Diastereoselective Synthesis of Nucleoside Analogues via Cyclization of Acyclic Precursors

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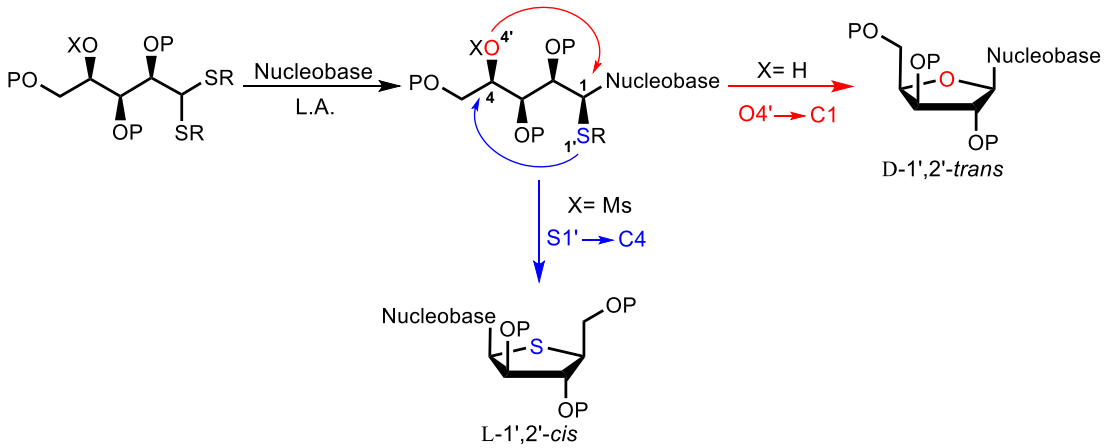
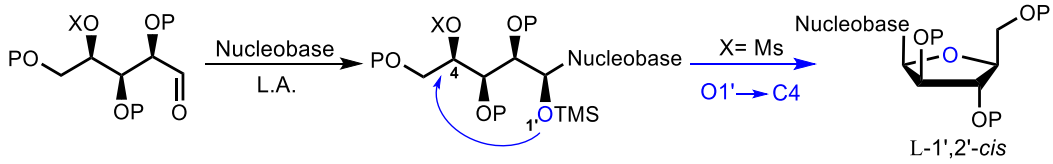
Schematic Abstract

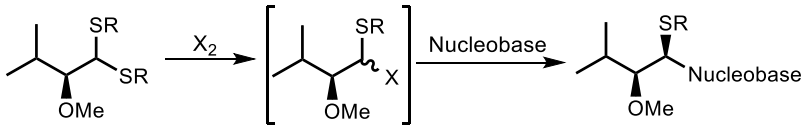
Chapter 1 : Introduction to Nucleoside Analogues and the Acyclic Approach

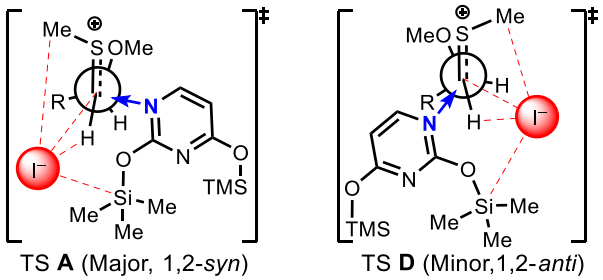


Chapter 2 : Synthesis and Cyclization of Acyclic 1,2-*syn N,O*-Acetals
(*J. Org. Chem.* **2012**, *77*, 7176)



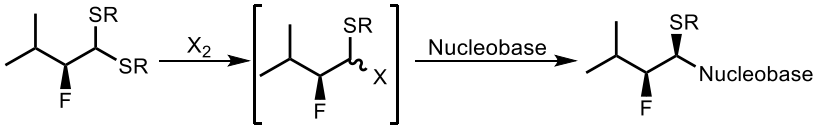
Chapter 3 : Investigation of Diastereoselective Acyclic Substitutions for the Synthesis of Thioaminals (*J. Org. Chem.* **2014**, *79*, 10504)

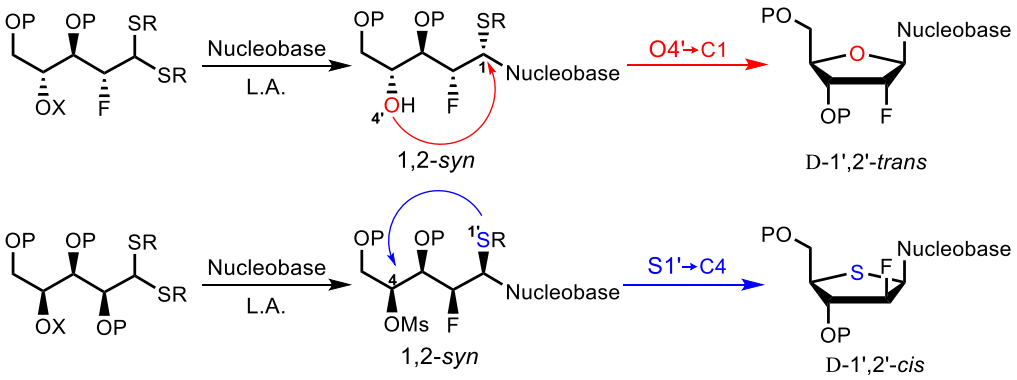




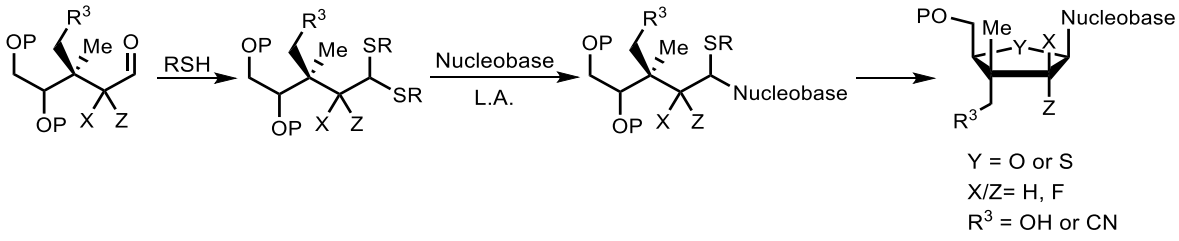
TS **A** (Major, 1,2-*syn*) TS **D** (Minor,1,2-*anti*)

Chapter 4 : Diastereoselective Synthesis of C2'-Fluorinated Nucleoside Analogues using the Acyclic Strategy





Chapter 5 : Synthesis of Novel Nucleoside Analogues bearing a C2'-F and a C3' all-Carbon Quaternary Center (*Org. Lett.* **2014**, *16*, 5698)



Abstract

Effective treatments against cancer and viral infections involve the administration of modified nucleosides that act as inhibitors of tumor growth and viral replication. The existing paradigm that governs nucleoside synthesis requires addition of nucleobases onto activated cyclic glycosyl donors. In such cases, the stereoselectivities depend on steric effects, anchimeric participation or displacement of an anomeric halide. A novel approach to nucleoside analogue synthesis using chiral acyclic thioaminals has been developed by our laboratory. A kinetically controlled cyclization of an acyclic precursor already containing the nucleobase is well suited to create such sterically encumbered molecules. Such cyclizations involve a stereogenic center bearing the nucleobase and a thioether moiety. This thioether may serve as a leaving group or as a nucleophile. In order to take advantage of the stereochemistry of the thioaminal at C1, both types of cyclizations involve intramolecular S_N2-like nucleophilic displacements. The first cyclization involves displacement of the activated thioalkyl group of the thioaminal by the secondary hydroxyl group at C4 (O4′-C1 cyclization) resulting in D-1',2'-*trans* furanosides. Alternatively, the sulfur of the thioaminal can serve as a nucleophile when the C4 hydroxyl is converted into a leaving group (S1′-C4 cyclization). This strategy gives access to L-1',2'-*cis* thioanalogues.

This acyclic approach addresses two key synthetic challenges in the synthesis of nucleoside analogues, namely, formation of L-nucleoside analogues along with a 1',2'-*cis* stereochemical arrangement between the nucleobase and the C2'-substituent. A protocol was developed in which acyclic *N,OTMS*-acetals were accessed with high 1,2-*syn* diastereoselectivities by addition of silylated pyrimidine and adenine nucleobases onto aldehydes in the presence of a bidentate Lewis acid. In the subsequent O1'-C4 cyclization, the oxygen of the acetal serves as the

nucleophile involved in the displacement of the leaving group at the C4 position. This strategy provides stereoselective access to unnatural L-nucleosides with a variety of nucleobases starting from easily accessible pools of D-sugars. As importantly, this methodology addresses the challenging synthesis of 1',2'-*cis* nucleosides.

The efficient synthesis of nucleoside analogues using this acyclic methodology relies on introduction of a pyrimidine or purine nucleobase in a stereocontrolled manner onto an acyclic precursor. It has been observed that nucleobases add to C2-alkoxydithioacetals with high 1,2-*syn* selectivity. An experimental and theoretical model compound study has been done to rationalize the origin of this 1,2-*syn* diastereocontrol (anti-Felkin-Anh) when silylated nucleobases add to acyclic dithioacetals.

A modification that improves the biological properties of nucleoside analogues is the introduction of fluorine, a common tool used in drug discovery. Access to two of the scaffolds that are difficult to synthesize using standard paradigms for nucleoside analogue formation, namely, 1',2'-*trans* furanosides and 1',2'-*cis* thiofuranosides bearing a fluorine in the C2'-position is possible using our acyclic approach. Nucleobase coupling onto acyclic dithioacetals bearing a C2-F maintains preference for 1,2-*syn* stereocontrol and subsequent intramolecular cyclization of these fluorinated thioaminals provides 1',2'-*trans* furanosides and 1',2'-*cis*-thiofurnaosides. Using these C2'-F scaffolds formation of SAM analogues, the cofactor implicated in methyltransferases, were designed.

Despite the availability of nucleoside analogues, there is a need to develop new agents with improved properties to overcome issues of resistance. In this regard, a new series of NAs bearing

a C3'-quaternary center and a C2'-F atom have been synthesized and are being investigated as potential antimetabolites.

Sommaire

Cet ouvrage explore de nouvelles voies pour la synthèse d'analogues de nucléosides. Nous allons décrire des travaux démontrant qu'il est possible de capitaliser sur la stéréochmie en C1 d'un précurseur thioaminal acyclique comportant une nucléobase pour générer stéréosélectivement des analogues de nucléosides et de thionucléosides. La possibilité d'accéder à deux types de nucleosides à partir d'un même intermédiaire, par deux modes de cyclisation intramolécularies différents, souligne l'efficacité et la versatilité de cette approche sur le plan de la diversité chimique. D'une part, le mode O4'-C1, où l'alcool en C4 est le nucléophile et le sulfide du thioaminal est le groupe partant, conduit à des nucléosides avec inversion de configuration en position anomérique. Le mode S1'-C4, où le sulfide est l'entité nucléophile déplaçant un mésylate en C4, conduit à des thionucléosides 1',2'-*cis* avec rétention de configuration en C1 et inversion en C4.

Nous allons démontrer qu'il est possible de générer diastéréosélectivement des intermédiaires de type *N,OTMS*-acétals, comportant des bases pyrimidines et adénine, par l'addition de bases silylées sur des polyalkoxyaldéhydes activés à l'aide d'acides de Lewis. Ces intermédiaires cyclisent par le déplacement S_N2 intramoléculaire d'un groupement partant en position C4 par l'oxygène à la position anomérique (C1). Les nucléosides obtenus par ce mode de cyclisation possèdent une géométrie 1',2'-*cis* difficilement accessible par les autres méthodologies et sont formés avec une configuration L- à partir de sucres naturels.

Afin de mieux comprendre l'obtention diastéréosélective de thioaminals 1,2-*syn* par l'addition de nucléobase silylées sur des C2-alkoxydithioacétals, nous avons effectué une étude expérimentale et théorique avec un modèle simple. Cette étude nous a amené à privilégier un modèle d'état de transition qui prend en compte la donation sigma, l'encombrement stérique et un effet gauche entre le groupement C2-alkoxy et le sulfonium. Ces travaux ont démontré que l'addition de nucléobases produit par un d'état de transition de type S_N2 où la nucleobase attaque sur la face moins encombrée de la paire d'ions impliquent le thionium.

Par la suite, nous allons nous intéresser à substituer diastéréosélectivement des dithioacétals, qui possède un fluor en C2, par une base azotée pour tenter de générer sélectivement des thioaminals. La cyclisation S1'-C4 ou O4'-C1 de ces adduits conduit ensuite très efficacement aux 1',2'-*trans* furanosides et 1',2'-*cis* thionucléosides. L'élaboration d'analogues de SAM, soit le cofacteur impliqué pour le transfert d'un groupe méthyle, dans les méthyltransférases qui a été associée au cancer, revêt une importance considérable pour la conception de molécules cibles (nucléosides et thioanalogues correspondants).

Le présent projet vise la découverte de nouveaux agents antiprolifératifs de la famille des analogues de nucléosides. Les drogues utilisées en clinique souffrent de nombreuses limitations. Nous allons utiliser notre méthode de synthèse acyclique pour donne accès aux nouveaux nucléosides qui possèdent un centre quaternaire carboné en C3' et un fluor en C2'.

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List of Abbreviations

Å	angstrom
Ac	acetyl
app	apparent
aq	aqueous
Bn	benzyl
bp	broad peak
Boc	*tert*-butoxycarbonyl
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
Bz	benzoyl
calcd	calculated
^{13}C NMR	carbon-13 nuclear magnetic resonance
Cbz	carboxybenzyl
CDA	cytosine deaminase
conc.	concentration
^{o}C	degrees Celsius
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
D-	sugar derived compound with D-configuration
d	doublet
dd	doublet of doublets
dt	doublet of triplets
ddd	doublet of doublets of doublets
DAST	diethylaminosulfur trifluoride
DCE	dichloroethane
dCK	deoxycytidine kinase
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DFT	density functional theory

DIBAL-H	diisobutylaluminium hydride
DIEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMBz	2,4-dimethoxybenzoyl
DMF	dimethylformamide
DMPD	1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine
DMSO	dimethyl sulfoxide
DMT	dimethoxytrityl
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
E	energy
EI	electron impact ionization
equiv.	equivalents
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
g	gram
G	Gibbs free energy
h	hours
hCNT	human concentrative nucleoside transporter
hENT	human equilibrative nucleoside transporter
^{1}H NMR	proton nuclear magnetic resonance
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
IC_{50}	inhibitory concentration for 50% of the population
IR	infrared
*i*Pr	*iso*-propyl

J	coupling constant
KIE	kinetic isotope effect
KHMDS	potassium bis(trimethylsilyl)amide
L-	sugar derived compound with L-configuration
L.A.	Lewis acid
LDA	lithium diisopropylamide
$LiAlH_4$	lithium aluminium hydride
LNAs	locked nucleoside analogues
LP	lone pair
m	multiplet
M	molar
Me	methyl
mg	milligram
MHz	megahertz
min	minute
ml	milliliter
mmol	millimole
MS	mass spectrometry
Ms	methylsulfonyl
MsCl	methanesulfonyl chloride
N	normal
NBO	natural bond orbital
n.d.	not determined
NBS	*N*-bromosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
NI	no inhibition
NIS	*N*-iodosuccinimide
NOE	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
NsCl	4-nitrobenzenesulfonyl chloride
Nu	nucleophile

P	protecting group
PCM	polarizable continuum model
Ph	phenyl
PMBz	*p*-methoxybenzoyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PMTs	protein methyltransferases
PTSA	*p*-toluenesufonic acid
Pr	propyl
Py	pyridine
q	quadruplet
R_f	retention factor on TLC
RNA	ribonucleic acid
RNR	ribonucleotide reductase
s	singlet
SAM	S-adenosylmethionine
sat.	saturated
t	triplet
T	temperature
*t*AmOH	*tert*-amylalcohol
TBABF	tetrabutylammonium bifluoride
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
td	triplet of doublets
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran

THP	tetrahydropyran
Thy	thymine
TIPS	triisopropylsilyl
$TIPDSCl_2$	1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
TLC	thin layer chromatography
TMS	trimethylsilyl
TS	transition structure
TTBP	2,4,6-tri-*tert*-butylpyrimidine
Tr	triphenylmethyl
µL	microliter
XtalFluor-E	diethylaminodifluorosulfinium tetrafluoroborate

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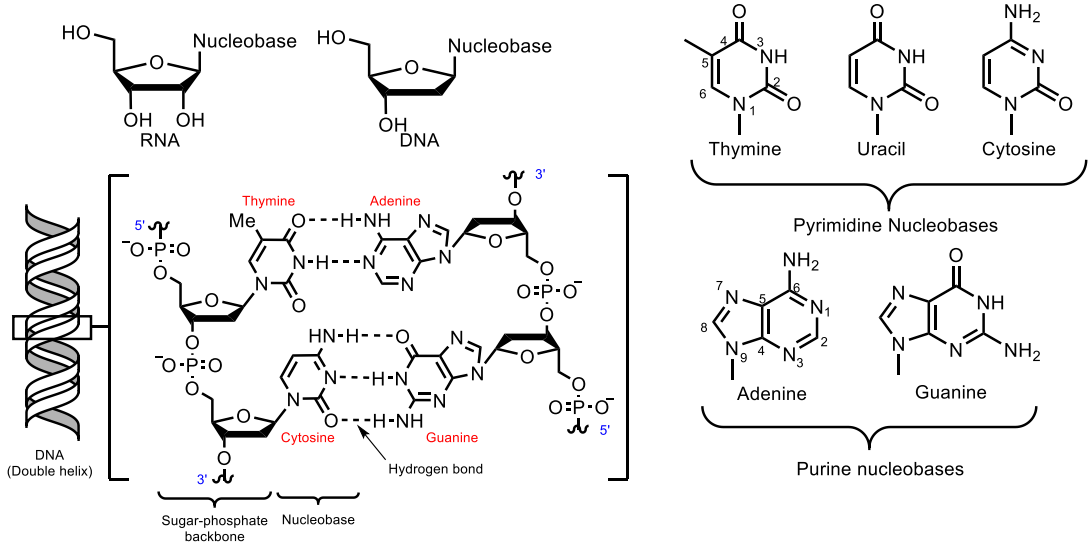
Chapter 1 Introduction to Nucleoside Analogues and the Acyclic Approach

1.1 Nucleoside Analogues

Nucleotides are the key building blocks that make up DNA and RNA and are involved in many cellular processes such as metabolism, cell signaling and regulation of enzymes.[1] The double stranded helix of DNA that stores our genetic information contains nucleotide units composed of a nitrogenous nucleobase, a five-membered ring sugar and a phosphate group (Figure 1.1). In DNA, thymine and cytosine are the pyrimidine nucleobases attached through a β-glycosidic bond between the C1 carbon of the D-2-deoxyribofuranose and the N1 nitrogen of the nucleobase. RNA displays a similar structure, but the nucleobase is attached to a D-ribofuranose sugar moiety and uracil replaces thymine. Both DNA and RNA contain adenine and guanine as the purine nucleobases attached via the N9 nitrogen. The sugar scaffold in RNA contains a hydroxy substituent at the C2 position that has a 1',2'-*trans* stereochemical relationship with the nucleobase. This element is absent in DNA, hence the deoxy prefix in deoxyribonucleic acid (DNA). The difference between nucleosides and nucleotides is the presence of a phosphate group at the C5- or C3-oxygen in the latter.

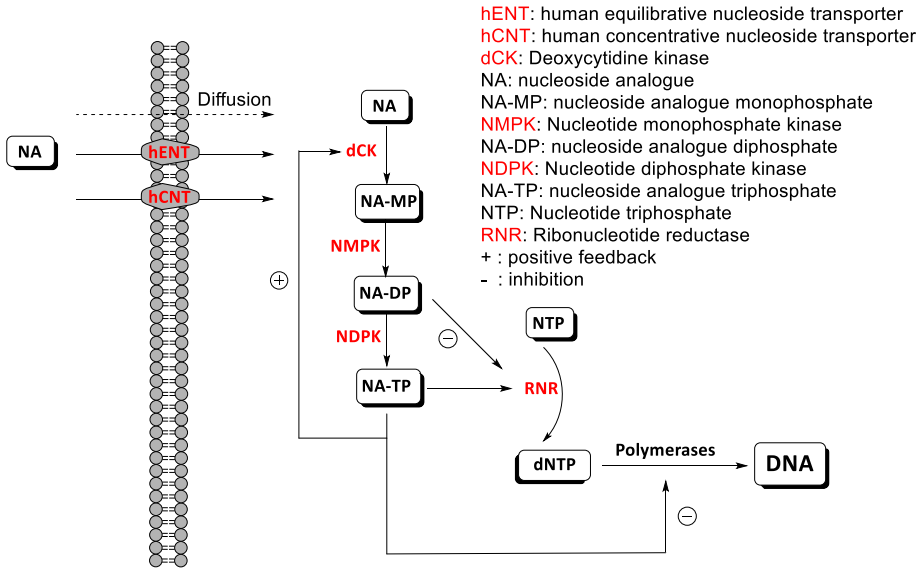
Figure 1.1 Natural nucleosides found in DNA and RNA.[2]



One of the most efficient treatments against cancer and viral infections involves administration of modified nucleosides (nucleoside analogue; NA) which are designed to interfere with cell division and viral replication through incorporation into nucleic acids (DNA and RNA) and/or inhibition of essential enzymes, such as human and viral polymerases, kinases, ribonucleotide reductase, and DNA methyltransferases.[1,3] NAs thus compete with their endogenous counterparts to inhibit the synthesis of nucleotides, which is the limiting process in cell proliferation.[4] Many of the enzymes involved in nucleotide synthesis are highly active in cancer cells, but barely detectable in non-proliferating cells.[5]

In order to act as antimetabolites, nucleoside analogues must first enter the cell through diffusion or with the help of nucleoside transporters, which are classified as human equilibrative nucleoside transporters (hENT) or human concentrative nucleoside transporters (hCNT) (Figure 1.2).[6] hENTs transport NAs across the cell membrane based on an equilibrium between the intra- and extra-cellular concentration gradients whereas hCNT rely on ATP to transport NAs against a concentration gradient.[7] In order to be active antimetabolites, NAs must be phosphorylated. The first step in this process is the monophosphorylation by dCK (deoxycytidine kinase),[6] which is often rate-limiting. A second and third phosphorylation results in the formation of the di- and triphosphate metabolites. The triphosphate species can lead to apoptosis through incorporation into nucleic acids or through mitrochondrial release of apoptosis inducing factors. Inhibition of RNR (ribonucleotide reductase) can also result in cell death through depletion of the deoxy nucleotides available for DNA synthesis. Diphosphorylated and triphosphorylated analogues can both inhibit RNR.[1]

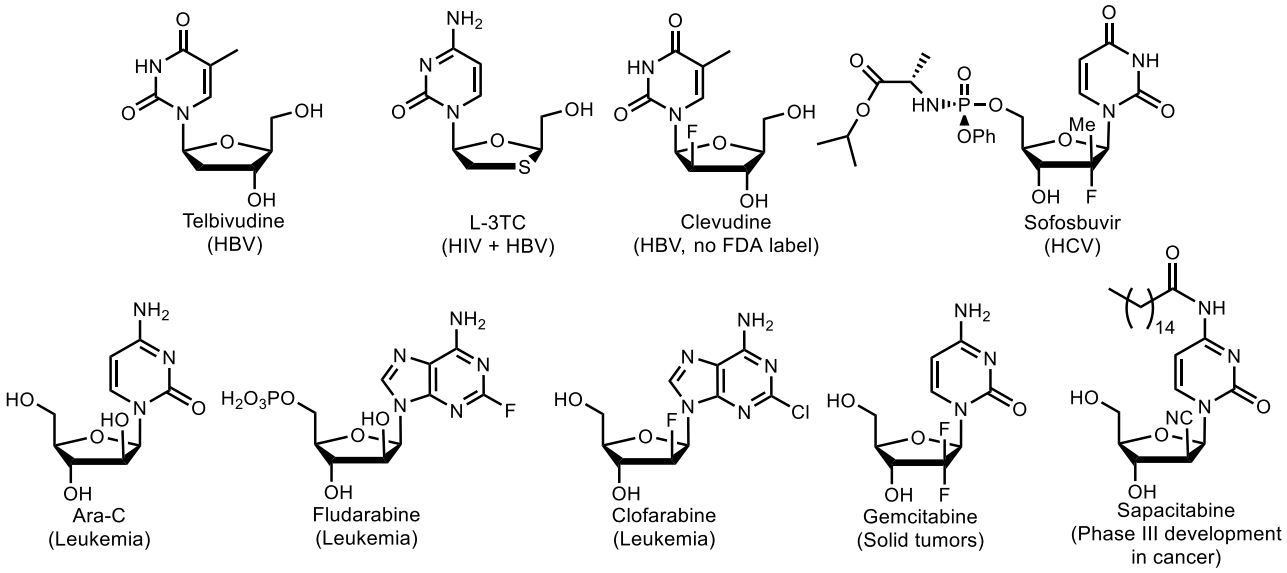
Figure 1.2 Mechanism of action of nucleoside analogues. Modified from reference 7.



Antiviral and anticancer FDA approved nucleoside analogues contain various modifications on the sugar ring, the nucleobase, or to the substituents and their stereochemical relationships (Figure 1.3). Many therapeutically relevant nucleoside analogues that have been accepted for the treatment of leukemia display arabino-scaffolds with 1',2'-*cis* arrangements between the nucleobase attached at the anomeric centre and an electron withdrawing group attached at C2 (for example Clevudine, Ara-C, Fludarabine, Clofarabine, Sapacitabine, Figure 1.3).[6-9] This particular stereochemical arrangement has been demonstrated to increase the rate of monophosphorylation by dCK through a series of favorable hydrogen bonding interactions with the surrounding amino acids.[10-12] The interest in synthesizing L-NAs (L-3TC, Telbivudine, Clevudine) has grown exponentially since the discovery of L-3TC as the first biologically active member of the L-series.[13-15] The unnatural L-configuration of these drugs reduces their cytotoxicity towards healthy cells while still being processed by viral enzymes.[16] Another important modification that is seen in NAs is the incorporation of fluorine in the C2' position of the sugar ring (for example Clevudine, Sofosbuvir, Clofarabine, Gemcitibine). Fluorinated NAs

have become useful anticancer and antiviral agents due in part to the increased stability of their glycosidic bond.[17] Gemcitabine with two C2-fluoro substituents is one of the most important chemotherapeutic agents used for the treatment of solid tumors.[18,19]

Figure 1.3 FDA approved antiviral and anticancer agents.[1]



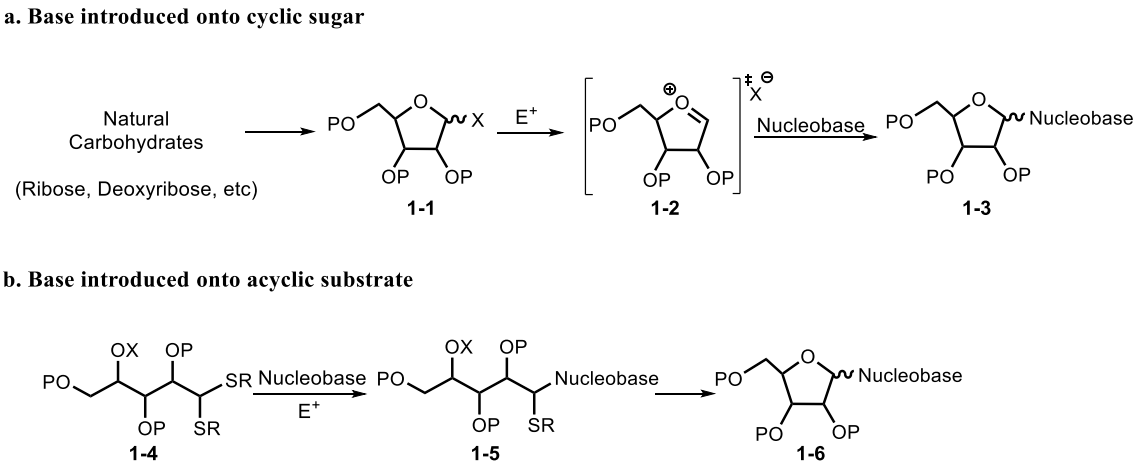
In addition to serving as anticancer and antiviral agents, NAs are finding use in the treatment of other conditions. For example, nucleosides and related compounds are used in the treatment of hyperuricaemia, as an immunosuppressive drug in organ transplantation, in autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, in obstructive pulmonary disease and asthma as well as potential agents for neuro- and cardioprotection.[1]

1.2 Synthesis of Nucleoside Analogues

Due to the potential of NAs as anticancer and antiviral agents, there has been much interest in developing various strategies for their synthesis. In broad terms, these strategies can be regarded as divergent or convergent.[20] The divergent approach transforms natural nucleosides into analogues allowing for the original configuration of the glycosidic bond to be maintained. This

approach is, however, limited to the natural pool of available nucleosides. Condensation of nucleobases onto sugar derivatives is the second strategy, which offers a convergent approach to their synthesis.[17] This methodology is not limited to natural nucleosides and thus results in increased substrate diversity. One drawback for this strategy is that the stereochemistry of the glycosidic bond must be controlled. In this respect, the development of stereocontrolled N-glycosylation reactions continues to be an important area of research. The general paradigm for nucleoside synthesis involves introduction of a nucleobase onto a preformed sugar scaffold (Scheme 1.1a). Using this approach, pyrimidine and purine nucleobases are coupled with activated cyclized carbohydrate precursors (**1-1**) bearing a leaving group at the anomeric position and occurs through formation of an intermediate oxonium (**1-2**). Various strategies have been developed to control the diastereoselectivity (1',2'-*trans* versus 1',2'-*cis*) for nucleobase addition using this approach, some of which will be highlighted below.

Scheme 1.1 Convergent strategies for NA synthesis.



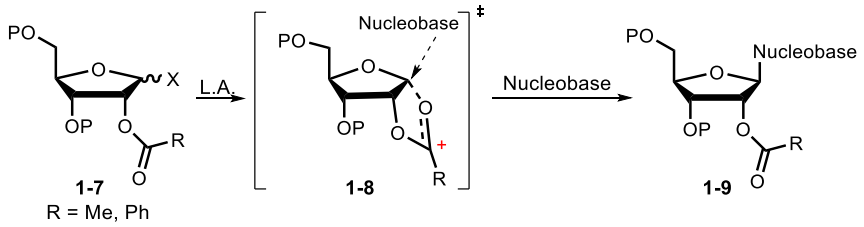
Research in the Guindon laboratory has focused on the development of an acyclic methodology for nucleoside analogue synthesis (Scheme 1.1b).[21] Coupling of a nucleobase to an activated acyclic dithioacetal precursor (**1-4**), results in diastereoselective formation of an acyclic

thioaminal (**1-5**). The stereochemistry of this thioaminal is maintained in the subsequent cyclization process allowing for NAs to be synthesized with a controlled *cis* or *trans* relationship between the nucleobase and C2' substituent.

1.2.1 General strategies for the synthesis of 1',2'-*trans* C2'-alkoxy furanosides

Using the standard paradigm of nucleobase addition onto preformed cyclic sugar scaffolds (Scheme 1.1a), the issue of controlling the 1',2'-stereochemistry between the nucleobase and the C2'-substituent has been the target of much research. Obtaining a 1',2'-*trans* relationship typically involves anchimeric assistance with the neighboring protecting group (Scheme 1.2).[22] Upon activation of the anomeric moiety of furanoside **1-7** with a Lewis acid, the C2 protecting group stabilizes the developing oxonium through formation of a bicyclic intermediate (**1-8**). This hinders the bottom α-face of the sugar moiety forcing the nucleobase to attack from the upper β-face resulting in the 1',2'-*trans* isomer **1-9**.

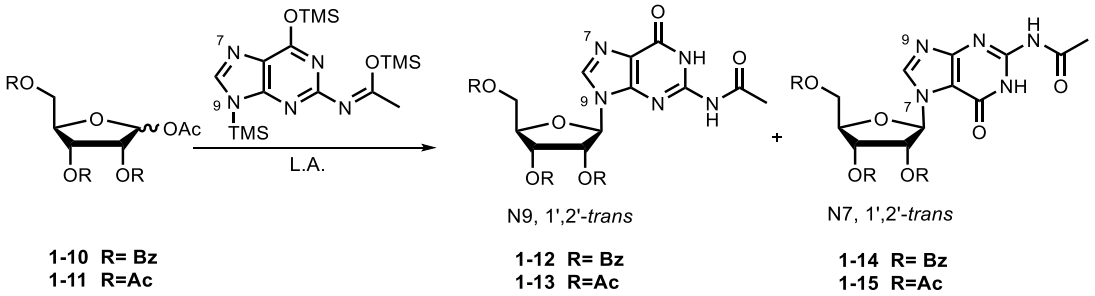
Scheme 1.2 1',2'-*trans* NA synthesis.



Addition of nucleobases onto such electrophilic intermediates can be done through the fusion method that involves reaction of the free nucleobase and the electrophilic sugar at high temperatures.[5] Alternatively, the metal salt procedure involving coupling the salt (mercury or sodium) of the nucleobase to activated sugars can be used as is often the case for addition of purines. This typically results in moderate yields of the desired NA.[5] Nucleobase silylation is a widely used strategy to enhance the yield of the glycosylation resulting from an increase in

solubility and nucleophilicity of the purine and pyrimidine nucleobases.[5] The multiple nitrogens present in purine and pyrimidine scaffolds can lead to mixtures of regioisomeric glycosylation products depending on the reaction conditions (substrate, solvent, Lewis acid, reaction time and temperature). Regioselectivity issues are typically more prevalent for the purine nucleobases. For example, additions of purines often result in a mixture of the N9- and N7-glycosylated products,[23] as can be seen in the following synthesis of 1',2'-*trans* nucleosides **1-12** to **1-15** (Table 1.1).[24,25]

Table 1.1 Synthesis of 1',2'-*trans* N9-and N7-regioisomers from reaction of guanine with ribofuranoside.[24,25]

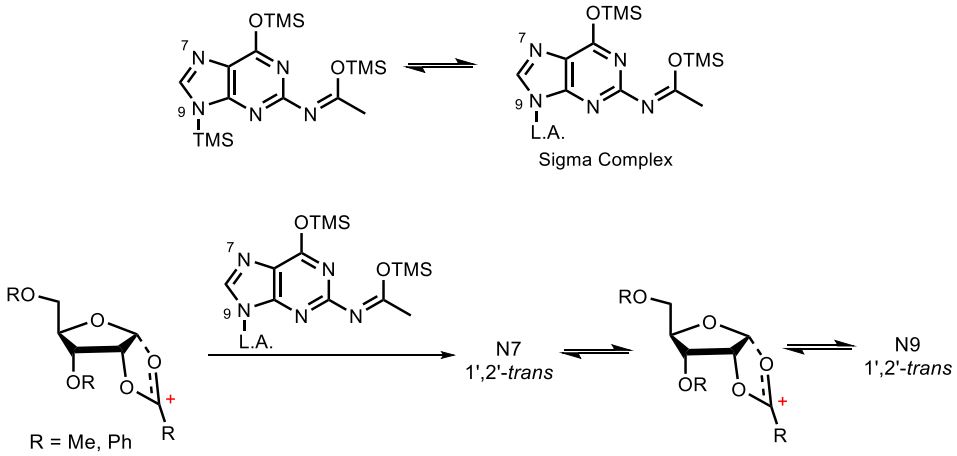


Entry	Substrate	Lewis Acid, Time	T	Solvent	Ratio (**N9**:**N7**)	Yield (%)
1	R = Bz	$SnCl_4$, 4h	25 ^oC	MeCN	1:3	81
2	R = Ac	$SnCl_4$, 4h	25 ^oC	MeCN	1:95	78
3	R = Bz	TMSOTf, 1.5h	84 ^oC	$ClCH_2CH_2Cl$	6:1	79
4	R = Bz	TMSOTf, 6h	84 ^oC	$ClCH_2CH_2Cl$	12 :1	88
5	R = Bz	TMSOTf, 6h	111 ^oC	Toluene	32:1	99

Coupling of silylated N^2-acetylguanine with protected ribo-configured anomeric acetates (**1-10** and **1-11**) resulted in a mixture of the N9-(**1-12** and **1-13**) and N7-(**1-14** and **1-15**) regioisomers with a 1',2'-*trans* stereochemistry. These results have been rationalized by considering the

affinity of the Lewis acid for the silylated nucleobase along with kinetic and thermodynamic factors.[23] Formation of the N7-regioisomer as the major product occurs with the use of $SnCl_4$ as the Lewis acid in MeCN at relatively low reaction temperatures (entries 1-2). Reaction with TMSOTf in DCE or toluene at higher temperatures and longer reaction times enhances the formation for the N9-regioisomer (entries 3-5). The difference in N9/N7 product distribution with the Lewis acid ($SnCl_4$ or TMSOTf) has been rationalized from the strength of the σ-complex formed between the Lewis acid and the nucleobase (Scheme 1.3). $SnCl_4$ forms a strong σ-complex with the less sterically hindered N9-nitrogen of the purine.[23] Therefore, N7 is more available for glycosylation. However, the weak σ-complex between the N9 nitrogen and TMSOTf allows for increased formation of the N9-regioisomer. The presence of an ester in the C2 position allows for an equilibrium to be established between the coupled product and the bicyclic oxonium intermediate (Scheme 1.3).

Scheme 1.3 Formation of σ-complex and equilibrium between N7-and N9-regioisomers.[5]



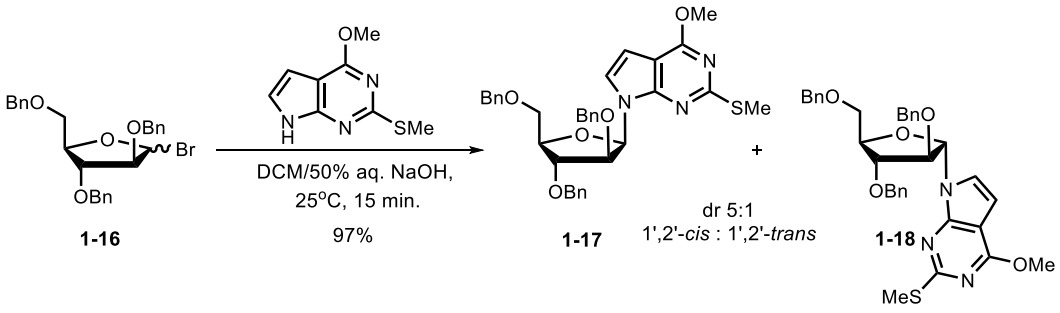
This equilibrium is favored in non- or weakly polar solvents (DCE, toluene, entries 3-5) where the Lewis acid facilitates removal of the nucleobase and thus leads to the thermodynamically favored N9-regioisomer.[5] More polar solvents like MeCN compete with the nucleobase for the Lewis acid and hinder these rearrangements thus preferring the N7-regiochemistry (entries 1-2,

Table 1.1).[23] The protecting group at C2 of the starting material (**1-10** and **1-11**) also influences the ratio of regioisomers (entries 1-2). Due to charge delocalization into the aromatic ring, a benzoate can more efficiently stabilize the positive charge in the bicyclic intermediate, as compared to an acetate. This shifts the equilibrium and decreases formation of the N7 regioisomer.[26] Therefore, although a 1',2'-*trans* stereochemistry is relatively easy to obtain, formation of the desired glycosylation product can be complicated by the presence of regioisomers.

1.2.2 General strategies for the synthesis of 1',2'-*cis* C2'-alkoxy furanosides

The 1',2'-*cis* configuration represents an important synthetic challenge since the anchimeric assistance approach cannot be used. As well, nucleobase addition has to occur on the more sterically hindered face of the sugar scaffold. Therefore, several different approaches have been developed to access the 1',2'-*cis* stereochemical relationship. One widely used strategy involves displacement of halofuranoses (Scheme 1.4).

Scheme 1.4 1',2'-*cis* NA synthesis via displacement of halofuranose.[27]

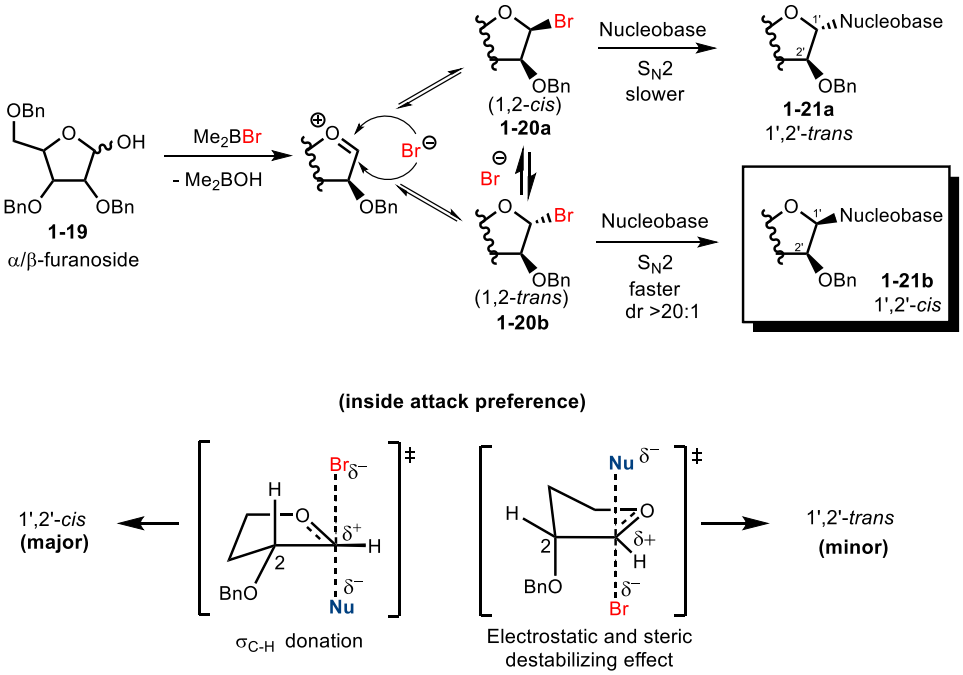


A 7-deazapurine nucleobase displaces an anomeric bromide (**1-16**) providing for example a 5:1 mixture of 1',2'-*cis* and 1',2'-*trans* diastereomers (**1-17** and **1-18**).[27] The preferred formation of

the 1',2'-*cis* nucleoside was thought to occur through S_N2 displacement of the dominant α-anomeric bromine.

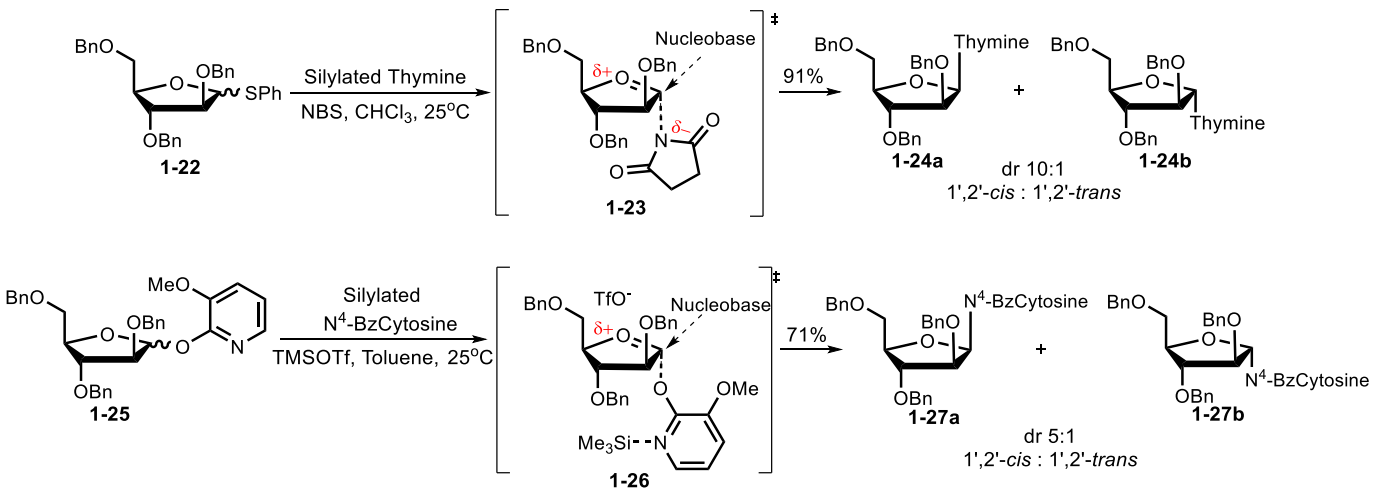
Addition onto halofuranoses to generate 1',2'-*cis* nucleosides has been further investigated in the Guindon lab.[28] Lactols of each sugar series (**1-19**, xylo-, ribo-, arabino-, lyxo-) were activated with dimethylboron bromide (Me_2BBr) to form a mixture of the corresponding bromofuranosides (**1-20**, Scheme 1.5). Reaction with pyrimidine nucleobases at 25 °C provided >20:1 diastereoselectivity in favor of the 1',2'-*cis* isomer (**1-21b**) independent of the starting ratio of bromides. This glycosylation proceeds through a fast equilibrium between the initially formed *cis* and *trans* bromofuranosides followed by preferential attack of the nucleobase onto the concave (inside) face of 1,2-*trans* bromothioether **1-20b** through an exploded S_N2 transition state.

Scheme 1.5 1',2'-*cis* NA synthesis via pyrimidine displacement of halofuranoses.[28]



Other approaches to synthesize 1',2'-*cis* NAs involve nucleobase displacement of 1,2-*trans* ion-pairs (Scheme 1.6). Activation of thioglycoside **1-22** with *N*-bromosuccinimide (NBS) and coupling with silylated thymine provided a 10:1 *cis*/*trans* ratio.[29] The preference for 1',2'-*cis* diastereoselectivity was rationalized from nucleobase attack onto oxonium intermediate **1-23** where the succinimide anion prefers a 1,2-*trans* relationship through minimization of steric and electrostatic repulsions with the C2-OBn substituent. The nucleobase, therefore, prefers to attack on the least hindered β-face giving preference to the 1',2'-*cis* isomer **1-24a**.

Scheme 1.6 1',2'-*cis* NA synthesis via ion-pair displacement.[29,30]

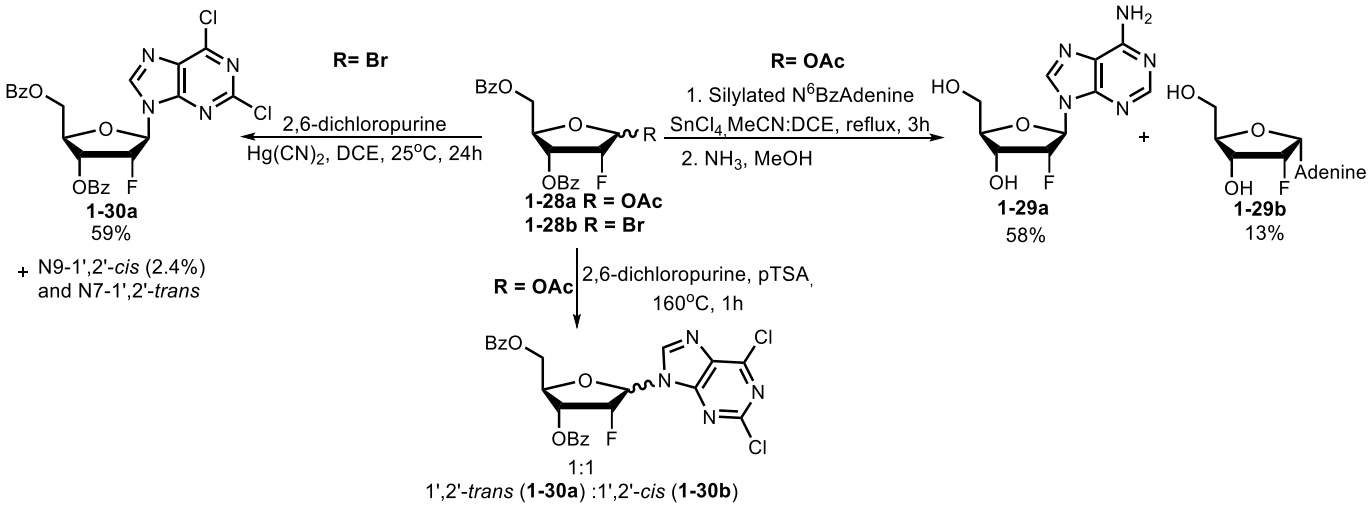


Activation of an anomeric MOP (3-methoxy-2-pyridyloxy) furanoside **1-25** with TMSOTf and coupling with silylated N^4-benzoylcytosine favored formation of the 1',2'-*cis* furanoside **1-27a**.[30] This also functions through ion-pair displacement where the nucleobase undergoes a S_N2 reaction on the less hindered face of the sugar moiety of intermediate **1-26**.

1.2.3 General strategies for the synthesis of 1',2'-*trans* C2'-F furanosides

Fluorination of molecules is a well-established strategy to increase pharmaceutical effectiveness in the design of new drugs.[31] Controlling the 1',2'-*trans* stereochemistry in NAs with a fluorine in the C2' position is challenging due to the lack of possible C2-neighboring group participation. Addition of nucleobases onto fluorinated sugars results in a variable mixture of 1',2'-*trans* and 1',2'-*cis* diastereomers. For example, activation of the ribo-fluorinated anomeric acetate **1-28a** (Scheme 1.7) with $SnCl_4$ and coupling with silylated N^6-benzoyladenine resulted in a 58% yield of the 1',2'-*trans* NA **1-29a** after benzoyl group deprotection along with 13% of the 1',2'-*cis* anomer **1-29b**.[32] Reaction of 2,6-dichloropurine with this same anomeric acetate (**1-28a**) resulted in a 1:1 mixture of the *trans* and *cis* diastereomers **1-30**.[33] Coupling anomeric bromide **1-28b** with 2,6-dichloropurine resulted in 59% of the N9-1',2'-*trans* isomer **1-30a** along with some of the N7-1',2'-*trans* and N9-1',2'-*cis* isomers.[33]

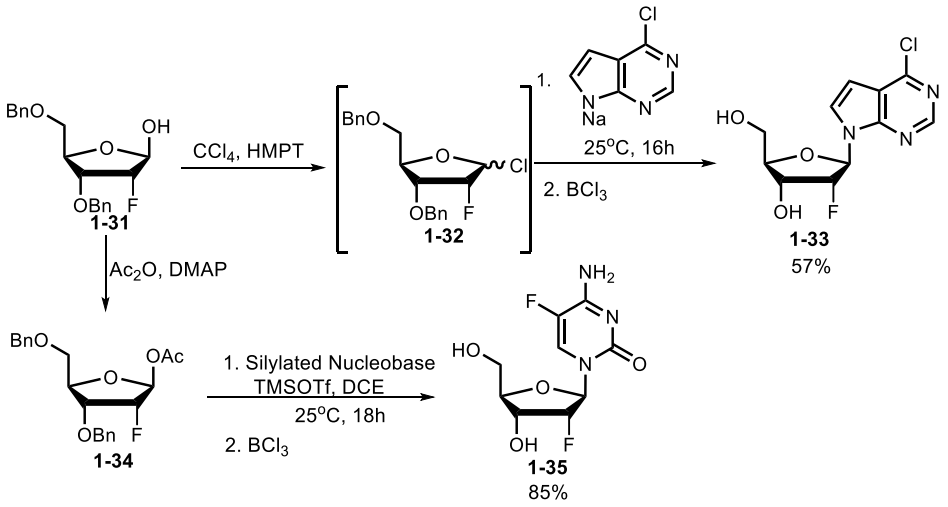
Scheme 1.7 Synthesis of 1',2'-*trans* C2'-fluorinated NA with benzoyl protecting groups.[32,33]



In a recent patent issued by Liotta,[34] the anomeric chloride (**1-32**) or acetate (**1-34**) of benzyl protected ribo-fluorinated precursor **1-31** was used to synthesis 1',2'-*trans* C2'-F nucleoside

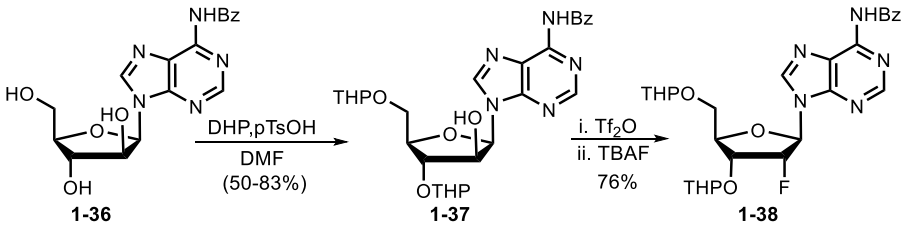
analogues (**1-33** and **1-35**, Scheme 1.8). Although the desired analogues were obtained in good yields, the selectivity of the glycosylations was not reported. It was mentioned, however, that the reactions resulted in a mixture of products.

Scheme 1.8 Synthesis of 1',2'-*trans* C2'-fluorinated NA with benzyl protecting groups.[34]



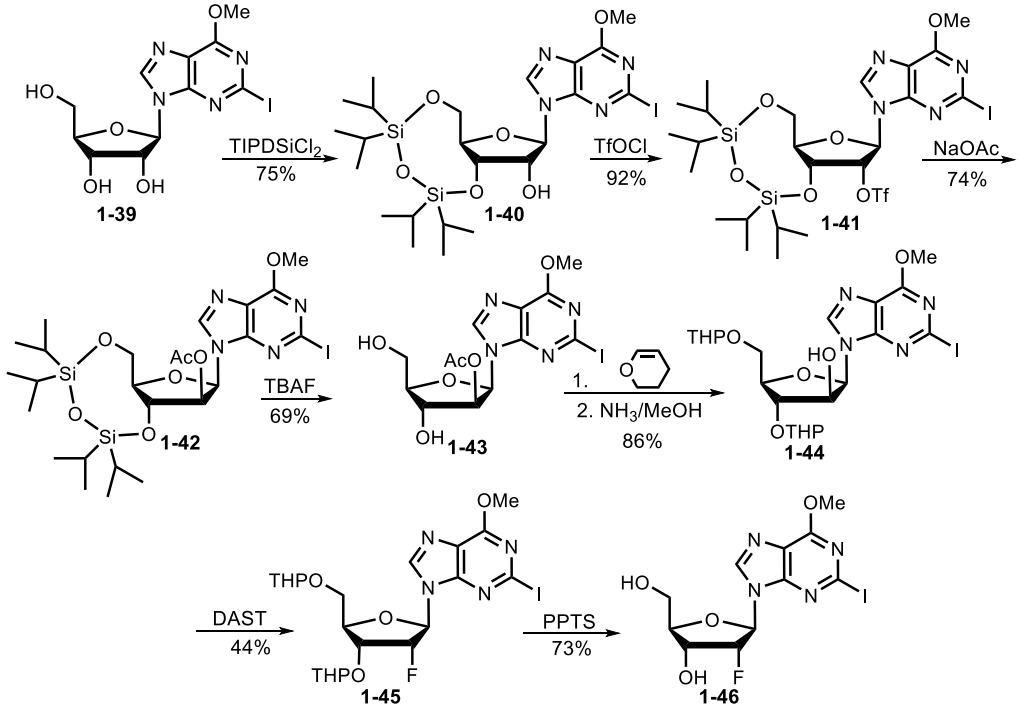
Due to the variable selectivity from condensation of nucleobases onto fluorinated furanoses, 1',2'-*trans* C2'-F nucleosides are often obtained from fluorination of preformed nucleosides.[35,36] For example, protection of the C3 and C5 hydroxyl groups of 1',2'-*cis* adenine furanoside **1-36** with tetrahydropyran (THP) (Scheme 1.9) leaves the C2 hydroxyl moiety of **1-37** open to triflate activation. Subsequent S_N2 displacement of the C2-triflate with a nucleophilic source of fluorine (TBAF) results in a high yield for the 1',2'-*trans* isomer **1-38**.

Scheme 1.9 1',2'-*trans* C2'-F NA synthesis via S_N2 displacement of C2-triflate.[36]



The 1',2'-*cis* stereochemical arrangement of the starting material (**1-36**, Scheme 1.9) was accessed through protecting group manipulations and inversion of the C2-stereocenter of 1',2'-*trans* furanoside **1.39** (Scheme 1.10).[37] Protection of the C3 and C5 oxygens with the tetraisopropyldisiloxane moiety (**1-40**) and introduction of a C2-triflate allowed for inversion of this stereocenter (**1-42**). Subsequent silyl group deprotection (**1-43**), protection with THP and displacement of the free C2-hydroxy group with DAST (**1-45**) allowed for formation of the 1',2'-*trans* C2-fluorinated nucleoside analogue **1-46**.

Scheme 1.10 1',2'-*trans* C2-F NA synthesis.[37]

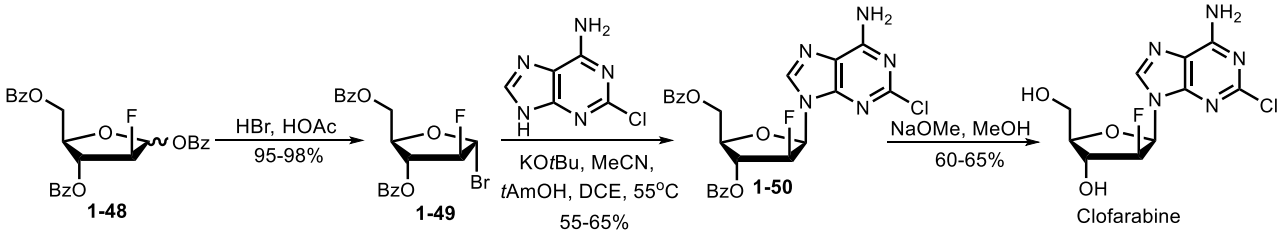


1.2.4 General strategies for the synthesis of 1',2'-*cis* C2'-F furanosides

S_N2 displacement of anomeric halofuranoses is the synthetic approach used for the formation of 1',2'-*cis* NAs with a fluorine in the C2' position and usually results in high ß-selectivity for pyrimidine nucleobases.[17,38] This procedure is also used with purine nucleobases (Scheme 1.11). For example, synthesis of Clofarabine occurs through addition of 2-chloroadenine to the 1',2'-

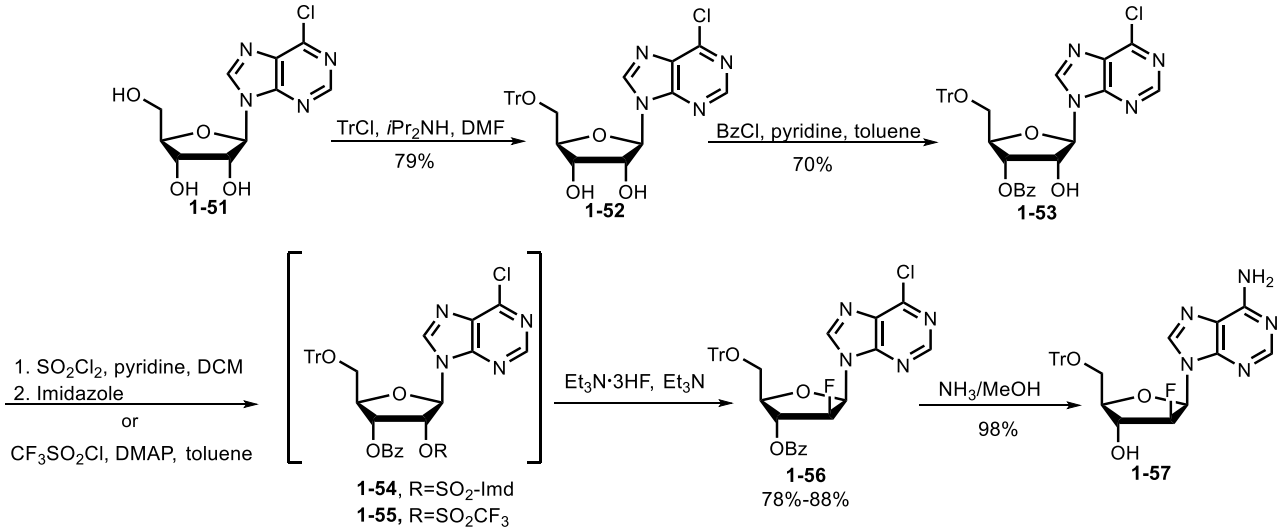
trans protected bromofuranose **1-49**.[39] The latter is proposed to undergo a stereospecific S_N2 displacement providing high 1',2'-*cis* selectivity.

Scheme 1.11 Synthesis of Clofarabine via displacement of bromofuranose.[6]



Fluorination of C2'-alkoxy 1',2'-*trans* analogues has been reported to access the 1',2'-*cis* stereochemistry (Scheme 1.12).[40] Following selective C5'-tritylation of the 6-chloropurine riboside (**1-51**) and C3'-benzoylation, the C2'-hydroxy group was converted to either the imidazolesulfonate (**1-54**) or the trifluoromethanesulfonate (**1-55**). Fluorination with 3HF•NEt_3 resulted in the C2'-fluorinated derivative **1-56** in good yield which was subsequently treated with ammonia to remove the C3'-benzoate and to introduce an amine on the purine ring.

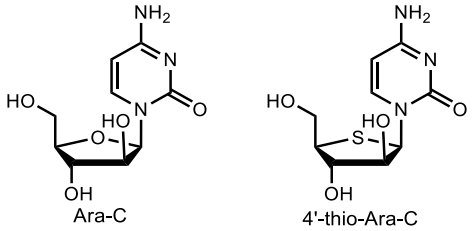
Scheme 1.12 Synthesis of 1',2'-*cis* C2'-F nucleoside analogues.[40]



1.3 Thiofuranosides

An important variation in the activity of nucleoside analogues has been demonstrated when the intracyclic oxygen of furanosides is replaced by sulfur. This is highlighted by 4′-thio-Ara-C (Figure 1.4), which has improved anticancer activity relative to Ara-C for solid tumors presumably due to an increase in bioavailability. The triphosphate form of 4'-thio-Ara-C has been shown to be a 20-fold more potent inhibitor of DNA synthesis while also being a poor substrate of cytidine deaminase allowing prolonged retention.[41,42] Another interesting property of this thiofuranoside is its possible dual mechanism of action with inherent antiangiogenic activity.[43] The development of thionucleoside analogues is therefore of interest to the medicinal chemistry community and various routes are being explored for their synthesis.

Figure 1.4 Ara-C versus 4′-thio-AraC.



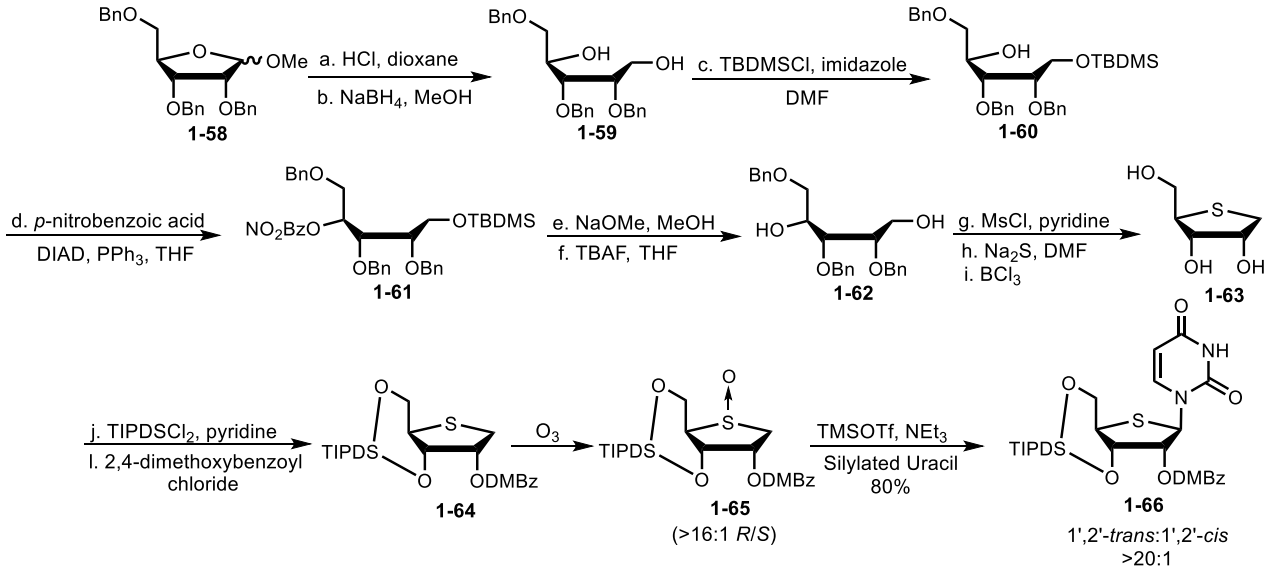
1.3.1 General strategies for the synthesis of C2'-alkoxy thiofuranosides

1.3.1.1 1',2'-*trans* thionucleoside analogues with a C2'-alkoxy group

The known methods for the synthesis of 1',2'-*trans* thioNAs require the appropriate choice of C2'-protecting group in order to make use of neighboring group participation. Access to these scaffolds therefore relies on coupling of a nucleobase to a cyclic thionium intermediate in which shielding of the α-face with the C2'-neighbouring group results in preferential formation of the ß-anomer. It has been shown that the net positive charge on the α-carbon of thioniums is quite

different than the corresponding oxygen congeners (+0.05 net positive charge for α-carbon of thionium versus +0.56 net positive charge for α-carbon of oxonium).[44] This implies that the resulting thiocarbonium intermediates are less susceptible to neighboring group effects and it has been suggested that a C2-acetyl is not an efficient protecting group for anchimeric participation. However, a C2-benzoyl bearing electron-donating substituents was found to provide high yields of desired ß-thiofuranosides. 1',2'-*trans*-4'-thioNAs have been synthesized from the corresponding tetrahydrothiophenes (Scheme 1.13).[45]

Scheme 1.13 Synthesis of 1',2'-*trans* thionucleoside analogues via anchimeric assistance.[45]



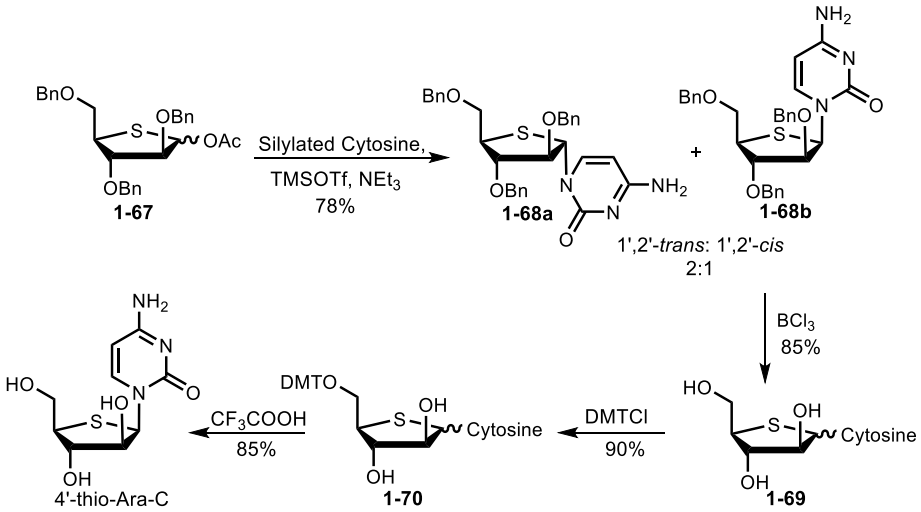
Acidic methanolysis of methyl 2,3,5-tri-O-benzyl-D-ribofuranoside (**1-58**) followed by reduction with $NaBH_4$ gave the corresponding diol **1-59**. The primary hydroxyl group was selectively protected with TBDMS and then converted to the L-lyxose derivative through a Mitsunobu reaction (**1-61**). Deprotection followed by formation of the dimesylate, reaction with sodium sulfide and benzyl group removal provided **1-63**. C3 and C5 protection with $TIPDSCl_2$ and installation of a 2,4-dimethoxybenzoyl group on the C2-hydroxyl moiety provided **1-64**. Oxidation using O_3 gave the desired sulfoxide **1-65**. Addition of silylated uracil to the cyclic

thionium formed *in situ* from a Pummerer reaction of the sulfoxide provided the 1',2'-*trans* thioNA **1-66**. The 2,4-dimethoxybenzoyl protecting group at C2' ensured high levels of 1',2'-*trans* selectivity.

1.3.1.2 1',2'-*cis* thionucleoside analogues with a C2'-alkoxy group

Synthesis of 1',2'-*cis* thionucleosides has not been studied to the same extent as with the oxygen analogues.[46] An efficient strategy to access this *cis* stereochemistry is lacking as can be seen by the poor selectivity obtained in the synthesis of 4′-thio-AraC (Scheme 1.14).[47] Activation of anomeric acetate **1-67** in the presence of TMSOTf and coupling with silylated cytosine provided a 2:1 selectivity in favor of the 1',2'-*trans* isomer (**1-68a**) that could not be separated from the desired 1',2'-*cis* product (**1-68b**). The mixture was therefore debenzylated and reprotected at C5' with a dimethoxytrityl (DMT) group to allow for separation of the two diastereomers. 4′-thio-Ara-C was obtained once the DMT group was removed in the presence of trifluoroacetic acid.

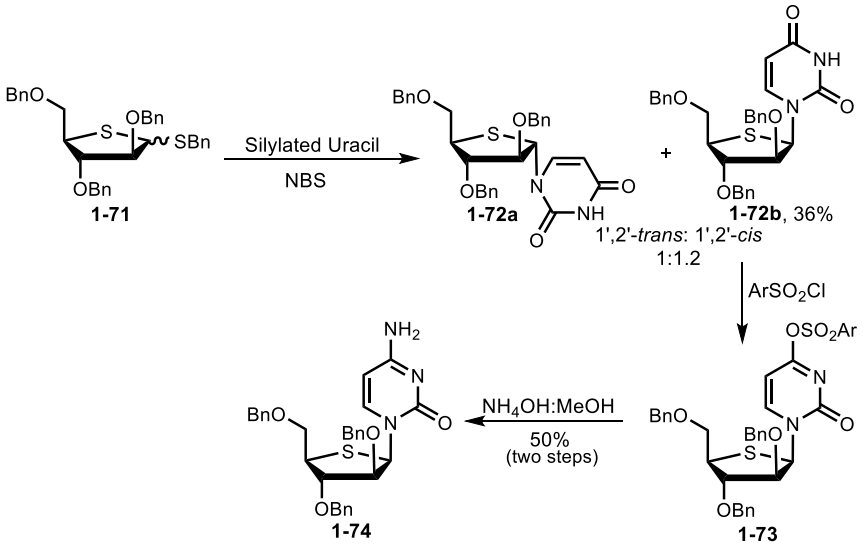
Scheme 1.14 Synthesis of 4′-thio-Ara-C: activation of anomeric acetate.[47]



In order to try to solve the issue of poor selectivity, activation of an anomeric thiobenzyl group (**1-71**) with NBS was attempted (Scheme 1.15).[47] Glycosylation with silylated uracil however,

resulted in a 1.2:1 ratio of the *cis* (**1-72b**) and *trans* isomers (**1-72a**). The 1',2'-*cis* isomer **1-72b** was isolated in 36% yield and conversion of the uracil nucleobase into cytosine resulted in 4′-thio-Ara-C.

Scheme 1.15 Synthesis of 4′-thio-AraC: activation of anomeric thiobenzyl. [47]

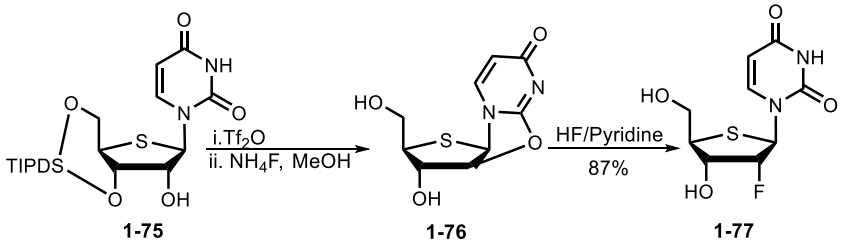


1.3.2 General Strategies for the Synthesis of C2'-F Thiofurnaosides

1.3.2.1 1',2'-*trans* thionucleoside analogues with a C2'-fluoro group

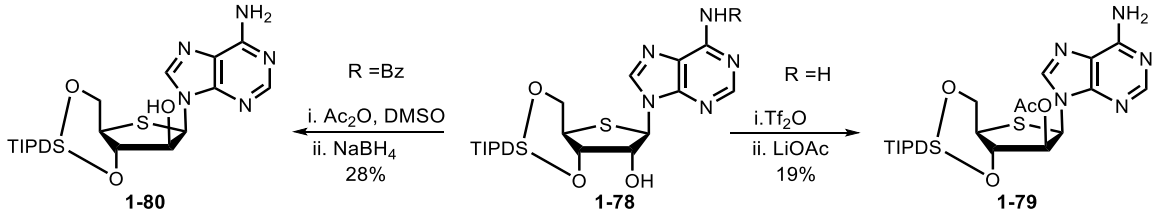
The known methods for the synthesis of 1',2'-*trans* thiofuranosides with a fluorine substituent in the C2' position and a pyrimidine nucleobase use similar strategies as those employed with an intracyclic oxygen.[48,49] The fluorine is introduced on a preformed scaffold that already has the nucleobase attached (Scheme 1.16). For example, the 4'-thio-uridine derivative **1-75** in which the C3' and C5'-hydroxy substituents are protected with a TIPDS group was converted into the anhydro-derivative **1-76** by treatment with trifluoromethanesulfonic anhydride followed by removal of the TIPDS group with ammonium fluoride. Treatment with HF-pyridine resulted in the 1',2'-*trans* 2'-deoxy-2'-fluoro-4'-thiouridine **1-77** in good yield.

Scheme 1.16 Synthesis of 1',2'-*trans* thio NA with a C2'-F and a pyrimidine nucleobase.[48]



This same strategy of forming an anhydro-derivative such as **1-76** cannot be applied with a purine nucleobase since there is no carbonyl oxygen to displace a leaving group at the C2' position. Therefore, other strategies were attempted for the synthesis of purine 1',2'-*trans* thio-nucleoside analogues (Scheme 1.17). Initial attempts involved conversion of a ribo-derivative (**1-78**) into one with an arabino-configuration (**1-79** or **1-80**) to set the stage for S_N2 displacement with a nucleophilic source of fluorine.

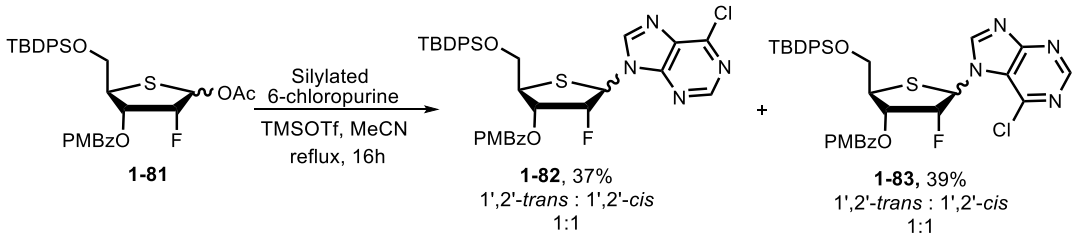
Scheme 1.17 Synthesis of arabino-thio NA with a purine nucleobase.[48]



However, after treatment of the TIPDS protected thio-derivative **1-78** with trifluoromethanesulfonic anhydride, and displacement with LiOAc, the desired product **1-79** was only obtained in 19% yield. As an alternative, oxidation with Ac_2O and DMSO followed by reduction with $NaBH_4$ resulting in a 28% yield of the desired arabino-derivative **1-80**. Due to the low yield of the necessary arabino-derivatives **1-79** and **1-80**, an alternate route involving condensation of a 2-F-4-thiosugar derivative and a purine nucleobase was investigated (Scheme 1.18).[48] Nucleobase coupling was done with thiosugar derivative **1-81** bearing a *p*-

methoxybenzoyl (PMBz) group in the C3-position in hopes of providing some C3-anchimeric assistance to favor the β-anomer. However, reaction with silylated 6-chloropurine in the presence of TMSOTf resulted in a mixture of the N9-(**1-82**) and N7-(**1-83**) regioisomers that lacked any 1',2'-diastereoselectivity.

Scheme 1.18 Synthesis of 1',2'-*trans* thio-NA with a C2'-F and a purine nucleobase.[48]



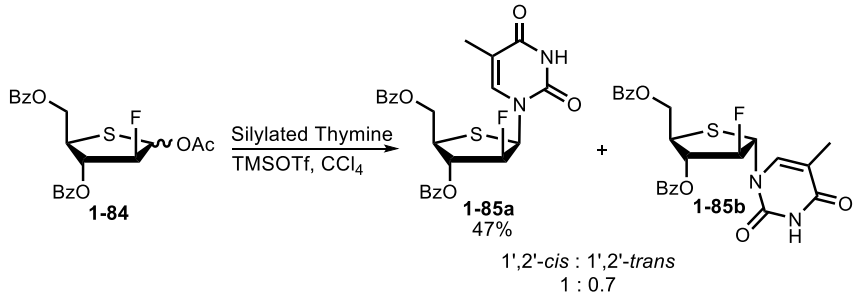
Therefore, it can be concluded that synthesis of 1',2'-*trans* thio-NA with a C2'-fluorine and a pyrimidine nucleobase occurs fairly easily through manipulation of a thioanalogue in which the stereochemistry of the glycosidic bond is already set. However, these manipulations cannot be used with purine nucleobases and methods for their synthesis result in poor selectivity for nucleobase addition.

1.3.2.2 1',2'-*cis* thionucleoside analogues with a C2'-F group

The synthesis of 1',2'-*cis* thioNA with a C2'-F and either a pyrimidine or purine nucleobase is also challenging. Methods to access such scaffolds rely on addition of nucleobases to anomeric acetates and result in poor selectivity.[50-52] Work from the laboratory of Professor Masad Damha at McGill University, demonstrated that 1',2'-*cis* thio-NA bearing a thymine nucleobase could be synthesized in 47% yield from condensation of silylated thymine with benzoyl protected thioacetate **1-84**.[50] They showed that the polarity of the solvent influenced the level of 1,2-

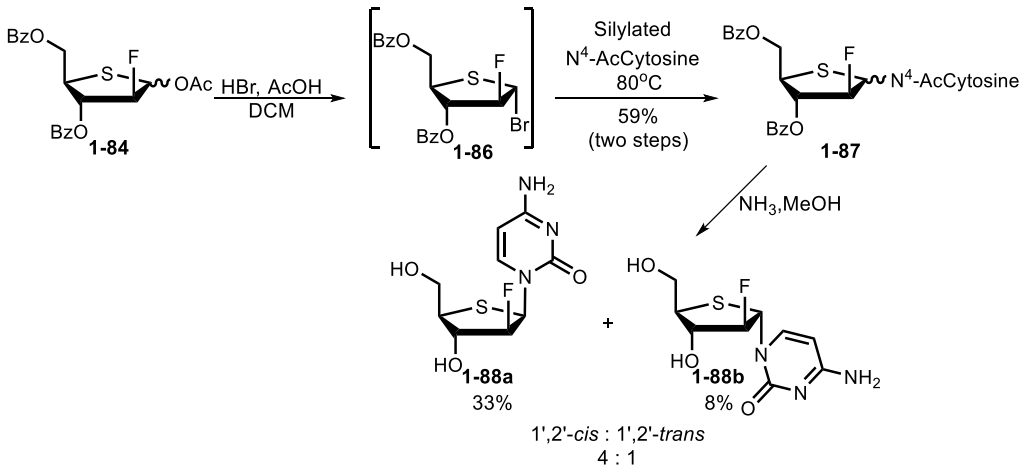
stereocontrol. Switching from MeCN to something less polar such as CCl_4 resulted in an increase in the diastereoselectivity of nucleobase addition from 3:1 (α-**1-85b**:β-**1-85a**) to 0.7:1(α-**1-85b**:β-**1-85a**). This was rationalized due to an increase in anchimeric assistance from the C3-OBz in solvents of decreasing polarity where the free thiacarbenium ion would be less stable.

Scheme 1.19 Synthesis of 1',2'-*cis* thio-NA with a C2'-F and a pyrimidine nucleobase.[50]



Formation of 2'-deoxy-2'-fluoro-4'-thio-NA have also been studied through condensation of halothiofuranoses with pyrimidine and purine nucleobases (Scheme 1.20).[53]

Scheme 1.20 Synthesis of 1',2'-*cis* thio-NA with a C2'-F via halogenothiosugars.[53]



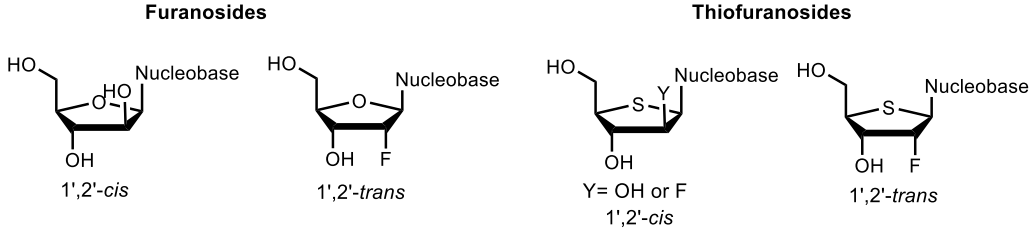
The desired 1',2'-*cis* thioNA **1-88a** was obtained in a 4:1 ratio with its 1',2'-*trans* anomer **1-88b** when bromothiofuranose **1-86** was coupled with silylated N^4-acetylcytosine followed by removal of the benzoyl protecting groups. Reacting 2,6-diaminopurine with the above

bromothiofuranose (**1-86**) in the presence of TMSOTf resulted in a 75% yield of a 1.2:1 mixture of the thio-NA in favor of the 1',2'-*trans* isomer. Thus, using the typical paradigm of nucleobase addition onto cyclic thio-derivatives bearing a C2'-F group leads to poor diastereoselectivity. Therefore, there is a need to find an alternative route to nucleoside synthesis in which the stereochemistry of the N-glycosidic bond can be better controlled.

1.3.3 Challenging nucleoside analogue scaffolds

It can be concluded that certain scaffolds are difficult to access using standard paradigms for nucleoside analogue synthesis. These include 1',2'-*cis* furanosides with an alkoxy group in C2' and furanosides with a 1',2'-*trans* relationship between the nucleobase and C2'-fluorine (Figure 1.5). In the thiofuranoside series, 1',2'-*cis* scaffolds with an alkoxy or fluorine substituent are hard to synthesize along with 1',2'-*trans* fluorinated compounds particularly those with purine nucleobases (Figure 1.5). This highlights the need for a novel strategy to be developed to access these challenging scaffolds. The acyclic approach developed in the Guindon laboratory (described below and the subject of this thesis) allows for an efficient method to access three of these challenging scaffolds, namely both of those in the furanoside series along with 1',2'-*cis* thiofuranosides.

Figure 1.5 Challenging NA scaffolds using standard paradigms.

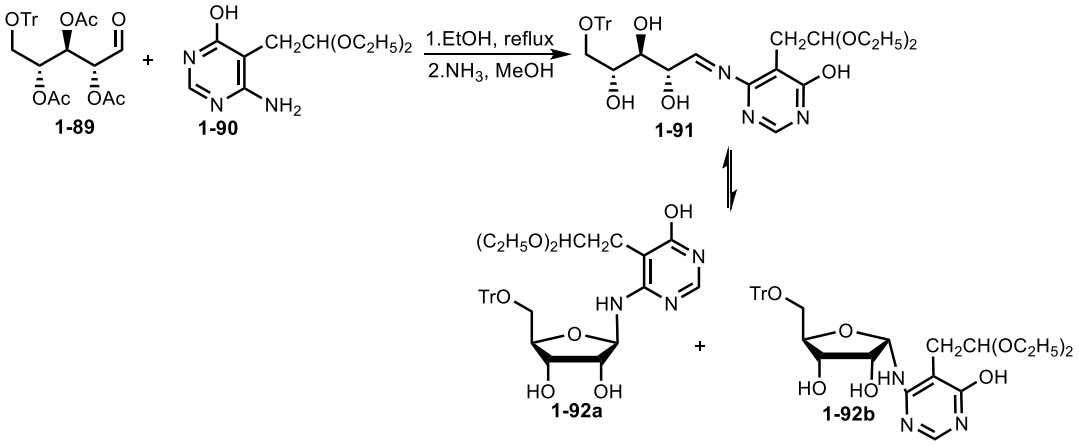


1.4 Acyclic approach for synthesis of nucleoside analogues

1.4.1 Precedent literature examples

Research in the Guindon laboratory has focused on stereoselective strategies to attach a nucleobase onto the C1 of acyclic intermediates where subsequent cyclization allows for the synthesis of nucleoside analogues (Scheme 1.1b). Although there are precedent reports involving nucleobase addition onto acyclic substrates, examples are scarce. One such example involves coupling onto acyclic aldehyde precursors with subsequent cyclization (Scheme 1.21).[54,55]

Scheme 1.21 Nucleobase addition onto acyclic aldehyde.[54]

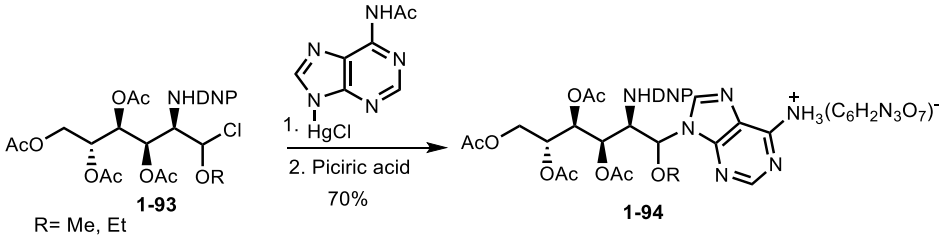


Reaction of substituted pyrimidine **1-90** with acetylated aldehyde **1-89** in refluxing ethanol followed by removal of the acetyl protecting groups resulted in **1-91** which exists in equilibrium with the cyclized *cis* and *trans* nucleosides (**1-92a** and **b**).

Synthesis of acyclic nucleosides has also been reported from addition of nucleobases onto 1-alkoxy-1-chloro derivatives (Scheme 1.22).[56] Reaction of the acetyl protected adenine nucleobase with **1-93** resulted in the formation of the *N,O*-acetal **1-94** which was N-deacetylated with picric acid. Although the exact selectivity was not determined, it was reported that each of

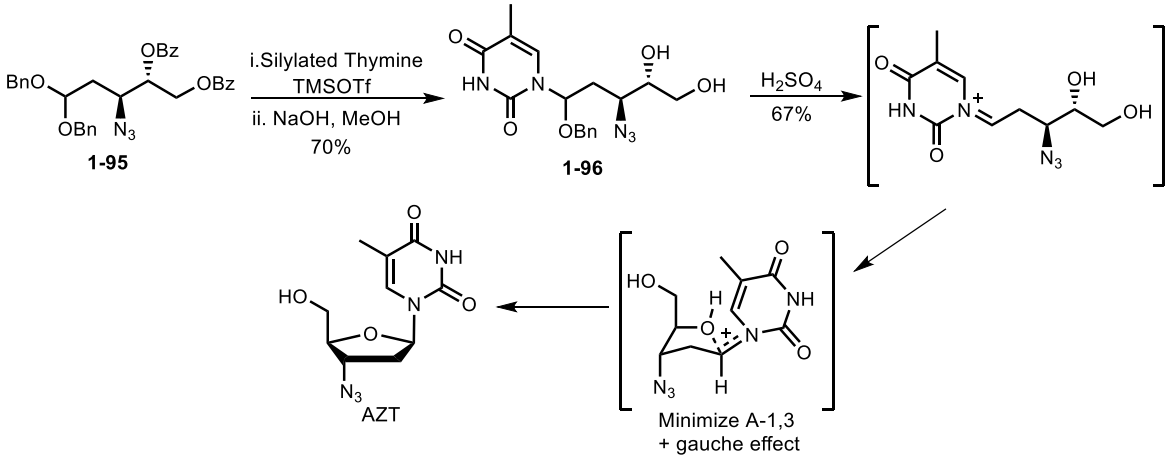
the picrate salts (R=Me or Et) behaved as a single compound, was homogeneous by thin layer chromatography, and exhibited a sharp melting point.

Scheme 1.22 Coupling of purine nucleobase to 1-alkoxy-1-chloro derivative.[56]



Liotta's synthesis of AZT[57] represents an important example in which an acyclic approach is used to generate a nucleoside analogue with high diastereoselectively (Scheme 1.23).

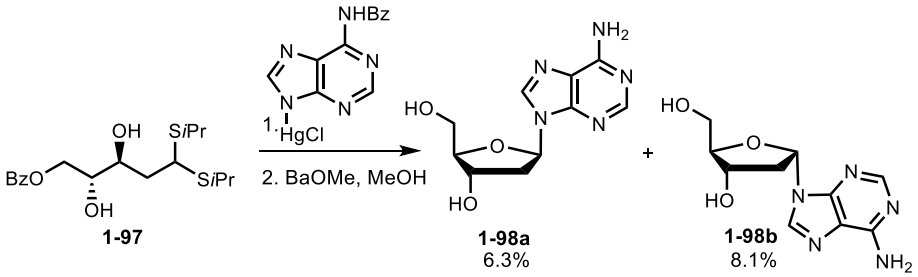
Scheme 1.23 Liotta's synthesis of AZT using an acyclic approach.[57]



In his synthesis, coupling of silylated thymine through TMSOTf activation of O-benzyl acetal **1-95** occurred unselectively. This was followed by cyclization in acidic media in which minimization of allylic 1,3-strain and a gauche interaction between the azide and endocyclic oxygen allowed for formation of only the β-anomer.

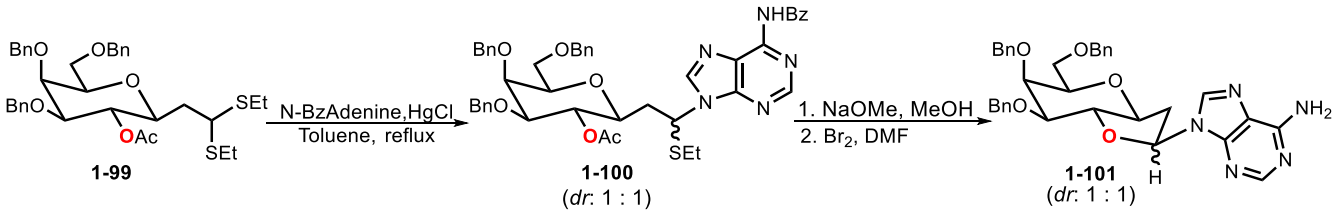
Although a precedent example has been reported in which a purine nucleobase reacts with an acyclic dithioacetal precursor (**1-97**, Scheme 1.24),[58] it is likely that intramolecular cyclization precedes nucleobase attack. Thus, it is reasonable to suggest that the purine nucleobase actually couples with the cyclized thioglycoside to form β-**1-98a** and α-**1-98b** anomers in low yields.

Scheme 1.24 Coupling of purine nucleobase to acyclic dithioacetal.[58]



In Hanessian's studies towards the synthesis of nucleoside antibiotics,[59] addition of benzoyl protected adenine to diethyl dithioacetal **1-99** resulted in an unselective synthesis of the thioaminal precursor **1-100** (Scheme 1.25). Removal of the acetyl protecting group and subsequent cyclization using bromine as the thiophilic activating agent resulted in the desired bicyclic system **1-101** albeit unselectively.

Scheme 1.25 Synthesis and cyclization of thioaminal intermediate.[59]



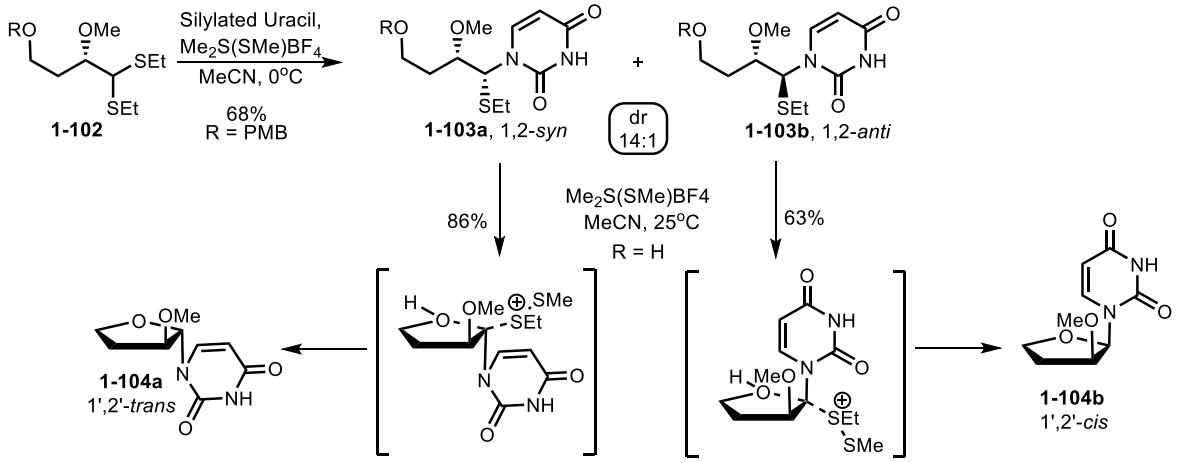
These precedent examples of nucleobase addition onto acyclic precursors with subsequent cyclization highlight the potential of this strategy for the synthesis of nucleoside analogues. However, in order to make this method efficient, a diastereoselective approach for nucleobase

coupling onto acyclic precursors is required along with being able to maintain this stereochemistry in the subsequent cyclization. Thus, a novel acyclic approach to nucleoside analogue synthesis has been investigated in the Guindon laboratory.

1.4.2 Diastereoselective acyclic approach

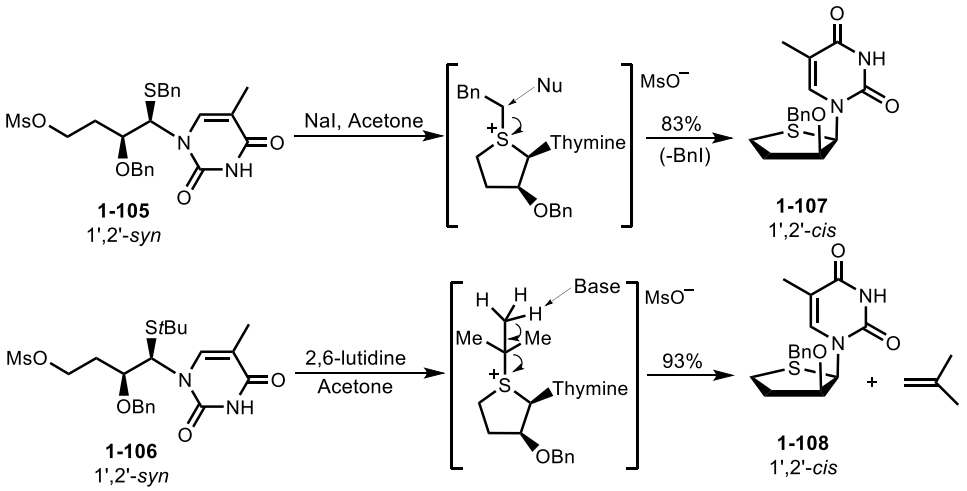
Synthesis of nucleoside analogues using an acyclic approach has focused on diastereoselective nucleobase addition to acyclic dithioacetals followed by intramolecular cyclization. Preliminary studies demonstrated that nucleobases add to acyclic dithioacetal precursors with preference for the 1,2-*syn* thioaminal.[61] This is exemplified by the 14:1 ratio obtained for coupling of silylated uracil to the diethyl dithioacetal **1-102** (Scheme 1.26). Separation and removal of the PMB protecting group allowed for O4'-C1 cyclization of both thioaminals. This cyclization occurs through chemoselective activation of the thioethyl moiety with dimethyl(methylthio)sulfonium tetrafluoroborate ($Me_2S(SMe)BF_4$)[60] followed by displacement with the oxygen at C4. It was shown that the 1,2-*syn* thioaminal **1-103a** cyclizes to provide the 1',2'-*trans* nucleoside analogue **1-104a** while 1,2-*anti* thioaminal **1-103b** results in only the 1',2'-*cis* furanoside **1-104b**.[61] Therefore, it was demonstrated that the 1,2-induction set in the coupling of the nucleobase to the acyclic precursor is maintained in the intramolecular cyclization. The cyclization therefore proceeds through an S_N2-like process and not through a S_N1 mechanism as was the case for Liotta's synthesis of AZT.

Scheme 1.26 Synthesis and O4'-C1 S_N2-like cyclization of thioaminals.[61]



An interesting feature of this methodology is the ability of the acyclic thioaminals to undergo two modes of cyclization and thus provide two different types of nucleoside analogues. As just described, an O4'-C1 cyclization where the oxygen at C4 acts as the nucleophile to displace an activated thioether moiety allows for the formation of furanosides (Scheme 1.26). A second mode of cyclization can also occur where the sulfur at C1 acts as the nucleophile to displace a leaving group at C4 (S1'-C4 cyclization, Scheme 1.27). Thioaminals containing either a thiobenzyl or thio-*t*-butyl functionality provide thionucleosides after S-dealklyation.[62] With a mesylate leaving group at C4 and a –SBn or –S*t*Bu thioaminal at C1, 1,2-*syn* thioaminals **1-105** and **1-106** underwent S1'-C4 cyclization generating 1',2'-*cis* thioanalogues **1-107** and **1-108** with good yields. In the presence of NaI, the -SBn thioaminal **1-105** undergoes debenzylation through nucleophilic attack of the iodide ion on the benzylic carbon of the sulfonium intermediate.[63-65] Cyclization with the -S*t*Bu thioaminal **1-106** occurs in refluxing 2,6-lutidine which serves as the base necessary to facilitate de-*t*-butylation with release of isobutene.[63]

Scheme 1.27 S1'-C4 cyclization.[62]

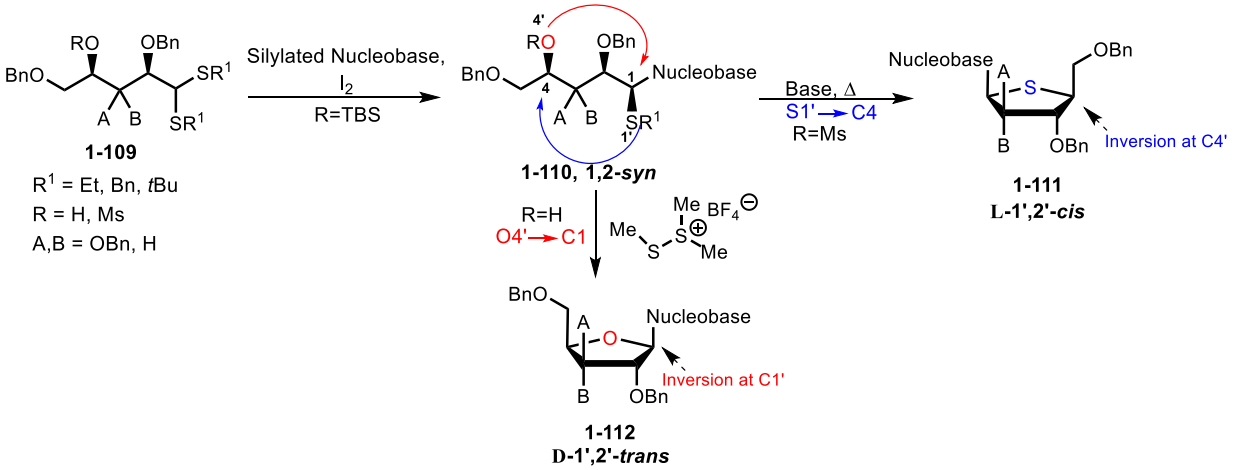


The successful cyclizations of these model acyclic thioaminal substrates highlighted a potential route for the synthesis of nucleoside analogues. The key features of this approach involve high levels of 1,2-*syn* diastereoselectivity for addition of nucleobases to acyclic dithioacetal precursors bearing an alkoxy group in the C2-position. The C1 stereochemistry in the thioaminal is then either inversed (O4'-C1 cyclization) or maintained (S1'-C4 cyclization) in the subsequent S_N2-like cyclization. This methodology has been extended to more complex substrates containing the necessary scaffolds to form nucleoside analogues.[21]

1.4.3 Acyclic approach for the synthesis of nucleoside analogues

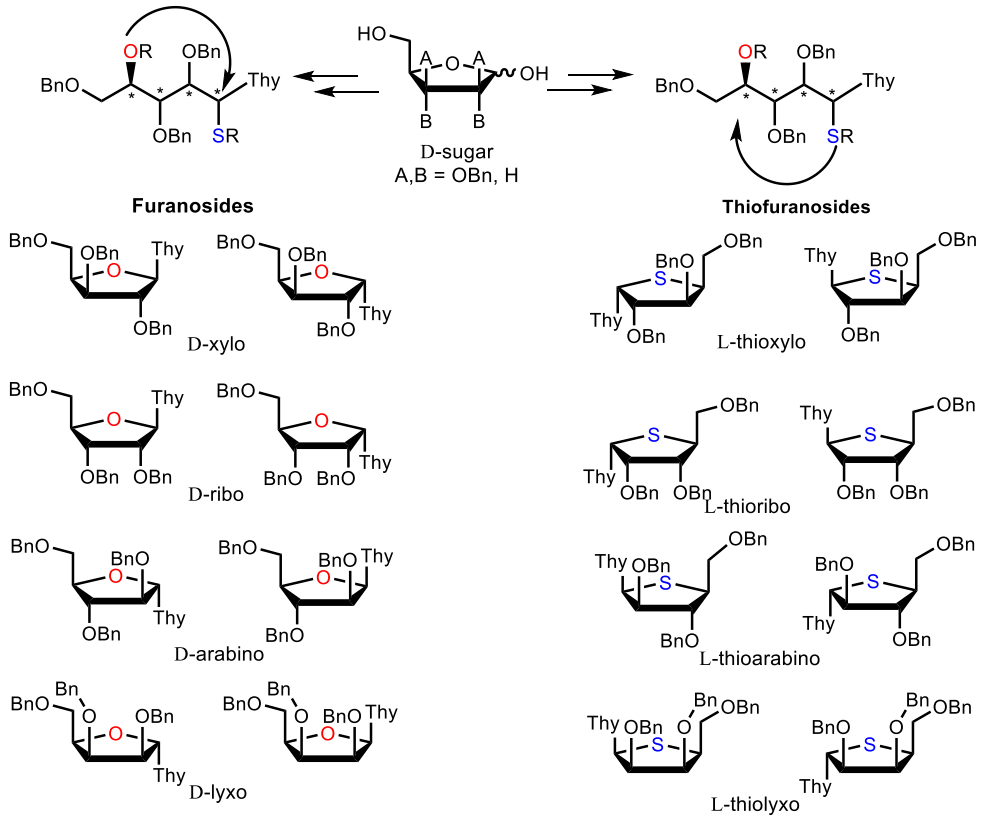
Extension of this methodology from model substrates to those bearing additional substituents, hence sugars in the xylo-, ribo-, arabino- or lyxo- series, demonstrate that acyclic thioaminals can be synthesized with good yields and preference for the 1,2-*syn* diastereomer from reaction of silylated nucleobases with dithioacetals (**1-109**) in the presence of a Lewis acid (I_2) (Scheme 1.28).[21]

Scheme 1.28 Acyclic paradigm for the synthesis of D-1',2'-*trans* furanosides and L-1',2'-*cis* 4'-thiofuranosides.[21]



These 1,2-*syn* thioaminals (**1-110**) successfully undergo the two types of cyclization previously described to generate 1',2'-*cis* 4'-thiofuranosides in the L-series (**1-111**) and 1',2'-*trans* furanosides in the D-series (**1-112**). All of the D-furanoside and L-thiofuranoside diastereomers in the xylo-, ribo-, arabino- and lyxo- series with thymine as the nucleobase have been synthesized (Scheme 1.29).[21] The 1,2-*anti* thioaminals obtained as the minor diastereomer were also isolated and subjected to the two modes of cyclization to generate the corresponding 1',2'-*cis* furanosides and 1',2'-*trans* 4'-thiofuranosides.

Scheme 1.29 Acyclic paradigm for the synthesis of D-furanosides and L-4'-thiofuranosides.[21]



1.5 Research Perspectives

The acyclic approach studied in our laboratory provides a novel methodology to access D-1',2'-*trans* furanosides and L-1',2'-*cis* thiofuranosides. Due to the importance of L-NAs as antiviral agents and the efficiency of our methodology in synthesizing L-NAs starting from D-sugars, the diasteroeselective synthesis and cyclization of 1,2-*syn* acyclic *N,O*-acetals was studied to access L-1',2'-*cis* furanosides (Chapter 2). One of the key features of this chemistry is the fact that acyclic thioaminals can be formed with high 1,2-*syn* diastereoselectivity from coupling of nucleobases to acyclic dithioacetals and therefore this reaction merited a thorough mechanistic investigation (Chapter 3). Introduction of a fluorine atom in the C2'-position of NAs provides significant variations to their biological properties and access to these scaffolds is typically

challenging using standard methods of nucleoside analogue synthesis. Therefore, the synthesis of fluorinated NAs using the acyclic methodology has been developed (Chapter 4). This approach to nucleoside synthesis allows for not only the stereochemistry of the glycosidic bond (C1') to be controlled but also for the substituents at C2' and C3' of the furanose ring to be varied thus increasing the diversity of nucleoside analogues. Novel scaffolds bearing a C2'-F and a C3'-all carbon quaternary center have been synthesized and evaluated as potential anticancer and antiviral agents (Chapter 5).

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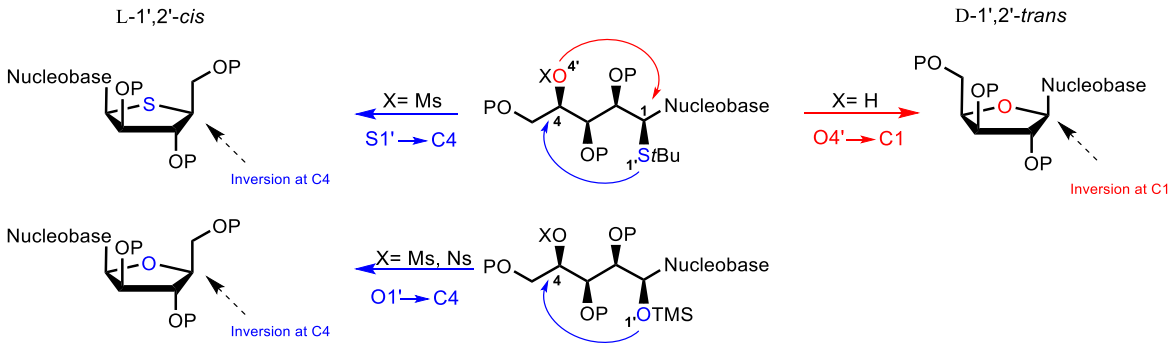
Chapter 2
Synthesis and Cyclization of Acyclic 1,2-*syn* *N,O*-Acetals

2.1 Research Perspectives

The acyclic methodology that has been developed for the synthesis of nucleoside analogues leads to D-1',2'-*trans* furanosides through a O4'-C1 cyclization and to L-1',2'-*cis* thiofuranosides through a S1'-C4 cyclization (Scheme 2.1).[1] In both processes, the stereochemistry of the nucleoside obtained is provided by the acyclic thioaminal precursor. Due to the importance of L-NAs as antiviral agents and the 1',2'-*cis* stereochemical arrangement between the nucleobase and the C2' substituent (Figure 1.3, Chapter 1), a single versatile method addressing these two synthetic challenges was envisioned. A cyclization protocol was developed in which acyclic *N,OTMS*-acetals (Scheme 2.1) were accessed with high 1,2-*syn* diastereoselectivities by addition of silylated pyrimidine and purine nucleobases to aldehydes using a bidentate Lewis acid ($MgBr_2 \cdot OEt_2$).

Scheme 2.1 Acyclic approach for the synthesis of nucleoside analogues.[1,2]



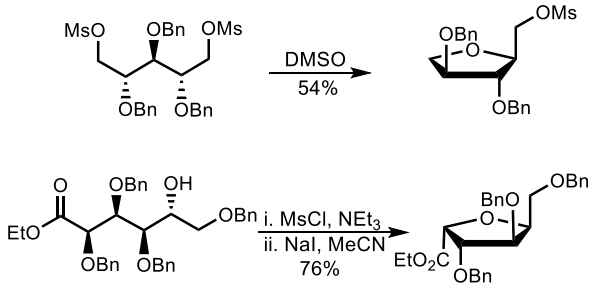
In the subsequent O1'-C4 cyclization reaction, the oxygen of the acetal serves as the nucleophile involved in the displacement of the leaving group at the C4 position with inversion of configuration (Scheme 2.1). This work merited a featured article in the Journal of Organic Chemistry for which I prepared the manuscript and supporting information. Its contents will be elaborated upon in this chapter.[2] My contribution to this work involved optimization of nucleobase coupling and cyclization in the C4-mesylate series following Dr. Michel Prévost's initial studies with thymine and adenine. I also developed the new series bearing a C4-nosylate and elucidated their mechanism of cyclization through ^{1}H NMR.

2.2 Synthesis and Cyclization of *N,OBn*-acetals

2.2.1 Literature precedents for cyclization of OBn ethers

The anticipated O1'-C4 cyclization was expected to be more challenging with an oxygen moiety than with sulfur functionalities as in the S1'-C4 cyclization due to the difference in polarizability between these two heteroatoms. Some precedent literature examples where benzyloxy substituents displaced leaving groups with subsequent dealkylation encouraged the initial work on this project. For example, it has been shown that a secondary benzyloxy ether can undergo an intramolecular cyclization with displacement of a primary[3] or secondary mesylate[4] followed by debenzylation to form the cyclic products (Scheme 2.2).

Scheme 2.2 Intramolecular cyclizations with nucleophilic benzyloxy ethers.[3,4]



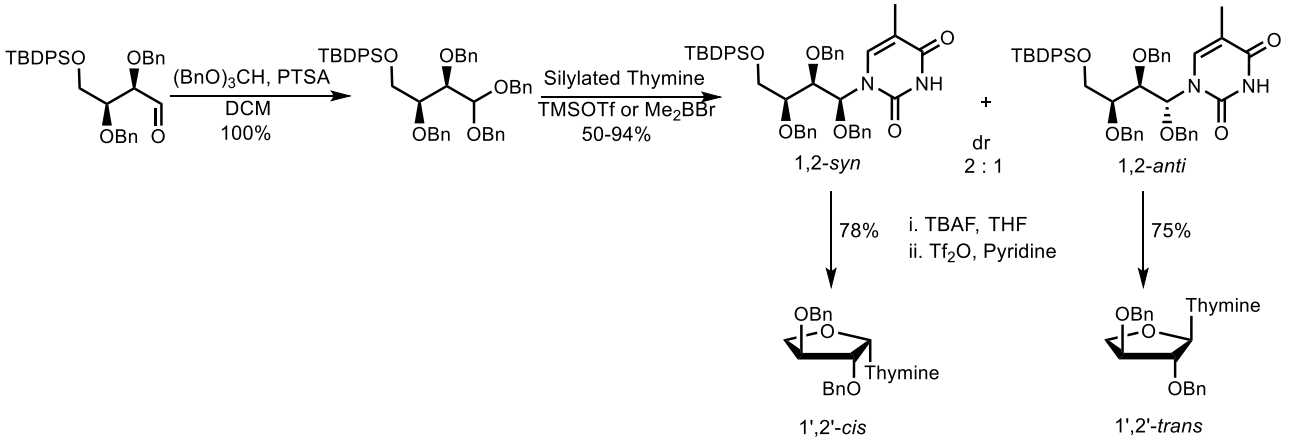
These examples involve cyclization of OBn ethers whereas our acyclic methodology relies on cyclization of *N,O*-acetals. Thus, the expected cyclization was further challenged due to the inherent anomeric effect,[5] which involves donation of the OBn oxygen lone pair into the antibonding σ* of the C1-N bond. This would therefore result in a less available lone pair for displacement of the C4 leaving group. It should be noted that there are no precedent literature examples involving cyclization of *N,O*-acetals.

2.2.2 Initial work on the synthesis and cyclization of *N,OBn*-acetals

The first step in determining whether or not an O1'-C4 cyclization would be successful involved the coupling of silylated thymine to an acyclic acetal. This work was done by Dr Michel Prévost during his PhD studies and was reported in a Journal of the American Chemical Society publication.[6] An acyclic dibenzyloxyacetal was prepared from the acetalization of the corresponding aldehyde with *p*-toluenesufonic acid (PTSA) and benzyl orthoformate (Scheme 2.3).[7] Coupling of the silylated thymine nucleobase was investigated using either TMSOTf or Me_2BBr Lewis acids. The yield of the coupling reaction ranged from 50-94% and resulted in a low diastereoselectivity (2:1) in favor of the 1,2-*syn N,OBn*-acetal. The two acetals could be separated and subjected to TBAF conditions to remove the silyl protecting group.[8] Subsequently, a triflate was installed at the primary position and upon warming the reaction mixture from –78 ^{o}C to 0 ^{o}C the cyclization occurred with dealkylation of the benzyloxy group. These results demonstrate that the OBn moiety in a *N,OBn*-acetal can indeed act as the nucleophilic source to displace a good leaving group with subsequent debenzylation. The cyclization reaction required a triflate in the primary position and did not work well with a primary mesylate. This study demonstrates that the 1,2-*syn N,OBn*-acetals cyclize to give 1',2'-*cis* products whereas the 1,2-

anti N,OBn-acetals provide the 1',2'-*trans* furanoside. Thus, the stereochemical information that is set in the coupling reaction is maintained in the cyclization process.

Scheme 2.3 Synthesis and cyclization of *N,OBn*-acetal.[6,8]



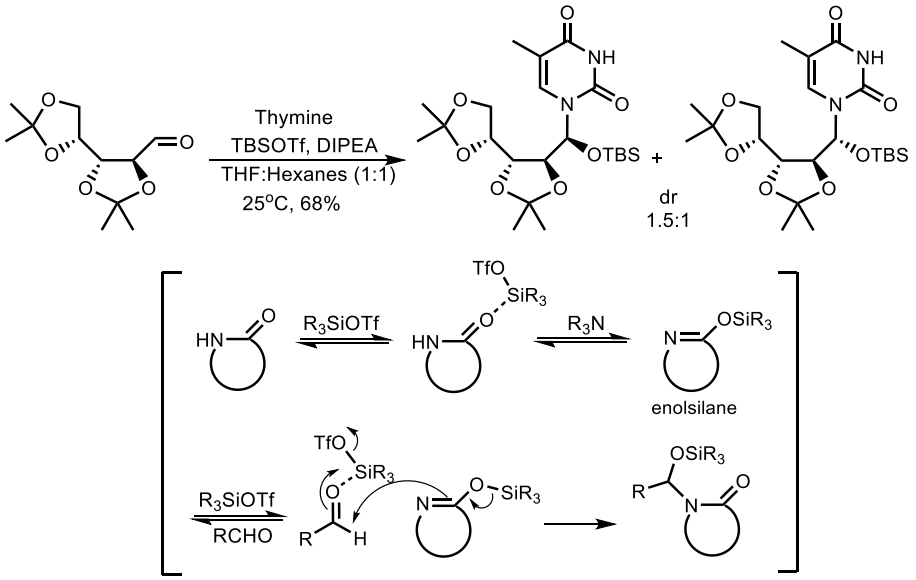
Cyclization of the 1,2-*syn N,OBn*-acetal highlighted the potential of this approach to synthesize nucleoside analogues with the challenging 1',2'-*cis* stereochemistry. However, this strategy was limited by the poor selectivity in obtaining the 1,2-*syn* acetal. Another type of *N,O*-acetal was investigated in hopes of increasing the diastereomeric ratio of the coupling step while still allowing for cyclization and dealkylation to occur.

2.3 Synthesis and cyclization of *N,OSilyl*-acetals

The reported synthesis of *N,OTBS*-acetals from coupling of thymine with a C2-alkoxy aldehyde (Scheme 2.4), led us to consider this type of reaction for the formation of *N,O*-acetals. An *N,O-silyl*-acetal species, albeit with low diastereoselectivity, was formed in the reaction of acyclic aldehydes with unsilylated nucleobases in the presence of a Lewis acid (TBSOTf)/ Lewis base (DIPEA) system.[9] It was rationalized that the use of a silyl triflate and a tertiary amine allowed for formation of an enolsilane with subsequent carbon-carbon bond formation and oxygen

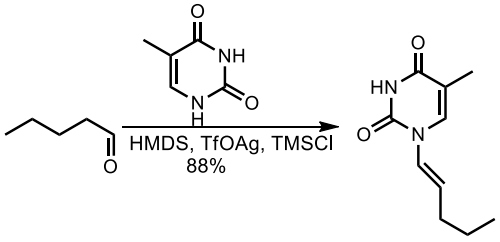
silylation. Although this reaction occurred with a good yield (68%), a poor diastereoselectivity (1.5:1) was obtained with a slight preference for the Felkin-Anh 1,2-*anti* diastereomer.

Scheme 2.4 Formation of *N,OTBS*-acetal from addition of thymine to C2-alkoxy aldehyde.[9]



Two major hurdles had to be overcome to render our acyclic strategy efficient. The acyclic *N,O-silyl*-acetals had to be generated with high *syn* diastereoselectivity and the chemical stability of these intermediates had to be sufficient to withstand cyclization. A precedent[10] (Scheme 2.5), involving the synthesis of enamine derivatives as potential nucleoside analogues made us aware that such by-products may occur in our synthetic plan.

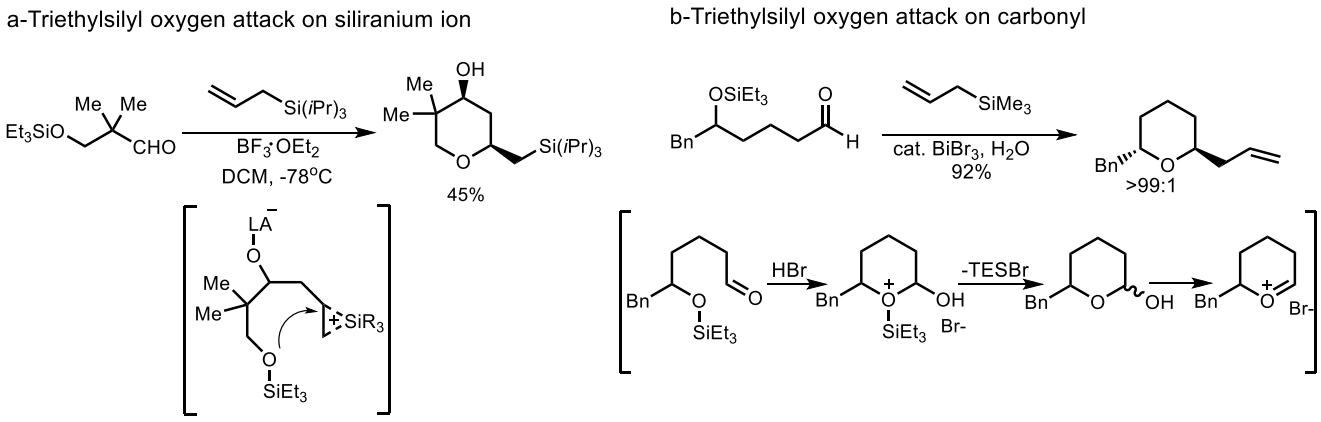
Scheme 2.5 Formation of enamine from addition of nucleobase to an aldehyde.[10]



Reaction of pentanal and thymine in the presence of HMDS, TfOAg and TMSCl (*in situ* formation of TMSOTf) resulted in the synthesis of the corresponding enamine in good yield.

Therefore, it was possible that such an elimination process would occur in our approach as well. It was also considered that the planned cyclization could be negatively influenced by the steric hindrance of the oxygen in a *N,O-silyl*-acetal. However, examples have been reported where silyloxy ethers have been suggested to be involved in intramolecular reactions (Scheme 2.6). For example, synthesis of tetrahydropyrans has been developed in which the triethylsilyl ether oxygen was proposed to act as the nucleophilic species in an intramolecular trapping of a β-silylcation/siliranium ion (Scheme 2.6a).[11]

Scheme 2.6 Intramolecular cyclizations of silyloxy ethers.[11,12]

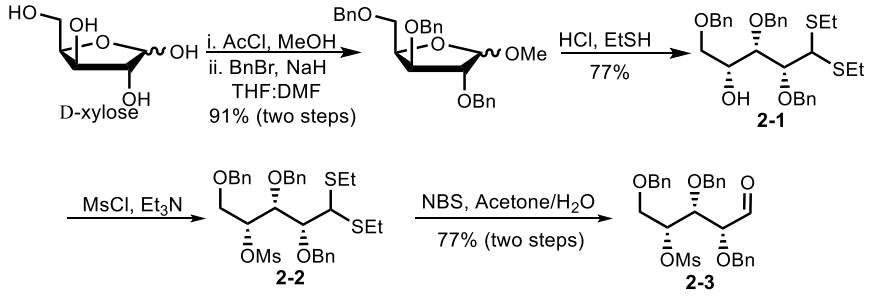


Similarly it has been proposed that the oxygen of a triethylsilyl ether moiety adds to an aldehyde with subsequent allylation of the oxocarbenium (Scheme 2.6b)[12]. This difference in chemoselectivity was rationalized by Evans to be caused by a low reactivity of the carbonyl in absence of a Lewis acid. $BiBr_3$ or triethylsilyl bromide provides a source of HBr, which functions as the catalyst in addition to BrBiO. With these examples in mind, the planned O1'-C4 cyclization of *N,O-silyl*-acetals was investigated.

2.3.1 Synthesis of C4-activated aldehydes

In order to investigate the nucleobase coupling onto an acyclic aldehyde and the potential for O1'-C4 cyclization, aldehydes bearing a good leaving group in the C4 position were synthesized. The aldehydes were prepared starting from D-xylose with protection of the anomeric position in acidic methanol (Schemes 2.7). Subsequent benzylation in the presence of NaH and BnBr in a mixture of THF:DMF (4:1) provided the known methylfuranoside in 91 % yield for the two steps.[13] Reaction of the methylfuranoside with ethanethiol and *conc.* HCl provided acyclic dithioacetal **2-1** in good yield, which was then activated at the C4 position with a mesylate (**2-2**). This intermediate was kept at low temperatures and used as a crude mixture due to potential S1'-C4 cyclization. Aldehyde **2-3** was then prepared in good yield (77%, two steps) by oxidation of dithioacetal **2-2** using NBS and 2,6-lutidine in a mixture of acetone:H_2O (3:1).

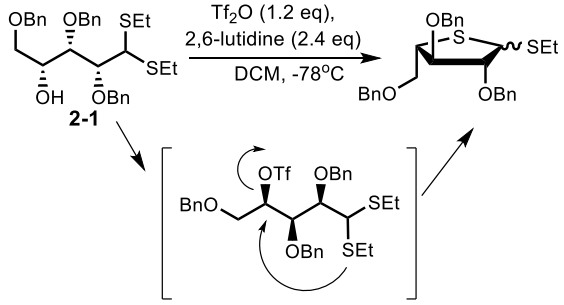
Scheme 2.7 Preparation of aldehyde **2-3** starting from D-xylose.



In an effort to enhance the envisioned O1'-C4 cyclization, attempts were made to introduce a better leaving group at the C4 position. It has previously been reported, in the solvolysis of disubstituted phosphinates, that a trifate is roughly a 10 000 times better leaving group than a mesylate and a nosylate about a 10 times better leaving group than a mesylate.[14] Therefore, using the above approach for the synthesis of aldehyde **2-3**, formation of the corresponding triflate

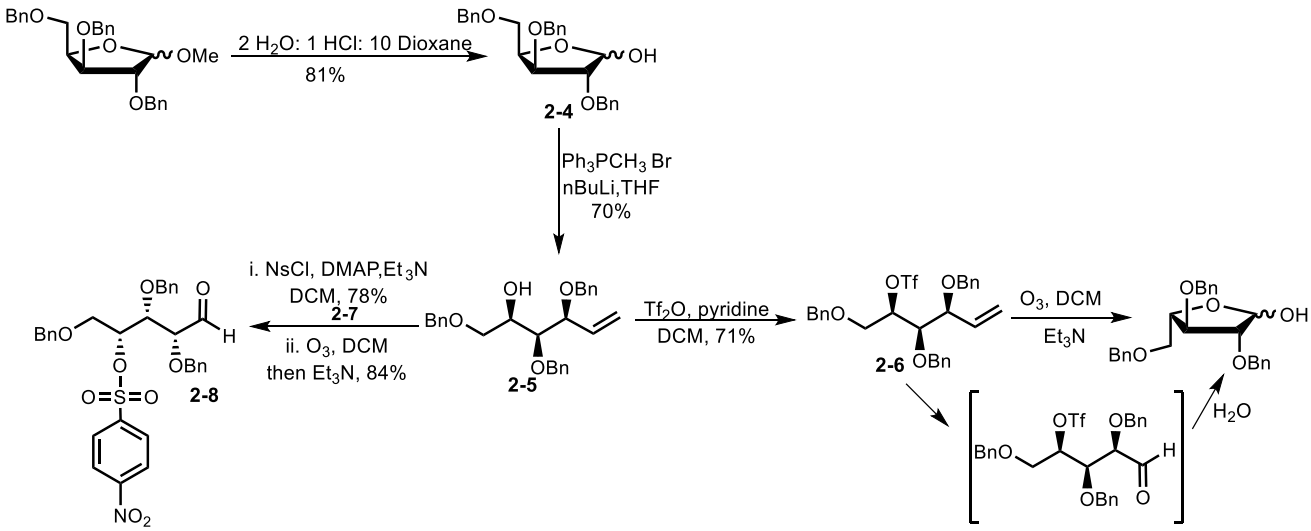
dithioacetal was attempted. This led however, to a mixture of products which included the cyclic thiofuranoside (Scheme 2.8).

Scheme 2.8 Cyclization of acyclic dithioacetal bearing a C4 triflate.



An alternate strategy to access the requisite aldehyde with a C4 triflate was therefore investigated (Scheme 2.9).

Scheme 2.9 Route investigated to form aldehyde with a C4 triflate or nosylate.



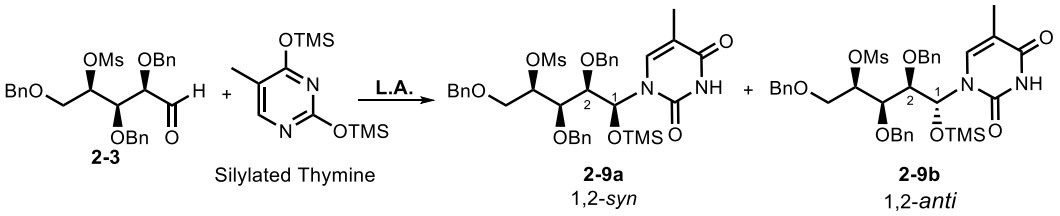
The partially protected lactol **2-4** derived from treating the methylfuranoside with a H_2O:HCl:dioxane mixture was subjected to a Wittig reaction providing known acyclic alkene **2-5** in 70% yield.[15-17] A triflate group was installed on the resulting secondary alcohol to provide **2-6**

in high yield (71%). Subsequent oxidation with ozone at –78°C and treatment with triethylamine did not yield the corresponding aldehyde but led instead to formation of the L-arabino-lactol. Therefore, it was concluded that a triflate group in the C4 position was serving as too good of a leaving group resulting in cyclization before the nucleobase could even be introduced. Introduction of a nosylate leaving group at C4 was then considered (Scheme 2.9). This leaving group was successfully inserted onto the secondary alcohol of alkene **2-5** by refluxing the reaction mixture for 16 hours. Subsequent ozonolysis provided the C4-nosylate aldehyde **2-8** in high yield (84%).

2.3.2 Diastereoselective synthesis of *N,OTMS*-acetals

The coupling reaction was initially investigated by Dr Michel Prévost with aldehyde **2-3** (Table 2.1).[8]

Table 2.1 Coupling of aldehyde **2-3** with silylated thymine in the presence of a Lewis acid.[8]

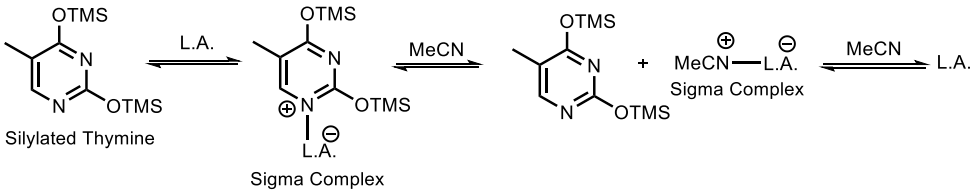


Entry	Conditions (equivalents)	Solvent	T, Time	Ratio(*syn*:*anti*)	Yield
1	TMSOTf (2.0), Thymine (2.0)	DCM	0 °C, 3h	1:3	60%
2	$MgBr_2$•OEt_2 (1.5), Thymine (2.0)	DCM	–40 °C, 4h	-	Traces
3	$MgBr_2$•OEt_2 (1.5), Thymine (2.0)	MeCN	–40 °C, 4h	>20:1	74%

When silylated thymine was added to the acyclic aldehyde in the presence of a monodentate Lewis acid (TMSOTf) in dichloromethane, a 1:3 mixture of 1,2-*syn* and 1,2-*anti* diastereoisomers was formed (entry 1). This observation is consistent with the low dr observed in

the work of Battistini.[9] When $MgBr_2$•OEt_2, a bidentate Lewis acid, was reacted in DCM with silylated thymine only traces of product were formed (entry 2). However, when the reaction was done in MeCN, a >20:1 diastereoselectivity was observed in favor of the 1,2-*syn* isomer (entry 3) in 74% yield. Contrary to our initial concerns, these *N,OTMS*-acetals could be isolated with standard aqueous work-up and flash chromatography. The effect of the solvent, as seen in entries 2 and 3, was counterintuitive because chelation controlled activations are typically more efficient in solvents that do not coordinate to the Lewis acid. DCM was therefore expected to provide enhanced reactivity as compared to MeCN which could itself serve as a ligand for $MgBr_2$•OEt_2. This coordination would thus decrease its ability to activate the starting material. However, silylated nucleobases also have high affinities for Lewis acids with the formation of sigma complexes (Scheme 2.10).[18] A polar solvent, such as MeCN could therefore facilitate an equilibrium in which some free Lewis acid becomes available allowing for the reaction to occur.

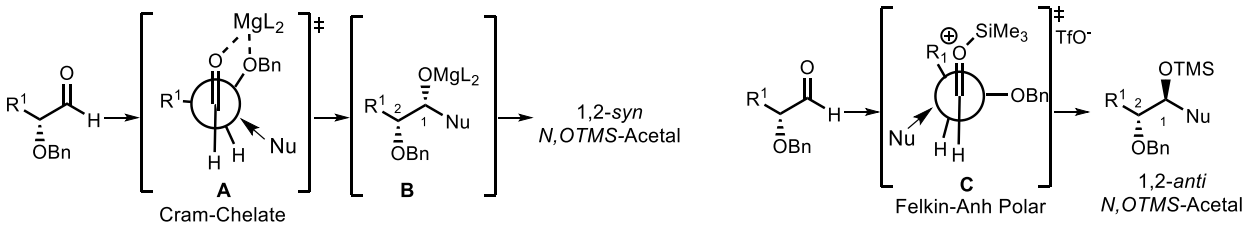
Scheme 2.10 Sigma complex equilibrium between nucleobase and Lewis acid in MeCN.



It is rationalized that the high 1,2-*syn* diastereoselectivity (Table 2.1, entry 3) in the presence of $MgBr_2$•OEt_2 results from the addition of the silylated nucleobase onto the opposite side of the C2 substituent in a five-membered ring magnesium chelate **A** (Scheme 2.11). Five-membered magnesium chelates have previously been shown to form preferentially over six-membered chelates.[19,20] The generated alkoxide intermediate **B** would then be either silylated intramolecularly, or intermolecularly by a second silylated nucleobase. The 1,2-*anti*

diastereoselectivity obtained upon activation with a monodentate Lewis acid is consistent with a polar Felkin-Anh transition state (Scheme 2.11, **C**).

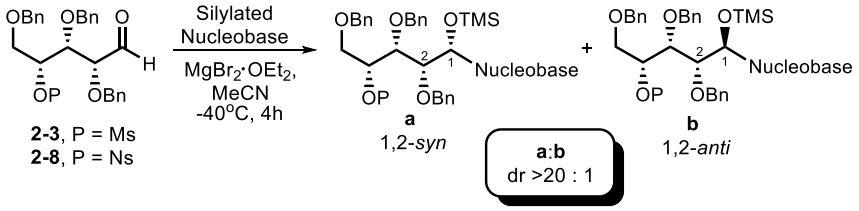
Scheme 2.11 Bidentate and monodentate pathways leading to 1,2-*syn* and 1,2-*anti N,OTMS*-acetals.



Nu = Silylated Nucleobase

With optimal conditions to generate the desired 1,2-*syn N,OTMS*-acetals, the mesylate aldehyde **2-3** and the nosylate aldehyde **2-8** were coupled with various silylated nucleobases (Table 2.2). Similar to the formation of the 1,2-*syn N,OTMS*-acetal **2-9a** (P= Ms, entry 1), **2-10a** (P= Ns) was obtained with high diastereoselectivity (>20:1) when silylated thymine and $MgBr_2 \cdot OEt_2$ were reacted in acetonitrile at –40 ^oC with aldehyde **2-8** (entry 1). Silylated uracil provided the *N,OTMS*-acetals **2-11a** and **2-12a** in high diastereoselectivity as well (Table 2.2, entry 2). Although introduction of purine nucleobases is known to be challenging in terms of obtaining selectively only the N9-regioisomer,[18] the adenosine *N,OTMS*-acetals **2-13a** and **2-14a** was synthesized with high regio-(N9) and diastereoselectivity (entry 3). Couplings of silylated 5F-uracil, cytosine and N^4-AcCytosine proved to be as effective (entries 4-6). Formation of the guanosine *N,OTMS*-acetal was unsuccessful (entry 7).[8]

Table 2.2 Formation of *N,OTMS*-acetals through coupling of aldehydes with silylated nucleobases.



Entry	Nucleobase	P =Ms	Yield(%)[a,b]	P =Ns	Yield(%)[a,b]
1	Thymine	**2-9a**	74	**2-10a**	62
2	Uracil	**2-11a**	61	**2-12a**	63
3	Adenine	**2-13a**	66	**2-14a**	54
4	5F-Uracil	**2-15a**	57	**2-16a**	58
5	Cytosine	**2-17a**	71	**2-18a**	65
6	N^4-AcCytosine	**2-19a**	49		
7[8]	Guanosine		-		

[a] All *N,OTMS*-acetals were formed with >20:1 diastereoselectivity for the 1,2-*syn* isomer based on the crude reaction mixtures. [b] Silylated nucleobase (2.0-4.0eq.), $MgBr_2$•OEt_2 (1.5-2.0eq.), MeCN, –40 °C, 4 hours.

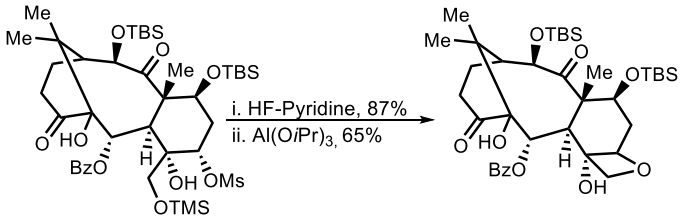
2.4 O1'-C4 Cyclization of *N,OTMS*-Acetals

2.4.1 C4-Mesylate *N,OTMS*-Acetal Cyclizations

The next challenge was to investigate conditions allowing for the O1'→C4 cyclization to occur without epimerization of the C1 stereogenic center of the 1,2-*syn N,OTMS*-acetals. The reaction was first studied with the *N,OTMS*-acetals bearing a mesylate at C4. It was observed that the cyclization did not occur spontaneously after coupling aldehyde **2-3** in the presence of $MgBr_2$•OEt_2 at low temperatures.[8] In fact, warming the reaction mixtures only provided the corresponding aldehyde. Addition of various external nucleophiles such as CsF, KF, KBr and

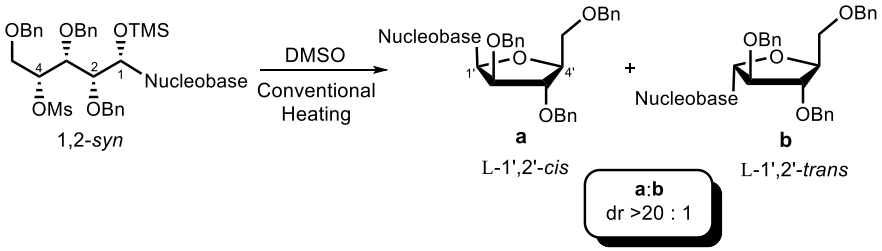
TBAF provided mainly the aldehyde and decomposition products.[8] However, when **2-9a** was heated in DMSO at 140 °C, trace amounts of the cyclized product was observed with the majority of the crude reaction mixture being aldehyde **2-3** (Table 2.3, entry 1). A literature search highlighted the use of Lewis acids such as Al(O*t*Bu)$_3$ to facilitate cyclization reactions as in Paquette's synthesis of taxol.[21,22] He demonstrated that addition of Al(O*i*Pr)$_3$ in isopropanol was the optimal conditions for mesylate displacement in the formation of his oxetane ring (Scheme 2.12).[23]

Scheme 2.12 Cyclization with Al(O*i*Pr)$_3$ to form oxetane ring.[23]



Upon addition of Al(O*t*Bu)$_3$ at 140 °C in DMSO, the desired L-1',2'-*cis* nucleoside analogue **2-20a** could be isolated in 34% yield (Table 2.3, entry 2) with a >20:1 diastereoselectivity. This is consistent with an S_N2-like intramolecular cyclization where the C1 stereochemistry in the *N,OTMS*-acetal is maintained. Other solvents such as toluene and isopropanol in the presence of Al(O*t*Bu)$_3$ gave only unreacted starting material (entry 3) or aldehyde **2-3** (entry 8). The uracil and adenine nucleoside analogues were also synthesized in 49% and 40% yields using 3.0 equivalents of Al(O*t*Bu)$_3$ in DMSO (entries 4 and 9). Optimization of the reaction conditions, revealed that lowering the number of equivalents of Al(O*t*Bu)$_3$ decreased the yield (entries 4-6). Upon switching from Al(O*t*Bu)$_3$ to Al(O*i*Pr)$_3$, the yield of product formation did not improve (entries 4 and 7). In all of the successful cyclization reactions, there was no remaining starting material in the crude mixtures.

Table 2.3 S_N2-like cyclization of C4-mesylate *N,OTMS*-acetals with conventional heating.

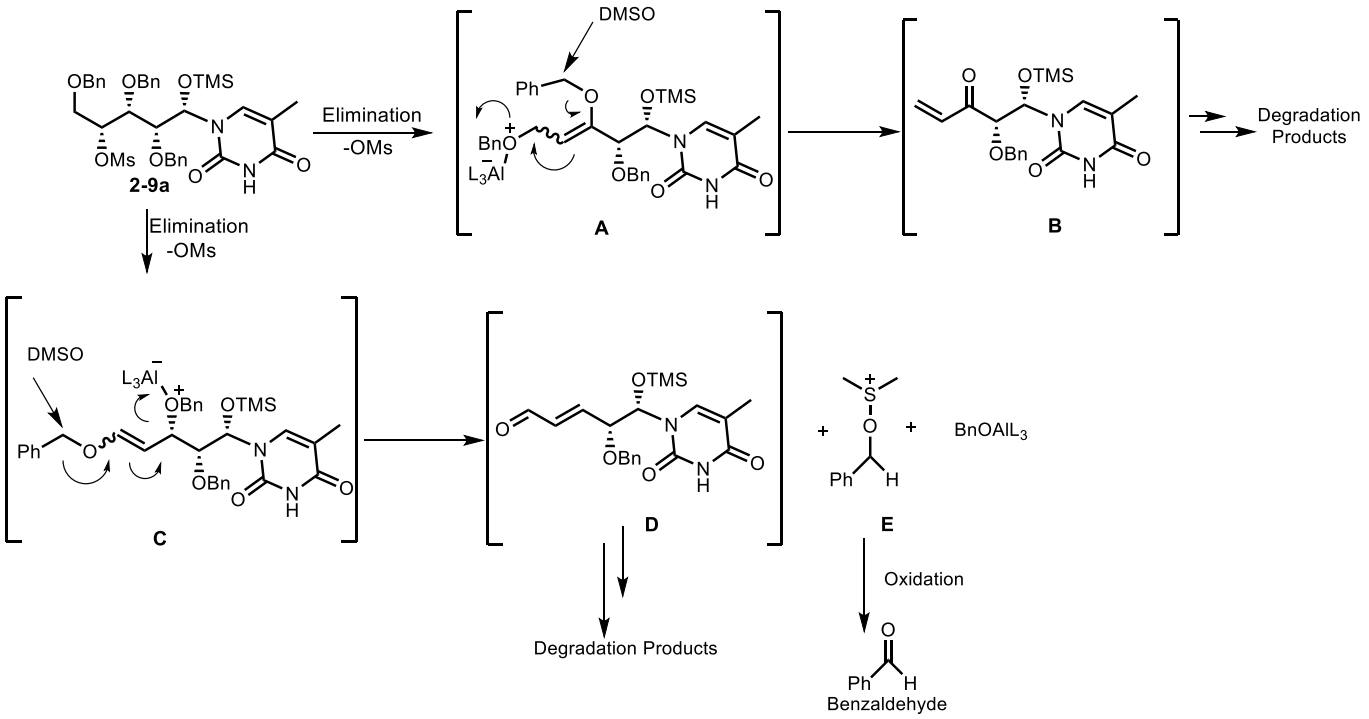


Entry	*N,OTMS*-Acetal	Conditions (equivalents)	Solvent	Product	Yield (%)
1	2-9a (Thymine)	140 °C, 3h	DMSO	**2-20a**	Traces
2	**2-9a (Thymine)**	**140 °C, 3h, Al(O*t*Bu)$_3$ (3.0)**	**DMSO**	**2-20a**	**34**
3	2-9a (Thymine)	110 °C, 3h, Al(O*t*Bu)$_3$ (3.0)	Toluene	Starting Material	
4	**2-11a (Uracil)**	**140 °C, 3h, Al(O*t*Bu)$_3$ (3.0)**	**DMSO**	**2-21a**	**49**
5	2-11a (Uracil)	140 °C, 3h, Al(O*t*Bu)$_3$ (2.0)	DMSO	**2-21a**	37
6	2-11a (Uracil)	140 °C, 3h, Al(O*t*Bu)$_3$ (1.0)	DMSO	**2-21a**	23
7	2-11a (Uracil)	140 °C, 3h, Al(O*i*Pr)$_3$ (3.0)	DMSO	**2-21a**	40
8	2-11a (Uracil)	80 °C, 3h, Al(O*i*Pr)$_3$ (3.0)	Isopropanol	Aldehyde **2-3**	
9	**2-13a (Adenine)**	**140°C, 3h, Al(O*t*Bu)$_3$ (3.0)**	**DMSO**	**2-22a**	**40**

The best conditions are shown in bold (entries 2, 4, 9).

Despite the complete conversion of the *N,OTMS*-acetals to product and a clean crude reaction mixture, the moderate isolated yields for these cyclizations were surprising. It was suspected that side products were forming that were either volatile or soluble in the aqueous phase. In this regard, the cyclization reaction was investigated in d_6-DMSO in order to study the reaction mixture prior to aqueous work-up or evaporation. This demonstrated the presence of benzaldehyde (about 40% with respect to the cyclized product **2-20a**) and unknown products that still contained an acetal center. In an effort to explain the formation of benzaldehyde, different modes of starting material decomposition were envisioned (Scheme 2.13).

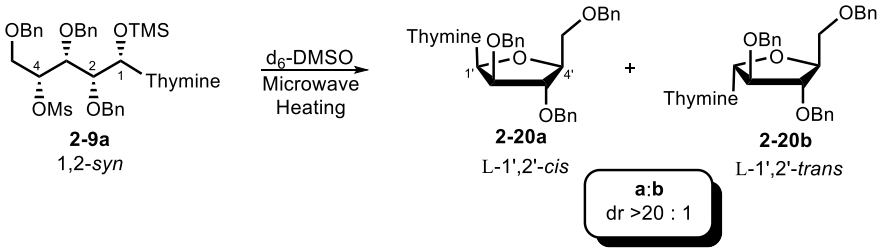
Scheme 2.13 Decomposition of **2-9a** in the presence of $Al(OR)_3$ in DMSO.



The C4 mesylate in the starting *N,OTMS*-acetal can eliminate with formation of enol ethers **A** or **C**. A nucleophilic attack at the benzylic position would form intermediates **B** and **D**. Since the solvent used in the reaction is DMSO, it is possible that it serves as the nucleophilic species allowing for the formation of species **E**, which upon oxidation, would explain the presence of benzaldehyde. The low reaction yields are therefore attributed to decomposition of the starting *N,OTMS*-acetals at such high reaction temperatures.

In hopes of further improving the O1'→C4 cyclization, microwave heating was considered.[24] Optimizations were done in d_6-DMSO so that the reaction mixtures could be studied. This also allowed for the residual CD_3SOCD_2H peak to function as an internal standard in order to provide NMR yields (shown in brackets in Table 2.4). It was seen that a Lewis acid was indeed necessary in microwave heating conditions since only trace amounts of product were observed when the reaction mixture was heated at 180 ^oC for 10 minutes (Table 2.4, entry 1).

Table 2.4 S_N2-like cyclization of C4-mesylate *N,OTMS*-acetals with microwave heating.



Entry	Conditions (equivalents)	NMR Yield[a]	Isolated Yield
1	180 °C, 10 min	Traces of **2-20a**	
2	180 °C, 10 min, Al(O*t*Bu)$_3$ (3.0)	decomposition	
3	180 °C, 10 min, Al(O*t*Bu)$_3$ (1.5)	23% of **2-20a**	-
4	180 °C, 10 min, Al(O*t*Bu)$_3$ (1.0)	26% of **2-20a**	41% of **2-20a**
5	180 °C, 10 min, Al(O*t*Bu)$_3$ (0.6)	48% of **2-20a**	45% of **2-20a**
6	120 °C, 10 min, Al(O*t*Bu)$_3$ (1.0)	96% of **2-9a**	-
7	160 °C, 10 min, Al(O*t*Bu)$_3$ (1.0)	22% of **2-9a** + 42% **2-20a**	-
8	**180 °C, 10 min, Al(O*i*Pr)$_3$ (0.6)**	**54 % of 2-20a**	**48% of 2-20a**
9	180 °C, 10 min, Al(O*i*Pr)$_3$ (0.3)	19% of **2-20a**	-
10	160 °C, 40 min, Al(O*i*Pr)$_3$ (0.6)	46% of **2-20a**	-
11	180 °C, 5 min, Al(O*i*Pr)$_3$ (0.6)	25% of **2-9a** + 38% **2-20a**	-
12	180 °C, 10 min, Al(O*i*Pr)$_3$ (0.6) + 10 min	51% of **2-20a**	-

a. CD_3SOCD_2H used as internal standard. **The best conditions are shown in bold (entry 8).**

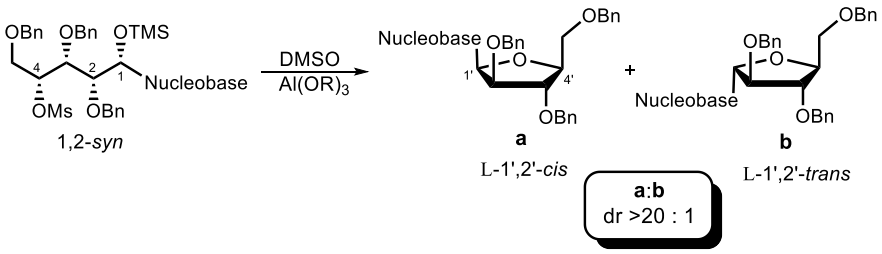
Upon addition of 3 equivalents of Al(O*t*Bu)$_3$ (amount that was ideal for conventional heating), only decomposition was observed (entry 2). However, lowering the equivalents of Lewis acid (entries 3-5), resulted in an increase in product formation with 0.6 equivalents of Al(O*t*Bu)$_3$ being optimal (entry 5). The nature of the Lewis acid (Al(O*i*Pr)$_3$ or Al(O*t*Bu)$_3$) gave comparable yields of cyclized product **2-20a** (entries 5 and 8) with 0.6 equivalents of Al(O*i*Pr)$_3$ again being best (entries 8-9). It should be noted that a similar optimization process was done to determine

the ideal temperature (180 ^{o}C) and reaction time (10 minutes) for this cyclization using microwave heating. For example, when heated at 120 ^{o}C or 160 ^{o}C for 10 minutes, the reaction did not go to completion with starting *N,OTMS*-acetal **2-9a** still being present (entries 4 versus 6 and 7). Upon comparison of these results, it can be seen that the NMR percent yields of product **2-20a** are similar at 160 ^{o}C (42%) versus 180 ^{o}C (36%) (entries 7 and 4) although there is no more starting material present in the latter. The remaining starting material likely therefore decomposed instead of being converted to product. However, running the reaction at 160 ^{o}C for a longer length of time (40 minutes) did not improve the yield significantly (entries 7 and 10). When the reaction was carried out for only 5 minutes at 180 ^{o}C starting material **2-9a** was still observed and subsequently converted to product when the reaction was left at this temperature for 10 minutes (entries 8 and 11). It was also observed that the decomposition products seemed to be arising from the instability of the starting material and not the product. This was verified by monitoring the NMR percent yield of product **2-20a** in the reaction media for an additional 10 minutes after the cyclization went to completion (entries 8 and 12). The NMR percent yields (entries 4, 5 and 8) are in agreement with the isolated yields. This confirmed that the low yields were not due to loss of product in the aqueous phase during extraction or from its purification using silica gel flash chromatography.

The optimized microwave cyclization conditions (DMSO, 180 ^{o}C for 10 minutes using 0.6 equivalent of Al(O*i*Pr)$_3$, Table 2.4, entry 8) resulted in improved yields for the thymine and uracil 1',2'-*cis* nucleoside analogues **2-20a** and **2-21a** (Table 2.5, entries 2 and 4) as compared to their formation using conventional heating (DMSO, 140 ^{o}C for 3 hours using 3.0 equivalent of Al(O*t*Bu)$_3$, Table 2.5, entries 1 and 3). The two sets of conditions resulted in similar yields for the adenosine nucleoside analogue **2-22a** (entries 5 and 6). O1'-C4 cyclization was attempted with

the optimized microwave conditions for the *N,OTMS*-acetals bearing 5F-uracil (**2-15a**), cytosine (**2-17a**) and N^4-AcCytosine (**2-19a**). These cyclizations resulted in low yields for their respective cyclized products (entries 7-9).

Table 2.5 S_N2-like cyclization of C4-mesylate *N,OTMS*-acetals.



Entry	*N,OTMS*-Acetal	Heating Source	Product	Yield (%)
1	**2-9a** (Thymine)	Conventional	**2-20a**	34
2	**2-9a** (Thymine)	Microwave	**2-20a**	52
3	**2-12a** (Uracil)	Conventional	**2-21a**	49
4	**2-12a** (Uracil)	Microwave	**2-21a**	57
5	**2-13a** (Adenine)	Conventional	**2-22a**	40
6	**2-13a** (Adenine)	Microwave	**2-22a**	38
7	**2-15a** (5F-Uracil)	Microwave	**2-23a**	32
8	**2-17a** (Cytosine)	Microwave	**2-24a**	27
9	**2-19a** (N^4-AcCytosine)	Microwave	**2-24a**	17

Conventional Heating Conditons: DMSO, 140 ^oC for 3 hours using 3.0 equivalent of Al(O*t*Bu)$_3$;
Microwave Heating Conditions: DMSO, 180 ^oC for 10 minutes using 0.6 equivalent of Al(O*i*Pr)$_3$

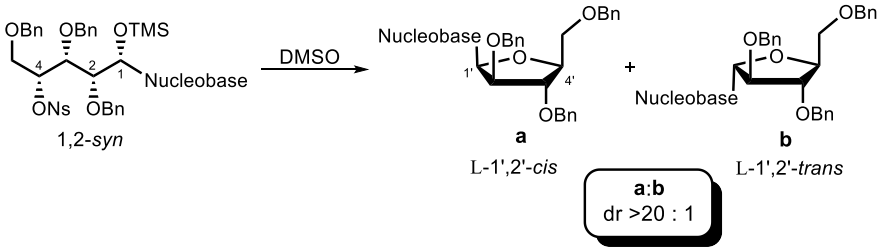
Therefore, the main advantages of using microwave conditions are a much faster reaction time (180 ^oC for 10 minutes versus 140 ^oC for 3 hours) with a lower amount of aluminum Lewis acid

(0.6 eq vs. 3.0 eq) required which also allowed for an enhancement in the yield of cyclized products.

2.4.2 C4-Nosylate *N,OTMS*-Acetal Cyclizations

The cyclization of the *N,OTMS*-acetals bearing a nosylate leaving group at C4 was then investigated (Table 2.6). When heated at only 90 ^{o}C in DMSO and in the absence of Lewis acid, *N,OTMS*-acetal **2-10a** bearing a nosylate leaving group and thymine nucleobase cyclized with a good yield (77%) to provide L-1',2'-*cis* nucleoside analogue **2-20a** (Table 2.6, entry 3). This was a significant improvement as compared to the traces of product observed from the cyclization of the corresponding C4-Ms *N,OTMS*-acetal **2-9a** in the absence of a Lewis acid (Table 2.3, entry 1). When reacted for the same length of time (1 hour) at lower temperatures, starting material remained in the crude reaction mixtures (entries 1 and 2). In the optimization of the reaction conditions, it was observed that DMSO still remained the solvent of choice.

Table 2.6 S_N2-like cyclization of C4-nosylate *N,OTMS*-acetals.



Entry	*N,OTMS*-Acetal	Conditions (equivalents)	Product	Yield(%)
1	2-10a (Thymine)	50 ^{o}C, 1 h	**2-20a**	41[a]
2	2-10a (Thymine)	60 ^{o}C, 1 h	**2-20a**	66[a]
3	**2-10a (Thymine)**	**90 ^{o}C, 1 h**	**2-20a**	**77**
4	2-10a (Thymine)	90 ^{o}C, 1 h, Al(O*i*Pr)$_3$ (3.0)	**2-20a**	63

5	**2-12a (Uracil)**	**90 °C, 3 h**	**2-21a**	**74**
6	2-12a (Uracil)	90 °C, 3 h, Al(O*i*Pr)$_3$ (3.0)	**2-21a**	61
7	2-14a (Adenine)	90 °C, 3 h	**2-22a**	17
8	**2-14a (Adenine)**	**90 °C, 3 h, Al(O*i*Pr)$_3$ (3.0)**	**2-22a**	**60**
9	**2-16a (5F-Uracil)**	**90 °C, 3 h**	**2-23a**	**63**
10	2-16a (5F-Uracil)	90 °C, 3 h, Al(O*i*Pr)$_3$ (3.0)	**2-23a**	45
11	2-18a (Cytosine)	90 °C, 3 h	**2-24a**	28
12	**2-18a (Cytosine)**	**90 °C, 3 h, Al(O*i*Pr)$_3$ (3.0)**	**2-24a**	**46**
13[b]	2-25a (N^4-AcCytosine)	90 °C, 3 h	**2-25a**	8
14	**2-26a (N^4-AcCytosine)**	**90 °C, 3 h, Al(O*i*Pr)$_3$ (3.0)**	**2-25a**	**52**

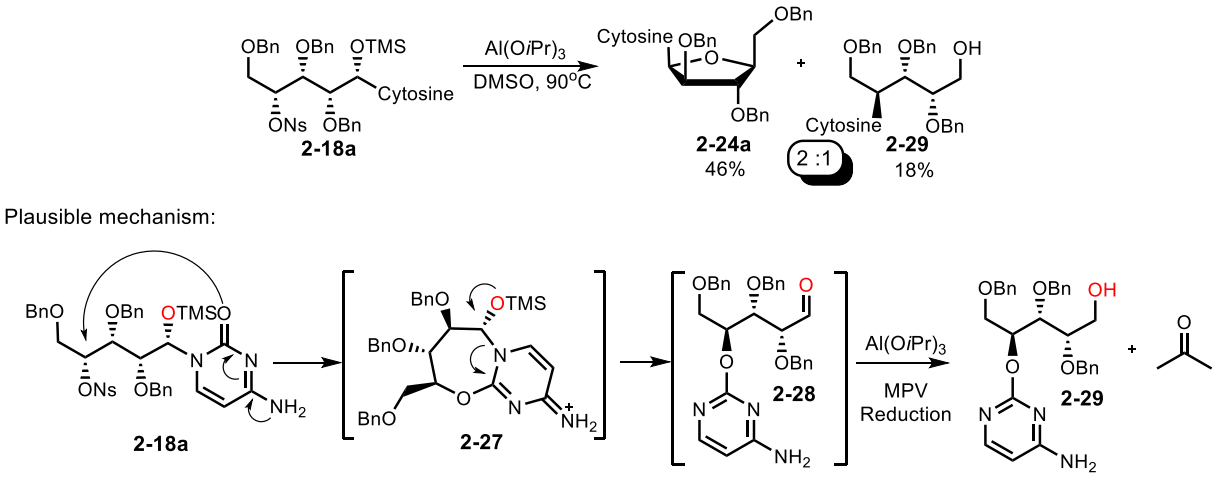
[a] Starting material **2-10a** remaining in crude reaction mixture. [b] *N,OTMS*-N^4-AcCytosine acetal **2-25a** was synthesized through acetylation of the 1,2-*syn* cytosine acetal **2-18a**. **Best conditions are shown in bold.**

Cyclization in toluene, MeCN or DMF provided various mixtures of the product **2-20a**, starting material **2-10a** and aldehyde **2-8** (results not shown). Cyclization of the *N,OTMS*-acetals with uracil and 5F-uracil in DMSO at 90 °C, in the absence of a Lewis acid also gave satisfying results (entries 5 and 9). Low yields were noted, however, for *N,OTMS*-acetals bearing adenine, cytosine and N^4-AcCytosine nucleobases (entries 7, 11 and 13). The addition of the Al(O*i*Pr)$_3$ Lewis acid was thus considered. Whereas no improvements were noted for the thymine, uracil and 5F-uracil cases (entries 4, 6 and 10), significantly higher yields were noted with adenine (entry 8, 60% yield), along with cytosine and its derivative (entries 12 and 14).

In the course of the synthesis of the 1',2'-*cis* analogue **2-24a** bearing cytosine as the nucleobase (Table 2.6, entry 12), formation of a secondary product in a 1:2 ratio with the cyclized nucleoside **2-24a** was observed. This secondary product still contained the cytosine but lacked

the proton characteristic of an anomeric center. It was thus identified as primary alcohol **2-29** (Scheme 2.14) which was confirmed by MS. This alcohol could form through an intramolecular addition of the carbonyl oxygen of the cytosine moiety displacing the C4-Ns. The resulting cyclic intermediate **2-27** could collapse to the corresponding aldehyde **2-28** with rearomatization of the cytosine. In the presence of Al(O*i*Pr)$_3$, the aldehyde could then undergo a Meerwein-Ponndorf-Verley (MPV) reduction[25-27] to furnish primary alcohol **2-29**. It is possible that a similar side product was formed when the other *N,OTMS*-acetals bearing a pyrimidine nucleobase (thymine, uracil, 5F-uracil and N^4-AcCytosine) were cyclized in the presence of Al(O*i*Pr)$_3$. Adenine precursors did not seem to form the corresponding side product.

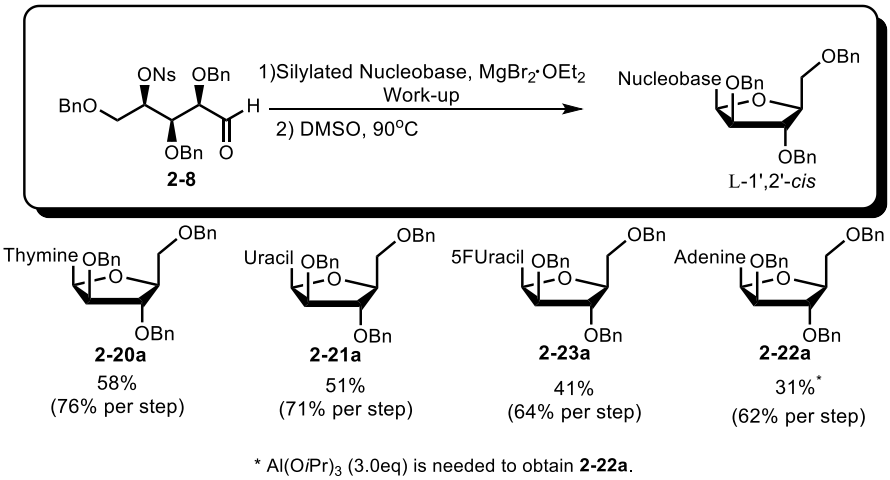
Scheme 2.14 Formation of side-product **2-29**.



In all of the nucleobase coupling reactions, the *N,OTMS*-acetals were purified prior to cyclization. Since some acetal cleavage was suspected on silica gel, cyclization of the crude acetals (after aqueous work-up) was tested. It was observed (Scheme 2.15) that the yields of L-1',2'-*cis* analogues obtained from cyclization of crude *N,OTMS*-acetals were consistent with

those obtained from cyclization of the purified acetals. This indicates that there is no need to purify the 1,2-*syn N,OTMS*-acetals prior to cyclization rendering the process even simpler.

Scheme 2.15 Silylated nucleobase coupling and cyclization using crude *N,OTMS*-acetals.



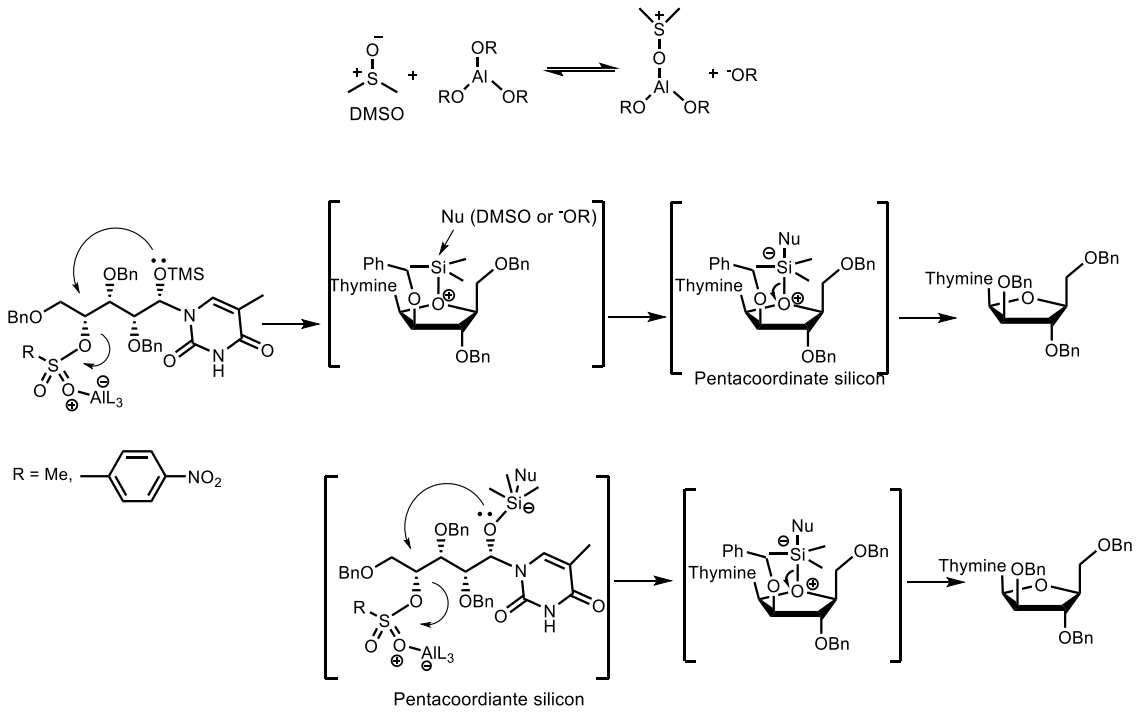
* $Al(OiPr)_3$ (3.0eq) is needed to obtain **2-22a**.

A two-step process was also tried in which DMSO was simply added to the reaction mixture (aldehyde **2-8** with silylated thymine, $MgBr_2 \cdot OEt_2$ in MeCN) once formation of the *N,OTMS*-acetal was complete (i.e., no work-up). After heating to 90 ^oC, the resulting nucleoside analogue **2-20a** was isolated in 39% yield.

2.5 Mechanistic Insights for the O1'→C4 Cyclization

The exact role of the $Al(OR)_3$ in these O1'-C4 cyclizations has not been elucidated, but its Lewis acid character could enhance the leaving group ability after complexation with the sulfonate oxygens of the mesylate or nosylate at C4 (Scheme 2.16). A similar complexation has been proposed for the formation of tetrahydrofurans through tosylate activation with Fe(III).[28]

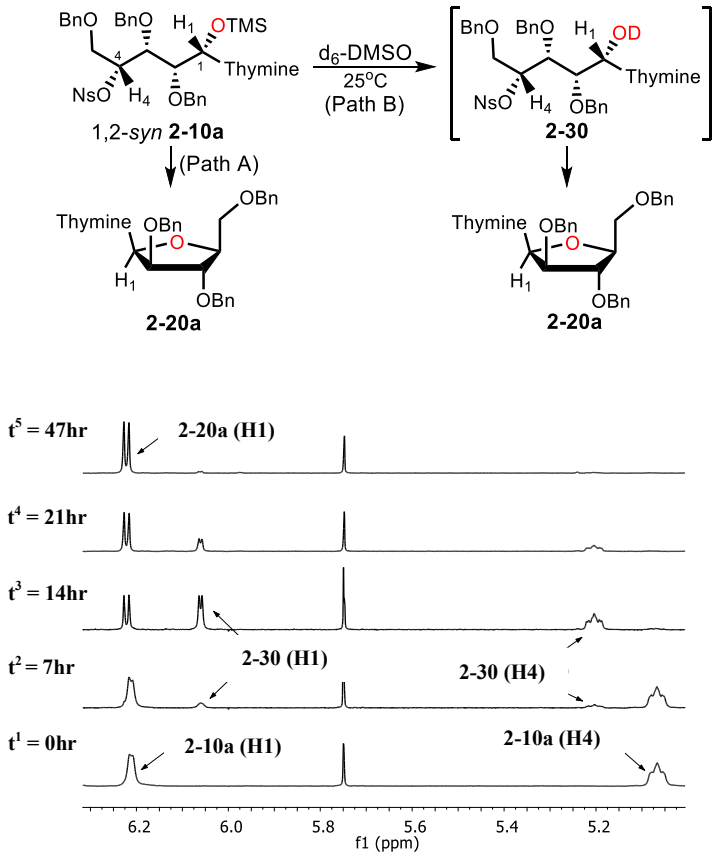
Scheme 2.16 C4 sulfonate activation with $Al(OR)_3$.



The oxygen lone pair of the –OTMS group could displace the activated leaving group at the C4 position. The subsequent desilylation could occur from addition of a nucleophilic species (either DMSO or an ⁻OR ion formed from the coordination of DMSO with $Al(O\textit{t}Bu)_3$ or $Al(O\textit{i}Pr)_3$) to the silicon atom forming a pentacoordinate species[29,30] that would decomplex to give the L-nucleoside. In a similar scenario, the pentacoordinate silicon species could form on the *N,OTMS*-acetal enhancing the nucleophilicity of the oxygen prior to displacement of the activated C4 leaving group. For the cyclization of the nosylate *N,OTMS*-acetals which did not always require $Al(O\textit{i}Pr)_3$, it was hypothesized that the oxygen of the *N,OTMS*-acyclic acetal could serve as the nucleophile displacing the better non-Lewis acid activated nosylate leaving group at C4 to form the L-nucleosides (Figure 2.1, Path A). The reacting intermediate in the cyclization could still involve a pentacoordinate silicon complex in the presence of DMSO, thus increasing the

nucleophilicity of the oxygen. ^{1}H NMR spectroscopic analysis of the O1'→C4 cyclizations of nosylated acetal **2-10a** in d_6-DMSO unveiled yet another possibility (Figure 2.1). This experiment indicated that cyclization of **2-10a** proceeded at room temperature with the formation of an intermediate species that completely converted to product after 47 hours. This intermediate could not be isolated but the observed ^{1}H NMR peaks are in good agreement with a hemiaminal arising from *in situ* deprotection of the OTMS acetal.

Figure 2.1 ^{1}H NMR spectra during cyclization of 1,2-*syn N,OTMS*-acetal **2-10a** at 25 °C.



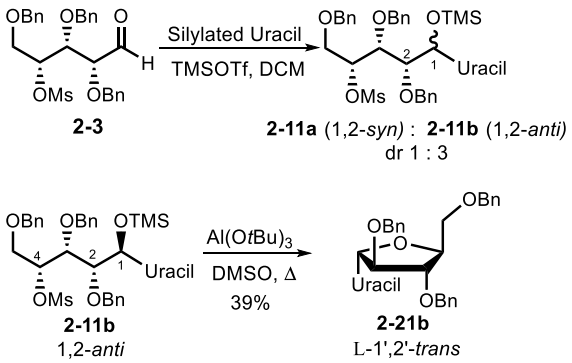
As seen in Figure 2.1, NMR chemical shifts that may correspond to H1 and H4 of intermediate **2-30** are very similar to those of the starting material, suggesting that the acetal center and nosylate activating group are still present. In addition, there were no NMR signals corresponding to additional silyl groups (other than TMSONs), further indicating that **2-10a** was indeed

deprotected to the corresponding hemiaminal **2-30**. An example of a similar adenosine hemiaminal has previously been reported in the literature.[31] Also, when silylated nucleobase or BSA (bis(trimethylsilyl)acetamide) was added to the cyclization reaction and montitored by NMR, the formation of the L-1',2'-*cis* nucleoside took longer (2 hours versus 1 hour at 90 ^{o}C) and no intermediate was observed. Cyclization of the hemiaminal generated after *in situ* deprotection of the *N,OTMS*-acetal (Figure 2.1, Path B) was therefore proposed. In the course of these NMR experiments, the decomposition of hemiaminal **2-30** to aldehyde **2-8** with loss of the thymine nucleobase was not observed most likely due to the absence of an acid**.**

2.6 Synthesis and Cyclization of 1,2-*anti N,OTMS*-acetals

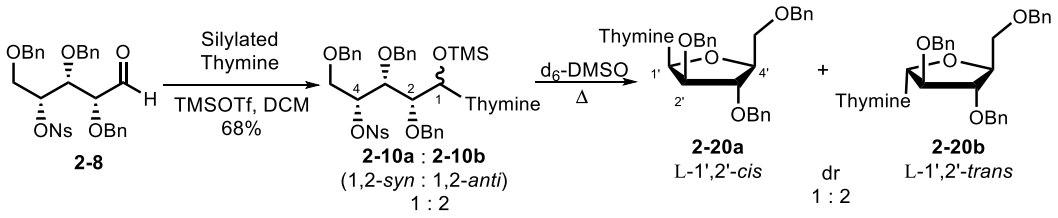
In order to confirm that the O1'→C4 cyclization proceeds with retention of configuration at C1, 1,2-*anti N,OTMS*-acetal **2-11b** was synthesized and cyclized (Scheme 2.17). This 1,2-*anti* configuration was generated with poor selectivity (1,2-*syn*:1,2-*anti*; 1:3) in presence of TMSOTf, but a pure fraction of the 1,2-*anti* product could be separated by flash chromatrography. Cyclization of **2-11b** provided only the L-1',2'-*trans* nucleoside analogue **2-21b** (>20:1), as determined by the ^{1}H NMR of the crude reaction mixture.

Scheme 2.17 Synthesis and cyclization of 1,2-*anti N,OTMS*-acetal **2-11b**.



The retention of configuration at C1 for the O1'→C4 cyclization was also further examined in the nosylate series (Scheme 2.18). A 1:2 mixture of **2-10a** : **2-10b** was prepared by coupling aldehyde **2-8** with silylated thymine in presence of TMSOTf. The 1,2-*syn* and *anti N,OTMS*-acetals could not be separated and were therefore cyclized as a mixture. The corresponding 1:2 mixture of the L-1',2'-*cis* and *trans* nucleoside analogues **2-20a** and **2-20b** was obtained cleanly.

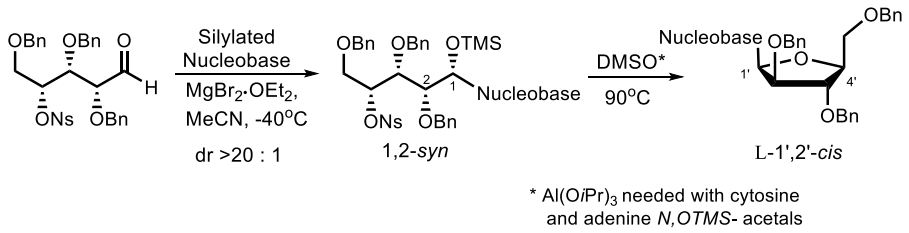
Scheme 2.18 Synthesis and cyclization of a mixture of *N,OTMS*-acetals **2-10a** and **2-10b**.



2.7 Conclusions

A novel strategy has been developed for the synthesis of valuable L-1',2'-*cis* nucleoside analogues from unusual 1,2-*syn N,OTMS*-acetals bearing pyrimidine as well as adenine nucleobases. In order to diastereoselectively generate these acyclic precursors, addition of silylated nucleobases onto polyalkoxyaldehydes in the presence of $MgBr_2 \cdot OEt_2$ through a suggested Cram-chelate transition state has been studied. These *N,OTMS*-acetals undergo unprecedented O1'→C4 cyclizations with complete retention of configuration at C1. NMR studies of the reaction may have unveiled a possible mechanism involving an *in situ* deprotection of the *N,OTMS*-acetals. This strategy provides stereoselective access to unnatural L-nucleosides with a variety of nucleobases starting from easily accessible pools of D-sugars. As importantly, this methodology addresses the challenging synthesis of 1',2'-*cis* nucleosides. In summary, the

most efficient way of synthesizing L-1',2'-*cis* NAs using the acyclic approach involves nucleobase addition onto C4-ONs activated aldehydes followed by a subsequent O1'→C4 cyclization in DMSO with conventional heating.



2.8 References

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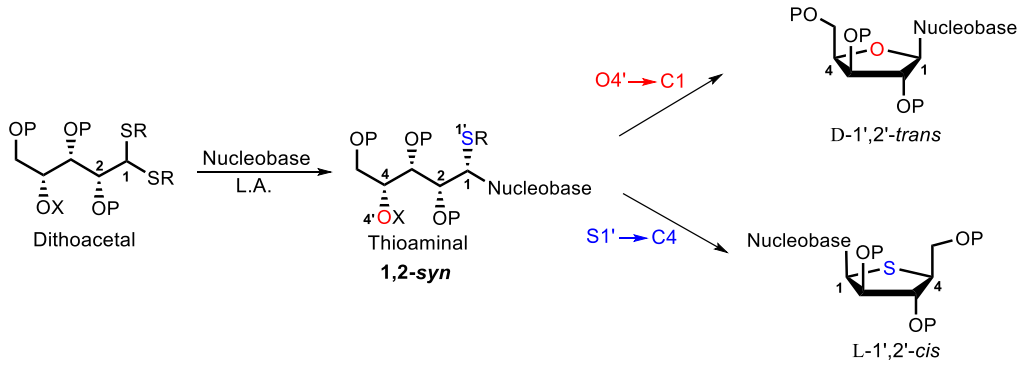
Chapter 3 Investigation of Diastereoselective Acyclic Substitutions for the Synthesis of Thioaminals

3.1 Research Perspectives

The efficient synthesis of nucleoside analogues, which involves the introduction of a pyrimidine or purine nucleobase onto a sugar scaffold in a stereocontrolled manner, remains an ongoing challenge. In the development of the acyclic approach for the synthesis of nucleoside analogues, it has been observed that nucleobases add to C2-alkoxydithioacetals with high 1,2-*syn* selectivity (Scheme 3.1).[1,2] These 1,2-*syn* acyclic thioaminals then undergo the two distinct and versatile stereoselective S_N2-like intramolecular cyclizations leading to D-1',2'-*trans* nucleoside analogues and L-1',2'-*cis* thionucleosides.

Scheme 3.1 Synthesis of 1,2-*syn* thioaminals from nucleobase addition to dithioacetals.



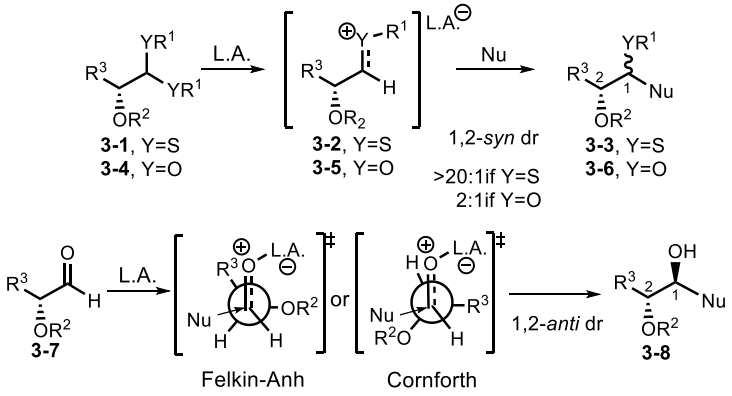
An experimental and theoretical study has been undertaken to rationalize the origin of this 1,2-*syn* diastereocontrol (anti-Felkin-Anh) when silylated nucleobases add to acyclic dithioacetals bearing an alkoxy group in the C2-position. This became the subject of a 2014 Journal of Organic Chemistry paper,[3] and its contents will be discussed within this chapter. My contribution to this work involved investigation of thymine coupling to the isopropyl model substrate with various solvents and activating agents. I also performed the experimental kinetic isotope studies

to support our mechanistic hypothesis. As highlighted throughout the chapter, Dr Michel Prévost performed all of the DFT calculations and had done the initial experimental model substrate study (Table 3.1) with the help of Marie-Ève Waltz.

3.2 Introduction to Substitution Mechanisms

The high 1,2-*syn* inductions observed for nucleobase coupling to dithioacetals with a C2-alkoxy group (**3-1**) are intriguing given that the corresponding acetals (**3-4**) provide only marginal selectivities under non-chelating conditions (Scheme 3.2).[4,5]

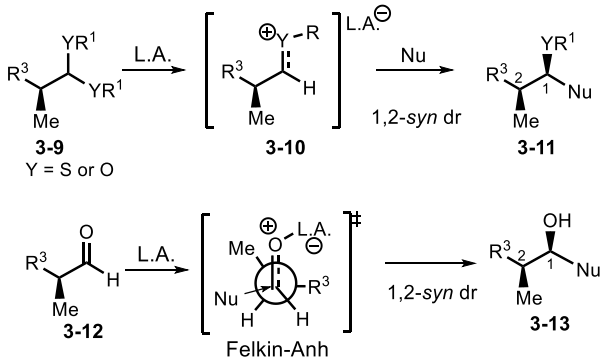
Scheme 3.2 Selectivity trends for Nu addition to C2-alkoxy dithioacetals, acetals and aldehydes.



It is generally expected that acyclic acetals react through free carbenium intermediates such as thiacarbenium[6] **3-2** and oxocarbenium[7,8] **3-5**. Therefore, they should intuitively provide selectivities comparable to those observed with the corresponding activated aldehydes **3-7,** with the R^1 group being replaced by a Lewis acid. However, C2-alkoxyaldehydes **3-7** are 1,2-*anti* selective (Felkin-Anh[9-11] or Cornforth[12,13]) in absence of chelate formation giving an opposite induction as to what is observed with **3-1** and **3-4**. Chiral carbenium precursors (**3-9**, Scheme 3.3) not bearing a C2-electron withdrawing group induce similar selectivities as their chiral

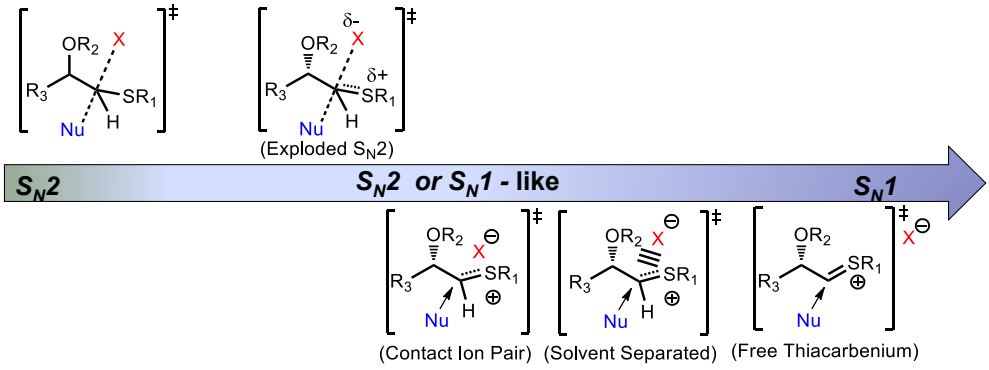
aldehyde congeners furnishing the 1,2-*syn* Felkin-Anh product where attack of the nucleophile occurs opposite of the largest alkyl group.[6,14,15]

Scheme 3.3 Selectivity trends for Nu addition to C2-chiral precursors.



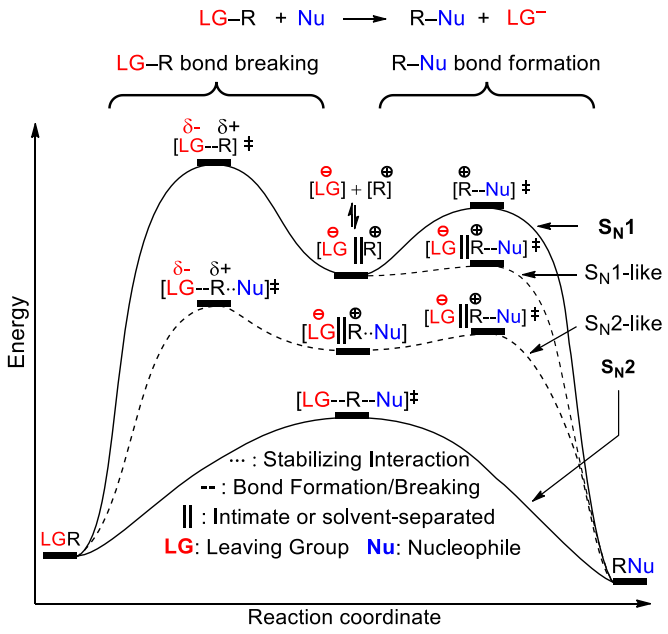
In order to rationalize the observed trends of selectivity for substitution of C2-alkoxydithioacetals (Scheme 3.2), mechanistic insights are essential. Although S_N1 and S_N2 reactions are often considered as discrete processes, the mechanism of a given substitution reaction lies somewhere on a continuum between these two extremes (Figure 3.1).[16] Therefore, substitution reactions may proceed through borderline S_N1-S_N2 mechanisms.[7,17-19]

Figure 3.1 Spectrum of substitution reaction mechanisms.



A representation of their potential energy diagrams (Figure 3.2) is helpful in differentiating among these reaction types.[20,21]

Figure 3.2 Potential energy diagrams for S_N1, S_N1-like, S_N2-like and S_N2 mechanisms.



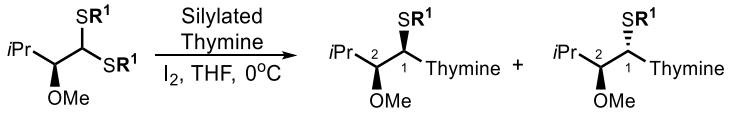
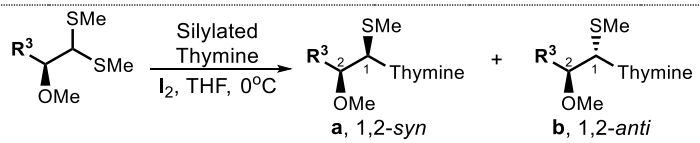
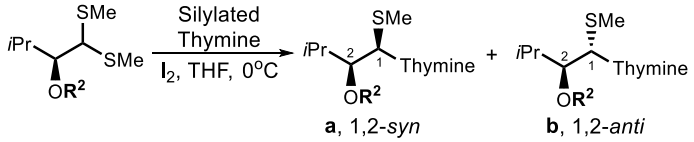
All substitution reactions involve two processes, namely, a bond breaking step between the leaving group and the substrate (R) and formation of a new bond with the incoming nucleophile.[22,23] The rates at which this ionization and addition occur determine the mechanism of substitution. A substitution qualifies as an S_N1 reaction if formation of the free carbenium species (thia-**3-1** or oxo-**3-5**) is rate determining (S_N1, Figure 3.2). The subsequent addition of the nucleophile is then regarded as the product determining step. It is suggested that only a small fraction of S_N1 reactions occur with a fully free carbenium.[24] Exchange of the leaving group and nucleophile actually takes place through solvent-separated or contact ion pairs (Figure 3.1). Although a clear distinction is difficult to make, solvent separated ion-pairs are considered to be different from free carbenium species since a measurable electrostatic attraction between the cation and anion exists despite the presence of the solvent. Therefore, in an S_N1-like mechanism, attack of the nucleophile occurs on ion pairs (intimate/contact-ion pair or solvent-separated) formed after cleavage of the LG−R covalent bond. If the slow step (ion pair or product

formation) involves the nucleophile, the substitution reaction functions more as an S_N2 mechanism.[25,26] S_N2 reactions involving an intermediate ion pair are termed S_N2-like ("exploded"),[27] since they do not meet the concerted bond forming/bond-breaking criteria of classical S_N2 reactions (Figure 3.2).[28] The degree of association between the reacting carbon, the counter ion and the nucleophile can thus vary and occurs through a range of mechanisms with more or less tightly associated transition states between the two formal extremes of the S_N2 and S_N1 pathways. Where a particular reaction is located on this spectrum depends on protecting groups, solvents, leaving groups and activating agents.[25]

3.3 Substitution of Model Dithioacetal Substrates

A substrate model study was investigated in order to identify the factors that contribute to the 1,2-*syn* induction when dithioacetals are substituted by nucleobases. Table 3.1 summarizes the work done by Dr Michel Prévost during his PhD studies on this model study. It can be seen that the alkyl chain (R^1) attached to the sulfur atoms of the dithioacetal does not influence the *syn* induction. Dimethyl-(**3-14**), di*iso*propyl-(**3-16**) and di*tert*butyl-(**3-18**) thioacetals all give high 1,2-*syn* selectivity (entries 1-3, Table 3.1) when reacted with I_2 in THF at 0 ^oC. However, with a phenyl (entry 4) or benzyl (entry 5) group attached at C2, the selectivity drops significantly. On the other hand, *i*Pr (entry 1) or *t*Bu (entry 6) side chains give high *syn* selectivity. Both methoxy and silyloxy C2-groups provide high 1,2-*syn* inductions (entries 1 and 7), which are comparable to what is typically observed for substrates bearing a benzyloxy group at C2.[1]

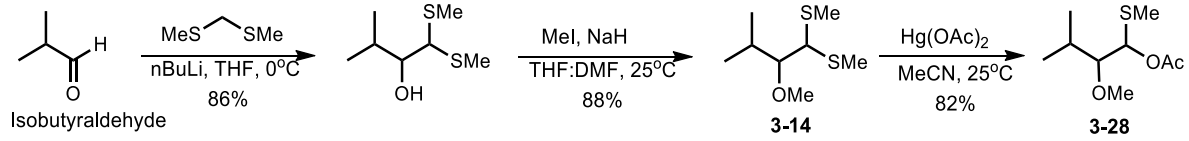
Table 3.1 Substitution of dithioacetals with various R^1, R^2 and R^3 groups.[29]

Entry	R^1, R^2 or R^3	Ratio (**a**:**b**)[a]	Yield (%)
			
1	**3-14** Me	11:1 **3-15a,b**	85
2	**3-16** *i*Pr	9:1 **3-17a,b**	82
3	**3-18** *t*Bu	9:1 **3-19a,b**	92
			
4	**3-20** Ph	3:1 **3-21a,b**	90
5	**3-22** -CH_2Ph	2:1 **3-23a,b**	83
6	**3-24** *t*Bu	>20:1 **3-25a,b**	81
			
7	**3-26** TBS	12:1 **3-27a,b**	86

a. Determined by ^{1}H NMR spectroscopic analysis of crude mixtures

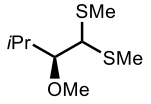
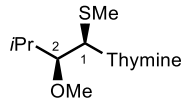
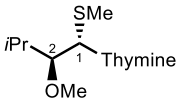
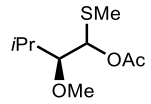
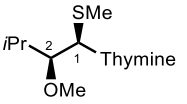
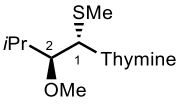
Dithioacetal **3-14** was selected to explore the different plausible mechanisms for this reaction both experimentally and theoretically (*in silico)*. This dithioacetal was synthesized from the reaction of isobutyraldehyde, bis(methylthio)methane and *n*BuLi in THF at 0 ^{o}C followed by protection of the C2-alcohol with MeI (Scheme 3.4).[2] Formation of the corresponding thioacetate **3-28** from dithioacetal **3-14** was accomplished from addition of $Hg(OAc)_2$ in MeCN.

Scheme 3.4 Preparation of dithioacetal **3-14** and acetate **3-28**.



As seen in Table 3.2, various activating agents were examined to perform the nucleophilic substitution. Reaction of dithioacetal **3-14** at 0 °C with silylated thymine provides comparable 1,2-*syn* selectivity in the presence of I_2, Br_2 or $Me_2S(SMe)BF_4$ (entries 1, 2, 5 and 7, Table 3.2).

Table 3.2 Substitution of **3-14** and **3-28** using various activation protocols.

Entry	Activating Agent, Time	T	Ratio(**a**:**b**)[a]	Yield(%)
 **3-14**	Silylated Thymine[b], THF	 **3-15a,** 1,2-*syn* +  **3-15b,** 1,2-*anti*		
1	I_2, 40 hr	0 °C	11:1	64[c]
2	I_2, 65 hr	0 °C	9:1	85
3	I_2, 16 hr	25 °C	4:1	
	+16 hr	70 °C	1:1	78
4	I_2, 16 hr	70 °C	1:1	81
5	Br_2, 16 hr	0 °C	9:1	82
6	Br_2, 4 hr	0 °C	11:1	83
7	$Me_2S(SMe)BF_4$, 16 hr	0 °C	14:1	79
8	$Hg(OAc)_2$, TMSOTf, 16 hr	0 °C	13:1	88
9	$Hg(OAc)_2$, TMSOTf, 16 hr	25 °C	5:1	82
 **3-28**	Silylated Thymine[b], THF	 **3-15a,** 1,2-*syn* +  **3-15b,** 1,2-*anti*		
10	TMSI, 4hr	0 °C	14:1	51
11	TMSBr, 4hr	0 °C	14:1	54
12	TMSOTf, 4hr	0 °C	13:1	38

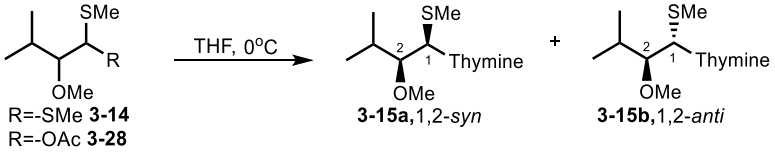
a. Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. b. Silylated thymine prepared as solution in DCM, therefore, a ~ 2:1 ratio of THF to DCM in the reaction mixture. c. Starting material **3-14** remaining in crude mixture.

Treatment of **3-14** with $Hg(OAc)_2$ generates acetate **3-28**, which was either treated *in situ* with TMSOTf and the nucleobase (entries 8-9), or purified by flash chromatography before being reacted with the nucleobase using TMSI, TMSBr or TMSOTf (entries 10-12). These two protocols provide the 1,2-*syn* product with comparable diastereoselectivity, but the *in situ* method (entries 8 and 9) gives higher yields. The observed variation in selectivity at different

reaction temperatures (entries 1-4 and 8-9) suggests that the substitution reaction is under kinetic control.

The reaction conditions presented in Table 3.2 required optimization of the reaction time and temperature along with the amount of reagents added and their order of addition. For example, the order of addition of the activating agent and silylated thymine was demonstrated to have an impact on the yield of product formation (Table 3.3). The typical conditions involved addition of the silylated nucleobase prior to addition of the activating agent (entry 1). When I_2 was added before the nucleobase, the reaction did not proceed with starting material **3-14** and only traces of product being recovered (entry 2).

Table 3.3 Variation of activating agent and silylated thymine addition.



Entry	R	Conditions	Ratio (**a** :**b**) [a]	Yield (%)
1	SMe	Silylated Thymine then I_2	9:1	85
2	SMe	I_2, –40 °C 30 min[b], then Silylated Thymine	**3-14** and traces of product	
3	SMe	Silylated Thymine then Br_2	11:1	83
4	SMe	Br_2, –40 °C 30 min[b], then Silylated Thymine	11:1	63
5	OAc	Silylated Thymine then TMSBr	**3-28** and traces of product	
6	OAc	TMSBr, –10 °C 1 hr[b], then Silylated Thymine	14:1	54

a. Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. b. Reaction time determined from ^{1}H NMR studies for conversion of starting material to halothioether (as discussed in Section 3.4).

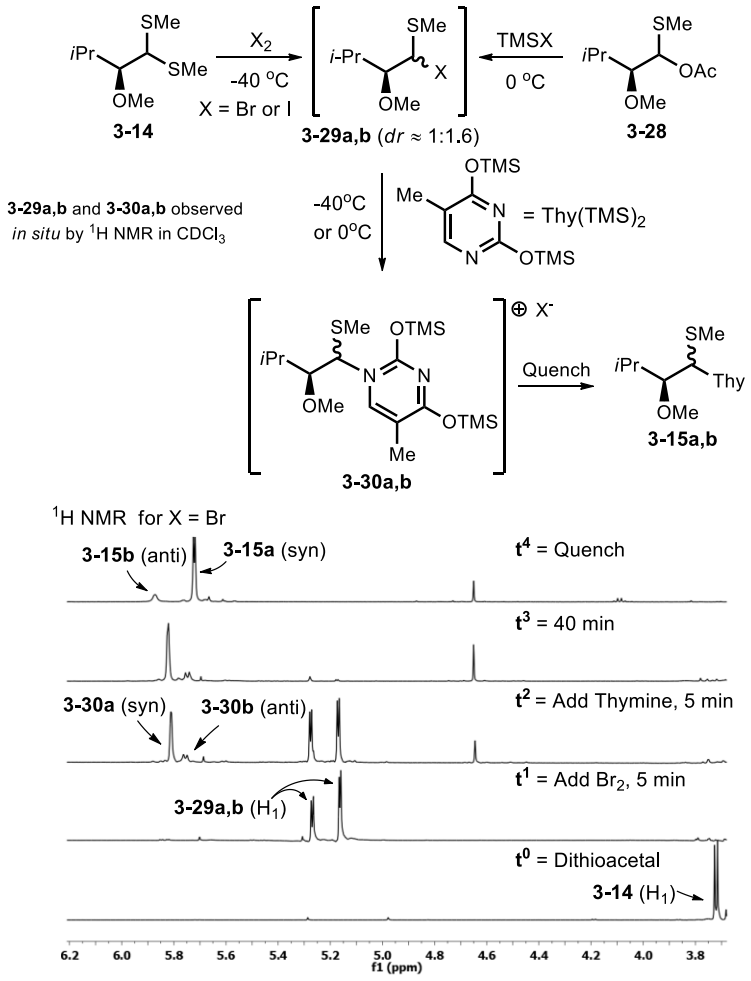
However, if bromine was added prior to the nucleobase, the reaction did proceed but resulted in a lower yield of thioaminal products **3-15** with the presence of undetermined impurities (entries 3 and 4). These undetermined impurities may be due to decomposition of the bromothioether **3-29**

(see section 3.4) before it reacts with the silylated nucleobase. In the coupling reactions of thioacetate **3-28**, the TMSX activating agent had to be added prior to nucleobase addition (entry 6). If the order was reversed starting material **3-28** with only traces of product formation was observed (entry 5). This lack of reactivity was most likely due to complexation between the TMSBr and the nucleobase.

3.4 ^{1}H NMR Study for Dithioacetal Substitution

In these substitution reactions, it is anticipated that upon activation of the dithioacetal substrate, a halothioether intermediate is first formed onto which the silyated nucleobase adds. This scenario is supported by a ^{1}H NMR spectroscopic study in $CDCl_3$ that shows formation of halothioether intermediates (Figure 3.3). Upon addition of the halogen to **3-14**, two new species, which display characteristic chemical shifts corresponding to bromothioethers **3-29a,b**, were rapidly formed in approximately a 1:1.6 ratio. These species convert to product intermediates **3-30a** and **3-30b** upon addition of the silylated thymine. **3-30a** and **3-30b** have anomeric protons characteristic of thioaminals but display a difference in chemical shift as compared to final thioaminals **3-15a,b**.It is thus proposed that these product intermediates still have the silyl groups attached to the thymine which after hydrolysis result in thioaminals **3-15a,b**. Based on these observations, the nucleobase coupling reaction seems to be under Curtin-Hammett control, since the product ratio of **3-15a,b** (5.6:1 in $CDCl_3$) does not correspond to the diastereomeric mixture of halides **3-29a,b** (1:1.6). It is recognized that the major and minor diastereoisomers may react through different mechanisms. Interestingly, activation of the thioacetate **3-28** with TMSBr also furnished the same intermediate species **3-29a,b**. The corresponding iodothioether intermediates were, however, difficult to observe *in situ* by ^{1}H NMR.

Figure 3.3 ^{1}H NMR spectroscopic study for the substitution of **3-14** or **3-28** by silylated thymine.



3.5 DFT Study

The substitution mechanism of halothioether **3-29**, which was experimentally identified as the most plausible reacting intermediate, was examined by density functional theory (DFT) calculations in Gaussian 09.[30] These calculations were performed by Dr Michel Prévost (IRCM, research associate). Various models have been developed to calculate molecular structures and these can be classified into two categories namely, quantum chemical models and molecular mechanics models.[31] Quantum chemical models stem from the Schrödinger equation in which molecules are described through interactions among nuclei and electrons whereas molecular

mechanics treats molecules in terms of atoms and bonds. Although the molecular mechanics approach is simpler than solving the Schrödinger equation only conformational analyses can be obtained from molecular mechanics.[31] Various quantum chemical models have been developed which differ in the approximations made to solve the Schrödinger equation for a many-electron system. In the Hartree-Fock (HF) approximation, electrons are modelled as independent particles where each electron sees the others as an average field. This approximation however, fails to predict how the motion of one electron affects the motions of all the others. Thus, HF is not good in accounting for the thermochemistry of reactions involving bond formation and cleavage. Two fundamentally different approaches for improvement of the Hartree-Fock model have emerged. One approach involves a more flexible description of the motion of electrons by combining the Hartree-Fock descriptions for ground and excited states (configuration interaction (CI) and Møller-Plesset (MP) models). An alternate approach that has proven to be successful for determination of equilibrium geometries and molecular conformations is density functional theory that calculates electron density instead of wavefunctions.[32] The total energy calculated in DFT ($E= E^T + E^V + E^J + E^{XC}$) takes into consideration the electronic kinetic energy (E^T), the potential energy (E^V), the electron-electron repulsions, and an exchange-correlation term (E^{XC}) which accounts for both the exchange interaction arising from the Pauli-exclusion principle and electron-electron correlation.[24] The accuracy of a DFT calculation depends on the quality of this exchange–correlation (XC) functional,[33] and has resulted in different levels of theory which include for example B3LYP, M05, M06-2X. The reported energies for these calculations were obtained for fully optimized structures through DFT calculations with the M06-2X[33-35] level of theory using a 6-311+G** basis set in combination with LANL2DZpd[36,37] effective core potentials for bromine and iodine. The 6-311+G** basis-set is a split-valence basis set implying

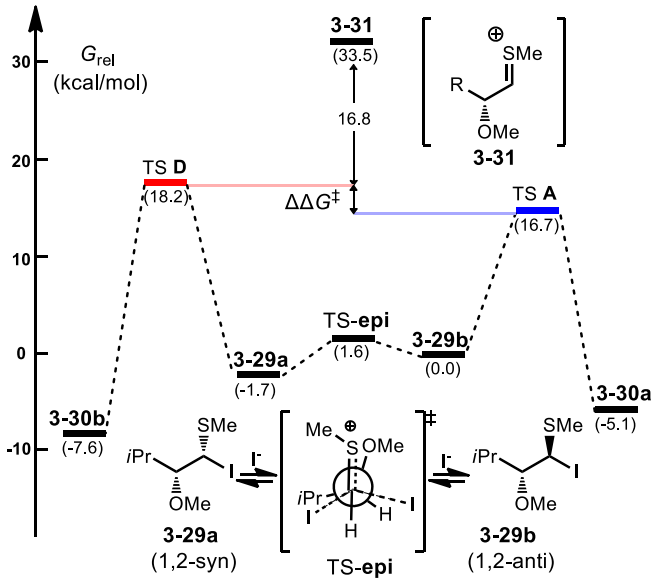
that a linear combination of 6 (6-311+G**) Gaussian-type orbitals was used to describe the core orbitals and the valence atomic orbitals were described using 5 Gaussian orbitals (6-311+G**) split into three functions with the first being a linear combination of three Gaussian orbitals and the second two functions being single diffuse Gaussians. Diffuse functions were also taken into consideration for everything larger than H (6-311+G**), d-orbitals were added to second and third row elements (6-311+G**) and p-orbitals were added to all of the s-orbitals of H (6-311+G**). The purpose of this elaborate basis-set is to increase the accuracy in properly describing the electron density. Calculations involving heavy elements can be simplified by considering only the valence electrons, while replacing the core by a potential. Thus, LANL2DZpd effective core potentials were used for bromide and iodide where the electron density is treated as a function of potential instead of as orbitals. Polarization and diffusion (LANL2DZpd) were also taken into account.

The different trajectories of nucleobase attack and positions of the leaving group were studied using uracil$(TMS)_2$ which provides experimental selectivities comparable to thymine$(TMS)_2$ and was therefore used to reduce the time of the calculations.[2] Mechanisms that ranged from S_N2-like to S_N1 were analyzed and compared *in silico.* Optimization of the transition structures and intermediates were performed in the gas phase as well as in various solvents using the polarizable continuum model (PCM), which treats solvents as a polarizable continuum taking into account electrostatic, dispersion-repulsion and cavitation factors. The solvent is modeled as a cavity of interlocking van der Waals spheres.[38]

An overview of the relevant intermediates and proposed transition structures for addition of the silylated nucleobase to halothioether **3-29** in THF is presented in Figure 3.4. Transition structures, TS **A** and TS **D** (shown in Figure 3.5), have been established to be at the rate and

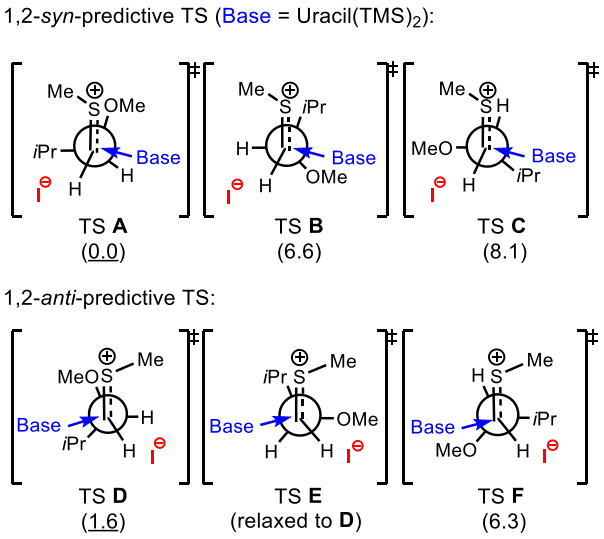
product determining steps. For reasons discussed in the solvent effect section, the Gibbs free energy values of TS **A** and **D** were obtained from optimized structures in toluene that were then solvated in THF. All the other intermediates presented were optimized in THF. Both TS display relative Gibbs free energy values significantly lower than the free thiacarbenium species **3-31**(Figure 3.4), which indicates that the substitution reaction is not likely to proceed through a classical S_N1 mechanism. The relative Gibbs free energy for the epimerization (TS-**epi**) of iodothioethers **3-29a,b** (15.1 kcal/mol lower than TS **A**) indicates that they undergo a rapid equilibrium. This is consistent with the ^{1}H NMR spectroscopic studies in which a fairly constant **3-29a**:**3-29b** ratio was observed throughout the coupling reaction (Figure 3.3). The profile presented in Figure 3.4 is consistent with Curtin-Hammett[39,40] kinetic control, where a fast equilibration exists between ion pairs and the rate of formation of the R−Nu bond dictates the stereochemistry of the substitution reaction. Therefore, $\Delta\Delta G^{\ddagger}$ between the lowest 1,2-*syn* (TS **A**) and 1,2-*anti* (TS **D**) transition structures provides a measure of the expected reaction selectivity.

Figure 3.4 Relative Gibbs free energy (kcal/mol) profile in THF for **3-29a,b** substitution.



A thorough examination of the different trajectories of base attack, counter-ion position and C1–C2 conformations was done in the gas phase. TS **A** and **D** (S_N2-like), the lowest 1,2-*syn* and 1,2-*anti* predictive transition structures are presented in Figure 3.5. In these TS, the counter ion is on the opposite side of nucleobase entrance and pyramidalization of the C1 center leads to staggered conformations. Both the lowest 1,2-*syn* and 1,2-*anti* predictive TS (**A** and **D**) adopt a C1–C2 conformation orienting the sulfur and C2-oxygen gauche to each other. No stationary point could be found in the C2-C3 TS **E** conformation, thus it led to TS **D** after transition structure optimization.

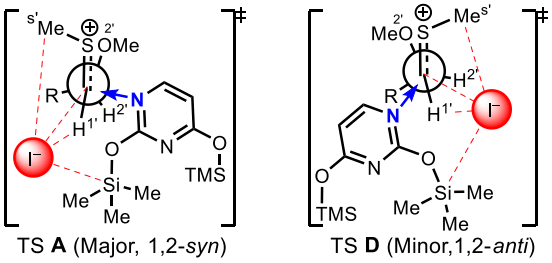
Figure 3.5 Lowest 1,2-*syn* and 1,2-*anti* predictive TS in the gas phase. Gibbs free energy (kcal/mol).



The stabilizing interactions obtained by natural bond orbital (NBO) analyses in the gas phase are helpful in rationalizing the preferred geometry of TS **A** and **D** (Table 3.4). Strong interactions are found between the antibonding π*(S–C1) and the nitrogen sp^2 lone pair of the nucleobase and, to a lesser extent, with lone pairs of the iodide (entries 1 and 2). These interactions are stronger in TS **D**, which is consistent with the shorter N–C1 (TS **D** 2.26 Å versus TS **A** 2.38 Å) and I–C1

(TS **D** 3.30 Å versus TS **A** 3.49 Å) bond lengths. Significant interactions of the iodide lone pairs are also found with the antibonding σ*(C–H) bonds involving H1', the methyl group attached to sulfur and also with the silicon group of the nucleobase (entries 3-5). These interactions all likely contribute to orienting the iodide below the thiacarbenium species. Interestingly, the R–C2 and H2'–C2 sigma bonds interact strongly with the thiacarbenium antibonding orbital π*(S–C1) (entries 6-7) and thus the preferred C1–C2 gauche conformation could be due to proper alignment of these sigma bonds in both TS **A** and **D** resulting in essentially hyperconjugative stabilization of the cation.

Table 3.4 Stabilizing interactions (NBO analysis) of the TS **A** and **D** in the gas phase.



Entry	Stabilizing interactions	TS **A** (kcal/mol)	TS **D** (kcal/mol)
1	LP(N) → π*(S–C1)	32.5	43.6
2	LP(I) → π*(S–C1)	6.4	14.0
3	LP(I) → σ*(H1'–C1)	8.5	3.8
4	LP(I) → σ*(Me: C–H)	5.3	4.3
5	LP(I) → σ*(TMS)	5.4	4.1
6	σ(C2–R) → π*(S–C1)	8.6	4.1
7	σ(C2–H2')→ π*(S–C1)	10.4	15.9
8	LP(O2')→ σ*(S–Me$^{s'}$)	0.92	1.30

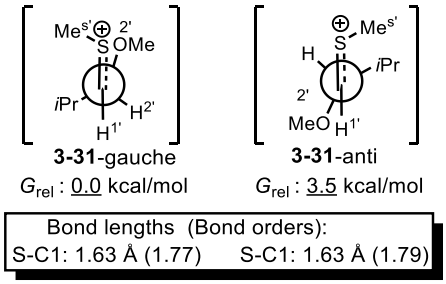
LP : lone pair

It is postulated that this orientation could also favor an electrostatic stabilization between the C2-OMe group and the positively charged thioether, which was observed for related oxocarbenium

species.[41] However, the calculated values from the NBO analysis suggest only a 0.92 and 1.30 kcal/mol stabilization for this type of interaction in TS **A** and **D** (entry 8). The S–C1 bond orders and bond lengths in TS **A** and **D** (Table 3.4) are close to the ones observed for the free thiacarbenium (**3-31**-gauche and **3-31**-anti, Table 3.5). This suggests that these TS are leaning towards contact ion pair intermediates with substantial thiacarbenium character. When comparing TS **A** and **D**, it can be seen that the N-C1 and I-C1 bond lengths are both shorter and their stabilizing interactions stronger in TS **D**. This indicates a somewhat more associative mechanism for formation of the 1,2-*anti* product.

The free thiacarbenium **3-31** also has the same C1–C2 conformational preference as TS **A** and **D**, where the C2-oxygen and C1-sulfur are gauche (Table 3.5).

Table 3.5 Stabilizing interactions (NBO analysis) of thiacarbenium **3-31** in the gas phase.



Entry	Stabilizing interaction	**3-31**-gauche (kcal/mol)	**3-31**-anti kcal/mol)
1	$\sigma(C2–C3_{iPr})\rightarrow\pi^*(S–C1)$	9.0	10.4
2	$\sigma(C2–H2')\rightarrow\pi^*(S–C1)$	12.0	2.8
3	$\sigma(C2–O2')\rightarrow\pi^*(S–C1)$	-	2.5
4	$LP(O2')\rightarrow\sigma^*(S–Me^{s'})$	1.6	-
5	$LP(O2')\rightarrow\pi^*(S–C1)$	-	2.4

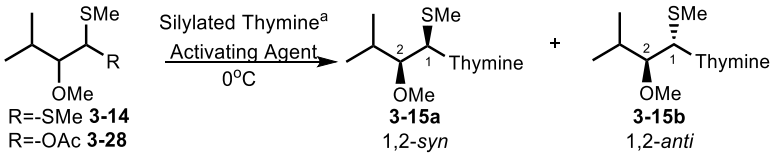
3-31-Gauche was calculated to be 3.5 kcal/mol lower in energy than the **3-31**-anti conformation in the gas phase. The stabilizing energy obtained for the sigma donation in **3-31**-gauche (entries 1-2, Table 3.5) is comparable to what was found at the TS level (entries 6-7, Table 3.4). The additional stabilization energy provided by the σ(C2–O2') bond in **3-31**-anti does not compensate for the sum of sigma donation calculated in **3-31**-gauche (entries 1-3, Table 3.5). Interactions between the LP(O2') provided only marginal stabilization to both **3-31**-gauche and **3-31**-anti by interactions with, respectively, the σ*(S–$Me^{s'}$) and π*(S–C1) (entries 4-5).

3.6 Solvent Effects

3.6.1 Experimental Study

The influence of the solvent on the substitution of dithioacetal **3-14** with a silylated nucleobase was studied both experimentally (thymine) and *in silico* (uracil). As seen in Table 3.6, a solvent such as toluene that has a low dielectric constant (2.38) as compared to THF (7.58), caused the 1,2-*syn* selectivity to decrease when either an iodide (entries 1-2 versus 5) or bromide (entries 8-10) activating agent was used. DCM, a solvent that has a comparable dielectric constant to THF (DCM 8.93) also resulted in lower selectivity (entries 3-5). However, solvents of higher dielectric constant, MeCN (37.5) and DMSO (46.7), furnished higher inductions (entries 5-7 and 9-11). For these reactions, the silylated thymine was prepared as a solution in the corresponding solvent. This could be the reason for the slight differences in selectivity for entries 5 and 9 (13:1, Table 3.6) as compared to entries 2 and 5 (9:1, Table 3.2).

Table 3.6 Experimental solvent effects.



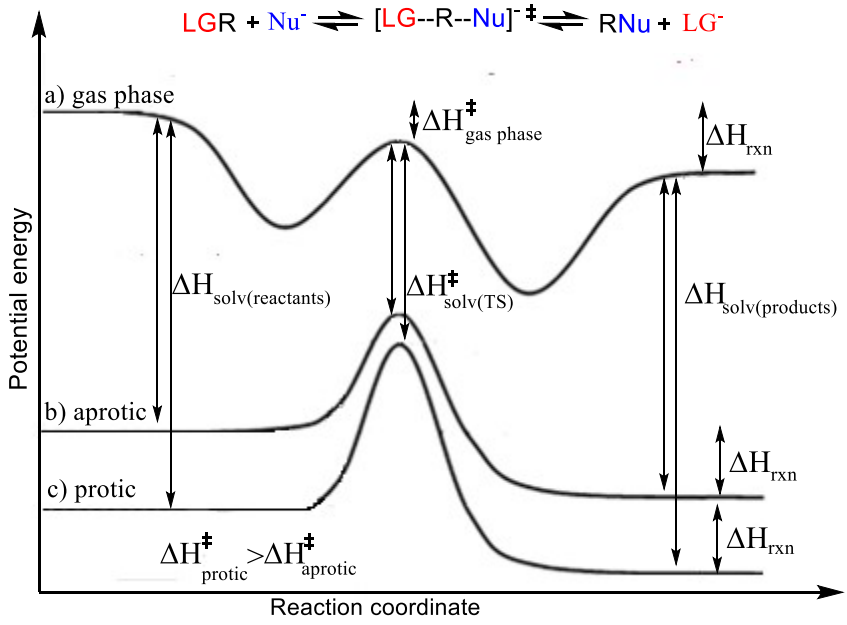
Entry	R	Activating Agent, Solvent	Ratio (**a** :**b**)[b]	Yield (%)
1	SMe	I_2, Toluene	5:1	85
2	OAc	TMSI, Toluene	11:1	50
3	SMe	I_2, DCM	8:1	83
4	OAc	TMSI, DCM	7:1	n.d.
5	SMe	I_2, THF	13:1	81
6	SMe	I_2, MeCN	>20:1	83
7	SMe	I_2, DMSO	>20:1	75
8	OAc	TMSBr, Toluene	5:1	n.d.
9	SMe	Br_2, THF	13:1	n.d.
10	OAc	TMSBr, THF	13:1	n.d.
11	SMe	Br_2, MeCN	>20:1	n.d.

a. Silylated thymine prepared as a solution in the corresponding solvent. b. Determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures. n.d. : not determined

At first glance, the increased 1,2-*syn* selectivity in solvents of higher dielectric constant may seem counterintuitive. It could be thought that these solvents would stabilize the counterion and hence provide more of a solvent-separated S_N1 product determining step, which could lower the *syn*:*anti* selectivities. However, solvents of increasing polarity lead to better solvation of developing charged intermediates and thus are preferred for both S_N1 and S_N2 mechanisms.[24] Polar protic (MeOH, H_2O) and polar aprotic (MeCN, DMSO) solvents cause a variation in reactivity dependant on the mechanism of substitution. Protic solvents are best for S_N1 reactions where hydrogen-bonding between the solvent and developing charged species allows for stabilization of the carbocation and leaving group. However, in an S_N2 reaction hydrogen-bonding between a polar protic solvent and the nucleophile would lessen its reactivity. Thus, S_N2

reactions are favored in polar aprotic solvents as demonstrated in Figure 3.6.[42] When reactants and products are placed in solution considerable energy is released due to solvation of charges. However, charges in the transition state are more dispersed causing the solvation energy to be much smaller. As discussed above, for substitutions proceeding through an S_N2 mechanism, reaction barriers are higher in protic solvents as compared to aprotic solvents (Figure 3.6 b and c).

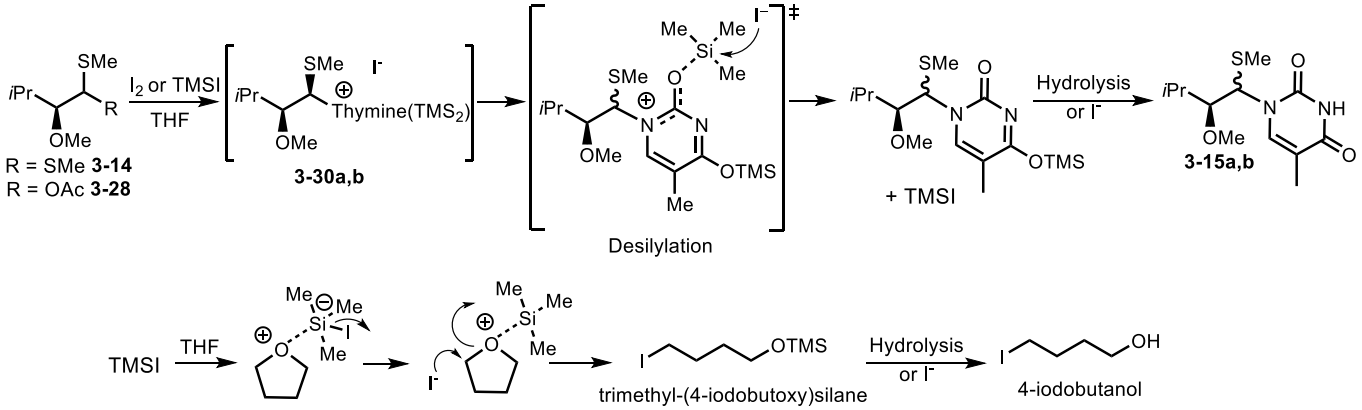
Figure 3.6 Solvent Effects for S_N2 Mechanisms in (a) gas phase, (b) polar aprotic solvents, (c) polar protic solvents. Modified from reference 42.



Based on polarity considerations, it was expected that the coupling reactions performed in DCM should have higher selectivities than in THF. However, the experimental results indicate higher selectivity in THF (13:1, entry 5, Table 3.6) as compared to DCM (8:1, entry 3, Table 3.6). A possible explanation for this may be due to formation of 4-iodobutanol[43] which was observed when the reaction was performed in THF. It has been reported that in the presence of TMSI,

THF undergoes a ring-opening reaction to from trimethyl-(4-iodobutoxy)silane (Scheme 3.5).[44] When our dithioacetal species react with silylated thymine in the presence of I_2, TMSI is generated as a by-product from desilylation of the nucleobase (Scheme 3.5). The presence of 4-iodobutanol in the crude reaction mixtures could thus result from desilylation of trimethyl-(4-iodobutoxy)silane with I^- or from hydrolysis during the aqueous work-up. It is hypothesized that when the substitution reaction is done in solvents that do not react with TMSI, its presence in the reaction mixture may cause resilylation of the nucleobase and a potential equilibration to the thermodynamic 1,2-*anti* product. This equilibrium would lower the observed selectivities, as is the case when the coupling reaction is done in DCM. Therefore, when THF is used as the solvent, these reactions may underlie a simpler (less thermodynamic) scenario because of this secondary reaction taking place to form 4-iodobutanol.

Scheme 3.5 Formation of 4-iodobutanol from activation of THF with TMSI.

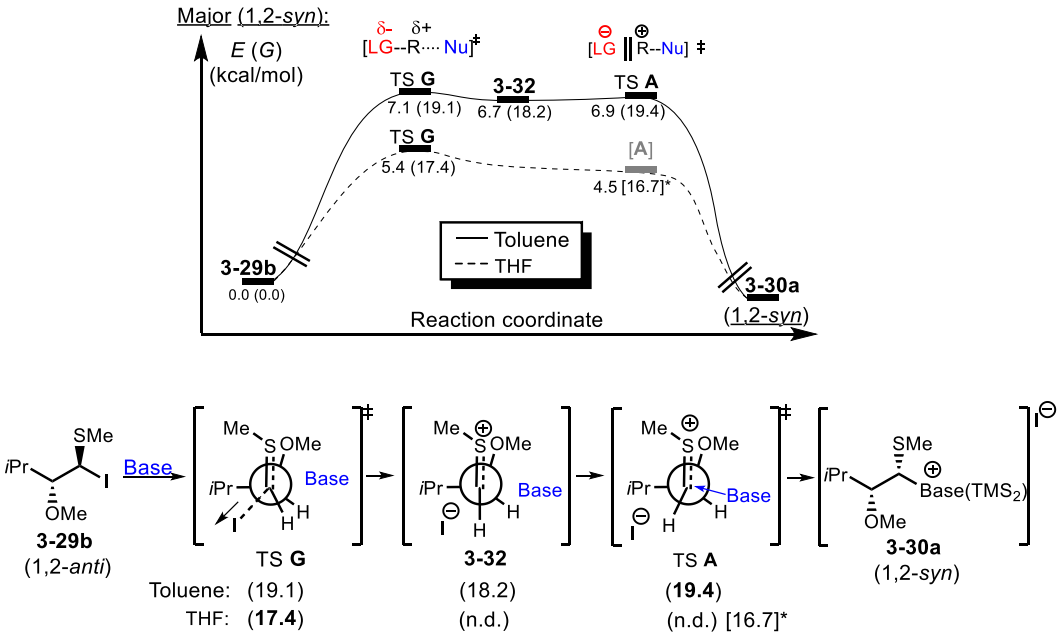


3.6.2 DFT Study

To examine these solvent effects *in silico*, the transition structures located in the gas phase were first reoptimized using the polarizable continuum (PCM) solvent model in toluene. Interestingly, after careful examination of the reaction potential surface, two TS close in energy were located

in the reaction path from the 1,2-*anti* iodothioether **3-29b** to the 1,2-*syn* product complex **3-30a** (Figure 3.7, toluene).

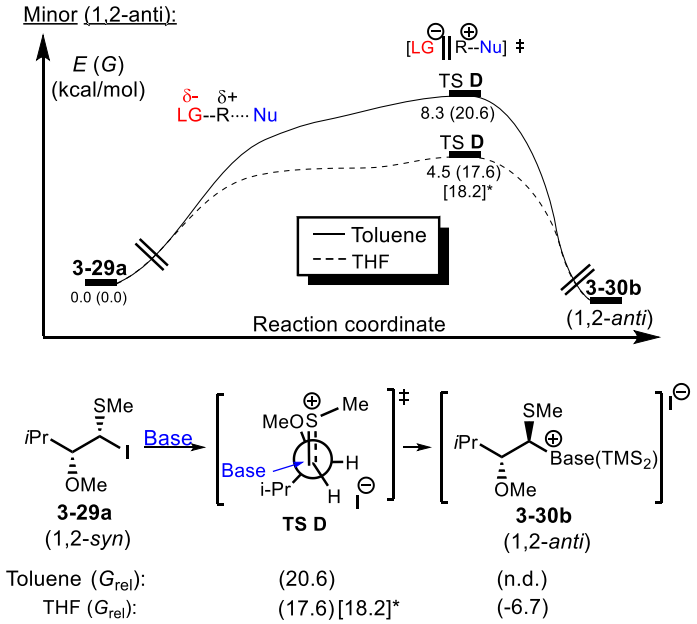
Figure 3.7 Reaction pathway leading to major (1,2-*syn*) product in toluene and THF.



The first transition structure, TS **G**, was characterized by the elongation of the I–C1 bond to furnish **3-32**, a thiacarbenium ion pair intermediate stabilized by interactions with the base. The subsequent transition structure, TS **A**, is much like the TS found in the gas phase, but with slightly longer N_{base}–C1 (2.47 Å vs 2.38 Å) and I–C1 bonds (3.57 Å vs 3.49 Å). This reaction profile is characteristic of an S_N2-like mechanism where the base is involved in the ionization step. In THF, only TS **G** could be located, and examination of the potential energy surface showed a weak downhill slope in the vicinity of TS **A**, followed by an abrupt drop in energy to **3-30a**. The electronic and Gibbs free energy shown for [**A**] in THF were thus obtained from the solvated structure identified in toluene. For formation of the 1,2-*anti* minor stereoisomer (Figure

3.8), the TS **D** found in toluene, THF or MeCN displayed slightly longer N_{base}–C1 and I–C1 bonds as compared to the gas phase, but were otherwise comparable.

Figure 3.8 Reaction pathway leading to minor (1,2-*anti*) thioaminal in toluene or THF.



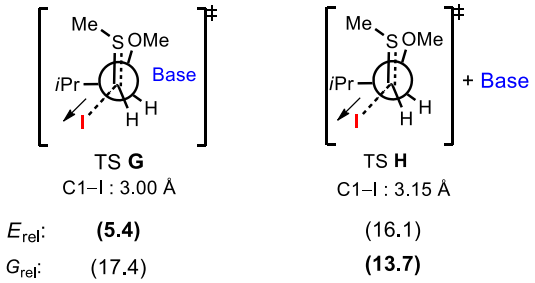
In both solvents, TS **D** was higher in energy than any intermediates in the ionization region of the reaction pathway. Therefore, in toluene, the calculated $\Delta\Delta G^{\ddagger}$ between TS **A** (highest TS between **3-29b** and **3-30a**) and TS **D** are in agreement with the experimental value (1.3 versus 1.25, entry 2, Table 3.7). In THF or MeCN, however, the $\Delta\Delta G^{\ddagger}$ between TS **G** (highest TS between **3-29b** and **3-30a**) and TS **D** predicts a loss of 1,2-*syn*-selectivity that does not agree with the measured experimental selectivities (entries 3-4, Table 6). This same loss in selectivity was also observed using other DFT functionals. The calculated $\Delta\Delta G^{\ddagger}$ with a bromide counter ion were found to be within the same range of energy than with the iodide (entries 6-8).

Table 3.7 Experimental and calculated $\Delta\Delta G^{\ddagger}$ in various solvents at 0 °C.

		$\Delta\Delta G^{\ddagger}$ in kcal/mol (1,2-*syn* : 1,2-*anti*)		
		Experimental	Calculated	
Entry	Solvent		($G^{TSD} - G^{TSA}$)	($G^{TSD} - G^{TSG}$)
Counter ion = I				
1	Vacuum	-	1.62 (20:1)	
2	Toluene	1.3 (11:1)	1.25 (10:1)	
3	THF	1.4 (13:1)		0.18 (1.4:1)
			1.50 (16:1)	
4	MeCN	>1.6 (>20:1)		– 0.88 (1:5)
			1.67 (22:1)	
5	DMSO	>1.6 (>20:1)	**1.68 (22:1)**	
Counter ion = Br				
6	Vacuum	-	2.29 (68:1)	
7	Toluene	0.98 (5:1)	1.89 (33:1)	
8	THF	1.4 (13:1)		0.53 (2.7:1)
			1.90 (34:1)	

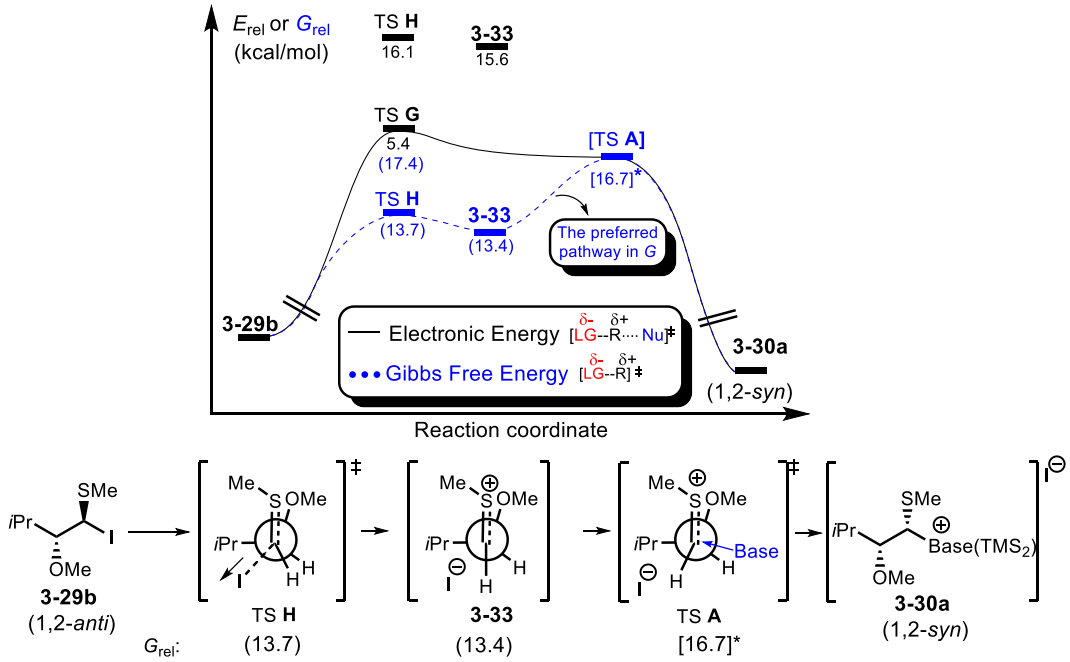
An important observation, however, was made in the solvent systems that predicted a loss of selectivity. Namely, if in THF, MeCN and DMSO the estimated TS **A**, rather than TS **G,** was used in calculating $\Delta\Delta G^{\ddagger}$, the values were in agreement with those obtained experimentally (Table 3.7, entries 3-5 and 8 in bold). This led to the possibility that the ionization could in fact occur through a different pathway that did not involve TS **G**. In accordance with this hypothesis, the ionization transition structure **H** was located (Figure 3.9). TS **H** differs from TS **G** in that the ionization occurs in absence of the base. TS **G** was found to be lower in relative electronic energy as compared to TS **H** (5.4 versus 16.1 kcal/mol), but higher than TS **H** in Gibbs free energy (17.4 versus 13.7 kcal/mol).

Figure 3.9 Ionization transition structures (R−I bond breaking) in presence (TS **G**) or absence (TS **H**) of the base in THF.



Thus, in electronic energy, TS **H** is 10.7 kcal/mol higher than TS **G** due to stabilization with the nucleophile in the latter. The most important difference between the calculated relative electronic and Gibbs free energies for TS **H** and TS **G** stems from the entropy correction values. The entropy contribution in TS **H** is greater (more disorder) than in TS **G** which is more ordered due to interactions with the base. From examination of the reaction pathway (Figure 3.10), it is seen that in electronic energy, TS **G** (LG−R bond breaking in presence of the base) is involved at the rate determining step. In relative Gibbs free energy (kcal/mol), however, the reaction preferably proceeds through TS **H** (LG−R bond breaking in absence of the base). This means that TS **A** (R−Nu bond forming step) is therefore clearly at the rate limiting and product determining step. The preferred pathway in Gibbs free energy (blue) would hence involve TS **H** rather than TS **G**. TS **H** leads to thiacarbenium ion pair intermediate **3-33**, which could then react with the nucleobase through TS **A**.

Figure 3.10 Reaction pathway in THF leading to major (1,2-*syn*) thioaminal through TS **H**.



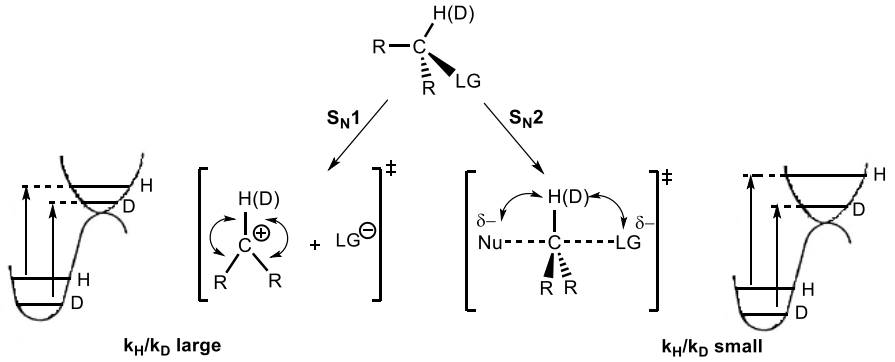
Taking this into consideration, TS **A** and **D** are both at the rate determining and product determining steps, and should be considered for determining the predicted selectivities in all the solvents studied. The calculated selectivities using the difference in Gibbs free energy between TS **A** and **D** are in agreement with those observed experimentally (Table 3.7). In order to gain further experimental mechanistic insight into the transition states involved at the rate-determining step in these substitution reactions, a secondary α-deuterium KIE study was done.

3.7 Kinetic Isotope Effects (KIEs)

Kinetic isotope effects (KIEs) have been considered to be the most useful tool for studying reaction mechanisms and determining the structure of transition states.[45] Variation in the rate of a reaction upon substitution of an atom with its isotope results from a change in vibrational frequency of the chemical bond with heavier atoms leading to lower vibrational frequencies and thus resulting in slower reactions.[45] KIEs are classified as either primary or secondary depending

on whether the labelled bond is involved (breaking or forming) in the transition state of the rate-determining step (primary) or remains unchanged (secondary). Therefore, a secondary α-KIE occurs when the hydrogen at the α- or reacting carbon is replaced by a deuterium. The magnitude of the KIE is determined by the amount of steric crowding from the leaving group and nucleophile in the transition state.[45] Thus, a substitution reaction involving a loose (less associative) transition state results in larger KIEs whereas tight (more associative) transition states give smaller KIEs. This can be understood by considering how the vibrations in a substitution reaction are affected in going from starting material to the transition state (Figure 3.11). In a S_N1 reaction, a tetrahedral substrate is converted to a trigonal planar carbenium ion making the C_α-H(D) out-of-plane bending vibrations easier and thus of lower energy resulting in a large KIE. Small or inverse KIE are expected for S_N2 reactions since a tetrahedral substrate is converted into a pentavalent transition state. Therefore, the out-of-plane bending vibrations are of higher energy when the transition state is more associative.

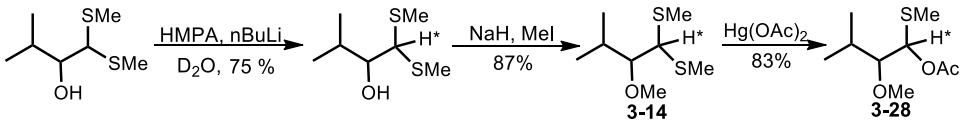
Figure 3.11 C_α-H(D) out-of-plane bending vibrations and magnitude of KIEs. Taken from reference 45.



Dithioacetal **3-14** and thioacetate **3-28** bearing an α-^{2}H were synthesized with ~ 80% enrichment of ^{2}H from reaction of the corresponding free alcohol with nBuLi and HMPA followed by

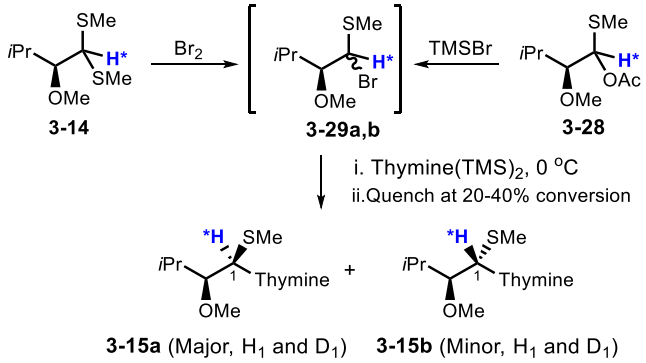
addition of D_2O (Scheme 3.6). Subsequent protection of the free alcohol furnished the dithioacetal **3-14** that was converted into the ^2H-enriched thioacetate **3-28**.

Scheme 3.6 Synthesis of ^2H-enriched **3-14** and **3-28**.



Substitution of bromothioether intermediate **3-29** that was 50% enriched with ^2H was investigated (Table 3.8). Complete conversion of starting materials **3-14** or **3-28** to the bromothioether **3-29** after addition of Br_2 or TMSBr was verified by ^1H NMR spectroscopic analysis of the reaction mixtures to ensure that the observed KIE was indeed due to the substitution of the bromothioether by the nucleobase and not from the activation of the dithioacetal. After addition of the silylated thymine, the reactions were quenched when 20 to 40% conversion was reached, as determined by ^1H NMR and confirmed after isolation and purification of the crude mixtures. The KIEs were determined using the equation[46,47]: KIE = $\ln(1-F)/\ln(1-F(R/R_o))$; where F is the fractional conversion (yield of **3-15a,b**) and R and R_o the percent of D in the product **3-15** (R) and in the bromothioether **3-29** (R_o). These results suggest that the nature of the S_N2-like transition state is not influenced by the solvent polarity (Table 3.8, entries 1-5). Large positive values ($k_H/k_D \approx 1.20$) suggest more dissociative TS with pronounced carbenium character, whereas small values ($k_H/k_D \approx 1.0$) are typically obtained for more associative S_N2 TS.[25,45,46] The calculated vacuum and toluene α-deuterium effects for 1,2-*syn* (1.28 and 1.24) and 1,2-*anti* (1.16 and 1.14) products (entries 1 and 2, Table 3.8) are consistent with these observations.

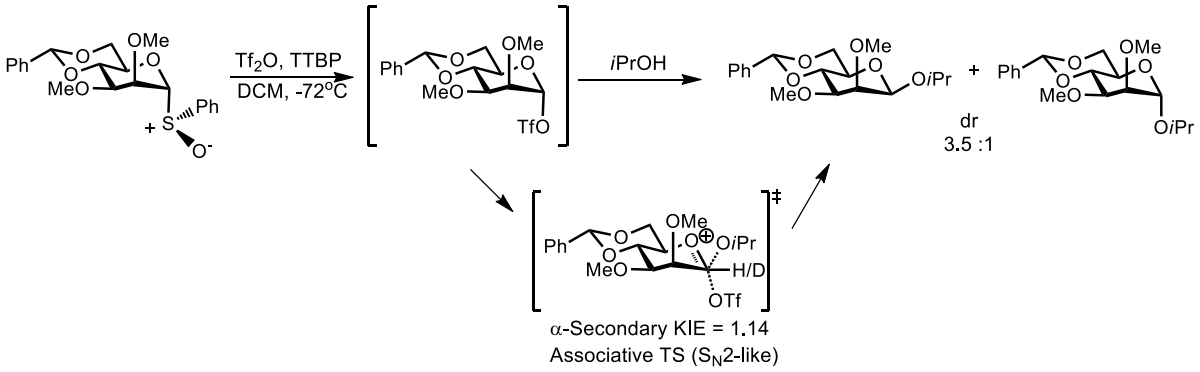
Table 3.8 ^{2}H Secondary KIEs for the substitution of bromothioethers **3-29a,b** (H* ≈ 50% ^{2}H-enrichment)



Entry	Solvent (Activating agent)	KIE (k_H/k_D) Major (**3-15a**, 1,2-*syn*)		KIE (k_H/k_D) Minor (**3-15b**, 1,2-*anti*)	
		exp	calcd	exp	calcd
1	vacuum		1.28		1.16
2	Toluene (TMSBr)	1.13 ± 0.01	1.24	0.99 ± 0.04	1.14
3	THF (Br_2)	1.18 ± 0.02	n.d.	0.92 ± 0.03	1.13
4	THF (TMSBr)	1.21± 0.02	n.d.	1.03 ± 0.03	1.13
5	MeCN (Br_2)	1.15 ± 0.04	n.d.	n.d.	1.14

From these KIEs, transition structure (TS **D**) leading to the minor thioaminal seems to be more associative in nature than TS **A**, which was also noted from the DFT calculations (Table 3.4). Although different factors have been shown to impact KIEs such as the leaving group, solvent and nucleophile,[45] and thus one should be careful in comparing KIEs between different reactions, the experimental KIE values for the 1,2-*syn* product (1.13-1.21) correspond to those reported for O-glycosylations occurring through exploded-S_N2 or CIP-mechanisms with pronounced oxocarbenium character at the transition state (1.14, Figure 3.12).[25,46]

Figure 3.12 Reported α-D KIE for O-glycosylations through associative S_N2-like TS.[25,46]



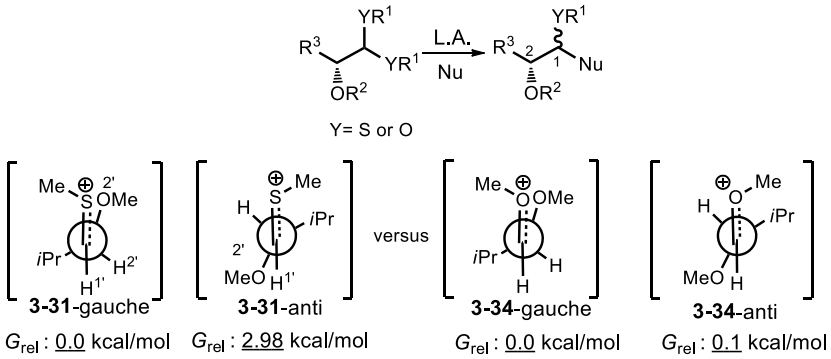
Therefore, from the observed KIEs, the S_N2-like TS **A** appears to be less associative and thus more ionized relative to TS **D.** This could be the reason for the higher 1,2-*syn* selectivity in solvents of increasing dielectric constant where TS **A** would be more stabilized in polar media relative to TS **D.** This results in an increased $\Delta\Delta G^{\ddagger}$ and supports the high (>20:1) selectivity observed both experimentally and *in silico* for formation of the 1,2-*syn* thioaminal in solvents of higher dielectric constant.

3.8 C2-alkoxyacetals versus C2-alkoxydithioacetals.

From this mechanistic investigation, it appears that the high 1,2-*syn* selectivity observed for C2-alkoxydithioacetals is due to a conformational preference, where the O2' and SR are gauche. DFT calculations for the free thiacarbenium intermediates in THF also show a preference for this gauche orientation (**3-31**-gauche) by 2.98 kcal/mol as compared to its anti-conformer (**3-31** anti) (Figure 3.13). As previously mentioned, C2-alkoxyacetals undergo unselective substitution reactions.[5] DFT calculations highlight a small difference in Gibbs free energy between **3-34**-gauche and **3-34**-anti conformations (0.1 kcal/mol, Figure 3.13, THF) for the free oxonium. Although the energy of the transition structures was not calculated, the very small difference in Gibbs free energy between the gauche and anti-conformations of free oxonium **3-34** suggests

that the preference for the gauche conformation is not present. This supports the lower 1,2-*syn* induction observed experimentally for nucleobase coupling to acyclic acetals.

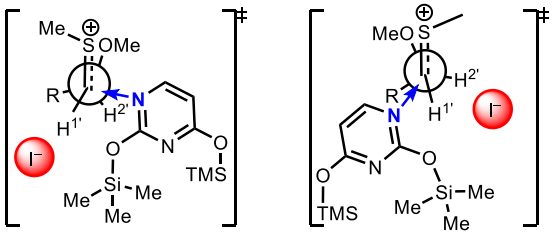
Figure 3.13 Selectivity for C2-alkoxyacetals versus C2-alkoxydithioacetals in substitution reactions.



3.9 Conclusions

Analysis of the *in silico* reaction pathways along with experimental studies allowed for a better understanding of the mechanism of dithioacetal substitution with nucleobases. In toluene, the pathway leading to the major (1,2-*syn*) thioaminal is characteristic of an S_N2-like mechanism, where the ionization occurs in presence of the nucleophile. In THF and solvents of increasing dielectric constant, the Gibbs free energy profile indicates that the ionization should be kinetically favored by an S_N1-like process (not involving the nucleophile during ion-pair formation). The subsequent base addition remains, however, both the rate limiting and product determining step. This substitution therefore functions as a stepwise S_N2-reaction and should reasonably be termed S_N2-like. The formation of the minor product (1,2-*anti*) is also characterized as an S_N2-like process. The established C1–C2 gauche conformational preference allows for an optimal stabilization of the thiacarbenium by sigma donation from the C2–H and the C2–R bonds. The counter ion provides significant additional stabilization by interacting with

the electron deficient thiacarbenium ion. Nucleobase addition occurs on the least hindered side of the thiacarbenium ion-pair species to minimize unfavorable interactions. Polar solvents provide higher 1,2-*syn* selectivities, which is in agreement with the calculated more ionized, or less associative, nature of the *syn*-predictive TS. These observations are also consistent with the secondary kinetic isotope effects. This study has thus allowed for a better understanding as to why nucleobases add to acyclic dithioacetals with high 1,2-*syn* selectivity, a key step used in our novel acyclic approach to generate nucleoside analogues. In summary, the 1,2-*syn* selectivity obtained for nucleobase addition onto dithioacetals is due to a gauche conformational preference between the C2-alkoxy group and the thioether moiety in the thiacarbenium contact ion pair. The substitution reaction is under Curtin-Hammett conditions and thus the selectivity of the reaction is based on the difference in free energies between the major and minor transition states, both of which are at the product-determining step. Thus, this substitution is classified as having a S_N2-like mechanism.



TS **A** (Major, 1,2-*syn*) TS **D** (Minor,1,2-*anti*)

3.10 References

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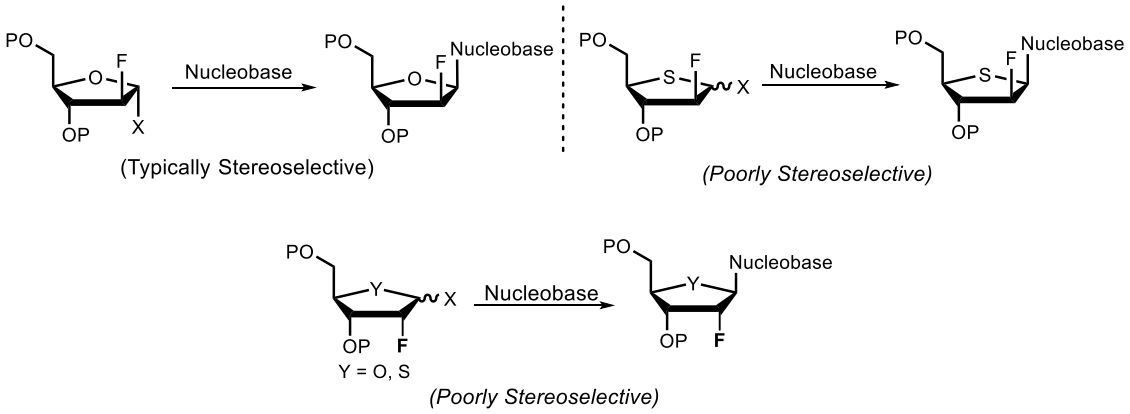
Chapter 4 Diastereoselective Synthesis of C2'-Fluorinated Nucleoside Analogues using the Acyclic Strategy

4.1 Research Perspectives

Nucleoside analogues bearing a fluorine atom in the C2' position have become useful anticancer (eg. Clofarabine, Gemcitabine) and antiviral (eg. Clevudine) agents due in part to the increased stability of their glycosidic bond towards hydrolysis.[1,2] Introduction of fluorine has become an important strategy in the design of novel biologically active compounds changing a molecule's metabolic stability, lipophilicity, acidity, and dipole properties.[3] The properties of fluorine that are responsible for these biological variations include its electronegativity, bond strength and size. The large carbon-fluorine bond energy makes it resistant to metabolic transformations.[4] Fluorine is the second smallest atom with an atomic radius between that of hydrogen and oxygen allowing for only a slight steric distortion upon replacing a hydrogen with fluorine.[5,6] It is also similar to a hydroxyl group in terms of its bond length (C-F bond length 1.35 Å versus C-O bond 1.43 Å). Fluorine serves as an isopolar mimic of oxygen due to its relatively large dipole and hence ability to undergo electrostatic interactions with neighboring functional groups (weak hydrogen-bond acceptor).[4,5] There have thus been many precedent efforts towards the synthesis of fluorinated nucleoside analogues. As discussed in detail in Chapter 1, two main approaches to access NAs with fluorine in the C2' position involve fluorination of natural nucleosides or nucleobase addition onto already fluorinated substrates.[1] The first approach allows for the original configuration of the glycosidic bond to be maintained and is limited to the natural pool of nucleosides. Alternatively, nucleobase addition onto substrates already possessing a C2-F group allows for increased substrate diversity, but the stereochemistry of the glycosidic bond must be controlled. Typically, a stereoselective 1',2'-*cis* relationship between the nucleobase

and the C2'-F group in the furanoside series is obtained through displacement of anomeric-halo sugars (Scheme 4.1).[7] However, to the best of our knowledge, no approach has been reported to provide high 1',2'-*cis* selectivity in the corresponding thiofuranoside series.[8-10]

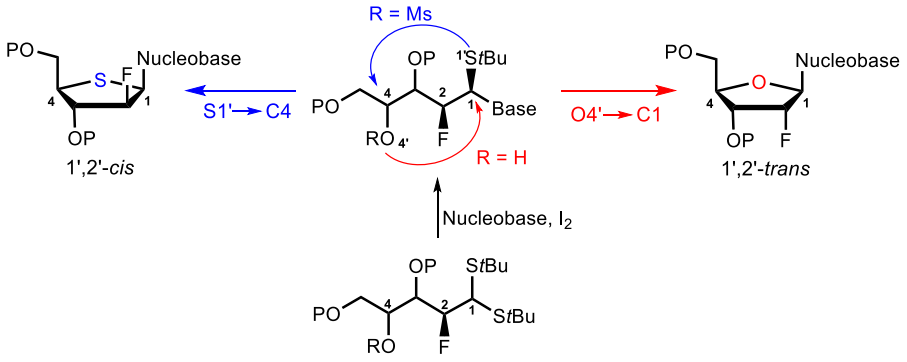
Scheme 4.1 Representative strategies to synthesize C2'-F NAs.



Controlling the 1',2'-*trans* stereochemistry for C2'-monofluorinated NAs is particularly challenging due to the lack of possible C2-neighboring group participation. Nucleobase addition results in variable 1',2'-*trans* selectivity.[11-13] Synthesis of such scaffolds often relies on fluorination of preformed NAs.[14-16] Therefore, an alternate strategy to synthesize fluorinated nucleoside analogues would be beneficial. Access to two of these challenging scaffolds namely, 1',2'-*trans* furanosides and 1',2'-*cis* thiofuranosides is possible using our acyclic methodology (Scheme 4.2). In the current study, nucleobase coupling onto acyclic dithioacetals bearing a C2-F with subsequent cyclization has been investigated. Preference for 1,2-*syn* stereocontrol is maintained and these fluorinated thioaminals cyclize to provide 1',2'-*trans* furanosides and 1',2'-*cis*-thiofuranosides. My contribution to this work involves all of the experimental investigation done on the synthesis of the model C2-F substrates as well as the C2-F nucleosides. Three undergraduate students worked on parts of this project under my supervision. As mentioned thoughout this chapter, Dr Michel Prévost performed the DFT calculations, and

nucleobase couplings with C2/C3-alkoxy substrates (Table 4.4) were done by Dr Michel Prévost and Dr Benoit Cardinal-David during their PhD studies.

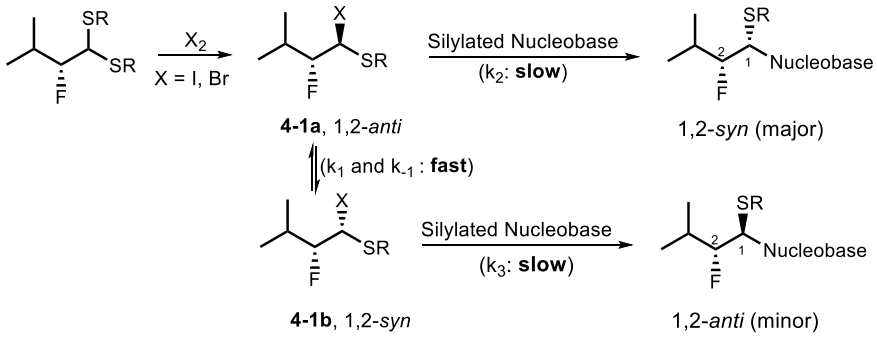
Scheme 4.2 Acyclic strategy for synthesis of C2'-F nucleoside analogues.



4.2 Theoretical and experimental model study

The proposed mechanism for this substitution first involves activation of the dithioacetal to generate interconverting halothioether intermediates **4-1a,b**[19] that subsequently react with the silylated nucleobase to generate the 1,2-*syn* and 1,2-*anti* thioaminals (Scheme 4.3).

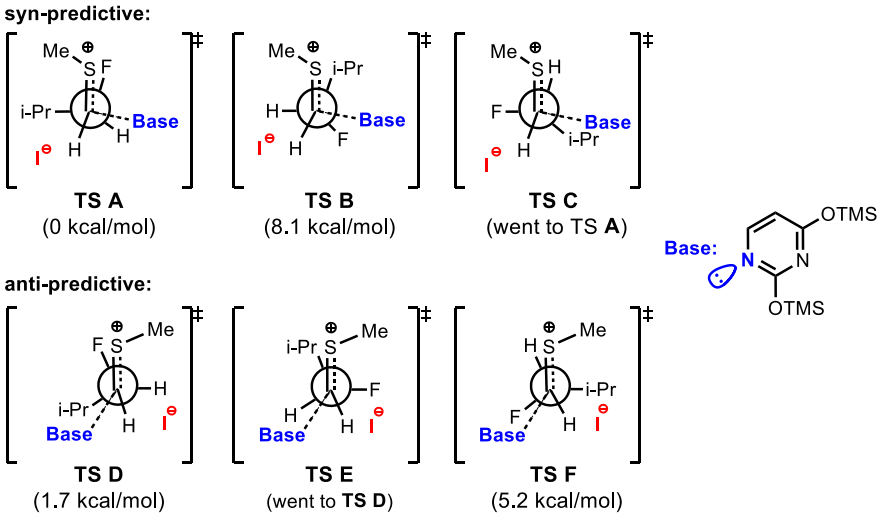
Scheme 4.3 Proposed Curtin-Hammett scenario for the substitution of halothioethers formed by activation of dithioacetals.



If the substitution steps (k_2 and k_3) are significantly slower than the anomerization (k1), the stereochemical outcome of the substitution reaction is due to the difference in transition state free energies leading to the 1,2-*syn* and 1,2-*anti* products, as stated by the Curtin-Hammett principle.

The substitution mechanism was examined by DFT calculations (done by Dr Michel Prévost) using the same parameters as described for the model substrate bearing a C2-OMe substituent (M06-2X level of theory using a 6-311+G** basis set in combination with LANL2DZpd effective core potentials for iodine). The transition structures obtained in the gas phase (Figure 4.1) suggest that both the lowest 1,2-*syn* and 1,2-*anti* predictive TS (**A** and **D**) adopt a C1–C2 conformation orienting the sulfur and C2-F gauche to each other. This is consistent with precedent reports in which a charge-dipole interaction between polar C-F bonds and a formal positive charge is stabilized by a gauche conformation.[5]

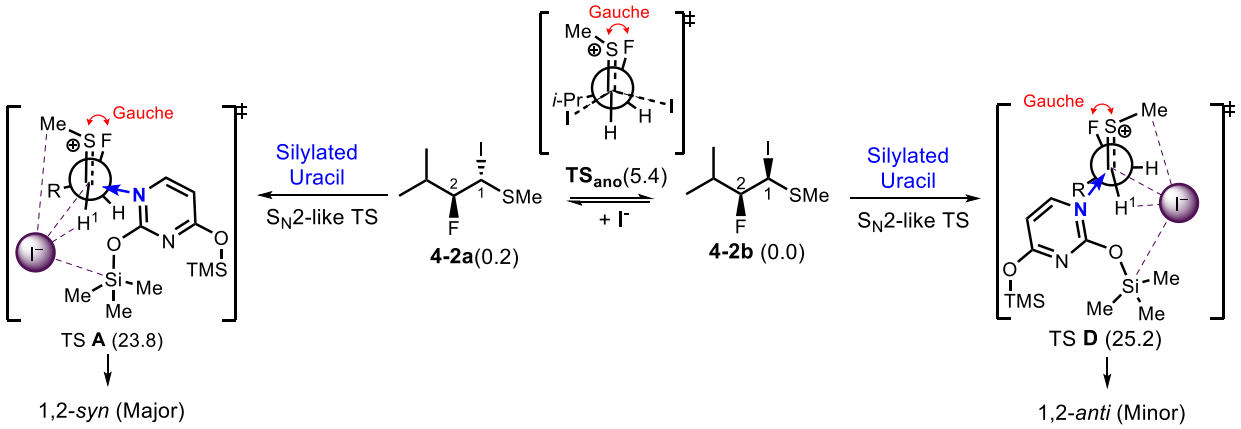
Figure 4.1 1,2-*syn* and 1,2-*anti* predictive TS in the gas phase (Gibbs free energy indicated in kcal/mol).



No stationary point could be found in the C2-C3 TS **C** or TS **E** conformations, thus they led to TS **A** or TS **D** after the transition structure optimization. The difference between the lowest *syn* (TS **A**) and *anti* (TS **D**) predictive transition structures in the gas phase corresponds to a Gibbs free energy difference of 1.7 kcal/mol and thus an expected *syn* to *anti*-selectivity of 23:1.

The reaction profile for this nucleobase substitution was then calculated in THF. The energy barrier for epimerization of the initially formed halothioethers **4-2a,b** (Scheme 4.4) suggests a fast anomerization. Substitution of these equilibrating intermediates by the nucleobase was found to proceed through a S_N2-like mechanism involving 1,2-*syn* and 1,2-*anti* predictive TS **A** and **D**. The calculated difference in Gibbs free energy between these TS in THF (1.4 kcal/mol) predicts a 13:1 selectivity in favor of the 1,2-*syn* thioaminal. This reaction pathway is thus similar to the substitutions of C2-alkoxy dithioacetals with the S_N1-pathway calculated to be prohibitively higher in energy.

Scheme 4.4 Lowest TS **A** (1,2-*syn)*, TS **D** (1,2-*anti*) and anomerization transition structures (Gibbs Free energy indicated in kcal/mol in THF).



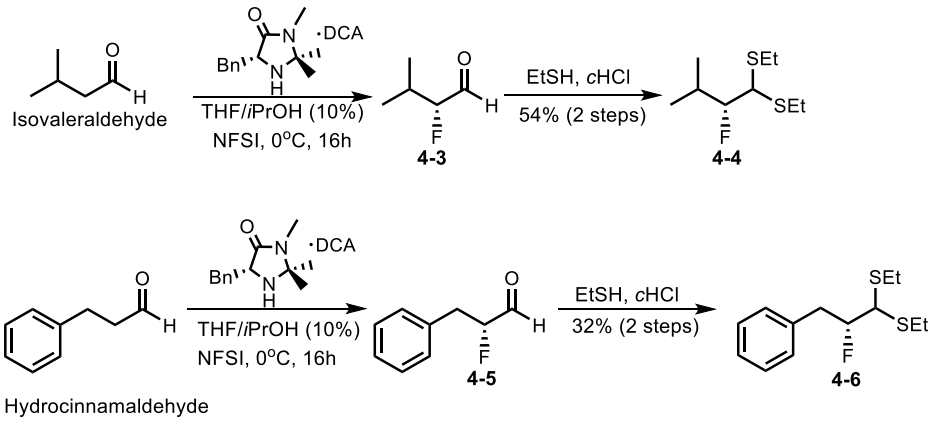
Solvent	$\Delta\Delta G^{\ddagger}$ in kcal/mol (1,2-*syn* : 1,2-*anti*) Calcd ($G^{TS\ D} - G^{TS\ A}$)
Vacuum	1.7 (23:1)
THF	1.4 (13:1)

The C1–C2 gauche conformational preference between the sulfur and C2-fluoro atom in TS **A**, TS **D** and TS_{ano} could be responsible for the particular reactivity of dithioacetals bearing an electron withdrawing group at C2. Apart from potentially providing electrostatic stabilization

from the high electron density on the C2-electronegative atom, this conformation allows for optimal σ(C2-R) and σ(C2-H) sigma donation to the π*(S–C1) center at the transition state.

An experimental model study was also done in order to determine the stereoselective outcome of nucleobase addition to dithioacetals in which the C2-stereogenic center contains a fluoride atom. Two model dithioacetal substrates **4-4** and **4-6** were prepared from fluorination of the corresponding aldehydes (isovaleraldehyde and hydrocinnamaldehyde, Scheme 4.5).

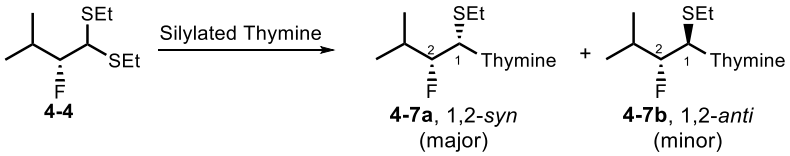
Scheme 4.5 Preparation of C2-F dithioacetals.

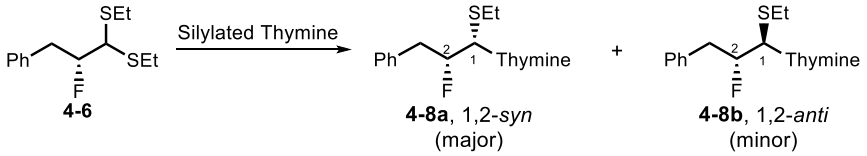


Introduction of the C2-F group onto these aldehydes was performed using MacMillan's commercially available (*R*)-imidazolidinone dichloroacetic acid catalyst and NFSI in a solution of THF and isopropanol.[17] Although we were only interested in the diastereoselectivity for the coupling of the nucleobase to the dithioacetal, and not the enantioselectivity for introduction of the fluorine, these conditions worked best in obtaining the desired fluorinated dithioacetals. For example, when the fluorination was done using either the free imidazolidinone catalyst or DL-proline and NFSI in DMF,[18] the fluorination did not go to completion and impurities were observed.

It is known that C2-F aldehydes are generally not stable enough to purify by flash chromatography and are more volatile than their starting aldehydes, thus making their manipulation difficult.[18] The fluorinated dithioacetals therefore were prepared from addition of ethanethiol and concentrated HCl to the reaction mixture without isolation of C2-F aldehydes **4-3** and **4-5**. Substitution of model dithioacetals **4-4** and **4-6** with silylated thymine was investigated (Table 4.1). Diethyl-dithioacetal **4-4** bearing an isopropyl group gave a moderate 6:1 ratio in favor of the 1,2-*syn* diastereomer when coupled with silylated thymine in the presence of iodine at 0 ^{o}C (entry 1), which is consistent with the selectivity obtained from the DFT calculations assuming that the reaction is under kinetic control (Scheme 4-4). This assumption was further confirmed by the fact that that selectivities measured at different reaction temperatures follow Arrhenius' equation with the ratios remaining constant over time at 0 ^{o}C, 25 ^{o}C and 70 ^{o}C in THF (entries 1-3). However, when heating at 70 ^{o}C in DCM for several days, a reaction mixture that reached completion at 25 ^{o}C with a 4.2:1 ratio of thioaminals resulted in a decreased 1.5:1.0 ratio (entry 5). This indicates that the reaction could be reversible at higher temperatures in certain solvents providing a thermodynamic distribution of products. The ratios were not affected if the silylated thymine was prepared as a solution in DCM or THF (entries 2 and 4).

Table 4.1 Nucleobase coupling onto model C2-F dithioacetals.

Entry	Activating Agent, Time	T	Solvent	Ratio(**a**:**b**)[a]	Yield (%)
	 **4-4** → **4-7a**, 1,2-*syn* (major) + **4-7b**, 1,2-*anti* (minor)				
1	I_2, 48h	0 ^{o}C	THF	6.3:1	37[b]
2	I_2, 48h	25 ^{o}C	THF	5.9:1	82
3	I_2, 24h	70 ^{o}C	THF	4.0:1	71

4	I_2, 48h	25 °C	THF[c]	6.3 :1	63[b]
5	I_2, 24h	25 °C	DCM	4.2 :1	
	+144 h	70 °C	DCM	1.5:1	80
6	I_2, 16h	0 °C	DMSO	7.7:1	91
7	Br_2, 16h	–20 °C	THF	3.5:1	67
8	$Me_2S(SMe)BF_4$, 48h	0 °C	THF	7.1:1	57[b]
9	$Me_2S(SMe)BF_4$, 70h	25 °C	THF	6.7:1	91
10	$Hg(OAc)_2$, TMSOTf, 48h	0 °C	THF	5.6:1	63[b]
11	$Hg(OAc)_2$, TMSOTf, 48h	25 °C	THF	6.3:1	91
	 **4-6** **4-8a**, 1,2-*syn* (major) **4-8b**, 1,2-*anti* (minor)				
12	I_2, 116h	25 °C	THF	2.3:1	52[b]

a. Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. b. Starting material remaining in crude mixture. c. Silylated thymine as a solution in THF opposed to DCM.

When the reaction was done at 0 °C in DMSO opposed to THF (entries 6 versus 1), the reaction occurred faster (16 h versus 48 h) with similar selectivity. Different activating agents were also examined for the substitution reaction. Activation with Br_2 provided lower 1,2-*syn* selectivity despite the reaction being carried out at –20 °C (entry 7). This may be due to a potential equilibration to the more stable 1,2-*anti* thioaminal **4-7b** in the presence of TMSBr, as discussed in Chapter 3. Alternatively, it is reasonable to suggest that the lower selectivity may be due to decomposition of either the 1,2-*anti* bromothioether or the 1,2-*syn* thioaminal, which would also result in lower selectivities. Although, undetermined impurities were observed in the crude reaction mixture (possibly due to decomposition) and a slightly lower isolated yield of thioaminals **4-7a**,**b** was obtained (67%, entry 7), decomposition of the 1,2-*anti* bromothioether

seems unlikely to affect the observed ratios since a fast equilibrium is expected between the two initially formed bromothioethers. The initial formation of halothioether intermediates is supported by ^{1}H NMR studies. Upon addition of bromine to dithioacetal **4-4** in d_8-THF at –20 ^{o}C, two new species that display characteristic chemical shifts corresponding to bromothioethers were rapidly formed in approximately a 1:1.4 ratio despite the 4:1 ratio of 1,2-*syn* and 1,2-*anti* thioaminals **4-7a** and **4-7b** obtained after nucleobase addition (entry 7). This supports the hypothesis that the substitution occurs through the proposed Curtin-Hammett scenario.

Addition to **4-4** provided comparable selectivity when activated with $Me_2S(SMe)BF_4$ (7:1, entries 8-9), as compared to I_2. Treatment with $Hg(OAc)_2$ generated the corresponding acetate *in situ*, which was treated with TMSOTf and the nucleobase, to provide the 1,2-*syn* diastereomer with similar selectivity (6:1, entries 10-11). With a secondary chain attached at C2 (dithioacetal **4-6**), the 1,2-*syn* induction dropped significantly (2:1, entry 12). This model study demonstrates that nucleobase addition onto C2-fluoro dithioacetals bearing a substituent in the C3-position furnishes synthetically useful 1,2-*syn* induction.

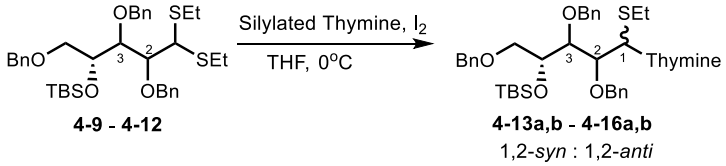
4.3 Additions onto C2-C3-alkoxy dithioacetals

With the encouraging 1,2-*syn* induction observed for model substrate **4-2** bearing a C2-F stereogenic center, nucleobase coupling onto more complex dithioacetals was investigated. This will provide an improved route to access fluorinated nucleoside analogues. A summary of the previous work done on additions to dithioacetals bearing C2 and C3 alkoxy stereogenic centers highlights some interesting features to consider when nucleobase additions are performed on more complex substrates.

4.3.1 Previous studies on additions to C2-C3-alkoxy dithioacetals

It was previously observed in our laboratory[20] that the relative stereochemistry between the substituents at C2 and C3 of acyclic dithioacetals influences the level of 1,2-*syn* induction (Table 4.2). Higher 1,2-*syn* selectivity is observed when there is a 2,3-*syn* relationship between the alkoxy substituents (entries 1 and 2) as compared to a 2,3-*anti* relative stereochemistry (entries 3 and 4).

Table 4.2 Diastereoselective synthesis of C2, C3-bis-OBn thioaminals.[20]



4-9 - 4-12 → **4-13a,b - 4-16a,b**

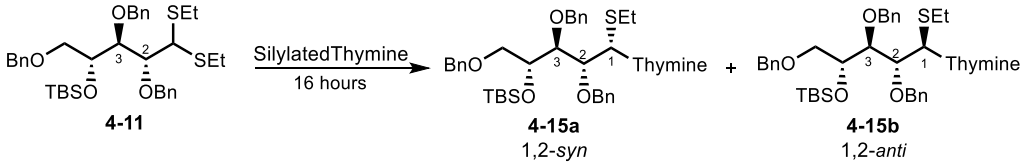
1,2-*syn* : 1,2-*anti*

Entry	Substrate	Ratio(**a**:**b**)	Yield (%)
1	2,3-*syn* (**4-9**, D-arabino)	15:1 (**4-13a,b)**	100
2	2,3-*syn* (**4-10**, D-xylo)	15:1 (**4-14a,b**)	90
3	2,3-*anti* (**4-11**, D-ribo)	4:1 (**4-15a,b**)	91
4	2,3-*anti* (**4-12**, D-lyxo)	8 :1 (**4-16a,b**)	100

4.3.2 Substitution of 2,3-*anti* bis-alkoxy dithioacetal

In an effort to improve the level of 1,2-*syn* induction for 2,3-*anti* bis-alkoxy dithioacetal **4-11**, some of the previous substitution conditions explored with the model dithioacetal substrates were investigated (Table 4.3).

Table 4.3 Nucleobase coupling onto 2,3-*anti* dithioacetal **4-11**.

Entry	Activating Agent	T	Solvent	Ratio(**a**:**b**)[a]	Yield (%)
					
1	I_2	0 °C	THF	4:1	54[b]
2	I_2	70 °C	THF	1:2	74
3	I_2	0 °C	DMSO	5 :1	62
4	Br_2	0 °C	THF	Undetermined Mixture	
5	$Me_2S(SMe)BF_4$	0 °C	THF	5:1	69[b]
6	$Hg(OAc)_2$, TMSOTf	0 °C	THF	4:1	83

a. Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. b. Starting material remaining in crude mixture.

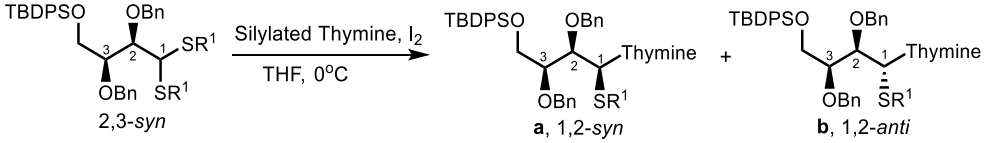
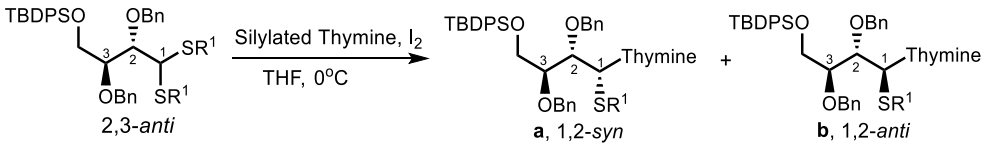
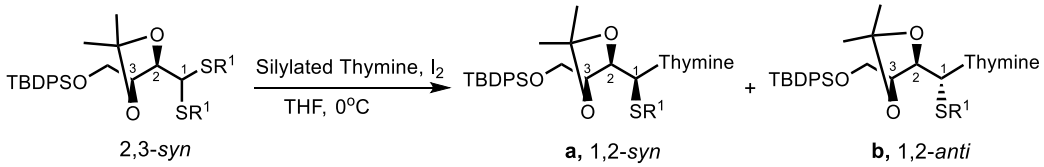
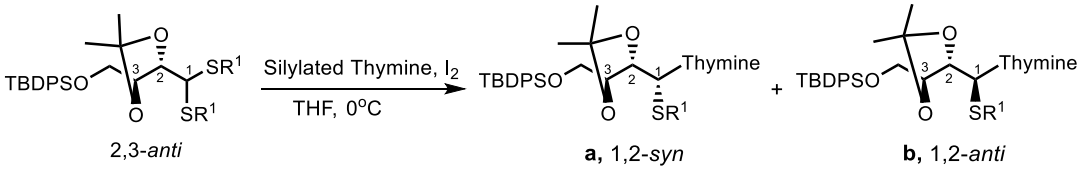
These results confirmed that the substitution of bis-alkoxy dithioacetals is under kinetic control with the 1,2-*anti* thioaminal **4-15b** being favored at 70 °C (entries 1-2). A variation in solvent (DMSO, entry 3) or activating agent (entries 4-6) did not seem to influence the level of 1,2-*syn* induction.

4.3.3 Additions to model 2,3-bis-alkoxy dithioacetals

This variation in diastereoselectivity for nucleobase addition to dithioacetals with different relative C2, C3-alkoxy group stereochemistries was studied both experimentally and theoretically by Dr. Michel Prévost using model substrates.[19] It was experimentally observed that 2,3-*syn* **4-17** and **4-19** provided high 1,2-*syn* dr (15:1) (entries 1-2, Table 4.4), while a loss of selectivity (2:1) was measured with 2,3-*anti* **4-21** (entry 3). Compounds with restricted conformational freedom were synthesized by linking the C2- and C3-alkoxy groups through

formation of acetonides **4-23**, **4-25** and **4-27**. 2,3-*anti* acetonide **4-27** provided the 1,2-*syn* thioaminal product with a large increase in selectivity (>20:1, entry 6), whereas the substitution of 2,3-*syn* acetonides (**4-23**, **4-25**) was poorly selective (2-4:1, entries 4-5).

Table 4.4 Nucleobase substitution of C2,C3-bis-alkoxy-dithioacetals. Taken from reference 19.

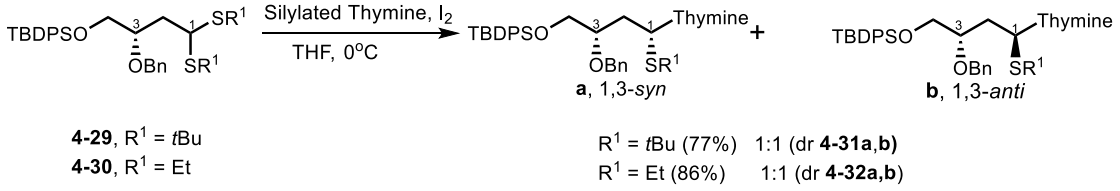
Entry	Substrate	R^1	Ratio (**a**:**b**)[a]	Yield(%)
				
1	(**4-17**)	*t*Bu	15:1 (**4-18a,b**)	85
2	(**4-19**)	Et	14:1 (**4-20a,b**)	84
				
3	(**4-21**)	*t*Bu	2.0:1 (**4-22a,b**)	82
				
4	(**4-23**)	*t*Bu	2.4:1 (**4-24a,b**)	74
5	(**4-25**)	Et	4.2:1 (**4-26a,b**)	70
				
6	(**4-27**)	Et	>20:1 (**4-28a,b**)	81

a. Determined by ^{1}H NMR spectroscopic analysis of crude mixtures

In order to examine the level of induction provided by the C3-stereogenic center, compounds **4-29** and **4-30** were also synthesized by Dr Michel Prévost and reacted with silylated thymine in presence of iodine (Scheme 4.6). The formation of the thioaminal products **4-31** and **4-32** in a

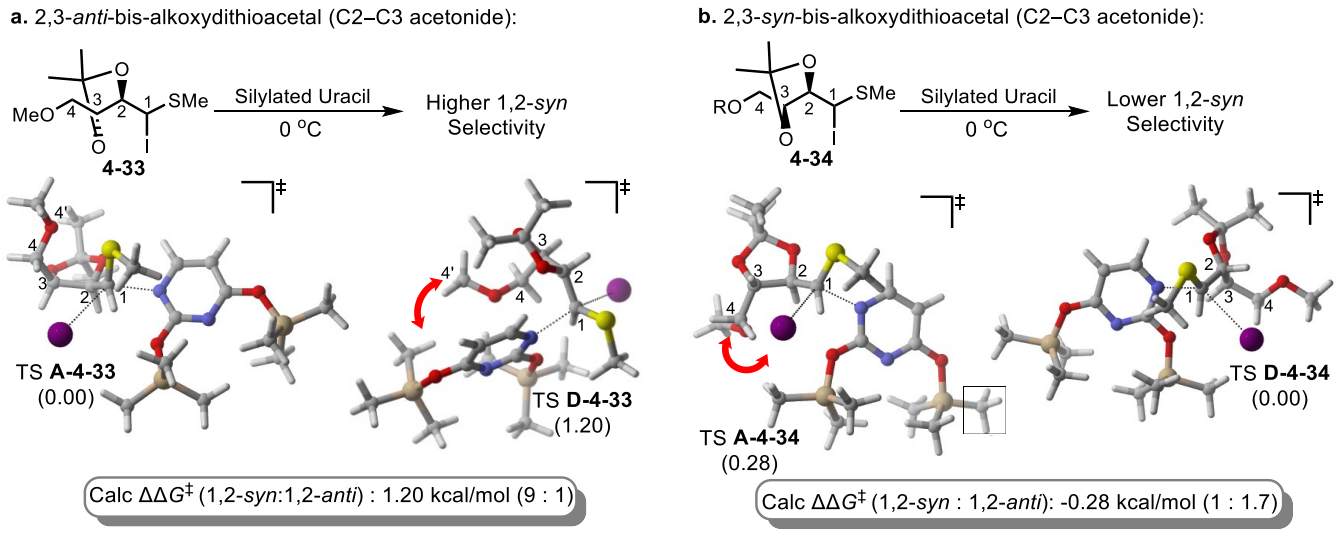
1:1 ratio indicates that the β-alkoxy center does not provide any 1,3-stereoinduction. This suggests that it is the relative configuration between the C2 and C3 centers that is influencing the level of 1,2-*syn* selectivity with bis-alkoxydithioacetals.

Scheme 4.6 Substitutions of 2-deoxydithioacetals.[19]



Nucleophilic substitution of C2-C3-alkoxy dithioacetals with 2,3-*syn* or 2,3-*anti* acetonides was examined *in silico* (Figure 4.2, gas phase).

Figure 4.2 Lowest 1,2-*syn* (TS **A**) and 1,2-*anti* (TS **D**) transition structures for a) 2,3-*anti* and b) 2,3-*syn* C2,C3-acetonides. Gas phase Gibbs free energies in kcal/mol.

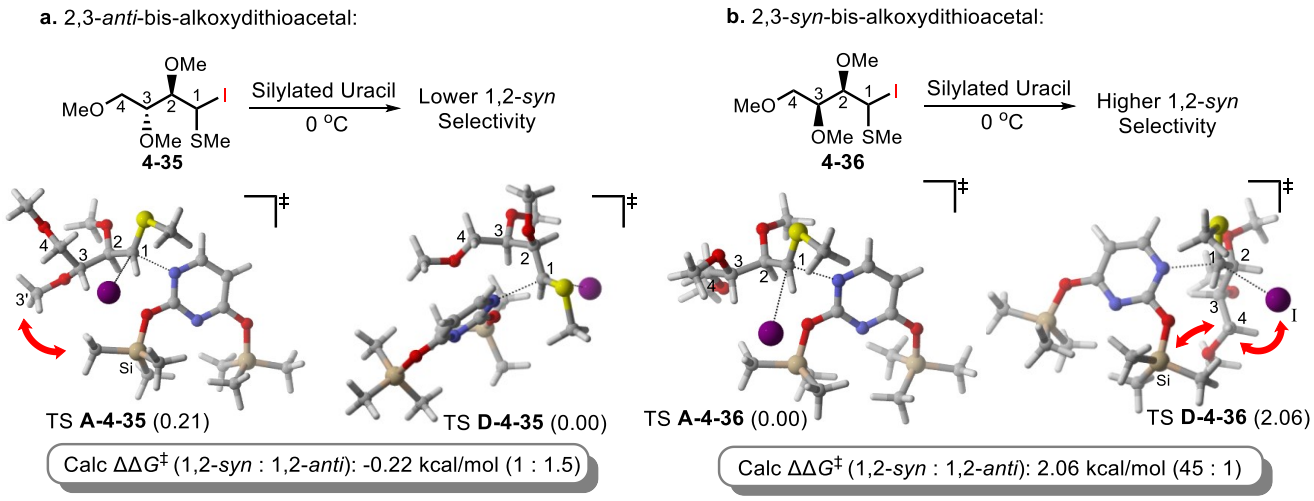


TS **A** and TS **D** in which the C2-alkoxy group is gauche to the thioether moiety were identified as the lowest 1,2-*syn* and 1,2-*anti* predictive transition structures for substitutions of **4-33** or **4-**

34. The $\Delta\Delta G^{\ddagger}$ between these TS correctly predicts higher 1,2-*syn* selectivity from 2,3-*anti* acetonide **4-33** than from 2,3-*syn* acetonide **4-34**. Based on the transition structures obtained, the higher 1,2-*syn* selectivity for **4-33** (2,3-*anti*) can be attributed to a destabilization of the TS **D-4-33** from interactions between the C4-stereocenter and the TMS group of the base (Figure 4.2a), whereas the loss of 1,2-*syn* selectivity for the substitution of **4-34** (2,3-*syn*) can stem from an unfavorable interaction between the iodide and the C4-stereocenter in TS **A-4-34** (Figure 4.2b).

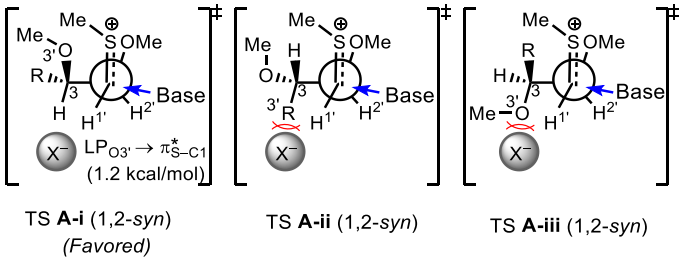
The DFT transition structure analysis of the 2,3-*syn* and 2,3-*anti*-dithioacetals **4-35** and **4-36** is also in agreement with the experimental trend (Figure 4.3, gas phase). The calculated $\Delta\Delta G^{\ddagger}$ (TS **A** vs **D**) predicts an unselective substitution of 2,3-*anti* **4-35** and a 1,2-*syn* selective coupling to 2,3-*syn* **4-36**. Unfavorable interactions between the TMS group of the base and the C3 center seemingly destabilize TS **A-4-35** relative to TS **D-4-35** (Figure 4.3a) leading to a loss of 1,2-*syn* selectivity $\Delta\Delta G^{\ddagger} = -0.22$). The highly diastereoselective substitution with 2,3-*syn* **4-36** could be attributed to destabilizing interactions involving the C4-stereocenter with both the TMS-group and the leaving iodide in TS **D-4-36** (Figure 4.3b).

Figure 4.3 Lowest 1,2-*syn* (TS **A**) and 1,2-*anti* (TS **D**) transition structures for a) 2,3-*anti* and b) 2,3-*syn* acyclic substrates. Gas phase Gibbs free energies in kcal/mol.



The presence of the counter ion has an important impact on the preferred conformation of the C3-stereocenter, which is oriented to avoid unfavorable steric or electronic interactions with the iodide (i.e. TS **A-i** vs TS **A-ii** or TS **A-iii**, Figure 4.4). A stabilizing donation between the LP(O3') and the π*(S–C1) (1.2 kcal/mol) could contribute to the C2−C3 conformational preference found in TS **A-4-36** (Figure 4.3b) and further increase the $\Delta\Delta G^{\ddagger}$. A related stabilizing orbital interaction was noted for the addition to 2,3-*anti* acetonide **4-33** in TS **A-4-33** (Figure 4.2a), but the latter was involving O4' rather than O3' (LP(O4') and the π*(S–C1).

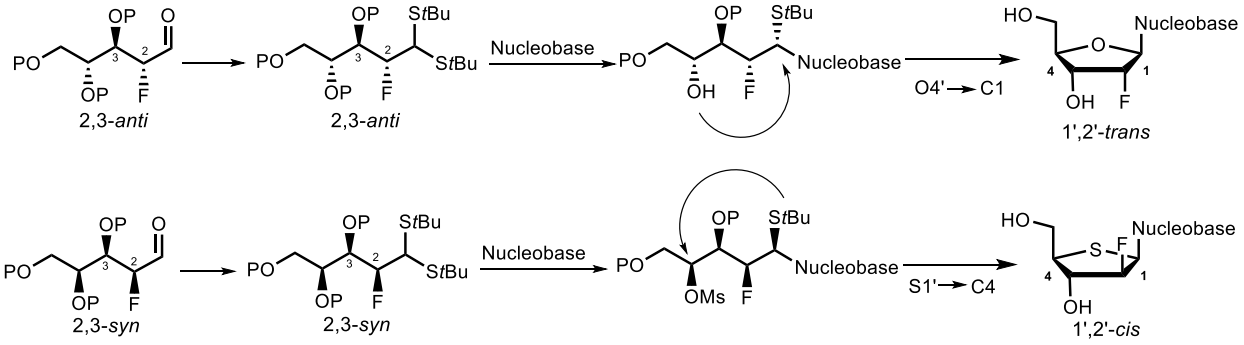
Figure 4.4 Important conformational preferences observed for the TS analysis of 2,3-bis-alkoxyhalothioethers.



4.4 Additions onto C2-F, C3-alkoxy dithioacetals

With these previous findings in mind, the synthesis of thioaminals containing a C2-F and a C3-alkoxy group was studied. The absolute stereochemistry of the starting aldehydes shown in Scheme 4.7 is necessary to synthesize D-1',2'-*trans* furanosides and D-1',2'-*cis* thiofuranosides.

Scheme 4.7 Requisite C2-F aldehydes for the formation of the targeted NAs.



The key synthetic challenge for the synthesis of the C2-F aldehydes is incorporation of the fluorine atom. It is known that synthesis of C2-F substrates that also contain a C3-alkoxy substituent is complicated by potential elimination of the group in C3.[3] The generated monofluorinated compounds are also more readily deprotonated than their nonfluorinated starting materials, making the enantioselective introduction of a fluorine atom difficult.[2] As discussed below, several strategies were examined to access these acyclic fluorinated precursors.

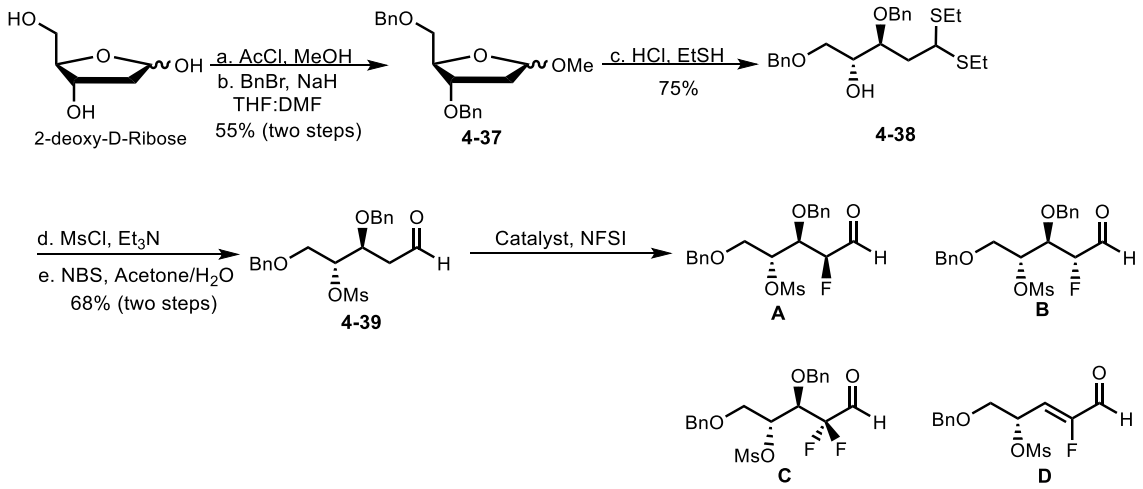
4.4.1 Synthesis of 2,3-*anti* C2-F, C3-alkoxy aldehydes

4.4.1.1 Fluorine incorporation onto aldehyde bearing a C3-alkoxy substituent

Addition of fluorine onto an acyclic aldehyde using MacMillan's imidazolidinone catalysts, as was done for synthesis of model substrate **4-2**, was investigated. To generate the requisite aldehyde (**4-39**, Scheme 4.8), 2-deoxy-D-ribose was protected at the anomeric position as a

methyl acetal and subsequently benzylated to provide the known compound **4-37**.[21] Conversion to dithioacetal **4-38**, with C4-mesylate protection and oxidative deprotection provided the corresponding aldehyde **4-39**.

Scheme 4.8 Introduction of fluorine onto aldehyde **4-39**.



Various conditions were investigated in order to incorporate fluorine into the C2-position of aldehyde **4-39**. These included MacMillan's fluorination conditions using (*R*)- or (*S*)-imidazolidinone salts in THF/*i*PrOH,[17] Barbas' conditions using the free imidazolidinones in DMF,[18] and attempts were also made using L-proline. In all reactions, NFSI served as the electrophilic source of fluorine. Precedent fluorinations of acyclic substrates bearing a OBn group at C3 using a oxazolidinone and NFSI (fluorination through formation of an enolate) are known,[22] however, examples using MacMillan's imidazolidinones (fluorination through enamine/iminium formation) have not been reported. Very recently, enantioselective fluorination of acyclic substrates bearing an acetonide protected hemiaminal ether in C3 have been published.[23]

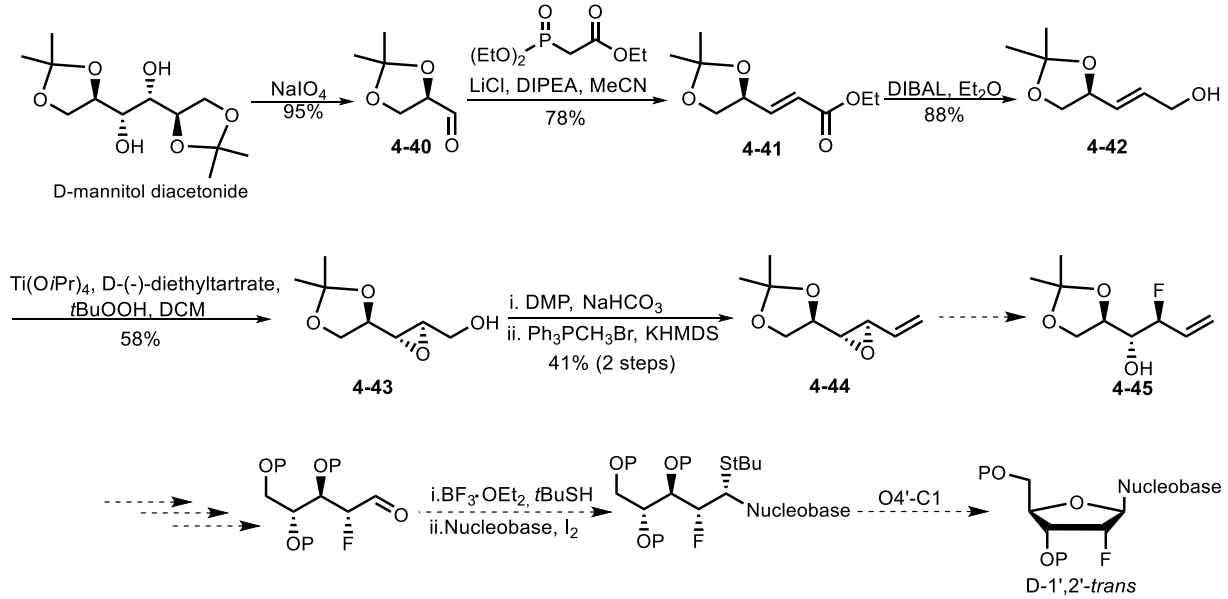
Although the (*R*)- and (*S*)- imidazolidinone catalysts did seem to be effective in introducing the C2-fluorine in a selective manner onto aldehyde **4-39** (different ^{1}H NMR shifts for the aldehydic

protons), the crude reaction mixtures also contained several other products. In addition to either the monofluorinated species **A** or **B** (Scheme 4.8), ^{1}H NMR chemical shifts consistent with the difluorinated product **C** were observed. Elimination of the C3-OBn group also seemed to occur (olefinic proton observed in ^{1}H NMR) forming products such a **D** which was identified by MS. Isolation of C2-F aldehydes **A** and **B** was not done since such species are known to decompose on silica gel.[24] Therefore, attempts were made to convert the crude C2-F aldehydes into products that could be isolated. For example, reduction to the corresponding alcohol with $NaBH_4$ and subsequent oxidation resulted in only low yields (~10%) of the desired C2-F aldehydes. Given these results other strategies were considered for fluorine incorporation.

4.4.1.2 Fluorine incorporation onto vinyl epoxide

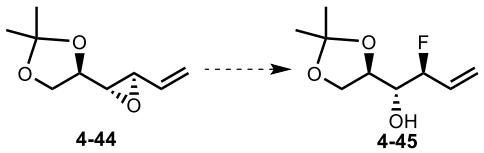
It was envisaged that addition of fluorine onto a vinyl epoxide could be a plausible route to synthesize C2'-fluorinated 1',2'-*trans* nucleoside analogues (Scheme 4.9).

Scheme 4.9 Introduction of fluorine onto vinyl epoxide **4-44**.



In this regard, aldehyde **4-40** was prepared from sodium periodate cleavage of D-mannitol diacetonide[25] with subsequent conversion to the known ester **4-41** through a Horner-Wadsworth-Emmons reaction.[26] Reduction to primary alcohol **4-42** with DIBAL occurred in good yield (88%). Sharpless epoxidation to the known epoxide **4-43**[26] followed by oxidation and a Wittig reaction provided vinyl epoxide **4-44**. A precedent literature example in which $3HF{\cdot}NEt_3$ in MeCN resulted in successful fluorination of a vinyl epoxide with inversion of configuration (substrate control for enantioselective fluorination) made this seem like a plausible route.[27] Various conditions[28-30] were studied to access fluorinated alkene **4-45** (Table 4.5)..

Table 4.5 Opening of vinyl epoxide **4-44** with fluorine.



4-44 **4-45**

Entry	Conditions	Solvent	Outcome
1	$3HF{\cdot}NEt_3$(6.0 eq), 25 °C, 3 days	MeCN	**4-44** and Undetermined Mixture
2	$3HF{\cdot}NEt_3$(2.0 eq), $LiClO_4$(2.0 eq), 25 °C, 16 hr	MeCN	Undetermined Mixture
3	$BF_3{\cdot}OEt_2$(4.0 eq), 25 °C, 6 days	Et_2O, benzene	Undetermined Mixture
4	HF-pyridine(16.0 eq), 25 °C, 4 hr	$CHCl_3$	**4-44**

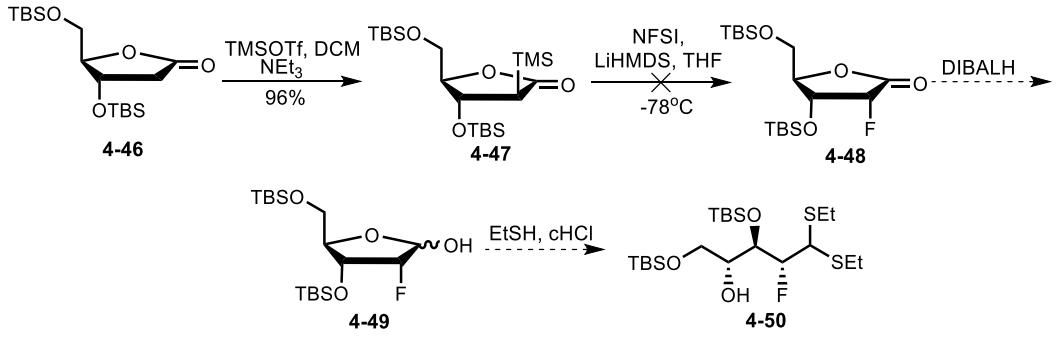
However, the reactions resulted in either an undetermined mixture of products (entries 1-3) or in unreacted starting material (entry 4). These low molecular weight compounds were volatile and thus difficult to manipulate. Also, this fluorination may have been complicated by the presence

of the labile acetonide protecting group. Although this route was not examined further, replacement of the acetonide by other protecting groups may be advantageous

4.4.1.3 Fluorine incorporation onto lactone bearing a C3-alkoxy substituent

A previously reported strategy involving electrophilic addition of fluorine (NFSI) to a silyl-protected lactone furnished ribo-lactol **4-49**.[3] This approach could provide the required acyclic 2,3-*anti* C2-F dithioacetal **4-50** (Scheme 4.10). Following Sauve's work, a TMS group was installed at the C2 position to allow for introduction of the fluorine with the ribo-configuration. They postulated that the bulky C2-TMS and C3-OTBS groups prefer a *trans*-orientation in the enolate allowing for fluorination to occur *syn* to the C3-protecting group. A low yield (33%) was reported for this fluorination reaction along with recovery of lactone **4-46** (61%). They speculated that a C-silyl to O-silyl isomerization of the C2-TMS group prior to fluorination resulted in the recovery of **4-46**.

Scheme 4.10 Introduction of fluorine onto lactone **4-47**.

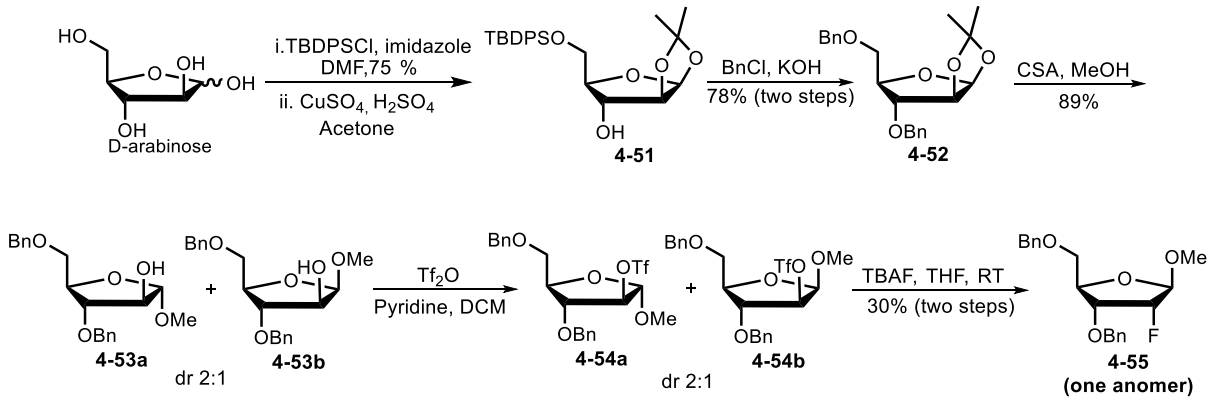


Efforts to reproduce this fluorination reaction were unsuccessful. A mixture of unreacted starting material **4-47**, lactone **4-46** and undetermined compounds were observed. Therefore, an alternative strategy for incorporation of a C2-F group was sought.

4.4.1.4 Fluorine incorporation onto cyclic acetal bearing a C3-alkoxy substituent

A previously reported synthesis in which a nucleophilic source of fluorine (TBAF) was used to displace a C2-triflate generating ribo-configured acetal **4-55**[31] was next considered (Scheme 4.11). Protection of the C5-hydroxyl of D-arabinose with TBDPS followed by C1-C2 acetonide protection resulted in **4-51**. Removal of the silyl protecting group and installation of C5 and C3 benzyl protecting groups provided **4-52** in 78% yield over two steps. Subsequent removal of the acetonide provided cyclic arabino-acetals **4-53** bearing a free hydroxyl group at C2.[31]

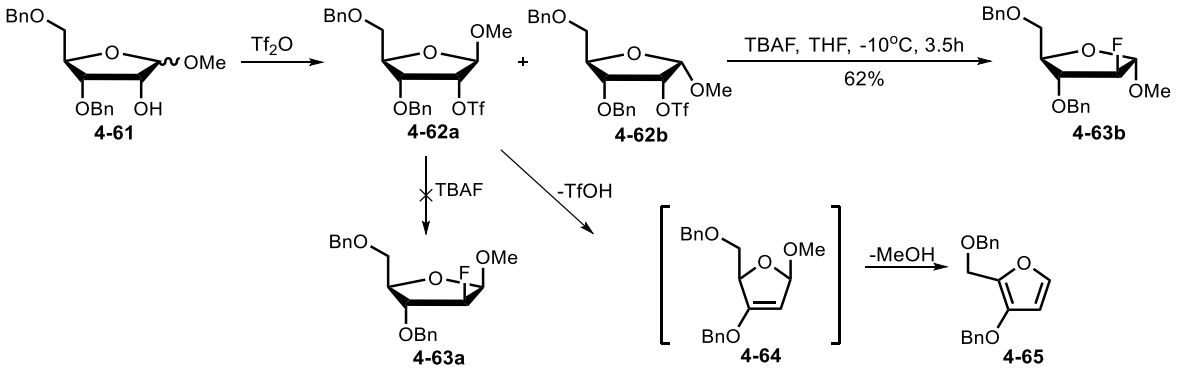
Scheme 4.11 Introduction of fluorine onto cyclic acetal **4-54**.



Introduction of the C2-F group was done according to the reported literature procedure with initial formation of the C2-triflate **4-54**.[31] Displacement with TBAF provided the fluorinated acetal **4-55** with the expected 30% yield. In an effort to better understand the low yield for this fluorination, the two steps of the reaction (installation of the triflate and fluorination) were analyzed. Conversion of the ~2:1 mixture of the known α-(**4-53a)** and ß-(**4-53b)**-methylfuranosides[32] proceeded smoothly to provide a ~2:1 mixture of α-(**4-54a)** and ß-(**4-54b)** C2-triflates. The crude ^{1}H NMR for fluorination of the unpurified triflates contained a mixture of fluorinated acetal **4-55** along with unidentified products. In some instances, the C2-triflate α-(**4-**

54a) anomer could be recovered, but seemingly decomposed under the same reaction conditions. It should also be noted that only one anomer, presumably the 1,2-*trans* methylfuranoside of **4-55** was isolated after purification (although 2D NMR experiments were not done to confirm the 1,2-stereochemistry). Due to formation of other side-products, it was difficult to determine from the crude ^{1}H NMR if this was the only anomer of **4-55** that was formed. When $3HF{\cdot}NEt_3$ was used as the nucleophilic source of fluorine, **4-55** was isolated with the same 30 % yield with refluxing the reaction at 80 ^{o}C for 16 hours, also with undetermined products in the crude reaction mixture. While the fluoride anion serves as a weak nucleophile, it is a rather strong base and is known to cause elimination reactions.[33] A similar fluorination was previously examined (Scheme 4.12) where a difference in reactivity was observed between the α- and ß-C2-triflates **4-62a,b**.[34] Treatment of the α-anomer (**4-62b**) with TBAF in THF resulted in the arabino-fluorinated product **4-63b** in 62% yield. However, similar treatment of the ß-anomer **(4-62a**) resulted in the furan derivative **4-65** through initial elimination of the C2-triflate followed by loss of methanol. They hypothesized that the difference in reactivity between the two anomers was due to a steric effect where the OMe group of the ß-anomer **(4-62a**) hinders nucleophilic attack at C2, especially when the OMe is in the preferred pseudoaxial conformation (anomeric effect). Therefore, for the ß-anomer **(4-62a**) direct substitution of the triflate with F^- competes unfavorably with the elimination pathway leading to furan **4-65** instead of fluorinated methylfuranoside **4-63a**. In the case of the α-anomer (**4-62b**), nucleophilic attack at C2 is unhindered by the anomeric OMe group resulting in the fluorinated product **4-63b**.

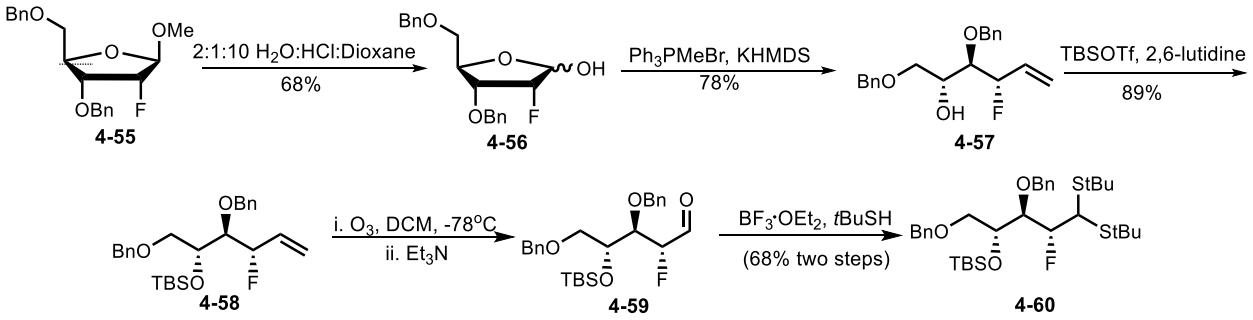
Scheme 4.12 Reported introduction of fluorine onto D-ribo-methylfuranosides.[34]



The marked difference in reactivity between the two anomers may also play a role in fluorination of **4-54**. If this same rational is used**,** only the C2-triflate ß-anomer **4-54b** (the minor anomer) undergoes nucleophilic displacement and the C2-triflate α-anomer **4-54a** decomposes. The ^{1}H NMR chemical shifts of the side-products formed for the fluorination of **4-54** with either TBAF or 3HF·NEt$_3$ do not correspond to furan **4-65**, however, it has been reported that this furan is unstable.[34] In a recent patent by Liotta,[35] fluorination of the free C2-OH of acetals **4-53** was accomplished with DAST. Although the yield for this fluorination reaction was not given, it may be an alternative to optimize this reaction sequence.

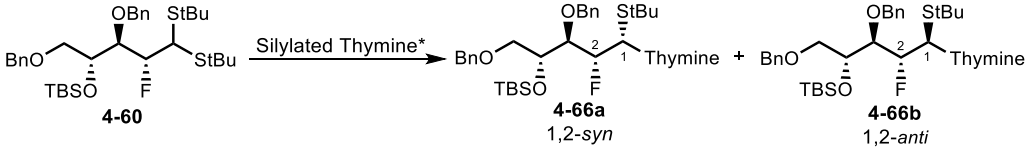
Nevertheless, with the C2-fluorinated product **4-55** in hand, the synthetic plan was carried forward to investigate if our acyclic strategy for nucleoside synthesis can be applied to substrates bearing a C2-F substituent. Conversion of fluorinated acetal **4-55** to the known lactol **4-56**[31] occurred with a good yield (68%, Scheme 4.13). The Wittig reaction of lactol **4-56** generated the terminal alkene **4-57** cleanly at 0 ^{o}C (78%).

Scheme 4.13 Synthesis of 2,3-*anti* C2-F dithioacetal.



Protection of the secondary alcohol at C4 followed by ozonolysis provided the TBS protected C2-F aldehyde **4-59** that was converted to dithioacetal **4-60** prior to purification. Coupling of silylated thymine with dithioacetal **4-60** was next investigated (Table 4.6). Addition of silylated thymine to **4-60** in THF using I_2 as the thiophilic activating agent resulted in a 2:1 ratio of 1,2-*syn* thioaminal **4-66a** and 1,2-*anti* thioaminal **4-66b** (entry 1). This low diastereoselectivity is consistent with nucleobase addition to the corresponding 2,3-*anti* bis-alkoxy dithioacetal **4-11** (Table 4.3). The selectivity remained the same when the reaction was done at 70 °C (entry 2), but the reaction went to completion faster (24 hours versus 48 hours).

Table 4.6 Addition of nucleobase to C2-F dithioacetal **4-60**.



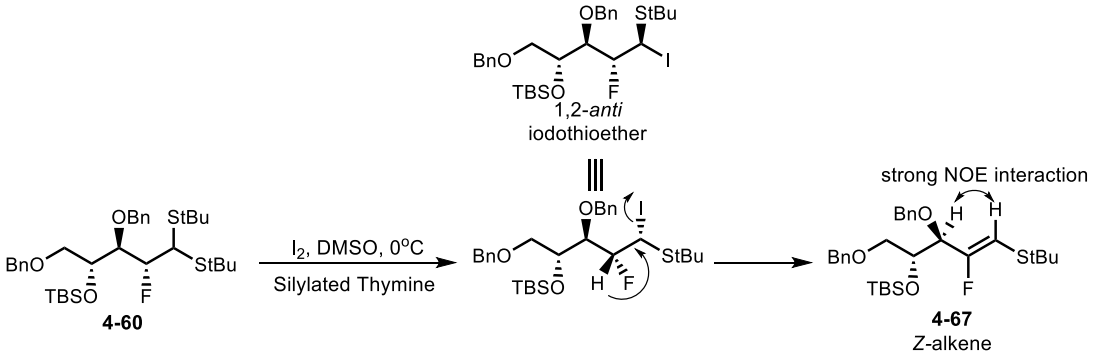
Entry	Activating Agent, Time	T	Solvent	Ratio(**a**:**b**)[a]	Yield (%)
1	I_2, 48h	25 °C	THF	2.4:1	89
2	I_2, 24h	70 °C	THF	2.3:1	80
3	I_2, 48h	0 °C	DMSO	3.1:1	73

4	Br_2, 16h	–20 °C	THF	1.4:1	n.d.
5	$Me_2S(SMe)BF_4$, 48h	25 °C	THF	3.9:1	57
6	$Hg(OAc)_2$, TMSOTf, 16h	25 °C	THF	4.5:1	52[b]
7	$Hg(OAc)_2$, TMSOTf, 16h	25 °C	DCM	6.3:1	49[b]
8	$Hg(OAc)_2$, TMSOTf, 72h	–20 °C	DCM	7.1:1	n.d.[b]
9	$Hg(OAc)_2$, TMSOTf, 16h	–20 °C	MeCN	8.3:1	n.d.

a. Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. b. Starting material remaining in crude mixture. *Silylated thymine as a solution in DCM. n.d. = not determined

When the solvent was changed to DMSO, a 3:1 ratio of the 1,2-*syn* thioaminal **4-66a** was observed at 0 °C (entry 3). The slightly lower yield of thioaminals **4-66a,b** in DMSO (73%, entry 3) as compared to THF (89%, entry 1) may be attributed to formation of Z-alkene **4-67** (Scheme 4.14). This side-product could result from elimination of the 1,2-*anti* iodothioether. It is unlikely that this elimination would affect the dr of thioaminals **4-66a,b** since the coupling reaction is thought to proceed through a fast equilibrium of the initially formed halothioethers.

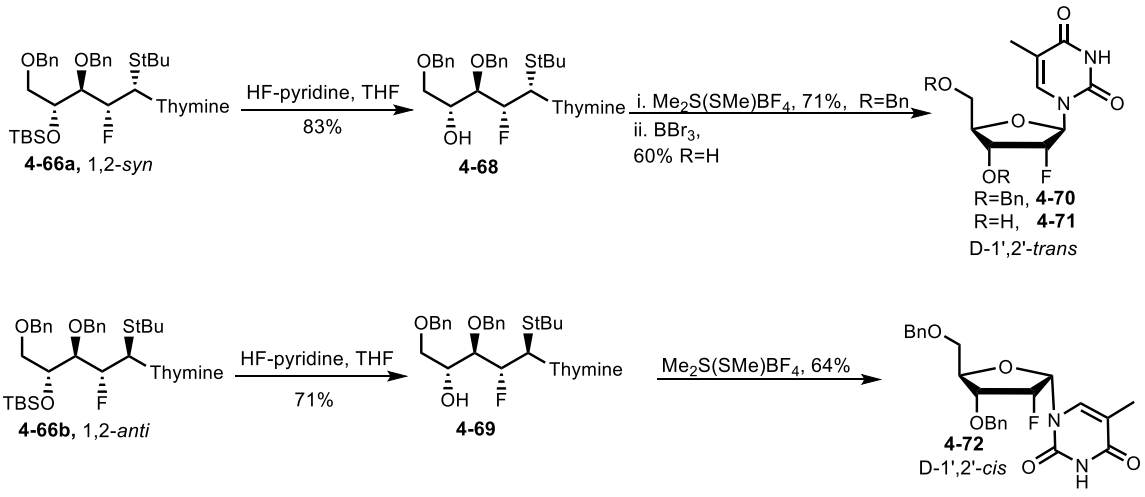
Scheme 4.14 Formation of Z-alkene **4-67** in DMSO.



Similar to the substitution of model substrate **4-2**, the activation of **4-60** with Br_2 in THF resulted in a loss of selectivity at –20 °C potentially due to equilibration in the presence of TMSBr (entry

4), as discussed in Chapter 3. Activation with $Me_2S(SMe)BF_4$ provided slightly higher selectivites (4:1, entry 5). Higher 1,2-*syn*/*anti* thioaminal ratios were also obtained with $Hg(OAc)_2$/TMSOTf in DCM or MeCN, albeit the reaction not going to completion (5-8:1, entries 6-9). Reaction in MeCN at –20 ^oC did provide the highest *syn*/*anti*-ratio (8:1) but the crude reaction mixture contained several other unidentified products (entry 10). This study demonstrates that the diastereoselectivity of nucleobase coupling onto 2,3-*anti* dithioacetals bearing a C2-F is consistent with that obtained for a C2-alkoxy group. The 1,2-*syn*:*anti* ratio for this nucleobase coupling reaction was improved with a variation of the activating agent and solvent although these coupling reactions should be done again allowing for the reaction to go to completion. Separation of the 1,2-*syn* and 1,2-*anti* **4-66a**,**b** isomers could be done with silica gel column chromatography but was easier after removal of the C4-TBS protecting group (Scheme 4.15) to provide **4-68** and **4-69**.

Scheme 4.15 O4'-C1 cyclization to provide D-furanosides.



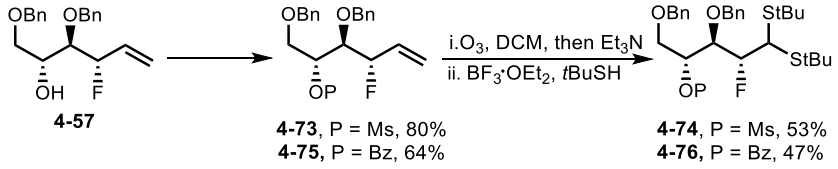
O4'-C1 cyclization of **4-68** with $Me_2S(SMe)BF_4$ provided the benzyl protected D-1',2'-*trans* furanoside **4-70** in 71% yield. Removal of the protecting groups with BBr_3 provided the known

nucleoside analogue **4-71**.[36] Cyclization of the minor 1,2-*anti* thioaminal **4-69** provided D-1',2'-*cis* furanoside **4-72** in 64% yield. This work demonstrates that our acyclic strategy of nucleobase coupling onto acyclic dithioacetals with subsequent S_N2-like cyclization allows for the synthesis of D-furanosides bearing a fluorine atom in the C2'-position.

4.4.1.5 Nucleobase coupling of 2,3-*anti* dithioacetals with various protecting groups

A brief examination of different C3, C4 and C5 protecting groups was done to investigate the selectivity of the nucleobase coupling with 2,3-*anti* C2-F dithioacetals (Scheme 4.16). The protecting group manipulation previously described in which a C2-C3 *anti* acetonide provides a higher 1,2-*syn* dr cannot be utilized in this case with a fluorine at C2. Therefore, other protecting groups were investigated. Installation of a mesylate at C4 onto alkene **4-57** with subsequent oxidation and conversion to dithioacetal provided **4-74**. Similarly, a benzoate was installed at C4 to furnish dithioacetal **4-76**.

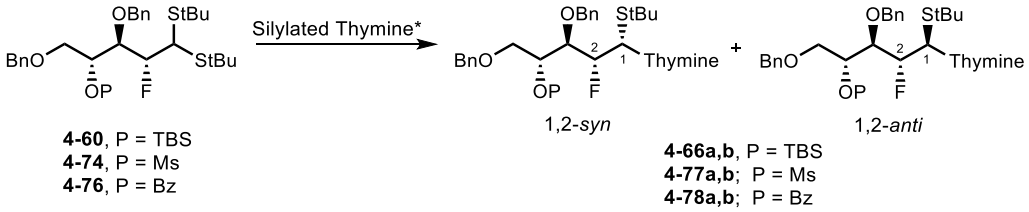
Scheme 4.16 Synthesis of various 2,3-*anti* C2-F dithioacetals.



Although thioaminals **4-77** and **4-78** (Table 4.7) were not characterized, coupling of silylated thymine in the presence of I_2 and THF at room temperature provided similar selectivities as compared to coupling with C4-TBS protected dithioacetal **4-60** (entries 1, 3, and 5). These results indicate that the protecting group at C4 does not seem to significantly influence the 1,2-selectivity of nucleobase coupling. Although coupling of **4-60** with $Hg(OAc)_2$ and TMSOTf at -

20 °C in MeCN provided an 8:1 mixture of thioaminals (entry 2), coupling of **4-74** and **4-76** provided an undetermined mixture of products (entries 4 and 6).

Table 4.7 Investigation of silylated thymine coupling with variation of C4-protecting group.

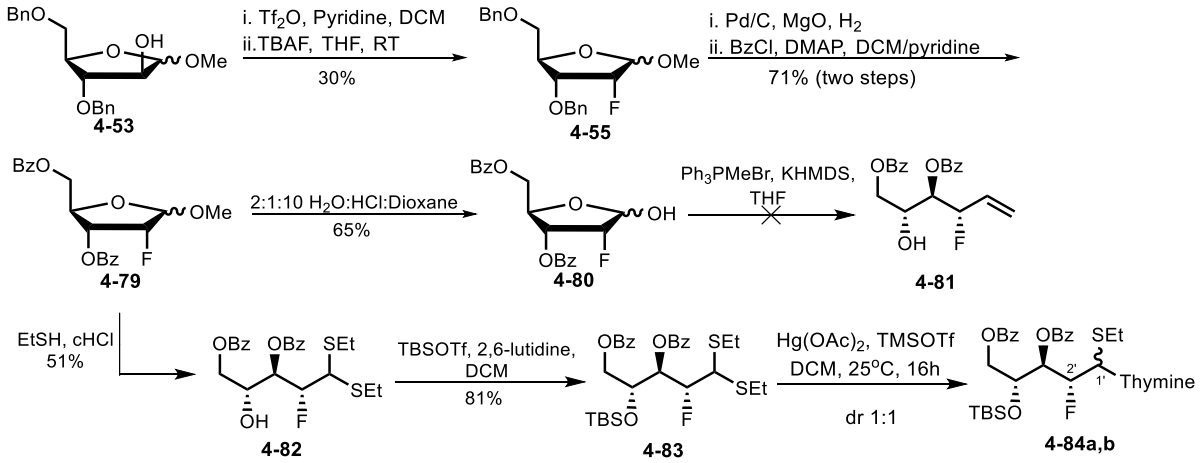


Entry	Substrate	Activating Agent, Time	T	Solvent	Ratio(**a**:**b**)[a]
1	**4-60**, P =TBS	I_2, 48h	25 °C	THF	2.4:1
2	**4-60**, P =TBS	$Hg(OAc)_2$,TMSOTf, 16h	–20 °C	MeCN	8.3:1
3	**4-74**, P = Ms	I_2, 72h	25 °C	THF	2.8:1[b]
4	**4-74**, P = Ms	$Hg(OAc)_2$, TMSOTf, 16h	–20 °C	MeCN	Undetermined Mixture
5	**4-76**, P = Bz	I_2, 16h	25 °C	THF	3.5:1[b]
6	**4-76**, P = Bz	$Hg(OAc)_2$, TMSOTf, 16h	–20°C	MeCN	Undetermined Mixture (Traces of Product)

a. Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. b. Starting material remaining in crude mixture. *Silylated thymine as a solution in DCM.

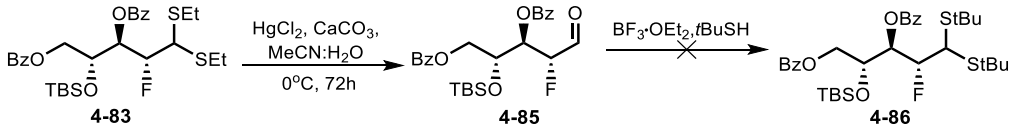
The selectivity of the reaction was also investigated with C3 and C5 benzoyl protecting groups (Scheme 4.17). Removal of the benzyl groups was done after the C2-F substituent was installed since fluorination in the presence of benzoyl groups was previously reported to give low yields and variable results.[13]

Scheme 4.17 Investigation of silylated thymine coupling with C3/C5 benzoyl protecting groups.



Removal of the C3 and C5 benzyl groups, installation of two benzoates and subsequent hydrolysis provided known lactol **4-80**.[13] Subjecting this lactol to the previously optimized Wittig conditions did not result in alkene **4-81** but rather in a mixture of unidentified products. Alternatively, acetal **4-79** was converted to diethyl-dithioacetal **4-82** using ethanethiol and concentrated HCl. TBS protection of the C4-hydroxyl group provided **4-83** onto which silylated thymine was added. Activation with I_2 in THF at 25 ^{o}C for 72 hours provided only traces of product with recovery of starting material **4-83**, whereas activation with $Hg(OAc)_2$ and TMSOTf at 25 ^{o}C in DCM resulted in what appeared to be a 1:1 ratio of thioaminals **4-84a,b**. Although they were not characterized, **4-84a,b** displayed ^{1}H NMR peaks characteristic of thioaminals. Attempts to convert diethyl-dithioacetal **4-83** into di*tert*butyl-dithioacetal **4-86** (Scheme 4.18) resulted in an undetermined mixture of products which lacked a TBS protecting group and could not be separated by silica gel column chromatography.

Scheme 4.18 Attempted conversion of diethyl- to di*ert*butyl-dithioacetal **4-86**.

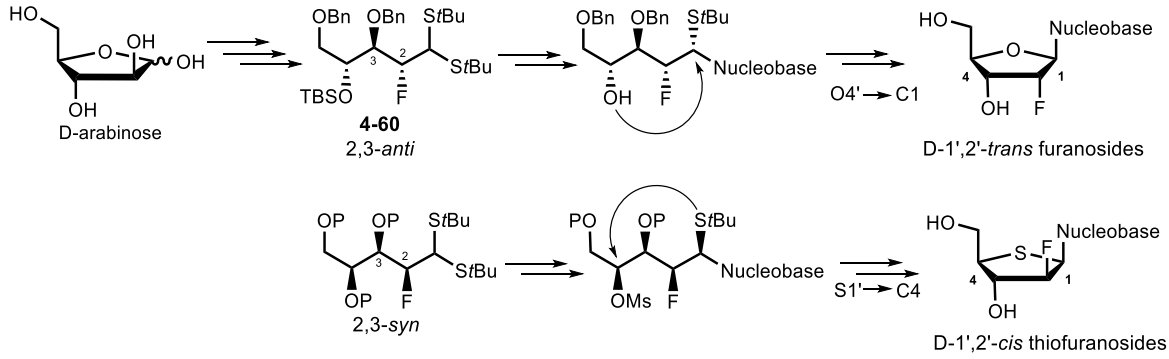


These experiments indicate that the C3, C4 and C5 protecting groups didn't provide a means to enhance the 1,2-selectivity for nucleobase addition onto C2-F dithioacetals. It would be interesting, however, to investigate the selectivity when a C3-C4 acetonide was present in these substrates.

4.4.2 Synthesis of 2,3-*syn* C2-F, C3-alkoxy aldehydes

The previous section highlighted the utility of our acyclic strategy in accessing D-1',2'-*trans* furanosides (Scheme 4.19) from nucleobase addition onto 2,3-*anti* C2-F dithioacetal **4-60** followed by a O4'-C1 cyclization. Coupling of nucleobases to C2-fluorinated dithioacetals with a 2,3-*syn* stereochemistry was next investigated in order to synthesize D-1',2'-*cis* thiofuranosides through a S1'-C4 cyclization.

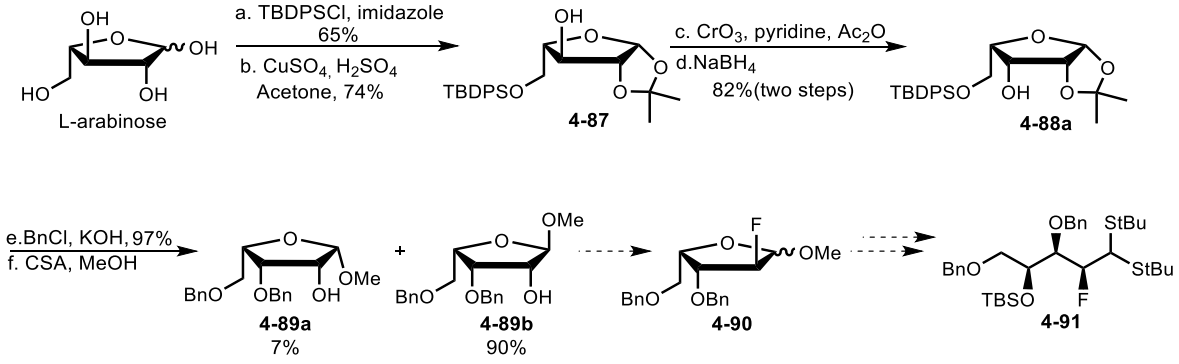
Scheme 4.19 Acyclic strategy to access furanosides and thiofuranosides.



4.4.2.1 Synthesis of 2,3-*syn* C2-F aldehyde from L-arabinose

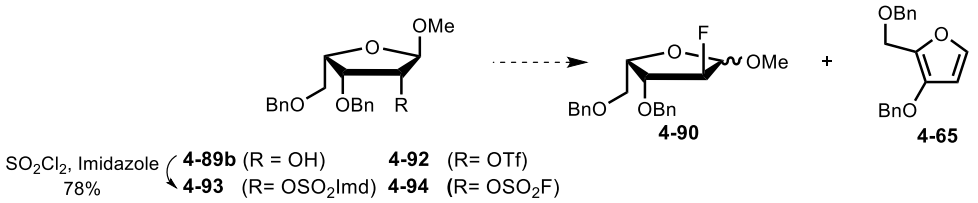
A synthetic strategy similar to the one used to access D-1',2'-*trans* furanosides was investigated to access D-1',2'-*cis* thiofuranosides, namely fluorination of a cyclic acetal (**4-89**) and conversion to acyclic dithioacetal **4-91** (Scheme 4.20). Following installation of a C5-TBDPS and a C1-C2 acetonide onto L-arabinose, the resulting free C3-hydroxyl of **4-87** was inverted through oxidization and reduction. This provided **4-88a** in good yield as was previously reported.[37]

Scheme 4.20 Strategy to access 2,3-*syn* C2-F dithioacetal **4-91** starting from L-arabinose.

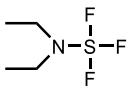
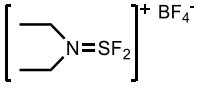


Silyl group removal and C3/C5 benzyl group protection followed by acetonide cleavage resulted in methylfuranosides **4-89a,b**. The two OMe anomers were separated and characterized providing 90% of the ß-anomer **4-89b** and 7% of the α-anomer **4-89a**. Incorporation of fluorine at C2 was envisioned to access **4-90**, however, this fluorination, proved to be challenging (Table 4.8). The initial approach to synthesize **4-90** was similar to the one previously used for synthesis of 2,3-*anti* dithioacetals in which a nucleophilic source of fluorine (TBAF) displaced a secondary triflate leaving group (Table 4.8, entry 1).

Table 4.8 Attempts to synthesize **4-90**.



Entry	R	Conditions (equivalents)	Solvent	Outcome
1	OTf	TBAF (5.0), 25 °C, 16h	THF	**4-92** and **4-65**
2	OTf	TBAF(1.2), AcOH (2.0), 25 °C, 72h	THF	**4-92** and traces of **4-65**
3	OTf	TBABF(1.2), 25 °C, 16h	DCM	**4-92** and **4-65**
4	OH	DAST(2.5), 25 °C, 16h	DCM	**4-89b** and unknown mixture
5	OH	3HF•NEt_3(2.0), XtalFluor-E(1.5), –40 °C to 25 °C, 4h	DCM	**4-89b**
6	OH	3HF•NEt_3(2.0), NEt_3(1.0), XtalFluor-E(1.5), –40 °C to 25 °C, 4 hr	DCM	**4-89b** and unknown mixture
7	OH	DBU(1.5), XtalFluor-E(1.5), –40 °C to 25 °C, 16h	DCM	**4-89b**
8	OSO_2Imd	CsF(10.0), 140 °C, 16h	2-methoxyethanol	**4-65**
9	OSO_2Imd	CsF(5.0), 130 °C, 1h	DMSO	**4-65**
10	OSO_2Imd	3HF•NEt_3(6.0), 70 °C, 16h	EtOAc	**4-65** and **4-94**
11	OSO_2F	3HF•NEt_3(6.0), NEt_3 (3.0), 70 °C, 16h	EtOAc	**4-65**

TBAF: nBu_4NF **TBABF**: nBu_4NHF_2 **DAST**:  **XtalFluor-E**: 

Based on the ^{1}H NMR of the crude reaction mixture, formation of the ß-anomer of triflate **4-92** occurred smoothly from ß-anomer **4-89b**. Upon reaction with TBAF at 25 °C for 16 hours,

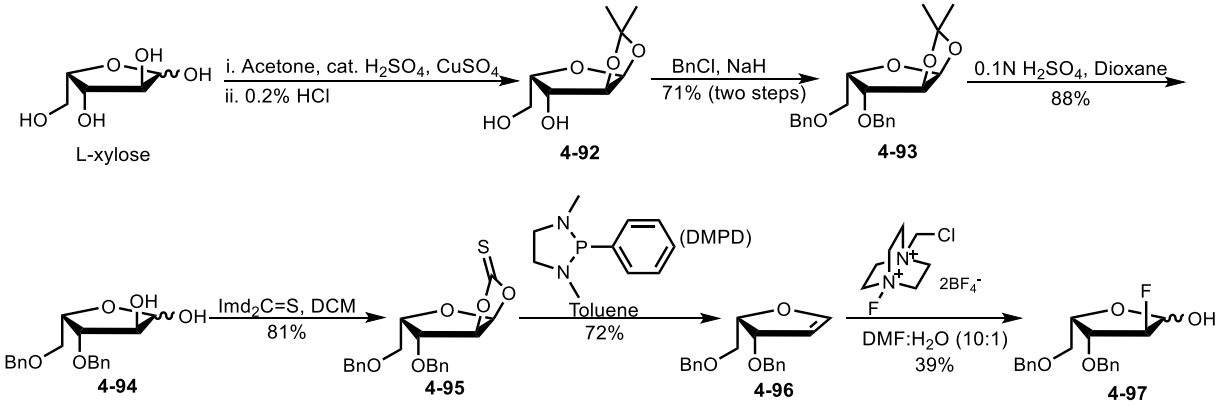
starting triflate **4-92** and undetermined products including furan **4-65** were isolated after purification. Formation of furan **4-65**[34] indicates that elimination reactions are indeed competing with the desired C2-nucleophilic fluorination reaction. In an effort to create a neutral reaction media, AcOH was added to the fluorination with TBAF (entry 2). This provided only the starting triflate **4-92** with traces of eliminated products. It has been reported that the less nucleophilic and less basic TBABF (tetrabutylammonium bifluoride) provides excellent yields in displacing triflates with minimal formation of eliminated side-products.[38] However, reaction of triflate **4-92** with TBABF in DCM still resulted in starting material and furan **4-65** (entry 3). Direct displacement of the free C2-OH of **4-89b** with DAST (diethylaminosulfur trifluoride) provided the starting material and an undetermined mixture of products (entry 4). Fluorinating agents, developed by OmegaChem, have been determined to be more stable than DAST, such as XtalFluor-E (diethylaminodifluorosulfinium tetrafluoroborate).[39] In a recent publication,[40] they reported its use in addition to promoters such as $3HF{\cdot}NEt_3$, $2HF{\cdot}NEt_3$, or DBU as an effective method for nucleophilic substitution with fluorine. The conditions that they employed were tried on substrate **4-89b**, but only resulted in starting material (entries 5-7). Introduction of fluorine onto sugar scaffolds has been done through nucleophilic (F^-) displacement of an imidazoyl sulfate leaving group.[9] Conversion of the C2-OH of **4-89b** into the imidazoyl sulfate **4-93** occurred with a 78% yield. Various conditions were examined to displace this leaving group such as reaction with CsF in either 2-methoxyethanol[9] (entry 8) or DMSO[41] (entry 9). In both cases only eliminated furan **4-65** was obtained. Displacement of **4-93** with $3HF{\cdot}NEt_3$ in ethyl acetate, a procedure used to access C2-F-D-arabino scaffolds,[42] resulted in what was thought to be initial displacement of the imidazole by the fluoride anion providing **4-94**. Reaction of the fluorosulfonate **4-94** did not lead to the desired product **4-90**, but rather to elimination. These

unsuccessful attempts to synthesize fluorinated acetal **4-90** through nucleophilic displacement of the oxygen moiety at C2 of ß-**4-89b** are in agreement with Klein's[34] previous work in which ß-acetals were shown to be more prone to eliminate rather than undergo substitution. Since the α-anomer **4-89a** was only formed in 7% yield, its fluorination was not investigated and an alternate strategy was considered.

4.4.2.2 Synthesis of 2,3-*syn* C2-F, C3-alkoxy aldehyde from L-xylose

Fluorination of carbohydrate based glycals has been a method previously used to introduce a C2-fluorine in a stereocontrolled manner, as well as serving to functionalize the anomeric center.[43] Applying this methodology, fluorination of glycal **4-96** was investigated (Scheme 4.21).

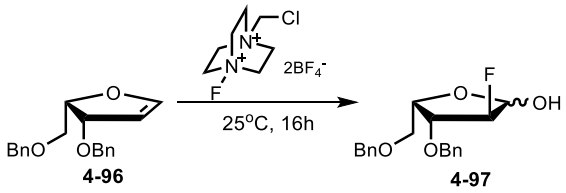
Scheme 4.21 Synthesis of C2-F lactol **4-97**.



Following a recent publication,[44] L-xylose was protected with a C1-C2 acetonide and C3/C5 benzyl groups to form **4-93**.[45] Cleavage of the acetonide resulted in diol **4-94**[46] which was converted to the cyclic thiocarbonate (**4-95**).[47,48] Treatment with DMPD (1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine) provided glycal **4-96** in good yield.[49] Cheaper sources of nucleophilic phosphorus such as $P(OEt_3)$, triethyl phosphite, typically used for the Corey-Winter synthesis of olefins could be used to optimize this sequence. The precedent reaction conditions[43] were used

for the fluorination of glycal **4-96**, namely reaction of Selectfluor in a solution of DMF:H_2O at 25 ^oC for 16 hours. We observed that the ratio of DMF:H_2O present in the reaction mixture influenced the nature of undesired side reactions.

Table 4.9 Synthesis of fluorinated lactol **4-97**.



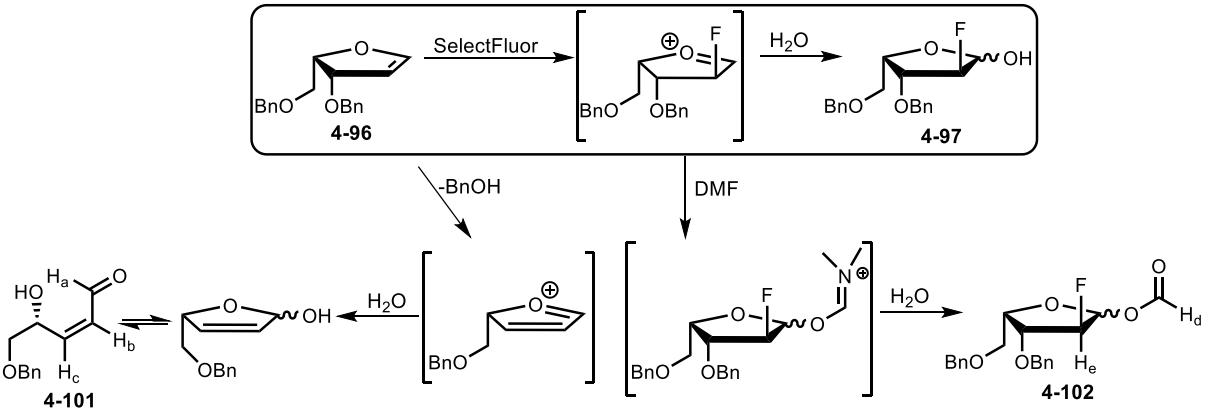
Entry	Solvent	Outcome	Yield
1	DMF:H_2O (1:1)	3:1 (**4-97** : **4-101**)	43%[a]
2	DMF:H_2O (3:1)	3:1:0.4 (**4-97** : **4-101**: **4-102**)	43% [a]
3	DMF:H_2O (5:1)	2:1 (**4-97** : **4-102**)	32%
4	DMF:H_2O (10:1)	3:1 (**4-97** : **4-102**)	39%

a. Yield of **4-97** mixed with **4-101**

With a higher amount of water (1:1 DMF:H_2O, Table 4.9, entry 1), a 3:1 ratio of the desired lactol **4-97** and aldehyde **4-101** was formed. ^1H NMR shifts characteristic of aldehydic and olefinic protons (H_a, H_b and H_c Scheme 4.22) suggest the formation of the unsaturated aldehyde **4-101**. Selectfluor serves as the electrophilic source of fluorine adding to C2 of the glycal (**4-96,** Scheme 4.22) generating the cyclic fluorinated oxonium.[43] The desired product **4-97** then results from addition of water at C1. Unsaturated aldehyde **4-101** may result from elimination of the C3-OBn group with subsequent addition of water. Separation of **4-101** from the desired product **4-97** was challenging and only possible after the subsequent Wittig reaction. When the fluorination

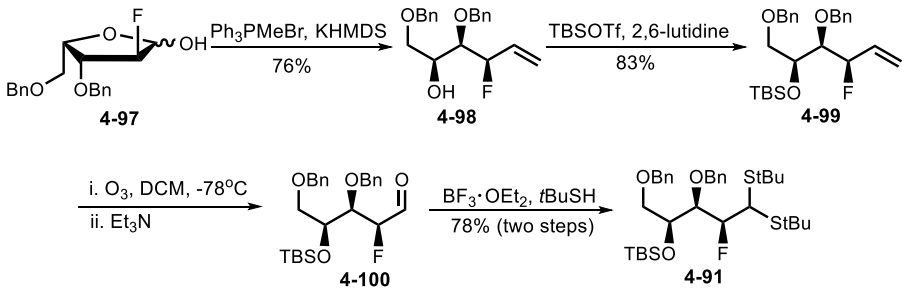
was done with higher amounts of DMF (entries 2-4, Table 4.9), less of the undesired **4-101** species was formed. Another secondary product was, however, detected. Characteristic ^{1}H NMR chemical shifts for H_d and H_e coupled with fluorine supported the formation of an anomeric mixture of **4-102**. This could result from addition of DMF to the fluorinated oxonium species followed by hydrolysis. This compound was identified by mass spectrometry and a similar side-reaction has been previously reported.[50] **4-102** could be separated from the desired lactol **4-97**. The best conditions thus far provide fluorinated lactol **4-97** in 39% yield using a 10:1 mixture of DMF:H_2O (entry 4, Table 4.9). Using a different source of electrophilic fluorine (NFSI, 2,6-dichloro-1-Fpyridinum triflate, or 2,6-dichloro-1-Fpyridinum tetrafluoroborate) did not result in the desired fluorinated lactol **4-97**. It should be noted that a similar yield (~40%)[43,51] was also obtained when the fluorination was repeated using the D-glycal, opposed to the 73% yield that is reported.[43]

Scheme 4.22 Formation of lactol **4-97** along with side products.



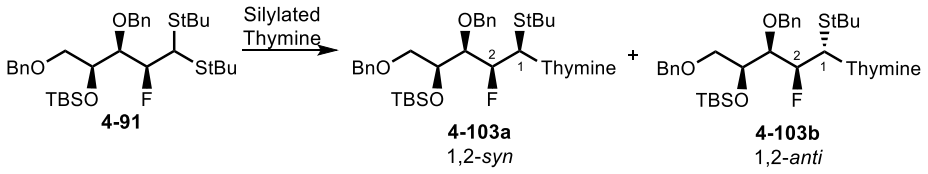
Optimization of this fluorination reaction is still necessary, but the reaction sequence was carried forward. Lactol **4-97** was subjected to a Wittig reaction, C4-silyl group protection, ozonolysis and conversion to 2,3-*syn* dithioacetal **4-91**, as shown in Scheme 4.23.

Scheme 4.23 Synthesis of 2,3-*syn* C2-F dithioacetal **4-91**.



The nucleobase coupling reaction onto the 2,3-*syn* dithioacetal **4-91** was next investigated (Table 4.10). Reaction of dithioacetal **4-91** with I_2 in THF at 25 ^oC and silylated thymine resulted in a 16:1 diastereomeric ratio in favor of 1,2-*syn* thioaminal **4-103a** (entry 1).

Table 4.10 Silylated thymine addition onto dithioacetal **4-91**.

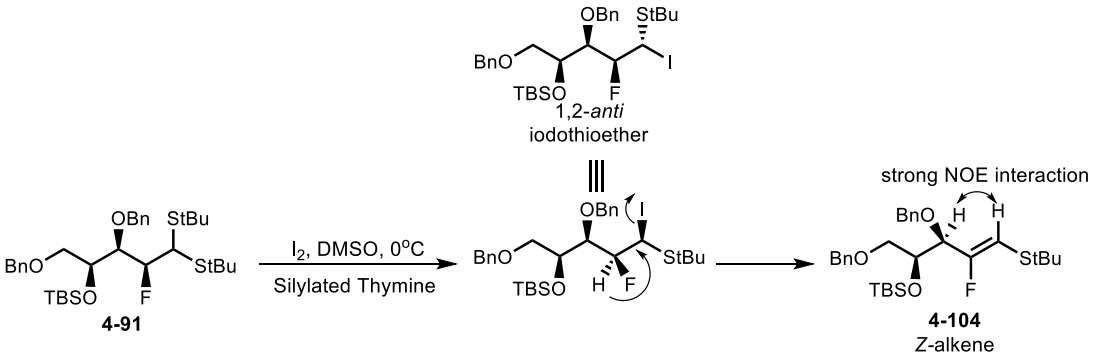


Entry	Activating Agent, Time	T	Solvent	Ratio(**a**:**b**)[a]	Yield (%)
1	I_2, 48h	25 ^oC	THF	16:1	70[b]
2	I_2, 16h	70 ^oC	THF	12:1	61[b,c]
3	I_2, 48h	25 ^oC	DCM	12:1	62
4	I_2, 16h	70 ^oC	DCM	1:1.4	50
5	I_2, 16h	0 ^oC	DMSO	20:1	60[b]

a. Determined by ^1H NMR spectroscopic analysis of crude mixtures. b. Yield of only *syn* isomer. c. Starting material **4-91** remaining in crude reaction mixture.

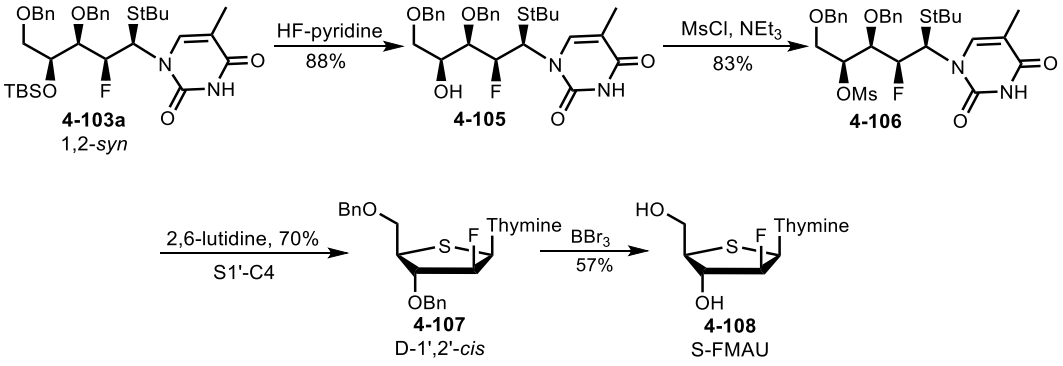
This higher 1,2-*syn* selectivity with a 2,3-*syn* relationship is consistent with the previous couplings with a C2- alkoxy group (Table 4.2). When the reaction was done at 70 ^{o}C a drop in selectivity was observed (12:1, entry 2). A lower selectivity (12:1) was also observed when the reaction was done at 25 ^{o}C in DCM (entry 3) with a reversal in selectivity noted at 70 ^{o}C (entry 4). When the coupling reaction was done with I_2 and DMSO at 0 ^{o}C, a 20:1 ratio of the 1,2-*syn* thioaminal **4-103a** was observed (entry 5) with a slightly lower yield (60%). As discussed with 2,3-*anti* dithioacetal **4-60**, nucleobase addition in DMSO resulted in the formation of side-product **4-104** identified by ^{1}H and NOESY NMR and mass spectrometry (see experimental section) (Scheme 4.24). This Z-alkene could result from elimination of the 1,2-*anti* iodothioether but is unlikely to influence the selectivity of the coupling reaction since it's thought to proceed through a fast equilibrium of halothioethers.

Scheme 4.24 Formation of Z-alkene **4-104** in DMSO.



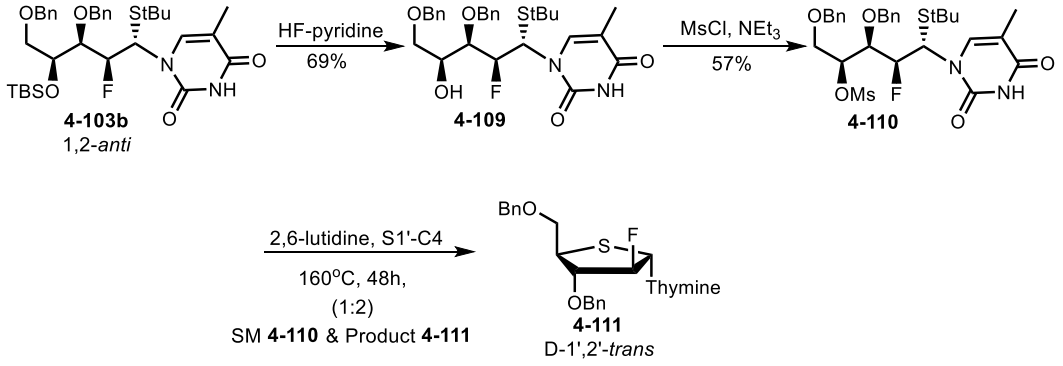
With the successful coupling of silylated thymine to dithioacetal **4-91**, the cyclization of 1,2-*syn* thioaminal **4-103a** was next examined (Scheme 4.25). Removal of the TBS protecting group and installation of a mesylate at C4 provided thioaminal **4-106**. Refluxing in 2,6-lutidine (160 ^{o}C for 4 hours) provided the D-1',2'-*cis* thiofuanoside **4-107** in good yield. Removal of the benzyl protecting groups resulted in the known nucleoside analogue S-FMAU (**4-108**).[8]

Scheme 4.25 S1'-C4 cyclization of thioaminal **4-103a**.



The minor 1,2-*anti* thioaminal **4-103b** was also deprotected with subsequent addition of a C4-mesylate providing **4-110** (Scheme 4.26). The S1'-C4 cyclization to generate the 1',2'-*trans* thionucleoside analogue **4-111** was much slower than formation of the 1',2'-*cis* NA **4-107**. Refluxing at 160 ^{o}C for 48 hours only resulted in a 2:1 mixture of the product and starting thioaminal **4-110**.

Scheme 4.26 S1'-C4 cyclization of thioaminal **4-103b**.



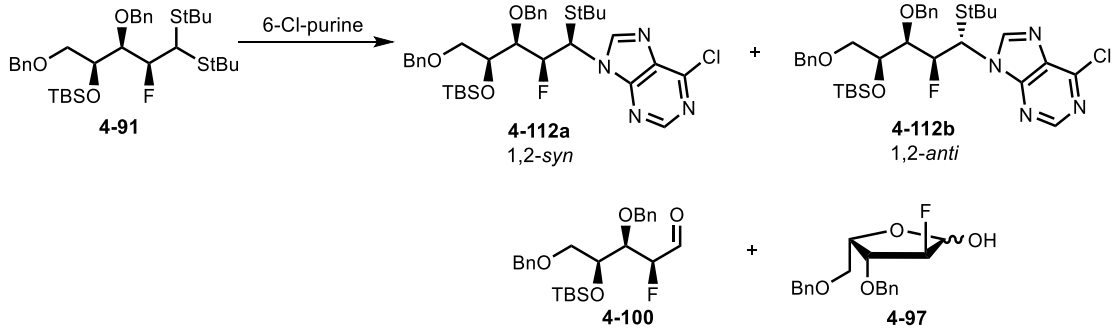
Nevertheless, these results demonstrate that the 1,2-stereochemistry obtained from nucleobase coupling onto C2-F acyclic dithioacetals is maintained in the cyclization step. Therefore, this

acyclic approach allows for the synthesis of D-1',2'-*cis* thiofuranosides that are difficult to synthesize using other methodologies.

4.4.2.3 Purine nucleobase coupling onto C2-F dithioacetals

Coupling of a purine nucleobase onto 2,3-*syn* dithioacetal **4-91** was also investigated (Table 4.11). Addition of 6-Cl-purine to dithioacetal **4-91** in the presence of I_2 in THF at 25 ^oC (entry 1) resulted in formation of the N9-1,2-*syn* thioaminal **4-112a**. The minor 1,2-*anti* thioaminal **4-112b** has not yet been identified, but the crude reaction mixture seemed to indicate the formation of only one isomer.

Table 4.11 Coupling of purine to dithioacetal **4-91.**

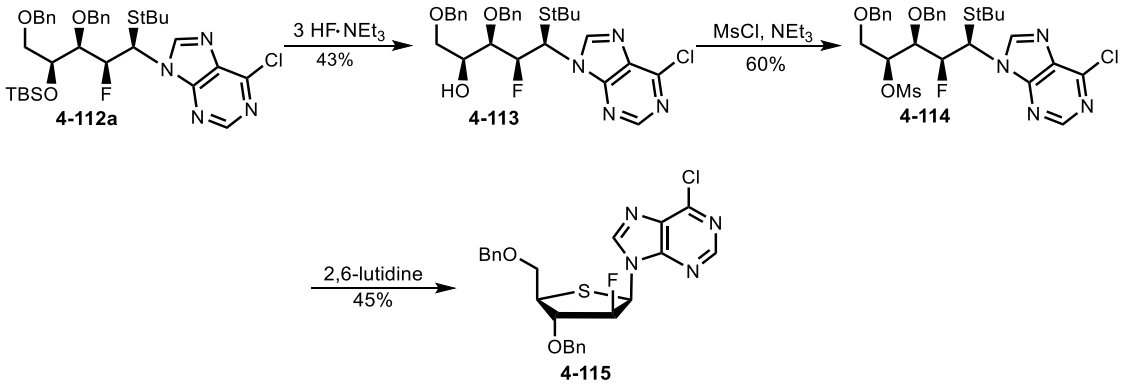


Entry	Activating Agent, Time	T	Solvent	Ratio (**syn**:**anti**)[a]	Ratio (**4-112a** : **4-100**)[a]	Yield (%)
1	I_2, 16h	25 ^oC	THF	One isomer	3:1	54[b]
2	I_2, 16h (6-Cl-purine, NaH, MeCN)	25 ^oC	THF	Starting material **4-91**		
3	I_2, 16h	25 ^oC	MeCN	**4-100** and **4-97**		

a. Determined by ^1H NMR spectroscopic analysis of crude mixtures. b. Aldehyde **4-100** is inseparable from **4-112a**

A 3:1 mixture of thioaminal **4-112a** and aldehyde **4-100** was obtained that could not be separated upon purification. Coupling with silylated 6-Cl-purine was not tried since formation of undesired N7-regioisomers was expected.[52,53] The sodium salt of 6-Cl-purine was added to dithioacetal **4-91** in the presence of I_2 (entry 2), but only starting material was observed. When the reaction was done in MeCN opposed to THF, aldehyde **4-100** and lactol **4-97** were isolated (entry 3). This coupling reaction of purine nucleobases with dithioacetals still needs to be optimized, but nevertheless, these results indicate that purines add to fluorinated dithioacetals with preference for the desired N9-1,2-*syn* thioaminal. The 3:1 mixture of thioaminal **4-112a** and aldehyde **4-100** was treated with $3HF{\cdot}NEt_3$ in THF to provide 43% yield of deprotected thioaminal **4-113** along with recovered lactol **4-97** (Scheme 4.27). The free C4-OH of **4-113** was activated with a mesylate (**4-114**) and cyclized. This provided the benzyl protected nucleoside analogue D-1',2'-*cis* thiofuranoside **4-115**. The N9-regiochemistry of **4-115** was confirmed from HSQC and HMBC experiments (see experimental section).

Scheme 4.27 Synthesis of D-1',2'-*cis* thiofuranoside **4-115**.

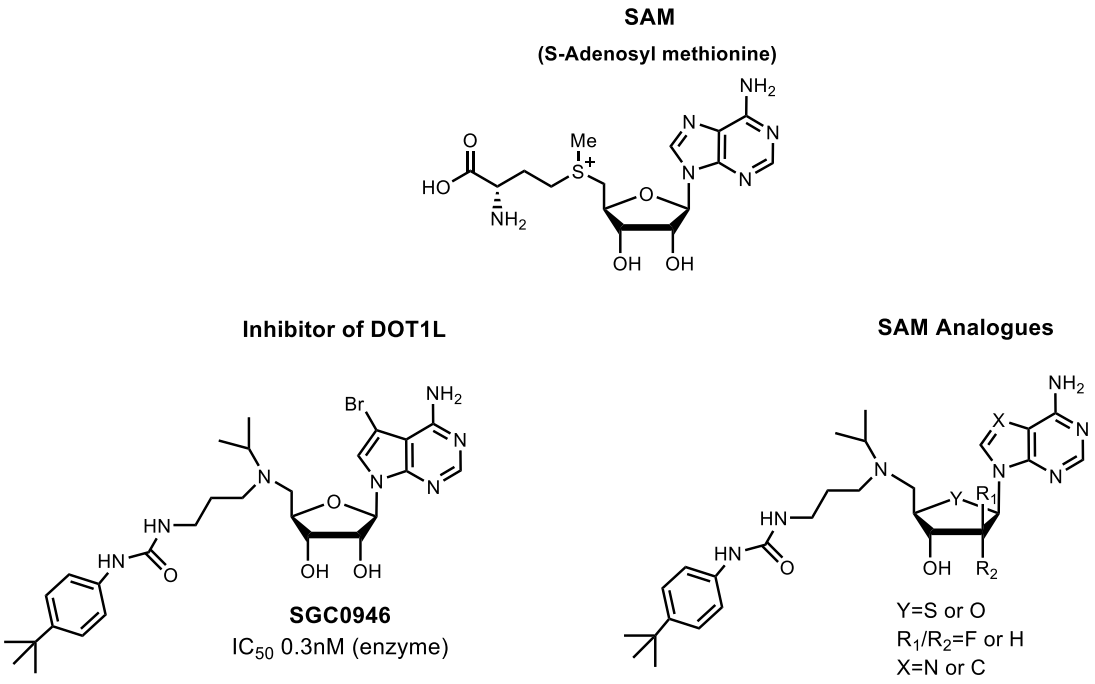


Although this reaction sequence still needs to optimized, these initial results highlight the utility of our methodology for the synthesis of D-1',2'-*cis* thiofuranosides bearing a purine nucleobase.

4.5 Protein MethylTransferase Inhibitors

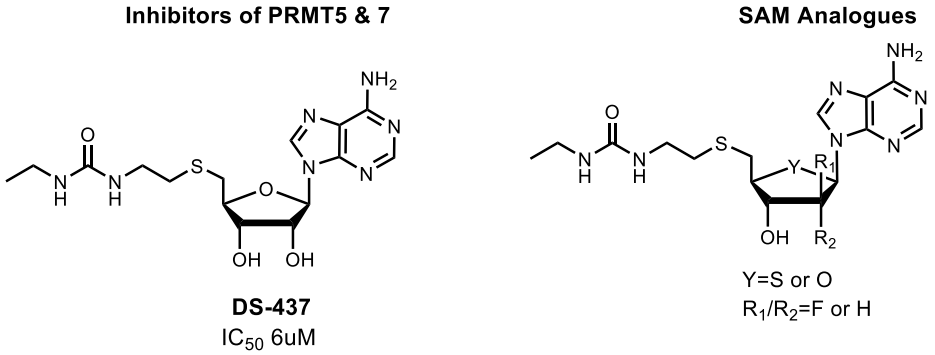
In collaboration with the SGC (Structural Genomics Consortium) in Toronto and as part of the ChemNet Create program supported by NSERC, we are synthesizing potential inhibitors of epigenetic targets. Epigenetics involve changes in gene expression without alteration of the DNA sequence.[54] Histone methylation is one such post-translational modification that is catalyzed by protein methyltransferases (PMTs). PMTs transfer a methyl group from the cofactor SAM (S-adenosylmethionine) to either lysine (PKMTs) or arginine (PRMTs) side-chains of histones.[54] Mutation or misregulation of PMTs is linked to cancer and thus this family of proteins may serve as potential drug targets. Inhibitors can be peptide-competitive, SAM-competitive, or allosteric (non-competitive with both SAM and peptide). PMT SAM-inhibitors have been developed that target DOT1L, a lysine methyltransferase.[55] For example, nucleoside analogue, SGC0946 (Figure 4.5), has been identified as a potent and selective inhibitor of DOT1L, killing cells containing a MLL (mixed lineage leukemia) translocation.[54] We plan to synthesize various analogues of these inhibitors in order to target DOT1L or other PMTs. Replacing the oxygen at C2' by a fluorine (ribo-or arabino-like) will modify the electronic parameters next to the anomeric center and influence binding to the protein. The intracyclic oxygen will also be replaced by a sulfur to potentially improve the pharmacokinetic profile of the nucleoside analogues.

Figure 4.5 Proposed SAM analogues for DOT1L.



DS-437 has recently been shown to be a SAM competitive inhibitor of PRMT5 and PRMT7 which are arginine methyltransferases.[56] Deletion of PRMT5 has been linked to activation of p53-mediated apoptosis and it has been suggested that PRMT5 and 7 work in conjunction to methylate their substrates.[56] Thus, these protein methyltransferases may also serve as potential cancer targets. DS-437 occupies the cofactor binding site in PRMT5 and its urea functionality was designed to mimic the guanidinium group in the arginine residue of histone H4R3. In an effort to synthesize more potent inhibitors, we plan to insert this urea moiety onto our nucleoside substrates bearing a C2'-fluorine while also varying the heteroatom in the five-membered sugar ring (Figure 4.6).

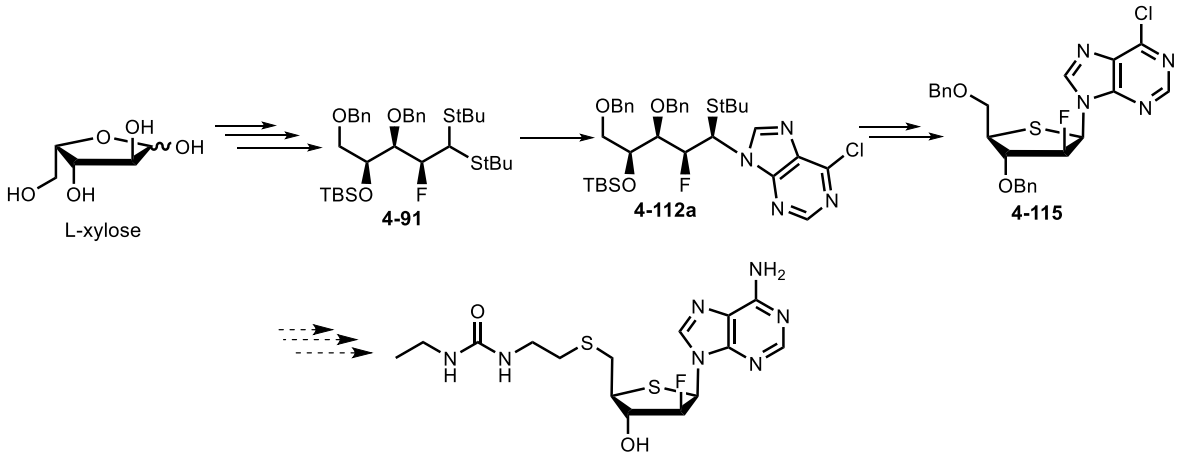
Figure 4.6 Proposed SAM analogues for PRMT5 and 7.



4.5.1 Towards the Synthesis of SAM analogues

Using the developed acyclic strategy to access D-1',2'-*cis* thiofuranosides bearing a purine nucleobase, analogues with the same urea side-chain as in DS-437 will be synthesized (Scheme 4.28).

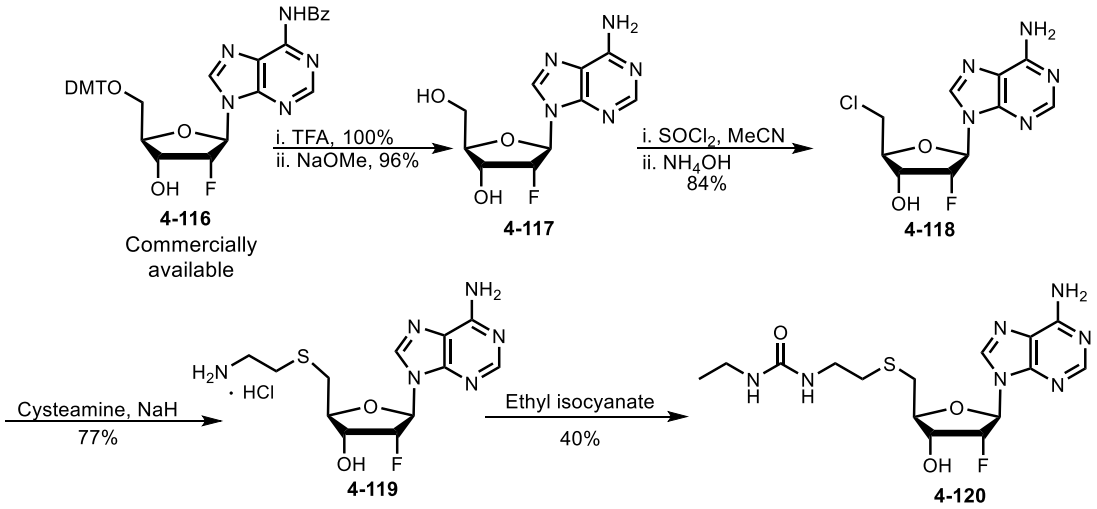
Scheme 4.28 Towards the synthesis of SAM analogues for PRMT5 and 7 inhibition.



Towards this objective, analogues bearing a C2'-F (ribo-) and intracyclic oxygen have been synthesized (Scheme 4.29) and sent for testing at the SGC. The known 1',2'-*trans* C2'-F adenine furanoside **4-117**[12,16,57] was obtained from DMT and benzoyl group deprotection of commercially available **4-116**. Following a similar synthesis as for DS-437,[56] a chlorine leaving group was installed at C5 (**4-118**) followed by displacement with cysteamine (**4-119**). Reaction

of the free amine with ethyl isocyanate provided the desired nucleoside analogue **4-120** in 36% yield.

Scheme 4.29 Synthesis of furanoside C2'-F analogues.



The activity of these compounds was determined at the SGC in Toronto. Compounds **4-119** and **4-120** showed no inhibitory activity for PRMT5 and only weak activity at PRMT7 (Table 4.12).

Table 4.12 IC_{50} for compounds **4-119** and **4-120**.

Compound	PRMT7	PRMT5	SETDB1	SUV39H1	SUV39H2	SETD2
	IC_{50}(μM)	IC_{50}(μM)	IC_{50}(μM)	IC_{50}(μM)	IC_{50}(μM)	IC_{50}(μM)
4-120	>200	NI	NI	NI	NI	NI
4-119	85	NI	12	32	76	69

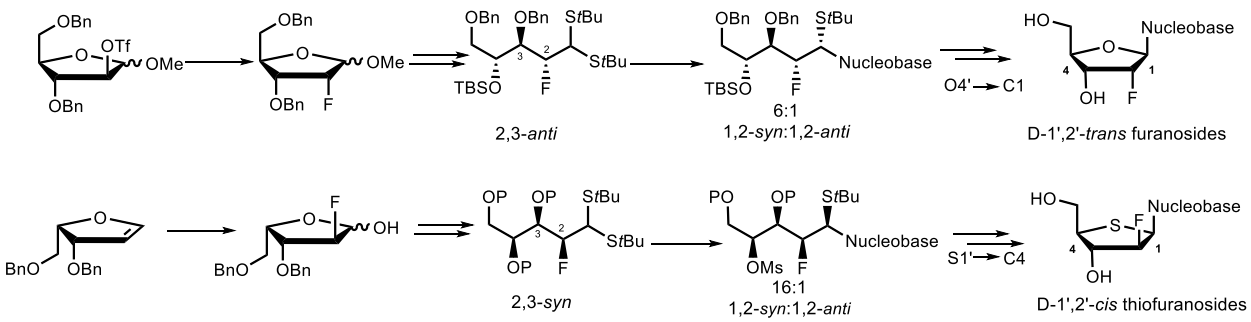
NI = No inhibition

Their IC_{50} values were about 10-30 times higher than DS-437 (IC_{50}=6μM). However, they did show some inhibition towards other PMTs. Interestingly, **4-119** shows reasonable activity against SETDB1, but is not selective also having activity at PRMT7, SUV39H1/H2 and SETD2.

There are currently no known inhibitors of SETDB1, thus, this PMT could also be an interesting target for our analogues.

4.6 Conclusions

The stereoselective nucleobase addition to acyclic dithioacetals bearing a C2-F stereogenic center is proposed to occur through a S_N2-like mechanism in which both the major and minor transition structures adopt a C1–C2 gauche conformation. Attack on the least hindered side of the contact-ion pair TS **A** results in preferential formation of the 1,2-*syn* diastereoisomer. Our acyclic methodology provides reasonable to high selectivities for coupling of pyrimidine and purine nucleobases to 2,3-*anti* and 2,3-*syn* C2-fluorinated dithioacetals. Cyclization of these thioaminals provides a new approach to synthesize nucleoside analogues bearing an alkoxy group in the C3'-position and a fluorine at C2'. To render such a strategy efficient for the synthesis of C2'-fluroinated nucleosides, alternate approaches to access acyclic dithioacetals bearing a C2-F and a C3-alkoxy group need to investigated. In collaboration with the SGC, analogues of these molecules are being tested as protein methyltransferase inhibitors. In conclusion, the results of this work demonstrate that the most efficient way to generate D-1`,2`-*trans* furanosides using the acyclic methodology, is through OTf displacement with TBAF to insert the C2-F followed by generation of the acyclic dithioacetal. Coupling with silylated nucleobase provides a 6:1 selectivity for the desired 1,2-*syn* thioaminal which can then undergo O4`-C1 cyclization. Formation of the 1`,2`-cis thiofuranosides, requires fluorination of the glycal with Selectfluor followed by subsequent synthesis of the dithioacetal species. Excellent (16:1) selectivity for the 1,2-*syn* thioaminal can be achieved after which activation with a C4-Ms allows for S1`-C4 cyclization.



4.7 References

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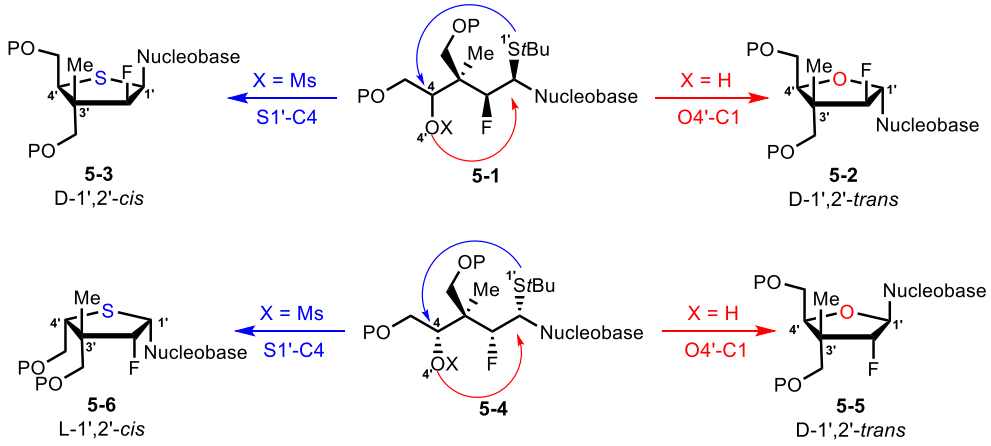
Chapter 5 Synthesis of Novel Nucleoside Analogues bearing a C2'-F and a C3'All-Carbon Quaternary Center

5.1 Research Perspectives

In search of new antimetabolites that may serve as antiviral and/or anticancer agents, our laboratory is developing a series of novel nucleoside analogues. In particular, we are interested in those bearing an all-carbon stereogenic quaternary center at C3' and various substituents at C2' including fluorine atoms.[1,2] The acyclic approach is particularly well suited for the efficient synthesis of these scaffolds and has allowed for the formation of novel nucleoside analogues bearing a fluorine in the C2' position and a C3' all-carbon quaternary center (Scheme 5.1). Cyclization of two 1,2-*syn* thioaminals **5-1** and **5-4** provides D-1',2'-*trans* furanosides **5-2** and **5-5** along with 1',2'-*cis* thiofuranosides **5-3** and **5-6**. My contribution to this work involves the synthesis of the nucleosides reported herein. Three undergraduate students worked on parts of this project under my supervision.

Scheme 5.1 Acyclic approach used for the synthesis of novel NA.

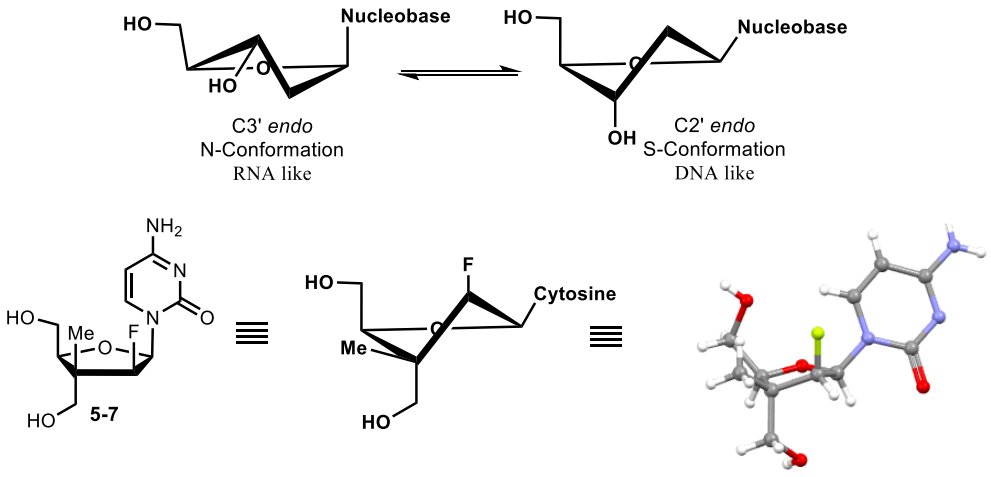


5.2 Novel nucleoside scaffolds

5.2.1 Conformation

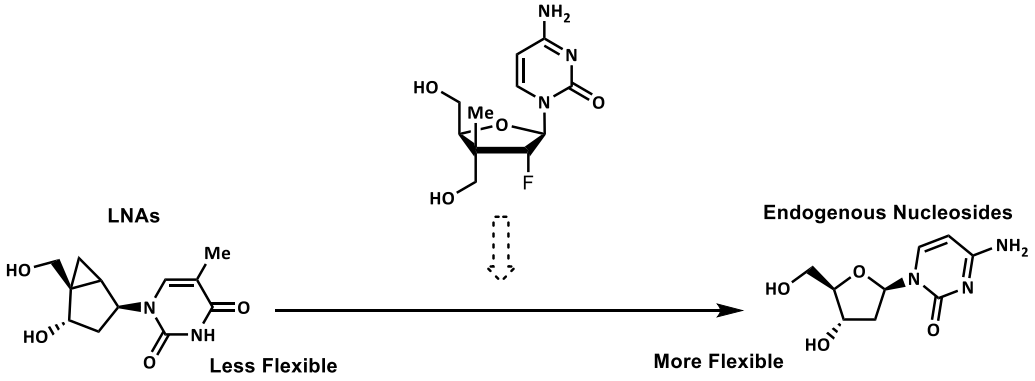
Nucleoside analogues interact with target proteins primarily in one conformation, it is therefore important to control the conformational bias of these molecules to optimize enzyme-substrate recognition.[3] For example, it has been demonstrated that human concentrative nucleoside transporters (hCNT) have strong preferences for north conformations, whereas human equilibrative nucleoside transporters (hENT) favor south conformations.[3] A dynamic equilibrium between north (C3-endo, RNA-like) and south (C2-endo, DNA-like) type-furanoses exists in solution (Figure 5.1).[3] The energy gap between these two conformers is ~4 kcal/mol, and can result in a difference between micromolar and nanomolar binding affinities.[4] We have postulated, that in our scaffolds bearing a quaternary center at C3', the south conformation should be favored due to minimization of steric constraints. The arabino- orientation of the C2`-F in **5-7** will also favor a south conformation.[5] Such a hypothesis is supported by X-ray analysis of D-1',2'-*cis* furanoside **5-7** which was prepared by Dr. Michel Prévost (Figure 5.1).

Figure 5.1 North and south furanose conformations and the postulated south-conformation of C3'-quaternary center analogues.



The sugar ring in these analogues, however, is still flexible and it is recognized that its conformation in solution can differ from that in the solid state. Replacement of the typical hydroxyl substituent by an all-carbon quaternary center may create a novel network of hydrogen bonds that can influence the preferred conformation in solution. Such a quaternary center allows for an intermediate conformational freedom between those of locked nucleoside analogues (LNAs)[6] that have a rigid conformation and endogenous nucleosides which are inherently flexible (Figure 5.2).

Figure 5.2 Conformational bias of novel C2'-F, C3'all-carbon quaternary center NAs.



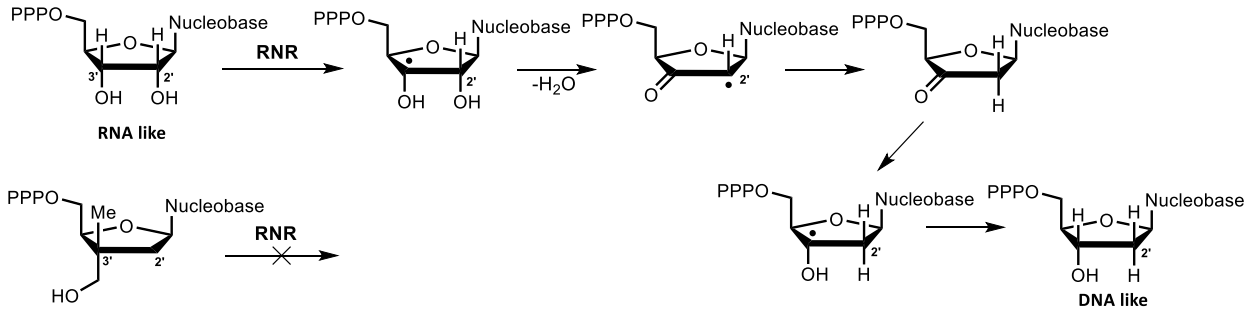
The potential conformational bias in our novel scaffolds may improve target recognition and affinity and provide a new class of antiviral or anticancer agents.

5.2.2 Interaction with RNR

RNR (ribonucleotide reductase) catalyzes the reduction of ribonucleotides to deoxyribonucleotides thus providing the deoxy- building blocks required for DNA synthesis.[7] This occurs through a radical transfer mechanism from the enzyme (cysteine and glutamate amino acids) to the substrate resulting in removal of the C2'-hydroxy moiety of RNA (Scheme 5.2).[8] Depletion of the pool of DNA monomers leads to cell death; hence RNR inhibition serves as a chemotherapeutic target. For example, gemcitabine diphosphate inhibits RNR causing

depletion of the dNTP (deoxy-nucleotide triphosphate pool), thus its triphosphate metabolite replaces dCTP during DNA synthesis. This prevents cellular growth and initiates apoptosis.[9] It has been reported that overexpression of RNR in pancreatic cells has been associated with gemcitabine chemoresistance.[9] We have hypothesized that this may be due to degradation by RNR.[7] Our novel nucleoside analogues could overcome this limitation where the first-step in the dehydroxylation pathway of RNR (C3'-hydrogen abstraction) will not be possible in our scaffolds bearing a quaternary center at C3'.

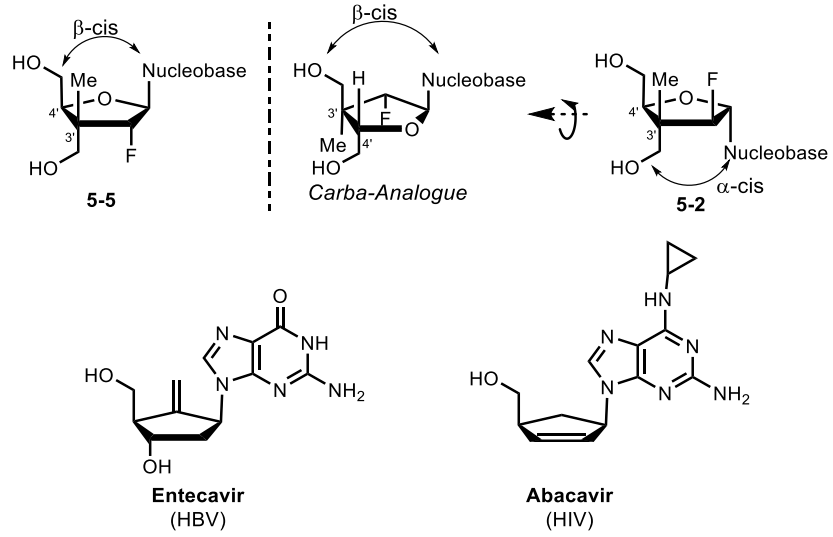
Scheme 5.2 Mechanism of RNR dehydroxylation.



5.2.3 Dual-face scaffolds

A hydroxymethyl group at C3' (Figure 5.3) may allow for a dual-face activity of these scaffolds. We hypothesized that the α-anomers, as in analogues such as **5-2**, could also be biologically relevant. The C3'-hydroxymethyl substituent in **5-2** has a *cis* relationship with the nucleobase at C1, which is similar to scaffolds such as **5-5** in which a *cis* relationship exists between the nucleobase in the ß-position and the C4 hydroxymethyl group.[1] This intriguing feature is best seen when the α-anomer is rotated, hence unveiling a carba-2-oxa analogue where the hydroxyl group at the quaternary center is now formerly at C4. Two examples of carba-analogues (Entecavir and Abacavir) approved by the FDA as antiviral agents are represented in Figure 5.3.

Figure 5.3 Dual-face scaffolds.



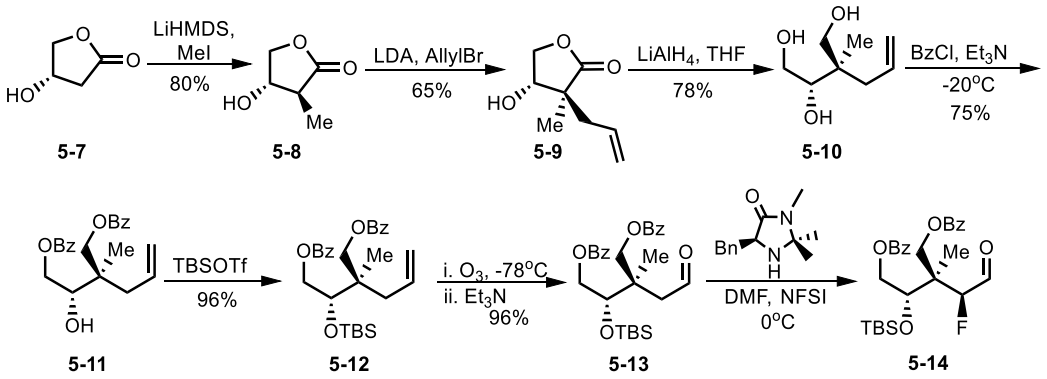
Nucleoside analogues combining this novel all-carbon quaternary center and a fluorine at C2' (second generation) may serve as new antiviral and anticancer agents. Their synthesis using the acyclic strategy was undertaken as part of my thesis.

5.3 Synthesis of novel nucleoside analogues

5.3.1 α-D-1',2'-*trans* furanosides (O4'-C1 cyclization)

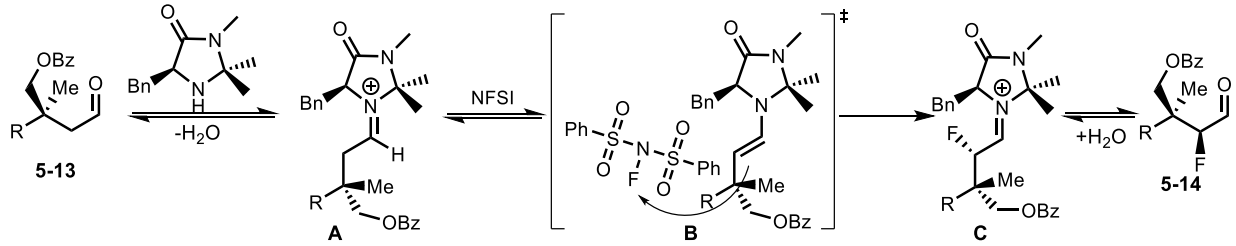
Formation of these novel scaffolds making use of our acyclic approach for nucleoside analogue synthesis started from commercially available (*S*)-β-hydroxy-γ-butyrolactone **5-7** (Scheme 5.3). Methylation followed by allylation provided lactone **5-9**, where the selectivity of the alkylations was controlled by the stereochemistry of the C3-hydroxyl group (Frater-Seebach alkylation). Reduction of this lactone using $LiAlH_4$ provided acyclic triol **5-10** in good yield (78%). After optimization of the reaction conditions, the two primary alcohols could be selectively benzoylated, providing **5-11**. TBS installation on the secondary C4-OH and ozonolysis of the terminal olefin provided aldehyde **5-13**.

Scheme 5.3 Synthesis of novel acyclic aldehydes.



One of the critical steps in this synthetic scheme was the selective introduction of the C2-fluorine. Contrary to fluorination of aldehydes bearing an alkoxy group in the C3-position (Chapter 4), fluorination of these substrates occurred smoothly. Selective introduction was accomplished using the free (*S*)-imidazolidinone catalyst[10,11] in DMF and NFSI at 0 °C. Formation of **5-14** occurred in a 17:1 ratio with its diastereomer. Diastereoselective fluorination of aldehyde **5-13** occurs through formation of iminium ion **A** (Scheme 5.4).

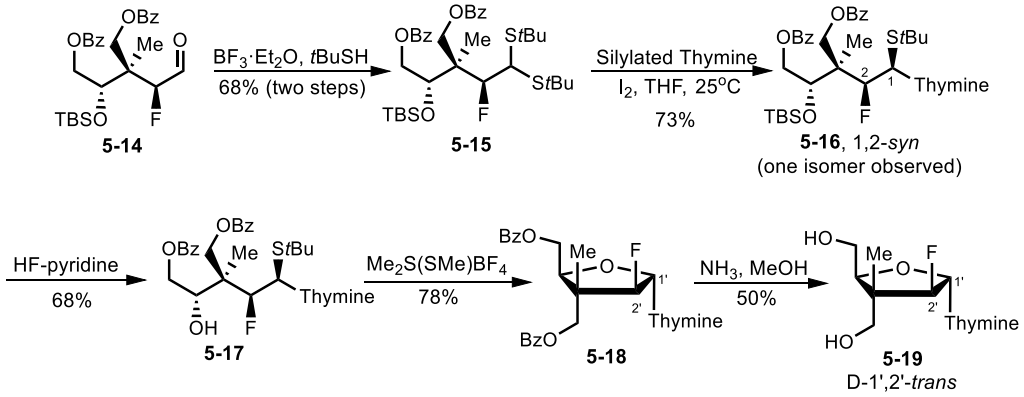
Scheme 5.4 Enantioselective fluorination.



Preference for this conformation results from minimization of steric interactions with the gem-dimethyl group of the imidazolidinone.[12-14] The imidazolidinone benzyl group shields one of the π–faces of the olefin thus allowing for enantioselective fluorination. In the case of the (*S*)-imidazolidinone catalyst (**B**, Scheme 5.4), the benzyl group blocks the re-face allowing for fluorination to occur from the si-face.

Reaction of crude C2-F aldehyde **5-14** with BF_3•OEt_2 and *t*BuSH at low temperatures (–40 ^oC) provided the TBS protected acyclic dithioacetal **5-15** in good yield (68% for two steps, Scheme 5.5). Coupling of **5-15** with silylated thymine using iodine as the thiophilic activating agent in THF at 25 ^oC resulted in formation of the 1,2-*syn* thioaminal **5-16**. Although the minor 1,2-*anti* diastereomer has not been identified, the ^1H NMR of the crude reaction mixture indicated formation of one isomer. TBS deprotection was carried out using HF-pyridine in THF at 25 ^oC and resulted in a good yield of **5-17** (68%). It should be noted that this desilylation required several days to reach completion, presumably due to steric hinderance from the neighboring quaternary center. With the acyclic thioaminal bearing a free hydroxyl at C4, an O4'-C1 cyclization could be performed. Activation of the –S*t*Bu functionality of **5-17** with $Me_2S(SMe)BF_4$ followed by intramolecular S_N2-displacement with the C4-OH provided the benzoyl protected D-1',2'-*trans* furanoside **5-18**. Debenzoylation using a saturated solution of NH_3/MeOH provided the novel analogue **5-19**.

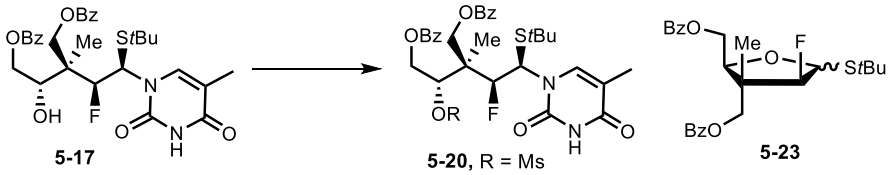
Scheme 5.5 Synthetic route to access α-D-1',2'-*trans* furanosides.



5.3.2 α-L-1',2'-*cis* thiofuranosides (S1'-C4 cyclization)

In order to determine if these novel acyclic thioaminals could undergo a S1'-C4 cyclization and thus provide novel thiofuranosides, installation of a leaving group on the secondary –OH was necessary. Reaction of **5-17** with MsCl resulted in the desired thioaminal **5-20** in 65 % yield (Table 5.1, entry 1).

Table 5.1 Installation of various C4-leaving groups.

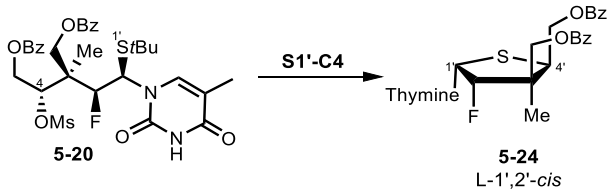


Entry	Conditions	Outcome
1	MsCl, Et_3N, 25 ^oC, 16h	65%
2	NsCl, DMAP, Et_3N, 50 ^oC, 16h	Undetermined Mixture
3	NsCl, DMAP, Et_3N, 25 ^oC, 66h	Undetermined Mixture
4	Tf_2O, 2,6-lutidine –40 ^oC (1h), 5 ^oC (2h)	Undetermined Compound and **5-23**

Attempts to synthesize C4-nosylate thioaminal **5-21** (entries 2 and 3) resulted in an undetermined mixture of compounds from which the desired compound (**5-21**) could be isolated in only trace amounts. Reaction of thioaminal **5-17** with triflic anhydride (entry 4) resulted in a mixture of an undetermined compound and thioglycoside **5-23** which was isolated and characterized by ^1H NMR and mass spectrometry (see experimental section). Although a single anomer of **5-23** was isolated, a NOESY experiment was not done to confirm the 1,2-stereochemistry. Such a species could form from O4'-C1 cyclization of **5-17** with loss of a triflate activated nucleobase. C4-mesylate thioaminal **5-20** was thus used to study the S1'-C4 cyclization (Table 5.2). The typical

cyclization and dealkylation conditions (refluxing in 2,6-lutidine) provided a 2:1 mixture of the starting thioaminal **5-20** and **5-24** (entry 1).

Table 5.2 Attempted S1'-C4 cyclization.



Entry	Conditions	Outcome
1	2,6-lutidine, 145 ^{o}C, 16h	2:1 (**5-20**:**5-24**)
2	2,6-lutidine, 145 ^{o}C, 9days	1:2 (**5-20**:**5-24**) (along with impurities)
3	Al(O*i*Pr)$_3$, DMSO, 140 ^{o}C, 3h	Undetermined Mixture

Despite being left for a longer reaction time (entry 2), starting material **5-20** still remained in the crude reaction mixture now in a 1:2 ratio with **5-24**. Other impurities were also present after this long reaction time. Mass spectrometry and ^{1}H NMR analysis of the crude mixture suggest the formation of the desired cyclized product **5-24**, but it was not possible to separate from the starting material and other impurities. Heating the reaction at 140 ^{o}C in DMSO using Al(O*i*Pr)$_3$ resulted in yet another undetermined mixture (entry 3).

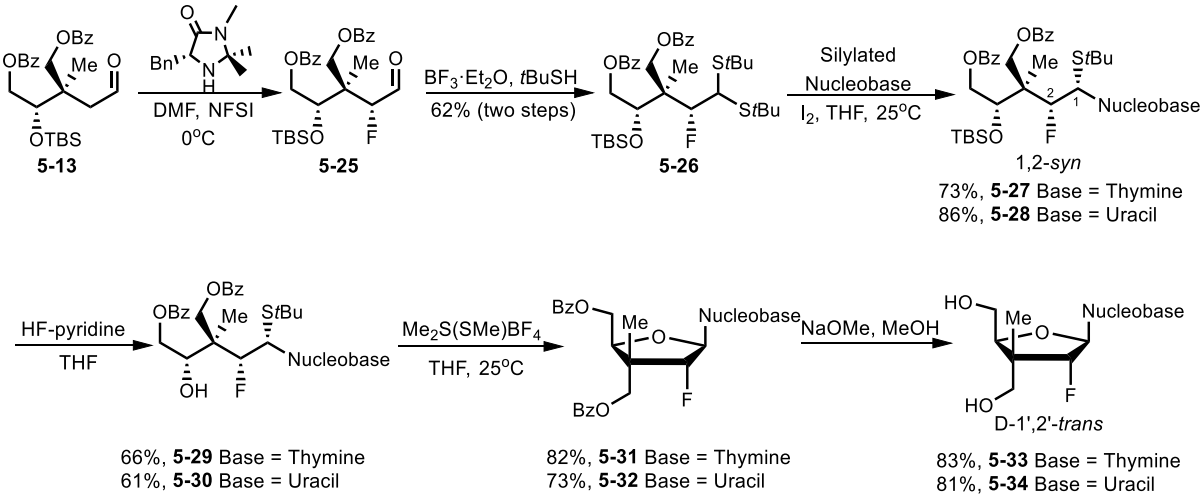
5.3.3 ß-D-1',2'-*trans* furanosides (O4'-C1 cyclization)

5.3.3.1 Thymine and Uracil

Selective fluorination of acyclic aldehyde **5-13** using the (*R*)-enantiomer of MacMillan's imidazolidinone catalyst[10,11] resulted in the corresponding C2-fluorinated aldehyde **5-25** also

with excellent diastereoselectivity (dr ~17:1) (Scheme 5.6). Conversion to the di-*t*-butyl dithioacetal provided **5-26** in good yield (62% two steps). Coupling with silylated thymine or silylated uracil resulted in the 1,2-*syn* thioaminals **5-27** and **5-28**. The minor thioaminal was not identified, but the ^{1}H NMR of the crude reaction mixture indicated the formation of only one isomer. Removal of the silyl protecting group followed by O4'-C1 cyclization provided analogues **5-31** and **5-32**. Benzoyl group deprotection occurred easily using NaOMe in MeOH to provide ß-D-1',2'-*trans* furanosides **5-33** and **5-34.**

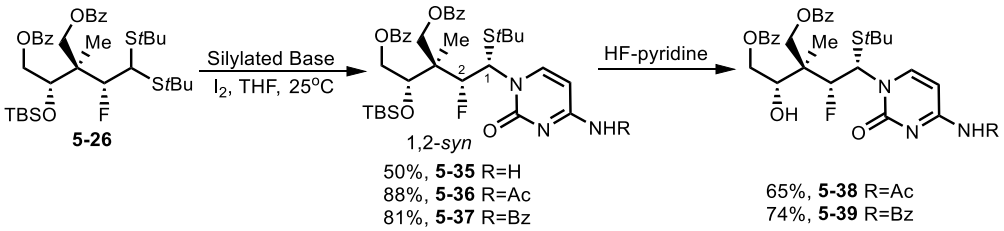
Scheme 5.6 Synthetic route to access ß-D-1',2'-*trans* furanosides.



5.3.3.2 Cytosine and its derivatives

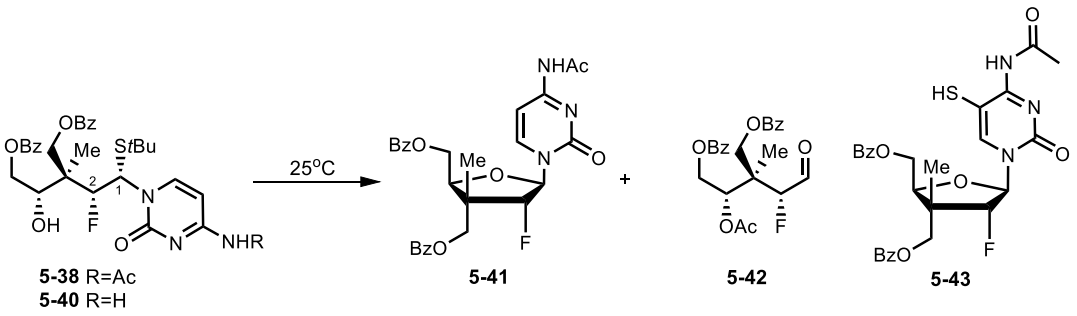
Coupling of dithioacetal **5-26** with silylated cytosine resulted in a 50% yield of 1,2-*syn* cytosine thioaminal **5-35** along with remaining starting material (Scheme 5.7) The yield of this coupling step was improved when silylated N^4-acetyl or N^4-benzoyl cytosine were used providing thioaminals **5-36** and **5-37** in good yield (88% and 81% respectively). Formation of deprotected thioaminals **5-38** and **5-39** resulted from TBS desilylation with HF-pyridine.

Scheme 5.7 Synthesis of cytosine thioaminals.



O4'-C1 cyclization of these thioaminals proved to be more challenging than with the corresponding thymine and uracil derivatives (Table 5.3).

Table 5.3 Cyclization of thioaminal **5-38**.



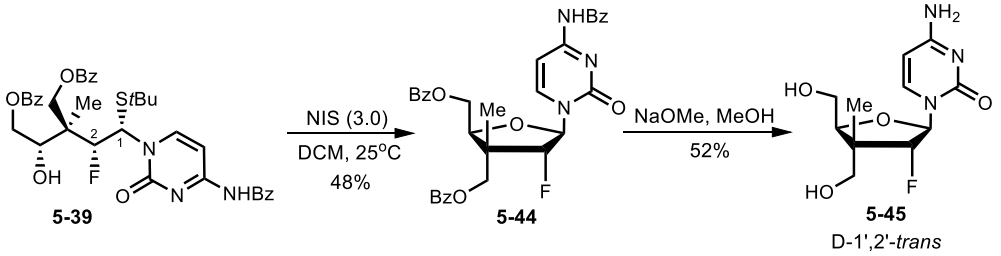
Entry	R	Conditions	Solvent	Outcome
1	Ac	$Me_2S(SMe)BF_4$ (2.0)	THF	**5-40**
2	H	$Me_2S(SMe)BF_4$ (2.0)	THF	Undetermined Mixture
3	Ac	$Me_2S(SMe)BF_4$ (2.0)	MeCN or DCM	**5-41** + Impurity
4	Ac	NIS (1.2)	DCM	**5-38**:**5-41** (1:1)
5	**Ac**	**NIS (3.0)**	**DCM (16 hr) or MeCN (4 hr)**	**5-41 (42%)**
6	Ac	NIS (3.0)	Toluene or DMF	**5-41** + **5-38** + Impurity
7	Ac	NIS (3.0), TMSOTf (0.1)*	DCM	**5-43**
8	Ac	I_2 (3.0) or $HgCl_2$ (3.0)	DCM	**5-38**
9	Ac	I_2 (3.0), AgOTf (2.0)	DCM	Undetermined mixture
10	Ac	$Hg(OAc)_2$(3.0)	DCM	**5-42**+ **5-38**

*Reaction done at –20 °C. **Optimal conditions in bold (entry 5).**

The conditions typically used for O4'-C1 cyclization ($Me_2S(SMe)BF_4$, THF, 25 ^oC, entry 1) resulted in N-deacetylation of starting material **5-38**, providing the free cytosine thioaminal **5-40**. When this thioaminal was subjected to the cyclization conditions (entry 2), an undetermined mixture of products was formed. Some of the desired cyclized product **5-41** was synthesized when cyclization of **5-38** was done in either MeCN or DCM (entry 3), but an inseparable impurity was also present. Thiophilic activation with 1.2 equivalents of NIS in DCM provided a 1:1 mixture of the desired analogue **5-41** and unreacted starting material **5-38** (entry 4). Increasing the equivalents of NIS to 3.0 and preforming the reaction in either DCM or MeCN (entry 5) resulted in the highest yield of furanoside **5-41** (42 %). Other solvents, such as toluene or DMF, in the presence of NIS (entry 6) resulted in an incomplete reaction along with an undetermined impurity. When NIS and TMSOTf were reacted with thioaminal **5-38** in DCM at –20 ^oC (entry 7), a compound that displayed ^1H NMR peaks characteristic of a cyclized compound was obtained. Analysis by MS was consistent with formation of **5-43**. This species could result from initial iodination[15] of the nucleobase followed by displacement and dealkylation of –S*t*Bu. I_2 or $HgCl_2$ did not promote the desired cyclization reaction and only unreacted starting material **5-38** was recovered (entry 8) whereas addition of AgOTf with I_2 provided an undetermined mixture of compounds (entry 9). Activation with $Hg(OAc)_2$ (entry 10) resulted in the formation of C4-acetyl protected aldehyde **5-42**, which was identified by ^1H NMR and mass spectrometry (see experimental section).

Cyclization of the N^4-Bz thioaminal **5-39** (Scheme 5.8) using the optimized cyclization conditions (NIS in DCM) provided the desired furanoside **5-44** in a similar yield (48%) as compared to the N^4-Ac thioaminal **5-38** (42 %). Deprotection of this ß-D-1',2'-*trans* furanoside generated the novel nucleoside analogue **5-45**.

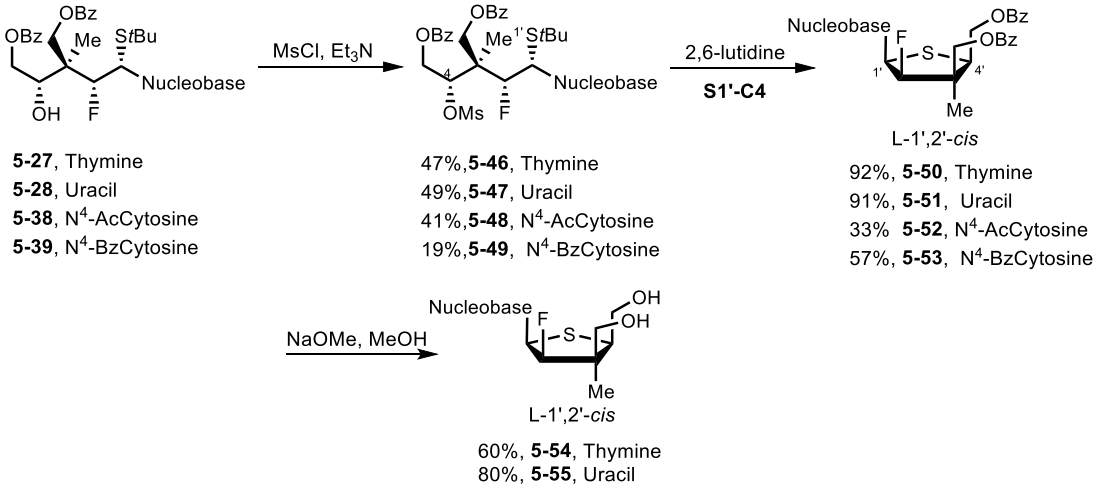
Scheme 5.8 Synthesis of ß-D-1',2'-*trans* furanoside bearing cytosine.



5.3.4 ß-L-1',2'-*cis* thiofuranosides (S1'-C4 cyclization)

A S1'-C4 cyclization of thioaminals **5-27**, **5-28**, **5-38** and **5-39** would provide access to novel ß-L-1',2'-*cis* thiofuranosides. Thus, a C4-mesylate leaving group was installed on these acyclic thioaminals bearing thymine, uracil, N^4-Ac cytosine, and N^4-Bz cytosine nucleobases (Scheme 5.9).

Scheme 5.9 S1'-C4 cyclization.



Although the C4-mesylate protected thioaminals **5-46** to **5-49** can be isolated in moderate yields, this secondary alcohol is difficult to manipulate presumably due to the sterically hindering quaternary center. Installation of the mesylate group requires a long reaction time (24 hours) and

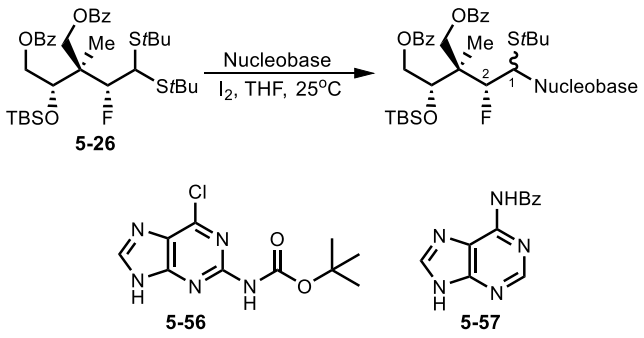
is often incomplete with the crude reaction mixture containing what appears to be dimesylated products. Nonetheless, these C4-Ms thioaminals were refluxed in 2,6-lutidine and provided ß-L-1',2'-*cis* thiofuranosides **5-50** to **5-53**. These S1'-C4 cyclizations proceeded smoothly to give high yields of the desired thiofuranosides **5-50** (thymine, 92%) and **5-51** (uracil, 91%). The low yield obtained for thiofuranoside **5-52** (N^4-Ac cytosine, 33%) may be due to N-deacetylation, the product of which was not isolated. In the case of **5-53**, (N^4-Bz cytosine, 57%) the crude reaction mixture did not contain any of the N-debenzoylated product but other minor impurities. Benzoyl group deprotection of **5-50** and **5-51** provided the thymine and uracil analogues **5-54** and **5-55** (Scheme 5.9). Deprotection of **5-52** and **5-53** has not yet been done.

5.3.5 Scaffolds bearing a purine nucleobase

5.3.5.1 Synthesis of D-1',2'-*trans* furanoside (O4'-C1 cyclization)

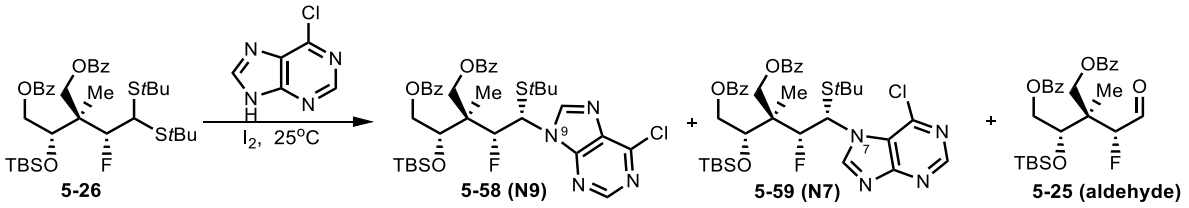
In this new series of nucleoside analogues bearing a C3'-quaternary center and a C2'-F atom it would be interesting to see if a purine nucleobase can add onto these acyclic precursors both regio- and diastereoselectively. The initial purine nucleobase considered was the 2-amino purine derivative **5-56** (Scheme 5.10) with the free amine protected with a Boc group.

Scheme 5.10 Coupling of purine nucleobases to dithioacetal **5-26**.



Coupling of **5-56** (either unsilylated or silylated) with dithioacetal **5-26** resulted in a mixture of products that were not identified but assumed to be the N9- and N7-regioisomers. Unsilylated 6-Bz adenine **5-57**, as well as the silylated derivative, were also coupled with the dithioacetal and resulted in 1 :1 ratio of two coupled products. As seen in Table 5.4, reaction of 6-Cl-purine with I_2 in THF at 25 ^oC resulted in a 4:1 mixture of the N9-regioisomer **5-58** along with the C2-fluorinated aldehyde **5-25** (entry 1). Coupling with this nucleobase was further optimized in an effort to enhance formation of the desired N9-regioisomer **5-58**. Addition of a non-nucleophilic base (entry 2), in order to quench any HI formed during the reaction, resulted in a mixture of aldehyde **5-25** and the N9-regioisomer along with a second coupled product. This product is assumed to be the N7-regioisomer **5-59**, although its characterization has not been done. Reaction of silylated 6-Cl-purine resulted in a 1:1 mixture of the N9-(**5-58**) and N7-(**5-59**) regioisomers (entry 3). Varying the length of the reaction (entries 4 and 5), addition of molecular sieves (entry 6) or decreasing the equivalents of I_2 (entry 7) still resulted in a mixture of regioisomers along with the aldehyde. Variation of the solvent was also investigated (entries 8-12) and in all cases these reactions showed no improvement as compared to THF (entry 1). Coupling in THF using the unsilylated nucleobase (entry 1) was thus the best reaction conditions to access the desired N9-regioisomer **5-58**. The C2-F aldehyde **5-25** could be separated from the desired product and recycled.

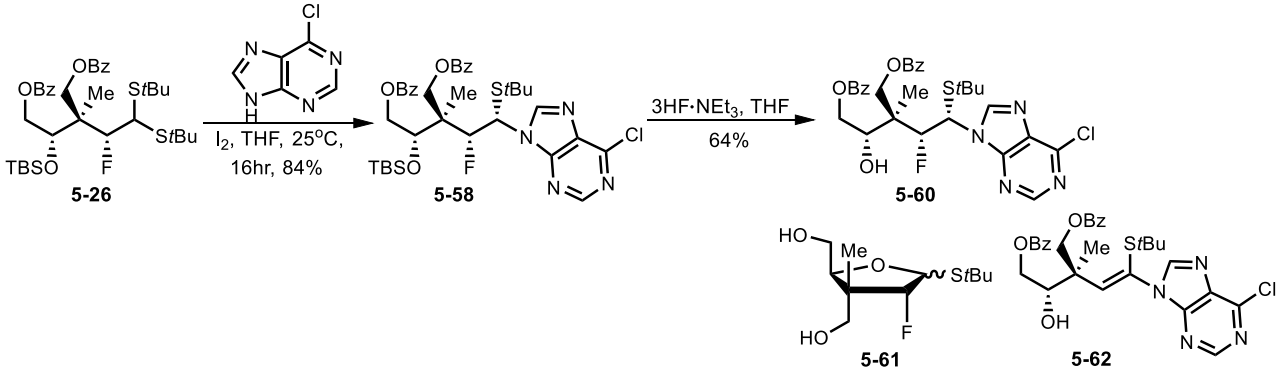
Table 5.4 Coupling of 6-Cl-purine to acyclic dithioacetal **5-26**.



Entry	Conditions	Solvent, Time	Outcome
1	6-Cl-purine (3.5), I_2 (2.0)	THF, 16 h	4:1 (N9:Aldehyde)
2	6-Cl-purine (3.5), I_2 (2.0), 2,6-di-*t*-butyl-4-methylpyridine (1.2)	THF, 16 h	3:1:1 (N9:N7:Aldehyde)
3	Silylated 6-Cl-purine (3.5), I_2 (2.0)	THF, 16 h	1:1 (N9:N7)
4	6-Cl-purine (3.5), I_2 (2.0)	THF, 69 h	2:1 (N9:Aldehyde)
5	6-Cl-purine (3.5), I_2 (2.0)	THF, 5 h	2:1:0.4 (N9:Aldehyde:N7)
6	6-Cl-purine (3.5), I_2 (2.0)	THF, 16 h + Molecular Sieves	5:1:1 (N9:Aldehyde:N7)
7	6-Cl-purine (3.5), I_2 (1.3)	THF, 16 h	2:1:1 (N9:Aldehyde:**5-26**)
8	6-Cl-purine (3.5), I_2 (2.0)	DCM, 16 h	Undetermined Mixture
9	6-Cl-purine (3.5), I_2 (2.0)	MeCN, 16 h	3:1 (N9:Aldehyde)
10	6-Cl-purine (3.5), I_2 (2.0)	Toluene, 16 h	Undetermined Mixture
11	6-Cl-purine (3.5), I_2 (2.0)	DMF, 16 h	4:1:2 (N9:Aldehyde:N7) +impurities
12	6-Cl-purine (3.5), I_2 (2.0)	*t*BuOH, 16 h	1:1:0.4 (N9:Aldehyde:N7)

When the coupling reaction was done on a larger scale (500 mg versus 50 mg) only trace amounts of the acyclic aldehyde was observed and the desired N9-1,2-*syn* thioaminal **5-58** was obtained in 84% yield (Scheme 5.11).

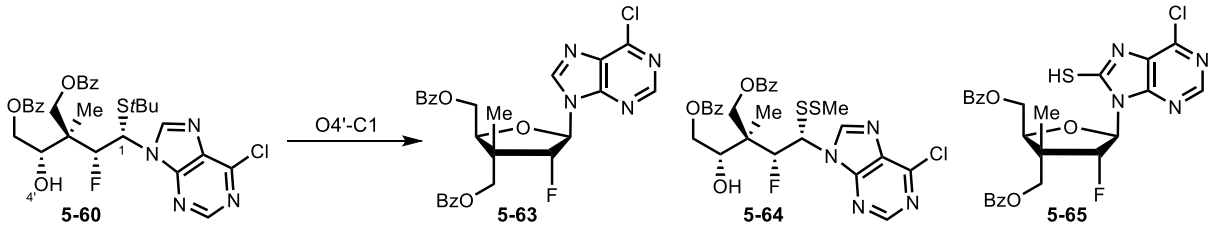
Scheme 5.11 Synthesis of N9-thioaminal **5-58**.



Optimization of the TBS deprotection was required to provide the desired thioaminal **5-60**. When a solution of HF-pyridine in THF was used, a cyclized product was obtained that may correspond to thioglycoside **5-61**. This species displayed similar ^{1}H NMR chemical shifts as **5-23**. Deprotection using TBAF resulted in elimination of the fluorine in C2 providing **5-62**, which was identified by ^{1}H, ^{13}C and mass spectrometry (see experimental section). Only one isomer was formed but the E/Z configuration was not confirmed by NOESY experiments although due to antiperiplanarity the Z-alkene is anticipated. The desired deprotected thioaminal **5-60**, however, was obtained in 64% yield using 3HF•NEt_3. The next step in the reaction sequence was the O4'-C1 cyclization to form the novel furanoside **5-63** (Table 5.5). Use of the thiophilic activating agent $Me_2S(SMe)BF_4$ in THF or MeCN (entry 1) resulted in acyclic thioaminal **5-64**. This acyclic thioaminal in which the -S*t*Bu group has been replaced with –SSMe was characterized by its ^{1}H NMR chemical shifts and was confirmed by mass spectrometry. Cyclization with N-iodosuccinimide in DCM (entry 2) or MeCN (entry 3) provided an unknown compound which could correspond to furanoside **5-65**. This structure correlates with the ^{1}H NMR and MS of the isolated product. Such a species could be formed through initial C8-

iodination of the purine ring (in the presence of NIS)[16,17] followed by nucleophilic displacement and dealkylation of –S*t*Bu.

Table 5.5 Attempted O4'-C1 cyclization of purine thioaminal **5-60**.



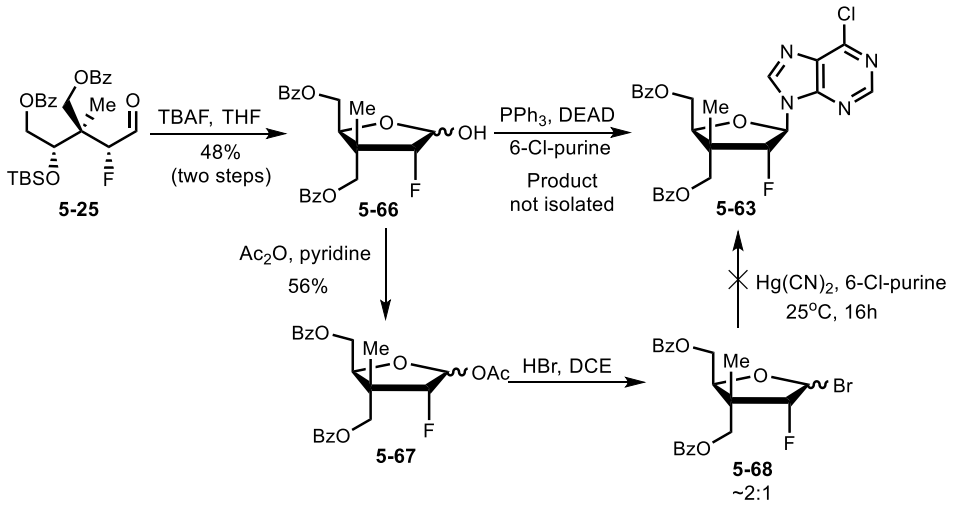
Entry	Conditions	Solvent	Outcome
1	$Me_2S(SMe)BF_4$ (2.0), 25 °C, 16h	THF or MeCN	**5-64**
2	NIS (3.0), 50 °C, 16h	DCM	**5-65**
3	NIS (3.0), 25 °C, 16h	MeCN	**5-65**
4	NIS (3.0), 25 °C, 16h	THF	**5-60**

Cyclization using NIS and THF (entry 4) resulted in the recovery of starting material **5-60**. These preliminary experiments, for the O4'-C1 cyclization with a purine thioaminal, need to be further examined. Problems with this mode of cyclization were also difficult with C2, C3-bis-alkoxy thioaminals bearing a purine nucleobase.[18] Formation of **5-65** could be verified through reaction of **5-63** in the presence of NIS and *t*BuSH. Therefore, alternate strategies were considered to access **5-63**.

5.3.5.2 Alternate routes to access D-1',2'-*trans* furanoside bearing a purine nucleobase

Alternative strategies involved condensation of 6-Cl-purine to activated cyclic furanosides (Scheme 5.12). Removal of the TBS protecting group of C2-fluorinated aldehyde **5-25** provided the requisite lactol **5-66** (Scheme 5.12).

Scheme 5.12 Addition of 6-Cl-purine to lactol **5-66**.

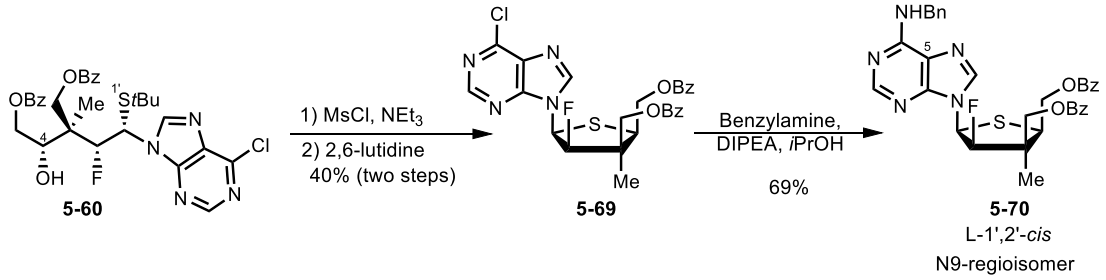


Activation of the anomeric hydroxyl group of **5-66** using PPh_3 and DEAD followed by displacement with 6-Cl-purine was attempted. The crude reaction mixture contained several products presumably the 1',2'-*cis* and 1',2'-*trans* isomers along with N9- and N7-regioisomers. The desired product **5-63** could not be isolated from this mixture. Synthesis of anomeric acetate **5-67** with subsequent conversion to bromide **5-68** was considered as an alternate strategy to access the desired nucleoside analogue **5-63**. Coupling of 6-Cl-purine with a 2:1 mixture of anomeric bromides **5-68** in the presence of $Hg(CN)_2$,[19] did not provide **5-63** but rather resulted in lactol **5-66**. Further optimization of these reaction conditions should allow for the generation of the desired furanoside.

5.3.5.3 S1'-C4 cyclization of purine thioaminals

Formation of the C4-mesylate thioaminal from **5-60** with subsequent S1'-C4 cyclization provided the L-1',2'-*cis* thiofuranoside **5-69** (Scheme 5.13). Displacement of the 6-chloro-substituent of the purine ring with benzylamine resulted in the formation of **5-70**. The ^{13}C NMR chemical shift of the C5 carbon (119.7 ppm) of the purine ring is in agreement with formation of the N9-regioisomer.[20,21]

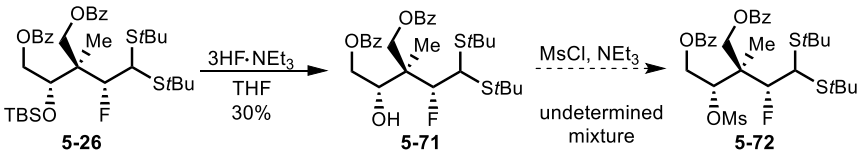
Scheme 5.13 S1'-C4 cyclization.



5.4 Synthesis of C4-mesylate aldehydes or dithioacetals

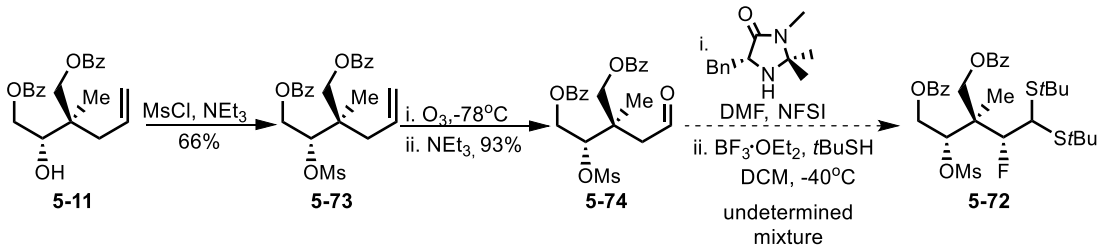
In order to develop a more efficient route for accessing thionucleosides, other approaches were considered to introduce the C4-leaving group at a different point in the synthesis. At the stage of the thioaminal, C4-leaving group incorporation is challenged by the presence of the quaternary center as well as by the nitrogens on the nucleobase. In a first attempt, installation of the mesylate onto dithioacetal **5-71**, hence before coupling with the nucleobase was tried (Scheme 5.14). Removal of the TBS from dithioacetal **5-26** using $3HF{\cdot}NEt_3$ resulted in **5-71** albeit in low yield (30%) due to the reaction not being complete. Mesylate installation did not occur smoothly and resulted in a mixture of products presumably with some S1`-C4 cyclization.

Scheme 5.14 Attempted formation of C4-mesylate dithioacetal.



This secondary C4-OH is hindered by the neighboring quaternary center thus making TBS deprotection difficult. Due to the inherent difficulty with its removal (reaction times of about 4 days), installation of a leaving group directly onto the unprotected olefin **5-11** was considered (Scheme 5.15).

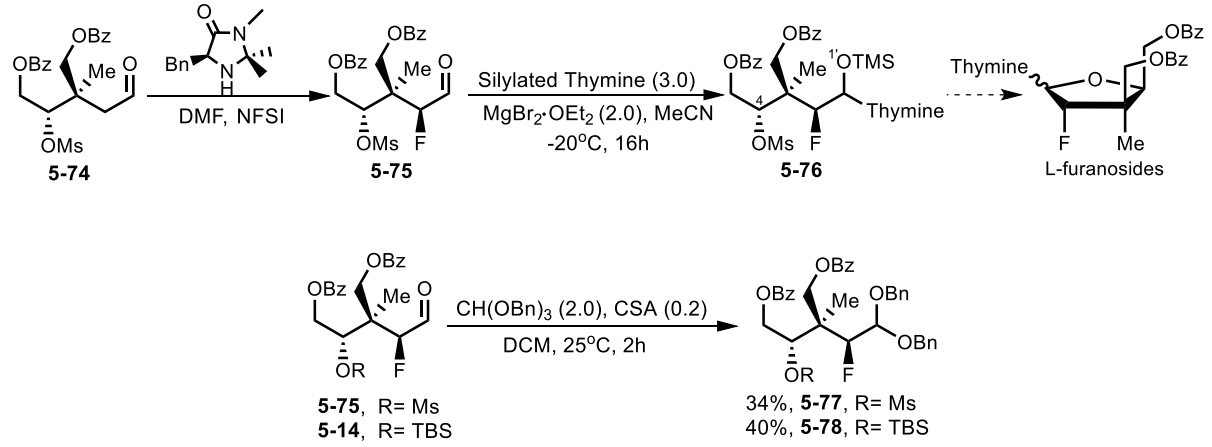
Scheme 5.15 Alternate route to access C4-mesylate dithioacetal **5-72**.



A C4-mesylate was installed onto olefin **5-11** resulting in **5-73**. It should be noted that efforts to introduce a nosylate leaving group on olefin **5-11** were unsuccessful. Ozonolysis provided aldehyde **5-74**, which was subjected to fluorination and dithioacetalization at low temperatures, but this treatment resulted in an undetermined mixture of products that may be due to S1'-C4 cyclization. The $BF_3{\cdot}OEt_2$ used for formation of the dithioacetal seems to be activating the mesylate leaving group and enhancing such a cyclization even at low reaction temperatures. It should be noted that the ^1H NMR of the C2-F aldehyde already contained some impurities possibly from cyclization at this stage as well. Although, formation of dithioacetal **5-72** may be possible using other conditions, at this point in time, it seems that mesylate group incorporation onto the thioaminal species remains the best method to generate thionucleoside analogues.

With the C4-Ms aldehyde **5-74** in hand, initial attempts were made to synthesize novel *N,OTMS*-acetals such as **5-76** that could cyclize to provide novel L-furanosides (Scheme 5.16). Reaction of crude silylated C2-fluorinated aldehyde **5-75** with silylated thymine at low temperatures in the presence of a Lewis acid was investigated. Although not all products were identified in the crude reaction mixture, the ^{1}H NMR of the major compound had characteristic peaks for *N,OTMS*-acetal species.

Scheme 5.16 Attempted synthesis of *N,OTMS*-acetals.

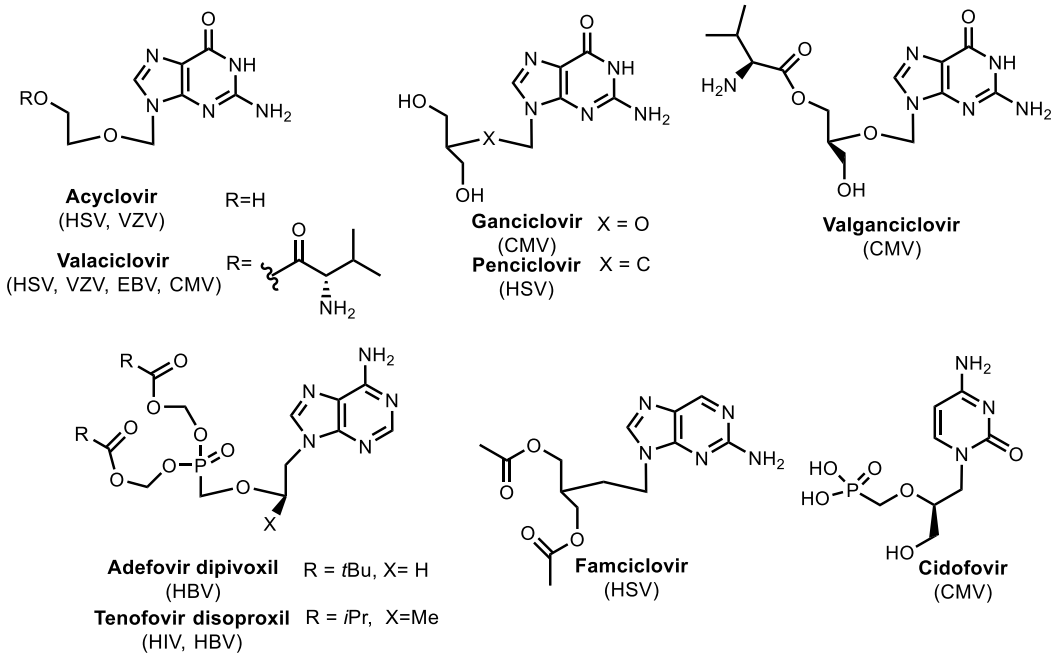


Coupling of silylated nucleobases with OBn-acetals was also considered to access novel L-furanosides. To this end, initial attempts were made to synthesize **5-77** and **5-78** from C2-fluorinated aldehydes **5-75** and **5-14**. The desired OBn-acetals were isolated in moderate yields (Scheme 5.16). Further development of this chemistry is needed to access such novel scaffolds.

5.5 Preparation of acyclic analogues

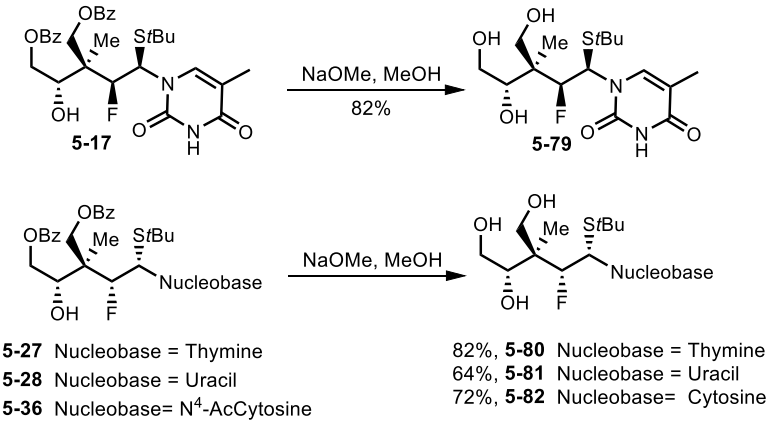
Acyclic nucleoside analogues can also be effective antimetabolites as exemplified by those approved by the FDA as antiviral agents (Figure 5.4).[22,23]

Figure 5.4 FDA approved acyclic antiviral agents.[22]



In this regard, the novel acyclic thioaminals that have been synthesized through diastereoselective nucleobase addition to dithioacetals may serve as potential antimetabolites. The C3 and C5 benzoyl groups of these substrates were removed to provide thioaminals **5-79** to **5-82**, which are being evaluated as potential antiviral agents.

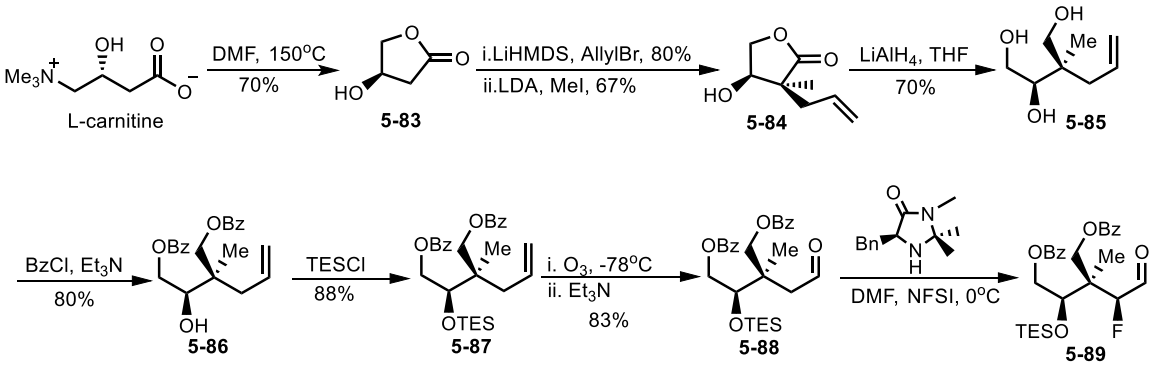
Scheme 5.17 Synthesis of acyclic nucleoside analogues.



5.6 ß-D-1',2'-*cis* thiofuranosides

Our acyclic approach for nucleoside synthesis provides a very effective route to generate thioanalogues. Access to novel ß-D-1',2'-*cis* thiofuranosides was possible starting from (*R*)-β-hydroxy-γ-butyrolactone **5-83** (Scheme 5.18). Formation of this lactone resulted from the known intramolecular nucleophilic displacement of the trimethylammonium ion of L-carnitine with heating in DMF.[24]

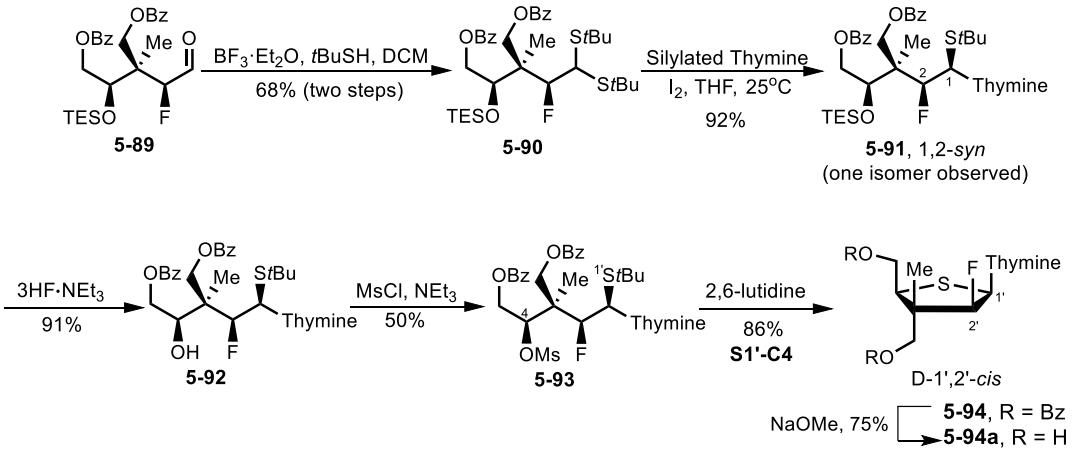
Scheme 5.18 Synthetic route to access ß-D-1',2'-*cis* thiofuranosides.



Allylation and subsequent methylation of lactone **5-83** generated the all-carbon quaternary center and led to lactone **5-84**. Reduction using $LiAlH_4$ provided acyclic triol **5-85**, which was selectively benzoylated at the two primary alcohol positions and silylated with a TES protecting group to obtain **5-87** in 88% yield. A C4-TES group was chosen since its removal proved to be much faster than the TBS group used in the previous scaffolds (16 hours versus 4 days). The terminal olefin **5-87** was then converted to the corresponding aldehyde **5-88** through ozonolysis at –78 °C. Selective introduction of the C2-fluoro group was accomplished using the (*S*)-imidazolidinone catalyst and NFSI to provide fluorinated aldehyde **5-89**. Once again the ^1H NMR spectroscopic analysis of the unpurified C2-F aldehyde indicated a 17:1 diastereomeric ratio for the fluorination. Conversion to acyclic dithioacetal **5-90** was done using boron

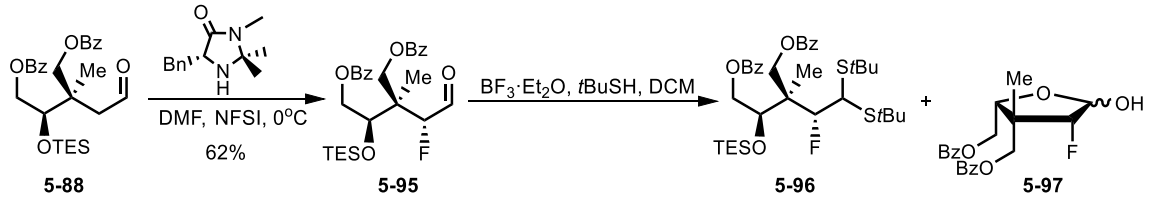
trifluoride diethyl etherate and *t*-butylthiol (Scheme 5.19). Coupling with silylated thymine in the presence of iodine at 25 °C resulted in the selective formation of the 1,2-*syn* thioaminal **5-91**. TES deprotection and mesylate installation followed by a S1'-C4 cyclization provided the novel D-1',2'-*cis* thiofuranoside **5-94**. After benzoyl group deprotection (**5-94a**) these thioanalogues will be evaluated for their antiviral and anticancer properties.

Scheme 5.19 Synthetic route to access ß-D-1',2'-*cis* thiofuranosides.



Fluorination of aldehyde **5-88** using the (*R*)-imidazolidinone catalyst provided the diastereomer **5-95**, which was purified and fully characterized (Scheme 5.20). Conversion to the corresponding dithioacetal however seemed to result in a mixture of **5-96** along with lactol **5-97** although these compounds have yet to be isolated and characterized.

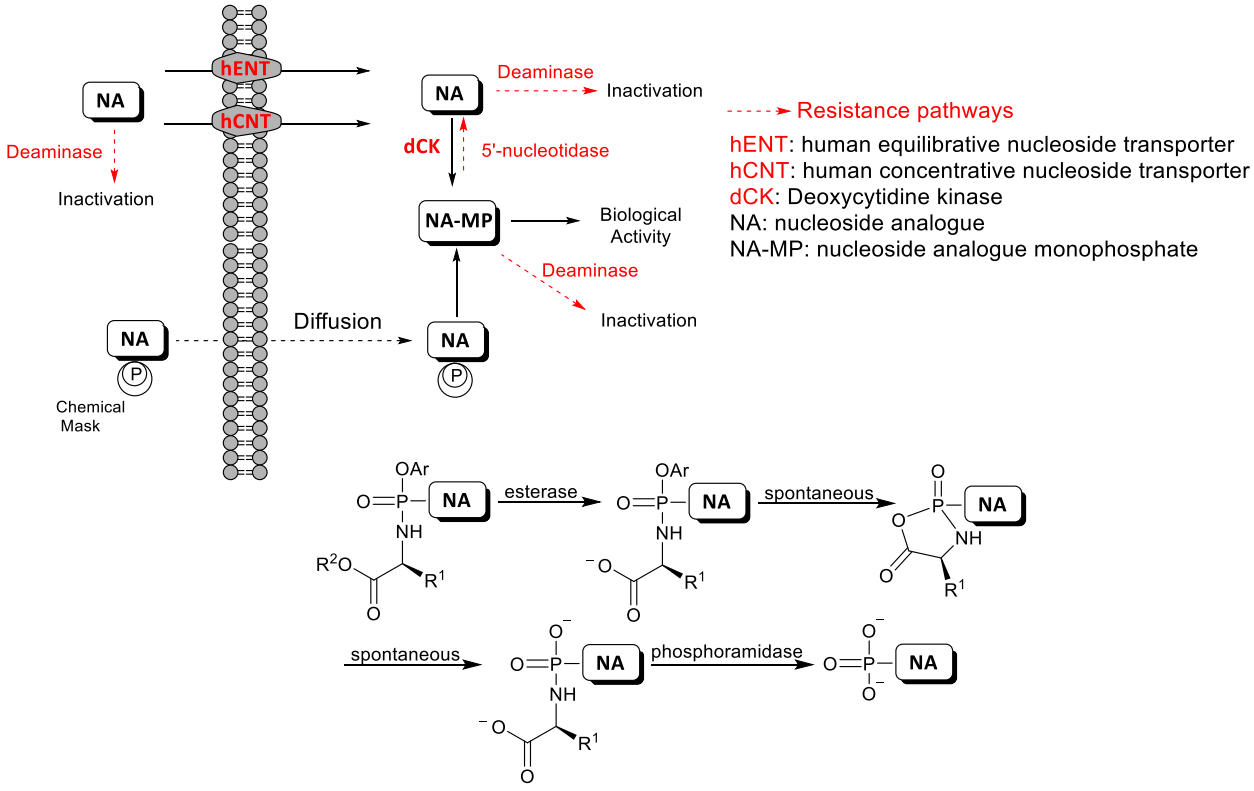
Scheme 5.20 Fluorination using (*R*)-imidazolidinone catalyst.



5.7 Pronucleotides and Conjugates

Nucleoside analogues face numerous resistance mechanisms that can limit their effectiveness. These include poor conversion of the drug into its active antimetabolite, degradation and limited uptake into the cell.[25] To overcome some of these limitations, the pronucleotide strategy (ProTide approach) has been developed in which a chemically masked phosphate moiety is added onto the nucleoside scaffold (Figure 5.5).[22,25] ProTides are specifically designed to overcome key resistance pathways and enhance antineoplastic effects.[25]

Figure 5.5 Pronucleotide strategy. Modified from reference 22 and 25.

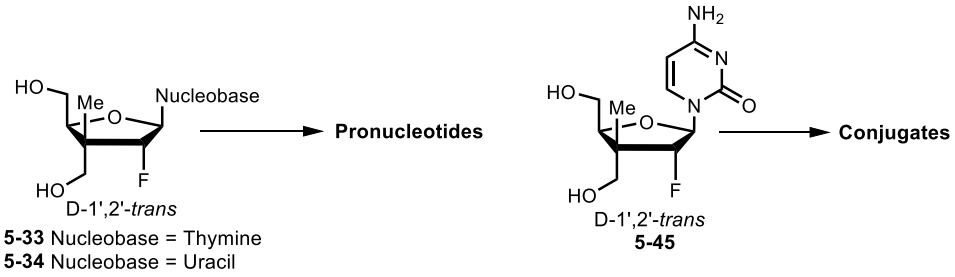


These chemical masks can increase the compound's hydrophobicity allowing for it to enter the cell through passive diffusion and thus overcoming the need of nucleoside transporters. Once inside the cell, this chemical mask is cleaved releasing the nucleoside monophosphate, bypassing

the initial and often rate-limiting step of monophosphorylation by DCK.[25] These chemical masks consist of two entities attached to the phosphate group and are classified as either phosphoesters (phosphorus-oxygen bond) or phosphoramidates (phosphorus-nitrogen bond). For example, Sofosbuvir (shown in Figure 1.3), a nucleoside analogue approved by the FDA in 2013 as an inhibitor of HCV replication, makes use of this pronucleotide strategy with a phosphoramidate moiety attached on the C5'-hydroxyl group.[26] It has been proposed that protide cleavage occurs through initial hydrolysis of the ProTide ester by an esterase enzyme followed by spontaneous cyclization (Fgiure 5.5).[25] Spontaneous hydrolysis and final cleavage of the P-N bond using a phosphoramidase enzyme generates the monophosphate. Pronucleotides are also insensitive to extra- and intracellular deamination,[22] thus protecting against cytosine deaminase (CDA) (cytidine to uridine conversion) and inactivation of the nucleoside. Nucleoside analogues can also be modified through addition of lipophilic moieties onto either the C5'-hydroxyl group of the sugar backbone or the N4-nitrogen of the cytosine nucleobase.[22] An example of this is Sapacitabine (shown in Figure 1.3) that is currently in Phase III development for cancer. Such species are referred to as conjugates and increase the lipophilicity of nucleosides. This overcomes some of the potential resistance pathways such as transport into the cell as well as degradation by cytidine deaminase.[22]

Applying such strategies to our novel scaffolds, pronucleotide and conjugate analogues have been synthesized (Scheme 5.21). A phosphate chemical mask was attached to **5-33** and **5-34** bearing thymine and uracil nucleobases. A lipid conjugate was also added onto furanoside **5-45**. At this time, their structures can not be elaborated upon further due to patent filing. These novel nucleoside analogue scaffolds are being evaluated as potential anticancer and antiviral agents.

Scheme 5.21 Formation of pronucleotides and conjugates using our novel NAs.



5-33 Nucleobase = Thymine
5-34 Nucleobase = Uracil

5.8 Bioisosteres

5.8.1 Kinase Inhibitors and Docking Experiments

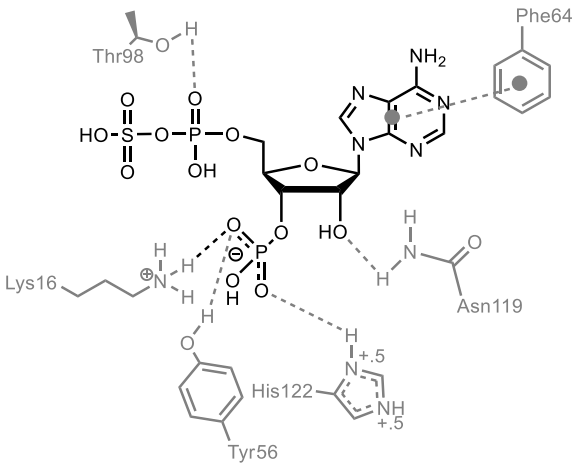
5.8.1.1 Nucleoside-diphosphate kinases

Docking of such scaffolds containing either a phosphate group or phosphate bioisotere at C5` or C3` has been done to evaluate potential targets for our novel nucleoside analogues. These initial docking studies were done using the Forecaster program developed by Professor Nicolas Moitessier at McGill University.[27]

Using ATP as the phosphate donor, nucleoside-diphosphate kinases (NDPKs) catalyze the phosphorylation of nucleotide diphosphates into triphosphates. The expression of NDPKs is strongly increased in proliferating neoplastic cells thus inhibition of these kinases may serve as a therapeutic target.[28] As part of the catalytic process, NDP kinase is phosphorylated on the histidine (His^{122}) residue. It has been demonstrated that PAPS (adenosine 3'-phosphate 5'-phosphosulfate) as well as PAP are inhibitors of these kinases.[28] PAPS is the major sulfate donor in living cells and PAP the reaction product. PAP is produced by transfer of the sulfate group of PAPS to acceptor molecules using sulfotransferases and is recycled into AMP using PAP-phosphatases. It has been demonstrated that it is the 3'-phosphate of PAPS or PAP that is located near the catalytic histidine residue (at the same position as the γ-phosphate of ATP).[28] The X-ray structure of the kinase revealed nucleotides bound at three independent sites with PAPS

occupying subunit A and PAP occupying subunits B and C. Polar interactions between the 3'-phospate and the δ nitrogen of His[122], the amino group of Lys[16] and hydroxyl of Tyr[56] have been identified (Figure 5.6).[28]

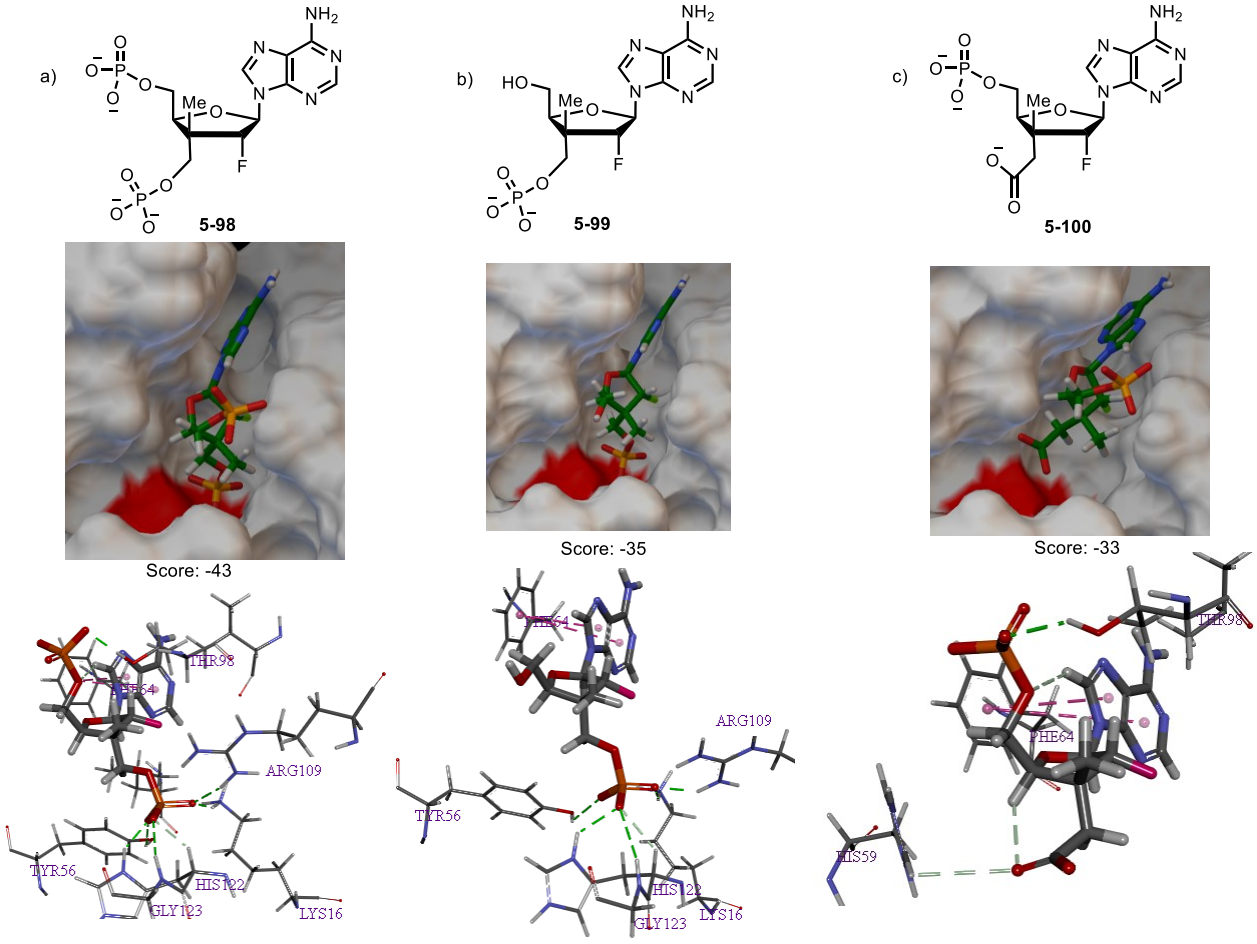
Figure 5.6 Interaction of PAPS in NDPKs (PDB ID: 1BUX).[28]



We thus speculated that a phosphate group or a carboxylic acid bioisostere located on the C3'-quaternary center of our analogues may also function as NDK inhibitors. Initial docking experiments (Figure 5.7) demonstrated that our analogues do occupy the same catalytic site as the PAP inhibitors. The three H-bonding interactions seen between His[122], Tyr[56] and Lys[16] with the 3'-phosphate of PAPS (Figure 5.6) are also observed with the 3'-phosphate in both our diphosphate analogue **5-98** (Figure 5.7a) and monophosphate analogue **5-99** (Figure 5.7b) along with an additional H-bond with Gly[123] and Arg[109]. Interactions similar to the ones observed for PAPS (Figure 5.6) between the adenine nucleobase and Phe[64] along with the 5'-phosphate and Thr[98] are also observed. With a carboxylic acid at the C3'-quaternary center (**5-100**, Figure 5.7c) only a weak H-bond between His[59] is present along with the adenine-Phe[64] and 5'-phosphate-Thy[98] interactions. These three analogues (Figure 5.7) had score values (measure of binding

affinity) similar to that obtained when PAPS (Score = -42) was docked into NDP kinase using the Forecaster program. Therefore, it can be concluded that our novel analogues may serve as inhibitors of nucleoside-diphosphate kinases.

Figure 5.7 Docking of novel nucleoside analogues to NDP kinase (His[122] represented in red).

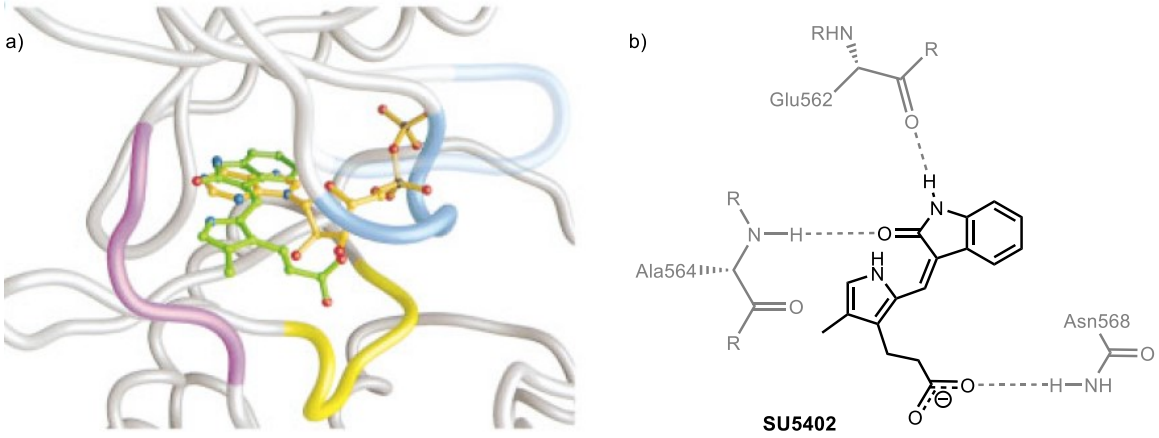


In a recent study, PAP has also been shown to be an inhibitor of PARP-1 [poly(ADP-ribose)polymerase 1].[29] This is a key enzyme in detecting DNA single-strand breaks and regulates the balance between DNA repair and cell death. Our novel analogues bearing a phosphate functionality at C3' or a bioisostere thereof may target PARP-1. Currently, there is only one PARP inhibitor (Olaparib) approved by the FDA for ovarian cancer.[30]

5.8.1.2 Protein tyrosine kinases

Carboxylic acid moieties have also been incorporated into protein tyrosine kinase inhibitors.[31] Cell signaling by tyrosine kinases plays a crucial role in disease pathogenesis and thus the design of inhibitors is used for the treatment of various cancers.[32-34] Binding of a growth factor to the extracellular domain of the kinase induces addition of the γ-phosphate of ATP to the hydroxyl group of the tyrosine residue in the cytoplasmic domain.[31] Oxindole containing molecules were found to inhibit the tyrosine kinase domain of fibroblast growth factor receptor 1 (FGFR1).[35] SU5402 competes with ATP for binding to the catalytic domain and its oxindole core occupies the site where the adenine of ATP binds (Figure 5.8).

Figure 5.8 a) Superposition of SU5402 and ATP bound to FGFR1 (γ-phosphate of ATP not shown due to disorder)[35] Reprinted with permission from AAAS. b) Interactions between SU5402 and FGFR1 (PDB ID: 1FGI)

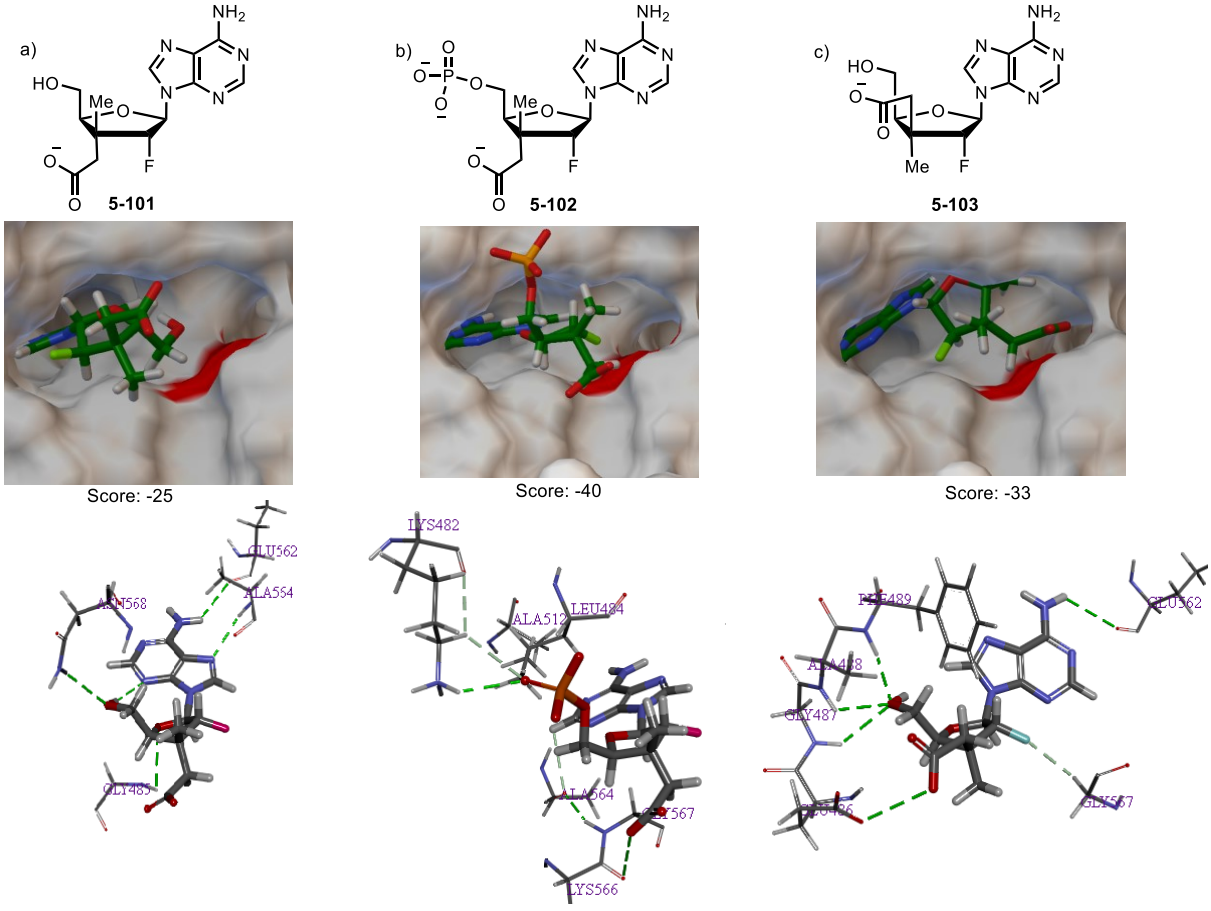


The moieties that extend from the oxindole interact with residues in the hinge region between the two lobes of the kinase where the carboxyethyl group of SU5402 hydrogen bonds to the side chain of asparagine (Asn^{568}). It was suggested that Asn^{568} is also likely to be involved in ATP binding due to a hydrogen-bond between the corresponding aspartic acid (Asp^{1083}) residue and

the O2' ribose hydroxyl group observed in the crystal structure of ATP bound to an insulin receptor tyrosine kinase.[36]

We have thus hypothesized that incorporation of a carboxylic acid functionality onto the quaternary center of our novel nucleoside scaffolds may serve as effective PTK inhibitors. Docking of our analogues into this PTK was investigated.

Figure 5.9 Docking of novel nucleoside analogues to FGFR1 (Asn^{568} represented in red, H-bonds are shown whether or not explicit H atoms are displayed).



Compound **5-101** bearing a fluorine in the C2`-position and a carboxylic acid on the C3'-quaternary center occupies the ATP binding site of FGFR1 (Figure 5.9a). Although the carboxylic acid functionality does not seem to interact with the Asn^{568} residue, the C5'-oxygen

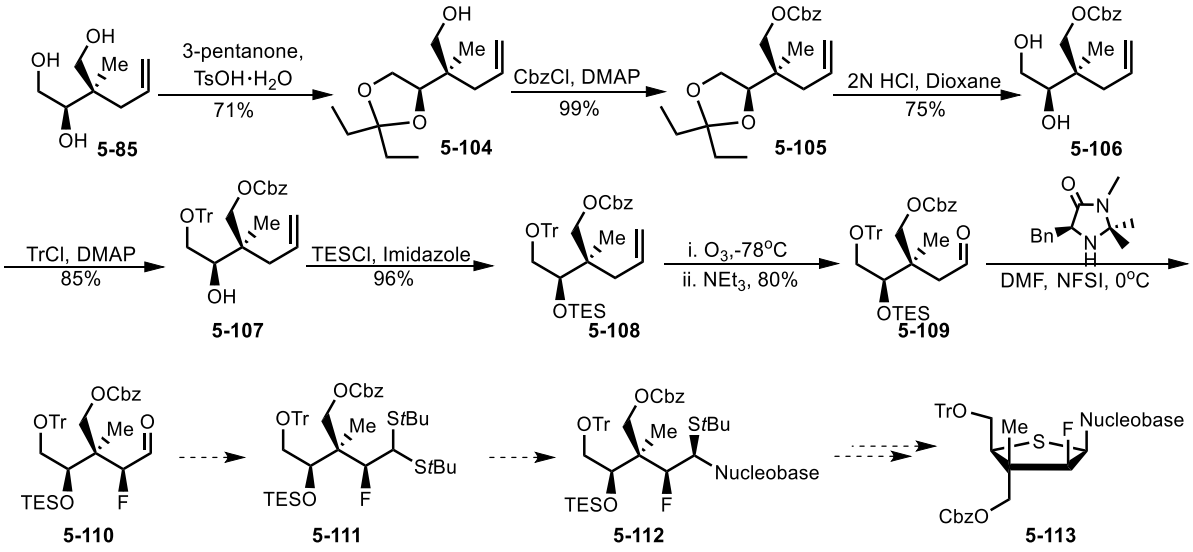
does. When a phosphate group is attached to the C5'-hydroxyl (**5-102**, Figure 5.9b) this H-bonding interaction is no longer present but the C3'-carboxylic acid interacts with Lys^{566} and Gly^{567}. With inversion of the C3'-quaternary center (**5-103**, Figure 5.9c) an H-bonding interaction between Glu^{486} and the C3'-carboxylic acid as well as Gly^{567} and the C2'-F group is observed. These three analogues (Figure 5.9) had score values similar to that obtained when SU5402 (Score = -41) was docked into FGFR1 using the Forecaster program.

It can be concluded that our novel scaffolds with a C3'-quaternary center do fit into the same pocket as the SU5402 inhibitor. Therefore, our analogues may compete with ATP for binding to the catalytic domain of FGFR. Currently, it has been demonstrated that FDA approved anticancer agents (ponatinib, regorafenib, and pazopanib) target fibroblast growth factor receptors however; their approval was not based on their activity against FGFR.[37] Therefore, these FGFR are a potential cancer target for which no drug is currently available.

5.8.2 Synthesis of novel analogues

In order to selectively functionalize the two primary alcohols in our novel scaffolds and thus selectively introduce a phosphate moiety, differentiation of the C3 and C5 hydroxyl moieties is necessary. Attempts to synthesize the protected thiofuranoside **5-113** were considered (Scheme 5.22). These protecting groups were chosen as they were useful for C3 and C5 hydroxyl group differentiation when similar furanoside scaffolds were synthesized from nucleobase condensation onto cyclic lactol species.[38] Hence, through protecting group manipulation a prodrug could be selectively installed at either the C3 or C5 positions.

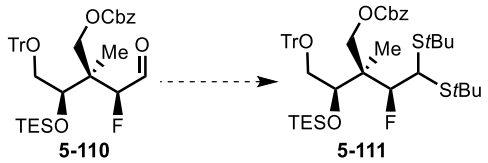
Scheme 5.22 Attempted synthesis of differentiated C3 and C5 alcohol moieties.



Protection of the 1,2-diol of **5-85** through formation of the diethyl ketal[39] **5-104** occurred smoothly. Installation of a primary carboxybenzyl (Cbz) followed by ketal protecting group removal under acidic conditions resulted in **5-106**. Subsequent protection of the primary hydroxyl group with trityl chloride and installation of a TES on the secondary –OH resulted in alkene **5-108**. Similar to the previously described syntheses of the acyclic thioaminals, ozonoylsis followed by selective introduction of the C2-F group provided acyclic aldehyde **5-110**. Although it was recognized that the primary trityl group may be sensitive to the typical conditions used for dithioacetal formation (BF_3•OEt_2, *t*BuSH), its conversion to dithioacetal **5-111** was studied (Table 5.6). Dithioacetalization of C2-fluroinated aldehyde **5-110** using the typical conditions of BF_3•OEt_2 and *t*BuSH at low reaction temperatures (-60 °C) provided an undetermined mixture of products (Table 5.6, entry 1). Upon purification of the mixture, species that seemingly still contained a trityl and TES group were isolated in trace amounts but their structure was not further elucidated. Reaction with $Hf(OTf)_4$ and *t*BuSH at room temperature (entry 2), conditions reported for synthesis of dithioacetals,[40] also resulted in an undetermined mixture. Performing the reaction at lower temperatures (entry 3) resulted in remaining starting

material **5-110** along with unknown compounds. Precedent uses of $LiClO_4$-Et_2O for the formation of dithioacetals in neutral reaction conditions have been reported.[41] When using these conditions only starting material **5-110** was recovered (entry 4).

Table 5.6 Attempted synthesis of dithioacetal **5-111**.

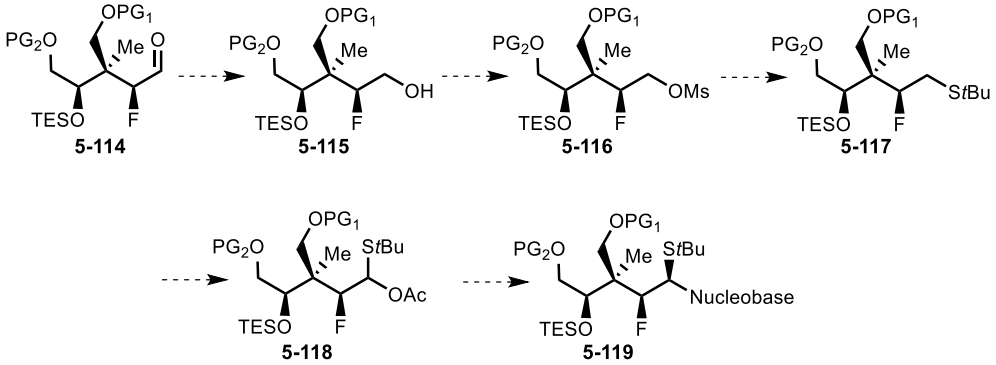


Entry	Conditions	Solvent	Outcome
1	BF_3•OEt_2 (1.4 eq), *t*BuSH (2.5 eq), –60 °C, 6 h	DCM	Undetermined mix
2	$Hf(OTf)_4$(0.001eq), *t*BuSH (3.0eq), 25 °C, 3 h	DCM	Undetermined mix
3	$Hf(OTf)_4$ (0.03eq), *t*BuSH(3.0eq), MS, –40 °C, 5 h	DCM	**5-110** & Undetermined mix
4	$LiClO_4$-Et_2O (4.0eq), *t*BuSH(4.0eq), 25 °C, 48 h	DCM	**5-110**

MS = molecular sieves

An alternative route can be envisioned to generate a thioaminal such as **5-119** bearing orthogonal protecting groups (PG_1 and PG_2) on the C3 and C5 hydroxyl moieties that alleviates the need for dithioacetal formation (Scheme 5.23).

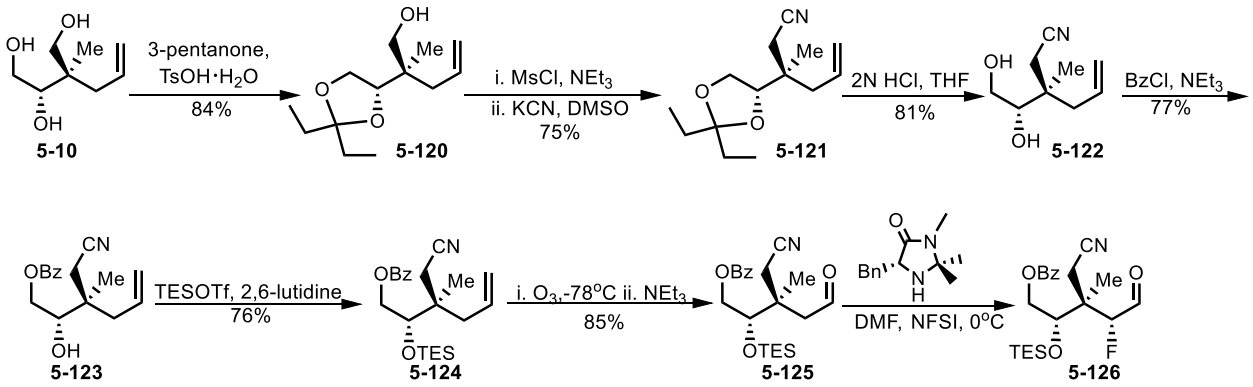
Scheme 5.23 Potential route to access acyclic thioaminals.



This would involve reduction of aldehyde **5-114** to alcohol **5-115** followed by displacement of a primary leaving group to generate **5-117**. A subsequent oxidation and Pummerer rearrangement would provide acetate **5-118** that could be used to generate the requisite thioaminal. Such a reaction scheme has yet to be explored.

The synthesis of analogues with a carboxylic acid moiety or biostere thereof[42] was envisioned through conversion of a nitrile functional group at the C3'-quaternary center. In this regard, the synthetic strategy shown in Scheme 5.24 was used.

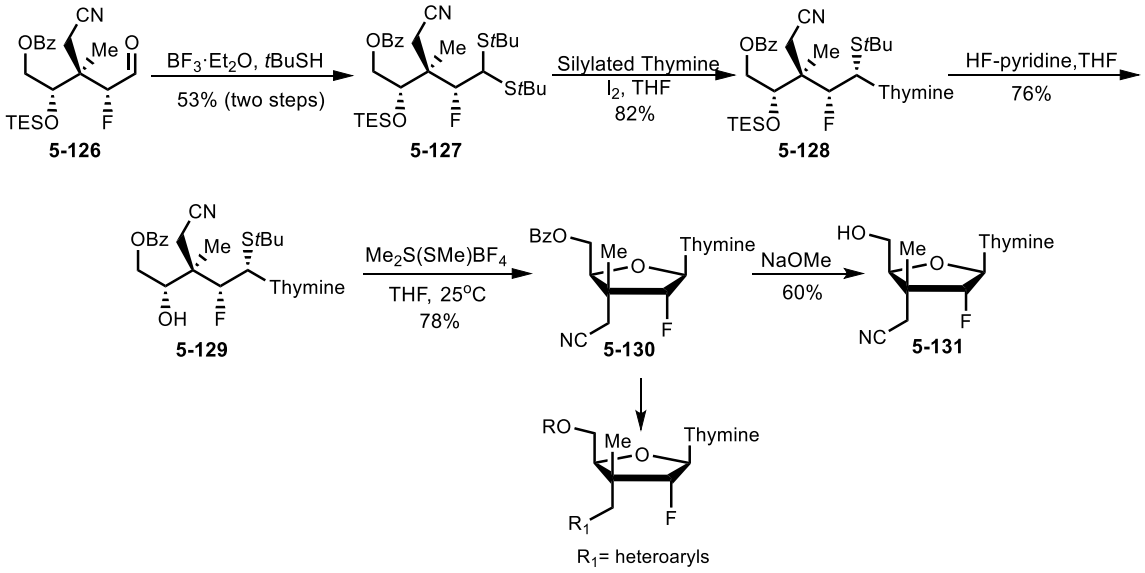
Scheme 5.24 Synthesis of analogues bearing a nitrile on the C3'-quaternary center.



Formation of the diethyl ketal **5-120** was followed by installation of a primary mesylate. Displacement with KCN provided **5-121** from which the ketal protecting group was removed. Primary hydroxyl group protection with a benzoate followed by installation of a secondary TES resulted in alkene **5-124**. Subsequent ozonolysis and selective introduction of the C2-F group provided aldehyde **5-126**. Dithioacetalization of **5-126** and coupling with silylated thymine resulted in the 1,2-*syn* thioaminal **5-128** (Scheme 5.25). O4'-C1 cyclization following removal of the TES protecting group provided 1',2'-*trans* furanoside **5-131**. This analogue has been used to introduce heteroaryl moieties that function as carboxylic acid biosteres onto the C3'-quaternary

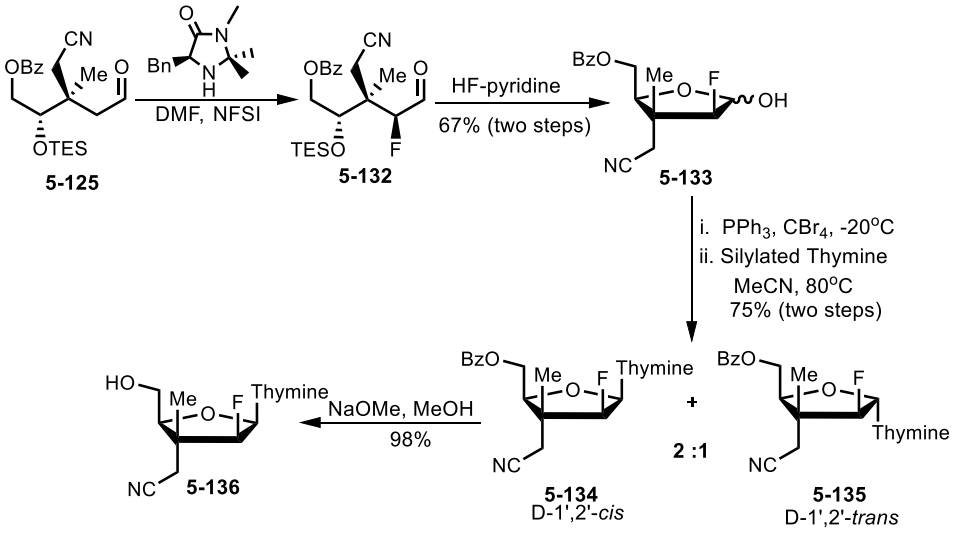
center. Such carboxylic acid biosteres improve membrane permeability by enhancing a compounds lipophilicity and reducing its polarity.[42]

Scheme 5.25 Synthesis of NA bearing a C3'-nitrile group.



Aldehyde **5-125** was also used for the synthesis of 1',2'-*cis* (**5-134**) and 1',2'-*trans* (**5-135**, potential carba-analogue) furanosides (Scheme 5.26).

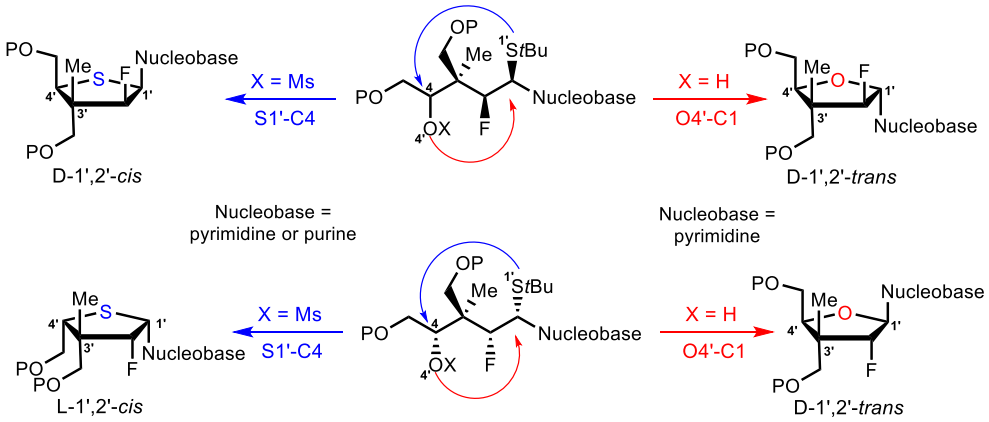
Scheme 5.26 Synthesis of 1',2'-*cis* and 1',2'-*trans* C2'-F analogues.



TES cleavage of C2-fluorinated aldehyde **5-132** using HF-pyridine resulted in lactol **5-133**. Formation of the anomeric bromide with subsequent displacement by silylated thymine provided the desired analogues **5-134** and **5-135**. Deprotection of the 1',2'-*cis* isomer provided **5-136**. Functional group conversion of these furanosides will provide access to potential novel antiviral and anticancer agents.

5.9 Conclusions

Novel nucleoside analogues bearing a quaternary center at C3' may provide a conformational bias and enhance enzyme-substrate specificity. It has been demonstrated that the acyclic approach for nucleoside synthesis developed in the Guindon lab is very effective in synthesizing such novel molecules. D-1',2'-*trans* furanosides along with D- or L-1',2'-*cis* thiofuranosides with a C2'-fluorine atom and a C3'-quaternary center can be formed by intramolecular cyclization of the corresponding 1,2-*syn* acyclic thioaminal precursors. These thioaminals are formed in a diastereoselective manner from nucleobase coupling onto acyclic C2-fluorinated dithioacetals. Fluorination of acyclic aldehydes bearing a C3-all-carbon quaternary center occurs with excellent diastereoselectivity using MacMillan's imidazolidinone catalysts. Pronucleotides and conjugates of these scaffolds are currently being analyzed as potential anticancer and antiviral agents. In summary, it can be concluded that the novel D-1`,2`-*trans* furanosides bearing pyrimidine nucleobases can be synthesized efficiently through an O4`-C1 cyclization of the thioaminal. D- or L-1`,2`-cis thiofuranosides bearing pyrimidine or purine nucleobases can be formed from an S1`-C4 cyclization through displacement of a C4-OMs. This mesylate is best installed after nucleobase coupling and C4-silyl group deprotection.



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Conclusions and Perspectives

A novel approach to nucleoside analogue synthesis from chiral acyclic thioaminals has been developed by our laboratory. Diastereoselective addition of nucleobases onto acyclic dithioacetals provides thioaminals in which the stereogenic center bears the nucleobase and a thioether moiety, which may serve as a leaving group or as a nucleophile. Taking advantage of the C1-stereochemistry of the thioaminal, two types of cyclizations involving S_N2-like nucleophilic displacements can occur. The first cyclization involves displacement of the activated thioalkyl group of the thioaminal by the secondary hydroxyl group at C4 (O4′-C1 cyclization) resulting in D-1',2'-*trans* furanosides. Alternatively, the sulfur of the thioaminal can serve as a nucleophile when the C4 hydroxyl is converted into a leaving group (S1′-C4 cyclization). This strategy gives access to L-1',2'-*cis* thioanalogues.

This acyclic approach addresses two key synthetic challenges in the synthesis of antiviral agents, namely, formation of L-nucleoside analogues along with a 1',2'-*cis* stereochemical arrangement between the nucleobase and the C2 substituent. A cyclization protocol was developed in which acyclic *N,OTMS*-acetals were accessed with high 1,2-*syn* diastereoselectivities by addition of silylated pyrimidine and adenine nucleobases onto aldehydes in the presence of a bidentate Lewis acid ($MgBr_2 \cdot OEt_2$). In the O1'-C4 cyclization reaction, the oxygen of the acetal serves as the nucleophile involved in the displacement of the leaving group at the C4 position, the mechanism of which was studied through ^1H NMR. This strategy provides stereoselective access to unnatural L-nucleosides with a variety of nucleobases starting from easily accessible pools of D-sugars while also resulting in the challenging synthesis of 1',2'-*cis* nucleosides.

The efficient formation of nucleoside analogues using this acyclic methodology relies on introduction of a pyrimidine or purine nucleobase in a stereocontrolled manner onto an acyclic precursor. It has been observed that nucleobases add to C2-alkoxydithioacetals with high 1,2-*syn* selectivity. An experimental and theoretical study has been done to rationalize the origin of this 1,2-*syn* diastereocontrol (anti-Felkin-Anh) when silylated nucleobases add to acyclic dithioacetals. It has been demonstrated that the substitution functions in a stepwise manner and can be classified as a S_N2-like reaction. The established C1–C2 gauche conformational preference allows for an optimal stabilization of the thiacarbenium by sigma donation from the C2–H and the C2–R bonds. The counter-ion provides significant additional stabilization by interacting with the electron deficient thiacarbenium ion. Nucleobase addition occurs on the least hindered side of the thiacarbenium ion-pair species to provide high diastereoselectivity in favor of the 1,2-*syn* thioaminal.

A modification that improves the biological properties of nucleoside analogues is the introduction of fluorine, a common tool used in drug discovery. Access to two of the scaffolds that are difficult to synthesize using standard paradigms, namely, 1',2'-*trans* furanosides and 1',2'-*cis* thiofuranosides bearing a fluorine in the C2'-position is possible using our acyclic approach. Nucleobase coupling onto acyclic dithioacetals bearing a C2-F maintains preference for 1,2-*syn* stereocontrol. Subsequent intramolecular cyclization of these fluorinated thioaminals provides 1',2'-*trans* furanosides and 1',2'-*cis*-thiofuranosides with thymine nucleobases. Such a strategy shows promising results in accessing scaffolds bearing a purine nucleobase which are being evaluated as potential SAM analogues. To render such a strategy efficient for the synthesis of C2'-fluorinated nucleosides, alternate approaches to access acyclic dithioacetals bearing a C2-

F and a C3-alkoxy group need to investigated. Using acyclic starting materials rather than starting from cyclic sugars would also improve our approach to nucleoside synthesis.

Despite the availability and use of nucleoside analogues as anticancer and antiviral drugs, development of newer agents with improved properties is needed to overcome issues of resistance. In this regard, a new series of NAs bearing a C3'-quaternary center and a C2'-F atom have been synthesized and are being investigated as potential antimetabolites. The acyclic methodology is well suited to access such scaffolds in which high enantioselective fluorination, high 1,2-*syn* diastereocontrol for thioaminal formation and efficient intramolecular S_N2-cyclization provides a series of novel nucleoside analogues. The conformation of such analogues remains to be elucidated and will shed light onto the bias imposed by the novel quaternary center. A limitation of this approach is seen with the O4'-C1 cyclization of the purine thioaminals and merits further investigation.

Contributions to Knowledge

1- **Dostie, S**.; Prévost, M.; Guindon, Y. *J. Org. Chem.* **2012**, *77*, 7176.

The strategy reported is addressing important synthetic challenges by providing stereoselective access to unnatural L-nucleosides and, as importantly, by allowing the formation of the sterically challenging 1',2'-cis nucleosides. These nucleosides represent a class of compounds from which many clinical drugs have been identified. In addition, the interest in nucleoside analogues in the L-series has grown exponentially because they display less toxicity than their D-counterparts in numerous clinical uses investigated (cancer, HBV, HIV). This work is of great interest to organic chemists and should furnish a useful tool to medicinal chemists for the development of new and improved biologically active nucleoside analogues.

2- Prévost, M.; **Dostie, S**.; Waltz, M. E.; Guindon, Y. *J. Org. Chem.* **2014**, *79*, 10504.

This work provides key insights on the reactivity of α-alkoxy thiacarbenium precursors and silylated nucleobase additions to haloethers. Chemists interested in reaction mechanisms will appreciate this first extensive study of an acyclic borderline S_N1-S_N2 mechanism by DFT calculations. Overall, this work sheds light onto the pathway followed by α-alkoxyacetal substitutions with silylated nucleobases. These insights could help further improve diastereoselective N-glycosylations to generate nucleoside analogues more efficiently.

3- Tambutet, G.; Becerril-Jimenez, F.; **Dostie, S**.; Simard, R.; Prevost, M.; Mochirian, P.; Guindon, Y. *Org. Lett.* **2014**, *16*, 5698.

This paper describes our first synthesis of novel nucleoside analogues having a quaternary center at C3' and the approach used for their synthesis. In this study, a dual-face nucleoside scaffold has been developed that allows both α- and β-anomers to have potential biological activity.

4- **Dostie, S**.; Prévost, M.; Guindon, Y. **2016**, Diastereoselective Synthesis of C2'-Fluorinated Nucleoside Analogues by an Acyclic Strategy, *Manuscript in Preparation*.

Our acyclic methodology provides reasonable to high selectivities for coupling of silylated nucleobases to 2,3-*anti* and 2,3-*syn* C2-fluorinated dithioacetals. This provides a new strategy to synthesize nucleoside analogues bearing an alkoxy group in the C3' position and F at C2' and allows for the synthesis of nucleoside analogues that are challenging to access using the current paradigms available. This approach has also allowed for the synthesis of a novel class of nucleoside analogues bearing a C2'-fluoro and a C3'-all carbon quaternary center that may serve as potential anticancer and antiviral agents.

EXPERIMENTAL SECTION

General Comments. All reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen or argon in flame-dried glassware using standard syringe techniques. All anhydrous solvents were dried with 4 Å molecular sieves prior to use. The 4 Å molecular sieves (1–2 mm beads) were activated by heating at 180 ^{o}C for 48 hours under vacuum prior to adding to new bottles of solvent purged with argon. Commercially available reagents were used as received. Ambersep 900 OH basic resin obtained from commercial sources was rinsed thoroughly with methanol and acetone, kept under vacuum for 16 h and stored at 25 °C. Flash chromatography was performed on Merck silica gel 60 (0.040 – 0.063 mm) using forced flow (flash chromatography) of the indicated solvent system or Biotage Isolera One. Analytical thin-layer chromatography (TLC) was carried out on pre-coated (0.25 mm) Merck F-254 silica gel aluminum plates. Visualization was performed with U.V. short wavelength and/or revealed with ammonium molybdate or potassium permanganate solutions. ^{1}H NMR spectra were recorded at room temperature on Varian VXR 400 and 500 MHz NMR spectrometers as indicated. The data are reported as follows: chemical shift in ppm referenced to residual solvent (CDCl3 δ 7.26 ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, td = triplet of doublets, m = multiplet, app = apparent), coupling constants (Hz), and integration.^{13}C NMR spectra were recorded at room temperature using 100.6 MHz or 125 MHz as indicated. The data are reported as follows: chemical shift in ppm referenced to residual solvent ($CDCl_3$ δ 77.16 ppm). Infrared spectra were recorded on a FTIR spectrophotometer on a NaCl support and signals are reported in cm^{-1}. Mass spectra were recorded either through electrospray ionization (ESI) or electron impact on an instrument operating at 70 eV and FAB mass spectra were recorded with or without ionization. An Orbitrap

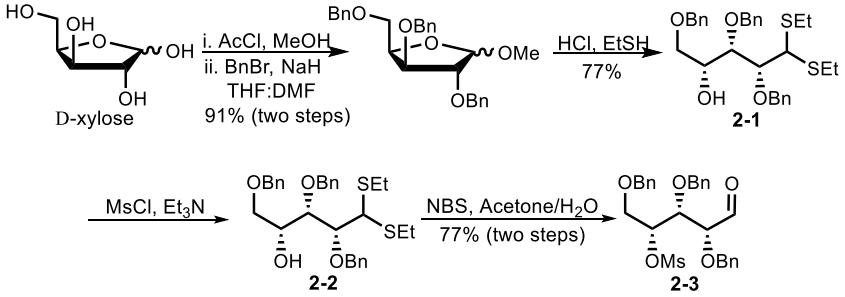
mass analyzer was used for HRMS measurements. Optical rotations were measured at room temperature from the sodium D line (589 nm) using $CDCl_3$ as solvent unless otherwise noted and calculated using the formula: $[\alpha]_D = (100)\alpha_{obs}/(\ell \cdot (c))$, where c = (g of substrate/100 mL of solvent) and ℓ = 1 dm.

Preparation of silylated nucleobases[1]

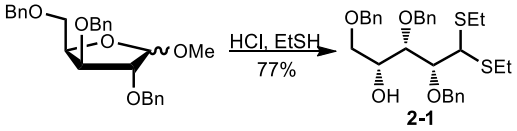
To a suspension of the nucleobase in HMDS (2.7 eq.) under inert atmosphere was added $(NH_4)_2SO_4$ (0.1 eq.). The reaction mixture was refluxed at 180 ^oC until a clear solution was obtained (typically three hours for pyrimidine nucleobases and 16 hours for purines). Upon cooling to 25 ^oC, the solution was placed under high vacuum for ~1 hour to remove excess HMDS. A solution of the silylated nucleobase was made in DCM (0.60 - 0.90 M) and transferred to an Aldrich bottle.

Chapter 2

Preparation of aldehyde 2-3 starting from D-xylose

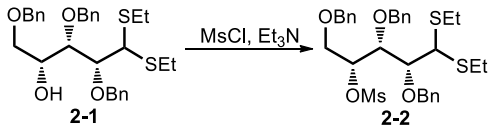


(–)-(2*R*,3*S*,4*R*)-1,3,4-tris(Benzyloxy)-5,5-bis(ethylthio)pentan-2-ol (2-1)



To a solution of methyl D-*xylo*-furanoside[2] (9.85 g, 23 mmol) in EtSH (9.8 ml, 131.5 mmol, 5.8 eq.) was added concentrated HCl (13.6 ml, 7.5 eq.). The reaction mixture was maintained for 16 hours at 25 °C and diluted with distilled water (50 ml). The aqueous layer was extracted with ether (3 × 50 ml) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 ml), brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 80:20) provided **2-1** (9.15 g, 77%) as a yellow solid: $\mathbf{R_f}$ = 0.2 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ –11 (*c* 1.0, CH_2Cl_2) ; P_{fus}: 55–57 °C; **Formula** : $C_{30}H_{38}O_4S_2$; **MW** : 526.7503 g/mol ; **IR** (neat) ν_{max} 3450, 2925, 1452 cm^{-1} ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 15H), 4.91 (d, *J* = 11.1 Hz, 1H), 4.81 (d, *J* = 2.1 Hz, 1H), 4.78 (d, *J* = 2.1 Hz, 1H), 4.56 – 4.43 (m, 3H), 4.12 (dd, *J* = 7.4, 3.0 Hz, 1H), 4.03 (d, *J* = 3.0 Hz, 1H), 3.99 – 3.94 (m, 2H), 3.54 (dd, *J* = 9.5, 6.7 Hz, 1H), 3.43 (dd, *J* = 9.5, 5.5 Hz, 1H), 2.81 – 2.61 (m, 4H), 2.50 (s, 1H), 1.26 (t, *J* = 4.7 Hz, 3H), 1.23 (t, *J* = 4.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.4, 138.1, 137.8, 128.31, 128.30, 128.23, 128.16, 127.73, 127.69, 127.67, 127.63, 127.4, 83.2, 79.8, 75.3, 75.0, 73.2, 71.3, 69.8, 53.2, 25.9, 25.2, 14.5, 14.4 ppm ; **HRMS** calcd for $C_{30}H_{38}O_4NaS_2$ [M+Na^+] : 549.2104, found: 549.2105 (-0.8 ppm).

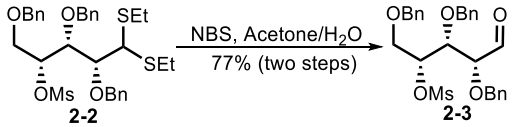
(–)-(2*R*,3*R*,4*R*)-1,3,4-tris(Benzyloxy)-5,5-bis(ethylthio)pentan-2-yl methanesulfonate (2-2)



To a 0.2 M solution of dithioacetal **2-1** (3.99 g, 7.57 mmol) in CH_2Cl_2 (38 ml) at –40 °C was added Et_3N (1.6 ml, 11.35 mmol, 1.5 eq.) and MsCl (0.77 ml, 9.84 mmol, 1.3 eq.). The reaction was maintained for 30 minutes at –40 °C and 2 hours at 0 °C. 1N HCl (5 ml) was then added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 ml) and the combined

organic layers were washed with saturated aqueous $NaHCO_3$ (50 ml), brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* **2-2** was obtained as a colorless oil and used as a crude mixture for the next reaction. Purification by flash chromatography (Hexanes/EtOAc, 80:20) of an aliquot of the reaction mixture allowed for characterization of **2-2** : $\mathbf{R_f}$ = 0.43 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ –9 (*c* 1.0, CH_2Cl_2) ; **Formula** : $C_{31}H_{40}O_6S_3$; **MW** : 604.8407 g/mol ; **IR** (neat) ν_{max} 3030, 2926, 1357, 1173 cm^{-1} ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 15H), 4.96 – 4.90 (m, 2H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.72 (d, *J* = 10.9 Hz, 1H), 4.63 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 4.23 (dd, *J* = 6.1, 4.4 Hz, 1H), 4.18 (d, *J* = 4.5 Hz, 1H), 4.00 (dd, *J* = 6.1, 4.5 Hz, 1H), 3.72 (dd, *J* = 11.2, 7.1 Hz, 1H), 3.57 (dd, *J* = 11.3, 3.1 Hz, 1H), 3.00 (s, 3H), 2.86 – 2.60 (m, 4H), 1.29 – 1.26 (m, 3H), 1.25 – 1.23 (m, 3H) ppm; **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 138.2, 137.8, 137.3, 128.53, 128.47, 128.43, 128.34, 128.0, 127.99, 127.93, 127.91, 127.7, 81.7, 81.4, 78.7, 75.4, 75.1, 73.3, 69.7, 52.7, 38.7, 25.5, 25.2, 14.6, 14.7 ppm ; **HRMS** calcd for $C_{31}H_{40}O_6NaS_3$ [M+Na^+] : 627.1879, found: 627.1902 (2.8 ppm).

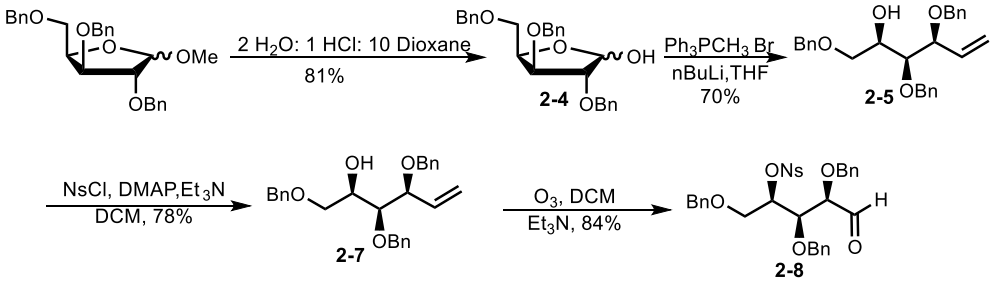
(–)-(2*R*,3*R*,4*R*)-1,3,4-tris(Benzyloxy)-5-oxopentan-2-yl methanesulfonate (2-3)



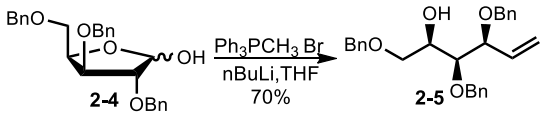
To a 0.1 M solution of **2-2** (4.58 g, 7.57 mmol) in a 3:1 mixture of acetone (90 ml) : H_2O (30 ml) at 0 ^oC was added 2,6-lutidine (7.0 ml, 60.5 mmol, 8.0 eq.) and NBS (11.0 g, 60.5 mmol, 8.0 eq.). After the reaction was maintained for 15 minutes at 0 ^oC, a 15% solution of $Na_2S_2O_3$ (100 ml) was added. The aqueous layer was extracted with ether (3 × 100 ml) and the combined organic layers were washed with 1N HCl (50 ml), saturated aqueous $NaHCO_3$ (50 ml), brine (50 ml),

dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 80:20) provided aldehyde **2-3** (2.89 g, 77%) as a yellowish oil : $\mathbf{R_f}$ = 0.13 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ –26 (*c* 1.0, CH_2Cl_2) ; **Formula** : $C_{27}H_{30}O_7S$; **MW** : 498.5879 g/mol ; **IR** (neat) ν_{max} 3031, 1732, 1357, 1175 cm^{-1} ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.62 (d, *J* = 0.8 Hz, 1H), 7.39 – 7.24 (m, 15H), 4.95 – 4.89 (m, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 4.19 (dd, *J* = 6.0, 3.9 Hz, 1H), 3.91 (dd, *J* = 3.9, 0.8 Hz, 1H), 3.75 (dd, *J* = 11.1, 3.7 Hz, 1H), 3.56 (dd, *J* = 11.1, 5.7 Hz, 1H), 2.94 (s, 3H) ppm ; **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 201.8, 137.3, 136.8, 136.4, 128.7, 128.58, 128.57, 128.56, 128.45, 128.42, 128.3, 128.1, 128.0, 81.4, 80.3, 77.3, 74.7, 73.39, 73.37, 68.4, 38.2 ppm; **HRMS** calcd for $C_{27}H_{30}O_7NaS$ [M+Na^+] : 521.1604, found: 521.1589 (-2.1 ppm).

Preparation of aldehyde 2-8 starting from D-xylose



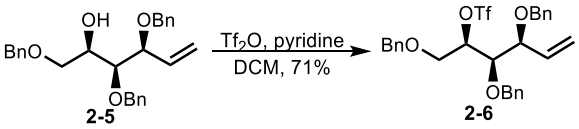
(2*R*,3*S*,4*S*)-1,3,4-tris(Benzyloxy)hex-5-en-2-ol (2-5)



The reported procedure for the formation of **2-5** was slightly modified.[3] *n*-Butyllithium (2.5 M in hexane, 2.86 ml, 7.15 mmol, 3.0 eq.) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (2.5 g, 7.15 mmol, 3.0 eq. previously dried with benzene)

in dry THF (0.55 M, 13 ml) at 0 °C. The resulting yellowish mixture was maintained for 2 hours at 25 °C. The reaction mixture was cooled to 0 °C before dropwise addition of 2,3,5-O-tribenzyl-D-*xylo*furanose[4,5] (1.0 g, 2.4 mmol) in dry THF (0.3 M, 8 ml). A cream-colored precipitate appeared and the reaction mixture was refluxed for 2 hours at 100 °C. After cooling to 25 °C, silica gel (1.5g) was added to the reaction mixture and the solvent was removed *in vacuo.* The resulting crude mixture was dissolved in ether (100 ml) and passed through a silica gel pad. The mixture was again concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **2-5** (0.70 g, 70%) as a yellow oil. ^{1}H NMR spectroscopic data correlate with the previously reported data for the enantiomer of **2-5**.[6] **Formula** : $C_{27}H_{30}O_4$; **MW** : 418.5247 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 15H), 5.87 (ddd, *J* = 17.9, 10.4, 7.8 Hz, 1H), 5.36 (d, *J* = 25.0 Hz, 1H), 5.36 (s, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.13 – 4.08 (m, 1H), 3.95 – 3.91 (m, 1H), 3.62 (dd, *J* = 6.5, 2.6 Hz, 1H), 3.45 (dd, *J* = 9.5, 6.1 Hz, 1H), 3.42 (dd, *J* = 9.5, 6.3 Hz, 1H), 2.43 (apps, 1H).

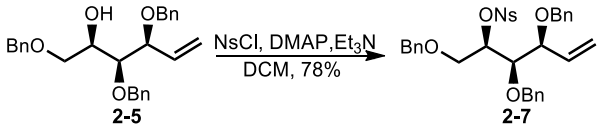
(2R,3R,4S)-1,3,4-tris(benzyloxy)hex-5-en-2-yl trifluoromethanesulfonate (2-6)



To a 1.0 M solution of pyridine (0.49 mmol, 0.48 ml, 2.0 eq.) in DCM was added Tf_2O (0.30 mmol, 0.30 ml) in CH_2Cl_2 (1.0 M) at –40 °C. After cooling for 20 minutes, **2-5** (0.10 g, 0.25 mmol, 1.0eq.) was added as a 0.30 M solution in DCM (0.82 ml). The reaction mixture was stireed for 2.5 hours at 0 °C and 1N HCl (0.50 ml) was added. The aqueous layer was extracted with Et_2O (3 × 1 ml) and the combined organic layers were washed with brine (2 ml), dried over

$MgSO_4$, filtered and concentrated *in vacuo.* The reaction mixture was not purified but provided **2-6** (96 mg, 71%): **Formula** : $C_{28}H_{29}F_3O_6S$; **MW** : 550.5892 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) 7.40 – 7.20 (m, 15H), 5.95 – 5.84 (m, 1H), 5.40 – 5.35 (m, 2H), 5.15 (ddd, *J* = 7.3, 4.7, 2.8 Hz, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 4.60 (d, *J* = 11.1 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.22 (d, *J* = 11.9 Hz, 1H), 3.90 (dd, *J* = 7.1, 3.8 Hz, 1H), 3.86 (dd, *J* = 7.2, 3.8 Hz, 1H), 3.69 (dd, *J* = 11.9, 2.7 Hz, 1H), 3.44 (dd, *J* = 11.9, 4.7 Hz, 1H).

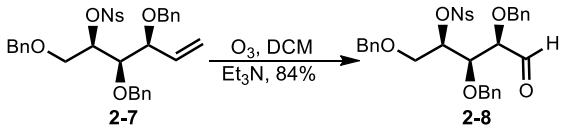
(+)-(2*R*,3*R*,4*S*)-1,3,4-tris(Benzyloxy)hex-5-en-2-yl 4-nitrobenzenesulfonate (2-7)



To a 0.2 M solution of **2-5** (2 g, 4.8 mmol) in CH_2Cl_2 (24 ml) at 0 ^oC was added NsCl (2.12 g, 9.6 mmol, 2.0eq.). A 0.4 M solution of DMAP (0.47 g, 3.83 mmol, 0.8 eq.) and Et_3N (2.4 ml, 17.2 mmol, 3.6 eq.) in CH_2Cl_2 (10 ml) was then added dropwise. The reaction mixture was refluxed for 16 hours at 50 ^oC and 1N HCl (5 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 ml) and the combined organic layers were washed with brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 85:15) provided **2-7** (2.25 g, 78%) as a yellow oil: $\mathbf{R_f}$ = 0.26 (Hexanes/EtOAc, 85:15); $\mathbf{[\alpha]^{25}_D}$ +0.95 (*c* 1.3, CH_2Cl_2) ; **Formula** : $C_{33}H_{33}NO_8S$; **MW** : 603.6820 g/mol ; **IR** (neat) ν_{max} 2869, 1531, 1349, 1185 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) 8.00 – 7.88 (m, 4H), 7.38 – 7.24 (m, 11H), 7.18 (dd, *J* = 6.8, 2.4 Hz, 2H), 7.14 (dd, *J* = 6.8, 2.4 Hz, 2H), 5.89 (ddd, *J* = 17.6, 10.0, 7.5 Hz, 1H), 5.38 (d, *J* = 5.1 Hz, 1H), 5.35 (s, 1H), 4.96 (ddd, *J* = 6.5, 5.8, 2.7 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.31 (d, *J* =

11.7 Hz, 1H), 4.24 (d, *J* = 11.8 Hz, 1H), 4.15 (d, *J* = 11.7 Hz, 1H), 3.95 (dd, *J* = 7.4, 4.0 Hz, 1H), 3.76 (dd, *J* = 6.6, 4.0 Hz, 1H), 3.66 (dd, *J* = 11.5, 2.7 Hz, 1H), 3.45 (dd, *J* = 11.5, 5.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 150.2, 142.9, 137.8, 137.7, 137.4, 134.4, 129.1, 128.55, 128.51, 128.4, 128.3, 128.1, 127.98, 127.96, 127.91, 127.8, 123.9, 120.1, 83.9, 79.8, 79.2, 74.9, 73.3, 70.5, 68.9 ppm ; **HRMS** calcd for $C_{33}H_{34}NO_8S$ [M+H$^+$] : 604.2000, found: 604.2018 (2.9 ppm).

(+)-(2*R*,3*R*,4*R*)-1,3,4-tris(Benzyloxy)-5-oxopentan-2-yl 4-nitrobenzenesulfonate (2-8)



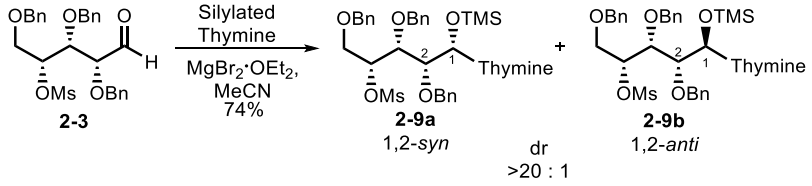
A 0.025M solution of **2-7** (1.27 g, 2.1 mmol) in CH_2Cl_2 (84 ml) was cooled to –78 ^oC and bubbled with O_3 in O_2 atmosphere for 40 minutes. TLC indicated the disappearance of the starting material. The system was purged with N_2 to remove the unreacted O_3. Et_3N (0.60 ml, 4.19 mmol, 2.0 eq.) was added to the reaction mixture and warmed to 25 ^oC for 30 minutes, followed by the addition of 1N HCl (2 ml). The aqueous layer was extracted with ether (3 × 50 ml) and the combined organic layers were washed with brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **2-8** (1.07 g, 84%) as a brown oil: $\mathbf{R_f}$ = 0.37 (Hexanes/EtOAc, 70:30); **$[\alpha]^{25}_D$** +15 (*c* 2.4, CH_2Cl_2) ; **Formula** : $C_{32}H_{31}NO_9S$; **MW** : 605.6548 g/mol ; **IR** (neat) ν_{max} 2870, 1535, 1369, 1186 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.03 – 8.00 (m, 2H), 7.93 – 7.89 (m, 2H), 7.39 – 7.34 (m, 3H), 7.34 – 7.25 (m, 8H), 7.18 – 7.12 (m, 4H), 4.96 (ddd, *J* = 6.2, 5.7, 3.0 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 1.2 Hz, 2H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 4.21 – 4.17 (m, 2H), 3.90 (d, *J* = 3.6 Hz, 1H), 3.69 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.45 (dd, *J* = 11.5, 5.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.9, 150.4, 142.2, 137.1,

136.9, 136.4, 129.3, 128.8, 128.72, 128.69, 128.59, 128.47, 128.36, 128.29, 128.04, 128.03, 124.0, 82.4, 81.7, 77.4, 74.8, 73.54, 73.45, 68.4 ppm ; **HRMS** calcd for $C_{32}H_{35}N_2O_9S$ [M+NH_4^+] : 623.2058, found: 623.2047 (-1.7 ppm).

Formation of *N,OTMS*-acetals

General Procedure 2-A for Preparation of *N,OTMS*-Acetals. To a solution of aldehyde **2-3** or **2-8** in MeCN (0.1 M) at –40 °C were successively added silylated base (2.0-4.0 eq. of a 0.6 M solution in CH_2Cl_2) and $MgBr_2$•OEt_2 (2.0 eq.). The reaction mixture was maintained for 4 hours at –40 °C, followed by addition of saturated aqueous $NaHCO_3$ (2 ml). The aqueous layer was extracted with ethyl acetate (3 × 5 ml) and the combined organic layers were washed with brine (5 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.*

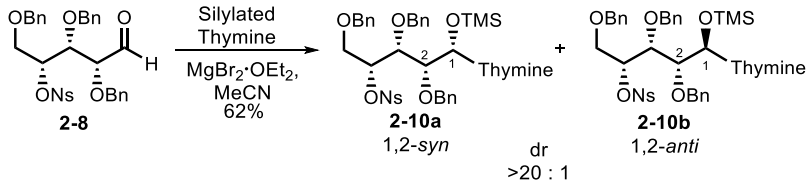
(–)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (2-9a)



Following general procedure 2-A, silylated thymine (0.56 ml of a 0.64 M solution in CH_2Cl_2, 0.36 mmol, 2.0 eq.) and $MgBr_2$•OEt_2 (92 mg, 0.36 mmol, 2.0 eq.) were added to a solution of aldehyde **2-3** (89 mg, 0.18 mmol) in MeCN (1.8 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **2-9a** (92 mg, 74%) as a white foam: $\mathbf{R_f}$ = 0.13 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –53 (*c* 1.7, $CDCl_3$) ; **Formula** : $C_{35}H_{44}N_2O_9SiS$; **MW** : 696.8824 g/mol ; **IR** (neat) ν_{max} 3191, 1691 cm^{-1} ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (m,

14H), 7.08 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.18 (d, *J* = 2.3 Hz, 1H), 4.99 – 4.93 (m, 1H), 4.81 (d, *J* = 11.1 Hz, 1H), 4.68 (d, *J* = 3.1 Hz, 1H), 4.65 (d, *J* = 3.1 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.29 (d, *J* = 11.1 Hz, 1H), 4.03 (dd, *J* = 6.7, 5.1 Hz, 1H), 3.89 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.84 (dd, *J* = 10.1, 5.8 Hz, 1H), 3.80 (dd, *J* = 6.6, 2.3 Hz, 1H), 3.11 (s, 3H), 1.83 (s, 3H), 0.15 (s, 9H) ppm. *NH signal missing possibly due to exchange in $CDCl_3$* ; **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 164.4, 150.2, 137.6, 137.48, 136.52, 128.6, 128.45, 128.41, 128.34, 128.25, 128.18, 127.9, 127.7, 127.6, 109.4, 79.6, 79.3, 77.5, 76.8, 75.3, 75.2, 73.3, 68.2, 38.7, 12.3, -0.40 ppm; **HRMS** calcd for $C_{35}H_{45}N_2O_9SiS$ [M+H$^+$] : 697.2610, found: 697.2619 (0.6 ppm).

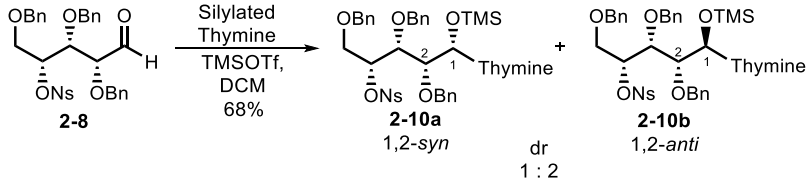
(–)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (2-10a)



Following general procedure 2-A, silylated thymine (1.4 ml of a 0.62 M solution in CH_2Cl_2, 0.84 mmol, 2.0 eq.) and $MgBr_2$•OEt_2 (218 mg, 0.84 mmol, 2.0 eq.) were added to a solution of aldehyde **2-8** (255 mg, 0.42 mmol) in MeCN (4.2 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **2-10a** (209 mg, 62%) as a white foam: **R_f** = 0.19 (Hexanes/EtOAc, 70:30); **[α]$^{25}_D$** –33 (*c* 0.84, CH_2Cl_2) ; **Formula** : $C_{40}H_{45}N_3O_{11}SiS$; **MW** : 803.9493 g/mol ; **IR** (neat) ν_{max} 3032, 1690, 1531 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.06 – 7.94 (m, 4H), 7.39 – 7.20 (m, 12H), 7.14 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.06 (dd, *J* = 7.2, 2.0 Hz, 2H), 6.29 (d, *J* = 3.1 Hz, 1H), 5.07 (ddd, *J* = 6.8, 6.3, 3.5 Hz, 1H), 4.66 (d, *J* = 11.4 Hz, 1H), 4.55 (dd, *J* = 12.6, 11.5 Hz, 2H), 4.33 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 2.8 Hz, 1H), 4.28

(d, J = 2.4 Hz, 1H), 3.95 (dd, J = 6.7, 5.8 Hz, 1H), 3.84 (dd, J = 10.9, 3.4 Hz, 1H), 3.72 – 3.65 (m, 2H), 1.84 (s, 3H), 0.18 (s, 9H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.7, 150.3, 149.7, 142.8, 137.5, 137.4, 137.3, 136.5, 129.3, 128.68, 128.62, 128.59, 128.53, 128.48, 128.28, 128.24, 128.1, 127.8, 123.9, 109.8, 83.7, 78.7, 77.4, 75.8, 74.79, 74.77, 73.5, 68.7, 12.5, -0.24 ppm; **HRMS** calcd for $C_{40}H_{46}O_{11}N_3SiS$ [M+H$^+$]: 804.2617, found: 804.2635 (2.3 ppm).

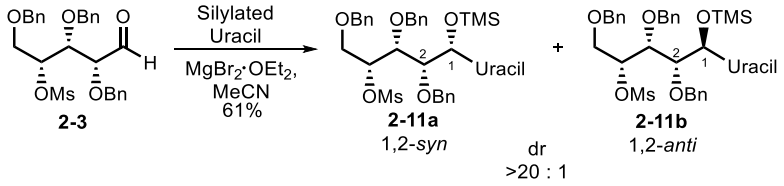
(2*R*,3*R*,4*R*)-1,3,4-tris(Benzyloxy)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (2-10a and 2-10b)



To a solution of aldehyde **2-8** (96 mg, 0.16 mmol) in CH_2Cl_2 (0.1 M, 1.6 ml) at 0 ^oC were successively added silylated thymine (0.87 ml of a 0.64 M solution in CH_2Cl_2, 0.55 mmol, 3.5 eq.) and TMSOTf (57 µl, 0.32 mmol, 2.0 eq.). The reaction mixture was maintained at 0 ^oC for 5 hours, followed by addition of saturated aqueous $NaHCO_3$ (2 ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml) and the combined organic layers were washed with brine (5 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1:2 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 70:30) did not allow for separation of the diastereomers and provided a mixture of **2-10a** and **2-10b** (87 mg, 68%) as a white foam: $\mathbf{R_f}$ = 0.19 (Hexanes/EtOAc, 70:30); Representative NMR resonances : **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.61 (s, 1H, isomer **a**), 8.51 (s, 1H, isomer **b**), 8.07 – 7.95 (m, 8H, isomer **a** & **b**), 7.35 – 7.24 (m, 24H, isomer **a** & **b**), 7.22 (dd, J = 7.3, 2.0 Hz, 2H, isomer **b**), 7.14 (dd, J = 6.5, 2.9 Hz, 2H, isomer **a**), 7.06 (dd, J = 7.2, 2.1 Hz, 2H, isomer **a**), 7.01 (dd, J = 6.9, 2.4 Hz, 2H, isomer

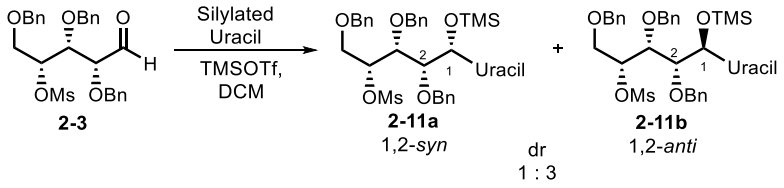
b), 6.29 (d, *J* = 3.1 Hz, 1H, isomer **a**), 6.21 (d, *J* = 5.2 Hz, 1H, isomer **b**), 5.26 – 5.20 (m, 1H, isomer **b**), 5.07 (ddd, *J* = 6.9, 6.4, 3.5 Hz, 1H, isomer **a**), 4.81 (dd, *J* = 21.4, 11.5 Hz, 2H, isomer **b**), 4.67 (d, *J* = 11.7 Hz, 1H, isomer **a**), 4.55 (appt, *J* = 11.7 Hz, 2H, isomer **a**), 4.34 (d, *J* = 11.5 Hz, 1H, isomer **a**), 4.30 (d, *J* = 5.2 Hz, 1H, isomer **a**), 4.28 (d, *J* = 4.9 Hz, 1H, isomer **a**), 4.20 (d, *J* = 11.6 Hz, 2H, isomer **b**), 4.05 – 3.98 (m, 2H, isomer **b**), 3.97 – 3.93 (m, 1H, isomer **a**), 3.85 (dd, *J* = 10.9, 3.4 Hz, 1H, isomer **a**), 3.73 – 3.68 (m, 2H, isomer **b**), 3.66 (dd, *J* = 7.4, 3.1 Hz, 2H, isomer **a**), 3.41 – 3.32 (m, 2H, isomer **b**), 1.84 (s, 3H, isomer **a**), 1.79 (d, *J* = 0.7 Hz, 3H, isomer **b**), 0.18 (s, 9H, isomer **a**), 0.14 (s, 9H, isomer **b**) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.7 (isomer **a**), 163.6 (isomer **b**), 150.6 (isomer **b**), 150.4 (isomer **b**), 150.3 (isomer **a**), 149.7 (isomer **a**), 142.8 (isomer **a**), 142.5 (isomer **b**), 137.5 (isomer **a**), 137.41 (isomer **a**), 137.38 (isomer **b**), 137.34, 137.1 (isomer **b**), 136.8 (isomer **b**), 136.5 (isomer **a**), 129.30 (isomer **b**), 129.25(isomer **a**), 128.68, 128.62 (isomer **a**), 128.58, 128.52 (isomer **a**), 128.49 (isomer **a**), 128.47 (isomer **b**), 128.44 (isomer **b**), 128.38 (isomer **b**), 128.28 (isomer **a**), 128.23 (isomer **a**), 128.20 (isomer **b**), 128.18 (isomer **b**), 128.07 (isomer **a**), 127.81 (isomer **a**, 127.79 (isomer **b**), 123.96 (isomer **b**), 123.94 (isomer **a**), 110.6 (isomer **b**), 109.8 (isomer **a**), 83.7 (isomer **a**), 82.9 (isomer **b**), 79.3 (isomer **b**), 78.7 (isomer **a**), 77.4 (isomer **a**), 76.9 (isomer **b**), 75.8 (isomer **a**), 75.5 (isomer **b**), 75.06 (isomer **b**), 74.77 (isomer **a**), 73.5 (isomer **a**), 73.1 (isomer **b**), 68.9 (isomer **b**), 68.6 (isomer **a**), 12.6 (isomer **b**), 12.5 (isomer **a**), -0.25 (isomer **a**), -0.29 (isomer **b**) ppm.

(–)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (2-11a)



Following general procedure 2-A, silylated uracil (0.45 ml of a 0.69 M solution in CH_2Cl_2, 0.312 mmol, 2.0 eq.) and $MgBr_2 \cdot OEt_2$ (81 mg, 0.312 mmol, 2.0 eq.) were added to a solution of aldehyde **2-3** (78 mg, 0.16 mmol) in MeCN (1.6 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-11a** (64 mg, 61%) as a white foam: $\mathbf{R_f}$ = 0.31 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –59 (*c* 0.9, CH_2Cl_2) ; **Formula** : $C_{34}H_{42}N_2O_9SiS$; **MW** : 682.8558 g/mol ; **IR** (neat) ν_{max} 3190, 2955, 1687 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.36 – 7.25 (m, 13H), 7.10 (dd, *J* = 7.0, 2.1 Hz, 2H), 6.18 (d, *J* = 2.6 Hz, 1H), 5.59 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.98 – 4.95 (m, 1H), 4.77 (d, *J* = 11.1 Hz, 1H), 4.66 (d, *J* = 11.1 Hz, 1H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.32 (d, *J* = 11.2 Hz, 1H), 4.02 – 3.98 (m, 1H), 3.88 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.82 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.76 (dd, *J* = 6.6, 2.7 Hz, 1H), 3.07 (s, 3H), 0.16 (s, 9H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.2, 149.7, 141.8, 137.6, 137.5, 136.5, 128.9, 128.68, 128.66, 128.56, 128.54, 128.4, 128.2, 127.99, 127.87, 101.3, 80.4, 78.6, 77.9, 76.6, 75.3, 75.1, 73.6, 68.6, 38.8, -0.26 ppm ; **HRMS** calcd for $C_{34}H_{43}N_2O_9SiS$ [M+H$^+$] : 683.2453, found: 683.2456 (0.5 ppm).

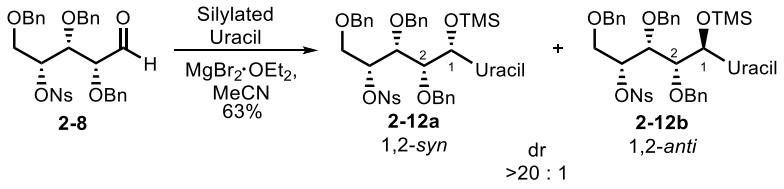
(+)-(2*R*,3*R*,4*R*,5*R*)-1,3,4-tris(Benzyloxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (2-11b)



To a solution of aldehyde **2-3** (54 mg, 0.11 mmol) in CH_2Cl_2 (0.1 M, 1.1 ml) at 0 °C were successively added silylated uracil (0.77 ml of a 0.5M solution in CH_2Cl_2, 0.38 mmol, 3.5 eq.) and TMSOTf (30 µl, 0.16 mmol, 1.5 eq.). The reaction mixture was maintained at 0 °C for 16

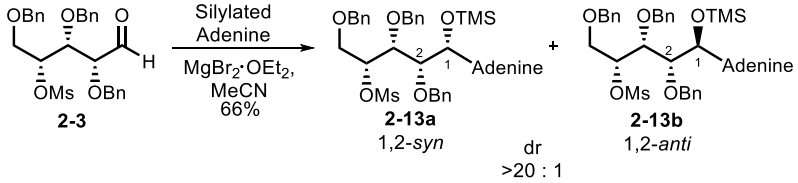
hours, followed by addition of saturated aqueous $NaHCO_3$ (2 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml) and the combined organic layers were washed with brine (5 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1:3 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-11b** as a white foam. A total of 33 mg (45%) of pure 1,2-*anti* diastereomer **2-11b** and a mixture of 1',2'- *syn* and *anti* diastereomers was obtained. **2-11b** : $\mathbf{R_f}$ = 0.49 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +25 (*c* 1.6, $CDCl_3$) ; **Formula** : $C_{34}H_{42}N_2O_9SiS$; **MW** : 682.8558 g/mol ; **IR** (neat) ν_{max} 3188, 2955, 1685 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.31 (m, 15H), 6.14 (d, *J* = 5.0 Hz, 1H), 5.53 (dd, *J* = 8.1, 2.1 Hz, 1H), 5.18 – 5.13 (m, 1H), 4.82 (d, *J* = 11.4 Hz, 1H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.97 (dd, *J* = 7.4, 5.2 Hz, 1H), 3.71 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.56 (dd, *J* = 7.5, 2.6 Hz, 1H), 3.40 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.05 (s, 3H), 0.11 (s, 9H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.7, 150.4, 141.2, 137.4, 137.34, 137.32, 128.8, 128.63, 128.62, 128.59, 128.34, 128.27, 128.18, 128.13, 128.0, 102.2, 80.9, 79.9, 78.7, 76.8, 75.5, 75.4, 73.3, 69.6, 38.8, -0.33 ppm ; **HRMS** calcd for $C_{34}H_{43}N_2O_9SiS$ $[M+H^+]$: 683.2453, found: 683.2459 (0.8 ppm).

(–)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (2-12a)



Following general procedure 2-A, silylated uracil (0.70 ml of a 0.74 M solution in CH_2Cl_2, 0.51 mmol, 2.0 eq.) and $MgBr_2{\cdot}OEt_2$ (132 mg, 0.51 mmol, 2.0 eq.) were added to a solution of aldehyde **2-8** (154 mg, 0.26 mmol) in MeCN (2.6 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-12a** (127 mg, 63%) as a white foam: $\mathbf{R_f}$ = 0.53 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –34 (*c* 1.3, CH_2Cl_2) ; **Formula** : $C_{39}H_{43}N_3O_{11}SiS$; **MW** : 789.9227 g/mol ; **IR** (neat) ν_{max} 3167, 2873, 1687, 1532 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.03 – 7.96 (m, 4H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.35 – 7.25 (m, 11H), 7.15 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.08 (dd, *J* = 7.4, 1.7 Hz, 2H), 6.31 (d, *J* = 2.9 Hz, 1H), 5.62 (dd, *J* = 8.1, 2.1 Hz, 1H), 5.11 (ddd, *J* = 6.7, 6.0, 3.4 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 4.6 Hz, 1H), 4.52 (d, *J* = 4.5 Hz, 1H), 4.37 – 4.27 (m, 3H), 3.94 (dd, *J* = 7.1, 5.7 Hz, 1H), 3.86 (dd, *J* = 10.9, 3.3 Hz, 1H), 3.72 – 3.66 (m, 2H), 0.20 (s, 9H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.47, 150.29, 149.75, 142.90, 141.73, 137.38, 137.27, 136.33, 129.19, 128.78, 128.68, 128.58, 128.55, 128.46, 128.29, 128.21, 128.06, 127.83, 123.91, 101.45, 83.94, 78.18, 77.52, 75.65, 74.71, 74.59, 73.49, 68.66, -0.30 ppm ; **HRMS** calcd for $C_{39}H_{44}O_{11}N_3SiS$ $[M+H^+]$: 790.2460, found: 790.2461 (0.12 ppm).

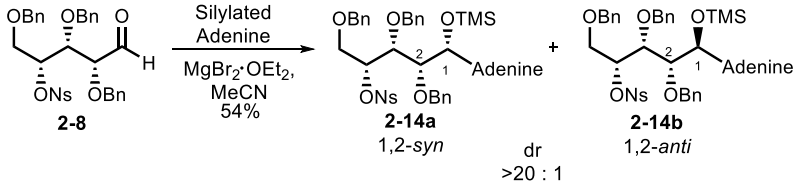
(–)-(2*R*,3*R*,4*R*,5*S*)-5-(6-Amino-9H-purin-9-yl)-1,3,4-tris(benzyloxy)-5-(trimethylsilyl)oxy)pentan-2-yl methanesulfonate (2-13a)



Following general procedure 2-A, silylated adenine (0.60 ml of a 0.71 M solution in CH_2Cl_2, 0.43 mmol, 4.0 eq.) and $MgBr_2{\cdot}OEt_2$ (28 mg, 0.11 mmol, 1.0 eq.) were added to a solution of aldehyde **2-3** (53 mg, 0.11 mmol) in MeCN (1.1 ml) and maintained at –20 °C for 16 hours. ^{1}H

NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 0:100) provided **2-13a** (50 mg, 66%) as a white foam: $\mathbf{R_f}$ =0.40 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ –14 (*c* 1.0, CH_2Cl_2) ; **Formula** : $C_{35}H_{43}N_5O_7SiS$; **MW** : 705.8957g/mol ; **IR** (neat) ν_{max} 3299, 3135, 1680, 1605 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.96 (s, 1H), 7.37 – 7.20 (m, 13H), 7.08 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.42 (d, *J* = 4.0 Hz, 1H), 5.80 (s, 2H), 5.02 (appdd, *J* = 10.3, 5.7 Hz, 1H), 4.64 (s, 2H), 4.54 (d, *J* = 11.1 Hz, 1H), 4.47 (s, 2H), 4.31 (d, *J* = 11.1 Hz, 1H), 4.00 – 3.95 (m, 1H), 3.90 (dd, *J* = 6.0, 5.5 Hz, 1H), 3.85 (dd, *J* = 10.6, 4.3 Hz, 1H), 3.74 (dd, *J* = 10.6, 5.9 Hz, 1H), 3.10 (s, 3H), 0.07 (s, 9H) ppm ; **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 155.4, 153.0, 148.9, 139.9, 137.64, 137.61, 136.8, 128.62, 128.60, 128.55, 128.458, 128.457, 128.16, 128.15, 127.95, 127.85, 119.4, 81.0, 79.1, 77.9, 76.5, 75.1, 74.9, 73.5, 68.8, 38.7, -0.29 ppm ; **HRMS** calcd for $C_{35}H_{44}N_5O_7SiS$ $[M+H^+]$: 706.2725, found: 706.2724 (-0.2 ppm).

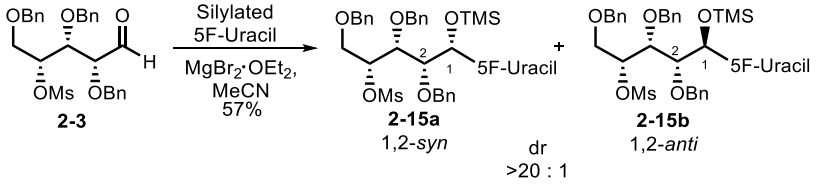
(–)-(2*R*,3*R*,4*R*,5*S*)-5-(6-Amino-9H-purin-9-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (2-14a)



Following general procedure 2-A, silylated adenine (1.5 ml of a 0.69 M solution in CH_2Cl_2, 0.99 mmol, 4.5 eq.) and $MgBr_2$•OEt_2 (58 mg, 0.22 mmol, 1.0 eq.) were added to a solution of aldehyde **2-8** (135 mg, 0.22 mmol) in MeCN (2.2 ml) and maintained at –40 °C for 6 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-**

14a (98 mg, 54%) as a white foam: $\mathbf{R_f}$ = 0.21 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –6.0 (*c* 1.0, CH_2Cl_2) ; **Formula** : $C_{40}H_{44}N_6O_9SiS$; **MW** : 812.9627 g/mol ; **IR** (neat) ν_{max} 3333, 3129, 1644, 1531 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.01 – 7.93 (m, 4H), 7.91 (s, 1H), 7.31 – 7.22 (m, 11H), 7.10 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.08 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.44 (d, *J* = 4.5 Hz, 1H), 5.66 (s, 2H), 5.11 – 5.06 (m, 1H), 4.49 (d, *J* = 13.1 Hz, 3H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.26 (dd, *J* = 27.3, 11.6 Hz, 2H), 3.93 (appt, *J* = 4.4 Hz, 1H), 3.82 – 3.78 (m, 2H), 3.59 (dd, *J* = 11.2, 6.0 Hz, 1H), 0.06 (s, 9H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.3, 153.1, 150.3, 149.1, 142.8, 139.9, 137.44, 137.38, 136.8, 129.2, 128.58, 128.54, 128.50, 128.49, 128.25, 128.24, 128.23, 128.1, 127.9, 123.9, 119.4, 83.9, 78.9, 77.7, 75.9, 74.7, 74.6, 73.4, 68.7, -0.30 ppm ; **HRMS** calcd for $C_{40}H_{45}N_6O_9SiS$ $[M+H^+]$: 813.2733, found: 813.2756 (2.9 ppm).

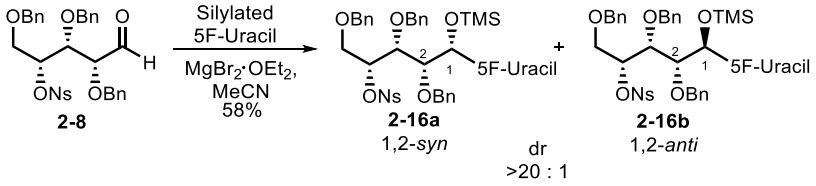
(–)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (2-15a)



Following general procedure 2-A, silylated 5F-uracil (1.0 ml of a 0.63 M solution in CH_2Cl_2, 0.62 mmol, 3.5 eq.) and $MgBr_2$•OEt_2 (92 mg, 0.355 mmol, 2.0 eq.) were added to a solution of aldehyde **2-3** (89 mg, 0.18 mmol) in MeCN (1.8 ml) and maintained at –20 °C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-15a** (71 mg, 57%) as a white foam: $\mathbf{R_f}$ = 0.49 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –29 (*c* 2.3, CH_2Cl_2) ; **Formula** : $C_{34}H_{41}FN_2O_9SiS$; **MW** : 700.8462 g/mol ; **IR** (neat) ν_{max} 3185, 2955, 1707 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.04 (d, *J* = 4.6 Hz, 1H), 7.48 (d, *J* = 6.2 Hz, 1H), 7.38 –

7.26 (m, 13H), 7.08 (dd, *J* = 6.4, 2.9 Hz, 2H), 6.13 (s, 1H), 4.98 – 4.95 (m, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.69 (d, *J* = 11.2 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.29 (d, *J* = 11.4 Hz, 1H), 4.01 (dd, *J* = 6.6, 5.6 Hz, 1H), 3.89 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.83 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.76 (dd, *J* = 6.8, 2.5 Hz, 1H), 3.09 (s, 3H), 0.16 (s, 9H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.8 (d, *J* = 26.6 Hz), 148.2, 140.6, 138.7, 137.5 (d, *J* = 9.6 Hz), 136.3, 129.090, 129.089, 128.75, 128.69, 128.56, 128.49, 128.3, 128.0, 127.9, 126.1 (d, *J* = 34.2 Hz), 80.3, 78.5, 78.1, 76.5, 75.4, 75.1, 73.6, 68.5, 38.9, -0.30 ppm ; **HRMS** calcd for $C_{34}H_{42}FN_2O_9SiS$ [M+H$^+$] : 701.2359, found: 701.2364 (0.7 ppm).

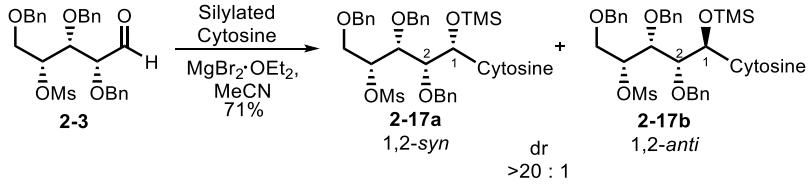
(–)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (2-16a)



Following general procedure 2-A, silylated 5F-uracil (1.3 ml of a 0.69 M solution in CH_2Cl_2, 0.89 mmol, 3.5 eq.) and $MgBr_2$•OEt_2 (132 mg, 0.51 mmol, 2.0 eq.) were added to a solution of aldehyde **2-8** (155 mg, 0.26 mmol) in MeCN (2.6 ml) and maintained at –20 ^{o}C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **2-16a** (121 mg, 58%, with ~10% aldehyde remaining in product) as a white foam: **R_f** = 0.24 (Hexanes/EtOAc, 70:30); **$[\alpha]^{25}_D$** –37 (*c* 0.99, $CDCl_3$) ; **Formula** : $C_{39}H_{42}FN_3O_{11}SiS$; **MW** : 807.9132 g/mol ; **IR** (neat) ν_{max} 3181, 2872, 1706, 1532 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 4H), 7.45 (d, *J* = 6.2 Hz, 1H), 7.36 – 7.25 (m, 11H), 7.14 (dd, *J* = 6.4, 2.9 Hz,

2H), 7.01 (dd, *J* = 7.6, 1.5 Hz, 2H), 6.22 (s, 1H), 5.11 (ddd, *J* = 7.0, 6.4, 3.4 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.20 (d, *J* = 11.5 Hz, 1H), 3.94 (dd, *J* = 7.0, 6.0 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.4 Hz, 1H), 3.70 – 3.61 (m, 2H), 0.20 (s, 9H) ppm ; *NH signal missing possibly due to exchange in $CDCl_3$*; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.4 (d, *J* = 26.9 Hz), 150.4, 147.8, 143.0, 140.6, 138.7, 137.3 (d, *J* = 12.3 Hz), 135.9, 129.2, 129.1, 128.9, 128.8, 128.7, 128.54, 128.46, 128.38, 128.1, 127.9, 126.1 (d, *J* = 34.1 Hz), 123.9, 83.9, 78.0, 77.7, 75.5, 74.9, 74.5, 73.6, 68.6, -0.27 ppm ; **HRMS** calcd for $C_{39}H_{43}O_{11}FN_3SiS$ [M+H$^+$] : 808.2366, found: 808.2360 (-0.72 ppm).

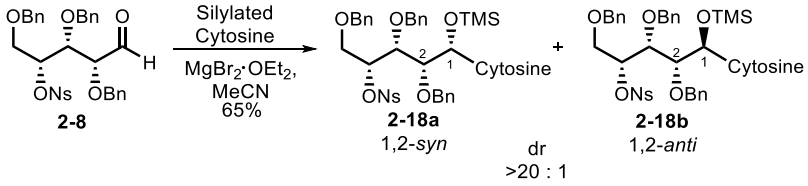
(–)-(2*R*,3*R*,4*R*,5*S*)-5-(4-Amino-2-oxopyrimidin-1(2H)-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (2-17a)



Following general procedure 2-A, silylated cytosine (1.3 ml of a 0.71 M solution in CH_2Cl_2, 0.92 mmol, 3.5 eq.) and $MgBr_2$•OEt_2 (102 mg, 0.39 mmol, 1.5 eq.) were added to a solution of aldehyde **2-3** (131 mg, 0.26 mmol) in MeCN (2.6 ml) and maintained at –20 ^{o}C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Acetone/DCM, 50:50) provided **2-17a** (128 mg, 71%) as a white foam: $\mathbf{R_f}$ = 0.19 (Acetone/DCM, 50:50); **[α]$^{25}_D$** –86 (*c*1.0, CH_2Cl_2) ; **Formula** : $C_{34}H_{43}N_3O_8SSi$; **MW** : 681.8710 g/mol ; **IR** (neat) ν_{max} 3333, 2955, 1645, 1494 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.4 Hz, 1H), 7.34 – 7.24 (m, 13H), 7.13 (dd, *J*

= 6.6, 2.8 Hz, 2H), 6.31 (d, *J* = 1.9 Hz, 1H), 5.71 (d, *J* = 7.4 Hz, 1H), 4.98 (appdd, *J* = 10.4, 5.7 Hz, 1H), 4.83 (d, *J* = 11.1 Hz, 1H), 4.59 (appt, *J* = 10.8 Hz, 2H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.26 (d, *J* = 10.9 Hz, 1H), 4.01 (dd, *J* = 7.1, 4.5 Hz, 1H), 3.92 – 3.83 (m, 3H), 3.15 (s, 3H), 0.14 (s, 9H) ppm. *NH_2 signal missing possibly due to exchange in $CDCl_3$* ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.9, 155.5, 142.7, 137.9, 137.7, 137.3, 128.531, 128.529, 128.5, 128.4, 128.3, 128.1, 127.9, 127.85, 127.81, 93.9, 79.9, 79.6, 78.3, 77.2, 75.6, 75.3, 73.5, 68.5, 38.8, -0.15 ppm ; **HRMS** calcd for $C_{34}H_{44}N_3O_8SiS$ [M+H$^+$] : 682.2613, found: 682.2626 (1.9 ppm).

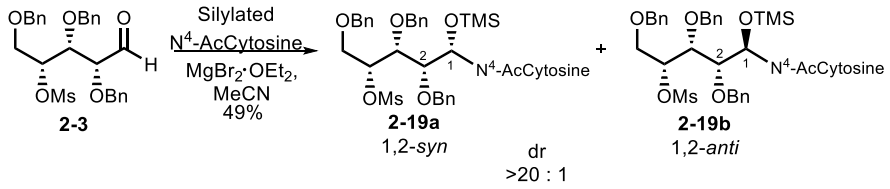
(–)-(2*R*,3*R*,4*R*,5*S*)-5-(4-Amino-2-oxopyrimidin-1(2H)-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (2-18a)



Following general procedure 2-A, silylated cytosine (1.1 ml of a 0.59 M solution in CH_2Cl_2, 0.66 mmol, 3.5 eq.) and $MgBr_2$•OEt_2 (73 mg, 0.28 mmol, 1.5 eq.) were added to a solution of aldehyde **2-8** (114 mg, 0.19 mmol) in MeCN (1.9 ml) and maintained at –40 °C for 6 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 0:100) provided **2-18a** (96 mg, 65%) as a white foam: **R_f** = 0.41 (Hexanes/EtOAc, 0:100); **$[\alpha]^{25}_D$** –57 (*c* 2.1, CH_2Cl_2) ; **Formula** : $C_{39}H_{44}N_4O_{10}SiS$; **MW** : 788.9380 g/mol ; **IR** (neat) ν_{max} 3331, 2956, 1658, 1529, 1486, 1185 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (apps, 4H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.30 – 7.22 (m, 11H), 7.17 – 7.13 (m, 2H), 7.09 – 7.06 (m, 2H), 6.42 (d, *J* = 2.8 Hz, 1H),

5.64 (d, *J* = 7.3 Hz, 1H), 5.12 – 5.08 (m, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.43 (dd, *J* = 11.2, 2.6 Hz, 2H), 4.36 – 4.25 (m, 3H), 3.89 (dd, *J* = 11.8, 5.4 Hz, 2H), 3.74 (dd, *J* = 10.8, 5.9 Hz, 2H), 0.16 (s, 9H) ppm ; *NH_2 signal missing possibly due to exchange in $CDCl_3$* ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ165.7, 155.4, 150.4, 143.0, 142.9, 137.70, 137.69, 137.2, 129.5, 128.7, 128.55, 128.54, 128.51, 128.294, 128.292, 128.09, 128.06, 127.9, 124.0, 93.8, 83.9, 78.8, 78.1, 76.3, 75.1, 74.6, 73.6, 68.9, -0.06 ppm; **HRMS** calcd for $C_{39}H_{45}N_4O_{10}SiS$ [M+H$^+$] : 789.2620, found: 789.2629 (1.1 ppm).

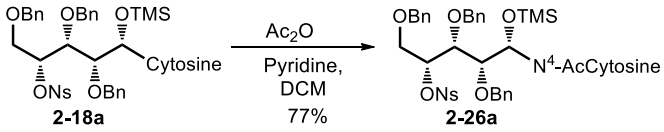
(–)-(2*R*,3*R*,4*R*,5*S*)-5-(4-Acetamido-2-oxopyrimidin-1(2H)-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (2-19a)



Following general procedure 2-A, silylated N^4-AcCytosine (1.3 ml of a 0.60 M solution in CH_2Cl_2, 0.75 mmol, 2.0 eq.) and $MgBr_2$•OEt_2 (193 mg, 0.75 mmol, 2.0 eq.) were added to a solution of aldehyde **2-3** (186 mg, 0.37 mmol) in MeCN (3.7 ml) and maintained at 0 ^oC for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-19a** (133 mg, 49%) as a white foam: $\mathbf{R_f}$ = 0.12 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –92 (*c* 1.4, CH_2Cl_2) ; **Formula** : $C_{36}H_{45}N_3O_9SiS$; **MW** : 723.9077 g/mol ; **IR** (neat) ν_{max} 3030, 2956, 1719, 1669, 1496 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.23 (m, 14H), 7.06 (dd, *J* = 6.8, 2.4 Hz, 2H), 6.32 (d, *J* = 1.8 Hz, 1H), 5.02 – 4.98 (m, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.16 (d, *J* = 11.1 Hz, 1H), 4.06 (dd, *J* = 7.2, 4.7 Hz, 1H), 3.96 – 3.88 (m, 3H), 3.18 (s, 3H), 2.27 (s, 3H), 0.14 (s, 9H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$)

δ 170.7, 162.8, 154.7, 146.4, 137.70, 137.66, 136.8, 128.7, 128.66, 128.59, 128.51, 128.311, 128.309, 128.1, 127.9, 127.8, 95.9, 79.7, 79.1, 78.6, 77.0, 75.6, 75.4, 73.6, 68.3, 38.8, 25.0, -0.20 ppm ; **HRMS** calcd for $C_{36}H_{46}N_3O_9SiS$ [M+H$^+$] : 724.2719, found: 724.2739 (2.8 ppm).

(–)-(2*R*,3*R*,4*R*,5*S*)-5-(4-Acetamido-2-oxopyrimidin-1(2H)-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (2-26a)



To a 0.3M solution of **2-18a** (0.33 g, 0.42 mmol) in CH_2Cl_2 (1.5 ml) at 0 ^oC was added Ac_2O (80 µl, 0.85 mmol, 2.0 eq.) and pyridine (0.14 ml, 1.69 mmol, 4.0 eq.). The reaction was maintained for 2 hours at 25 ^oC and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-26a** (271 mg, 77%) as a white form: $\mathbf{R_f}$ = 0.35 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –63 (*c* 1.4, CH_2Cl_2) ; **Formula** : $C_{41}H_{46}N_4O_{11}SSi$; **MW** : 830.9746 g/mol ; **IR** (neat) ν_{max} 3031, 2956, 1662, 1529, 1492 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.02 (apps, 4H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.32 – 7.25 (m, 10H), 7.24 – 7.21 (m, 2H), 7.18 – 7.15 (m, 2H), 7.00 (d, *J* = 6.5 Hz, 2H), 6.42 (d, *J* = 2.3 Hz, 1H), 5.15 – 5.11 (m, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.15 (d, *J* = 11.3 Hz, 1H), 3.95 (appt, *J* = 6.6 Hz, 1H), 3.92 (dd, *J* = 10.8, 3.7 Hz, 1H), 3.79 (dd, *J* = 10.8, 5.9 Hz, 1H), 3.75 (dd, *J* = 6.0, 2.5 Hz, 1H), 2.26 (s, 3H), 0.15 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.4, 162.4, 154.5, 150.3, 146.5, 142.8, 137.5, 137.4, 136.5, 129.4, 128.70, 128.67, 128.51, 128.47, 128.41, 128.35, 128.1, 128.0, 127.9, 123.9, 95.7, 83.8, 78.8, 77.8, 75.9, 74.9, 74.7, 73.5, 68.6, 25.1, -0.20 ppm ; **HRMS** calcd for $C_{41}H_{47}N_4O_{11}SiS$ [M+H$^+$] : 831.2726, found: 831.2734 (0.95 ppm).

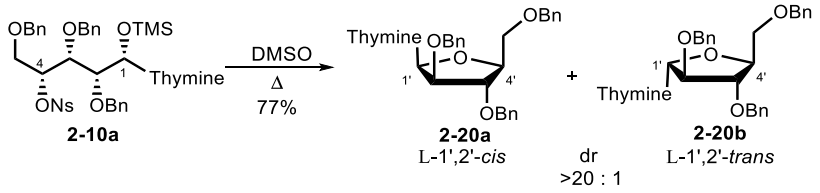
General Procedure 2-B: O1'→C4cyclization of *N,OTMS*-acetals with C4-Ms using conventional heating. L-nucleoside analogues **2-20a**, **2-21a** and **2-22a** were first cyclized from their respective *N,OTMS*-acetals **2-9a**, **2-11a**, and **2-13a** with a C4'-Ms using conventional heating. A 0.06 M solution of *N,OTMS*-acetal in anhydrous DMSO was added to a 15ml thick-walled glass test tube and heated with $Al(O\textit{t}Bu)_3$ (3.0eq.). The test tube was sealed with a teflon cap and the reaction mixture was maintained for 3 hours in a 140 ^{o}C sand bath. The reaction mixture was cooled to 25 ^{o}C followed by addition of brine (2 ml) and 1M NaOH (1 ml, to break emulsion formation). The aqueous layer was extracted with ethyl acetate (3 × 5 ml). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo.*

General Procedure 2-C: O1'→C4 cyclization of *N,OTMS*-acetals with C4-Ms using microwave heating. L-nucleoside analogues were cyclized from their respective *N,OTMS*-acetals with a C4'-Ms using microwave heating. A 0.06 M solution of *N,OTMS*-acetal in anhydrous DMSO was added to a glass test tube fitted for microwave conditions and heated with $Al(O\textit{i}Pr)_3$ (0.6 eq.). The test tube was sealed and the reaction mixture was maintained for 10 minutes at 180 ^{o}C in the microwave. The reaction mixture was cooled to 25 ^{o}C followed by addition of brine (2 ml) and 1M NaOH (1 ml, to break emulsion formation). The aqueous layer was extracted with ethyl acetate (3 × 5 ml). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo.*

General Procedure 2-D: O1'→C4 cyclization of *N,OTMS*-acetals with C4-Ns using conventional heating. A 0.06 M solution of *N,OTMS*-acetal in anhydrous DMSO was added to a 15ml thick-walled glass test tube and heated with $Al(O\textit{i}Pr)_3$ (0 or 3.0eq.). The test tube was

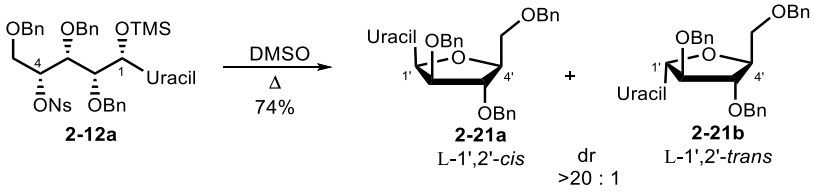
sealed with a teflon cap and the reaction mixture was maintained for 3 hours in a 90 °C sand bath. The reaction mixture was cooled to 25 °C followed by addition of brine (2 ml) and 1M NaOH (1 ml, to break emulsion formation). The aqueous layer was extracted with ethyl acetate (3 × 5 ml). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo.*

(–)-1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (2-20a)



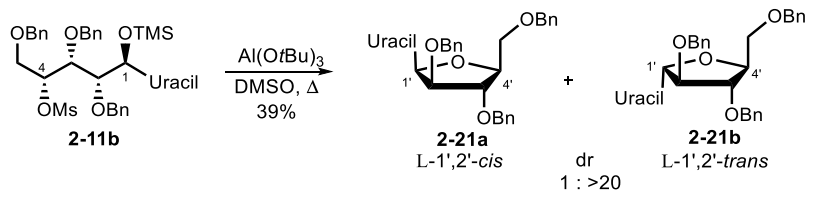
Following general procedure 2-D, a solution of *N,OTMS*-acetal **2-10a** (100 mg, 0.12 mmol) was heated in DMSO (2.1 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-20a** (50 mg, 77%) as a colorless gum. ^{1}H NMR spectroscopic data correlate with the previously reported data for the enantiomer of **2-20a**.[7] $\mathbf{R_f}$ = 0.26 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –53 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{31}H_{32}N_2O_6$; **MW** : 528.5956 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.44 (d, *J* = 1.1 Hz, 1H), 7.38 – 7.25 (m, 13H), 7.15 (dd, *J* = 7.2, 2.0 Hz, 2H), 6.31 (d, *J* = 5.2 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.57 – 4.50 (m, 3H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.24 (dd, *J* = 5.0, 4.2 Hz, 1H), 4.13 (dd, *J* = 5.5, 4.1 Hz, 1H), 4.08 – 4.05 (m, 1H), 3.72 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.66 (dd, *J* = 10.5, 4.3 Hz, 1H), 1.68 (d, *J* = 0.7 Hz, 3H).; **HRMS** calcd for $C_{31}H_{33}N_2O_6$ [M+H$^+$] : 529.2333, found: 529.2342 (1.7 ppm).

(–)-1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (2-21a)



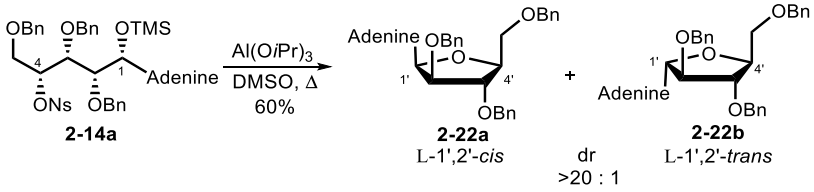
Following general procedure D, a solution of *N,OTMS*-acetal **2-12a** (151 mg, 0.19 mmol) was heated in DMSO (3.2 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-21a** (73 mg, 74%) as a colorless gum : $\mathbf{R_f}$ = 0.38 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –71 (*c* 1.5, $CDCl_3$) ; **Formula** : $C_{30}H_{30}N_2O_6$; **MW** : 514.5690 g/mol ; **IR** (neat) ν_{max} 3190, 2919, 1690 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.62 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.37 – 7.24 (m, 13H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.30 (d, *J* = 4.9 Hz, 1H), 5.47 (d, *J* = 8.1 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.54 – 4.46 (m, 3H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.26 – 4.22 (m, 1H), 4.10 – 4.08 (m, 2H), 3.69 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.64 (dd, *J* = 10.3, 2.4 Hz, 1H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.7, 150.6, 142.1, 137.6, 137.4, 136.7, 128.6, 128.57, 128.55, 128.2, 128.1, 128.04, 127.89, 127.869, 127.867, 101.2, 84.4, 81.9, 80.9, 80.5, 73.5, 73.2, 72.2, 68.7 ppm ; **HRMS** calcd for $C_{30}H_{31}N_2O_6$ [M+H$^+$] : 515.2177, found: 515.2159 (-3.4 ppm).

(+)-1-((2*R*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (2-21b)



Following general procedure 2-B, a solution of *N,OTMS*-acetal **2-11b** (70 mg, 0.10 mmol) and Al(O*i*Pr)$_3$ (63 mg, 0.31 mmol, 3.0 eq.) was heated in DMSO (1.7 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-21b** (21 mg, 39%) as a colorless gum : $\mathbf{R_f}$ = 0.31 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +32 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{30}H_{30}N_2O_6$; **MW** : 514.5690 g/mol ; **IR** (neat) ν_{max} 3171, 2923, 1686 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.37 – 7.25 (m, 13H), 7.13 (dd, *J* = 6.6, 2.8 Hz, 2H), 6.07 (s, 1H), 5.60 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.76 (d, *J* = 12.1 Hz, 1H), 4.64 – 4.57 (m, 3H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 11.8 Hz, 1H), 4.11 (s, 1H), 3.99 (s, 1H), 3.65 (dd, *J* = 9.8, 6.7 Hz, 1H), 3.57 (dd, *J* = 9.8, 6.8 Hz, 1H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.2, 150.1, 140.6, 137.9, 137.3, 136.8, 128.72, 128.67, 128.60, 128.3, 128.2, 127.98, 127.935, 127.932, 127.90, 101.4, 91.2, 86.5, 85.6, 82.9, 73.6, 72.3, 72.0, 69.8 ppm ; **HRMS** calcd for $C_{30}H_{31}N_2O_6$ [M+H$^+$] : 515.2177, found: 515.2177 (0.07 ppm).

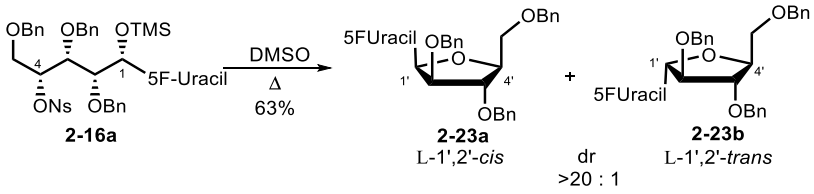
(–)-9-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)-9H-purin-6-amine (2-22a)



Following general procedure 2-D, a solution of *N,OTMS*-acetal **2-14a** (205 mg, 0.25 mmol) and Al(O*i*Pr)$_3$ (155mg, 0.76 mmol, 3.0 eq.) was heated in DMSO (4.2 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 0:100) provided **2-22a** (81 mg, 60%) as a colorless gum. ^{1}H NMR spectroscopic data correlate with the reported data for the enantiomer of **2-22a**. The enantiomer of **2-22a** 9-(2′,3′,5′-Tri-O-benzyl-β-D-arabinofuranosyl)adenine (CAS:

3257-73-6) is commercially available. $\mathbf{R_f}$ = 0.37 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ –9.5 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{31}H_{31}N_5O_4$; **MW** : 537.5089 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.18 (s, 1H), 7.37 – 7.25 (m, 10H), 7.22 – 7.17 (m, 3H), 6.92 (dd, *J* = 7.3, 1.7 Hz, 2H), 6.51 (d, *J* = 4.3 Hz, 1H), 5.73 (s, 2H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 3H), 4.27 (dd, *J* = 5.1, 2.3 Hz, 2H), 4.26 (s, 1H), 4.22 (s, 1H), 4.21 – 4.18 (m, 1H), 3.69 (d, *J* = 4.9 Hz, 2H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.4, 153.0, 149.9, 141.1, 137.8, 137.5, 136.6, 128.65, 128.62, 128.55, 128.2, 128.1, 128.0, 127.93, 127.92, 127.89, 119.2, 83.4, 81.9, 81.5, 80.9, 73.5, 72.9, 72.3, 69.2 ppm ; **HRMS** calcd for $C_{31}H_{32}N_5O_4$ $[M+H^+]$: 538.2449, found: 538.2443 (-1.0 ppm).

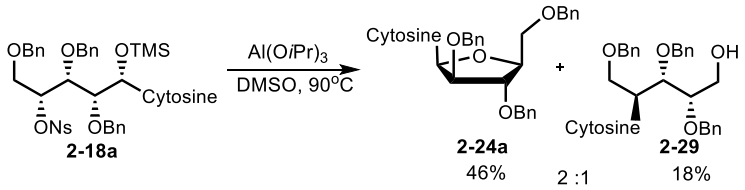
(–)-1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)-5-fluoropyrimidine-2,4(1H,3H)-dione (2-23a)



Following general procedure 2-D, a solution of *N,OTMS*-acetal **2-16a** (119 mg, 0.15 mmol) was heated in DMSO (2.5 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **2-23a** (50 mg, 63%) as a colorless gum : $\mathbf{R_f}$ = 0.36 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –36 (*c* 0.8, $CDCl_3$) ; **Formula** : $C_{30}H_{29}FN_2O_6$; **MW** : 532.5595 g/mol ; **IR** (neat) ν_{max} 3186, 2922, 1717 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.31 (d, *J* = 4.2 Hz, 1H), 7.85 (d, *J* = 6.4 Hz, 1H), 7.40 – 7.25 (m, 13H), 7.16 (d, *J* = 7.4 Hz, 2H), 6.28 (d, *J* = 5.0 Hz, 1H), 4.58 (dd, *J* = 11.8, 4.6 Hz, 2H), 4.55 – 4.49 (m, 2H), 4.45 (s, 2H), 4.26 (appt, *J* = 4.2 Hz, 1H), 4.14 – 4.08 (m, 2H), 3.70 (dd, *J* = 10.3, 3.6 Hz, 1H), 3.63 (dd, *J* = 10.4, 3.8 Hz, 1H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.9 (d, *J* = 26.5 Hz), 149.1, 139.9 (d, *J* = 235.8 Hz),

137.40, 137.36, 136.7, 128.7, 128.671, 128.666, 128.4, 128.2, 128.1, 128.0, 127.93, 127.88, 126.4 (d, J = 34.8 Hz), 84.6, 82.1, 80.8, 80.7, 73.6, 73.4, 72.4, 68.5 ppm ; **HRMS** calcd for $C_{30}H_{30}FN_2O_6$ [M+H$^+$] : 533.2082, found: 533.2074 (-1.5 ppm).

(–)-4-Amino-1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (2-24a) and (+)-(2S,3R,4S)-4-((4-aminopyrimidin-2-yl)oxy)-2,3,5-tris(benzyloxy)pentan-1-ol (2-29)



Following general procedure 2-D, a solution of *N,OTMS*-acetal **2-18a** (95 mg, 0.12 mmol) and Al(O*i*Pr)$_3$ (74 mg, 0.36 mmol, 3.0 eq.) was heated in DMSO (2.0 ml). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1), however, with a 2:1 mixture of nucleoside analogue **2-24a** and primary alcohol **2-29**. Purification by flash chromatography (Hexanes/EtOAc, 0:100) provided **2-24a** (28 mg, 46%) and **2-29** (11 mg, 18%) as colorless gums.

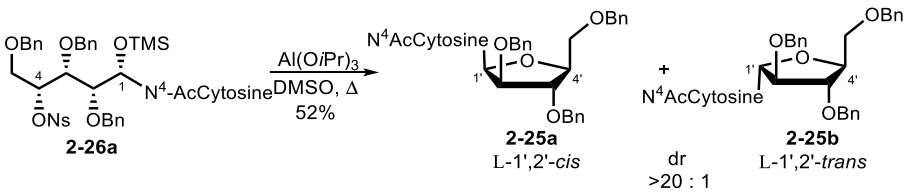
2-24a : $\mathbf{R_f}$ = 0.06 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ –109 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{30}H_{31}N_3O_5$; **MW** : 513.5842 g/mol ; **IR** (neat) ν_{max} 3347, 2925, 1626, 1481 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (d, J = 7.4 Hz, 1H), 7.37 – 7.22 (m, 13H), 7.16 – 7.12 (m, 2H), 6.38 (d, J = 4.6 Hz, 1H), 5.57 (d, J = 7.4 Hz, 1H), 4.57 – 4.49 (m, 3H), 4.46 – 4.39 (m, 2H), 4.35 – 4.29 (m, 2H), 4.14 – 4.11 (m, 1H), 4.01 (dd, J = 4.5, 3.0 Hz, 1H), 3.65 (d, J = 4.9 Hz, 2H) ppm. *NH_2 signal missing possibly due to exchange in $CDCl_3$* ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.3, 155.6, 143.8, 137.9, 137.5, 137.3, 128.60, 128.58, 128.55, 128.07, 128.06, 127.96, 127.90, 127.892, 127.890,

93.2, 85.9, 82.1, 81.4, 80.8, 73.5, 73.2, 72.1, 69.2 ppm ; **HRMS** calcd for $C_{30}H_{32}N_3O_5$ [M+H$^+$] : 514.2336, found: 514.2346 (1.9 ppm).

The N1 regiochemistry and 1',2'-*cis* configuration of **2-24a** was confirmed by comparison of the ^{13}C NMR spectrum of the debenzylated nucleoside with its commercially available enantiomer Cytosine β-D-arabinofuranoside (CAS: 147-94-4) **^{13}C NMR** (125 MHz, DMSO) δ 165.6, 155.2, 142.9, 92.4, 85.7, 84.8, 76.3, 74.8, 61.1 ppm.

2-29 : **R_f** = 0.31 (Hexanes/EtOAc, 0:100); **[α]$^{25}_D$** +3.5 (*c* 0.7, DCM) ; **Formula** : $C_{30}H_{33}N_3O_5$; **MW** : 515.6001 g/mol ; **IR** (neat) ν_{max} 3340, 3207, 2923, 1626, 1595 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 5.8 Hz, 1H), 7.34 – 7.24 (m, 15H), 6.08 (d, *J* = 5.7 Hz, 1H), 5.37 – 5.33 (m, 1H), 4.95 (s, 2H), 4.82 (d, *J* = 11.2 Hz, 1H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 1.2 Hz, 2H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.17 (dd, *J* = 7.0, 2.8 Hz, 1H), 4.00 (dd, *J* = 10.7, 4.0 Hz, 1H), 3.94 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.86 (d, *J* = 3.1 Hz, 2H), 3.73 – 3.69 (m, 1H) ppm. *OH signal missing possibly due to exchange in $CDCl_3$* ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.9, 164.5, 157.2, 138.6, 138.5, 138.3, 128.5, 128.42, 128.38, 128.273, 128.271, 128.1, 127.8, 127.70, 127.69, 99.8, 80.4, 80.3, 76.4, 75.1, 73.7, 73.1, 68.9, 62.5 ppm ; **HRMS** calcd for $C_{30}H_{34}N_3O_5$ [M+H$^+$] : 516.2493, found: 516.2498 (0.9 ppm).

(–)-N-(1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide (2-25a)

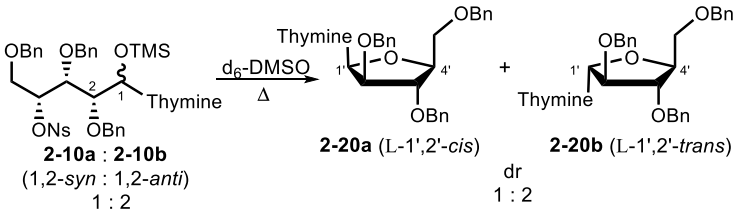


Following general procedure 2-D, a solution of *N,OTMS*-acetal **2-26a** (55 mg, 0.07 mmol) and Al(O*i*Pr)$_3$ (40 mg, 0.20 mmol, 3.0 eq.) was heated in DMSO (1.1 ml). ^{1}H NMR spectroscopic

analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (Hexanes/EtOAc, 0:100) provided **2-25a** (19 mg, 52%) as a colorless gum : $\mathbf{R_f}$ = 0.26 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ –104 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{32}H_{33}N_3O_6$; **MW** : 555.6209 g/mol ; **IR** (neat) ν_{max} 3030, 2924, 1665, 1495 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.38 – 7.22 (m, 14H), 7.08 (dd, *J* = 6.9, 2.4 Hz, 2H), 6.37 (d, *J* = 4.5 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 2H), 4.43 (d, *J* = 8.5 Hz, 1H), 4.40 (d, *J* = 8.2 Hz, 1H), 4.37 (dd, *J* = 4.5, 2.9 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.21 – 4.17 (m, 1H), 4.01 (dd, *J* = 4.1, 3.0 Hz, 1H), 3.65 (d, *J* = 5.2 Hz, 2H), 2.23 (s, 3H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.3, 162.5, 155.2, 146.7, 137.7, 137.4, 137.1, 128.7, 128.63, 128.59, 128.15, 128.13, 127.97, 127.94, 127.93, 127.91, 95.8, 86.7, 81.7, 81.5, 81.2, 73.5, 73.3, 72.1, 69.0, 25.1 ppm ; **HRMS** calcd for $C_{32}H_{34}N_3O_6$ $[M+H^+]$: 556.2442, found: 556.2446 (0.7 ppm).

Preparation of L-Nucleoside Analogues using d_6-DMSO.

1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (2-20a and 2-20b).

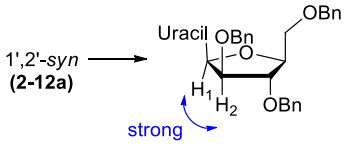


A 1:2 mixture of *N,OTMS*-acetals **2-10a** and **2-10b** (25 mg, 0.031 mmol) in d_6-DMSO (0.06 M, 0.52 ml) was placed in an NMR tube. The reaction mixture was maintained at 90 °C for 3 hours in a sand bath and then cooled to 25 °C. Nucleoside analogue **2-20a** was formed in 33% and analogue **2-20b** in 54% based on comparison of the area of the residual d_6-DMSO solvent peak at 2.50 ppm (d_1 relaxation time was set to 10s) with the area of the acetal center peak of the

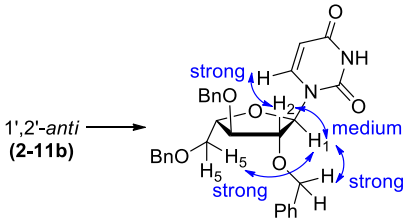
starting material taken before heating the reaction mixture. Brine (0.2 ml) and 1M NaOH (0.2 ml, to break emulsion formation) were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3 × 0.5 ml) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The expected corresponding 1 : 2 mixture of L-1',2'-*cis* and *trans* nucleoside analogues **2-20a** and **2-20b** was obtained. ^{1}H NMR spectroscopic data of the crude reaction mixture in $CDCl_3$ correlate with the enantiomers of **2-20a** and **2-20b** that have previously been reported in the literature.[7]

Stereochemical Proofs

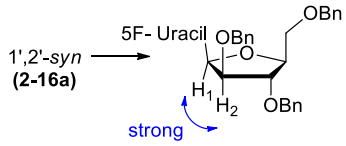
In all cases, the selectivities were determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixtures. The C1'−C2' relative configurations of the synthesized nucleoside analogues were determined by relevant nuclear Overhauser effect (nOe) enhancements (2D NOESY), ^{1}H NMR coupling constant data and correlations of chemical shifts. The peaks in the ^{1}H NMR spectra were assigned using ^{1}H/^{1}H COSY experiments, chemical shifts, and coupling constants. Nucleoside analogues **2-20a**, **2-20b**, **2-22a**, and the debenzylated analogue of **2-24a**, were found to have identical ^{1}H and ^{13}C NMR spectra to their corresponding enantiomers that have been reported in the literature (see experimental procedures). Proofs of structure for the C1'-C2' relative stereochemistry of nucleoside analogues **2-21a, 2-21b, 2-23a** and **2-26a** were provided by NOESY experiments which are detailed below.



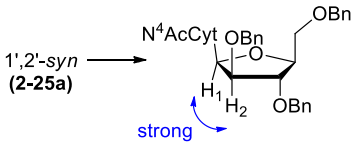
2-21a, L-1',2'-*cis*



2-21b, L-1',2'-*trans*

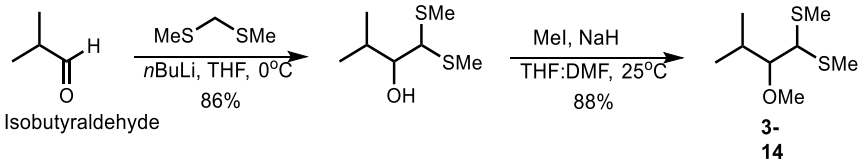


2-23a, L-1',2'-*cis*

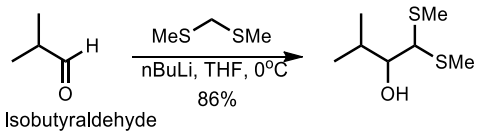


2-26a, L-1',2'-*cis*

Chapter 3

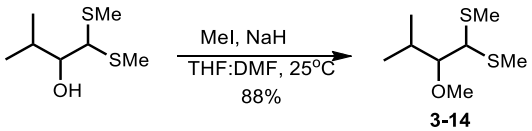


(±)-3-methyl-1,1-bis(methylthio)butan-2-ol



To a solution of bis(methylthio)methane (4.5 ml, 26.3 mmol, 1.2 eq.) in anhydrous THF (105 ml, 0.25 M) at –78 °C was added *n*BuLi (9.7 ml, 24.1 mmol, 1.1 eq.). The reaction mixture was maintained for 1 hour at –78 °C, followed by 30 minutes at –30 °C. After cooling to –78 °C, the mixture was cannulated onto a solution of isobutyraldehyde (2.0 ml, 21.9 mmol, 1.0 eq.) also at –78 °C in anhydrous THF (28 ml, 0.8 M). The reaction was stirred at 0 °C for 16 hours. A 0.5 N HCl (10 ml) solution was added and the aqueous layer was extracted with hexanes (3 × 60 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash chromatography (Hexanes/EtOAc, 90:10) and provided the product as a colorless oil (3.4 g, 86%). Complete characterization was previously done in our laboratory.[8]

(±)-(2-methoxy-3-methylbutane-1,1-diyl)bis(methylsulfane) (3-14)



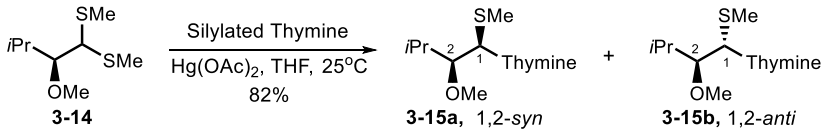
To a solution of the alcohol (2.3 g, 12.9 mmol, 1.0 eq.) in an anhydrous mixture of THF:DMF (55 ml THF, 10 ml DMF, 0.20 M, 85:15) at 0 °C was added NaH (0.62 g, 25.8 mmol, 2.0 eq., of

60% oil dispersion). MeI (1.7 ml, 25.8 mmol, 2.0 eq.) was added and the reaction was stirred at room temperature for 16 hours. A saturated aqueous NH_4Cl solution (20 ml) was added and the aqueous layer was extracted with a mixture of diethyl ether : hexanes (50:50, 3 × 60 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude reaction mixture was purified by flash chromatography (Hexanes/EtOAc, 90:10) and provided dithioacetal **3-14** as a colorless oil (2.2 g, 88%). Complete characterization was previously done in our laboratory.[8]

General Procedure 3-A:

To a solution of the corresponding C2-protected dithioacetal in anhydrous solvent at 0 °C were added silylated thymine and the activating agent. The reaction mixture was stirred until complete by TLC. In certain cases, additional silylated thymine and activating agent were added in order for the reaction to go to completion. (N.B. Addition of silylated thymine as a solution in THF gave slightly higher 1,2-syn selectivity as compared to a solution in DCM.) A saturated solution (1 ml) of $Na_2S_2O_3$ (with I_2 or Br_2) or $NaHCO_3$ (with $Hg(OAc)_2$/TMSOTf or $Me_2S(SMe)BF_4$) was added and the aqueous layer was extracted with ethyl acetate (3 × 5 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.*

(±)-1-(2-methoxy-3-methyl-1-(methylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (3-15a and 3-15b)

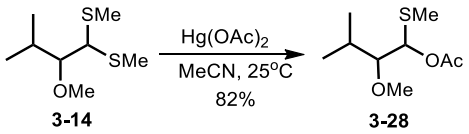


Following general procedure 3-A, $Hg(OAc)_2$ (80 mg, 0.25 mmol, 1.05 eq.), silylated thymine (1.0 ml, 0.72 mmol, 3.0 eq. of a 0.70 M solution in DCM), and TMSOTf (0.25 mmol, 50 µl, 1.05

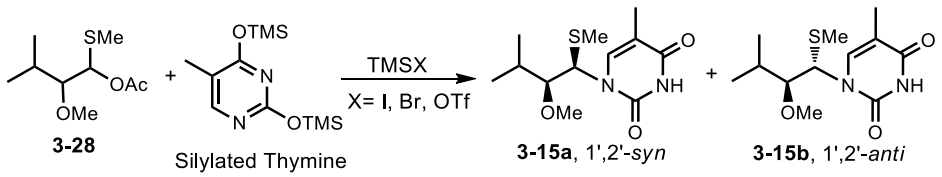
eq.), were added to a solution of **3-14** (46 mg, 0.24 mmol) in anhydrous THF (2.4 ml, 0.10 M) and stirred at room temperature. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 5 : 1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 40:60) did not allow separation of the diastereomers and provided a mixture of **3-15a** and **3-15b** (53 mg, 82%) as a white solid : $\mathbf{R_f}$ = 0.39 (Hexanes/EtOAc, 40:60); **Formula** : $C_{12}H_{20}N_2O_3S$; **MW** : 272.3638 g/mol ; **IR** (neat) ν_{max} 3423, 2952, 1677 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.71 (s, 1H, isomer **a**), 8.60 (s, 1H, isomer **b**), 7.83 (s, 1H, isomer **a**), 7.75 (s, 1H, isomer **b**), 5.89 (s, 1H, isomer **b**), 5.74 (d, *J* = 3.3 Hz, 1H, isomer **a**), 3.52 (s, 3H, isomer **b**), 3.36 (s, 3H, isomer **a**), 3.18 (dd, *J* = 7.1, 2.9 Hz, 1H, isomer **b**), 3.02 (dd, *J* = 8.1, 3.3 Hz, 1H, isomer **a**), 2.09 (s, 3H, isomer **b**), 2.02 (s, 3H, isomer **a**), 1.98 (s, 3H, isomer **a**), 1.96 (s, 3H, isomer **b**), 1.95 (m, 1H, isomer **a**), 1.73 – 1.65 (m, 1H, isomer **b**), 1.03 (d, *J* = 1.5 Hz, 3H, isomer **a**), 1.02 (d, *J* = 1.4 Hz, 3H, isomer **a**), 0.99 (d, *J* = 6.7 Hz, 3H, isomer **b**), 0.93 (d, *J* = 6.7 Hz, 3H, isomer **b**) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.74 (isomer **a**), 163.66 (isomer **b**), 151.6 (isomer **b**), 151.2 (isomer **a**), 139.0 (isomer **b**), 138.0 (isomer **a**), 111.2 (isomer **b**), 110.8 (isomer **a**), 89.8 (isomer **a**), 77.4 (isomer **b**), 65.3 (isomer **a**), 63.2 (isomer **b**), 62.4 (isomer **b**), 61.7 (isomer **a**), 32.2 (isomer **a**), 31.7 (isomer **b**), 19.2 (isomer **b**), 19.1 (isomer **a**), 18.8 (isomer **a**), 18.6 (isomer **b**), 14.12 (isomer **a**), 14.08 (isomer **b**), 12.9 (isomer **b**), 12.7 (isomer **a**) ppm ; **HRMS** calcd for $C_{12}H_{20}N_2O_3SNa$ [M+Na^+] : 295.1087, found: 295.1087 (0.06 ppm).

Dithioacetals **3-16, 3-18, 3-20, 3-22, 3-24** and **3-26** and thioaminals **3-17, 3-19, 3-21, 3-23, 3-25** and **3-27** were synthesized and characterized by Dr Michel Prévost.[9]

(±)-2-methoxy-3-methyl-1-(methylthio)butyl acetate (3-28)



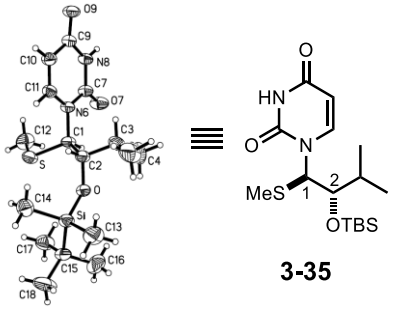
To a solution of **3-14** (0.52 g, 2.7 mmol, 1.0 eq.), in anhydrous acetonitrile (26 ml, 0.10 M) at 0 °C was added $Hg(OAc)_2$ (1.0 g, 3.2 mmol, 1.2 eq.). The reaction mixture was stirred at room temperature for two hours, filtered on a pad of Celite®, rinsed with diethyl ether and concentrated *in vacuo.* ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 90:10) provided **3-28** (0.45 g, 82%) as a colorless oil : $\mathbf{R_f}$ = 0.37 (Hexanes/EtOAc, 90:10); **Formula** : $C_9H_{18}O_3S$; **MW** : 206.3024 g/mol ; **IR** (neat) ν_{max} 2963, 1743 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.07 (d, *J* = 3.5 Hz, 1H), 3.51 (s, 3H), 3.06 (dd, *J* = 6.7, 3.6 Hz, 1H), 2.20 (s, 3H), 2.13 (s, 3H), 1.95 – 1.84 (m, 1H), 0.97 (at, *J* = 6.5 Hz, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.6, 88.3, 83.3, 61.0, 31.0, 21.4, 19.8, 18.1, 14.7 ppm ; **HRMS** calcd for $C_9H_{18}O_3SNa$ $[M+Na^+]$: 229.0869, found: 229.0863 (-2.5 ppm).



To a solution of **3-28** in anhydrous THF (0.10 M) at -20 °C was added TMSX (1.5 eq.). The reaction mixture was stirred at -10 °C for one hour. Silylated thymine (3.0 eq.) was then added and the reaction mixture was stirred at 0 °C overnight. Workup and purification were done according to General Procedure 3-A.

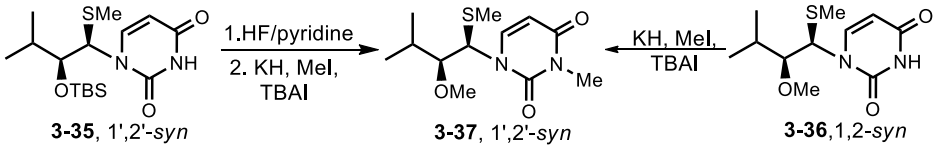
Stereochemical Proofs of Structures:

The X-ray structure shown below confirms the 1,2-*syn* stereochemistry with a C2-OTBS (**3-35**) and uracil nucleobase.[8]



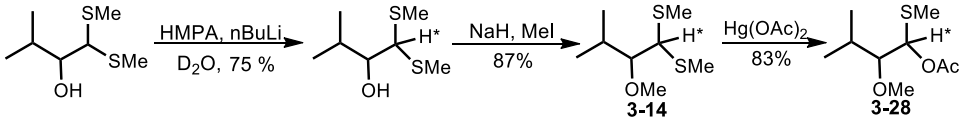
3-35

In order to confirm that the 1,2-*syn* product is also the major diastereomer with a C2-OMe (**3-36**)[8], deprotection and methylation from **3-35** along with methylation of **3-36** were previously done in our lab to ensure formation of the same product **3-37**.



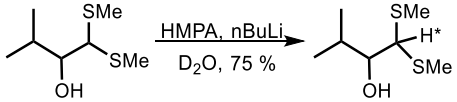
3-35, 1',2'-*syn* **3-37**, 1',2'-*syn* **3-36**,1,2-*syn*

Kinetic isotope effects:

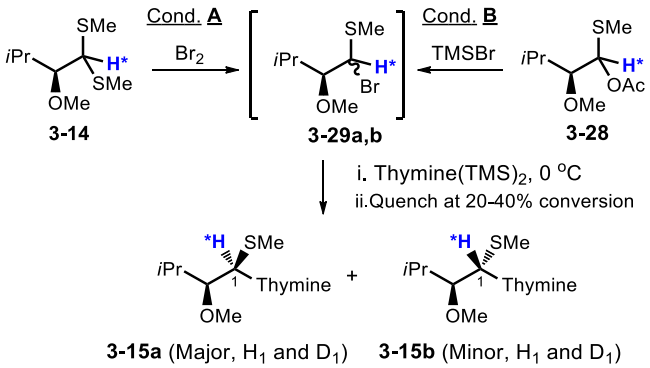


3-14 **3-28**

Preparation of ^{2}H enriched dithioacetal 3-14.



To a solution of starting material (1.8 g, 9.9 mmol, 1.0 eq.), in anhydrous THF (50 ml, 0.20 M) at –78 °C was added HMPA (17 ml, 99 mmol, 10 eq.) followed by *n*BuLi (13 ml, 25 mmol, 2.5 eq. of 2.0 M solution in hexanes). The reaction mixture was stirred at –78 °C for 1.5 hours. D_2O (1.0 ml, 50 mmol, 5.0 eq) was added and the mixture was brought to room temperature. The aqueous layer was extracted with hexanes (3 × 50 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexane/EtOAc, 90:10) provided the product (1.35 g, 75%) as a colorless oil that was ~ 80% enriched in ^2H.



Measurement of the Kinetic Isotope Effect (KIE) in Table 3.8. An ~50% mixture of ^2H enriched substrate **3-14** or **3-28** was used to perform the KIE study. The ^1H NMR of the starting mixture was taken prior to the reaction (d_1 relaxation delay 10s). Complete conversion to the bromothioether intermediates **3-29a**,**b** was confirmed by ^1H NMR. The reactions were quenched after 10-40% conversion, as judged by disappearance of the H1 signal of **3-29**, and by the yield obtained for **3-15a,b** after purification of the crude mixtures. Incorporation of ^2H into thioaminals **3-15a** and **3-15b** was determined using the ^1H NMR spectra of the pure mixtures. Each spectrum was integrated at least three times and the values were recorded in the following tables. The kinetic isotope effects were determined using the following equation[10,11]: KIE = ln(1-

F)/ln(1-F(R/R_o)); where F is the fractional conversion (yield of **3-15a,b**) and R and R_o the % of D in the products **3-15** (R) and in the bromothioether **3-29a,b** (R_o).

Conditions A:

To a solution of ^{2}H enriched **3-14** in anhydrous solvent (0.10 M) was added Br_2 (1.1 eq.) at -40 ^{o}C, the resulting mixture was stirred for 10 minutes (The activation occurred much faster in MeCN, therefore the mixture was only stirred for 30 seconds). Silylated thymine (1.4 eq) was then added and the reaction was warmed to 0 ^{o}C. The reaction was quenched with a saturated solution of $Na_2S_2O_3$ after one hour at 0 ^{o}C in THF or 15 minutes in MeCN.

Conditions B:

To a solution of ^{2}H enriched **3-28** in deteurated anhydrous solvent (0.10 M) was added TMSBr (1.5 eq.) at 0 ^{o}C (20 min.). Silylated thymine (1.4 eq) was added and the reaction was maintained at 0 ^{o}C for ~1 hour after which a saturated solution of $NaHCO_3$ was added. The standard deviation was calculated from the following equation:

$$\sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{(n-1)}}$$

where n denotes the number of integrations, x_i denotes the KIE calculated for each spectrum and $\bar{x}$ denotes the average of all KIE.

Experimental Determination of KIE for the major 1,2-*syn* thioaminal **3-15a**.

Entry	Solvent (Conditions)	Yield	1-F	ln(1-F)	R	R_o	R/ R_o	1-(FR/ R_o)	ln[1-(FR/R_o)]	KIE (k_H/k_D) at 0°C
										Major (15a, 1,2-syn)
1	Toluene (**B**, TMSBr)	42%	0.58	-0.5447	0.46	0.51	0.9019	0.6212	-0.4761	1.14
					0.45	0.49	0.9184	0.6143	-0.4873	1.12
					0.46	0.50	0.9200	0.6136	-0.4884	1.12
2	Toluene (**B**, TMSBr)	39%	0.61	-0.4943	0.48	0.53	0.9057	0.6468	-0.4357	1.13
					0.48	0.52	0.9231	0.64	-0.4463	1.11
					0.46	0.51	0.9019	0.6482	-0.4335	1.14
									Average KIE	**1.13 ± 0.01**
3	THF (**A**, Br_2)	22%	0.78	-0.2485	0.46	0.53	0.8679	0.8091	-0.2119	1.17
					0.46	0.54	0.8519	0.8126	-0.2075	1.20
					0.47	0.53	0.8868	0.8049	-0.2170	1.15
4	THF (**A**, Br_2)	7.4%	0.926	-0.0769	0.46	0.54	0.8519	0.9369	-0.0651	1.18
					0.46	0.53	0.8679	0.9358	-0.0664	1.16
					0.44	0.53	0.8302	0.9386	-0.0634	1.21
									Average KIE	**1.18 ± 0.02**
5	THF (**B**, TMSBr)	24%	0.76	-0.2744	0.49	0.58	0.8448	0.7972	-0.2266	1.21
					0.49	0.57	0.8597	0.7937	-0.2311	1.19
					0.49	0.59	0.8305	0.8007	-0.2223	1.23
									Average KIE	**1.21 ± 0.02**
6	MeCN (**A**, Br_2)	34%	0.66	-0.4155	0.47	0.53	0.8868	0.6985	-0.3588	1.16
					0.48	0.52	0.9231	0.6862	-0.3767	1.10
					0.44	0.51	0.8627	0.7067	-0.3472	1.20
7	MeCN (**A**, Br_2)	10%	0.90	-0.1054	0.46	0.53	0.8679	0.9132	-0.0908	1.16
					0.45	0.52	0.8654	0.9135	-0.0905	1.16
					0.46	0.51	0.9019	0.9098	-0.0945	1.12
									Average KIE	**1.15 ± 0.04**

Experimental Determination of KIE for the minor 1,2-*anti* thioaminal **3-15b**.

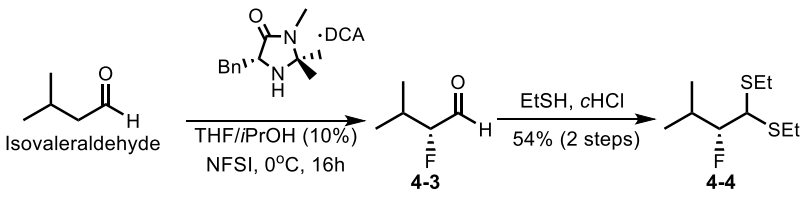
Entry	Solvent (Conditions)	Yield	1-F	ln(1-F)	R	R_o	R/ R_o	1-(FR/ R_o)	ln[1-(FR/R_o)]	KIE (k_H/k_D) at 0°C
										Minor (15b, 1,2-anti)
1	Toluene (**B**, TMSBr)	42%	0.58	-0.544	0.51	0.51	1.0	0.58	-0.5447	1.0
					0.52	0.49	1.0612	0.5543	-0.5901	0.92
					0.51	0.50	1.02	0.5716	-0.5593	0.97

2	Toluene (**B**, TMSBr)	39%	0.61	-0.4943	0.52	0.53	0.9811	0.6174	-0.4823	1.03
					0.52	0.52	1.0	0.61	-0.4943	1.0
					0.50	0.51	0.9804	0.6176	-0.4818	1.03
									Average KIE	**0.99 ± 0.04**
3	THF (**A**, Br_2)	22%	0.78	-0.2485	0.55	0.53	1.0377	0.7717	-0.2592	0.96
					0.57	0.54	1.0556	0.7678	-0.2643	0.94
					0.57	0.53	1.0755	0.7634	-0.2699	0.92
4	THF (**A**, Br_2)	7.4%	0.926	-0.0769	0.59	0.54	1.0926	0.9192	-0.0843	0.91
					0.58	0.53	1.0943	0.9190	-0.0845	0.91
					0.60	0.53	1.1321	0.9162	-0.0875	0.88
									Average KIE	**0.92 ± 0.03**
5	THF (**B**, TMSBr)	24%	0.76	-0.2744	0.57	0.58	0.9828	0.7641	-0.2691	1.02
					0.57	0.57	1.0	0.76	-0.2744	1.0
					0.56	0.59	0.9492	0.7722	-0.2585	1.06
									Average KIE	**1.03 ± 0.03**

Full details for the DFT calculations can be found in the JOC 2014 paper.[9]

Chapter 4

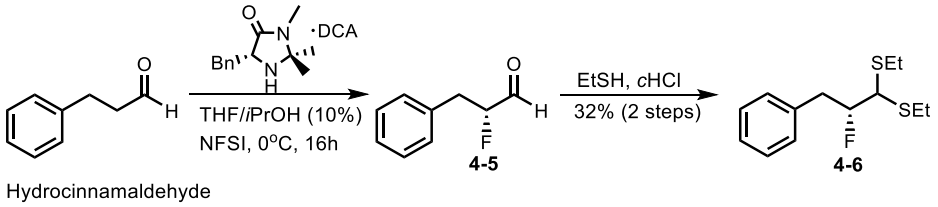
(2-fluoro-3-methylbutane-1,1-diyl)bis(ethylsulfane) (4-4)



Isovaleraldehyde (1.0 ml, 9.3 mmol, 1.0 eq.) was added to a solution of (*R*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt (0.64 g, 1.9 mmol, 0.20 eq.), and NFSI (4.4 g, 14.0 mmol, 1.5 eq.) in THF:*i*PrOH(10%) (31.0 ml, 0.30 M) at –20 °C. The reaction mixture was stirred for 16 hours at 0 °C. To verify that the reaction was complete, an aliquot was diluted with ether, filtered through a pad of silica gel, quenched with Me_2S, washed with a saturated solution of $NaHCO_3$, extracted with Et_2O and dried with $MgSO_4$. Due to the volatility of the C2-F aldehyde, the diethyl ether was removed by a stream of air. Directly to the reaction mixture at 0 °C was added ethanethiol (2.8 ml, 37.3 mmol, 4.0 eq.) and conc. HCl (6.0 ml, 74.6 mmol, 8.0 eq.). The reaction was stirred for 72 hours at 25 °C followed by addition of NEt_3 (5 ml) and dilution with Et_2O (40 ml). A saturated solution (40 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with diethyl ether (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 95:5), provided **4-4** as a colorless oil (1.1 g, 54%): $\mathbf{R_f}$ = 0.50 (Hexanes/EtOAc, 95:5); **Formula** : $C_9H_{19}FS_2$; **MW** : 210.3756 g/mol ; **IR** (neat) ν_{max} 2965, 2928, 2873 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.34 (ddd, *J* = 47.2, 6.2, 5.4 Hz, 1H), 3.93 (dd, *J* = 22.6, 5.2 Hz, 1H), 2.82 – 2.65 (m, 4H), 2.35 – 2.23 (m, 1H), 1.27 (t, *J* = 7.4Hz, 3H), 1.27 (t, *J* = 7.4Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 101.1 (d, *J* = 180.8 Hz), 52.8 (d, *J* = 22.2 Hz), 30.7 (d, *J* = 20.4 Hz), 25.0 (d, *J* = 2.5

Hz), 24.8 (d, J = 1.1 Hz), 19.0 (d, J = 6.7 Hz), 16.9 (d, J = 4.9 Hz), 14.59, 14.57 ppm ; **HRMS** calcd for $C_9H_{19}FS_2Na$ [M+Na$^+$] : 233.0804, found: 233.0797 (-3.3 ppm). Since we were only interested in the diastereoselectivity for the coupling of the nucleobase to the dithioacetal, the enantioselectivity for introduction of the fluorine was not determined.

(2-fluoro-3-phenylpropane-1,1-diyl)bis(ethylsulfane) (4-6)



Hydrocinnamaldehyde (0.30 ml, 2.3 mmol, 1.0 eq.) was added to a solution of (*R*)-5-benzyl-2,2,3,-trimethylimidazolidin-4-one dichloroacetic acid salt (0.16 g, 0.45 mmol, 0.20 eq.), and NFSI (1.1 g, 3.4 mmol, 1.5 eq.) in THF:*i*PrOH(10%) (7.0 ml, 0.30 M) at –20 ^{o}C. The reaction mixture was stirred for 16 hours at 0 ^{o}C. To verify that the reaction was complete, an aliquot was diluted with ether, filtered through a pad of silica gel, quenched with Me_2S, washed with a saturated solution of $NaHCO_3$, extracted with Et_2O and dried with $MgSO_4$. Due to the volatility of the C2-F aldehyde, the diethyl ether was removed by a stream of air. Directly to the reaction mixture at 0 ^{o}C was added ethanethiol (0.67 ml, 9.1mmol, 4.0 eq.) and conc. HCl (1.5 ml, 18.2 mmol, 8.0 eq.). The reaction was stirred for 16 hours at 25 ^{o}C followed by addition of NEt_3 (2 ml) and dilution with Et_2O (10 ml). A saturated solution (10 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with diethyl ether (3 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 95:5), provided **4-6** as a colorless oil (0.19 g, 32%): $\mathbf{R_f}$ = 0.32 (Hexanes/EtOAc, 95:5); **Formula** : $C_{13}H_{19}FS_2$; **MW** : 258.4184 g/mol ; **IR** (neat) ν_{max}

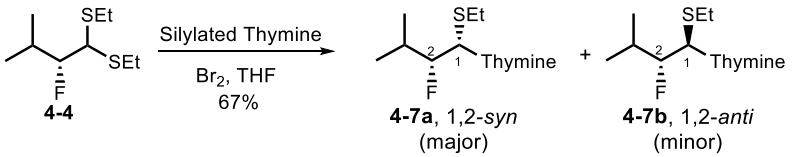
2963, 2926, 2869 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 4.99 – 4.85 (m, 1H), 3.92 (dd, *J* = 18.3, 4.4 Hz, 1H), 3.22 (ddd, *J* = 20.4, 14.1, 5.5 Hz, 2H), 2.83 – 2.69 (m, 4H), 1.33 – 1.26 (m, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.9 (d, *J* = 3.6 Hz), 129.6, 128.7, 126.9, 96.8 (d, *J* = 181.9 Hz), 53.8 (d, *J* = 21.8 Hz), 38.8 (d, *J* = 21.5 Hz), 25.63, 25.61, 14.64, 14.61 ppm ; **HRMS** calcd for $C_{13}H_{19}FS_2Na$ [M+Na^+] : 281.0804, found: 281.0802 (-0.73 ppm). Since we were only interested in the diastereoselectivity for the coupling of the nucleobase to the dithioacetal, the enantioselectivity for introduction of the fluorine was not determined.

Preparation of Thioaminals 4-7 and 4-8:

General Procedure 4-A:

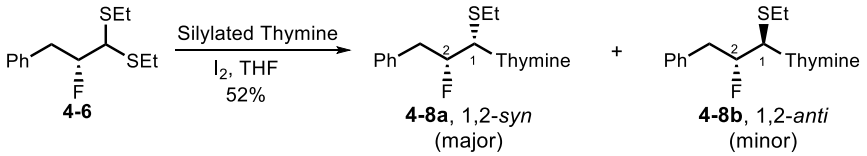
To a solution of the corresponding C2-F dithioacetal in anhydrous solvent at 0 °C were added silylated thymine and the activating agent. The reaction mixture was stirred until complete by TLC. In certain cases, additional silylated thymine and activating agent were added in order for the reaction to go to completion. A saturated solution (1 ml) of $Na_2S_2O_3$ (with I_2 or Br_2) or $NaHCO_3$ (with $Hg(OAc)_2$/TMSOTf or $Me_2S(SMe)BF_4$) was added and the aqueous layer was extracted with ethyl acetate (3 × 5 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.*

1-(1-(ethylthio)-2-fluoro-3-methylbutyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-7a and 4-7b)



Following general procedure 4-A, silylated thymine (0.90 ml, 0.63 mmol, 3.0 eq. of a 0.71 M solution in DCM), and Br_2 (22 µl, 0.42 mmol, 2.0 eq.) were added to a solution of **4-4** (44 mg, 0.21 mmol) in anhydrous THF (2.0 ml, 0.10 M) and stirred at –20 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 3.5:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 70:30) did not allow separation of the diastereomers and provided a mixture of **4-7a** and **4-7b** (39 mg, 67%) as a white foam: $\mathbf{R_f}$ = 0.30 (Hexanes/EtOAc, 70:30); **Formula** : $C_{12}H_{19}FN_2O_2S$; **MW** : 274.3549 g/mol ; **IR** (neat) ν_{max} 3183, 2967, 1686 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.89 (s, 1H, isomer **a**), 8.87 (s, 1H, isomer **b**), 7.68 (s, 1H, isomer **a**), 7.51 (s, 1H, isomer **b**), 6.09 – 5.94 (m, 2H, isomer **a** & **b**), 4.38 (ddd, *J* = 46.9, 7.6, 3.9 Hz, 1H, isomer **b**), 4.23 (ddd, *J* = 48.7, 9.4, 1.6 Hz, 1H, isomer **a**), 2.66 – 2.54 (m, 2H, isomer **b**), 2.51 (q, *J* = 7.4 Hz, 2H, isomer **a**), 2.20 – 2.08 (m, 1H, isomer **a**), 1.96 (s, 6H, isomer **a** & **b**), 1.90 – 1.78 (m, 1H, isomer **b**), 1.28 (t, *J* = 7.4 Hz, 3H, isomer **a**), 1.28 (t, *J* = 7.3Hz, 3H, isomer **b**), 1.06 – 0.99 (m, 12H, isomer **a** & **b**) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.7 (isomer **a**), 163.6 (isomer **b**), 151.5 (isomer **b**), 151.1 (isomer **a**), 138.0 (d, *J* = 5.0 Hz, isomer **a**), 137.8 (d, *J* = 6.6 Hz, isomer **b**), 111.9 (isomer **b**), 111.3 (isomer **a**), 101.0 (d, *J* = 180.6 Hz, isomer **a**), 99.1 (d, *J* = 52.8 Hz, isomer **b**), 61.1 (d, *J* = 19.3 Hz, isomer **a**), 59.3 (d, *J* = 22.0 Hz, isomer **b**), 30.9 (d, *J* = 19.1 Hz, isomer **a**), 30.3 (d, *J* = 19.6 Hz, isomer **b**), 25.2 (isomer **b**), 24.9 (isomer **a**), 18.5 (d, *J* = 4.8 Hz, isomer **a**), 18.4 (d, *J* = 10.1 Hz, isomer **b**), 17.8 (d, *J* = 8.6 Hz, isomer **a**), 17.5 (d, *J* = 6.5 Hz, isomer **b**), 14.7 (isomer **b**), 14.6 (isomer **a**), 12.83 (isomer **b**), 12.76 (isomer **a**) ppm ; **HRMS** calcd for : $C_{12}H_{19}FN_2O_2SNa$ $[M+Na^+]$: 297.1043, found: 297.1047 (1.07 ppm).

1-(1-(ethylthio)-2-fluoro-3-phenylpropyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-8a and 4-8b)

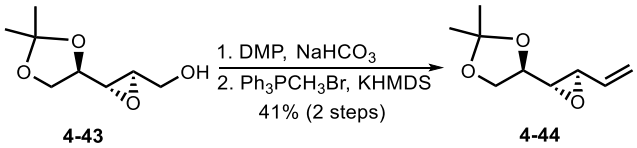


Following general procedure 4-A, silylated thymine (0.70 ml, 0.45 mmol, 3.0 eq. of a 0.71 M solution in DCM), and I_2 (76 mg, 0.30 mmol, 2.0 eq.) were added to a solution of **4-6** (39 mg, 0.15 mmol) in anhydrous THF (1.5 ml, 0.10 M) and stirred at 25 ^{o}C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 2.3:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 70:30) did not allow separation of the diastereomers and provided a mixture of **4-8a** and **4-8b** (25 mg, 52%) as a white foam: $\mathbf{R_f}$ = 0.19 (Hexanes/EtOAc, 70:30); **Formula** : $C_{16}H_{19}FN_2O_2S$; **MW** : 322.3977 g/mol ; **IR** (neat) ν_{max} 3183, 3027, 1692 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.57 (s, 1H, isomer **b**), 8.50 (s, 1H, isomer **a**), 7.61 (s, 1H, isomer **a**), 7.48 (s, 1H, isomer **b**), 7.33 – 7.17 (m, 10H, isomer **a** & **b**), 5.94 (dd, *J* = 24.0, 4.0 Hz, 1H, isomer **b**), 5.81 (dd, *J* = 29.2, 1.9 Hz, 1H, isomer **a**), 4.96 – 4.80 (m, 2H, isomer **a** & **b**), 3.24 (td, *J* = 13.9, 8.1 Hz, 1H, isomer **a**), 3.09 – 2.95 (m, 2H, isomer **a** & **b**), 2.91 – 2.79 (m, 1H, isomer **b**), 2.59 – 2.46 (m, 4H, isomer **a** & **b**), 1.93 (s, 3H, isomer **b**), 1.90 (s, 3H, isomer **a**), 1.27 (t, *J* = 7.2 Hz, 3H, isomer **b**), 1.26 (t, *J* = 7.3Hz, 3H, isomer **a**) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.5 (isomer **a**), 163.4 (isomer **b**), 151.4 (isomer **b**), 150.9 (isomer **a**), 137.7 (d, *J* = 4.8 Hz, isomer **a**), 137.4 (d, *J* = 4.6 Hz, isomer **b**), 135.4 (d, *J* = 1.6 Hz, isomer **b**), 135.3 (d, *J* = 6.0 Hz, isomer **a**), 129.4 (isomer **b**), 129.2 (isomer **a**), 128.9 (isomer **a**), 128.8 (isomer **b**), 127.4 (isomer **a**), 127.3 (isomer **b**), 112.0 (isomer **b**), 111.5 (isomer **a**), 96.9 (d, *J* = 181.5 Hz, isomer **a**), 95.1 (d, *J* = 183.0 Hz, isomer **b**), 62.3 (d, *J* = 19.7 Hz, isomer **a**), 61.1 (d, *J* = 17.1 Hz, isomer **b**), 39.4 (d, *J* = 21.3 Hz, isomer **a**), 38.8 (d, *J*

= 21.0 Hz, isomer **b**), 25.4 (isomer **b**), 25.1 (isomer **a**), 14.7 (isomer **a** & **b**), 12.8 (isomer **b**), 12.7 (isomer **a**) ppm ; **HRMS** calcd for : $C_{16}H_{19}FN_2O_2SNa$ [M+Na$^+$] : 345.1043, found: 345.1045 (0.47 ppm).

Compounds **4-9** to **4-16**[12] and **4-17** to **4-32**[9] were previously reported.

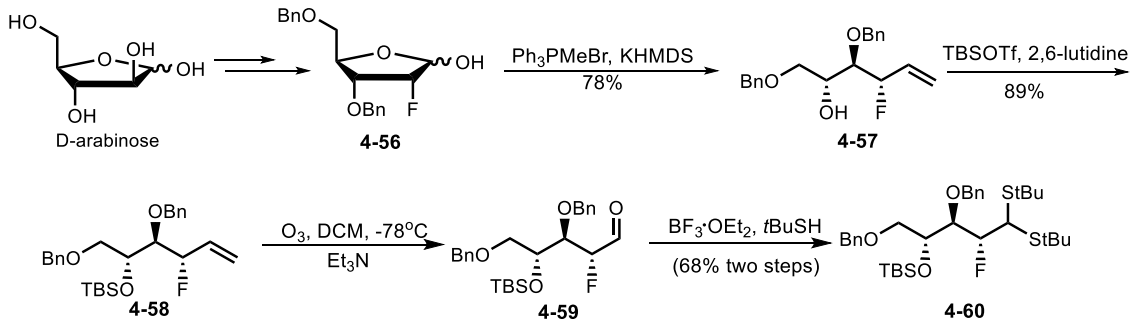
(*R*)-2,2-dimethyl-4-((2S,3R)-3-vinyloxiran-2-yl)-1,3-dioxolane (4-44)



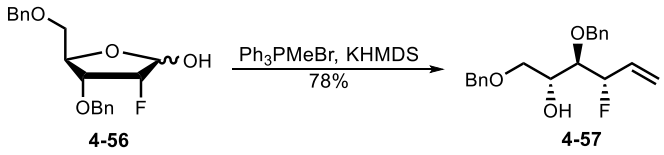
To a solution of **4-43** (68 mg, 0.39 mmol, 1.0 eq.) in anhydrous DCM (3.9 ml, 0.10 M) was added $NaHCO_3$ (0.33 g, 3.9 mmol, 10.0eq.) followed by DMP (0.21 g, 0.51 mmol, 1.3 eq.). The reaction mixture was stirred at 25 ^oC for 30 minutes. The DCM was evaporated and the reaction mixture was re-dissolved in diethyl ether and filtered over a silica pad before being evaporated. To a solution of dry methyltriphenylphosphonium bromide (0.24 g, 0.67 mmol, 1.7 eq., dried with benzene and left 16 hours under high vacuum) in anhydrous THF (2.8 ml, 0.24 M) was added potassium bis(trimethylsilyl) amide (1.2 ml, 0.59 mmol, 1.5 eq. of a 0.5 M solution in toluene). The reaction mixture was stirred at 25 ^oC for 1 hour. Upon cooling to 0 ^oC, the crude aldehyde (68 mg, 0.39 mmol, 1.0 eq.) as a solution in anhydrous THF (0.50 ml, 0.80 M) was added and stirred for 3 hours at 0 ^oC. The reaction mixture was diluted with diethyl ether and filtered over a pad of Celite®. Careful evaporation of the solvents (no heating of rotovap) was done as the product seemed to be volatile. Purification by flash chromatography (Hexanes/EtOAc, 60:40), provided **4-44** (27 mg, 41%, two steps) **Formula** : $C_9H_{14}O_3$; **MW** : 170.2057 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.59 (ddd, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.50 (dd,

J = 17.2, 1.4 Hz, 1H), 5.31 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.16 – 4.07 (m, 1H), 3.96 – 3.87 (m, 2H), 3.29 (dd, *J* = 7.3, 2.0 Hz, 1H), 2.95 (dd, *J* = 5.4, 2.0 Hz, 1H), 1.45 (s, 3H), 1.36 (s, 3H) ppm; **HRMS** calcd for $C_9H_{14}O_3Na$ [M+Na^+] : 190.0835, found: 190.0835 (-0.19 ppm).

Synthesis of Dithioacetal 4-60



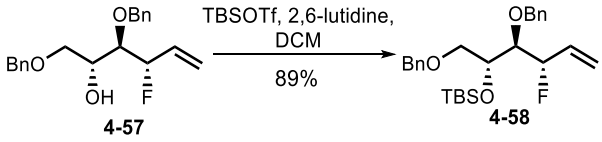
(+)-(2*R*,3*R*,4*S*)-1,3-bis(benzyloxy)-4-fluorohex-5-en-2-ol (4-57)



To a solution of dry methyltriphenylphosphonium bromide (1.6 g, 4.5 mmol, 3.0 eq., dried with benzene and left 16 hours under high vacuum) in anhydrous THF (8.0 ml, 0.55 M) at 0 °C was added potassium bis(trimethylsilyl) amide (9.0 ml, 4.5 mmol, 3.0eq. of a 0.5 M solution in toluene). The reaction mixture was stirred at 25 °C for 2 hours. Upon cooling to 0 °C, the starting lactol[13](0.50 g, 1.5 mmol, 1.0 eq.) as a solution in anhydrous THF (5.0 ml, 0.30 M) was added and stirred for 3 hours at 0 °C. Silica gel (0.80 g) was added and the reaction was concentrated to remove THF. The crude mixture was dissolved in diethyl ether (30.0 ml) and passed through a pad of silica gel. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **4-57** (0.39 g, 78%) as a colorless oil: : $\mathbf{R}_f$ = 0.59 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +58 (*c* 1.4, $CDCl_3$) ;

Formula : $C_{20}H_{23}FO_3$; **MW** : 330.3932 g/mol ; **IR** (neat) ν_{max} 3468, 2925, 2860 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 10H), 6.09 (dddd, *J* = 17.5, 13.4, 10.7, 6.9 Hz, 1H), 5.47 (ddd, *J* = 17.4, 2.5, 1.3 Hz, 1H), 5.39 (d, *J* = 10.7 Hz, 1H), 5.34 – 5.21 (m, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.56 – 4.48 (m, 3H), 3.84 (ddd, *J* = 14.1, 8.3, 2.7 Hz, 1H), 3.71 (ddd, *J* = 14.0, 7.1, 4.5 Hz, 1H), 3.67 – 3.63 (m, 1H), 3.60 (dd, *J* = 9.5, 5.6 Hz, 1H), 2.42 (d, *J* = 5.9 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.2, 137.9, 132.3 (d, *J* = 19.9 Hz), 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 120.0 (d, *J* = 12.2 Hz), 95.1 (d, *J* = 168.6 Hz), 80.1 (d, *J* = 21.1 Hz), 74.3 (d, *J* = 2.6 Hz), 73.6, 70.7 (d, *J* = 1.4 Hz), 69.9 (d, *J* = 8.1 Hz) ppm ; **HRMS** calcd for $C_{20}H_{23}FO_3Na$ $[M+Na^+]$: 353.1523, found: 353.1525 (0.54 ppm).

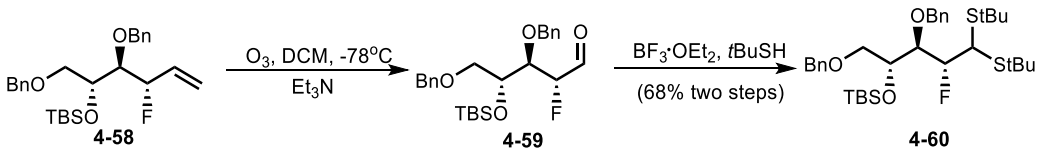
(+)-(((2*R*,3*R*,4*S*)-1,3-bis(benzyloxy)-4-fluorohex-5-en-2-yl)oxy)(tert-butyl)dimethylsilane (4-58)



To a solution of **4-57** (0.80 g, 2.4 mmol, 1.0 eq.) in anhydrous DCM (5.0 ml, 0.50 M) at 0 °C was added 2,6-lutidine (0.70 ml, 6.0 mmol, 2.5 eq.) and TBSOTf (0.85 ml, 3.6 mmol, 1.5 eq.). The reaction was stirred for 3 hours at 25 °C. A saturated solution (2 ml) of NH_4Cl was added and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **4-58** (0.96 g, 89%) as a colorless oil: : **R_f** = 0.25 (Hexanes/EtOAc, 95:5); **$[\alpha]^{25}_D$** +5.9 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{26}H_{37}FO_3Si$; **MW** : 444.6541 g/mol ; **IR** (neat) ν_{max} 2954, 2929, 2857 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 10H), 6.08 (dddd, *J* = 17.1, 15.1, 10.8, 6.2 Hz, 1H), 5.50 – 5.44 (m, 1H), 5.38 (d, *J* =

10.8 Hz, 1H), 5.29 – 5.15 (m, 1H), 4.73 (d, *J* = 11.3 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.52 (apps, 2H), 3.96 – 3.91 (m, 1H), 3.85 (ddd, *J* = 12.9, 5.9, 4.4 Hz, 1H), 3.67 (dd, *J* = 9.5, 3.1 Hz, 1H), 3.59 (dd, *J* = 10.0, 5.1 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.5, 138.4, 133.1 (d, *J* = 18.7 Hz), 128.44, 128.40, 128.1, 127.9, 127.72, 127.67, 119.2 (d, *J* = 12.3 Hz), 93.7 (d, *J* = 169.0 Hz), 81.4 (d, *J* = 22.7 Hz), 74.3 (d, *J* = 1.7 Hz), 73.4, 72.0 (d, *J* = 6.5 Hz), 71.8 (d, *J* = 2.0 Hz), 26.1, 18.3, -4.0, -4.7 ppm ; **HRMS** calcd for $C_{26}H_{37}FO_3SiNa$ [M+Na^+] : 467.2388, found: 467.2383 (-1.1 ppm).

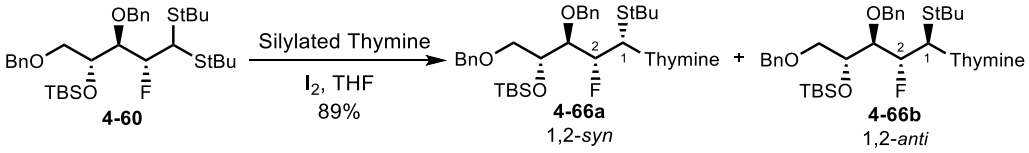
(–)-(((2*R*,3*R*,4*R*)-1,3-bis(benzyloxy)-5,5-bis(tert-butylthio)-4-fluoropentan-2-yl)oxy)(tert-butyl)dimethylsilane (4-60)



To a solution of **4-58** (0.37 g, 0.82 mmol, 1.0 eq.) in DCM (33.0 ml, 0.025 M) at –78 °C was bubbled O_3 under vacuum until the solution turned pale blue (about 15 minutes). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (0.23 ml, 1.6 mmol, 2.0 eq.), the reaction was warmed to 25 °C for 45 minutes. A 1 N HCl solution (20 ml) was added and the aqueous layer was extracted with dichloromethane (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* To the crude C2-F aldehyde **4-59** in anhydrous DCM (8.0 ml, 0.10 M) at –60 °C was added *t*BuSH (0.37 ml, 3.3 mmol, 4.0 eq.) and BF_3•OEt_2 (0.26 ml, 2.1 mmol, 2.5 eq.). The reaction was stirred at –40 °C for four hours. NEt_3 (0.46 ml, 3.3 mmol, 4.0 eq.) was added and stirring at –40 °C was maintained for 15 minutes. A saturated solution (5 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were

washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 95:5), provided **4-60** (0.34 g, 68%) as a colorless oil: : $\mathbf{R_f}$ = 0.43 (Hexanes/EtOAc, 90:10); $\mathbf{[\alpha]^{25}_D}$ –15 (*c* 1.0, $CDCl_3$) ; **Formula** : $C_{33}H_{53}FO_3S_2Si$; **MW** : 608.9860 g/mol ; **IR** (neat) ν_{max} 2958, 2936, 2855 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 10H), 5.02 (dd, *J* = 45.8, 9.0 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 4.53 (appt, *J* = 11.0 Hz, 3H), 4.49 – 4.32 (m, 2H), 4.11 (dd, *J* = 9.0, 3.1 Hz, 1H), 3.70 (dd, *J* = 9.8, 5.5 Hz, 1H), 3.57 – 3.52 (m, 1H), 1.35 (s, 9H), 1.35 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.6, 138.5, 128.41, 128.38, 127.8, 127.6, 127.5, 127.2, 95.3 (d, *J* = 177.4 Hz), 80.8 (d, *J* = 25.3 Hz), 73.5, 73.1, 72.1 (d, *J* = 5.8 Hz), 71.4, 47.3 (d, *J* = 20.2 Hz), 45.8, 44.0, 31.8, 31.6, 26.0, 18.3, -4.5, -4.6 ppm ; **HRMS** calcd for $C_{33}H_{53}FO_3S_2SiNa$ $[M+Na^+]$: 631.3082, found: 631.3076 (-0.93 ppm).

(–)-1-((1*S*,2*R*,3*R*,4*R*)-3,5-bis(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-1-(tert-butylthio)-2-fluoropentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-66a) and (+)- (1-((1*R*,2*R*,3*R*,4*R*)-3,5-bis(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-1-(tert-butylthio)-2-fluoropentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-66b)



Following general procedure 4-A, silylated thymine (0.90 ml, 0.62 mmol, 3.0 eq. of a 0.71 M solution in DCM), and I_2 (0.11 g, 0.41 mmol, 2.0 eq.) were added to a solution of **4-60** (0.13 g, 0.21 mmol) in anhydrous THF (2.0 ml, 0.10 M) and stirred at 25 ^oC. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 2.4:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **4-66a** (5

mg), a mix of **4-66a** & **4-66b** (88 mg) and **4-66b** (25 mg) for a total percent yield of 89% of white foams.

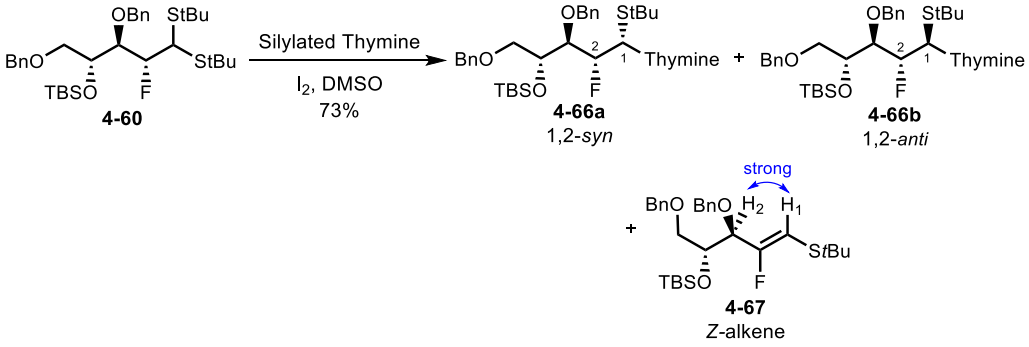
4-66a: $\mathbf{R_f}$ = 0.42 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –22 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{34}H_{49}FN_2O_5SSi$; **MW** : 644.9122 g/mol ; **IR** (neat) ν_{max} 3183, 3054, 2920, 1685 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.63 (s, 1H), 7.40 – 7.23 (m, 10H), 6.39 (appd, *J* = 33.0 Hz, 1H), 5.00 (d, *J* = 11.7 Hz, 1H), 4.90 (dd, *J* = 47.8, 9.2 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.49 (appq, *J* = 11.9 Hz, 2H), 4.25 (appt, *J* = 6.0 Hz, 1H), 4.01 (dd, *J* = 9.2, 4.7 Hz, 1H), 3.67 (dd, *J* = 9.6, 6.5 Hz, 1H), 3.54 – 3.46 (m, 1H), 1.95 (s, 3H), 1.22 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.6, 150.1, 138.7 (d, *J* = 3.3 Hz), 138.3, 138.1, 128.48, 128.46, 127.74, 127.71, 127.5, 126.8, 110.8, 95.4 (d, *J* = 178.5 Hz), 80.3 (d, *J* = 24.2 Hz), 73.53, 73.49, 71.4 (d, *J* = 4.4 Hz), 71.1, 59.2 (d, *J* = 17.3 Hz), 44.8, 31.1, 26.0, 18.3, 12.7, -4.6, -4.7 ppm ; **HRMS** calcd for : $C_{34}H_{49}FN_2O_5SSiNa$ $[M+Na^+]$: 667.3008, found: 667.3021 (2.1 ppm).

4-66b: $\mathbf{R_f}$ = 0.44 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +27 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{34}H_{49}FN_2O_5SSi$; **MW** : 644.9122 g/mol ; **IR** (neat) ν_{max} 3183, 3033, 2928, 1700, 1683 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.50 (s, 1H), 7.35 – 7.23 (m, 10H), 6.28 (appd, *J* = 27.8 Hz, 1H), 5.00 (ddd, *J* = 7.0, 6.3, 1.6 Hz, 1H), 4.63 (d, *J* = 10.5 Hz, 1H), 4.54 (d, *J* = 10.4 Hz, 1H), 4.47 (apps, 2H), 4.24 (appq, *J* = 4.7 Hz, 1H), 3.75 (dd, *J* = 12.5, 7.0 Hz, 1H), 3.61 (dd, *J* = 9.9, 4.4 Hz, 1H), 3.57 (dd, *J* = 9.9, 4.9 Hz, 1H), 1.82 (s, 3H), 1.29 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.3, 150.7, 139.0 (d, *J* = 5.9 Hz), 138.2, 137.9, 128.5, 128.4, 128.2, 127.9, 127.81, 127.75, 110.7, 95.5 (d, *J* = 180.4 Hz), 79.9 (d, *J* = 23.0 Hz), 74.6, 73.4, 71.3 (d, *J* = 5.4 Hz), 71.1 (d, *J* = 2.3 Hz), 56.7 (d, *J* = 18.0 Hz), 45.4,

31.2, 26.0, 18.3, 12.6, -4.2, -4.7 ppm ; **HRMS** calcd for : $C_{34}H_{49}FN_2O_5SSiNa$ [M+Na^+] : 667.3008, found: 667.3012 (0.57 ppm).

Coupling of silylated thymine with the dithioacetal using DMSO as a solvent resulted in the following impurity which was identified as the *Z*-alkene based on strong coupling between H_1 and H_2 in a NOESY experiment.

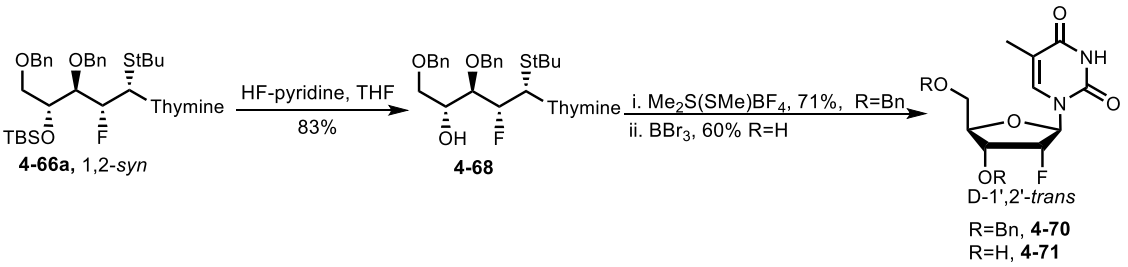
(((2*R*,3*R*,*Z*)-1,3-bis(benzyloxy)-5-(tert-butylthio)-4-fluoropent-4-en-2-yl)oxy)(tert-butyl)dimethylsilane (4-67)



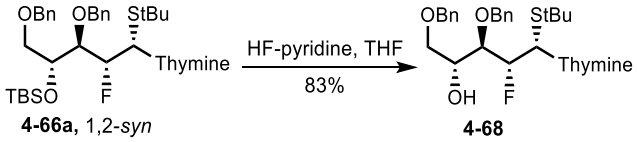
Following general procedure 4-A, silylated thymine (0.50 ml, 0.37 mmol, 3.0 eq. of a 0.74 M solution in DCM), and I_2 (61 mg, 0.24 mmol, 2.0 eq.) were added to a solution of **4-60** (74 mg, 0.12 mmol) in anhydrous DMSO (1.2 ml, 0.10 M) and stirred at 0 ^oC for 16 hours. An aliquot of the reaction mixture indicated that the presence of starting material, so an additional 3.0 eq. of silylated thymine and 2.0 eq. of I_2 were added and the reaction was stirred for 16 additional hours at 0 ^oC. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a 3:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **4-67** and a mix of **4-66a** & **4-66b** (52 mg, 73%).

4-67: Formula : $C_{29}H_{43}FO_3SSi$; **MW** : 518.7988 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 10H), 5.58 (d, *J* = 34.3 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.53 (appd, *J* = 1.9 Hz, 2H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.03 – 3.93 (m, 2H), 3.61 (ddd, *J* = 12.7, 10.0, 3.3 Hz, 2H), 1.37 (s, 9H), 0.86 (s, 9H), 0.03 (s, 6H) ppm; **HRMS** calcd for : $C_{29}H_{43}FO_3SSiNa$ [M+Na^+] : 541.2578, found: 541.2585 (1.3 ppm).

Preparation of D-1,2-*trans* furanoside 4-71:



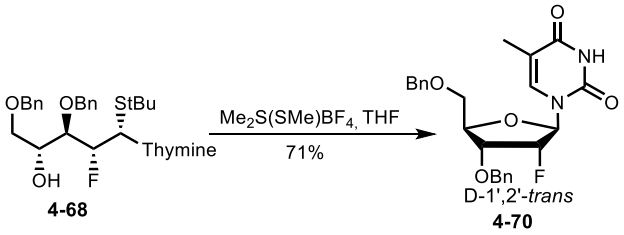
(–)-1-((1*S*,2*R*,3*R*,4*R*)-3,5-bis(benzyloxy)-1-(tert-butylthio)-2-fluoro-4-hydroxypentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-68)



To a solution of **4-66a** (76 mg, 0.12 mmol, 1.0 eq.) in anhydrous THF (1.2 ml, 0.10 M) in a plastic vial at 0 ^oC was added HF-pyridine (0.24 ml, 2ml/mmol, ~70% HF). The reaction was stirred for 16 hours at 25 ^oC. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 1 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 60:40), provided **4-68** (51.5 mg, 83%): $\mathbf{R_f}$ = 0.22 (Hexanes/EtOAc, 60:40); $\mathbf{[\alpha]^{25}_D}$ –17 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{28}H_{35}FN_2O_5S$; **MW** : 530.6513 g/mol ; **IR** (neat) ν_{max}

3435, 3194, 2931, 1680 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.56 (s, 1H), 7.36 – 7.21 (m, 10H), 6.35 (appd, *J* = 30.8 Hz, 1H), 4.86 – 4.71 (m, 2H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.54 – 4.47 (m, 2H), 4.18 (apps, 1H), 3.99 (apps, 1H), 3.59 (dd, *J* = 11.5, 6.4 Hz, 2H), 2.61 (d, *J* = 3.5 Hz, 1H), 1.92 (s, 3H), 1.22 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.6, 150.3, 138.3, 137.9, 137.7, 128.612, 128.610, 127.99, 127.98, 127.91, 127.5, 111.2, 95.3 (d, *J* = 182.6 Hz), 78.4 (d, *J* = 23.5 Hz), 73.7, 73.6, 70.6 (d, *J* = 4.7 Hz), 70.3, 58.9 (d, *J* = 15.9 Hz), 45.0, 31.1, 12.8 ppm ; **HRMS** calcd for $C_{28}H_{35}FN_2O_5SNa$ [M+Na^+] : 553.2143, found: 553.2153 (1.8 ppm).

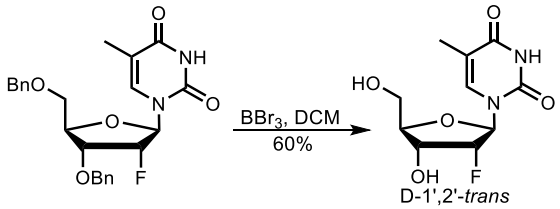
(+)-1-((2*R*,3*R*,4*R*,5*R*)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-70)



To a solution of **4-68** (47 mg, 0.09 mmol, 1.0 eq.) in anhydrous THF (1.0 ml, 0.10 M) was added $Me_2S(SMe)BF_4$ (35 mg, 0.18 mmol, 2.0 eq.). The reaction was stirred for 5 hours at 25 ^oC. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 x 1 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 60:40), provided **4-70** (28 mg, 71%): **R_f** = 0.28 (Hexanes/EtOAc, 60:40); **$[\alpha]^{25}_D$** +60 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{24}H_{25}FN_2O_5$; **MW** : 440.4641 g/mol ; **IR** (neat) ν_{max} 3183, 3033, 2920, 1695 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.55 (d, *J* = 1.1 Hz, 1H), 7.39 – 7.23 (m, 10H), 6.07 (dd, *J* = 16.3, 1.9 Hz, 1H), 5.05 (ddd, *J* = 52.3, 4.0, 1.9 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.55 (dt, *J* = 17.6, 8.1 Hz, 3H), 4.30 (d, *J* = 6.7 Hz, 1H), 4.22 (ddd, *J* = 18.6, 7.5, 4.1 Hz, 1H), 3.94 (dd, *J* = 11.1, 1.9 Hz, 1H), 3.67 (dd, *J* = 11.1, 2.3 Hz, 1H), 1.52 (s, 3H) ppm; **^{13}C**

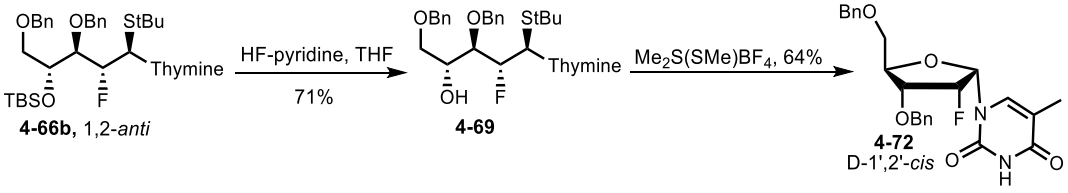
NMR (125 MHz, $CDCl_3$) δ 163.4, 150.0, 137.4, 137.2, 135.8, 128.80, 128.75, 128.4, 128.3, 128.0, 127.9, 111.1, 91.8 (d, *J* = 192.3 Hz), 88.7 (d, *J* = 34.1 Hz), 81.2 (d, *J* = 1.4 Hz), 74.9 (d, *J* = 15.8 Hz), 73.9, 73.1 (d, *J* = 1.1 Hz), 68.2, 12.1 ppm ; **HRMS** calcd for $C_{24}H_{25}FN_2O_5Na$ $[M+Na^+]$: 463.1640, found: 463.1631 (-1.9 ppm).

(+)-1-((2*R*,3*R*,4*R*,5*R*)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-71)

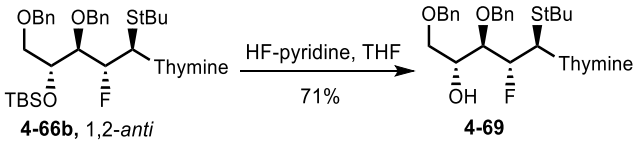


To a solution of **4-70** (29 mg, 0.07 mmol, 1.0 eq.) in anhydrous DCM (0.70 ml, 0.10 M) at –78 ^oC was added BBr_3 (0.26 ml, 0.26 mmol, 4.0 eq., 1M soln in DCM). The reaction was stirred for 4 hours at –78 ^oC and a 1:1 mixture of MeOH:DCM (1.0 ml) was added followed by $AgCO_3$ (0.28 g, 0.97 mmol, 15.0 eq.). Stirring was continued for 30 minutes at 25 ^oC followed by filtration on celite and concentration. Purification by flash chromatography (DCM/MeOH, 90:10), provided **4-71** (10 mg, 60%): $\mathbf{R_f}$ = 0.26 (DCM/MeOH, 90:10); $\mathbf{[\alpha]^{25}_D}$ +20 (*c* 1.0, CD_3OD) ; **Formula** : $C_{10}H_{13}FN_2O_5$; **MW** : 260.2214 g/mol ; **IR** (neat) ν_{max} 3392, 3070, 2936, 1696, 1664 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.89 (s, 1H), 6.01 (dd, *J* = 17.6, 2.0 Hz, 1H), 5.03 (ddd, *J* = 53.2, 4.5, 2.0 Hz, 1H), 4.35 (ddd, *J* = 19.7, 7.6, 4.6 Hz, 1H), 4.02 (d, *J* = 7.6 Hz, 1H), 3.97 (dd, *J* = 12.5, 2.2 Hz, 1H), 3.79 (dd, *J* = 12.5, 3.0 Hz, 1H), 1.89 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in CD_3OD*; The proton NMR data in $(CD_3)_2SO$ has previously been reported[14] however, we observed slight differences in the coupling constants. **^{1}H NMR** (500 MHz, $(CD_3)_2SO$) δ 11.35 (s, 1H), 7.78 (s, 1H), 5.91 (dd, *J* = 17.6, 2.2 Hz, 1H), 5.59

(d, *J* = 6.3 Hz, 1H), 5.23 (t, *J* = 5.1 Hz, 1H), 5.01 (ddd, *J* = 53.2, 4.3, 2.2 Hz, 1H), 4.22 – 4.12 (m, 1H), 3.86 (d, *J* = 7.2 Hz, 1H), 3.76 (dd, *J* = 7.2, 5.0 Hz, 1H), 3.62 – 3.55 (m, 1H), 1.75 (s, 3H) ppm; **^{13}C NMR** (125 MHz, CD_3OD) δ 166.4, 152.2, 138.3, 111.4, 95.0 (d, *J* = 186.8 Hz), 89.6 (d, *J* = 34.4 Hz), 84.7, 69.5 (d, *J* = 16.7 Hz), 61.1, 12.4 ppm ; **HRMS** calcd for $C_{10}H_{13}FN_2O_5Na$ [M+Na^+] : 283.0701, found: 283.0698 (-0.87 ppm).



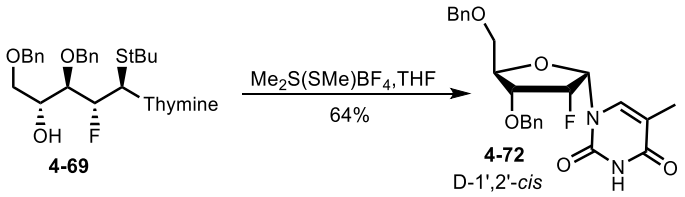
(+)-1-((1*R*,2*R*,3*R*,4*R*)-3,5-bis(benzyloxy)-1-(tert-butylthio)-2-fluoro-4-hydroxypentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-69)



To a solution of **4-66b** (31 mg, 0.05 mmol, 1.0 eq.) in anhydrous THF (0.50 ml, 0.10 M) in a plastic vial at 0 ^oC was added HF-pyridine (0.10 ml, 2ml/mmol, ~70% HF). The reaction was stirred for 16 hours at 25^oC. A saturated solution (0.50 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 0.50 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 60:40), provided **4-69** (18.1 mg, 71%): $\mathbf{R_f}$ = 0.22 (Hexanes/EtOAc, 60:40); **$[\alpha]^{25}_D$** +81 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{28}H_{35}FN_2O_5S$; **MW** : 530.6513 g/mol ; **IR** (neat) ν_{max} 3419, 3182, 2961, 1675 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.47 (s, 1H), 7.37 – 7.14 (m, 10H), 6.37 (dd, *J* = 25.2, 3.5 Hz, 1H), 5.02 (dt, *J* = 44.7, 3.6 Hz, 1H), 4.58 (d, *J* = 10.9 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.44 (d, *J* = 10.9 Hz, 1H), 4.24 –

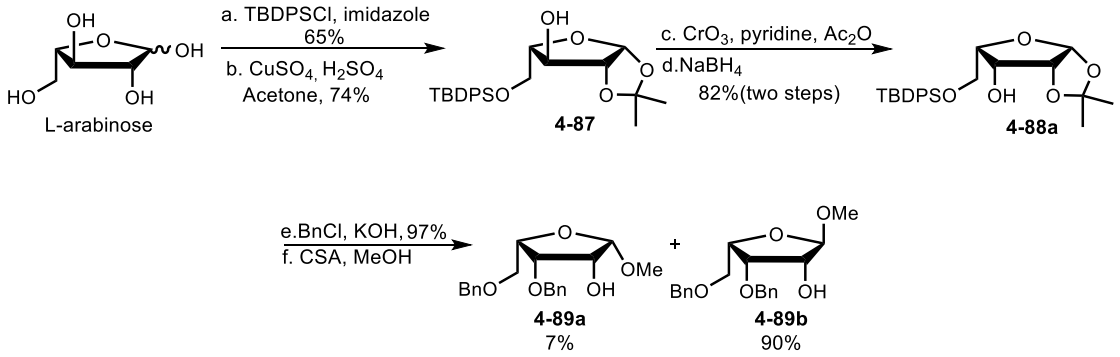
4.17 (m, 1H), 3.91 (ddd, *J* = 14.3, 7.7, 3.0 Hz, 1H), 3.65 – 3.55 (m, 2H), 2.77 (d, *J* = 5.5 Hz, 1H), 1.86 (s, 3H), 1.31 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.3, 150.8, 138.6, 137.8, 137.4, 128.6, 128.5, 128.2, 128.12, 128.09, 128.06, 110.8, 95.9 (d, *J* = 181.8 Hz), 79.1 (d, *J* = 19.7 Hz), 74.6, 73.6, 70.7, 69.8 (d, *J* = 8.9 Hz), 56.4 (d, *J* = 19.2 Hz), 45.8, 31.1, 12.7 ppm ; **HRMS** calcd for $C_{28}H_{35}FN_2O_5SNa$ [M+Na^+] : 553.2143, found: 553.2151 (1.4 ppm).

(+)-1-((2*S*,3*R*,4*R*,5*R*)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-72)

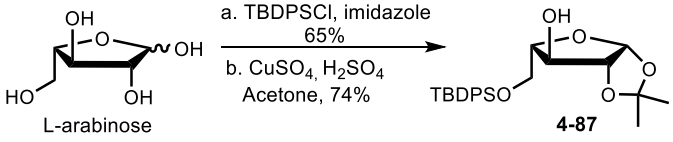


To a solution of **4-69** (17 mg, 0.03 mmol, 1.0 eq.) in anhydrous THF (0.32 ml, 0.10 M) was added $Me_2S(SMe)BF_4$ (13 mg, 0.06 mmol, 2.0 eq.). The reaction was stirred for 5 hours at 25 ^oC. A saturated solution (0.50 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 x 0.50 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 60:40), provided **4-72** (8.9 mg, 64%): $\mathbf{R_f}$ = 0.28 (Hexanes/EtOAc, 60:40); $\mathbf{[\alpha]^{25}_D}$ +29 (*c* 0.7, $CDCl_3$) ; **Formula** : $C_{24}H_{25}FN_2O_5$; **MW** : 440.4641 g/mol ; **IR** (neat) ν_{max} 3193, 3038, 2861, 1685 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.41 – 7.27 (m, 11H), 6.25 (dd, *J* = 17.8, 3.5 Hz, 1H), 5.15 (dt, *J* = 53.9, 3.6 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.57 (appt, *J* = 11.3 Hz, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.46 – 4.42 (m, 1H), 4.25 (ddd, *J* = 19.3, 6.9, 3.8 Hz, 1H), 3.73 (dd, *J* = 10.9, 2.2 Hz, 1H), 3.57 (dd, *J* = 11.0, 3.3 Hz, 1H), 1.88 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.5, 150.3, 137.6, 136.9, 136.8, 128.8, 128.7, 128.6,

128.2, 128.1, 127.9, 110.2, 88.7 (d, J = 196.9 Hz), 84.6 (d, J = 15.6 Hz), 81.6, 77.0, 73.9, 73.3 (d, J = 1.2 Hz), 69.1, 12.6 ppm ; **HRMS** calcd for $C_{24}H_{25}FN_2O_5Na$ [M+Na^+] : 463.1640, found: 463.1645 (1.1 ppm).



(–)-(3a*R*,5*S*,6*S*,6a*R*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-imethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (4-87)

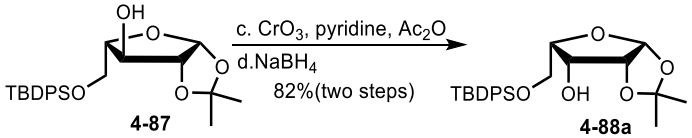


Following the literature procedure,[15,16] a slurry of L-arabinose (7.7 g, 50.9 mmol, 1.0 eq.) in anhydrous DMF (110 ml, 0.45 M) was heated at 100 ^oC until a homogenous solution was obtained (~ 20 minutes). The solution was brought to 55 ^oC and imidazole (6.9 g, 102 mmol, 2.0eq.) and TBDPSCl (13.3 ml, 50.9 mmol, 1.0 eq.) were added. The reaction mixture was stirred at 55 ^oC for 3 hours. Upon cooling to 25 ^oC, a 1 N HCl solution was added (25 ml) and the aqueous layer was extracted with dichloromethane (3 × 100 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided the TBDPS-protected L-arabinose (12.9 g, 65%) which has been reported in the literature.[15] To a

solution of the TBDPS-protected L-arabinose (12.8 g, 32.8 mmol, 1.0 eq.) in anhydrous acetone (164 ml, 0.20 M) was added c. H_2SO_4 (0.70 ml) and $CuSO_4$ (12.6 g, 78.8 mmol, 2.4 eq.). The reaction mixture was stirred at 25 ^oC for 16 hours, the solids filtered off and washed with acetone. Concentrated NH_4OH (2.5 ml) was added and the precipitated $(NH_4)_2SO_4$ was removed by filtration and the filtrate was concentrated. Purification by flash chromatography (Hexanes/EtOAc, 80:20) provided **4-87** (10.8 g, 77%). ^1H NMR spectroscopic data and $[\alpha]^{25}_D$ correlate with the previously reported data for **4-87**.[15,16]

4-87: $\mathbf{R_f}$ = 0.15 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ –3.8 (*c* 1.0, $CDCl_3$); **Formula** : $C_{24}H_{32}O_5Si$; **MW** : 428.5934 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 – 7.65 (m, 4H), 7.45 – 7.35 (m, 6H), 5.88 (d, *J* = 4.0 Hz, 1H), 4.54 (appd, *J* = 4.0 Hz, 1H), 4.43 (appt, *J* = 2.9 Hz, 1H), 4.07 – 4.02 (m, 1H), 3.87 – 3.79 (m, 2H), 1.78 (d, *J* = 4.1 Hz, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 1.07 (s, 9H) ppm.

(–)-(3a*R*,5*S*,6*R*,6a*R*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-methyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (4-88a)

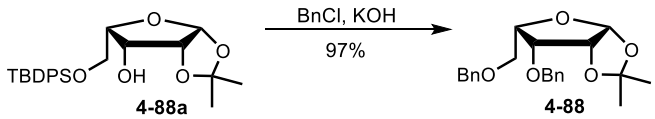


Following the literature procedure,[15,16] a suspension of CrO_3 (1.01 g, 10.0 mmol, 4.0 eq.) in anhydrous DCM (14.0 ml, 0.70 M) was added anhydrous pyridine (1.7 ml, 20.1 mmol, 8.0 eq.). The dark brown mixture was stirred for 30 minutes and a solution of **4-87** (1.07 g, 2.5 mmol, 1.0 eq.) in anhydrous DCM (9.0 ml, 0.28 M) was added followed by acetic anhydride (1.0 ml, 10.5 mmol, 4.2 eq.). Stirring was maintained for 15 minutes and a 1:1 mixture of ethyl acetate: toluene was added, resulting in precipitation of a black solid. The supernatant was decanted and

the solid was washed twice. The combined solutions were applied to a short silica gel column and the organic solvents were evaporated and dried with o-xylene to remove the acetic anhydride. The resulting ketone was used immediately without characterization. To a solution of crude starting material in ethanol (6.0 ml, 0.42 M) at 0 °C was added $NaBH_4$ (0.27 g, 7.02 mmol, 2.8 eq.). The ice bath was removed and stirring was maintained for 2 hours at 25 °C. The reaction was transferred to a separatory funnel containing DCM, brine and NH_4Cl (to remove excess $NaBH_4$). The aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **4-88a** (0.62 g, 57%). ^{1}H NMR spectroscopic data and $[\alpha]^{25}_D$ correlate with the previously reported data for **4-87**.[15,16]

4-87: $\mathbf{R_f}$ = 0.24 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ –6.4 (*c* 4.1, $CHCl_3$)[15]; **Formula** : $C_{24}H_{32}O_5Si$; **MW** : 428.5934 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.46 – 7.34 (m, 6H), 5.71 (d, *J* = 4.1 Hz, 1H), 4.62 (dd, *J* = 5.8, 4.1 Hz, 1H), 4.33 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.19 – 4.10 (m, 2H), 3.92 – 3.85 (m, 1H), 3.04 (d, *J* = 6.4 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.06 (s, 9H) ppm.

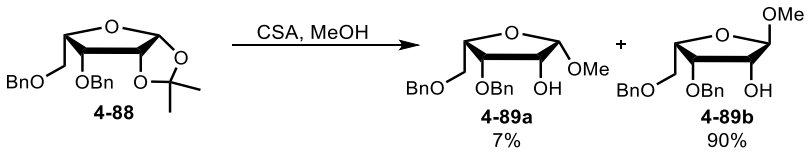
(–)-(3a*R*,5*S*,6*R*,6a*R*)-6-(benzyloxy)-5-((benzyloxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (4-88)



To a solution of **4-88a** (7.5 g, 17.5 mmol, 1.0 eq.) in anhydrous THF (88.0 ml, 0.20 M) was added freshly ground KOH (9.8 g, 175 mmol, 10.0 eq.) and BnCl (12.2 ml, 105 mmol, 6.0 eq.). The reaction was refluxed at 100 °C for 16 hours, filtered on celite, washed with DCM and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **4-88** (6.3

g, 97%): $\mathbf{R_f}$ = 0.18 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ –13 (*c* 1.2, $CDCl_3$) corresponds to that reported in the literature[17]; **Formula** : $C_{22}H_{26}O_5$; **MW** : 370.4388 g/mol ; **IR** (neat) ν_{max} 2985, 2936, 2867 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 10H), 5.72 (d, *J* = 4.0 Hz, 1H), 4.71 – 4.56 (m, 5H), 4.34 (appdd, *J* = 12.7, 6.0 Hz, 1H), 4.07 (dd, *J* = 7.2, 5.1 Hz, 1H), 3.89 (appd, *J* = 5.7 Hz, 2H), 1.50 (s, 3H), 1.32 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.6, 137.6, 128.6, 128.5, 128.1, 128.0, 127.97, 127.6, 113.7, 104.8, 80.2, 78.6, 77.4, 73.5, 72.8, 70.0, 26.7, 26.2 ppm ; **HRMS** calcd for $C_{22}H_{26}O_5Na$ $[M+Na^+]$: 393.1672, found: 393.1665 (-1.8 ppm).

(–)-(2*R*,3*R*,4*S*,5*S*)-4-(benzyloxy)-5-((benzyloxy)methyl)-2-methoxytetrahydrofuran-3-ol (4-89b) and (+)-(2*S*,3*R*,4*S*,5*S*)-4-(benzyloxy)-5-((benzyloxy)methyl)-2-methoxytetrahydrofuran-3-ol (4-89a)



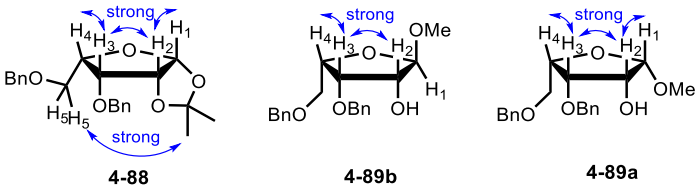
To a solution of **4-88a** (6.3 g, 16.9 mmol, 1.0 eq.) in anhydrous MeOH (240 ml, 0.07 M) was added CSA (120 mg). The reaction was refluxed at 90 ^oC for 16 hours, quenched with NEt_3 (2.0 ml) and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **4-89b** (5.24 g, 90%) and **4-89a** (0.44 g, 7%).

4-89b: $\mathbf{R_f}$ = 0.18 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ –68 (*c* 0.95, $CDCl_3$); **Formula** : $C_{20}H_{24}O_5$; **MW** : 344.4016 g/mol ; **IR** (neat) ν_{max} 3382, 3027, 2915 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 10H), 4.86 (apps, 1H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.41 (dd, *J* = 8.0, 4.9 Hz, 1H), 4.34 – 4.26 (m, 2H), 4.05 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.67 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.61 (dd, *J* = 10.5, 2.3 Hz, 1H), 3.34 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.9, 137.4, 128.57, 128.55, 128.1,

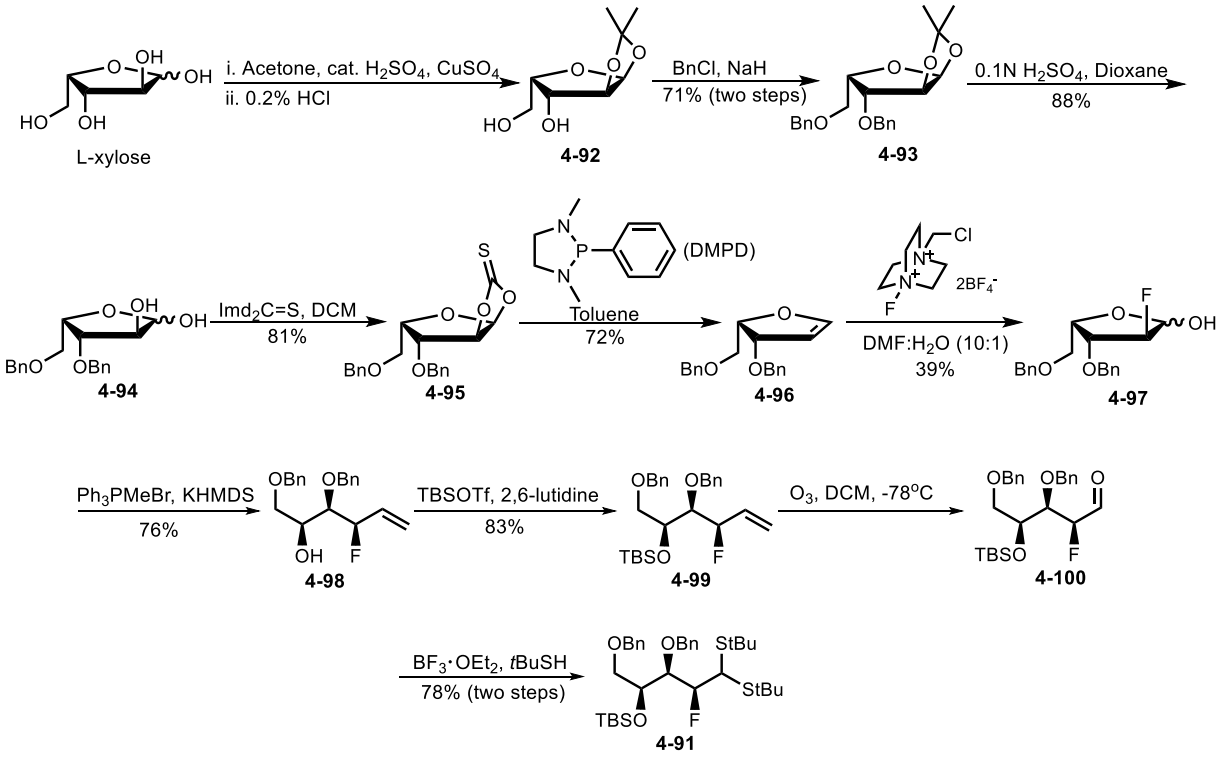
128.0, 127.98, 127.97, 108.6, 77.8, 77.6, 74.1, 72.7, 72.2, 68.0, 55.2 ppm ; **HRMS** calcd for $C_{20}H_{24}O_5Na$ [M+Na^+] : 367.1516, found: 367.1527 (2.9 ppm).

4-89a: $\mathbf{R_f}$ = 0.11 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +74 (*c* 0.8, $CDCl_3$); **Formula** : $C_{20}H_{24}O_5$; **MW** : 344.4016 g/mol ; **IR** (neat) ν_{max} 3553, 3022, 2925 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 10H), 4.79 (d, *J* = 4.9 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.59 – 4.53 (m, 2H), 4.25 (dd, *J* = 11.9, 5.8 Hz, 1H), 4.17 – 4.11 (m, 1H), 4.02 (appt, *J* = 5.8 Hz, 1H), 3.71 (dd, *J* = 9.8, 5.7 Hz, 1H), 3.64 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.43 (s,3H), 3.00 (d, *J* = 11.4 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.2, 138.1, 128.6, 128.5, 128.0114, 128.0095, 127.96, 127.8, 102.2, 79.3, 76.6, 74.5, 73.7, 73.0, 70.1, 56.1 ppm ; **HRMS** calcd for $C_{20}H_{24}O_5Na$ [M+Na^+] : 367.1516, found: 367.1522 (1.5 ppm).

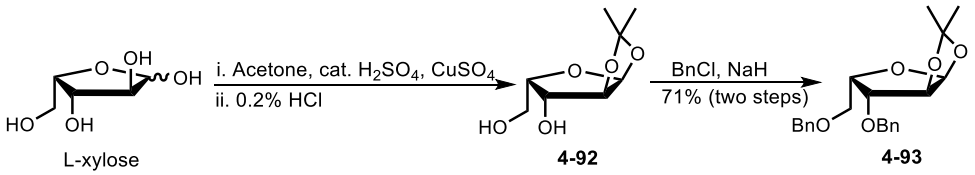
Proof of structure for the C1'-C2' relative stereochemistry were provided by NOESY experiments.



Synthesis of Dithioacetal 4-91.



(+)-(3*S*,5*S*)-6-(benzyloxy)-5-((benzyloxy)methyl)-2,2-imethyltetrahydrofuro[2,3][1,3]dioxole (4-93)

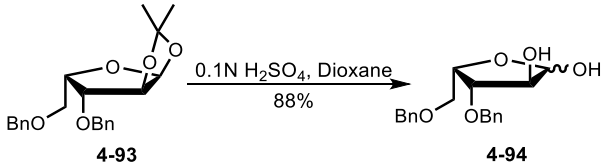


Following the literature procedure,[18] to a solution of dry acetone (20.0 ml, 0.33 M), conc. H_2SO_4 (0.10 ml) and anhydrous $CuSO_4$ (2.02 g, 12.6 mmol, 1.9 eq., dried by heating at 130 ^oC for 16 hours under high vacuum) was added L-xylose (1.0 g, 6.7 mmol, 1.0 eq.) The reaction mixture was stirred vigorously at 25 ^oC for 22 hours. The $CuSO_4$ was removed by filtration through Celite® and washed with acetone. The filtrate and washing were basified by addition of conc. NH_4OH (0.35 ml) and the precipitated $(NH_4)_2SO_4$ was filtered off and the solvent evaporated.

The residue was treated with 0.2% HCl (165 ml, 0.24M) and stirred for four hours. The reaction mixture was neutralized with solid $NaHCO_3$ (0.23 g), concentrated and co-evaporated once with a mixture of toluene (4.0 ml) and ethanol (4.0 ml). The residue was then dissolved in chloroform (7.0 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* To the crude **4-92** in anhydrous THF : DMF (20%) (23.0 ml, 0.30 M) at 0 ^oC was added BnBr (2.0 ml, 16.1 mmol, 2.4 eq.) and NaH (0.97 g, 24.2 mmol, 3.6 eq. of a 60% oil dispersion). The reaction was stirred at 25 ^oC for 16 hours. Water (7.0 ml) was added and the aqueous layer was extracted with diethyl ether (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **4-93** (1.8 g, 71%) as a pale yellow oil. Characterization data correlate with the previously reported data for the enantiomer.[18]

4-93: $\mathbf{R_f}$ = 0.34 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +42 (*c* 1.8, $CDCl_3$) ; **Formula** : $C_{22}H_{26}O_5$; **MW** : 370.4388 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 10H), 5.94 (d, *J* = 3.8 Hz, 1H), 4.69 – 4.59 (m, 3H), 4.53 (d, *J* = 4.4 Hz, 1H), 4.51 (d, *J* = 4.4 Hz, 1H), 4.41 (td, *J* = 6.1, 3.2 Hz, 1H), 3.98 (d, *J* = 3.2 Hz, 1H), 3.77 (qd, *J* = 9.9, 6.2 Hz, 2H), 1.49 (s, 3H), 1.32 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.2, 137.7, 128.6, 128.5, 128.0, 127.9, 127.8, 127.7, 111.8, 105.2, 82.6, 81.9, 79.4, 73.7, 72.2, 67.7, 27.0, 26.5 ppm.

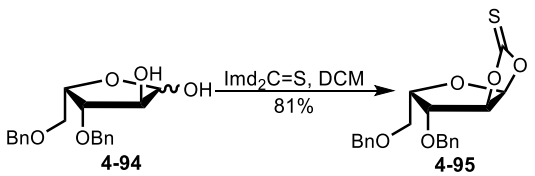
(–)-(3*S*,4*S*,5*S*)-4-(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2,3-diol (4-94)



Following the literature procedure,[18] to a solution of **4-93** (25.9 g, 70.0 mmol, 1.0 eq.), in 1,4-dioxane (230 ml, 0.30 M) was added 1 N H_2SO_4 (42 ml) The reaction mixture was refluxed for 4 hours. A saturated solution (50 ml) of $NaHCO_3$ was added and the reaction was concentrated. The aqueous layer was extracted with dichloromethane (5 × 40 ml) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **4-94** (20.2 g, 88%). Characterization data correlate with the previously reported data for the enantiomer.[18]

4-94: $\mathbf{R_f}$ = 0.22 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –7 (*c* 1.0, $CDCl_3$); **Formula** : $C_{19}H_{22}O_5$; **MW** : 330.3800 g/mol ; **IR** (neat) ν_{max} 3317, 2915, 2855 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 20H), 5.50 (appt, *J* = 4.6 Hz, 1H), 5.11 (d, *J* = 11.7 Hz, 1H), 4.71 – 4.47 (m, 9H), 4.43 (appq, *J* = 5.1 Hz, 1H), 4.26 (s, 1H), 4.22 (dt, *J* = 5.8, 4.4 Hz, 1H), 4.01 (ddd, *J* = 10.5, 5.1, 2.9 Hz, 2H), 3.88 (d, *J* = 11.8 Hz, 1H), 3.80 – 3.65 (m, 5H), 2.77 (d, *J* = 6.0 Hz, 1H), 2.06 (d, *J* = 4.4 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.3, 138.1, 137.9, 137.5, 128.8, 128.62, 128.58, 128.5, 128.3, 128.0, 127.99, 127.932, 127.930, 127.8, 127.738, 127.736, 103.7, 96.2, 83.8, 83.2, 80.1, 79.9, 77.9, 76.2, 73.9, 73.7, 73.1, 72.3, 69.1, 69.0 ppm ; **HRMS** calcd for : $C_{19}H_{22}O_5Na$ $[M+Na^+]$: 353.1359, found: 353.1358 (-0.32 ppm).

(–)-(3a*S*,5*S*,6*R*,6a*S*)-6-(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuro[2,3-d][1,3]dioxole-2-thione (4-95)

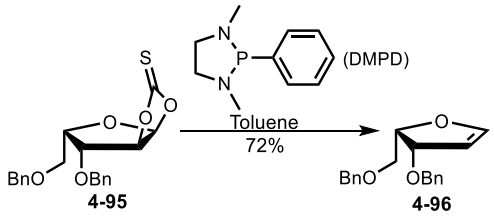


Following a slightly modified procedure,[19] to a solution of **4-94** (6.4 g, 19.5 mmol, 1.0 eq.) in anhydrous DCM (98 ml, 0.20 M) was added thiocarbonyldiimidazole (5.2 g, 29.2 mmol, 1.5 eq.).

The reaction mixture was stirred at 25 °C for 16 hours, diluted with DCM, washed with 10% HCl and evaporated. Co-evaporation with toluene was done opposed to a liquid-liquid extraction due to difficulty in separating the aqueous and organic layers. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **4-95** (5.9 g, 81%). Characterization data correlate with the previously reported data for the enantiomer.[19]

4-95: $\mathbf{R_f}$ = 0.53 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –26 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{20}H_{20}O_5S$; **MW** : 372.4348 g/mol ; **IR** (neat) ν_{max} 2866, 1313 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 10H), 6.40 (d, *J* = 4.6 Hz, 1H), 5.08 (d, *J* = 4.7 Hz, 1H), 4.59 (ddd, *J* = 33.7, 22.8, 11.9 Hz, 4H), 4.36 (td, *J* = 5.8, 3.5 Hz, 1H), 4.21 (d, *J* = 3.4 Hz, 1H), 3.78 (d, *J* = 5.8 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 189.8, 137.7, 136.5, 128.9, 128.69, 128.66, 128.10, 128.09, 128.0, 107.8, 86.1, 80.8, 79.6, 73.9, 73.1, 66.5 ppm ; **HRMS** calcd for : $C_{20}H_{20}O_5SNa$ [$M+Na^+$] : 395.0924, found: 395.0931 (1.7 ppm).

(+)-(2*S*,3*S*)-3-(benzyloxy)-2-((benzyloxy)methyl)-2,3-dihydrofuran (4-96)

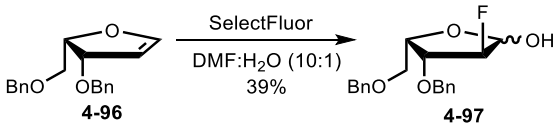


Following the literature procedure,[20] to a solution of **4-95** (3.06 g, 8.2 mmol, 1.0 eq.) in anhydrous toluene (16 ml, 0.50 M) was added DMPD (1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine) (3.7 ml, 19.7 mmol, 2.4 eq.). The reaction mixture was stirred at 70 °C for 4 hours, cooled to 25 °C and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **4-96** (1.75 g, 72%).

Characterization data correlates with the previously reported data for the enantiomer.[20]

4-96: $\mathbf{R_f}$ = 0.32 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +128 (*c* 1.4, $CDCl_3$); **Formula** : $C_{19}H_{20}O_3$; **MW** : 296.3603 g/mol ; **IR** (neat) ν_{max} 3030, 2914, 2861, 1607 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 10H), 6.65 (d, *J* = 2.7 Hz, 1H), 5.28 (appt, *J* = 2.6 Hz, 1H), 4.70 – 4.44 (m, 6H), 3.99 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.87 (dd, *J* = 10.6, 7.7 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 150.7, 138.8, 138.5, 128.54, 128.50, 128.0, 127.8, 127.7, 127.6, 101.6, 83.7, 79.8, 73.8, 71.0, 68.0 ppm ; **HRMS** calcd for : $C_{19}H_{20}O_3Na$ [M+Na^+] : 319.1305, found: 319.1303 (-0.55 ppm).

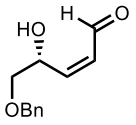
(–)-(3*S*,4*R*,5*S*)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrofuran-2-ol (4-97)



To a solution of **4-96** (1.75 g, 5.9 mmol, 1.0 eq.) in 10:1 DMF: H_2O (30 ml, 0.18 M) was added Selectfluor (3.1 g, 8.8 mmol, 1.5 eq.). The reaction mixture was stirred at 25 ^oC for 16 hours and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **4-97** (0.77 g, 39%): $\mathbf{R_f}$ = 0.27 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –5 (*c* 0.9, $CDCl_3$); **Formula** : $C_{19}H_{21}FO_4$; **MW** : 332.3714 g/mol ; **IR** (neat) ν_{max} 3419, 2920, 2861 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 20H), 5.56 – 5.48 (m, 1H), 5.30 (appt, *J* = 12.8 Hz, 1H), 4.97 (dd, *J* = 52.3, 2.6 Hz, 1H), 4.93 (dt, *J* = 52.0, 3.2 Hz, 1H), 4.74 – 4.47 (m, 7H), 4.41 (dd, *J* = 9.6, 4.3 Hz, 1H), 4.27 (tdd, *J* = 18.0, 5.5, 3.0 Hz, 2H), 4.09 (d, *J* = 11.9 Hz, 1H), 3.78 – 3.64 (m, 4H), 3.23 (d, *J* = 5.5 Hz, 1H) ppm *OH signals missing possibly due to exchange in $CDCl_3$*; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.3, 137.51, 137.48, 137.2, 128.8, 128.71, 128.70, 128.5, 128.4, 128.20, 128.16, 128.1, 128.0, 127.9, 127.83, 127.81, 101.2 (d, *J* = 34.2 Hz), 99.1 (d, *J* = 185.5 Hz), 96.0

(d, *J* = 17.3 Hz), 93.9 (d, *J* = 190.2 Hz), 81.2 (d, *J* = 24.6 Hz), 80.7, 80.5, 80.2 (d, *J* = 3.2 Hz), 74.1, 73.8, 73.3, 73.0, 68.52, 68.49 ppm ; **HRMS** calcd for : $C_{19}H_{21}FO_4Na$ [M+Na^+] : 355.1316, found: 355.1320 (1.05 ppm).

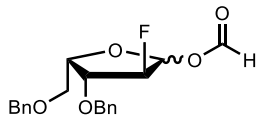
(*R*,*Z*)-5-(benzyloxy)-4-hydroxypent-2-enal (4-101)



4-101

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.26 (m, 5H), 7.13 (d, *J* = 16.1 Hz, 1H), 6.87 (dd, *J* = 16.1, 7.5 Hz, 1H), 4.69 (s, 2H), 4.64 (s, 2H), 4.30 (s, 2H) ppm.

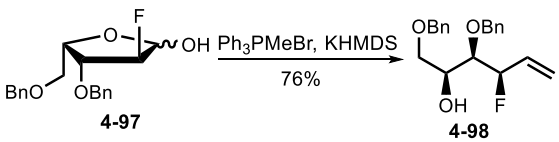
(3*S*,4*R*,5*S*)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrofuran-2-yl formate (4-102)



4-102

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.39 – 7.25 (m, 20H), 6.46 (dd, *J* = 4.1, 1.5 Hz, 1H), 6.34 (d, *J* = 13.3 Hz, 1H), 5.24 (appdt, *J* = 52.6, 4.7 Hz, 1H), 5.08 (appd, *J* = 49.6 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.63 – 4.50 (m, 8H), 4.43 – 4.37 (m, 1H), 4.24 (dd, *J* = 14.8, 5.5 Hz, 1H), 3.81 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.76 – 3.69 (m, 2H), 3.65 (dd, *J* = 10.6, 5.1 Hz, 1H) ppm; **HRMS** calcd for $C_{20}H_{21}FO_5Na$ [M+Na^+] : 383.1265, found: 383.1263 (-0.58 ppm).

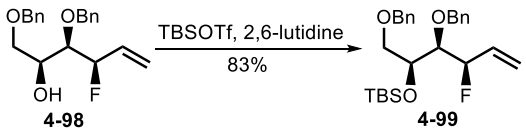
(+)-(2*S*,3*R*,4*R*)-1,3-bis(benzyloxy)-4-fluorohex-5-en-2-ol (4-98)



4-97 **4-98**

To a solution of dry methyltriphenylphosphonium bromide (2.5 g, 6.9 mmol, 3.0 eq., dried with benzene and left 16 hours under high vacuum) in anhydrous THF (13.0 ml, 0.55 M) at 0 °C was added potassium bis(trimethylsilyl) amide (14.0 ml, 6.9 mmol, 3.0eq. of a 0.5 M solution in toluene). The reaction mixture was stirred at 25 °C for 2 hours. Upon cooling to 0 °C, **4-97** (0.77 g, 2.3 mmol, 1.0 eq.) as a solution in anhydrous THF (8.0 ml, 0.30 M) was added and stirred for 3 hours at 0 °C. Silica gel (1.2 g) was added and the reaction was concentrated to remove THF. The crude mixture was dissolved in diethyl ether (30.0 ml) and passed through a pad of silica gel. Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **4-98** (0.58 g, 76%) as a colorless oil: : $\mathbf{R_f}$ = 0.34 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +23 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{20}H_{23}FO_3$; **MW** : 330.3994 g/mol ; **IR** (neat) ν_{max} 3392, 3027, 2850 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 10H), 6.02 – 5.91 (m, 1H), 5.50 – 5.45 (m, 1H), 5.36 (d, *J* = 10.7 Hz, 1H), 5.15 (appdt, *J* = 48.4, 6.6 Hz, 1H), 4.84 (d, *J* = 11.2 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.49 (appq, *J* = 11.9 Hz, 2H), 3.91 – 3.84 (m, 1H), 3.66 (ddd, *J* = 15.3, 6.6, 2.8 Hz, 1H), 3.56 – 3.44 (m, 2H), 2.28 (d, *J* = 7.4 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.2, 138.1, 133.2 (d, *J* = 18.9 Hz), 128.61, 128.57, 128.4, 128.1, 128.02, 127.98, 119.6 (d, *J* = 12.2 Hz), 94.7 (d, *J* = 171.8 Hz), 80.1 (d, *J* = 20.5 Hz), 75.0 (d, *J* = 2.7 Hz), 73.6, 71.2, 69.8 (d, *J* = 5.9 Hz) ppm ; **HRMS** calcd for $C_{20}H_{23}FO_3Na$ [M+Na^+] : 353.1523, found: 353.1529 (1.55 ppm).

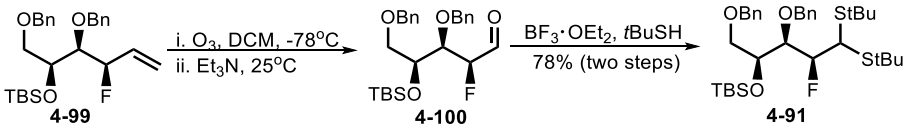
(–)-(((2*S*,3*R*,4*R*)-1,3-bis(benzyloxy)-4-fluorohex-5-en-2-yl)oxy)(tert-butyl)dimethylsilane (4-99)



To a solution of **4-98** (1.6 g, 4.7 mmol, 1.0 eq.) in anhydrous DCM (10 ml, 0.50 M) at 0 °C was added 2,6-lutidine (1.4 ml, 11.8 mmol, 2.5 eq.) and TBSOTf (1.7 ml, 7.1 mmol, 1.5 eq.). The

reaction was stirred for 5 hours at 0 °C. A saturated solution (5 ml) of NH_4Cl was added and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 95:5), provided **4-99** (1.74 g, 83%) as a colorless oil: : $\mathbf{R_f}$ = 0.53 (Hexanes/EtOAc, 95:5); $\mathbf{[\alpha]^{25}_D}$ –11 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{26}H_{37}FO_3Si$; **MW** : 444.6624 g/mol ; **IR** (neat) ν_{max} 2925, 2855 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 10H), 6.05 – 5.94 (m, 1H), 5.43 – 5.38 (m, 1H), 5.28 (d, *J* = 10.7 Hz, 1H), 5.25 – 5.12 (m, 1H), 4.70 (dd, *J* = 27.0, 11.7 Hz, 2H), 4.52 (apps, 2H), 4.05 (ddd, *J* = 6.5, 4.9, 3.4 Hz, 1H), 3.73 (dd, *J* = 10.1, 3.2 Hz, 1H), 3.59 – 3.53 (m, 1H), 3.49 (dt, *J* = 24.1, 4.4 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.6, 138.5, 134.4 (d, *J* = 19.7 Hz), 128.5, 128.4, 128.1, 127.82, 127.79, 127.6, 117.8 (d, *J* = 12.2 Hz), 92.6 (d, *J* = 173.7 Hz), 81.8 (d, *J* = 18.5 Hz), 74.3 (d, *J* = 1.1 Hz), 73.5, 72.22 (d, *J* = 4.1 Hz), 72.16 (d, *J* = 3.2 Hz), 26.1, 18.3, -4.1, -4.7 ppm ; **HRMS** calcd for $C_{26}H_{37}FO_3SiNa$ $[M+Na^+]$: 467.2388, found: 467.2396 (1.6 ppm).

(–)-(((2*S*,3*R*,4*S*)-1,3-bis(benzyloxy)-5,5-bis(tert-butylthio)-4-fluoropentan-2-yl)oxy)(tert-butyl)dimethylsilane (4-91)

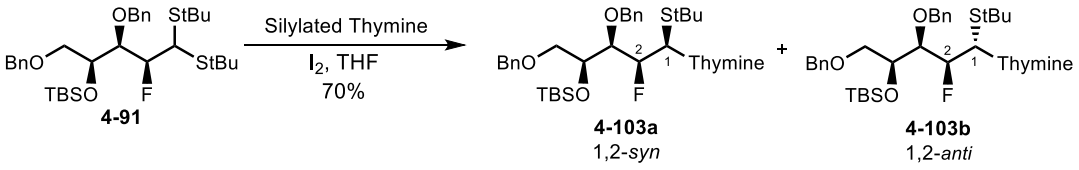


To a solution of **4-99** (1.74 g, 3.9 mmol, 1.0 eq.) in DCM (150 ml, 0.026 M) at –78 °C was bubbled O_3 under vacuum until the solution turned pale blue (about 20 minutes). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (1.1 ml, 7.8 mmol, 2.0 eq.), the reaction was warmed to 25 °C for 30 minutes. A 1 N HCl solution (20 ml) was added and the aqueous layer was extracted with dichloromethane (3 × 50 ml). The combined

organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* To the crude C2-F aldehyde **4-100** in anhydrous DCM (40 ml, 0.10 M) at –60 °C was added *t*BuSH (1.8 ml, 15.7 mmol, 4.0 eq.) and $BF_3{\cdot}OEt_2$ (1.3 ml, 9.8 mmol, 2.5 eq.). The reaction was stirred at -60 °C for five hours. NEt_3 (2.2 ml, 15.7 mmol, 4.0 eq.) was added and stirring at –60 °C was maintained for 15 minutes. A saturated solution (10 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **4-91** (1.85 g, 78%) as a colorless oil: : $\mathbf{R_f}$ = 0.48 (Hexanes/EtOAc, 90:10); $\mathbf{[\alpha]^{25}_D}$ –1.9 (*c* 1.3, $CDCl_3$) ; **Formula** : $C_{33}H_{53}FO_3S_2Si$; **MW** : 608.9874 g/mol ; **IR** (neat) ν_{max} 2958, 2925, 2861 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 10H), 4.77 – 4.63 (m, 3H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.35 (dd, *J* = 8.5, 7.0 Hz, 1H), 4.20 – 4.11 (m, 2H), 3.80 (d, *J* = 10.4 Hz, 1H), 3.57 – 3.51 (m, 1H), 1.39 (s, 9H), 1.37 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.9, 138.6, 128.44, 128.35, 127.8, 127.73, 127.69, 127.5, 92.0 (d, *J* = 187.5 Hz), 78.4 (d, *J* = 17.1 Hz), 73.5, 73.4, 72.7 (d, *J* = 7.0 Hz), 72.0, 47.4 (d, *J* = 24.6 Hz), 46.0, 45.5, 32.1 (d, *J* = 2.0 Hz), 31.9, 26.1, 18.4, -4.2, -4.4 ppm ; **HRMS** calcd for $C_{33}H_{53}FO_3S_2SiNa$ $[M+Na^+]$: 631.3082, found: 631.3087 (0.91 ppm).

4-100 (crude): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.75 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.27 (m, 10H), 5.09 (dd, *J* = 48.2, 3.5 Hz, 1H), 4.59 (apps, 2H), 4.53 (appq, *J* = 11.9 Hz, 2H), 4.05 (dd, *J* = 5.5, 2.7 Hz, 1H), 3.85 (ddd, *J* = 26.8, 5.5, 3.5 Hz, 1H), 3.76 – 3.71 (m, 1H), 3.62 (ddd, *J* = 10.2, 5.8, 2.6 Hz, 1H), 0.85 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H) ppm.

(+)-1-((1*R*,2*S*,3*R*,4*S*)-3,5-bis(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-1-(tert-butylthio)-2-fluoropentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-103a) and (–)-1-((1*S*,2*S*,3*R*,4*S*)-3,5-bis(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-1-(tert-butylthio)-2-fluoropentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-103b)



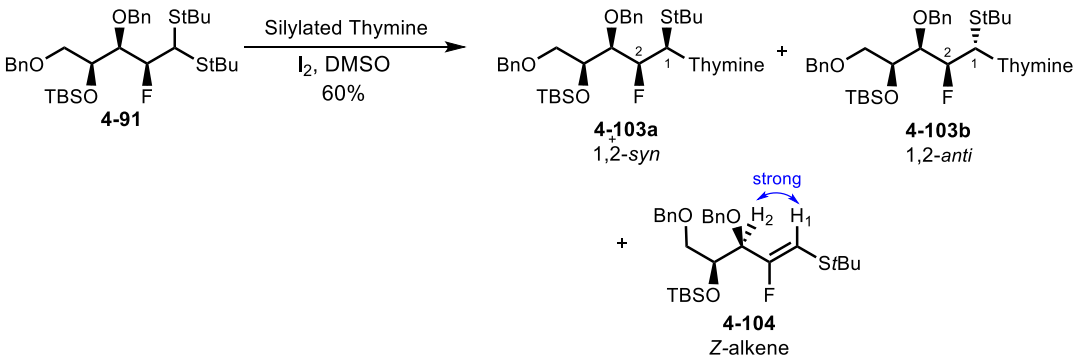
Following general procedure 4-A, silylated thymine (1.0 ml, 0.67 mmol, 3.0 eq. of a 0.70 M solution in THF), and I_2 (0.11 g, 0.45 mmol, 2.0 eq.) were added to a solution of **4-91** (0.14 g, 0.22 mmol, 1.0 eq.) in anhydrous THF (2.3 ml, 0.10 M) and stirred at 25 ^{o}C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 16:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **4-103a** (0.10 g, 70%) as a white foam: $\mathbf{R_f}$ = 0.28 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +46 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{34}H_{49}FN_2O_5SSi$; **MW** : 644.9184 g/mol ; **IR** (neat) ν_{max} 3199, 2920, 2861, 1680 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.44 (s, 1H), 7.38 – 7.26 (m, 10H), 6.18 (dd, *J* = 16.6, 5.9 Hz, 1H), 4.84 (appd, *J* = 46.5 Hz, 1H), 4.74 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 11.1 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.12 – 4.07 (m, 1H), 3.69 (dd, *J* = 9.8, 2.9 Hz, 1H), 3.59 (appd, *J* = 22.0 Hz, 1H), 3.48 – 3.41 (m, 1H), 1.89 (s, 3H), 1.32 (s, 9H), 0.82 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.2, 150.2, 138.5, 138.2, 138.0, 128.5, 128.4, 128.2, 127.9, 127.7, 127.6, 111.6, 92.2 (d, *J* = 188.1 Hz), 78.1 (d, *J* = 16.3 Hz), 74.0, 73.4, 71.7, 70.9, 58.5 (d, *J* = 25.6 Hz), 45.3, 31.3, 26.0, 18.2, 12.7, -4.0, -4.8 ppm ; **HRMS** calcd for : $C_{34}H_{49}FN_2O_5SSiNa$ [M+Na^+] : 667.3008, found: 667.3027 (2.91 ppm).

Following general procedure 4-A, silylated thymine (1.0 ml, 0.65 mmol, 3.0 eq. of a 0.74 M solution in DCM), and I_2 (0.12 g, 0.44 mmol, 2.0 eq.) were added to a solution of **4-91** (0.13 g, 0.22 mmol, 1.0 eq.) in anhydrous DCM (2.2 ml, 0.10 M) and stirred at 70 ^{o}C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1:1.4 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **4-103a** (35 mg) and **4-103b** (35 mg) for a total of a 50% yield.

4-103b: $\mathbf{R_f}$ = 0.24 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –45 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{34}H_{49}FN_2O_5SSi$; **MW** : 644.9184 g/mol ; **IR** (neat) ν_{max} 3188, 2925, 2850, 1674 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.36 (s, 1H), 7.35 – 7.25 (m, 10H), 6.25 (dd, *J* = 17.2, 6.6 Hz, 1H), 4.88 (dd, *J* = 45.7, 6.5 Hz, 1H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.46 (apps, 2H), 4.24 – 4.20 (m, 1H), 3.83 (dd, *J* = 28.1, 5.3 Hz, 1H), 3.73 (appd, *J* = 10.3 Hz, 1H), 3.47 – 3.41 (m, 1H), 1.90 (s, 3H), 1.29 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.2, 150.8, 138.5, 137.7, 137.5 (d, *J* = 2.3 Hz), 128.6, 128.4, 127.9, 127.7, 127.6, 127.4, 111.3, 91.1 (d, *J* = 187.9 Hz), 78.6 (d, *J* = 16.2 Hz), 77.4, 73.3, 71.9 (d, *J* = 6.3 Hz), 70.7, 58.0 (d, *J* = 20.5 Hz), 45.7, 31.1, 26.0, 18.2, 12.8, -4.2, -4.9 ppm ; **HRMS** calcd for : $C_{34}H_{49}FN_2O_5SSiNa$ [M+Na^+] : 667.3008, found: 667.3017 (1.46 ppm).

Coupling of silylated thymine with the dithioacetal using DMSO as a solvent resulted in the following impurity which was identified as the *Z*-alkene based on strong coupling between H1 and H2 in a NOESY experiment:

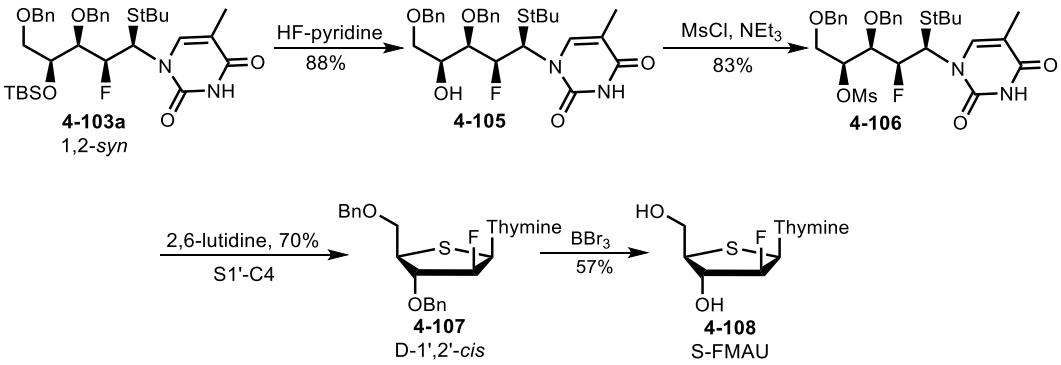
(((2*S*,3*R*,*Z*)-1,3-bis(benzyloxy)-5-(tert-butylthio)-4-fluoropent-4-en-2-yl)oxy)(tert-butyl)dimethylsilane (4-104)



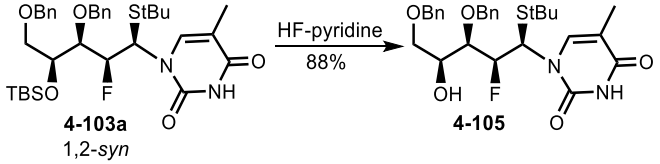
Following general procedure 4-A, silylated thymine (0.52 ml, 0.38 mmol, 3.0 eq. of a 0.74 M solution in DCM), and I_2 (65 mg, 0.26 mmol, 2.0 eq.) were added to a solution of **4-91** (78 mg, 0.13 mmol) in anhydrous DMSO (1.3 ml, 0.10 M) and stirred at 0 ^{o}C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 20:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **4-104** and **4-103a** (49 mg, 60%).

4-104: **Formula** : $C_{29}H_{43}FO_3SSi$; **MW** : 518.7988 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 10H), 5.58 (d, *J* = 34.2 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.46 (appd, *J* = 2.0 Hz, 2H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.05 – 3.92 (m, 2H), 3.62 (dd, *J* = 9.8, 4.4 Hz, 1H), 3.45 (dd, *J* = 9.7, 5.2 Hz, 1H), 1.35 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm; **HRMS** calcd for : $C_{29}H_{43}FO_3SSiNa$ [M+Na^+] : 541.2578, found: 541.2579 (0.14 ppm).

Preparation of D-1',2'-*cis* thiofuranoside 4-108 (S-FMAU).



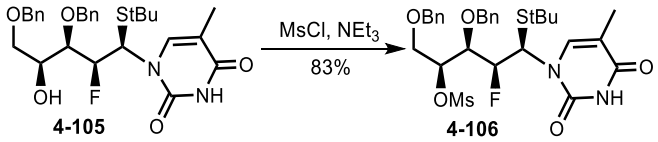
(+)-1-((1*R*,2*S*,3*R*,4*S*)-3,5-bis(benzyloxy)-1-(tert-butylthio)-2-fluoro-4-hydroxypentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-105)



To a solution of **4-103a** (104 mg, 0.16 mmol, 1.0 eq.) in anhydrous THF (1.7 ml, 0.10 M) in a plastic vial at 0 ^{o}C was added HF-pyridine (0.40 ml, 2ml/mmol, ~70% HF). The reaction was stirred for 16 hours at 25 ^{o}C. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 2 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **4-105** (75.2 mg, 88%): $\mathbf{R_f}$ = 0.20 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +74 (*c* 1.3, $CDCl_3$) ; **Formula** : $C_{28}H_{35}FN_2O_5S$; **MW** : 530.6554 g/mol ; **IR** (neat) ν_{max} 3425, 3188, 2958, 1680 cm^{-1} ; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ8.72 (s, 1H), 7.67 (s, 1H), 7.38 – 7.24 (m, 10H), 6.17 (appd, *J* = 31.7 Hz, 1H), 5.00 (appdd, *J* = 50.1, 8.3 Hz, 1H), 4.80 (d, *J* = 11.1 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.03 (apps, 1H), 3.94 (appt, *J* = 9.1 Hz, 1H), 3.62 – 3.55 (m, 1H), 3.42 (dd, *J* = 9.0, 5.8 Hz, 1H), 2.94 (s, 1H), 1.96 (s, 3H), 1.29 (s, 9H) ppm; ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 163.4, 150.6, 138.2 (d, *J* = 2.5 Hz), 138.03, 137.98, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 111.1, 98.3 (d, *J* =

181.7 Hz), 77.9 (d, *J* = 16.7 Hz), 75.1 (d, *J* = 3.3 Hz), 73.5, 70.9, 69.4 (d, *J* = 7.3 Hz), 58.7 (d, *J* = 18.7 Hz), 45.0, 31.2, 12.7 ppm ; **HRMS** calcd for $C_{28}H_{35}FN_2O_5SNa$ [M+Na^+] : 553.2143, found: 553.2149 (1.02 ppm).

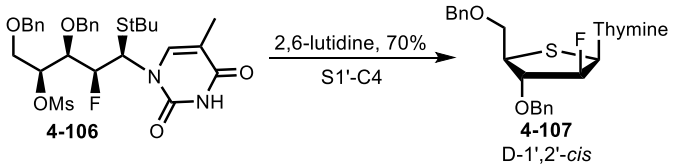
(+)-(2*S*,3*R*,4*S*,5*R*)-1,3-bis(benzyloxy)-5-(tert-butylthio)-4-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)pentan-2-yl methanesulfonate (4-106)



To a solution of **4-105** (75 mg, 0.14 mmol, 1.0 eq.) in anhydrous DCM (0.50 ml, 0.30 M) at 0 °C was added triethylamine (40 µl, 0.28 mmol, 2.0 eq.) and methanesulfonyl chloride (20 µl, 0.21 mmol, 1.5 eq). The reaction was stirred for 5 hours at 25 °C. A 1.0 N solution (0.50 ml) of HCl was added and the aqueous layer was extracted with dichloromethane (3 × 2 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **4-106** (75.9 mg, 83%): $\mathbf{R_f}$ = 0.15 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +64 (*c* 0.8, $CDCl_3$) ; **Formula** : $C_{29}H_{37}FN_2O_7S_2$; **MW** : 608.7404 g/mol ; **IR** (neat) ν_{max} 3178, 3038, 2963, 1688 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.65 (s, 1H), 7.37 – 7.28 (m, 10H), 6.14 (appd, *J* = 28.1 Hz, 1H), 5.03 (apptd, *J* = 6.1, 3.5 Hz, 1H), 4.85 (appd, *J* = 50.2 Hz, 1H), 4.78 (d, *J* = 10.9 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.12 (ddd, *J* = 10.9, 5.5, 2.8 Hz, 1H), 3.89 – 3.82 (m, 2H), 3.14 (s, 3H), 1.95 (s, 3H), 1.34 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.2, 150.3, 138.2, 137.6, 137.5, 128.7, 128.6, 128.4, 128.3, 128.1, 127.9, 111.1, 95.5 (d, *J* = 192.9 Hz), 77.1, 75.5, 73.7, 67.9, 58.5, 45.8, 38.7, 31.7,

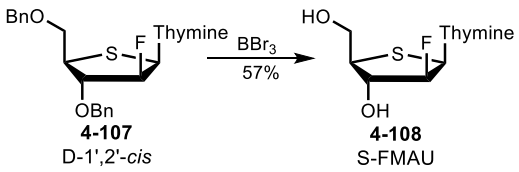
31.3, 12.6 ppm ; **HRMS** calcd for $C_{29}H_{37}FN_2O_7S_2Na$ [M+Na^+] : 631.1918, found: 631.1940 (3.35 ppm).

(+)-1-((2*R*,5*R*)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-107)



A solution of **4-106** (20 mg, 0.03 mmol, 1.0 eq.) in 2,6-lutidine (1.0 ml, 0.03 M) was refluxed for 4 hours at 160 ^oC. Upon cooling to room temperature, the reaction mixture was concentrated. Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **4-107** (10.5 mg, 70%): $\mathbf{R_f}$ = 0.33 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +60 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{24}H_{25}FN_2O_4S$; **MW** : 456.5324 g/mol ; **IR** (neat) ν_{max} 3183, 3065, 2861, 1691 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.85 (s, 1H), 7.39 – 7.27 (m, 10H), 6.46 (dd, *J* = 14.4, 5.0 Hz, 1H), 5.09 (dt, *J* = 50.8, 5.1 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.56 – 4.49 (m, 2H), 4.33 – 4.27 (m, 1H), 3.71 – 3.62 (m, 2H), 3.57 (appq, *J* = 5.1 Hz, 1H), 1.75 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.2, 150.9, 138.0 (d, *J* = 2.1 Hz), 137.6, 137.1, 128.75, 128.74, 128.4, 128.29, 128.25, 128.0, 110.7, 95.9 (d, *J* = 193.8 Hz), 80.8 (d, *J* = 22.7 Hz), 73.6, 72.8, 69.6, 59.7 (d, *J* = 16.9 Hz), 48.4, 12.4 ppm ; **HRMS** calcd for : $C_{24}H_{25}FN_2O_4S$ Na [M+Na^+] : 479.1411, found: 479.1423 (2.36 ppm).

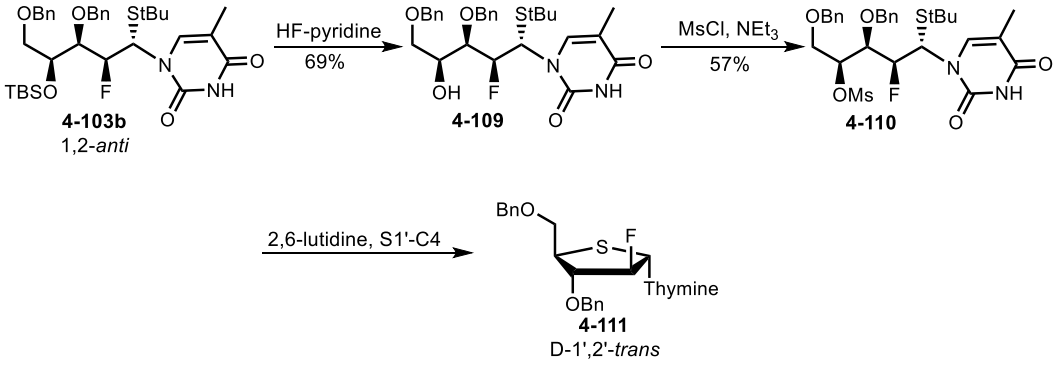
(+)-1-((2*R*,3*S*,4*S*,5*R*)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-108)



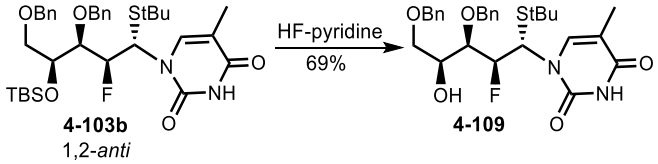
To a solution of **4-107** (26.3 mg, 0.058 mmol, 1.0 eq.) in anhydrous DCM (0.60 ml, 0.10 M) at –78 ^{o}C was added BBr_3 (0.25 ml, 0.23 mmol, 4.0 eq., 1.0 M solution in DCM). The reaction was stirred for 2 hours at -78 ^{o}C. A 1:1 mixture of MeOH : DCM (1.0 ml) and Ag_2CO_3 (0.24 g, 0.86 mmol, 15.0 eq.) was added and the reaction mixture was increased to room temperature with stirring for 30 minutes followed by filtration on celite and concentration. Purification by flash chromatography (DCM/MeOH, 90:10), provided **4-108** (9.1 mg, 57%). ^{1}H and ^{13}C NMR spectroscopic data correlate with the previously reported data.[21]

4-108: $\mathbf{R_f}$ = 0.41 (DCM/MeOH, 90:10); $\mathbf{[\alpha]^{25}_D}$ +37 (*c* 0.8, CD_3OD) ; **Formula** : $C_{10}H_{13}FN_2O_4S$; **MW** : 276.2824 g/mol ; **IR** (neat) ν_{max} 3360, 3054, 1681 cm^{-1} ; **^{1}H NMR** (500 MHz, D_2O) δ 8.26 (s, 1H), 6.34 (dd, *J* = 7.5, 6.0 Hz, 1H), 5.17 (ddd, *J* = 50.4, 7.2, 6.0 Hz, 1H), 4.41 (appdt, *J* = 12.5, 7.1 Hz, 1H), 3.94 (appd, *J* = 4.5 Hz, 2H), 3.41 (dt, *J* = 6.4, 4.8 Hz, 1H), 1.92 (s, 3H) ppm; **^{13}C NMR** (125 MHz, CD_3OD) δ 166.1, 152.9, 140.0 (d, *J* = 1.4 Hz), 111.0, 97.5 (d, *J* = 194.9 Hz), 74.5 (d, *J* = 23.0 Hz), 62.1, 59.7 (d, *J* = 16.9 Hz), 52.6 (d, *J* = 4.1 Hz), 12.4 ppm ; **HRMS** calcd for : $C_{10}H_{14}FN_2O_4S$ [M+H^{+}] : 277.0653, found: 277.0650 (-0.95 ppm).

Preparation of D-1',2'-*trans* thiofuranoside 4-111.



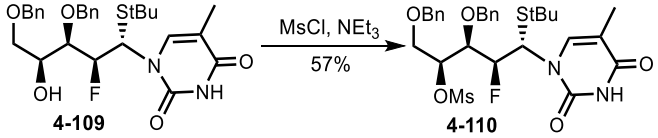
(–)-1-((1*S*,2*S*,3*R*,4*S*)-3,5-bis(benzyloxy)-1-(tert-butylthio)-2-fluoro-4-hydroxypentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-109)



To a solution of **4-103b** (64 mg, 0.099 mmol, 1.0 eq.) in anhydrous THF (1.0 ml, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.20 ml, 2ml/mmol, ~70% HF). The reaction was stirred for 16 hours at 25 °C. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 1 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **4-109** (36.1 mg, 69%): $\mathbf{R_f}$ = 0.14 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –35 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{28}H_{35}FN_2O_5S$; **MW** : 530.6554 g/mol ; **IR** (neat) ν_{max} 3425, 3188, 2925, 1684 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.44 (s, 1H), 7.38 – 7.27 (m, 10H), 6.23 (dd, *J* = 22.7, 4.8 Hz, 1H), 4.93 (appdt, *J* = 46.2, 5.1 Hz, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.50 (apps, 2H), 4.23 – 4.17 (m, 1H), 3.80 – 3.73 (m, 1H), 3.54 (appd, *J* = 5.7 Hz, 2H), 2.46 (d, *J* = 6.3 Hz, 1H), 1.95 (s, 3H), 1.31 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.2, 150.7, 137.95, 137.92, 137.5, 128.63, 128.58, 128.13, 128.05, 128.02, 127.96, 111.6, 94.8 (d, *J* = 185.3 Hz), 77.4, 74.5, 73.4, 70.8 (d, *J* = 3.2 Hz), 69.1 (d, *J* =

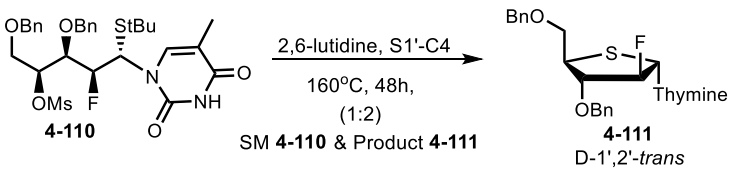
4.1 Hz), 57.2 (d, J = 19.5 Hz), 45.7, 31.2, 12.8 ppm ; **HRMS** calcd for $C_{28}H_{35}FN_2O_5SNa$ [M+Na^+] : 553.2143, found: 553.2157 (2.49 ppm).

(–)-(2*S*,3*R*,4*S*,5*S*)-1,3-bis(benzyloxy)-5-(tert-butylthio)-4-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)pentan-2-yl methanesulfonate (4-110)



To a solution of **4-109** (38 mg, 0.072 mmol, 1.0 eq.) in anhydrous DCM (0.30 ml, 0.30 M) at 0 ^oC was added triethylamine (20 µl, 0.14 mmol, 2.0 eq.) and methanesulfonyl chloride (10 µl, 0.11 mmol, 1.5 eq). The reaction was stirred for 5 hours at 25 ^oC. A 1.0 N solution (0.25 ml) of HCl was added and the aqueous layer was extracted with dichloromethane (3 × 0.50 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **4-110** (24.9 mg, 57%): $\mathbf{R_f}$ = 0.41 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –32 (*c* 0.95, $CDCl_3$) ; **Formula** : $C_{29}H_{37}FN_2O_7S_2$; **MW** : 608.7404 g/mol ; **IR** (neat) ν_{max} 3178, 3027, 2925, 1675 cm^{-1} ; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.44 (s, 1H), 7.37 – 7.24 (m, 10H), 6.37 (dd, J = 17.0, 6.7 Hz, 1H), 5.07 – 5.02 (m, 1H), 4.76 (ddd, J = 46.3, 6.8, 3.1 Hz, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.68 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.12 – 4.02 (m, 1H), 3.77 – 3.69 (m, 2H), 3.00 (s, 3H), 1.96 (s, 3H), 1.30 (s, 9H) ppm; ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 163.2, 150.9, 137.4, 137.2, 137.0, 128.73, 128.70, 128.4, 128.2, 128.0, 127.9, 111.7, 92.1 (d, J = 188.0 Hz), 79.6, 76.4 (d, J = 16.8 Hz), 74.5, 73.4, 68.7 (d, J = 6.1 Hz), 57.1 (d, J = 20.8 Hz), 46.2, 38.4, 31.2, 12.8 ppm ; **HRMS** calcd for $C_{29}H_{37}FN_2O_7S_2Na$ [M+Na^+] : 631.1918, found: 631.1936 (2.77 ppm).

1-((2*S*,5*R*)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (4-111)

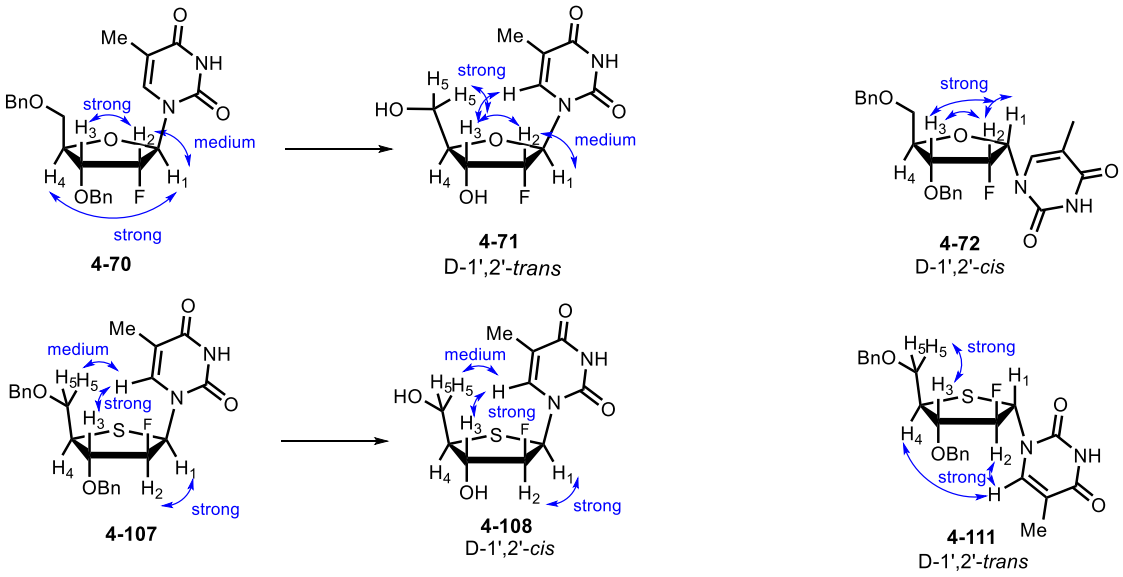


A solution of **4-110** (20 mg, 0.032 mmol, 1.0 eq.) in 2,6-lutidine (1.0 ml, 0.03 M) was refluxed for 48 hours at 160 °C. Upon cooling to room temperature, the reaction mixture was concentrated and a 2:1 mixture of product **4-111** and starting material **4-110** was obtained. Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided an inseparable mixture (11.5 mg): $\mathbf{R}_f$ = 0.30 (Hexanes/EtOAc, 50:50); **Formula** : $C_{24}H_{25}FN_2O_4S$; **MW** : 456.5324 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 (s, 1H, product), 8.08 (s, 1H, starting material), 7.58 (s, 1H, product), 7.44 (s, 1H, starting material), 7.39 – 7.22 (m, 20H, product & starting material), 6.40 – 6.35 (m, 1H, starting material), 6.33 (dd, *J* = 17.0, 2.8 Hz, 1H, product), 5.09 (dt, *J* = 48.0, 3.0 Hz, 2H, product & starting material), 4.76 (ddd, *J* = 46.3, 6.9, 3.3 Hz, 1H, starting material), 4.75 (d, *J* = 11.5 Hz, 1H, starting material), 4.68 (d, *J* = 11.5 Hz, 1H, starting material), 4.60 (q, *J* = 11.2 Hz, 2H, product), 4.54 (apps, 2H, product), 4.46 (dd, *J* = 31.1, 11.8 Hz, 2H, starting material), 4.32 (appdt, *J* = 11.6, 3.3 Hz, 1H, product), 4.07 (appdt, *J* = 8.0, 3.0 Hz, 1H, starting material), 3.98 – 3.93 (m, 1H, product), 3.77 – 3.71 (m, 2H, starting material), 3.66 (t, *J* = 8.8 Hz, 1H, product), 3.55 – 3.50 (m, 1H, product), 3.00 (s, 3H, starting material), 1.96 (s, 3H, starting material), 1.74 (s, 3H, product), 1.31 (d, *J* = 7.3 Hz, 9H, starting material) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.16 (product), 163.15 (starting material), 150.9 (starting material), 150.6 (product), 137.7 (product), 137.5 (product), 137.4 (starting material), 137.2(starting material), 137.0 (starting material), 136.6 (product), 128.8 (product), 128.73 (starting material), 128.69 (starting material),

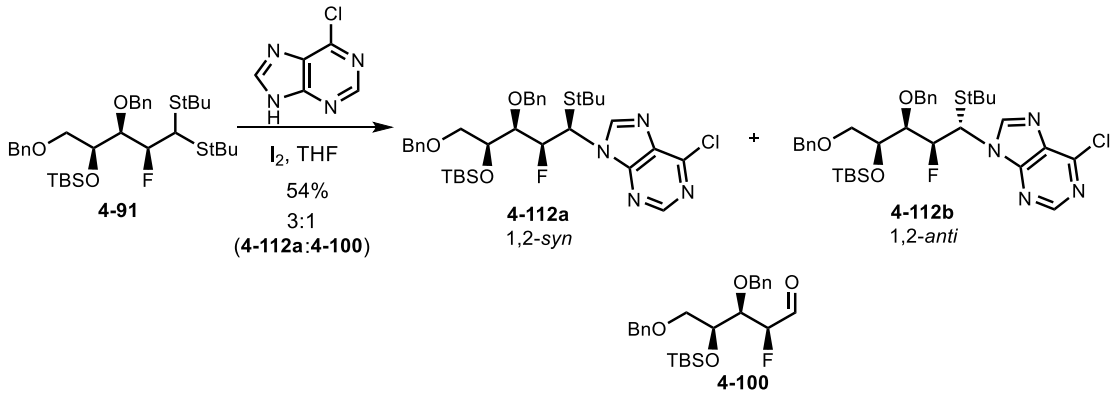
128.65 (product), 128.5 (product), 128.3 (starting material), 128.19 (product), 128.18 (starting material), 128.1 (product), 128.0 (starting material), 127.88 (product), 127.87 (starting material), 111.7 (starting material), 111.0 (product), 100.7 (d, *J* = 190.5 Hz, product), 92.1 (d, *J* = 187.6 Hz, starting material),83.3 (d, *J* = 26.5 Hz, product), 79.6 (starting material), 76.4 (d, *J* = 17.4 Hz, starting material), 74.5 (starting material), 73.6 (d, *J* = 3.1 Hz, product), 73.4 (starting material), 72.9 (product), 71.4 (product), 68.7 (d, *J* = 6.0 Hz, starting material), 64.9 (d, *J* = 32.2 Hz, product), 57.1 (d, *J* = 20.1 Hz, starting material), 52.0 (product), 46.2 (starting material), 38.4 (starting material), 31.2 (starting material), 12.8 (starting material), 12.5 (product) ppm ; **HRMS** calcd for : $C_{24}H_{25}FN_2O_4SNa$ [M+Na^+] : 479.1411, found: 479.1416 (1.01 ppm).

Stereochemical Proofs

In all cases, the selectivities were determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixtures. The C1'−C2' relative configurations of the synthesized nucleoside analogues were determined by relevant nuclear Overhauser effect (NOE) enhancements (2D NOESY), ^{1}H NMR coupling constant data and correlations of chemical shifts. The peaks in the ^{1}H NMR spectra were assigned using ^{1}H/^{1}H COSY experiments, chemical shifts, and coupling constants. Proof of structure for the C1'-C2' relative stereochemistry were provided by NOESY experiments.



(+)-9-((1*R*,2*S*,3*R*,4*S*)-3,5-bis(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-1-(tert-butylthio)-2-fluoropentyl)-6-chloro-9H-purine (4-112a)

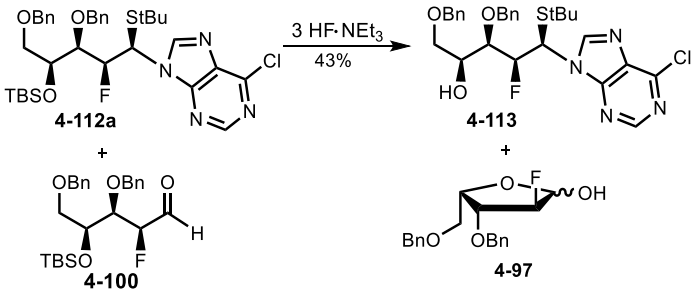


To a solution of **4-91** (0.44 g, 0.73 mmol, 1.0 eq.) in anhydrous THF (7.3 ml, 0.10 M) at 0 °C was added 6-Cl-purine (0.40 g, 2.55 mmol, 3.5 eq.), and I_2 (0.37 g, 1.46 mmol, 2.0 eq.). The reaction mixture was stirred at 25 °C for 16 hours. A saturated solution (5 ml) of $Na_2S_2O_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 7 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a 3:1 mixture of the 1,2-*syn* diastereoisomer **4-112a** with the corresponding aldehyde **4-100**. The minor 1,2-*anti*

diastereoisomer has not yet been identified. Purification by flash chromatography (Hexanes/EtOAc, 90:10) did not allow separation of the thioaminal from the aldehyde providing 0.28 g of a 3:1 mixture of **4-112a** : **4-100** that was used in the next step. Isolation of **4-112a** and and its full characterization was done from recovered starting material in the following TBS deprotection step.

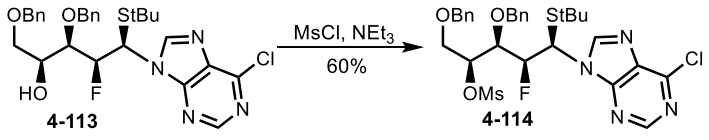
4-112a: $\mathbf{R_f}$ = 0.19 (Hexanes/EtOAc, 90:10); $\mathbf{[\alpha]^{25}_D}$ +41 (*c* 0.3, $CDCl_3$) ; **Formula** : $C_{34}H_{46}ClFN_4O_3SSi$; **MW** : 673.3604 g/mol ; **IR** (neat) ν_{max} 2958, 2925, 2850, 1556 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.22 (s, 1H), 7.39 – 7.26 (m, 10H), 6.08 (dd, *J* = 16.0, 5.9 Hz, 1H), 5.24 – 5.12 (m, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 12.1 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.16 (appdt, *J* = 7.9, 4.0 Hz, 1H), 3.67 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.56 (appdt, *J* = 23.3, 4.0 Hz, 1H), 3.49 (ddd, *J* = 10.1, 6.7, 3.6 Hz, 1H), 1.21 (s, 9H), 0.78 (s, 9H), 0.03 (s, 3H), -0.03 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 152.2, 151.4, 151.1, 145.4, 138.3, 137.8, 131.6, 128.7, 128.4, 128.2, 128.1, 127.68, 127.65, 91.8 (d, *J* = 186.5 Hz), 78.1 (d, *J* = 16.6 Hz), 73.8, 73.3, 71.6 (d, *J* = 4.9 Hz), 71.0, 57.7 (d, *J* = 25.7 Hz), 45.5, 31.0, 25.9, 18.2, -4.0, -4.7 ppm ; **HRMS** calcd for : $C_{34}H_{46}ClFN_4O_3SSiNa$ $[M+Na^+]$: 695.2625, found: 695.2631 (0.95 ppm).

(+)-(2*S*,3*R*,4*S*,5*R*)-1,3-bis(benzyloxy)-5-(tert-butylthio)-5-(6-chloro-9H-purin-9-yl)-4-fluoropentan-2-ol (4-113)



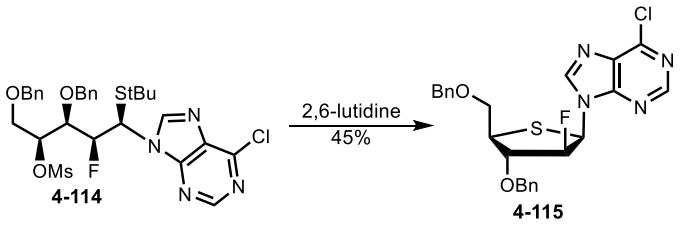
To a solution of **4-112a** (75 mg, 0.11 mmol, 1.0 eq.) (mixed with **4-100**) in anhydrous THF (1.2 ml, 0.10 M) in a plastic vial at 0 °C was added trihydrofluoride triethylamine (0.18 ml, 1.1 mmol, 10 eq.). The reaction took 48 hours at 25 °C to go to completion with additional trihydrofluoride triethylamine (total of 40 equivalents). A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 3 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 30:70), provided lactol **4-97** (13 mg) which could be separated from **4-113** (26.9 mg, 43%): $\mathbf{R_f}$ = 0.13 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +90 (*c* 0.8, $CDCl_3$) ; **Formula** : $C_{28}H_{32}ClFN_4O_3S$; **MW** : 559.0974 g/mol ; **IR** (neat) ν_{max} 3355, 2958, 2866, 1583, 1562 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.61 (s, 1H), 7.38 – 7.27 (m, 10H), 6.25 (dd, *J* = 28.9, 2.0 Hz, 1H), 5.04 (ddd, *J* = 48.8, 7.7, 2.0 Hz, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 11.1 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.15 – 4.11 (m, 1H), 4.07 (dd, *J* = 11.9, 8.0 Hz, 1H), 3.64 (dd, *J* = 9.1, 6.6 Hz, 1H), 3.51 (dd, *J* = 9.3, 5.8 Hz, 1H), 2.52 (brs, 1H), 1.19 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 152.3, 151.4, 151.0, 145.6, 137.9, 137.7, 131.7, 128.63, 128.60, 128.4, 128.2, 128.1, 127.9, 96.7 (d, *J* = 182.8 Hz), 77.8 (d, *J* = 17.3 Hz), 75.1 (d, *J* = 3.5 Hz), 73.7, 70.7, 69.7 (d, *J* = 7.6 Hz), 57.6 (d, *J* = 20.2 Hz), 45.3, 31.0 ppm ; **HRMS** calcd for $C_{28}H_{32}ClFN_4O_3SNa$ [M+Na^+] : 581.1760, found: 581.1779 (3.3 ppm).

(+)-(2*S*,3*R*,4*S*,5*R*)-1,3-bis(benzyloxy)-5-(tert-butylthio)-5-(6-chloro-9H-purin-9-yl)-4-fluoropentan-2-yl methanesulfonate (4-114)



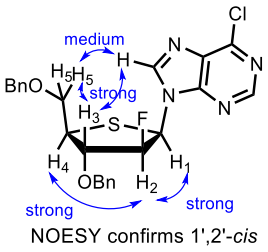
To a solution of **4-113** (33 mg, 0.06 mmol, 1.0 eq.) in anhydrous DCM (0.20 ml, 0.30 M) at 0 °C was added triethylamine (20 µl, 0.12 mmol, 2.0 eq.) and methanesulfonyl chloride (7 µl, 0.09 mmol, 1.5 eq). The reaction was stirred for 4 hours at 25 °C. Water (0.50 ml) was added and the aqueous layer was extracted with dichloromethane (3 × 1 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **4-114** (22.6 mg, 60%): $\mathbf{R_f}$ = 0.15 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +79 (*c* 1.5, $CDCl_3$) ; **Formula** : $C_{29}H_{34}ClFN_4O_5S_2$; **MW** : 637.1824 g/mol ; **IR** (neat) ν_{max} 3022, 2958, 2861, 1588, 1561cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.47 (s, 1H), 7.37 – 7.25 (m, 10H), 6.23 (dd, *J* = 23.7, 3.8 Hz, 1H), 5.11 – 4.98 (m, 2H), 4.72 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.14 (ddd, *J* = 16.8, 6.0, 3.8 Hz, 1H), 3.90 – 3.85 (m, 1H), 3.80 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.14 (s, 3H), 1.23 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 152.1 (d, *J* = 2.2 Hz), 151.5, 151.0, 145.7, 137.3, 137.1, 131.8, 128.74, 128.68, 128.5, 128.4, 128.2, 127.9, 94.0 (d, *J* = 185.2 Hz), 78.0 (d, *J* = 5.8 Hz), 76.7 (d, *J* = 18.7 Hz), 75.3 (d, *J* = 2.5 Hz), 73.6, 68.0, 57.1 (d, *J* = 21.8 Hz), 46.0, 38.8, 31.1ppm ; **HRMS** calcd for $C_{29}H_{34}ClFN_4O_5S_2Na$ $[M+Na^+]$: 659.1535, found: 659.1558 (3.42 ppm).

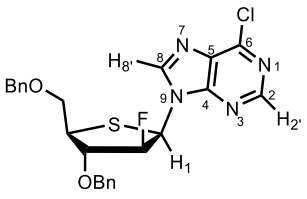
(+)-9-((2*R*,3*S*,4*S*,5*R*)-4-(benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrothiophen-2-yl)-6-chloro-9H-purine (4-115)



A solution of **4-114** (21 mg, 0.03 mmol, 1.0 eq.) in 2,6-lutidine (1.0 ml, 0.03 M) was refluxed for 4 hours at 160 °C. Upon cooling to room temperature, the reaction mixture was concentrated. Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **4-115** (7.0 mg, 45%): $\mathbf{R_f}$ = 0.46 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +47 (*c* 0.6, $CDCl_3$) ; **Formula** : $C_{24}H_{22}ClFN_4O_2S$; **MW** : 484.9744 g/mol ; **IR** (neat) ν_{max} 3033, 2866, 1583, 1562 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.75 (s, 1H), 7.41 – 7.27 (m, 10H), 6.47 (dd, *J* = 12.0, 4.9 Hz, 1H), 5.21 (appdt, *J* = 50.6, 5.3 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.58 (apps, 2H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.47 (appdt, *J* = 10.5, 5.2 Hz, 1H), 3.72 – 3.64 (m, 3H) ppm; **^{13}C NMR** (175 MHz, $CDCl_3$) δ 152.3, 152.2, 151.3, 145.7, 137.4, 136.9, 131.9, 128.768, 128.767, 128.5, 128.31, 128.30, 128.1, 95.4 (d, *J* = 196.3 Hz), 80.4 (d, *J* = 22.1 Hz), 73.5, 73.1, 68.9, 58.0 (d, *J* = 17.5 Hz), 47.8 (d, *J* = 4.2 Hz) ppm ; **HRMS** calcd for : $C_{24}H_{22}ClFN_4O_2SNa$ $[M+Na^+]$: 507.1028, found: 507.1034 (1.17 ppm).

Proof of N9 regiochemistry of the 6-Cl-purine ring was determined from HSQC and HMBC experiments.[22]





4-115

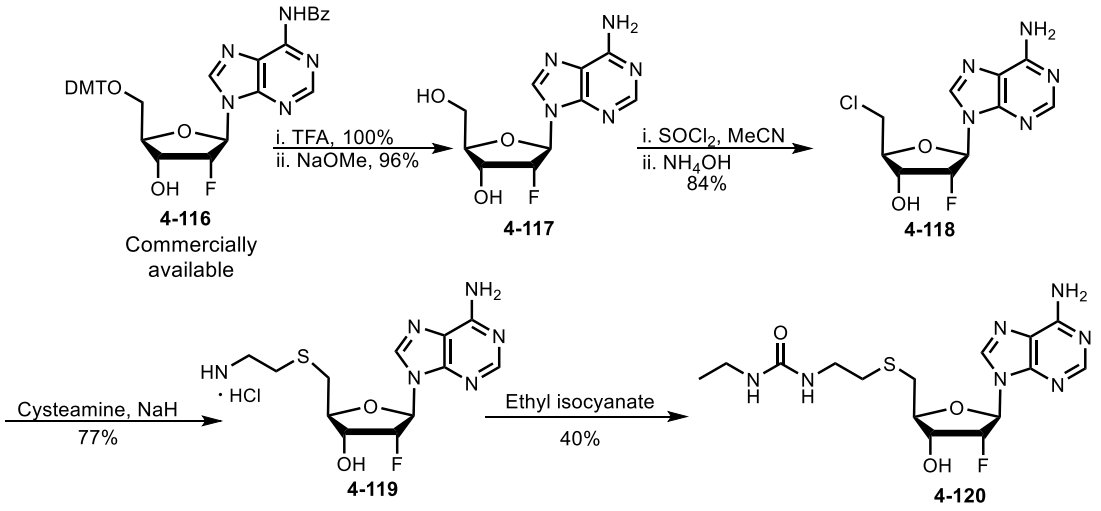
From HSQC

$H_{8'}$ (8.84 ppm) ⟷ C_8 (145.7 ppm)
$H_{2'}$ (8.75 ppm) ⟷ C_2 (152.2 ppm)

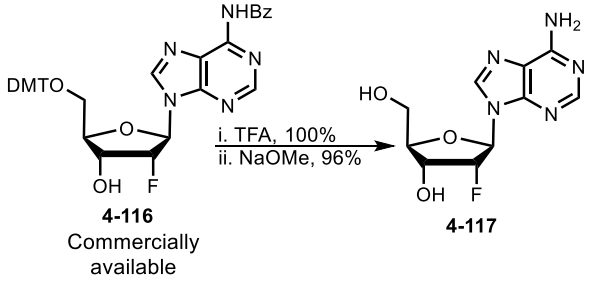
From HMBC

H_1 (6.47 ppm) ⟷ C_8 (145.7 ppm)
H_1 (6.47 ppm) ⟷ C_4 (152.3 ppm)
$H_{8'}$ (8.84 ppm) ⟷ C_4 (152.3 ppm)
$H_{8'}$ (8.84 ppm) ⟷ C_5 (131.9 ppm)
$H_{2'}$ (8.75 ppm) ⟷ C_4 (152.3 ppm)
$H_{2'}$ (8.75 ppm) ⟷ C_6 (151.3 ppm)

SAM Analogues



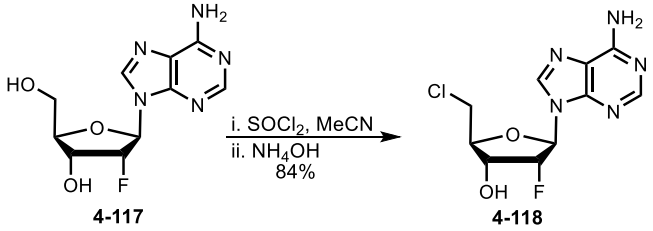
(–)-(2*R*,3*R*,4*R*,5*R*)-5-(6-amino-9H-purin-9-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (4-117)



Following a slightly modified procedure,[23-25] to a 95:4:1 mixture of DCM:TFA:H_2O (11.4 ml:0.48 ml:0.12 ml, 0.10M) was added **4-116** (0.81 g, 1.19 mmol, 1.0 eq.). The reaction mixture was stirred at 25 ^{o}C for 3 hours and a saturated solution of $NaHCO_3$ (5 ml) was added. The aqueous layer was extracted with ethyl acetate (3 × 15 ml) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (DCM/MeOH, 90:10), provided **4-117** as a white solid which has been previously reported in the literature[23-25]: $\mathbf{R_f}$ = 0.26 (DCM/MeOH, 90:10); $\mathbf{[\alpha]^{25}_D}$ –30 (*c* 0.96, CD_3OD); **Formula** : $C_{10}H_{12}FN_5O_3$; **MW** : 269.2364 g/mol ; **IR** (neat) ν_{max} 3328, 3113, 2931, 1669, 1605 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 8.38 (s, 1H), 8.20 (s, 1H), 6.29 (dd, *J* = 15.7, 3.3 Hz, 1H), 5.50 –

5.37 (m, 1H), 4.65 – 4.57 (m, 1H), 4.16 (d, *J* = 2.0 Hz, 1H), 3.94 (dd, *J* = 12.6, 2.1 Hz, 1H), 3.77 (dd, *J* = 12.6, 3.0 Hz, 1H) ppm *OH and NH_2 signals missing possibly due to exchange in CD_3OD*; **^{1}H NMR** (500 MHz, $(CD_3)_2SO$) δ 8.36 (s, 1H), 8.15 (s, 1H), 7.36 (s, 2H), 6.23 (dd, *J* = 16.9, 2.9 Hz, 1H), 5.72 (d, *J* = 6.0 Hz, 1H), 5.51 – 5.35 (m, 1H), 5.26 (appt, *J* = 5.6 Hz, 1H), 4.54 – 4.42 (m, 1H), 3.98 (apps, 1H), 3.78 – 3.70 (m, 1H), 3.62 – 3.54 (m, 1H) ppm ; **^{13}C NMR** (125 MHz, CD_3OD) δ 157.5, 153.8, 150.0, 141.4, 120.7, 94.7 (d, *J* = 189.2 Hz), 88.6 (d, *J* = 33.0 Hz), 86.2 (d, *J* = 1.7 Hz), 70.4 (d, *J* = 16.0 Hz), 62.1 ppm ; **HRMS** calcd for $C_{10}H_{13}FN_5O_3$ $[M+H^+]$: 270.0997, found: 270.1000 (1.22 ppm).

(+)-(2*S*,3*R*,4*R*,5*R*)-5-(6-amino-9H-purin-9-yl)-2-(chloromethyl)-4-fluorotetrahydrofuran-3-ol (4-118)

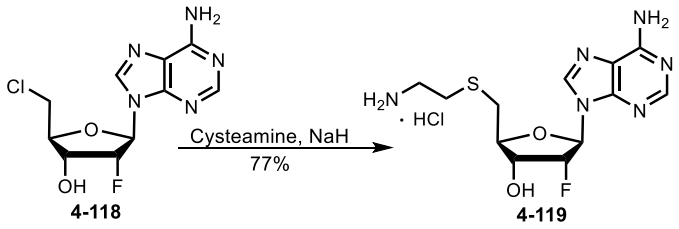


4-117 **4-118**

To **4-117** (0.30 g, 1.11 mmol, 1.0 eq.) in anhydrous MeCN (5.0 ml, 0.22 M) at 0 °C was added anhydrous pyridine (20 µl, 2.22 mmol, 2.0 eq.) and thionyl chloride (0.55 ml, 7.54 mmol, 6.0 eq.) The reaction mixture was stirred for 4 hours at 5 °C and 25 °C for 16 hours and then concentrated. The crude mixture was dissolved in 5:1 MeOH:H_2O (7.0 ml MeOH, 1.4 ml H_2O, 0.13 M) and concentrated NH_4OH (0.70 ml) was added. Stirring was maintained for 30 minutes at 25 °C followed by concentration. Purification by flash chromatography (DCM/MeOH, 95:5), provided **4-118** (0.27 g, 84%) : $\mathbf{R_f}$ = 0.17 (DCM/MeOH, 95:5); $\mathbf{[\alpha]^{25}_D}$ +3 (*c* 0.9, CD_3OD); **Formula** : $C_{10}H_{11}ClFN_5O_2$; **MW** : 287.6794 g/mol ; **IR** (neat) ν_{max} 3422, 2527, 1646 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 8.26 (s, 1H), 8.21 (s, 1H), 6.30 (dd, *J* = 18.7, 1.9 Hz, 1H), 5.54

(ddd, *J* = 52.7, 4.6, 2.0 Hz, 1H), 4.75 (ddd, *J* = 19.8, 7.5, 4.7 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.00 (dd, *J* = 12.3, 3.5 Hz, 1H), 3.86 (dd, *J* = 12.3, 5.0 Hz, 1H) ppm, *OH and NH_2 signals missing possibly due to exchange in CD_3OD*; **^{1}H NMR** (500 MHz, $(CD_3)_2SO$) δ 8.29 (s, 1H), 8.16 (s, 1H), 7.36 (s, 2H), 6.28 (dd, *J* = 19.6, 2.1 Hz, 1H), 5.95 (d, *J* = 6.4 Hz, 1H), 5.59 (ddd, *J* = 52.7, 4.6, 2.2 Hz, 1H), 4.72 – 4.62 (m, 1H), 4.16 – 4.12 (m, 1H), 3.99 (dd, *J* = 12.1, 3.3 Hz, 1H), 3.86 (dd, *J* = 12.1, 6.2 Hz, 1H) ppm ; **^{13}C NMR** (125 MHz, CD_3OD) δ 157.4, 154.1, 150.3, 141.2, 120.5, 94.6 (d, *J* = 187.6 Hz), 88.4 (d, *J* = 34.5 Hz), 83.4 (d, *J* = 1.2 Hz), 71.5 (d, *J* = 16.5 Hz), 44.8 ppm ; **HRMS** calcd for $C_{10}H_{12}ClFN_5O_2$ $[M+H^+]$: 288.0658, found: 288.0661 (0.90 ppm).

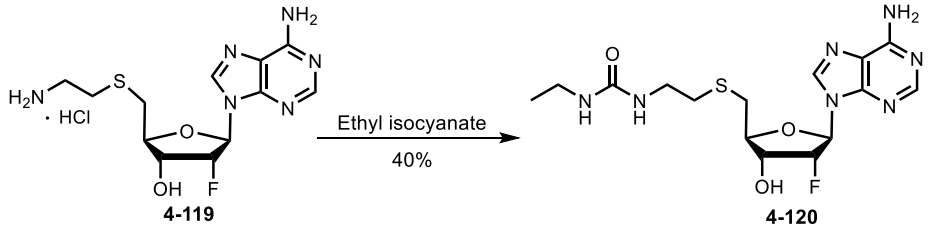
(+)-(2*S*,3*R*,4*R*,5*R*)-5-(6-amino-9H-purin-9-yl)-2-(((2-aminoethyl)thio)methyl)-4fluorotetrahydrofuran-3-ol (4-119)



To a solution of cysteamine (12 mg, 0.16 mmol, 0.85 eq.) in anhydrous DMF (0.60 ml, 0.26 M) at 0 ^oC was slowly added NaH (6.5 mg, 0.16 mmol, 0.85 eq.). When evolution of H_2 stopped (~15 minutes), **4-118** (54 mg, 0.19 mmol, 1.0 eq.) was added as a solution in anhydrous DMF (0.60 ml, 0.33 M). The reaction was warmed to 25 ^oC for 5 hours, quenched with H_2O (0.80 ml) and neutralized to pH=7 with a 1N HCl solution. The solvents were evaporated and purification by flash chromatography (reverse phase C18, 100% H_2O), provided **4-119** (52.1 mg, 85%). (N.B. the product could not be separated from minor impurities by reverse phase but the product stuck to the silica gel column and was difficult to isolate using normal phase even with 100% MeOH) : **$[\alpha]^{25}_D$** +31 (*c* 0.4, CD_3OD); **Formula** : $C_{12}H_{18}ClFN_6O_2S$; **MW** : 364.8244 g/mol ; **IR** (neat) ν_{max}

3344, 3204, 1648 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 8.27 (s, 1H), 8.22 (s, 1H), 6.27 (dd, *J* = 20.1, 1.6 Hz, 1H), 5.51 (ddd, *J* = 53.1, 4.7, 1.5 Hz, 1H), 4.75 (ddd, *J* = 20.8, 8.0, 4.7 Hz, 1H), 4.22 (td, *J* = 7.6, 3.5 Hz, 1H), 3.12 – 3.04 (m, 3H), 2.97 (dd, *J* = 15.0, 7.3 Hz, 1H), 2.81 (t, *J* = 6.6 Hz, 2H) ppm, *OH and NH_2 signals missing possibly due to exchange in CD_3OD*; **^{1}H NMR** (500 MHz, $(CD_3)_2SO$) δ 8.32 (s, 1H), 8.16 (s, 1H), 7.90 (s, 3H), 7.37 (s, 2H), 6.24 (dd, *J* = 19.7, 2.2 Hz, 1H), 5.90 (d, *J* = 6.0 Hz, 1H), 5.55 (ddd, *J* = 53.3, 4.5, 2.3 Hz, 1H), 4.63 – 4.54 (m, 1H), 4.09 – 4.03 (m, 1H), 3.05 – 2.85 (m, 4H), 2.73 (t, *J* = 7.5 Hz, 2H) ppm ; **^{13}C NMR** (125 MHz, CD_3OD) δ 157.4, 154.1, 150.3, 141.6, 120.6, 94.6 (d, *J* = 186.9 Hz), 88.6 (d, *J* = 35.0 Hz), 84.2, 73.3 (d, *J* = 16.6 Hz), 39.8, 34.2, 30.9 ppm ; **HRMS** calcd for $C_{12}H_{18}FN_6O_2S$ $[M+H^+]$: 329.1190, found: 329.1198 (2.19 ppm).

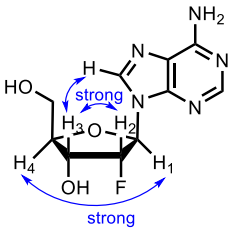
(+)-1-(2-((((2*S*,3*R*,4*R*,5*R*)-5-(6-amino-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl)thio)ethyl)-3-ethylurea (4-120)



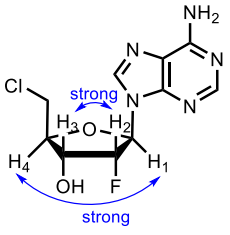
To a solution of **4-119** (38 mg, 0.10 mmol, 1.0 eq.) in anhydrous MeCN : DMF (2.5 ml MeCN : 0.3 ml DMF, 0.04 M) was added ethyl isocyanate (9 µl, 0.12 mmol, 1.2 eq.). The reaction was refluxed at 80 ^oC for 3 hours, the precipitate removed by filtration washing with MeCN and the filtrate was concentrated. Purification by flash chromatography (DCM/MeOH, 90:10), provided **4-120** (16.6 mg, 40%) : **R_f** = 0.16 (DCM/MeOH, 90:10); **$[\alpha]^{25}_D$** +32 (*c* 1.2, CD_3OD); **Formula** : $C_{15}H_{22}FN_7O_3S$; **MW** : 399.4454 g/mol ; **IR** (neat) ν_{max} 3339, 3199, 2979, 1637, 1573 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 8.30 (s, 1H), 8.21 (s, 1H), 6.26 (dd, *J* = 19.3, 1.8 Hz, 1H), 5.49

(ddd, J = 53.0, 4.7, 1.9 Hz, 1H), 4.68 (ddd, J = 20.2, 7.7, 4.6 Hz, 1H), 4.23 – 4.18 (m, 1H), 3.25 (t, J = 6.8 Hz, 2H), 3.13 – 3.04 (m, 3H), 2.91 (dd, J = 14.4, 6.3 Hz, 1H), 2.66 – 2.60 (m, 2H), 1.07 (t, J = 7.2 Hz, 3H) ppm, *OH and NH_2 signals missing possibly due to exchange in CD_3OD*; **^{1}H NMR** (500 MHz, $(CD_3)_2SO$) δ 8.31 (s, 1H), 8.16 (s, 1H), 7.35 (s, 2H), 6.22 (dd, J = 19.4, 2.4 Hz, 1H), 5.92 – 5.86 (m, 2H), 5.84 (d, J = 6.3 Hz, 1H), 5.54 (ddd, J = 52.9, 4.6, 2.5 Hz, 1H), 4.59 – 4.50 (m, 1H), 4.06 – 4.01 (m, 1H), 3.11 (t, J = 6.8 Hz, 2H), 3.00 – 2.94 (m, 3H), 2.82 (dd, J = 14.0, 7.3 Hz, 1H), 2.55 – 2.51 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H) ppm ; **^{13}C NMR** (125 MHz, CD_3OD) δ 160.9, 157.4, 154.1, 150.3, 141.4, 120.5, 94.7 (d, J = 187.2 Hz), 88.3 (d, J = 34.5 Hz), 84.0, 73.0 (d, J = 16.4 Hz), 40.6, 35.8, 34.5, 34.3, 15.7 ppm ; **HRMS** calcd for $C_{15}H_{22}FN_7O_3SNa$ $[M+Na^+]$: 422.1381, found: 422.1385 (0.86 ppm).

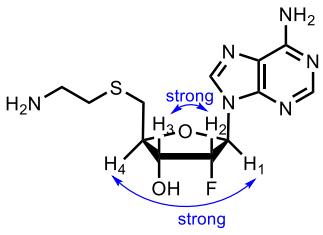
Proof of structure for the C1'-C2' relative stereochemistry were provided by NOESY experiments which are detailed below.



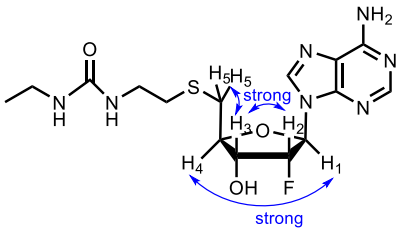
4-117



4-118

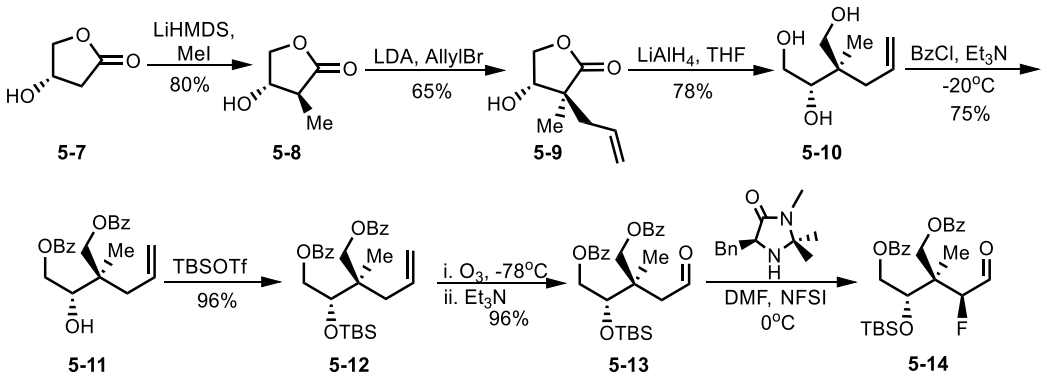


4-119

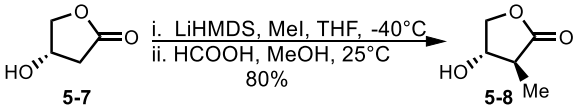


4-120

Chapter 5



(3*S*,4*S*)-4-hydroxy-3-methyldihydrofuran-2(3H)-one (5-8)

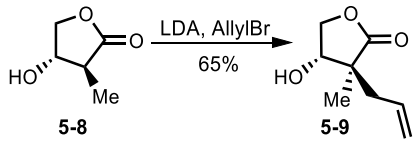


To LiHMDS (202 ml, 202 mmol, 2.2 eq., 1M THF) at -78 °C was added a solution of (*S*)-β-hydroxy-γ-butyrolactone **5-7** (9.4 g, 91.7 mmol, 1.0 eq.) in anhydrous THF (150 mL, 0.61 M). Stirring was maintained for 10 minutes at –78 °C and for 2 hours at -40 °C. Upon cooling to –78 °C, MeI (7.4 ml, 119 mmol, 1.3 eq.) as a solution in anhydrous THF (50 mL, 2.4 M) was added and stirred for 2.5 hours at –40 °C. The reaction was quenched with formic acid (10 ml) and warmed to 25 °C with stirring for 16 hours. Concentration of the reaction mixture was followed by passing it through a silica pad made of 100% EtOAc and re-concentrating. PPTS (2.28 g) was added to the crude mixture dissolved in MeOH (100 ml) to remove the TMS protecting group with stirring for 2 hours at 25 °C followed by evaporation. Purification by flash chromatography (Hexanes/EtOAc, 20:80) provided the known compound **5-8** (8.5 g, 80%). ^{1}H NMR spectroscopic data correlate with the previously reported data.[26]

5-8: $\mathbf{R_f}$ = 0.36 (Hexanes/EtOAc, 20:80); **Formula** : $C_5H_8O_3$; **MW** : 116.1152 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.47 – 4.42 (m, 1H), 4.26 (appq, *J* = 5.5 Hz, 1H), 4.09 – 4.04 (m, 1H), 2.59

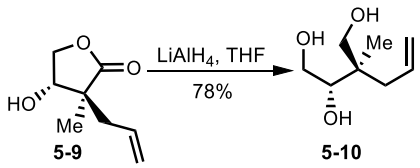
– 2.51 (m, 1H), 1.29 (d, *J* = 7.4 Hz, 3H) ppm, *OH signal missing possibly due to exchange in* $CDCl_3$.

(–)-(3*S*,4*S*)-3-allyl-4-hydroxy-3-methyldihydrofuran-2(3H)-one (5-9)



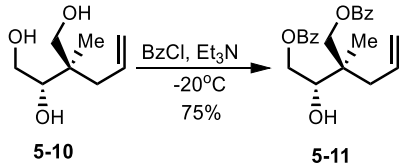
To a solution of DIPA (6.4 ml, 45.3 mmol, 2.5 eq.) in anhydrous THF (45 ml, 1.0 M) at –78 °C was added *n*-BuLi (18.2 ml, 45.3 mmol, 2.5 eq., 2.5 M solution in Hexanes). The reaction mixture was stirred at 25 °C for 30 minutes. Upon cooling to –40°C, **5-8** (2.1 g, 18.1 mmol, 1.0 eq.) as a solution in anhydrous THF (36 mL, 0.5 M) was added and stirred for 2 hours at –40 °C. A solution of allyl bromide (2.5 ml, 29 mmol, 1.6 eq.) and DMI (4.4 mL, 40 mmol, 2.2 eq.) in anhydrous THF (36 ml, 0.80 M) was added with stirring for 2 hours at –35 °C. The reaction mixture was quenched with 6N HCl (10 ml) and concentrated. The aqueous layer was extracted with isopropyl acetate (4 × 20 ml) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 20:80), provided **5-9** (1.84 g, 65%): $\mathbf{R_f}$ = 0.45 (Hexanes/EtOAc, 20:80); $\mathbf{[\alpha]^{25}_D}$ –12 (*c* = 1.0, DCM) ; **Formula** : $C_8H_{12}O_3$; **MW** : 156.1791 g/mol ; **IR** (neat) ν_{max} 3456, 3079, 2979, 2931, 1756, 1641 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.83–5.72 (m, 1H), 5.21–5.14 (m, 2H), 4.47–4.34 (m, 2H), 4.06 (dd, *J* = 9.8, 4.4 Hz, 1H), 2.37–2.27 (m, 2H), 1.23 (s, 3H) ppm, *OH signal missing possibly due to exchange in* $CDCl_3$; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 180.8, 132.3, 120.0, 72.9, 72.0, 47.2, 40.5, 15.8 ppm ; **HRMS** calcd for $C_8H_{12}O_3Na$ [M+Na^+] : 179.0679, found: 179.0677 (-0.88 ppm).

(+)- (2*S*,3*R*)-3-allyl-3-methylbutane-1,2,4-triol (5-10)



To a solution of **5-9** (1.76 g, 11.3 mmol, 1.0 eq.) in anhydrous THF (38 ml, 0.30 M) at 0 °C was added $LiAlH_4$ (17 ml, 16.9 mmol, 1.5 eq., 1M solution in THF). The reaction was stirred for 3.5 hours at 10 °C, quenched with Na_2SO_4•$10H_2O$ (8.5 g) and stirred for an additional 1.5 hours at 25 °C. After dilution with EtOAc, the mixture was dried over Na_2SO_4, washed with THF (3 × 20 ml), filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-10** (1.4 g, 78%): $\mathbf{R_f}$ = 0.20 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ +5 (*c* 2.5, DCM) ; **Formula** : $C_8H_{16}O_3$; **MW** : 160.2108 g/mol ; **IR** (neat) ν_{max} 3371, 3076, 2934, 1631 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.85 – 5.71 (m, 1H), 5.09 – 5.06 (m, 1H), 5.05 (s, 1H), 4.13 (brs, 3H), 3.75 – 3.60 (m, 2H), 3.58 (apps, 1H), 3.45 (appq, *J* = 11.1 Hz, 2H), 2.24 (dd, *J* = 13.8, 7.0 Hz, 1H), 1.94 (dd, *J* = 13.7, 7.7 Hz, 1H), 0.87 (s, 3H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.1, 118.2, 78.0, 67.8, 62.6, 40.8, 37.6, 19.4 ppm ; **HRMS** calcd for $C_8H_{16}O_3Na$ $[M+Na^+]$: 183.0992, found: 183.0987 (-2.5 ppm).

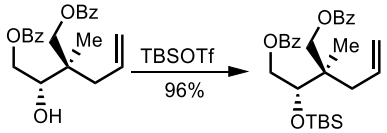
(+)-(2*R*,3*S*)-2-allyl-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-11)



To a solution of **5-10** (3.8 g, 23.8 mmol, 1.0 eq.) in anhydrous DCM (30 ml, 0.80 M) at –40 °C was added NEt_3 (27 ml, 191 mmol, 8.0 eq.) followed by stirring for 30 minutes. BzCl (6.1 ml,

52.5 mmol, 2.2 eq.) was added and the reaction mixture was placed at –20 °C for 16 hours. The reaction was quenched with 1 N HCl solution (20 ml) and the aqueous layer was extracted with dichloromethane (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-11** (6.6 g, 75%): $\mathbf{R_f}$ = 0.44 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +3 (*c* 1.0, DCM) ; **Formula** : $C_{22}H_{24}O_5$; **MW** : 368.4230 g/mol ; **IR** (neat) ν_{max} 3510, 3071, 2968, 1712 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 – 8.01 (m, 4H), 7.61 – 7.53 (m, 2H), 7.47 – 7.40 (m, 4H), 5.96 – 5.86 (m, 1H), 5.16 (d, *J* = 6.1 Hz, 1H), 5.13 (s, 1H), 4.64 (dd, *J* = 11.5, 2.5 Hz, 1H), 4.43 (dd, *J* = 11.5, 8.6 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.23 (d, *J* = 11.3 Hz, 1H), 4.00 (dd, *J* = 8.6, 2.5 Hz, 1H), 2.73 (brs, 1H), 2.45 (dd, *J* = 13.9, 7.7 Hz, 1H), 2.29 (dd, *J* = 13.9, 7.4 Hz, 1H), 1.14 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 166.7, 133.5, 133.31, 133.26, 130.1, 129.9, 129.8, 129.7, 128.6, 128.5, 119.0, 73.8, 68.5, 66.7, 41.0, 38.6, 19.0 ppm ; **HRMS** calcd for : $C_{22}H_{24}O_5Na$ [M+Na^+] : 391.1516, found: 391.1520 (1.12 ppm).

(+)-(2*R*,3*S*)-2-allyl-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl dibenzoate (5-12)

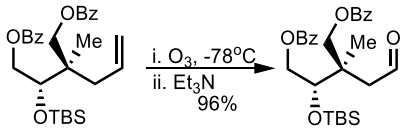


5-11 **5-12**

To a solution of **5-11** (6.7 g, 18.1 mmol, 1.0 eq.) in anhydrous DCM (40 ml, 0.50 M) at 0 °C was added 2,6-lutidine (5.3 ml, 45.2 mmol, 2.5 eq.) and TBSOTf (6.3 ml, 27.1 mmol, 1.5 eq.) The reaction mixture was stirred at 25 °C for 3 hours. A saturated solution of NH_4Cl (10 ml) was added and the aqueous layer was extracted with dichloromethane (3 x 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **5-12** (8.4 g, 96%): $\mathbf{R_f}$ = 0.63 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +15 (*c* 2.2, DCM) ; **Formula** : $C_{28}H_{38}O_5Si$; **MW** : 482.6838 g/mol ; **IR** (neat) ν_{max} 2975, 2932, 1728 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 – 8.01 (m, 4H), 7.58 – 7.53 (m, 2H), 7.47 – 7.40 (m, 4H), 5.94 – 5.84 (m, 1H), 5.11 (s, 1H), 5.08 (d, *J* = 7.0 Hz, 1H), 4.66 (dd, *J* = 11.8, 3.5 Hz, 1H), 4.35 (dd, *J* = 11.8, 6.0 Hz, 1H), 4.29 (d, *J* = 11.1 Hz, 1H), 4.24 (d, *J* = 11.1 Hz, 1H), 4.09 (dd, *J* = 5.9, 3.5 Hz, 1H), 2.41 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.29 (dd, *J* = 14.0, 7.8 Hz, 1H), 1.11 (s, 3H), 0.89 (s, 9H), 0.08 (s,3H), 0.08 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.8, 166.5, 133.8, 133.2, 133.1, 130.4, 130.1, 129.8, 129.6, 128.6, 128.5, 118.6, 74.8, 68.4, 67.6, 41.8, 38.8, 26.1, 19.5, 18.4, -3.8, -4.8 ppm ; **HRMS** calcd for : $C_{28}H_{38}O_5SiNa$ [$M+Na^+$] : 505.2381, found: 505.2377 (-0.81 ppm).

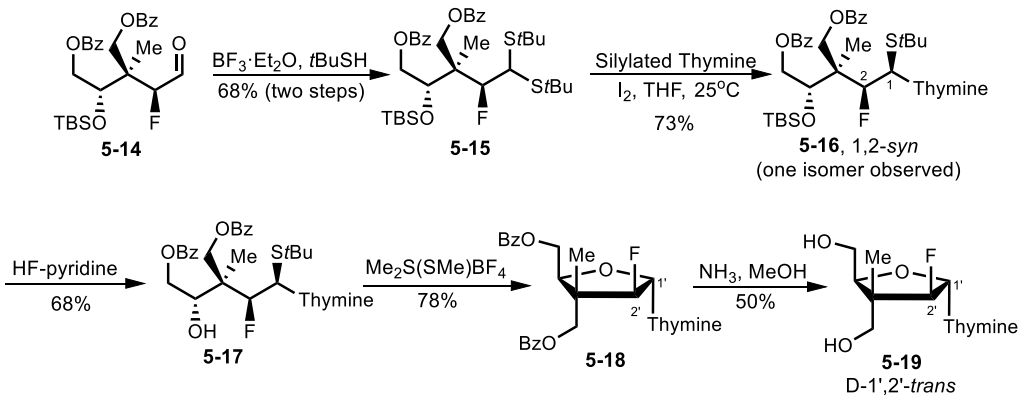
(+)-(2*R*,3*S*)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-2-(2-oxoethyl)butane-1,4-diyl dibenzoate (5-13)



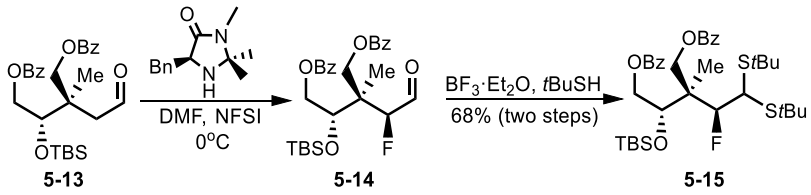
5-12 **5-13**

To a solution of **5-12** (8.7 g, 18.1 mmol, 1.0 eq.) in DCM (200 ml, 0.09 M) at –78 °C was bubbled O_3 under vacuum until the solution turned pale blue (about 45 minutes). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (18 ml, 126 mmol, 7.0 eq.), the reaction was warmed to 25 °C for 3 hours and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-13** (8.4 g, 96%): $\mathbf{R_f}$ = 0.66 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +5 (*c* 0.8, DCM) ; **Formula** : $C_{27}H_{36}O_6Si$; **MW** : 484.6566 g/mol ; **IR** (neat) ν_{max} 2956, 2930, 1721 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.93 (t, *J* = 2.7 Hz, 1H), 8.05 – 7.99 (m, 4H), 7.60 – 7.55 (m, 2H), 7.45 (td, *J* = 7.8, 3.9 Hz, 4H), 4.62 (dd, *J* = 12.0,

4.1 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.41 (d, *J* = 11.1 Hz, 1H), 4.38 (dd, *J* = 12.0, 5.1 Hz, 1H), 4.17 (t, *J* = 4.6 Hz, 1H), 2.72 (dd, *J* = 15.5, 3.1 Hz, 1H), 2.55 (dd, *J* = 15.5, 2.3 Hz, 1H), 1.28 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.9, 166.6, 166.3, 133.4, 133.3, 130.0, 129.84, 129.81, 129.7, 128.68, 128.65, 74.3, 68.7, 66.7, 48.2, 42.7, 26.0, 20.4, 18.4, -4.0, -4.8 ppm ; **HRMS** calcd for : $C_{27}H_{36}O_6SiNa$ [M+Na^+] : 507.2173, found: 507.2178 (0.92 ppm).



(–)-(2*R*,3*S*)-2-((*S*)-2,2-bis(tert-butylthio)-1-fluoroethyl)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl dibenzoate (5-15)

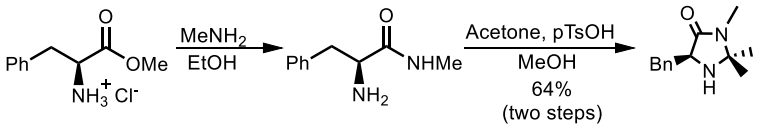


To the (*S*)-imidazolidinone catalyst (1.1 g, 5.1 mmol, 1.05 eq.) at –40 °C, was added **5-13** (2.4 g, 4.9 mmol, 1.0 eq.) as a solution in anhydrous DMF (5.0 ml, 1.0 M). After stirring for 10 minutes, NFSI (1.6 g, 4.96 mmol, 1.02 eq.) was added. Once homogeneous, it was left at 0 °C for 72 hours. The reaction mixture was diluted with Et_2O and water (3.0 ml) and treated with Me_2S (0.70 ml, 9.7 mmol, 2.0 eq.). The aqueous layer was extracted with Et_2O (3 × 5 ml) and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution

of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR spectroscopic analysis of the unpurified C2-F aldehyde indicated ~17:1 diastereomeric ratio for the fluorination. To the crude C2-F aldehyde **5-14** in anhydrous DCM (50 ml, 0.10 M) at –60 ^{o}C was added *t*BuSH (2.2 ml, 19.5 mmol, 4.0 eq.) and BF_3•OEt_2 (1.6 ml, 12.2 mmol, 2.5 eq.). The reaction was stirred at –60 ^{o}C for 5 hours. Upon addition of NEt_3 (14 ml, 97.3mmol, 20 eq.) stirring at –60 ^{o}C was maintained for 15 minutes. A saturated solution (10 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane (3 × 40 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-15** (2.2 g, 68% for two steps): $\mathbf{R_f}$ = 0.37 (Hexanes/EtOAc, 90:10); $\mathbf{[\alpha]^{25}_D}$ –61 (*c* 1.2, DCM) ; **Formula** : $C_{35}H_{53}FO_5S_2Si$; **MW** : 665.0062 g/mol ; **IR** (neat) ν_{max} 2958, 2928, 1721 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 4H), 7.53 – 7.48 (m, 2H), 7.41 – 7.31 (m, 4H), 5.12 (dd, *J* = 43.8, 1.6 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.63 – 4.57 (m, 2H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.44 – 4.40 (m, 1H), 4.36 (dd, *J* = 26.1, 1.9 Hz, 1H), 1.42 (s, 9H), 1.39 (s, 9H), 1.23 (s, 3H), 0.89 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 166.5, 133.1, 132.9, 130.4, 129.9, 129.74, 129.68, 128.44, 128.43, 98.9 (d, *J* = 186.4 Hz), 71.2 (d, *J* = 6.0 Hz), 67.2, 65.6 (d, *J* = 1.2 Hz), 46.7 (d, *J* = 17.7 Hz), 46.5 (d, *J* = 22.7 Hz), 46.2, 44.7, 32.0, 31.6, 26.1, 18.4, 15.5 (d, *J* = 6.4 Hz), -4.3, -4.6 (d, *J* = 1.9 Hz) ppm ; **HRMS** calcd for : $C_{35}H_{53}FO_5S_2SiNa$ [M+Na^+] : 687.2980, found: 687.2974 (-0.90 ppm).

5-14 (crude): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.85 (dd, *J* = 6.6, 1.5 Hz, 1H), 8.07 – 7.96 (m, 4H), 7.61 – 7.53 (m, 2H), 7.46 (m, 4H), 4.81 (dd, *J* = 47.7, 1.5 Hz, 1H), 4.65 (dd, *J* = 12.1, 4.0 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.45 – 4.38 (m, 2H), 4.21 (dt, *J* = 11.9, 6.0 Hz, 1H), 1.33 (d, *J* = 1.5 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H) ppm.

(*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one



Following a known procedure,[27] L-phenylalanine methyl ester hydrochloride (10 g, 46.4 mmol, 1.0 eq.) and methylamine (23.2 ml, 185.4 mmol, 4.0 eq., 8.0 M EtOH) were stirred at 25 ^{o}C for 24 hours. The reaction mixture was concentrated and coevaporated with Et_2O (15 ml). The aqueous layer was extracted with $CHCl_3$ (3 x 15 ml) and a saturated solution of $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* To the crude amide in MeOH (93 ml, 0.50 M) was added pTsOH (89 mg, 0.46 mmol, 0.01 eq.) and acetone (14 ml, 232 mmol, 5.0 eq.) and stirred at 70 ^{o}C for 16 hours. The reaction mixture was brought to 25 ^{o}C and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided the known MacMillan imidazolidinone (6.5 g, 64% for two steps). ^{1}H NMR spectroscopic data correlate with the previously reported data.[27] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.18 (m, 5H), 3.80 (dd, *J* = 6.7, 4.5 Hz, 1H), 3.16 (dd, *J* = 14.2, 4.4 Hz, 1H), 3.02 (dd, *J* = 14.2, 6.8 Hz, 1H), 2.76 (s, 3H), 1.69 (s, 1H), 1.27 (s, 3H), 1.17 (s, 3H) ppm.

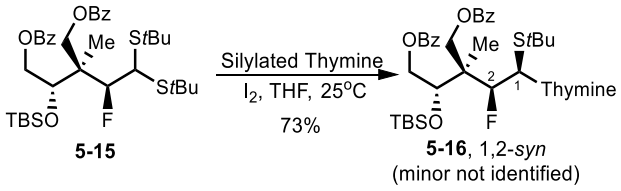
(*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one was prepared the same way starting from D-phenylalanine methyl ester hydrochloride.

General Procedure 5-A

To a solution of the corresponding C2-F dithioacetal in anhydrous solvent at 25 ^{o}C were added the silylated nucleobase and the activating agent. The reaction mixture was stirred until complete by TLC. A saturated solution of $Na_2S_2O_3$ was added and the aqueous layer was extracted with

ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.*

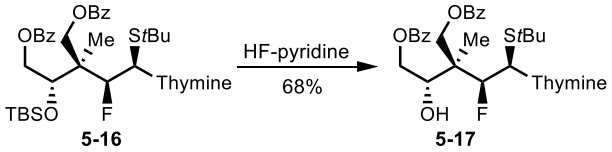
(+)-(2*R*,3*S*)-3-((tert-butyldimethylsilyl)oxy)-2-((1S,2R)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methylbutane-1,4-diyl dibenzoate (5-16)



Following general procedure 5-A, silylated thymine (0.51 ml, 0.32 mmol, 2.0 eq. of a 0.60 M solution in DCM), and I_2 (80 mg, 0.32 mmol, 2.0 eq.) were added to a solution of **5-15** (0.11 g, 0.16 mmol, 1.0 eq.) in anhydrous THF (1.6 ml, 0.10 M) and stirred at 25 °C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **5-16** (81 mg, 73%) as a white foam: $\mathbf{R}_f$ = 0.27 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +71 (*c* 1.1, DCM) ; **Formula** : $C_{36}H_{49}FN_2O_7SSi$; **MW** : 700.9324 g/mol ; **IR** (neat) ν_{max} 3185, 2958, 2930, 1722 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.00 – 7.86 (m, 4H), 7.68 (s, 1H), 7.57 – 7.45 (m, 2H), 7.45 – 7.37 (m, 2H), 7.35 – 7.30 (m, 2H), 6.19 (appd, *J* = 29.6 Hz, 1H), 4.90 (appd, *J* = 46.0 Hz, 1H), 4.70 (d, *J* = 12.2 Hz, 1H), 4.57 (dd, *J* = 11.6, 4.2 Hz, 1H), 4.53 – 4.49 (m, 2H), 4.45 (dd, *J* = 11.6, 5.0 Hz, 1H), 1.96 (s, 3H), 1.29 (s, 9H), 1.24 (s, 3H), 0.84 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.5, 166.2, 163.4, 150.1, 137.7 (d, *J* = 2.6 Hz), 133.2, 133.0, 130.3, 129.9, 129.70, 129.66, 128.52, 128.46, 111.6, 99.7 (d, *J* = 188.0 Hz), 70.9 (d, *J* = 5.5 Hz), 66.6, 64.9, 58.4 (d, *J* = 20.1 Hz), 45.6 (d, *J* = 16.5 Hz), 45.0 (d, *J* = 0.8 Hz),

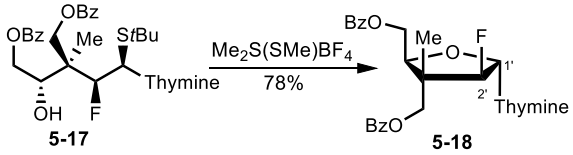
31.0, 25.9, 18.4, 14.3 (d, *J* = 6.6 Hz), 12.6, -4.0, -5.3 (d, *J* = 1.8 Hz) ppm ; **HRMS** calcd for : $C_{36}H_{49}FN_2O_7SSiNa$ [M+Na^+] : 723.2906, found: 723.2905 (-0.17 ppm).

(+)-(2*R*,3*S*)-2-((1S,2R)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-17)



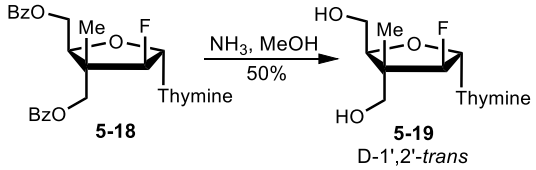
To a solution of **5-16** (71 mg, 0.10 mmol, 1.0 eq.) in anhydrous THF (1.0 ml, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.40 ml, 4ml/mmol, ~70% HF). The reaction was stirred for 72 hours at 25 °C. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 1 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-17** (40 mg, 68%): $\mathbf{R_f}$ = 0.29 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +44 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{30}H_{35}FN_2O_7S$; **MW** : 586.6715 g/mol ; **IR** (neat) ν_{max} 3468, 3172, 2963, 1686 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.01 – 7.97 (m, 4H), 7.73 (s, 1H), 7.58 – 7.51 (m, 2H), 7.45 – 7.37 (m, 4H), 6.52 (appd, *J* = 31.1 Hz, 1H), 4.89 (appd, *J* = 46.2 Hz, 1H), 4.65 (dd, *J* = 11.7, 3.5 Hz, 2H), 4.51 (dd, *J* = 11.6, 7.6 Hz, 1H), 4.43 – 4.35 (m, 2H), 3.20 (d, *J* = 5.0 Hz, 1H), 1.96 (s, 3H), 1.31 (s, 12H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.9, 166.2, 163.7, 150.6, 137.9 (d, *J* = 2.1 Hz), 133.5, 133.3, 129.9, 129.84 , 129.77, 129.6, 128.7, 128.6, 111.7, 100.4 (d, *J* = 187.1 Hz), 70.7 (d, *J* = 4.9 Hz), 66.1 (d, *J* = 2.1 Hz), 65.6 (d, *J* = 5.0 Hz), 59.3 (d, *J* = 20.1 Hz), 45.2, 45.0 (d, *J* = 17.0 Hz), 31.1, 13.7 (d, *J* = 3.9 Hz), 12.8 ppm ; **HRMS** calcd for $C_{30}H_{36}FN_2O_7S$ [M+H^+] : 587.2222, found: 587.2221 (-0.07 ppm).

(+)-((2*S*,3*R*,4*S*,5*S*)-4-fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-18)



To a solution of **5-17** (0.19 g, 0.33 mmol, 1.0 eq.) in anhydrous THF (3.3 ml, 0.10 M) was added $Me_2S(SMe)BF_4$ (0.13 g, 0.65 mmol, 2.0 eq.). The reaction was stirred for 4 hours at 25 ^oC. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 3 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-18** (0.13 g, 78%): $\mathbf{R_f}$ = 0.30 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +35 (*c* 1.4, $CDCl_3$) ; **Formula** : $C_{26}H_{25}FN_2O_7$; **MW** : 496.4843 g/mol ; **IR** (neat) ν_{max} 3062, 2894,1712 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.10 – 8.01 (m, 4H), 7.61 – 7.54 (m, 2H), 7.49 – 7.40 (m, 4H), 7.06 (s, 1H), 5.75 (dd, *J* = 24.6, 4.8 Hz, 1H), 5.67 (dd, *J* = 14.5, 4.8 Hz, 1H), 4.89 (dd, *J* = 6.9, 4.6 Hz, 1H), 4.59 – 4.50 (m, 2H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 1.92 (s, 3H), 1.31 (d, *J* = 3.7 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.3, 166.2, 163.7, 150.2, 138.1, 133.6, 133.5, 129.90, 129.87, 129.53, 129.45, 128.7, 128.6, 111.5, 95.9 (d, *J* = 195.0 Hz), 93.0 (d, *J* = 35.0 Hz), 81.9 (d, *J* = 3.7 Hz), 66.7, 63.7, 47.9 (d, *J* = 17.8 Hz), 12.5, 11.6 (d, *J* = 11.7 Hz) ppm ; **HRMS** calcd for $C_{26}H_{25}FN_2O_7Na$ [M+Na^+] : 519.1538, found: 519.1533 (-0.99 ppm).

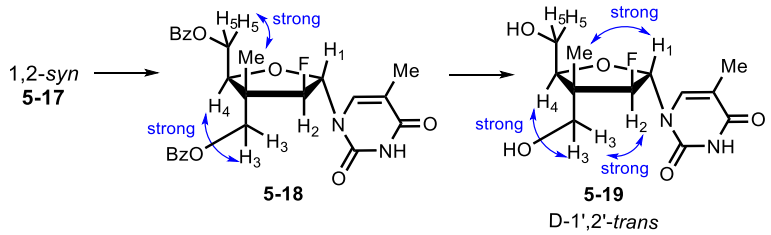
(+)-1-((2*S*,3*S*,4*R*,5*S*)-3-fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (5-19)



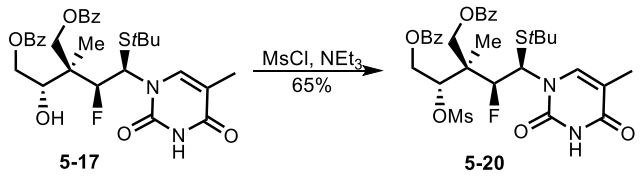
To a solution of **5-18** (0.11 g, 0.22 mmol, 1.0 eq.) in MeOH (8.0 ml, 0.03 M) was bubbled NH_3. The reaction was stirred for 72 hours at 25 ^{o}C and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-19** (31.9 mg, 50%): $\mathbf{R_f}$ = 0.09 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ +49 (*c* 1.4, CD_3OD) ; **Formula** : $C_{12}H_{17}FN_2O_5$; **MW** : 288.2722 g/mol ; **IR** (neat) ν_{max} 3392, 2941,1691 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.50 (s, 1H), 5.97 (dd, *J* = 15.6, 5.0 Hz, 1H), 5.28 (dd, *J* = 54.2, 5.0 Hz, 1H), 4.43 – 4.39 (m, 1H), 3.74 – 3.66 (m, 2H), 3.59 – 3.53 (m, 2H), 1.90 (s, 3H), 1.07 (d, *J* = 3.5 Hz, 3H) ppm *OH signals missing possibly due to exchange in* CD_3OD; **^{13}C NMR** (125 MHz, CD_3OD) δ 166.4, 152.5, 138.6, 111.9, 97.9 (d, *J* = 193.0 Hz), 90.8 (d, *J* = 34.7 Hz), 85.7 (d, *J* = 3.7 Hz), 65.9, 62.4 (d, *J* = 0.8 Hz), 49.7 (d, *J* = 16.9 Hz), 12.4, 11.0 (d, *J* = 11.3 Hz) ppm; **HRMS** calcd for $C_{12}H_{17}FN_2O_5Na$ [M+Na^+] : 311.1014, found: 311.1012 (-0.71 ppm).

Stereochemical Proofs

Proof of structure for the C1'-C2' relative stereochemistry were provided by NOESY experiments.

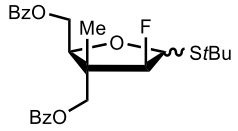


(+)-((2*R*,3*S*)-2-((1S,2R)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl dibenzoate (5-20)



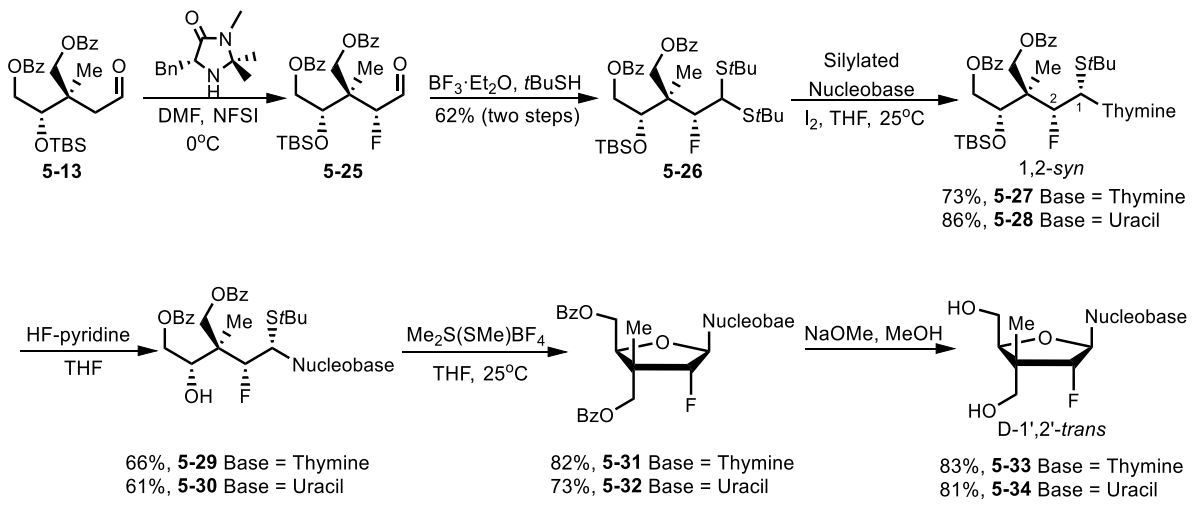
To a solution of **5-17** (0.11 g, 0.19 mmol, 1.0 eq.) in anhydrous DCM (1.9 ml, 0.10 M) at 0 °C was added triethylamine (40 µl, 0.29 mmol, 1.5 eq.) and methanesulfonyl chloride (40 µl, 0.48 mmol, 2.5 eq). The reaction was stirred for 16 hours at 25 °C. A 1.0 N solution (0.50 ml) of HCl was added and the aqueous layer was extracted with dichloromethane (3 × 2 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (DCM/Acetone, 90:10), provided **5-20** (82 mg, 65%): $\mathbf{R_f}$ = 0.33 (DCM/Acetone, 90:10); $\mathbf{[\alpha]^{25}_D}$ +54 (*c* 0.98, $CDCl_3$) ; **Formula** : $C_{31}H_{37}FN_2O_9S_2$; **MW** : 664.7619 g/mol ; **IR** (neat) ν_{max} 2965, 1687 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.08 – 8.03 (m, 4H), 7.70 (s, 1H), 7.61 – 7.55 (m, 2H), 7.50 – 7.41 (m, 4H), 6.19 (appd, *J* = 30.4 Hz, 1H), 5.49 (dd, *J* = 8.0, 2.2 Hz, 1H), 4.93 – 4.89 (m, 1H), 4.85 (appd, *J* = 30.1 Hz, 1H), 4.68 – 4.57 (m, 3H), 3.06 (s, 3H), 1.97 (s, 3H), 1.40 (s, 3H), 1.33 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 166.1, 163.3, 150.3, 137.5 (d, *J* = 2.2 Hz), 133.7, 133.5, 129.91, 129.90, 129.6, 129.3, 128.79, 128.76, 111.8, 98.5 (d, *J* = 193.5 Hz), 80.7, 64.6 (d, *J* = 2.1 Hz), 64.0, 58.3 (d, *J* = 19.7 Hz), 45.6, 44.9 (d, *J* = 17.5 Hz), 39.4, 31.0, 16.1 (d, *J* = 6.2 Hz), 12.8 ppm ; **HRMS** calcd for $C_{31}H_{37}FN_2O_9S_2Na$ [M+Na^+] : 687.1817, found: 687.1844 (4.0 ppm).

((2*S*,3*R*,4*S*,5*S*)-5-(tert-butylthio)-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-23)

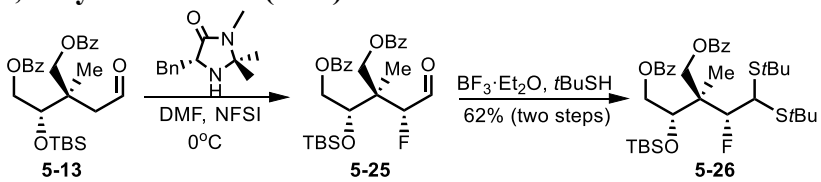


5-23

To a solution of **5-17** (97 mg, 0.17 mmol, 1.0 eq.) in anhydrous DCM (1.7 ml, 0.10 M) at –40 ^{o}C was added Tf_2O (0.5 ml µl, 0.50 mmol, 3.0 eq., 0.99 M in DCM) and 2,6-lutidine (0.12 ml, 0.98 mmol, 6.0 eq). The reaction was stirred for 1 hour at –40 ^{o}C and then for 2 hours at 25 ^{o}C. A 1.0 N solution (0.50 ml) of HCl was added and the aqueous layer was extracted with dichloromethane (3 × 2 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (EtOAc/Hexane, 50:50), provided **5-23**: **Formula** : $C_{25}H_{29}FO_5S$; **MW** : 460.5604 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (t, *J* = 7.9 Hz, 4H), 7.64 – 7.52 (m, 2H), 7.45 (dd, *J* = 16.7, 8.0 Hz, 4H), 5.53 (dd, *J* = 26.8, 4.1 Hz, 1H), 4.99 (dd, *J* = 53.2, 4.1 Hz, 1H), 4.60 – 4.49 (m, 2H), 4.38 – 4.26 (m, 2H), 4.24 (t, *J* = 6.2 Hz, 1H), 1.40 (s, 9H), 1.36 (d, *J* = 3.5 Hz, 3H) ppm; **HRMS** calcd for : $C_{25}H_{29}FO_5SNa$ [M+Na^+] : 483.1612, found: 483.1620. A NOESY experiment was not done to confirm the 1,2-stereochemistry.



(–)-(2*R*,3*S*)-2-((*R*)-2,2-bis(tert-butylthio)-1-fluoroethyl)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl dibenzoate (5-26)

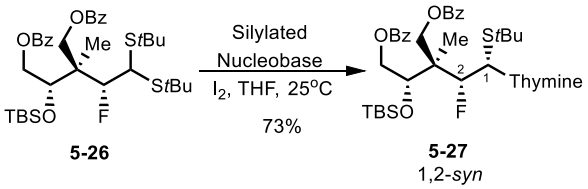


To the (*R*)-imidazolidinone catalyst (0.29 g, 1.3 mmol, 1.05 eq.) at –40 °C, was added **5-13** (0.60 g, 1.2 mmol, 1.0 eq.) as a solution in anhydrous DMF (1.3 ml, 1.0 M). After stirring for 10 minutes, NFSI (0.40 g, 1.3 mmol, 1.02 eq.) was added. Once homogeneous, it was left at 0 °C for 72 hours. The reaction mixture was diluted with Et_2O and water (1.0 ml) and treated with Me_2S (0.20 ml, 2.5 mmol, 2.0 eq.). The aqueous layer was extracted with Et_2O (3 × 3 ml) and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR spectroscopic analysis of the unpurified C2-F aldehyde indicated ~17:1 diastereomeric ratio for the fluorination. To the crude C2-F aldehyde **5-25** in anhydrous DCM (12.5 ml, 0.10 M) at –60 °C was added *t*BuSH (0.60 ml, 4.97 mmol, 4.0 eq.) and BF_3•OEt_2 (0.40 ml, 3.1 mmol, 2.5 eq.). The reaction was stirred at -60 °C for 5 hours. Upon addition of NEt_3 (3.5 ml, 24.9 mmol, 20 eq.)

stirring at –60 °C was maintained for 15 minutes. A saturated solution (5 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-26** (0.51 g, 62% for two steps): $\mathbf{R_f}$ = 0.39 (Hexanes/EtOAc, 90:10); $\mathbf{[\alpha]^{25}_D}$ –17 (*c* 1.0, DCM) ; **Formula** : $C_{35}H_{53}FO_5S_2Si$; **MW** : 665.0062 g/mol ; **IR** (neat) ν_{max} 2959, 2929, 1722 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 – 8.02 (m, 4H), 7.60 – 7.55 (m, 2H), 7.49 – 7.42 (m, 4H), 5.25 (dd, *J* = 44.5, 2.5 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 10.4 Hz, 1H), 4.43 – 4.31 (m, 3H), 4.24 (dd, *J* = 26.1, 2.4 Hz, 1H), 1.462 (s, 9H), 1.456 (s, 3H), 1.43 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.8, 166.5, 133.3, 133.1, 130.4, 130.1, 129.8, 129.7, 128.7, 128.5, 95.4 (d, *J* = 183.3 Hz), 74.9, 68.7 (d, *J* = 9.6 Hz), 66.2 (d, *J* = 8.9 Hz), 47.6 (d, *J* = 16.2 Hz), 47.4 (d, *J* = 18.9 Hz), 46.0, 45.3, 32.0, 31.9, 26.1, 18.5, 17.1 (d, *J* = 6.8 Hz), -4.3, -4.5 ppm ; **HRMS** calcd for : $C_{35}H_{53}FO_5S_2SiNa$ $[M+Na^+]$: 687.2980, found: 687.2976 (-0.62 ppm).

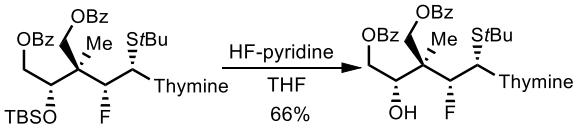
5-25 (crude): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.82 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.92 (m, 4H), 7.60 – 7.50 (m, 2H), 7.49 – 7.34 (m, 4H), 5.00 (dd, *J* = 48.0, 1.3 Hz, 1H), 4.58 (dd, *J* = 13.4, 6.1 Hz, 1H), 4.49 – 4.39 (m, 4H), 1.31 (d, *J* = 1.6 Hz, 3H), 0.91 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H) ppm.

(–)-(2*R*,3*S*)-3-((tert-butyldimethylsilyl)oxy)-2-((1R,2S)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methylbutane-1,4-diyl dibenzoate (5-27)



Following general procedure 5-A, silylated thymine (0.48 ml, 0.29 mmol, 2.0 eq. of a 0.60 M solution in DCM), and I_2 (75 mg, 0.29 mmol, 2.0 eq.) were added to a solution of **5-26** (98 mg, 0.15 mmol, 1.0 eq.) in anhydrous THF (1.5 ml, 0.10 M) and stirred at 25 °C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **5-27** (75 mg, 73%) as a white foam: $\mathbf{R_f}$ = 0.16 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –42 (*c* 0.97, DCM); **Formula** : $C_{36}H_{49}FN_2O_7SSi$; **MW** : 700.9324 g/mol ; **IR** (neat) ν_{max} 3180, 2957, 2929, 1696 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 – 7.98 (m, 4H), 7.94 (s, 1H), 7.65 (s, 1H), 7.60 – 7.55 (m, 2H), 7.47 – 7.42 (m, 4H), 6.11 (dd, *J* = 30.5, 1.3 Hz, 1H), 5.11 (dd, *J* = 46.8, 1.3 Hz, 1H), 4.67 (d, *J* = 11.0 Hz, 2H), 4.41 (d, *J* = 10.9 Hz, 1H), 4.39 – 4.34 (m, 1H), 4.34 – 4.31 (m, 1H), 1.92 (s, 3H), 1.39 (s, 3H), 1.33 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 166.2, 163.2, 150.0, 138.0 (d, *J* = 3.2 Hz), 133.4, 133.3, 130.2, 130.0, 129.74, 129.69, 128.67, 128.60, 111.2, 97.3 (d, *J* = 185.8 Hz), 73.7, 67.7 (d, *J* = 6.4 Hz), 65.0 (d, *J* = 7.5 Hz), 58.7 (d, *J* = 20.2 Hz), 46.5 (d, *J* = 19.2 Hz), 45.5, 31.2, 26.0, 18.4, 16.6 (d, *J* = 6.8 Hz), 12.7, -3.8, -4.8 ppm ; **HRMS** calcd for : $C_{36}H_{49}FN_2O_7SSiNa$ [M+Na^+] : 723.2906, found: 723.2908 (0.26 ppm).

(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-29)

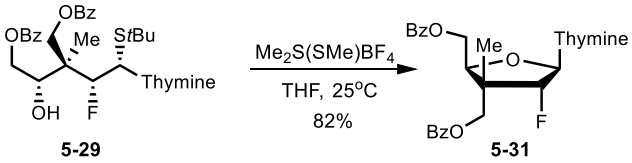


5-27 **5-29**

To a solution of **5-27** (66 mg, 0.095 mmol, 1.0 eq.) in anhydrous THF (0.95 ml, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.40 ml, 4ml/mmol, ~70% HF). The reaction was stirred for 96 hours at 25 °C. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the

aqueous layer was extracted with ethyl acetate (3 × 1 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-29** (37 mg, 66%): $\mathbf{R_f}$ = 0.39 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –26 (*c* 1.3, $CDCl_3$) ; **Formula** : $C_{30}H_{35}FN_2O_7S$; **MW** : 586.6715 g/mol ; **IR** (neat) ν_{max} 3446, 3202, 2962, 1718 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.07 – 8.03 (m, 4H), 7.71 (s, 1H), 7.60 – 7.53 (m, 2H), 7.48 – 7.38 (m, 4H), 6.45 (appd, *J* = 31.2 Hz, 1H), 4.96 (appd, *J* = 46.4 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.69 (dd, *J* = 11.6, 2.3 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.47 (dd, *J* = 11.2, 8.7 Hz, 1H), 4.27 – 4.22 (m, 1H), 3.65 (d, *J* = 3.8 Hz, 1H), 1.95 (s, 3H), 1.35 (s, 3H), 1.32 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.9, 166.7, 163.5, 150.9, 137.9 (d, *J* = 2.8 Hz), 133.43, 133.35, 129.91, 129.89, 129.83, 128.68, 128.64, 128.5, 111.8, 99.8 (d, *J* = 184.8 Hz), 72.7 (d, *J* = 3.2 Hz), 66.5 (d, *J* = 3.7 Hz), 65.7 (d, *J* = 3.2 Hz), 58.8 (d, *J* = 20.0 Hz), 45.6 (d, *J* = 17.8 Hz), 45.4, 31.1, 16.2 (d, *J* = 6.2 Hz), 12.8 ppm ; **HRMS** calcd for $C_{30}H_{35}FN_2O_7SNa$ $[M+Na^+]$: 609.2041, found: 609.2056 (-2.48 ppm).

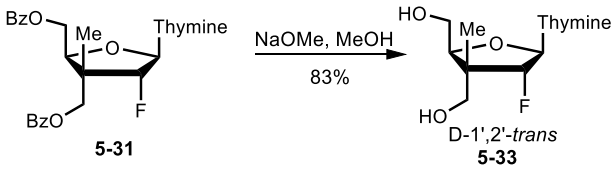
(+)-((2*S*,3*R*,4*R*,5*R*)-4-fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-31)



To a solution of **5-29** (91 mg, 0.16 mmol, 1.0 eq.) in anhydrous THF (1.6 ml, 0.10 M) was added $Me_2S(SMe)BF_4$ (61 mg, 0.31 mmol, 2.0 eq.). The reaction was stirred for 4 hours at 25 °C. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 3 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-31** (63 mg, 82%): $\mathbf{R_f}$ = 0.24 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +11 (*c* 1.3,

DCM) ; **Formula** : $C_{26}H_{25}FN_2O_7$; **MW** : 496.4843 g/mol ; **IR** (neat) ν_{max} 3193, 3062,1718, 1692 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.09 – 8.02 (m, 4H), 7.63 – 7.57 (m, 2H), 7.51 – 7.44 (m, 4H), 7.40 (s, 1H), 5.96 (dd, *J* = 18.6, 2.5 Hz, 1H), 5.07 (dd, *J* = 51.5, 2.5 Hz, 1H), 4.66 (d, *J* = 5.1 Hz, 2H), 4.61 (appt, *J* = 5.0 Hz, 1H), 4.55 (dd, *J* = 11.3, 1.2 Hz, 1H), 4.50 (dd, *J* = 11.4, 2.3 Hz, 1H), 1.83 (s, 3H), 1.28 (d, *J* = 1.0 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.3, 166.2, 163.3, 150.2, 134.6, 133.8, 133.6, 129.83, 129.79, 129.5, 129.4, 128.83, 128.78, 111.5, 100.2 (d, *J* = 192.8 Hz), 90.0 (d, *J* = 37.7 Hz), 81.9, 65.6 (d, *J* = 12.2 Hz), 63.4, 46.6 (d, *J* = 16.4 Hz), 16.1 (d, *J* = 4.0 Hz), 12.6 ppm ; **HRMS** calcd for $C_{26}H_{25}FN_2O_7Na$ $[M+Na^+]$: 519.1538, found: 519.1537 (-0.19 ppm).

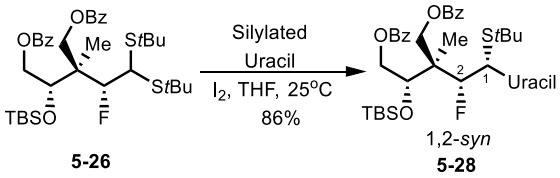
(+)-1-((2*R*,3*R*,4*R*,5*S*)-3-fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (5-33)



To a solution of **5-31** (68 mg, 0.14 mmol, 1.0 eq.) in MeOH (1.0 ml, 0.13 M) at 0 °C was added NaOMe (20 µl, 0.07 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 °C. Formic acid (~ 2 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-33** (33 mg, 83%): $\mathbf{R_f}$ = 0.13 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ +4 (*c* 0.8, CD_3OD) ; **Formula** : $C_{12}H_{17}FN_2O_5$; **MW** : 288.2722 g/mol ; **IR** (neat) ν_{max} 3363, 2936,1694 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.92 (s, 1H), 6.06 (dd, *J* = 17.1, 4.2 Hz, 1H), 4.97 (dd, *J* = 53.1, 4.2 Hz, 1H), 4.18 (appt, *J* = 4.1 Hz, 1H), 3.82 (dd, *J* = 11.9, 3.7 Hz, 1H), 3.74 (dd, *J* = 12.0, 4.6 Hz, 1H), 3.70 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.62 (dd, *J* = 11.1, 2.0 Hz, 1H), 1.90 (s, 3H), 1.13 (s, 3H) ppm *OH*

and NH signals missing possibly due to exchange in CD_3OD; **^{13}C NMR** (125 MHz, CD_3OD) δ 166.3, 152.6, 137.7, 111.7, 101.4 (d, *J* = 189.8 Hz), 89.2 (d, *J* = 35.9 Hz), 85.8 (d, *J* = 3.4 Hz), 65.0 (d, *J* = 12.1 Hz), 62.4, 15.7 (d, *J* = 2.3 Hz), 12.5 ppm *one carbon missing due to same chemical shift as CD_3OD*; **^{13}C NMR** (125 MHz, $(CD_3)_2SO$) δ 163.7, 150.7, 135.7, 109.7, 99.4 (d, *J* = 189.1 Hz), 85.9 (d, *J* = 34.6 Hz), 83.7 (d, *J* = 3.4 Hz), 63.3 (d, *J* = 11.3 Hz), 60.9, 46.6 (d, *J* = 15.9 Hz), 15.4 (d, *J* = 1.2 Hz), 12.3 ppm; **HRMS** calcd for $C_{12}H_{17}FN_2O_5Na$ [M+Na$^+$] : 311.1014, found: 311.1018 (1.53 ppm).

(–)-(2*R*,3*S*)-3-((tert-butyldimethylsilyl)oxy)-2-((1R,2S)-2-(tert-butylthio)-2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-1-fluoroethyl)-2-methylbutane-1,4-diyl dibenzoate (5-28)

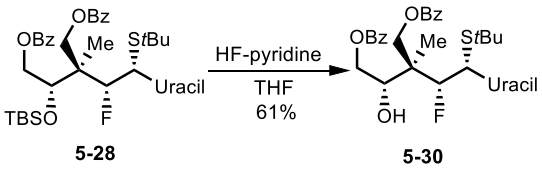


5-26 **5-28**

Following general procedure 5-A, silylated uracil (1.1 ml, 0.79 mmol, 3.0 eq. of a 0.74 M solution in DCM), and I_2 (0.13 g, 0.53 mmol, 2.0 eq.) were added to a solution of **5-26** (0.18 g, 0.27 mmol, 1.0 eq.) in anhydrous THF (2.6 ml, 0.10 M) and stirred at 25 °C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **5-28** (0.16 g, 86%) as a white foam: $\mathbf{R_f}$ = 0.41 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –42 (*c* 1.3, $CDCl_3$) ; **Formula** : $C_{35}H_{47}FN_2O_7SSi$; **MW** : 686.9058 g/mol ; **IR** (neat) ν_{max} 3172, 2963, 2861, 1696 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.06 – 7.98 (m, 4H), 7.89 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.50 – 7.42 (m, 4H), 6.08 (dd, *J* = 31.2, 0.9 Hz, 1H), 5.76 (dd, *J* = 8.2, 1.7 Hz, 1H), 5.13 (dd, *J* = 46.8, 1.1 Hz, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.65 (d, *J* = 11.9 Hz,

1H), 4.41 (d, *J* = 10.8 Hz, 1H), 4.36 (dd, *J* = 6.3, 2.8 Hz, 1H), 4.30 (ddd, *J* = 11.9, 6.4, 2.5 Hz, 1H), 1.39 (d, *J* = 1.3 Hz, 3H), 1.33 (s,9), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 166.2, 162.6, 150.0, 142.5 (d, *J* = 3.0 Hz), 133.4, 133.3, 130.1, 129.9, 129.71, 129.66, 128.7, 128.6, 102.5, 96.9 (d, *J* = 184.9 Hz), 73.6, 67.6 (d, *J* = 6.7 Hz), 64.9 (d, *J* = 7.7 Hz), 59.1 (d, *J* = 20.1 Hz), 46.4 (d, *J* = 18.9 Hz), 45.5, 31.1, 26.0, 18.4, 16.4 (d, *J* = 7.1 Hz), -3.9, -4.9 ppm ; **HRMS** calcd for : $C_{35}H_{47}FN_2O_7SSiNa$ [M+Na^+] : 709.2749, found: 709.2763 (1.94 ppm).

(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(tert-butylthio)-2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-1-fluoroethyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-30)

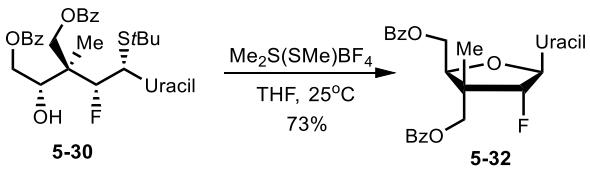


5-28 **5-30**

To a solution of **5-28** (0.10 g, 0.15 mmol, 1.0 eq.) in anhydrous THF (1.5 ml, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.45 ml, 3 ml/mmol, ~70% HF). The reaction was stirred for 96 hours at 25 °C. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 2 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-30** (52 mg, 61%): $\mathbf{R_f}$ = 0.37 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –26 (*c* 1.3, $CDCl_3$) ; **Formula** : $C_{29}H_{33}FN_2O_7S$; **MW** : 572.6449 g/mol ; **IR** (neat) ν_{max} 3441, 2957, 1691 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.07 – 8.01 (m, 4H), 7.94 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.48 – 7.40 (m, 4H), 6.45 (appd, *J* = 31.9 Hz, 1H), 5.80 (d, *J* = 8.2 Hz, 1H), 4.96 (appd, *J* = 46.3 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.68 (dd, *J* = 11.6, 2.3 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.50 – 4.45 (m, 1H), 4.24 – 4.16 (m, 1H), 3.54 (d, *J* = 3.7 Hz, 1H), 1.36 (d, *J* = 1.7 Hz, 3H), 1.33 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.9,

166.8, 162.8, 150.7, 142.4 (d, *J* = 3.0 Hz), 133.44, 133.41, 129.88, 129.85, 129.823, 129.817, 128.7, 128.6, 102.9, 99.5 (d, *J* = 185.1 Hz), 72.9 (d, *J* = 3.0 Hz), 66.4 (d, *J* = 3.8 Hz), 65.6 (d, *J* = 4.4 Hz), 59.4 (d, *J* = 20.0 Hz), 45.6 (d, *J* = 17.8 Hz), 45.5, 31.1, 16.5 (d, *J* = 6.0 Hz) ppm ; **HRMS** calcd for $C_{29}H_{33}FN_2O_7SNa$ [M+Na^+] : 595.1885, found: 595.1890 (0.97 ppm).

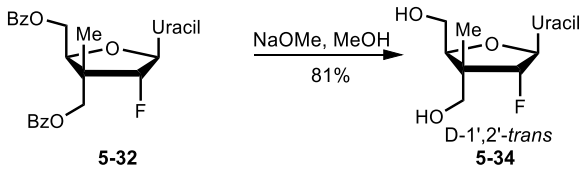
(+)-((2*S*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-32)



To a solution of **5-30** (0.27 g, 0.46 mmol, 1.0 eq.) in anhydrous THF (5.0 ml, 0.10 M) was added $Me_2S(SMe)BF_4$ (0.18 g, 0.93 mmol, 2.0 eq.). The reaction was stirred for 4 hours at 25 °C. A saturated solution (3.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 5 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 30:70), provided **5-32** (0.16 g, 73%): $\mathbf{R_f}$ = 0.41 (Hexanes/EtOAc, 30:70); $\mathbf{[\alpha]^{25}_D}$ +38 (*c* 0.7, $CDCl_3$) ; **Formula** : $C_{25}H_{23}FN_2O_7$; **MW** : 482.4577 g/mol ; **IR** (neat) ν_{max} 3204, 3054,1712, 1685 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.07 – 8.02 (m, 4H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.50 – 7.45 (m, 4H), 5.91 (dd, *J* = 19.0, 1.8 Hz, 1H), 5.74 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.06 (dd, *J* = 50.9, 1.8 Hz, 1H), 4.72 – 4.61 (m, 3H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.50 (dd, *J* = 11.3, 2.6 Hz, 1H), 1.23 (d, *J* = 1.3 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ166.3, 166.2, 162.5, 150.0, 138.8, 133.8, 133.7, 129.83, 129.78, 129.5, 129.3, 128.80, 128.79, 102.8, 100.4 (d, *J* = 192.6 Hz), 90.5 (d, *J* = 38.7 Hz), 82.4, 65.4 (d, *J* = 12.1 Hz), 63.2, 46.7 (d, *J*

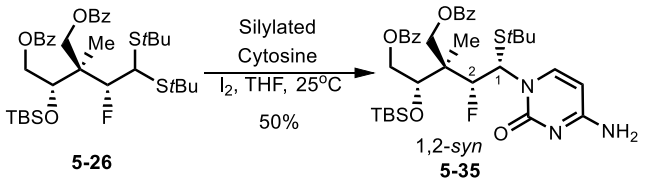
= 16.5 Hz), 15.8 (d, *J* = 4.5 Hz) ppm ; **HRMS** calcd for $C_{25}H_{23}FN_2O_7Na$ [M+Na^+] : 505.1382, found: 505.1384 (0.56 ppm).

(+)-1-((2*R*,3*R*,4*R*,5*S*)-3-fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (5-34)



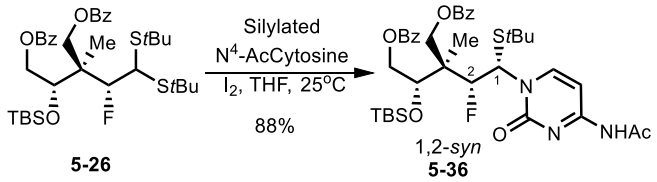
To a solution of **5-32** (96 mg, 0.20 mmol, 1.0 eq.) in MeOH (1.6 ml, 0.13 M) at 0 ^oC was added NaOMe (25 µl, 0.10 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 ^oC. A 1N HCl solution (~ 10 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (DCM/MeOH, 95:5), provided **5-34** (44 mg, 81%): $\mathbf{R}_f$ = 0.29 (DCM/MeOH, 95:5); $\mathbf{[\alpha]^{25}_D}$ +28 (*c* 1.4, CD_3OD) ; **Formula** : $C_{11}H_{15}FN_2O_5$; **MW** : 274.2456 g/mol ; **IR** (neat) ν_{max} 3392, 2941,1686 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 8.07 (d, *J* = 8.2 Hz, 1H), 6.03 (dd, *J* = 17.5, 3.7 Hz, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 4.96 (dd, *J* = 52.7, 3.6 Hz, 1H), 4.19 (appt, *J* = 4.3 Hz, 1H), 3.81 (dd, *J* = 12.0, 3.9 Hz, 1H), 3.75 (dd, *J* = 11.9, 4.9 Hz, 1H), 3.69 (dd, *J* = 11.1, 2.0 Hz, 1H), 3.64 (dd, *J* = 11.1, 2.0 Hz, 1H), 1.10 (d, *J* = 0.7 Hz, 3H) ppm *OH and NH signals missing possibly due to exchange in* CD_3OD; **^{13}C NMR** (125 MHz, CD_3CN) δ 163.9, 151.6, 140.9, 102.7, 101.7 (d, *J* = 188.3 Hz), 89.3 (d, *J* = 36.8 Hz), 85.7 (d, *J* = 1.8 Hz), 64.5 (d, *J* = 12.2 Hz), 61.9, 48.2 (d, *J* = 16.2 Hz), 15.4 (d, *J* = 3.4 Hz) ppm; **HRMS** calcd for $C_{11}H_{15}FN_2O_5Na$ [M+Na^+] : 297.0857, found: 297.0863 (1.53 ppm).

(–)-(2*R*,3*S*)-2-((1R,2S)-2-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl dibenzoatedibenzoate (5-35)



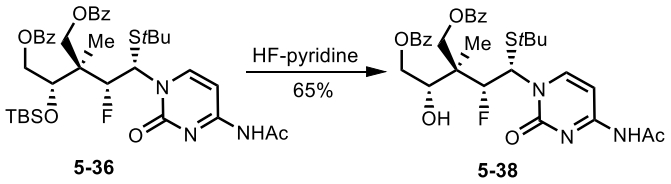
Following general procedure 5-A, silylated cytosine (0.40 ml, 0.28 mmol, 3.5 eq. of a 0.72 M solution in DCM), and I_2 (40 mg, 0.16 mmol, 2.0 eq.) were added to a solution of **5-26** (53 mg, 0.08 mmol, 1.0 eq.) in anhydrous THF (1.0 ml, 0.10 M) and stirred at 25 °C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 0:100) provided **5-35** (27.2 mg, 50%) as a white foam: $\mathbf{R_f}$ = 0.21 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ –31 (*c* 1.5, $CDCl_3$) ; **Formula** : $C_{35}H_{48}FN_3O_6SSi$; **MW** : 685.9210 g/mol ; **IR** (neat) ν_{max} 3425, 3341, 2958, 1717, 1648 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 – 8.02 (m, 4H), 8.00 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 4H), 6.32 (appd, *J* = 32.4 Hz, 1H), 5.86 (d, *J* = 7.4 Hz, 1H), 5.05 (appd, *J* = 46.9 Hz, 1H), 4.70 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 10.7 Hz, 1H), 4.45 (dd, *J* = 6.2, 2.0 Hz, 1H), 4.34 – 4.27 (m, 1H), 1.43 (s, 3H), 1.31 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H) ppm *NH_2 signal missing possibly due to exchange in* $CDCl_3$; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.7, 166.5, 165.8, 155.6, 143.9, 133.3, 133.1, 130.3, 130.0, 129.762, 129.760 , 128.7, 128.6, 98.2, 95.7 (d, *J* = 244.7 Hz), 73.9, 68.3 (d, *J* = 8.9 Hz), 65.4 (d, *J* = 7.5 Hz), 59.1 (d, *J* = 18.6 Hz), 46.4 (d, *J* = 17.9 Hz), 45.3, 31.3, 26.0, 18.4, 17.2 (d, *J* = 6.7 Hz), -3.8, -4.8 ppm ; **HRMS** calcd for : $C_{35}H_{49}FN_3O_6SSi$ [M+H$^+$] : 686.3090, found: 686.3101 (1.57 ppm).

(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl dibenzoate (5-36)



Following general procedure 5-A, silylated N^4-AcCytosine (4.5 ml, 2.1 mmol, 3.5 eq. of a 0.48 M solution in DCM), and I_2 (0.31 g, 1.2 mmol, 2.0 eq.) were added to a solution of **5-26** (0.40 g, 0.61 mmol, 1.0 eq.) in anhydrous THF (6.0 ml, 0.10 M) and stirred at 25 °C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 0:100) provided **5-36** (0.39 g, 88%) as a white foam: $\mathbf{R_f}$ = 0.59 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ –22 (*c* 1.7, $CDCl_3$) ; **Formula** : $C_{37}H_{50}FN_3O_7SSi$; **MW** : 727.9577 g/mol ; **IR** (neat) ν_{max} 2958, 2929, 1721, 1664 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.36 (dd, *J* = 7.5, 1.8 Hz, 1H), 8.03 (appd, *J* = 8.0 Hz, 4H), 7.59 – 7.52 (m, 2H), 7.47 – 7.39 (m, 5H), 6.31 (appd, *J* = 32.1 Hz, 1H), 5.08 (appd, *J* = 47.4 Hz, 1H), 4.72 – 4.66 (m, 2H), 4.48 (d, *J* = 10.7 Hz, 1H), 4.41 (dd, *J* = 6.3, 2.5 Hz, 1H), 4.28 (ddd, *J* = 12.0, 6.4, 2.7 Hz, 1H), 2.24 (s, 3H), 1.43 (s, 3H), 1.30 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.7, 166.7, 166.3, 162.8, 155.1, 147.8, 133.3, 133.2, 130.2, 130.0, 129.744, 129.736, 128.7, 128.6, 97.0, 96.2 (d, *J* = 184.1 Hz), 74.0, 68.0 (d, *J* = 7.6 Hz), 65.0 (d, *J* = 7.9 Hz), 60.4 (d, *J* = 19.6 Hz), 46.5 (d, *J* = 18.7 Hz), 45.8, 31.2, 26.0, 25.1, 18.4, 16.7 (d, *J* = 7.2 Hz), -3.9, -4.8 ppm ; **HRMS** calcd for : $C_{37}H_{51}FN_3O_7SSi$ $[M+H^+]$: 728.3196, found: 728.3221 (3.46 ppm).

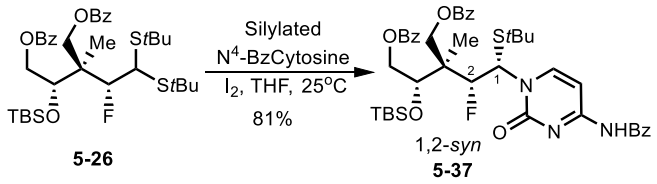
(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-38)



5-36 **5-38**

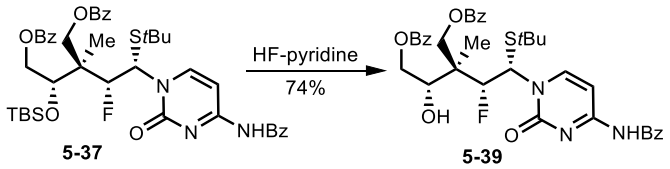
To a solution of **5-36** (0.20 g, 0.27 mmol, 1.0 eq.) in anhydrous THF (3.0 ml, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (1.2 ml, 4ml/mmol, ~70% HF). The reaction was stirred for 90 hours at 25 °C. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 3 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-38** (0.11 g, 65%): $\mathbf{R_f}$ = 0.43 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ –34 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{31}H_{36}FN_3O_7S$; **MW** : 613.6968 g/mol ; **IR** (neat) ν_{max} 3303, 3072, 2966, 1717, 1658 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.43 (dd, *J* = 7.5, 1.1 Hz, 1H), 8.07 – 8.02 (m, 4H), 7.58 – 7.53 (m, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.47 – 7.40 (m, 4H), 6.56 (appd, *J* = 31.9 Hz, 1H), 4.91 (appd, *J* = 46.1 Hz, 1H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.71 (dd, *J* = 11.6, 2.2 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.49 (dd, *J* = 11.3, 8.8 Hz, 1H), 4.29 (apps, 1H), 3.93 (d, *J* = 4.6 Hz, 1H), 2.25 (s, 3H), 1.35 (d, *J* = 1.6 Hz, 3H), 1.28 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.5, 166.9, 166.7, 162.7, 155.9, 147.5, 133.4, 133.3, 129.98, 129.95, 129.86, 129.85, 128.7, 128.5, 99.2 (d, *J* = 185.8 Hz), 97.4, 72.9 (d, *J* = 3.1 Hz), 66.3 (d, *J* = 3.5 Hz), 65.7 (d, *J* = 3.9 Hz), 60.8 (d, *J* = 19.8 Hz), 45.8 (d, *J* = 17.4 Hz), 45.7, 31.1, 25.1, 16.1 (d, *J* = 6.0 Hz) ppm ; **HRMS** calcd for $C_{31}H_{36}FN_3O_7SNa$ [$M+Na^+$] : 636.2150, found: 636.2167 (2.61 ppm).

(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl dibenzoate (5-37)



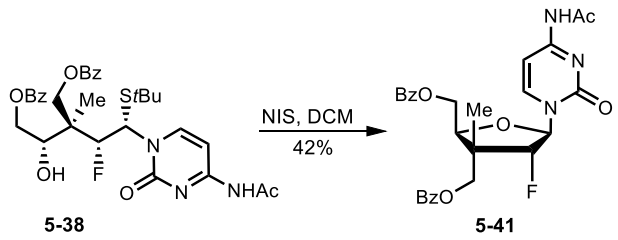
Following general procedure 5-A, silylated N^4-BzCytosine (3.5 ml, 2.38 mmol, 3.0 eq. of a 0.68 M solution in DCM), and I_2 (0.40 g, 1.6 mmol, 2.0 eq.) were added to a solution of **5-26** (0.53 g, 0.79 mmol, 1.0 eq.) in anhydrous THF (8.0 ml, 0.10 M) and stirred at 25 °C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **5-37** (0.51 g, 81%) as a white foam: $\mathbf{R_f}$ = 0.56 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –64 (*c* 1.4, $CDCl_3$) ; **Formula** : $C_{42}H_{52}FN_3O_7SSi$; **MW** : 790.0271 g/mol ; **IR** (neat) ν_{max} 2963, 2850, 1722, 1661 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.43 (d, *J* = 7.0 Hz, 1H), 8.07 – 8.02 (m, 4H), 7.89 (d, *J* = 6.4 Hz, 2H), 7.65 – 7.42 (m, 10H), 6.32 (appd, *J* = 32.1 Hz, 1H), 5.14 (dd, *J* = 46.7, 0.8 Hz, 1H), 4.73 (d, *J* = 10.6 Hz, 1H), 4.68 (dd, *J* = 12.1, 2.1 Hz, 1H), 4.51 (d, *J* = 10.6 Hz, 1H), 4.43 (dd, *J* = 6.3, 2.4 Hz, 1H), 4.29 (ddd, *J* = 12.0, 6.4, 2.7 Hz, 1H), 1.44 (d, *J* = 1.0 Hz, 3H), 1.33 (s, 9H), 0.87 (s, 9H), 0.08 (s, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.7, 166.31, 166.26, 162.3, 155.0, 148.0, 133.4, 133.3, 133.2, 130.2, 130.0, 129.76, 129.74, 129.3, 128.651, 128.649, 128.57, 127.6, 96.5, 96.2 (d, *J* = 185.1 Hz), 73.8, 67.9 (d, *J* = 7.6 Hz), 65.0 (d, *J* = 7.8 Hz), 60.5 (d, *J* = 19.8 Hz), 46.5 (d, *J* = 18.6 Hz), 45.8, 31.2, 26.0, 18.4, 16.7 (d, *J* = 7.6 Hz), -3.8, -4.8 ppm ; **HRMS** calcd for : $C_{42}H_{52}FN_3O_7SSiNa$ [M+Na^+] : 812.3171, found: 812.3189 (2.21 ppm).

(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-39)



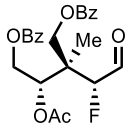
To a solution of **5-37** (0.41 g, 0.52 mmol, 1.0 eq.) in anhydrous THF (5.0 ml, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (2.0 ml, 4ml/mmol, ~70% HF). The reaction was stirred for 79 hours at 25 °C. A saturated solution (3.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 3 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-39** (0.26 g, 74%): $\mathbf{R_f}$ = 0.34 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –44 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{36}H_{38}FN_3O_7S$; **MW** : 675.7662 g/mol ; **IR** (neat) ν_{max} 3306, 3066, 2963, 1712, 1648 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.51 (d, *J* = 6.2 Hz, 1H), 8.09 – 8.00 (m, 4H), 7.89 (s, 2H), 7.72 – 7.39 (m, 10H), 6.58 (appd, *J* = 31.8 Hz, 1H), 4.96 (appd, *J* = 46.1 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.74 (d, *J* = 11.3 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.53 – 4.46 (m, 1H), 4.32 (apps, 1H), 3.92 (s, 1H), 1.37 (s, 3H), 1.31 (s, 9H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.9, 166.7, 166.2, 162.5, 155.8, 147.7, 133.5, 133.4, 133.3, 130.0, 129.96, 129.89, 129.86, 129.3, 128.7, 128.520, 128.518, 127.7, 99.3 (d, *J* = 185.4 Hz), 97.3, 72.9 (d, *J* = 3.3 Hz), 66.3 (d, *J* = 3.7 Hz), 65.7 (d, *J* = 3.5 Hz), 60.9 (d, *J* = 19.9 Hz), 45.8 (d, *J* = 17.4 Hz), 45.77, 31.1, 16.0 (d, *J* = 6.2 Hz) ppm; **HRMS** calcd for $C_{36}H_{38}FN_3O_7SNa$ $[M+Na^+]$: 698.2307, found: 698.2324 (2.43 ppm).

(+)-((2*S*,3*R*,4*R*,5*R*)-5-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-41)



To a solution of **5-38** (49 mg, 0.08 mmol, 1.0 eq.) in anhydrous DCM (0.80 ml, 0.10 M) at 0 ^{o}C was added NIS (54 mg, 0.24 mmol, 3.0 eq.). The reaction was stirred for 4 hours at 25 ^{o}C. A saturated solution (1.0 ml) of $Na_2S_2O_3$•$5H_2O$ was added and the aqueous layer was extracted with ethyl acetate (3 × 3 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-41** (18 mg, 42%): $\mathbf{R_f}$ = 0.37 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ +115 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{27}H_{26}FN_3O_7$; **MW** : 523.5096 g/mol ; **IR** (neat) ν_{max} 3303, 3073, 2979, 1723, 1664 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.08 – 7.99 (m, 4H), 7.63 – 7.51 (m, 3H), 7.50 – 7.42 (m, 4H), 5.93 (appd, *J* = 19.8 Hz, 1H), 5.14 (appd, *J* = 49.6 Hz, 1H), 4.79 (dd, *J* = 11.8, 7.3 Hz, 1H), 4.71 (dd, *J* = 7.3, 3.4 Hz, 1H), 4.62 (dd, *J* = 11.8, 3.4 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.50 (dd, *J* = 11.3, 2.6 Hz, 1H), 2.28 (s, 3H), 1.09 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.7, 166.3, 166.1, 163.2, 155.1, 143.6, 133.7, 133.6, 129.9, 129.8, 129.5, 129.4, 128.76, 128.74, 100.5 (d, *J* = 191.4 Hz), 97.1, 92.0 (d, *J* = 39.3 Hz), 83.2, 65.4 (d, *J* = 11.6 Hz), 63.1, 47.1 (d, *J* = 16.7 Hz), 25.2, 15.4 (d, *J* = 5.3 Hz) ppm ; **HRMS** calcd for $C_{27}H_{27}FN_3O_7$ [M+H^+] : 524.1828, found: 524.1826 (-0.30 ppm).

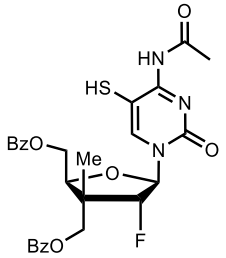
(2*R*,3*S*)-3-acetoxy-2-((*R*)-1-fluoro-2-oxoethyl)-2-methylbutane-1,4-diyl dibenzoate (5-42)



5-42

To a solution of **5-38** (26 mg, 0.04 mmol, 1.0 eq.) in anhydrous DCM (0.50 ml, 0.10 M) at 0 °C was added $Hg(OAc)_2$ (42 mg, 0.13 mmol, 3.0 eq.). The reaction was stirred for 16 hours at 25 °C. The reaction mixture was filtered on a pad of Celite® and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-42**: **Formula** : $C_{23}H_{23}FO_7$; **MW** : 430.4229 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.80 (dd, *J* = 7.6, 1.1 Hz, 1H), 8.03 – 7.93 (m, 4H), 7.63 – 7.52 (m, 2H), 7.44 (dt, *J* = 26.7, 7.8 Hz, 4H), 5.63 (dd, *J* = 7.0, 3.7 Hz, 1H), 4.92 (dd, *J* = 47.5, 1.1 Hz, 1H), 4.72 (dd, *J* = 12.2, 3.7 Hz, 1H), 4.51 – 4.41 (m, 3H), 2.08 (s, 3H), 1.37 (d, *J* = 1.6 Hz, 3H) ppm; **HRMS** calcd for : $C_{23}H_{27}FO_7N$ $[M+NH_4^+]$: 448.1766, found: 448.1756 (-2.2 ppm).

((2*S*,3*R*,4*R*,5*R*)-5-(4-acetamido-6-mercapto-2-oxopyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-43)

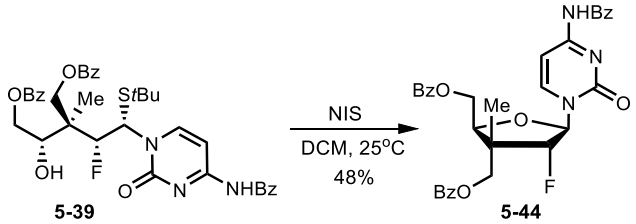


5-43

To a solution of **5-38** (55 mg, 0.09 mmol, 1.0 eq.) in anhydrous DCM (1.0 ml, 0.10 M) at -40 °C was added NIS (62 mg, 0.27 mmol, 3.0 eq.) and TMSOTf (85 µl, 0.10 eq., 0.11 M in DCM). The reaction was stirred for 1 hour at -40 °C. A saturated solution (0.5 ml) of $Na_2S_2O_3 \cdot 5H_2O$ was added and the aqueous layer was extracted with ethyl acetate (3 × 1 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.*

Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-43**: **Formula** : $C_{27}H_{26}FN_3O_7S$; **MW** : 555.5774 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.10 – 7.97 (m, 4H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.59 (dt, *J* = 7.3, 5.8 Hz, 2H), 7.46 (dd, *J* = 15.2, 7.4 Hz, 4H), 7.39 (d, *J* = 7.5 Hz, 1H), 6.88 (dd, *J* = 28.2, 1.6 Hz, 1H), 5.03 (dd, *J* = 49.9, 1.7 Hz, 1H), 4.60 (dd, *J* = 11.1, 1.4 Hz, 1H), 4.51 – 4.39 (m, 4H), 2.24 (s, 3H), 1.40 (s, 3H) ppm; **HRMS** calcd for : $C_{27}H_{27}FN_3O_7S$ [M+H$^+$] : 556.1548, found: 556.1545 (-0.59 ppm).

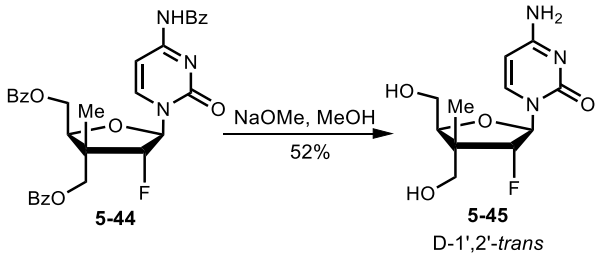
(+)-((2*S*,3*R*,4*R*,5*R*)-5-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-44)



To a solution of **5-39** (0.104 g, 0.15 mmol, 1.0 eq.) in anhydrous DCM (1.6 ml, 0.10 M) at 0 °C was added NIS (0.104 g, 0.46 mmol, 3.0 eq.). The reaction was stirred for 16 hours at 25 °C. A saturated solution (1.0 ml) of $Na_2S_2O_3$•$5H_2O$ was added and the aqueous layer was extracted with DCM (3 × 3 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-44** (43 mg, 48%): $\mathbf{R_f}$ = 0.20 (Hexanes/EtOAc, 50:50); **[α]$^{25}_D$** +90 (*c* 1.0, $CDCl_3$) ; **Formula** : $C_{32}H_{28}FN_3O_7$; **MW** : 585.5790 g/mol ; **IR** (neat) ν_{max} 3301, 1723, 1675 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.24 (d, *J* = 7.3 Hz, 1H), 8.10 – 8.01 (m, 4H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.71 – 7.42 (m, 10H), 5.97 (appd, *J* = 19.8 Hz, 1H), 5.20 (appd, *J* = 49.6 Hz, 1H), 4.80 (dd, *J* = 11.8, 7.4 Hz, 1H), 4.74 (dd, *J* = 7.4, 3.3 Hz, 1H), 4.63 (dd, *J* = 11.8, 3.3 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.52 (dd, *J* = 11.2, 2.7 Hz, 1H), 1.11 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.4, 166.2, 166.1, 162.9, 155.1, 143.7, 133.7, 133.6, 133.5, 132.9,

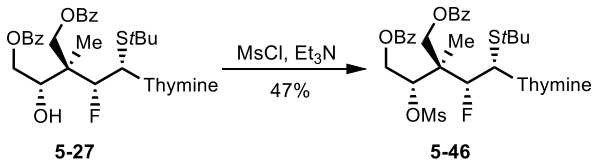
129.9, 129.8, 129.5, 129.4, 129.3, 128.78, 128.75, 127.66, 100.4 (d, *J* = 191.8 Hz), 96.9, 92.1 (d, *J* = 39.3 Hz), 83.2, 65.4 (d, *J* = 11.8 Hz), 63.2, 47.1 (d, *J* = 16.7 Hz), 15.4 (d, *J* = 5.5 Hz) ppm ; **HRMS** calcd for $C_{32}H_{28}FN_3O_7Na$ [M+Na^+] : 608.1803, found: 608.1814 (1.66 ppm).

(+)-4-amino-1-((2*R*,3*R*,4*R*,5*S*)-3-fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrofuran-2-yl)pyrimidin-2(1H)-one (5-45)



To a solution of **5-44** (83 mg, 0.14 mmol, 1.0 eq.) in MeOH (1.3 ml, 0.13 M) at 0 ^oC was added NaOMe (0.14 ml, 0.57 mmol, 4.0 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 ^oC. Formic acid (~ 2 drops) was added to neutralize the reaction mixture before concentration. Purification by reverse phase C18 (H_2O/MeOH, 90:10), provided **5-45** (20 mg, 52%): $[\alpha]^{25}_D$ +58 (*c* 1.2, CD_3OD) ; **Formula** : $C_{11}H_{16}FN_3O_4$; **MW** : 273.2608 g/mol ; **IR** (neat) ν_{max} 3445, 2528,1651 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.98 (d, *J* = 7.5 Hz, 1H), 5.94 (d, *J* = 7.5 Hz, 1H), 5.90 (dd, *J* = 18.9, 2.3 Hz, 1H), 4.90 (dd, *J* = 51.7, 2.3 Hz, 1H), 4.19 (appt, *J* = 5.0 Hz, 1H), 3.83 – 3.75 (m, 2H), 3.70 (d, *J* = 10.9 Hz, 1H), 3.64 (dd, *J* = 11.1, 2.3 Hz, 1H), 1.01 (s, 3H) ppm *OH and NH_2 signals missing possibly due to exchange in* CD_3OD; **^{13}C NMR** (125 MHz, CD_3OD) δ 167.8, 158.3, 142.0, 102.6 (d, *J* = 188.4 Hz), 96.1, 91.5 (d, *J* = 37.5 Hz), 86.5, 64.6 (d, *J* = 12.2 Hz), 62.2, 49.9, 15.2 (d, *J* = 4.5 Hz) ppm; **HRMS** calcd for $C_{11}H_{16}FN_3O_4Na$ [M+Na^+] : 296.1017, found: 296.1006 (-3.69 ppm).

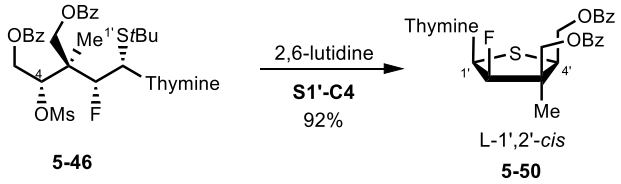
(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl dibenzoate (5-46)



5-27 **5-46**

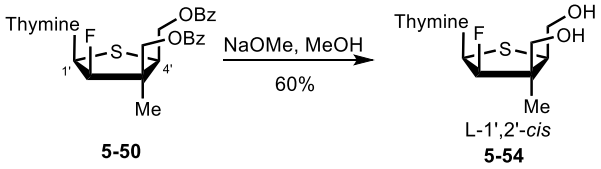
To a solution of **5-27** (0.10 g, 0.17 mmol, 1.0 eq.) in anhydrous DCM (1.8 ml, 0.10 M) at 0 ^{o}C was added triethylamine (40 µl, 0.26 mmol, 1.5 eq.) and methanesulfonyl chloride (35 µl, 0.43 mmol, 2.5 eq). The reaction was stirred for 16 hours at 25 ^{o}C. A 1.0 N solution (0.50 ml) of HCl was added and the aqueous layer was extracted with dichloromethane (3 × 2 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (DCM/Acetone, 90:10), provided **5-46** (54 mg, 47%): $\mathbf{R_f}$ = 0.41 (DCM/Acetone, 90:10); $\mathbf{[\alpha]^{25}_D}$ –31 (*c* 1.6, $CDCl_3$) ; **Formula** : $C_{31}H_{37}FN_2O_9S_2$; **MW** : 664.7619 g/mol ; **IR** (neat) ν_{max} 3186, 3066, 2965, 1712, 1685 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.11 – 8.03 (m, 4H), 7.67 (s, 1H), 7.61 – 7.56 (m, 2H), 7.50 – 7.42 (m, 4H), 6.28 (appd, *J* = 31.7 Hz, 1H), 5.69 (appd, *J* = 8.2 Hz, 1H), 4.95 (d, *J* = 46.6 Hz, 1H), 4.90 (dd, *J* = 12.5, 1.3 Hz, 1H), 4.69 (d, *J* = 11.3 Hz, 1H), 4.57 (dd, *J* = 12.6, 8.7 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 3.09 (s, 3H), 1.92 (s, 3H), 1.49 (s, 3H), 1.35 (s, 9H) ppm contains ~ 5% of cyclized product ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.166, 166.157, 163.4, 150.4, 137.6 (d, *J* = 2.7 Hz), 133.7, 133.6, 129.91, 129.89, 129.52, 129.45, 128.8, 128.7, 111.7, 98.8 (d, *J* = 187.6 Hz), 82.2, 64.5 (d, *J* = 7.5 Hz), 64.3 (d, *J* = 4.9 Hz), 58.2 (d, *J* = 19.9 Hz), 45.9, 45.5 (d, *J* = 18.1 Hz), 39.5, 31.1, 18.1 (d, *J* = 6.3 Hz), 12.8 ppm; **HRMS** calcd for $C_{31}H_{37}FN_2O_9S_2Na$ [M+Na^{+}] : 687.1817, found: 687.1828 (1.6 ppm).

(–)-((2*R*,3*S*,4*R*,5*S*)-4-fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrothiophene-2,3-diyl)bis(methylene) dibenzoate (5-50)



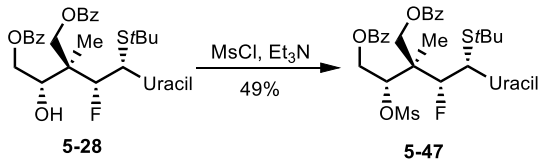
A solution of **5-46** (0.20 g, 0.30 mmol, 1.0 eq.) in 2,6-lutidine (30 ml, 0.01 M) was refluxed for 3 hours at 160 ^{o}C. A 1.0 N solution (5.0 ml) of HCl was added and the aqueous layer was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 30:70), provided **5-50** (0.14 g, 92%): $\mathbf{R_f}$ = 0.51 (Hexanes/EtOAc, 30:70); $\mathbf{[\alpha]^{25}_D}$ –74 (*c* 2.0, $CDCl_3$) ; **Formula** : $C_{26}H_{25}FN_2O_6S$; **MW** : 512.5499 g/mol ; **IR** (neat) ν_{max} 3188, 3070, 2979, 1723, 1686 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.08 – 7.99 (m, 4H), 7.79 (s, 1H), 7.62 – 7.55 (m, 2H), 7.48 – 7.42 (m, 4H), 6.61 (dd, *J* = 25.5, 3.8 Hz, 1H), 5.03 (dd, *J* = 52.6, 3.8 Hz, 1H), 4.93 – 4.86 (m, 1H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.65 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 3.73 (dd, *J* = 8.5, 6.7 Hz, 1H), 1.96 (s, 3H), 1.47 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 166.1, 163.3, 151.1, 138.7 (d, *J* = 4.8 Hz), 133.63, 133.58, 129.9, 129.8, 129.6, 129.4, 128.73, 128.69, 110.8, 98.7 (d, *J* = 191.8 Hz), 65.4 (d, *J* = 6.0 Hz), 64.7 (d, *J* = 7.5 Hz), 62.3 (d, *J* = 16.7 Hz), 55.4, 51.7 (d, *J* = 15.6 Hz), 21.4 (d, *J* = 7.7 Hz), 12.7 ppm ; **HRMS** calcd for : $C_{26}H_{25}FN_2O_6SNa$ [M+Na^+] : 535.1310, found: 535.1309 (-0.11 ppm).

(–)-1-((2*S*,3*R*,4*S*,5*R*)-3-fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (5-54)



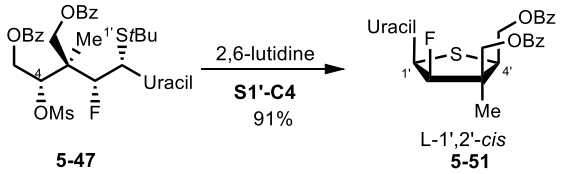
To a solution of **5-50** (0.14 g, 0.27 mmol, 1.0 eq.) in MeOH (4.0 ml, 0.07 M) at 0 ^{o}C was added NaOMe (30 µl, 0.14 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 ^{o}C. Amberlite R (120, H^{+}) (0.7g) was added to neutralize the reaction mixture before filtration and concentration. Purification by flash chromatography (Isopropanol/DCM, 20:80), provided **5-54** (50 mg, 60%): $\mathbf{R_f}$ = 0.54 (Isopropanol/DCM, 20:80); $\mathbf{[\alpha]^{25}_D}$ –186 (*c* 1.0, CD_3OD) ; **Formula** : $C_{12}H_{17}FN_2O_4S$; **MW** : 304.3378 g/mol ; **IR** (neat) ν_{max} 3427, 2530, 1655 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.90 (s, 1H), 6.44 (dd, *J* = 25.6, 3.8 Hz, 1H), 4.82 (dd, *J* = 53.0, 3.8 Hz, 1H), 3.97 (dd, *J* = 11.0, 5.6 Hz, 1H), 3.73 (d, *J* = 11.1 Hz, 1H), 3.71 – 3.62 (m, 2H), 3.30 – 3.26 (m, 1H), 1.87 (s, 3H), 1.28 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in* CD_3OD ; **^{13}C NMR** (125 MHz, CD_3OD) δ 166.1, 152.8, 140.8 (d, *J* = 4.6 Hz), 110.5, 100.3 (d, *J* = 188.9 Hz), 64.4 (d, *J* = 5.3 Hz), 63.5 (d, *J* = 16.8 Hz), 62.9 (d, *J* = 7.7 Hz), 60.9 (d, *J* = 1.4 Hz), 54.4 (d, *J* = 15.8 Hz), 21.2 (d, *J* = 8.6 Hz), 12.4 ppm ; **HRMS** calcd for $C_{12}H_{17}FN_2O_4SNa$ $[M+Na^{+}]$: 327.0785, found: 327.0798 (3.82 ppm).

(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(tert-butylthio)-2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-1-fluoroethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl dibenzoate (5-47)



To a solution of **5-28** (0.18 g, 0.31 mmol, 1.0 eq.) in anhydrous DCM (1.0 ml, 0.30 M) at 0 °C was added triethylamine (20 µl, 1.24 mmol, 4.0 eq.) and methanesulfonyl chloride (80 µl, 0.96 mmol, 3.1 eq). The reaction was stirred for 16 hours at 25 °C. A 1.0 N solution (0.50 ml) of HCl was added and the aqueous layer was extracted with dichloromethane (3 × 2 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (DCM/Acetone, 90:10), provided **5-47** (100 mg, 49%): $\mathbf{R_f}$ = 0.53 (DCM/Acetone, 90:10); $\mathbf{[\alpha]^{25}_D}$ –27 (*c* 1.3, $CDCl_3$) ; **Formula** : $C_{30}H_{35}FN_2O_9S_2$; **MW** : 650.7353 g/mol ; **IR** (neat) ν_{max} 3221, 2966, 1690 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.13 – 8.02 (m, 4H), 7.90 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.49 – 7.45 (m, 4H), 6.24 (appd, *J* = 31.9 Hz, 1H), 5.80 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.69 (appd, *J* = 7.7 Hz, 1H), 5.01 – 4.86 (m, 2H), 4.68 (d, *J* = 11.3 Hz, 1H), 4.55 (dd, *J* = 12.3, 9.1 Hz, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 3.08 (s, 3H), 1.49 (d, *J* = 1.4 Hz, 3H), 1.36 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.17, 166.15, 162.6, 150.3, 142.0 (d, *J* = 2.7 Hz), 133.7, 133.6, 129.91, 129.89, 129.5, 129.4, 128.8, 128.7, 103.0, 98.4 (d, *J* = 187.5 Hz), 82.2, 64.4 (d, *J* = 8.0 Hz), 64.3 (d, *J* = 5.3 Hz), 58.6 (d, *J* = 19.8 Hz), 46.0, 45.5 (d, *J* = 18.0 Hz), 39.5, 31.1, 17.9 (d, *J* = 6.5 Hz) ppm; **HRMS** calcd for $C_{30}H_{35}FN_2O_9S_2Na$ [M+Na^+] : 673.1660, found: 673.1674 (2.0 ppm).

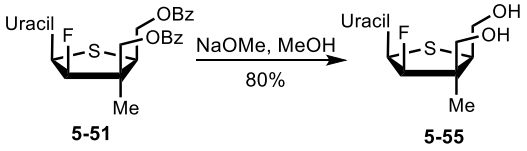
(–)-((2*R*,3*S*,4*R*,5*S*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrothiophene-2,3-diyl)bis(methylene) dibenzoate (5-51)



A solution of **5-47** (89 mg, 0.14 mmol, 1.0 eq.) in 2,6-lutidine (3.0 ml, 0.05 M) was refluxed for 5 hours at 160 °C. A 1.0 N solution (2.0 ml) of HCl was added and the aqueous layer was

extracted with ethyl acetate (3 × 3 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Hexanes/EtOAc, 30:70), provided **5-51** (62 mg, 91%): $\mathbf{R_f}$ = 0.50 (Hexanes/EtOAc, 30:70); $\mathbf{[\alpha]^{25}_D}$ –94 (*c* 0.8, $CDCl_3$) ; **Formula** : $C_{25}H_{23}FN_2O_6S$; **MW** : 498.5233 g/mol ; **IR** (neat) ν_{max} 3199, 3065, 1691 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.06 – 7.98 (m, 5H), 7.62 – 7.53 (m, 2H), 7.48 – 7.42 (m, 4H), 6.60 (dd, *J* = 25.2, 3.8 Hz, 1H), 5.80 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.04 (dd, *J* = 52.5, 3.8 Hz, 1H), 4.82 – 4.76 (m, 1H), 4.73 – 4.66 (m, 2H), 4.53 (dd, *J* = 11.2, 2.0 Hz, 1H), 3.78 – 3.71 (m, 1H), 1.48 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 166.0, 162.4, 150.9, 143.0 (d, *J* = 4.8 Hz), 133.7, 133.6, 129.9, 129.8, 129.5, 129.4, 128.74, 128.69, 102.4, 98.6 (d, *J* = 191.6 Hz), 65.6 (d, *J* = 6.1 Hz), 64.6 (d, *J* = 7.4 Hz), 62.6 (d, *J* = 16.7 Hz), 55.4, 51.8 (d, *J* = 15.6 Hz), 21.3 (d, *J* = 7.8 Hz) ppm ; **HRMS** calcd for : $C_{25}H_{23}FN_2O_6SNa$ $[M+Na^+]$: 521.1153, found: 521.1157 (0.79 ppm).

(–)-1-((2*S*,3*R*,4*S*,5*R*)-3-fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrothiophen-2-yl)pyrimidine-2,4(1H,3H)-dione (5-55)

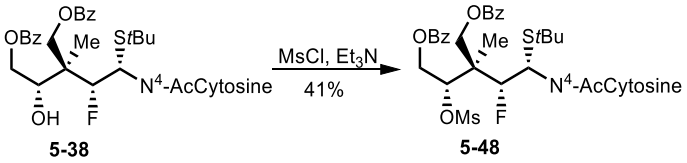


5-51 **5-55**

To a solution of **5-51** (54 mg, 0.11 mmol, 1.0 eq.) in MeOH (0.9 ml, 0.13 M) at 0 °C was added NaOMe (20 µl, 0.054 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 °C. A 1N HCl solution (~ 10 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (DCM/MeOH, 95:5), provided **5-55** (25 mg, 80%): $\mathbf{R_f}$ = 0.31 (DCM/MeOH, 95:5); $\mathbf{[\alpha]^{25}_D}$ –63 (*c* 0.7, CD_3OD) ; **Formula** : $C_{11}H_{15}FN_2O_4S$; **MW** : 290.3112 g/mol ; **IR** (neat) ν_{max} 3333, 2883, 1701 cm^{-1} ; **^{1}H NMR** (500

MHz, $(CD_3)_2CO$) δ 8.03 (d, *J* = 6.9 Hz, 1H), 6.47 (appd, *J* = 25.4 Hz, 1H), 5.64 (d, *J* = 7.9 Hz, 1H), 4.91 (appd, *J* = 53.3 Hz, 1H), 4.11 – 4.01 (m, 1H), 3.87 – 3.69 (m, 3H), 3.36 (appt, *J* = 7.1 Hz, 1H), 1.34 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in* $(CD_3)_2CO$; **^{13}C NMR** (125 MHz, CD_3OD) δ 165.9, 152.7, 145.3 (d, *J* = 4.7 Hz), 101.8, 100.2 (d, *J* = 188.9 Hz), 64.5 (d, *J* = 5.3 Hz), 63.8 (d, *J* = 16.8 Hz), 62.9 (d, *J* = 7.6 Hz), 60.9 (d, *J* = 1.5 Hz), 54.5 (d, *J* = 15.8 Hz), 21.2 (d, *J* = 8.7 Hz) ppm ; **HRMS** calcd for $C_{11}H_{15}FN_2O_4SNa$ $[M+Na^+]$: 313.0629, found: 313.0635 (1.94 ppm).

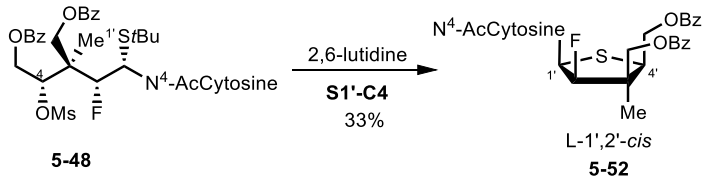
(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl dibenzoate (5-48)



To a solution of **5-38** (0.099 g, 0.16 mmol, 1.0 eq.) in anhydrous DCM (0.60 ml, 0.30 M) at 0 °C was added triethylamine (0.10 ml, 0.65 mmol, 4.0 eq.) and methanesulfonyl chloride (0.04 ml, 0.50 mmol, 3.1 eq). The reaction was stirred for 16 hours at 25 °C. A 1.0 N solution (0.20 ml) of HCl was added and the aqueous layer was extracted with dichloromethane (3 × 2 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (DCM/Acetone, 80:20), provided **5-48** (46 mg, 41%): $\mathbf{R_f}$ = 0.33 (DCM/Acetone, 80:20); $\mathbf{[\alpha]^{25}_D}$ –38 (*c* 0.8, $CDCl_3$) ; **Formula** : $C_{32}H_{38}FN_3O_9S_2$; **MW** : 691.7872 g/mol ; **IR** (neat) ν_{max} 3427, 2965, 1718, 1658 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.37 (dd, *J* = 7.5, 1.6 Hz, 1H), 8.12 – 8.03 (m, 4H), 7.60 – 7.55 (m, 2H), 7.50 – 7.42 (m, 5H), 6.42 (appd, *J* = 32.6 Hz, 1H), 5.76 (d, *J* = 8.5 Hz, 1H), 4.92 (appd, *J* = 46.7 Hz, 1H), 4.90 (dd, *J* = 12.7, 1.5 Hz, 1H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.58 – 4.54 (m, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 3.07 (s, 3H), 2.24 (s, 3H),

1.54 (s, 3H), 1.32 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.2, 166.23, 166.18, 162.6, 155.3, 147.4, 133.55, 133.51, 130.0, 129.9, 129.6, 129.5, 128.8, 128.7, 97.7 (d, *J* = 187.7 Hz), 97.1, 82.3, 64.5 (d, *J* = 8.4 Hz), 64.3 (d, *J* = 5.3 Hz), 60.0 (d, *J* = 19.5 Hz), 46.2, 45.5 (d, *J* = 17.8 Hz), 39.5, 31.1, 25.1, 18.0 (d, *J* = 6.8 Hz) ppm; **HRMS** calcd for $C_{32}H_{38}FN_3O_9S_2Na$ [M+Na^+] : 714.1926, found: 714.1927 (0.12 ppm).

(–)-((2*R*,3*S*,4*R*,5*S*)-5-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrothiophene-2,3-diyl)bis(methylene) dibenzoate (5-52)

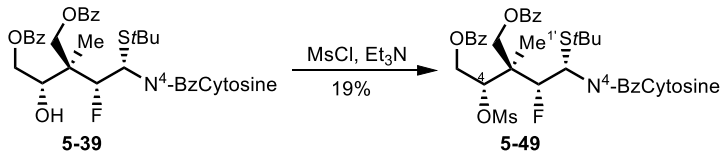


5-48 **5-52**

A solution of **5-48** (45 mg, 0.07 mmol, 1.0 eq.) in 2,6-lutidine (2.5 ml, 0.025 M) was refluxed for 5 hours at 160 ^oC. A 1.0 N solution (1.0 ml) of HCl was added and the aqueous layer was extracted with ethyl acetate (3 × 2 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-52** (12 mg, 33%): $\mathbf{R_f}$ = 0.30 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ –105 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{27}H_{26}FN_3O_6S$; **MW** : 539.5752 g/mol ; **IR** (neat) ν_{max} 3237, 2973, 1722, 1666 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.43 (dd, *J* = 7.6, 2.5 Hz, 1H), 8.07 – 7.96 (m, 4H), 7.60 – 7.54 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.42 (m, 4H), 6.76 (dd, *J* = 24.4, 3.7 Hz, 1H), 5.16 (dd, *J* = 52.3, 3.7 Hz, 1H), 4.81 (appt, *J* = 10.0 Hz, 1H), 4.68 (dd, *J* = 11.0, 8.4 Hz, 2H), 4.53 (d, *J* = 11.1 Hz, 1H), 3.79 – 3.73 (m, 1H), 2.26 (s, 3H), 1.49 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.2, 166.2, 166.1, 162.5, 155.9, 148.4, 133.60, 133.57, 129.9, 129.8, 129.5, 129.4, 128.71, 128.67, 97.8 (d, *J* = 191.5 Hz), 96.7, 65.7 (d, *J* = 6.3

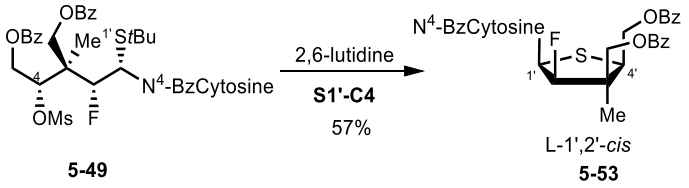
Hz), 64.8 (d, *J* = 7.0 Hz), 64.5 (d, *J* = 17.0 Hz), 55.5, 52.1 (d, *J* = 15.7 Hz), 25.2, 21.3 (d, *J* = 7.8 Hz) ppm ; **HRMS** calcd for : $C_{27}H_{27}FN_3O_6S$ [M+H$^+$] : 540.1599, found: 540.1595 (-0.83 ppm).

(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl dibenzoate (5-49)



To a solution of **5-39** (0.13 g, 0.20 mmol, 1.0 eq.) in anhydrous DCM (1.0 ml, 0.30 M) at 0 ^oC was added triethylamine (0.10 ml, 0.78 mmol, 4.0 eq.) and methanesulfonyl chloride (0.05 ml, 0.61 mmol, 3.1 eq). The reaction was stirred for 16 hours at 25 ^oC. A 1.0 N solution (0.20 ml) of HCl was added and the aqueous layer was extracted with dichloromethane (3 × 2 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-49** (28 mg, 19%): $\mathbf{R_f}$ = 0.11 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –50 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{37}H_{40}FN_3O_9S_2$; **MW** : 753.8566 g/mol ; **IR** (neat) ν_{max} 2973, 1723, 1658 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.44 (d, *J* = 7.7 Hz, 1H), 8.13 – 8.04 (m, 4H), 7.89 (d, *J* = 7.0 Hz, 2H), 7.69 – 7.42 (m, 10H), 6.45 (appd, *J* = 32.6 Hz, 1H), 5.78 (appd, *J* = 8.5 Hz, 1H), 4.97 (appd, *J* = 54.3 Hz, 1H), 4.93 (d, *J* = 4.3 Hz, 1H), 4.72 (d, *J* = 11.2 Hz, 1H), 4.59 – 4.51 (m, 2H), 3.09 (s, 3H), 1.56 (s, 3H), 1.35 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.24, 166.18, 166.1, 162.5, 155.2, 147.5, 133.54, 133.50, 133.49, 130.0, 129.93, 129.6, 129.5, 129.3, 128.76, 128.74, 128.69, 127.65, 97.6 (d, *J* = 188.1 Hz), 97.0, 82.3, 64.5 (d, *J* = 7.9 Hz), 64.3 (d, *J* = 5.3 Hz), 60.1 (d, *J* = 18.8 Hz), 46.3, 45.6 (d, *J* = 17.7 Hz), 39.5, 31.1, 18.0 (d, *J* = 6.8 Hz) ppm; **HRMS** calcd for $C_{37}H_{40}FN_3O_9S_2Na$ [M+Na$^+$] : 776.2082, found: 776.2074 (-1.07 ppm).

(–)-((2*R*,3*S*,4*R*,5*S*)-5-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrothiophene-2,3-diyl)bis(methylene) dibenzoate (5-53)

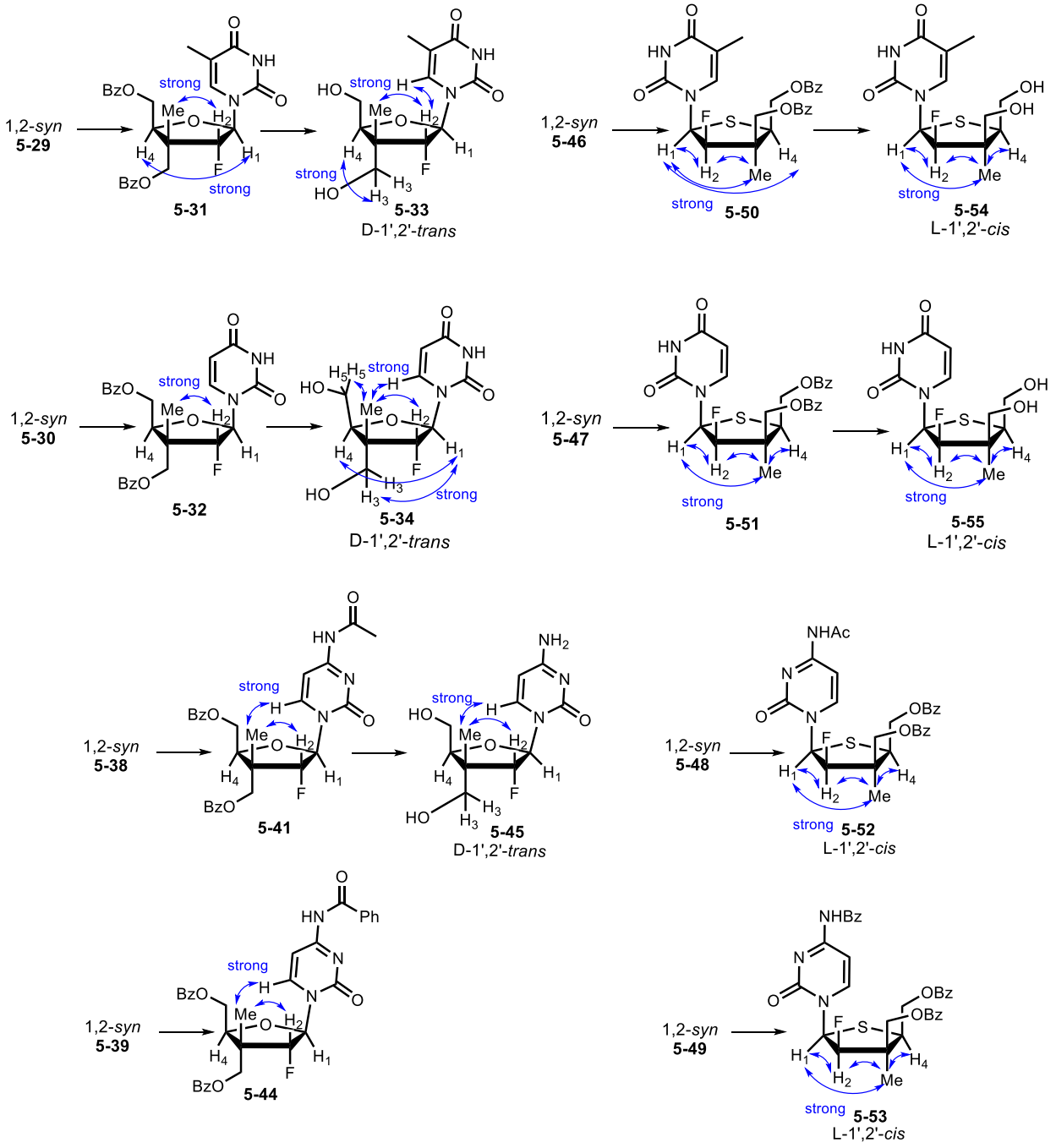


A solution of **5-49** (24 mg, 0.03 mmol, 1.0 eq.) in 2,6-lutidine (1.0 ml, 0.03 M) was refluxed for 4 hours at 160 ^{o}C. Upon cooling to 25 ^{o}C, the reaction was concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 30:70), provided **5-53** (11.1 mg, 57%): $\mathbf{R_f}$ = 0.16 (Hexanes/EtOAc, 30:70); $\mathbf{[\alpha]^{25}_D}$ –87 (*c* 0.7, $CDCl_3$) ; **Formula** : $C_{32}H_{28}FN_3O_6S$; **MW** : 601.6446 g/mol ; **IR** (neat) ν_{max} 3247, 3076, 2968, 1723, 1664 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.50 (d, *J* = 7.2 Hz, 1H), 8.08 – 7.98 (m, 4H), 7.92 – 7.40 (m, 12H), 6.81 (dd, *J* = 24.5, 3.6 Hz, 1H), 5.20 (dd, *J* = 52.4, 3.7 Hz, 1H), 4.87 – 4.81 (m, 1H), 4.73 – 4.67 (m, 2H), 4.59 – 4.53 (m, 1H), 3.80 – 3.75 (m, 1H), 1.51 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 166.1, 166.0 162.6, 148.4, 133.57, 133.54, 133.4, 132.1, 130.0, 129.83, 129.75, 129.6, 129.3, 128.8, 128.74 128.70, 127.7, 127.5, 98.0 (d, *J* = 190.8 Hz), 65.8, 64.8 (d, *J* = 7.1 Hz), 64.5 (d, *J* = 16.6 Hz), 55.8, 52.3 (d, *J* = 15.6 Hz), 21.4 (d, *J* = 8.0 Hz) ppm ; **HRMS** calcd for : $C_{32}H_{28}FN_3O_6SNa$ [M+Na^+] : 624.1575, found: 624.1584 (1.46 ppm).

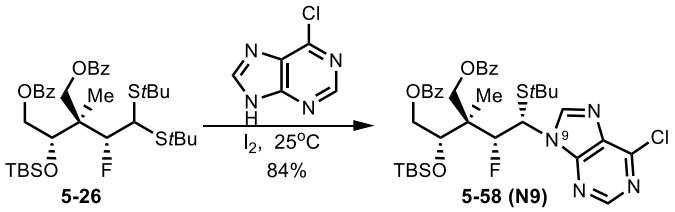
Stereochemical Proofs

The peaks in the ^{1}H NMR spectra were assigned using ^{1}H/^{1}H COSY experiments, chemical shifts, and coupling constants. Proof of structure for the C1'-C2' relative stereochemistry were provided by NOESY experiments. For the thioanalogues, weak interactions between the proton

of the nucleobase and the H3 or H5 hydrogens suggests that the nucleobase is oriented anti to the sugar ring.

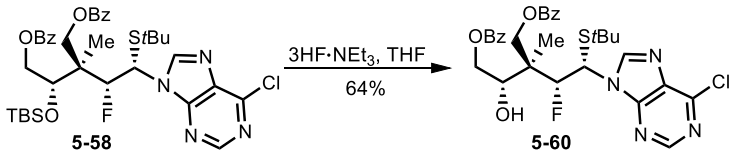


(–)-(2*R*,3*S*)-3-((tert-butyldimethylsilyl)oxy)-2-((1R,2S)-2-(tert-butylthio)-2-(6-chloro-9H-purin-9-yl)-1-fluoroethyl)-2-methylbutane-1,4-diyl dibenzoate (5-58)



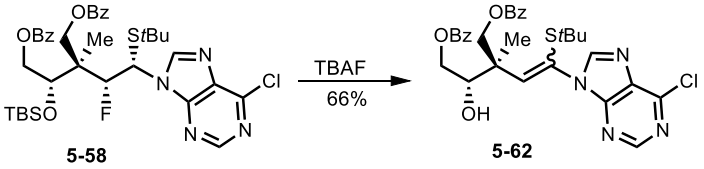
Following general procedure 5-A, 6-Cl-purine (0.37 g, 2.37 mmol, 3.5 eq.), and I_2 (0.34 g, 1.4 mmol, 2.0 eq.) were added to a solution of **5-26** (0.45 g, 0.68 mmol, 1.0 eq.) in anhydrous THF (7.0 ml, 0.10 M) and stirred at 25 ^{o}C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **5-58** (0.42 g, 84%) as a white foam: $\mathbf{R_f}$ = 0.49 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –71 (*c* 1.4, $CDCl_3$) ; **Formula** : $C_{36}H_{46}ClFN_4O_5SSi$; **MW** : 729.3761 g/mol ; **IR** (neat) ν_{max} 2958, 2930, 2858, 1723 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.9 Hz, 1H), 8.49 (s, 1H), 8.00 – 7.89 (m, 4H), 7.61 – 7.54 (m, 2H), 7.46 – 7.37 (m, 4H), 6.10 (dd, *J* = 30.6, 1.3 Hz, 1H), 5.20 (dd, *J* = 46.3, 1.3 Hz, 1H), 4.70 (d, *J* = 10.7 Hz, 1H), 4.64 (dd, *J* = 12.0, 3.4 Hz, 1H), 4.55 (d, *J* = 10.7 Hz, 1H), 4.32 (dd, *J* = 6.2, 3.5 Hz, 1H), 4.23 (ddd, *J* = 12.0, 6.3, 2.5 Hz, 1H), 1.50 (d, *J* = 1.3 Hz, 3H), 1.21 (s, 9H), 0.81 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.5, 166.3, 152.2, 151.2, 150.4, 145.5 (d, *J* = 1.8 Hz), 133.5, 133.3, 131.7, 129.9, 129.71, 129.65, 129.55, 128.7, 128.6, 95.5 (d, *J* = 186.0 Hz), 73.6, 67.4 (d, *J* = 5.7 Hz), 65.1 (d, *J* = 7.8 Hz), 57.9 (d, *J* = 21.4 Hz), 46.3 (d, *J* = 19.0 Hz), 45.7, 31.0, 25.9, 18.4, 16.2 (d, *J* = 7.2 Hz), -3.9, -5.0 ppm ; **HRMS** calcd for : $C_{36}H_{46}ClFN_4O_5SSiNa$ [M+Na^{+}] : 751.2523, found: 751.2526 (0.47 ppm).

(–)-(2*R*,3*S*)-2-((1*R*,2*S*)-2-(tert-butylthio)-2-(6-chloro-9H-purin-9-yl)-1-fluoroethyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-60)



To a solution of **5-58** (0.11 g, 0.16 mmol, 1.0 eq.) in anhydrous THF (0.6 ml, 0.26 M) in a plastic vial at 0 °C was added 3HF•NEt_3 (0.20 ml, 0.78 mmol, 5.0 eq.). The reaction was stirred for 120 hours at 25 °C. A saturated solution (0.5 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 2 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-60** (61 mg, 64%): $\mathbf{R_f}$ = 0.29 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –47 (*c* 0.7, $CDCl_3$) ; **Formula** : $C_{30}H_{32}ClFN_4O_5S$; **MW** : 615.1153 g/mol ; **IR** (neat) ν_{max} 3317, 2964, 1717 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 1.8 Hz, 1H), 8.61 (s, 1H), 8.08 – 7.97 (m, 4H), 7.63 – 7.55 (m, 2H), 7.49 – 7.40 (m, 4H), 6.58 (dd, *J* = 31.3, 0.7 Hz, 1H), 5.09 (d, *J* = 11.5 Hz, 1H), 5.00 (dd, *J* = 45.7, 0.7 Hz, 1H), 4.65 (dd, *J* = 11.7, 2.3 Hz, 1H), 4.58 – 4.53 (m, 2H), 4.22 – 4.16 (m, 1H), 3.51 (d, *J* = 3.7 Hz, 1H), 1.41 (d, *J* = 1.8 Hz, 3H), 1.21 (s, 9H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 166.9, 152.3, 151.4, 150.5, 145.5 (d, *J* = 2.1 Hz), 133.7, 133.5, 131.8, 129.9, 129.8, 129.7, 129.6, 128.7, 128.6, 98.1 (d, *J* = 186.3 Hz), 73.6 (d, *J* = 2.9 Hz), 66.2 (d, *J* = 3.5 Hz), 66.1 (d, *J* = 4.7 Hz), 58.2 (d, *J* = 21.1 Hz), 45.7, 45.6 (d, *J* = 17.8 Hz), 31.0, 17.2 (d, *J* = 6.0 Hz) ppm; **HRMS** calcd for $C_{30}H_{32}ClFN_4O_5SNa$ [M+Na^+] : 637.1658, found: 637.1672 (2.1 ppm).

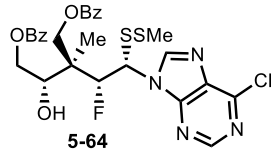
(–)-(2*R*,3*S*)-2-(tert-butylthio)-2-(6-chloro-9H-purin-9-yl)vinyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-62)



5-58 **5-62**

To a solution of **5-58** (36 mg, 0.05 mmol, 1.0 eq.) in anhydrous THF (0.20 ml, 0.24 M) was added TBAF (0.25 ml, 1M THF, 5.0 eq.). The reaction was stirred for 24 hours at 25 ^{o}C. The reaction mixture was quenched with H_2O (0.2 ml) and the aqueous layer was extracted with ethyl acetate (3 × 0.5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-62** (19 mg, 66%). Only one isomer was formed but the E/Z configuration was not confirmed by NOESY experiments. $\mathbf{R_f}$ = 0.19 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –5 (*c* 1.4, $CDCl_3$) ; **Formula** : $C_{30}H_{31}ClN_4O_5S$; **MW** : 595.1089 g/mol ; **IR** (neat) ν_{max} 3398, 2963, 1723 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.48 (s, 1H), 8.09 (dd, *J* = 10.6, 9.3 Hz, 2H), 8.03 – 7.97 (m, 2H), 7.62 – 7.54 (m, 2H), 7.47 (dd, *J* = 13.8, 6.2 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 6.63 (s, 1H), 4.80 – 4.74 (m, 2H), 4.63 – 4.55 (m, 2H), 4.26 (dd, *J* = 8.0, 2.2 Hz, 1H), 3.28 (s, 1H), 1.71 (s, 3H), 1.13 (s, 9H) ppm ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 166.8, 152.9, 151.74, 151.66, 145.3, 140.6, 133.6, 133.5, 132.0, 130.0, 129.78, 129.77, 129.72, 128.69, 128.6, 127.9, 74.0, 67.9, 66.7, 49.8, 44.8, 31.6, 19.9 ppm; **HRMS** calcd for $C_{30}H_{31}ClN_4O_5SNa$ [M+Na$^+$] : 617.1596, found: 617.1618 (3.6 ppm).

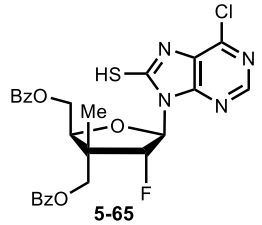
(2*R*,3*S*)-2-((1*R*,2*S*)-2-(6-chloro-9H-purin-9-yl)-1-fluoro-2-((*R*)-methylsulfinothioyl)ethyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-64)



5-64

To a solution of **5-60** (22 mg, 0.04 mmol, 1.0 eq.) in anhydrous THF (0.40 ml, 0.10 M) was added $Me_2S(SMe)BF_4$ (20 mg, 0.07 mmol, 2.0 eq.). The reaction was stirred for 4 hours at 25 ^oC. The reaction mixture still contained starting material so an additional 2.0 eq. of $Me_2S(SMe)BF_4$ was added and stirring at 25 ^oC was continued for 16 hours. The reaction was quenched with a saturated solution of $NaHCO_3$ (0.20 ml) and the aqueous layer was extracted with ethyl acetate (3 × 0.5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-64**: **Formula** : $C_{27}H_{26}ClFN_4O_5S_2$; **MW** : 605.0964 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.53 (s, 1H), 7.99 (dd, *J* = 45.0, 7.2 Hz, 4H), 7.59 (dt, *J* = 14.7, 7.4 Hz, 2H), 7.43 (dt, *J* = 21.4, 7.8 Hz, 4H), 6.56 (dd, *J* = 25.5, 2.7 Hz, 1H), 5.39 (dd, *J* = 45.5, 2.7 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.68 (dd, *J* = 11.8, 2.3 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.47 – 4.41 (m, 1H), 4.25 – 4.22 (m, 1H), 3.25 (d, *J* = 3.2 Hz, 1H), 2.11 (s, 3H), 1.35 (s, 3H) ppm; **HRMS** calcd for : $C_{27}H_{26}ClFN_4O_5S_2Na$ [M+Na^+] : 627.0909, found: 627.0907 (-0.39 ppm).

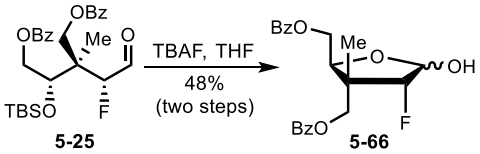
((2*S*,3*R*,4*R*,5*R*)-5-(6-chloro-8-mercapto-9H-purin-9-yl)-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-65)



5-65

To a solution of **5-60** (9 mg, 0.015 mmol, 1.0 eq.) in anhydrous MeCN (0.20 ml, 0.10 M) was added NIS (10 mg, 0.04 mmol, 3.0 eq.). The reaction was stirred for 24 hours at 25 °C. The reaction was quenched with a saturated solution of $NaHCO_3$ (0.20 ml) and the aqueous layer was extracted with ethyl acetate (3 × 0.5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-65**: **Formula** : $C_{26}H_{22}ClFN_4O_5S$; **MW** : 556.9934 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.34 (d, *J* = 3.1 Hz, 1H), 8.10 – 7.97 (m, 4H), 7.63 – 7.54 (m, 2H), 7.46 (dt, *J* = 20.7, 7.8 Hz, 4H), 6.89 (dd, *J* = 28.5, 1.5 Hz, 1H), 5.07 (dd, *J* = 49.4, 1.5 Hz, 1H), 4.69 – 4.63 (m, 2H), 4.56 – 4.45 (m, 3H), 1.47 (d, *J* = 1.3 Hz, 3H) ppm; **HRMS** calcd for : $C_{26}H_{22}ClFN_4O_5SNa$ [M+Na^+] : 579.0876, found: 579.0875.

(+)-((2*S*,3*R*,4*R*)-4-fluoro-5-hydroxy-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-66)

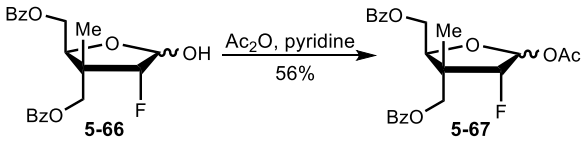


5-25 **5-66**

To a solution of **5-25** (0.19 g, 0.38 mmol, 1.0 eq.) in anhydrous THF (0.80 ml, 0.50 M) was added TBAF (1.2 ml, 1.15 mmol, 3.0 eq., 1M THF). The reaction was stirred at 25 °C for 16 hours and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-66** (71 mg, 48%): $\mathbf{R_f}$ = 0.44 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +8 (*c* 0.96, $CDCl_3$) ; **Formula** : $C_{21}H_{21}FO_6$; **MW** : 388.3862 g/mol ; **IR** (neat) ν_{max} 3425, 2953, 1717 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 – 8.00 (m, 8H), 7.63 – 7.53 (m, 4H), 7.49 – 7.40 (m, 8H), 5.64 (appd, *J* = 13.1 Hz, 1H), 5.58 (appd, *J* = 15.8 Hz, 1H), 4.89 (appd, *J* = 52.3 Hz, 1H), 4.81 (appd, *J* = 51.6 Hz, 1H), 4.61 – 4.41 (m, 10H), 1.41 (d, *J* = 1.8 Hz, 3H), 1.28 (d, *J* = 4.2 Hz, 3H) ppm *OH signals missing*

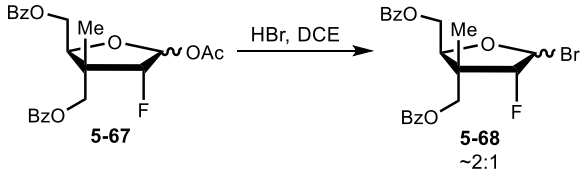
possibly due to exchange in $CDCl_3$. **HRMS** calcd for : $C_{21}H_{21}FO_6Na$ [M+Na^+] : 411.1214, found: 411.1210 (-0.99 ppm).

((2*S*,3*R*,4*R*)-5-acetoxy-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-67)



To a solution of **5-66** (68 mg, 0.18 mmol, 1.0 eq.) in anhydrous pyridine (0.50 ml, 0.35 M) at 0 ^oC was added Ac_2O (50 µl, 0.53 mmol, 3.0 eq.). The reaction was stirred at 25 ^oC for 16 hours and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-67** (42 mg, 56%): $\mathbf{R_f}$ = 0.38 (Hexanes/EtOAc, 70:30); **Formula** : $C_{23}H_{23}FO_7$;**MW** : 430.4284 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 8H), 7.63 – 7.54 (m, 4H), 7.51 – 7.40 (m, 8H), 6.39 (dd, *J* = 13.0, 0.9 Hz, 1H), 6.34 (d, *J* = 15.3 Hz, 1H), 5.03 (dd, *J* = 52.1, 1.1 Hz, 1H), 4.92 (d, *J* = 51.2 Hz, 1H), 4.63 – 4.38 (m, 10H), 2.10 (d, *J* = 2.7 Hz, 3H), 2.09 (s, 3H), 1.38 (d, *J* = 1.5 Hz, 3H), 1.32 (d, *J* = 4.2 Hz, 3H) ppm.

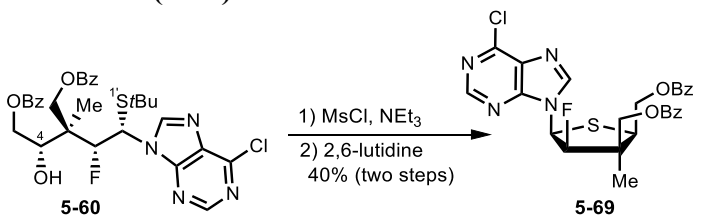
((2*S*,3*R*,4*R*)-5-bromo-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) dibenzoate (5-68)



To a solution of **5-67** (42 mg, 0.09 mmol, 1.0 eq.) in anhydrous DCM (0.50 ml, 0.20 M) at 0 ^oC was added HBr (30% in acetic acid) (60 µl). The reaction was stirred at 25 ^oC for 72 hours. A saturated solution of $NaHCO_3$ was added and the aqueous layer was extracted with DCM (3 × 1.0 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The compound was not purified but washed with toluene three times and the crude

mixture (~ 2:1 of anomeric bromides) was used for the next step. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 – 8.01 (m, 8H), 7.64 – 7.53 (m, 4H), 7.46 (m, 8H), 6.57 (d, *J* = 15.4 Hz, 1H), 6.43 (d, *J* = 18.5 Hz, 1H), 5.50 (d, *J* = 53.9 Hz, 1H), 5.34 (d, *J* = 52.7 Hz, 1H), 4.77 – 4.43 (m, 10H), 1.27 (s, 3H), 1.26 (s, 3H) ppm.

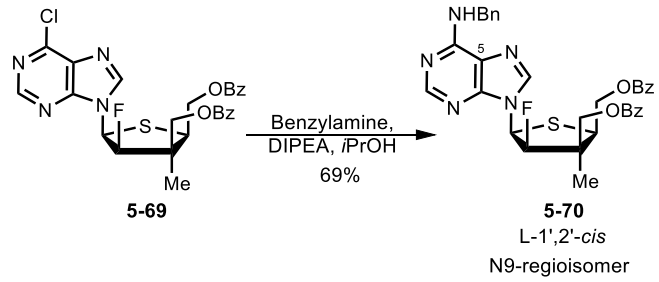
((2*R*,3*S*,4*R*,5*S*)-5-(6-chloro-9H-purin-9-yl)-4-fluoro-3-methyltetrahydrothiophene-2,3-diyl)bis(methylene) dibenzoate (5-69)



To a solution of **5-60** (46 mg, 0.08 mmol, 1.0 eq.) in anhydrous DCM (0.30 ml, 0.30 M) at 0 ^oC was added triethylamine (42 µl, 0.30 mmol, 4.0 eq.) and methanesulfonyl chloride (20 µl, 0.23 mmol, 3.1 eq). The reaction was stirred for 16 hours at 25 ^oC. H_2O (0.20 ml) was added and the aqueous layer was extracted with dichloromethane (3 × 2 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30) resulted in the C4-Ms thioaminal but it was not clean and used as is for the cyclization. A solution of C4-Ms thioaminal (37 mg, 0.05 mmol, 1.0 eq.) in 2,6-lutidine (1.0 ml, 0.05 M) was refluxed for 4 hours at 160 ^oC. Upon cooling to 25 ^oC, the reaction was concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-69** (11.4 mg, 40%): $\mathbf{R_f}$ = 0.28 (Hexanes/EtOAc, 50:50); **Formula** : $C_{26}H_{22}ClFN_4O_4S$; **MW** : 540.99376 g/mol; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.68 (s, 1H), 8.02 (dd, *J* = 31.4, 7.1 Hz, 4H), 7.57 (dd, *J* = 13.3, 7.0 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 4H), 6.70 (dd, *J* = 23.7, 2.8 Hz, 1H), 5.09 (dd, *J* = 52.4, 2.6 Hz, 1H), 4.91 (appt, *J* = 9.7 Hz, 1H), 4.85 – 4.75 (m, 2H), 4.62 (d, *J* = 11.1 Hz, 1H), 3.86 (appt, *J* = 7.3 Hz, 1H), 1.57 (s, 3H) ppm; **HRMS** calcd $C_{26}H_{22}ClFN_4O_4SNa$ $[M+Na^+]$: 563.0927, found:

563.0934 (1.30 ppm). Full characterization was not done as the product still contained some 2,6-lutidine.

((2*R*,3*S*,4*R*,5*S*)-5-(6-(benzylamino)-9H-purin-9-yl)-4-fluoro-3-methyltetrahydrothiophene-2,3-diyl)bis(methylene) dibenzoate (5-70)



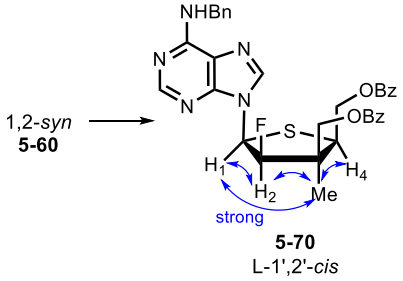
5-69 **5-70**
L-1',2'-*cis*
N9-regioisomer

To a solution of **5-69** (11 mg, 0.02 mmol, 1.0 eq.) in isopropanol (0.20 ml, 0.10 M) was added benzylamine (3 µl, 0.03 mmol, 1.3 eq.) and DIPEA (10 µl, 0.06 mmol, 3.0 eq.). The reaction mixture was refluxed for 16 hours at 70 °C. A saturated solution of NH_4Cl (0.1 ml) was added and the aqueous layer was extracted with ethyl acetate (3 × 1 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50) provided **5-70** (8.8 mg, 69%): $\mathbf{R_f}$ = 0.17 (Hexanes/EtOAc, 50:50); **Formula** : $C_{33}H_{30}FN_5O_4S$; **MW** : 611.6858 g/mol ; **IR** (neat) ν_{max} 3263, 3065, 2941, 1717, 1620 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.29 (d, *J* = 3.3 Hz, 1H), 8.02 (ddd, *J* = 32.0, 5.0, 3.2 Hz, 4H), 7.59 – 7.54 (m, 2H), 7.48 – 7.27 (m, 9H), 6.64 (dd, *J* = 24.7, 3.6 Hz, 1H), 6.10 (s, 1H), 5.06 (dd, *J* = 52.0, 3.6 Hz, 1H), 4.91 – 4.79 (m, 4H), 4.77 (d, *J* = 11.3 Hz, 1H), 4.60 (dd, *J* = 11.3, 1.4 Hz, 1H), 3.80 (appt, *J* = 7.6 Hz, 1H), 1.55 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.14, 166.08, 155.0, 153.4, 141.03, 140.99, 138.5, 133.6, 133.5, 129.9, 129.8, 129.7, 129.6, 128.9, 128.70, 128.67, 127.9, 127.7, 119.7, 98.1 (d, *J* = 192.0 Hz), 66.1 (d, *J* = 6.1 Hz), 64.9 (d, *J* = 6.9 Hz), 60.3 (d, *J* = 18.0 Hz), 55.1, 52.0 (d, *J* = 15.7

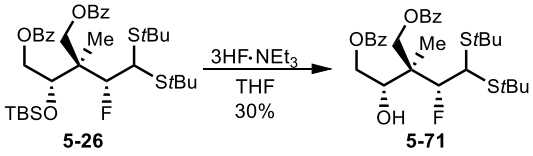
Hz), 44.9, 21.6 (d, J = 7.7 Hz) ppm ; **HRMS** calcd for : $C_{33}H_{31}FN_5O_4S$ [M+H$^+$] : 612.2075, found: 612.2073 (-0.40 ppm).

Stereochemical Proofs

The peaks in the ^{1}H NMR spectra were assigned using ^{1}H/^{1}H COSY experiments, chemical shifts, and coupling constants. Proof of structure for the C1'-C2' relative stereochemistry were provided by NOESY experiments. Proof of the N9-regiochemistry was based on the chemical shift of the C5 carbon of the purine ring. Weak interactions between the proton of the nucleobase and the H5 or H3 hydrogens suggests that the nucleobase is oriented anti to the sugar ring.



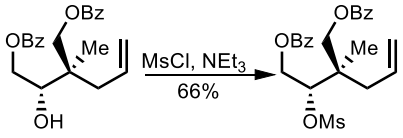
(2*R*,3*S*)-2-((*R*)-2,2-bis(tert-butylthio)-1-fluoroethyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-71)



To a solution of **5-26** (0.14 g, 0.22 mmol, 1.0 eq.) in anhydrous THF (2.0 ml, 0.10 M) at 0 ^{o}C was added 3HF•NEt$_3$ (1.2 ml, 7.4 mmol, 36.0 eq.). The reaction was stirred at 25 ^{o}C for 72 hours. A saturated solution of $NaHCO_3$ was added and the aqueous layer was extracted with EtOAc (3 × 1.0 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-71** (36 mg, 30%): **R$_f$** = 0.10 (Hexanes/EtOAc, 90:10); **Formula** : $C_{29}H_{39}FO_5S_2$; **MW** : 550.7444

g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 – 7.99 (m, 4H), 7.61 – 7.52 (m, 2H), 7.43 (m, 4H), 5.26 (dd, *J* = 44.3, 1.9 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.68 (dd, *J* = 11.9, 1.9 Hz, 1H), 4.50 – 4.42 (m, 2H), 4.36 (dd, *J* = 26.8, 2.0 Hz, 1H), 4.20 – 4.16 (m, 1H), 3.29 (d, *J* = 3.4 Hz, 1H), 1.46 (s, 9H), 1.42 (s, 9H), 1.41 (d, *J* = 4.8 Hz, 3H) ppm.

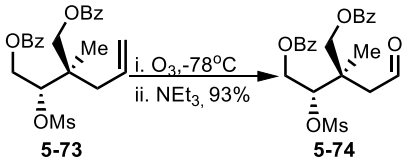
(+)-(2*R*,3*S*)-2-allyl-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl dibenzoate (5-73)



5-11 **5-73**

To a solution of **5-11** (2.9 g, 7.9 mmol, 1.0 eq.) in anhydrous DCM (27 ml, 0.30 M) at 0 °C was added triethylamine (5.1 ml, 36.4 mmol, 4.6 eq.) and MsCl (2.5 ml, 31.6 mmol, 4.0 eq.) The reaction mixture was stirred at 25 °C for 16 hours. A 1.0 N HCl solution (10 ml) was added and the aqueous layer was extracted with dichloromethane (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **5-73** (2.3 g, 66%): $\mathbf{R_f}$ = 0.17 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +27 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{23}H_{26}O_7S$; **MW** : 446.5133 g/mol ; **IR** (neat) ν_{max} 3072, 2977, 1717 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (m, 4H), 7.61 – 7.56 (m, 2H), 7.50 – 7.43 (m, 4H), 5.87 (m, 1H), 5.22 – 5.16 (m, 3H), 4.83 (dd, *J* = 12.5, 2.1 Hz, 1H), 4.56 (dd, *J* = 12.5, 8.6 Hz, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 4.27 (d, *J* = 11.6 Hz, 1H), 3.05 (s, 3H), 2.46 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.35 (dd, *J* = 14.0, 7.6 Hz, 1H), 1.21 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.4, 166.3, 133.6, 133.4, 131.9, 129.9, 129.81, 129.80, 129.5, 128.74, 128.73, 120.2, 84.2, 67.4, 64.1, 40.9, 39.3, 39.0, 19.5 ppm ; **HRMS** calcd for : $C_{23}H_{26}O_7SNa$ [M+Na^+] : 469.1291, found: 469.1283 (-1.84 ppm).

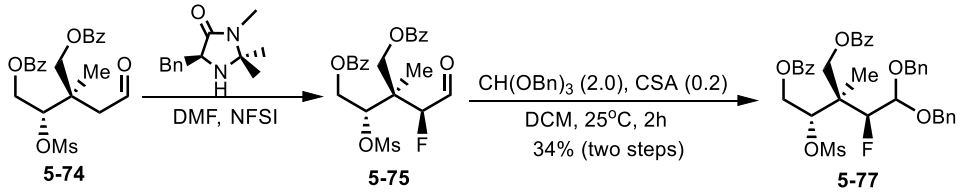
(+)-(2*R*,3*S*)-2-methyl-3-((methylsulfonyl)oxy)-2-(2-oxoethyl)butane-1,4-diyl dibenzoate dibenzoate (5-74)



5-73 **5-74**

To a solution of **5-73** (2.2 g, 5.0 mmol, 1.0 eq.) in DCM (150 ml, 0.03 M) at -78 °C was bubbled O_3 under vacuum until the solution turned pale blue (about 1 hour and 45 minutes). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (2.1 ml, 15.0 mmol, 3.0 eq.), the reaction was warmed to 25 °C for 30 minutes. A 1.0 N HCl solution (10 ml) was added and the DCM was evaporated. The aqueous layer was then extracted with diethyl ether (3 × 30 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-74** (2.09 g, 93%): $\mathbf{R_f}$ = 0.36 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +16 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{22}H_{24}O_8S$; **MW** : 448.4862 g/mol ; **IR** (neat) ν_{max} 2975, 1723 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.89 (t, *J* = 1.9 Hz, 1H), 8.10 – 8.00 (m, 4H), 7.63 – 7.54 (m, 2H), 7.51 – 7.42 (m, 4H), 5.32 (dd, *J* = 7.9, 2.6 Hz, 1H), 4.79 (dd, *J* = 12.5, 2.6 Hz, 1H), 4.55 (dd, *J* = 12.5, 7.9 Hz, 1H), 4.50 (apps, 2H), 3.07 (s, 3H), 2.85 (dd, *J* = 16.7, 2.0 Hz, 1H), 2.71 (dd, *J* = 16.6, 1.9 Hz, 1H), 1.37 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.4, 166.3, 166.1, 133.7, 133.6, 129.9, 129.8, 129.5, 129.3, 128.79, 128.78, 82.6, 67.3, 63.7, 48.0, 40.9, 39.3, 19.4 ppm ; **HRMS** calcd for : $C_{22}H_{24}O_8SNa$ [M+Na^+] : 471.1084, found: 471.1073 (-2.31 ppm).

(2R,3S)-2-((S)-2,2-bis(benzyloxy)-1-fluoroethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl dibenzoate (5-77)

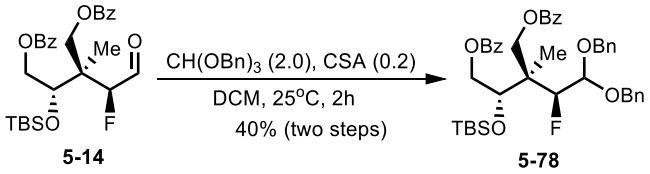


5-74 **5-75** **5-77**

To the (*S*)-imidazolidinone catalyst (52 mg, 0.24 mmol, 1.05 eq.) at –40 °C, was added **5-74** (0.10 g, 0.23 mmol, 1.0 eq.) as a solution in anhydrous DMF (0.3 ml, 1.0 M). After stirring for 10 minutes, NFSI (73 mg, 0.23 mmol, 1.02 eq.) was added. Once homogeneous, it was left at –20°C for 48 hours. The reaction mixture was diluted with Et_2O and water (1.0 ml) and treated with Me_2S (35 µl, 0.46 mmol, 2.0 eq.). The aqueous layer was extracted with Et_2O (3 × 1 ml) and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR spectroscopic analysis of the unpurified C2-F aldehyde indicated ~ 17:1 diastereomeric ratio for the fluorination. To the crude C2-F aldehyde **5-75** (0.16 g, 0.36 mmol, 1.0 eq.) in anhydrous DCM (1.8 ml, 0.20 M) was added $(BnO)_3CH$ (0.22 ml, 0.72 mmol, 1.0 eq.) and CSA (17 mg, 0.07 mmol, 0.20 eq.). After stirring for 5 hours at 25 °C, a saturated NH_4Cl solution was added (1.0 ml) to hydrolyze the excess $(BnO)_3CH$ and stirring was maintained for 1 hour. The aqueous layer was extracted with EtOAc (3 x 1 ml) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-77** (82 mg, 34% for two steps): $\mathbf{R_f}$ = 0.49 (Hexanes/EtOAc, 70:30); **Formula** : $C_{36}H_{37}FO_9S$; **MW** : 664.7370 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 – 7.93 (m, 4H), 7.63 – 7.18 (m, 16H), 5.53 (dd, *J* = 8.7, 1.3 Hz, 1H), 5.03 (t, *J* = 6.3 Hz, 1H), 4.90 – 4.64 (m, 6H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.39 (dd, *J* = 11.7, 2.1 Hz, 1H), 2.98 (s, 3H), 1.26 (s, 3H) ppm; **HRMS** calcd for : $C_{36}H_{37}FO_9SNa$ $[M+Na^+]$: 687.2035, found: 687.2037 (0.29 ppm).

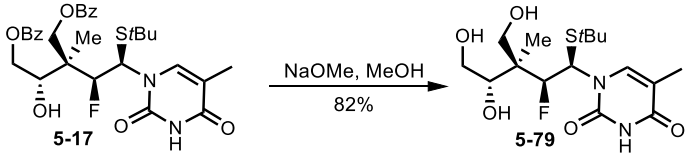
5-75 (crude): **^{1}H NMR** (500 MHz, $CDCl_3$) 9.87 (dd, *J* = 6.2, 1.0 Hz, 1H), 8.12 – 7.97 (m, 4H), 7.62 – 7.54 (m, 2H), 7.50 – 7.40 (m, 4H), 5.32 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.92 – 4.80 (m, 2H), 4.60 (dd, *J* = 12.0, 8.8 Hz, 1H), 4.53 – 4.45 (m, 2H), 3.08 (s, 3H), 1.39 (s, 3H) ppm.

(2*R*,3*S*)-2-((S)-2,2-bis(benzyloxy)-1-fluoroethyl)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl dibenzoate (5-78)



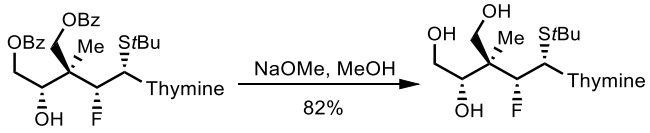
To the crude C2-F aldehyde **5-14** (0.11 g, 0.22 mmol, 1.0 eq.) in anhydrous DCM (1.2 ml, 0.20 M) was added $(BnO)_3CH$ (0.14 ml, 0.45 mmol, 1.0 eq.) and CSA (10 mg, 0.05 mmol, 0.20 eq.). After stirring for 3 hours at 25 ^oC, a saturated NH_4Cl solution was added (1.0 ml) to hydrolyze the excess $(BnO)_3CH$ and stirring was maintained for 1 hour. The aqueous layer was extracted with EtOAc (3 x 1 ml) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-78** (63 mg, 40% for two steps): $\mathbf{R_f}$ = 0.31 (Hexanes/EtOAc, 70:30); **Formula** : $C_{41}H_{49}FO_7Si$; **MW** : 700.9075 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 – 7.90 (m, 4H), 7.58 – 7.19 (m, 16H), 5.06 (t, *J* = 6.9 Hz, 1H), 4.90 (dd, *J* = 44.8, 6.2 Hz, 1H), 4.75 – 4.36 (m, 9H), 1.11 (s, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm; **HRMS** calcd for : $C_{41}H_{49}FO_7SiNa$ $[M+Na^+]$: 723.3124, found: 723.3141 (2.4 ppm).

(+)-1-((1*R*,2*S*,3*R*,4*S*)-1-(tert-butylthio)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)-3-methylpentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (5-79)



To a solution of **5-17** (0.12 g, 0.20 mmol, 1.0 eq.) in MeOH (1.6 ml, 0.13 M) at 0 °C was added NaOMe (30 µl, 0.10 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 °C. A 1 N HCl solution (~ 10 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (DCM/MeOH, 95:5), provided **5-79** (62 mg, 82%): $\mathbf{R_f}$ = 0.24 (DCM/MeOH, 95:5); $\mathbf{[\alpha]^{25}_D}$ +54 (*c* 1.6, $CDCl_3$) ; **Formula** : $C_{16}H_{27}FN_2O_5S$; **MW** : 378.4594 g/mol ; **IR** (neat) ν_{max} 3403, 3188, 2963, 1683 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.73 (s, 1H), 6.49 (appd, *J* = 31.3 Hz, 1H), 4.83 (appd, *J* = 46.1 Hz, 1H), 4.00 – 3.95 (m, 1H), 3.91 – 3.86 (m, 1H), 3.75 – 3.67 (m, 2H), 3.53 (dd, *J* = 12.0, 2.4 Hz, 1H), 1.95 (s, 3H), 1.32 (s, 9H), 1.03 (s, 3H) ppm *OH signals missing possibly due to exchange in $CDCl_3$.*; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.2, 151.4, 138.1, 112.0, 100.8 (d, *J* = 184.1 Hz), 72.9 (d, *J* = 4.6 Hz), 64.5 (d, *J* = 5.1 Hz), 62.8, 59.7 (d, *J* = 20.0 Hz), 45.9 (d, *J* = 16.6 Hz), 45.3, 31.1, 13.7 (d, *J* = 2.7 Hz), 12.8 ppm ; **HRMS** calcd for $C_{16}H_{27}FN_2O_5SNa$ $[M+Na^+]$: 401.1517, found: 401.1522 (1.34 ppm).

(–)-1-((1*S*,2*R*,3*R*,4*S*)-1-(tert-butylthio)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)-3-methylpentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (5-80)

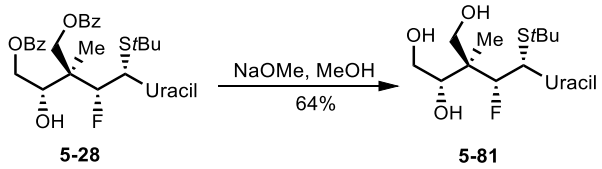


5-27 **5-80**

To a solution of **5-27** (89 mg, 0.15 mmol, 1.0 eq.) in MeOH (1.2 ml, 0.13 M) at 0 °C was added NaOMe (20 µl, 0.08 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 °C. A 1 N HCl solution (~ 10 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (DCM/MeOH, 95:5), provided **5-80** (47 mg, 82%): $\mathbf{R_f}$ = 0.19 (DCM/MeOH, 95:5); $\mathbf{[\alpha]^{25}_D}$ –69 (*c* 1.1, CD_3OD) ; **Formula** :

$C_{16}H_{27}FN_2O_5S$; **MW** : 378.4594 g/mol ; **IR** (neat) ν_{max} 3386, 2962, 1684 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.78 (s, 1H), 6.47 (dd, *J* = 30.5, 1.1 Hz, 1H), 4.90 (dd, *J* = 46.8, 1.0 Hz, 1H), 3.84 (d, *J* = 11.1 Hz, 1H), 3.79 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.72 (dd, *J* = 11.6, 2.7 Hz, 1H), 3.65 (d, *J* = 11.0 Hz, 1H), 3.54 – 3.49 (m, 1H), 1.92 (s, 3H), 1.32 (s, 9H), 1.11 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in* CD_3OD ; **^{13}C NMR** (125 MHz, CD_3OD) δ 166.2, 152.3, 139.9 (d, *J* = 3.4 Hz), 111.9, 100.6 (d, *J* = 182.2 Hz), 77.3 (d, *J* = 0.7 Hz), 65.0 (d, *J* = 6.5 Hz), 64.1 (d, *J* = 5.6 Hz), 60.1 (d, *J* = 19.9 Hz), 47.0 (d, *J* = 17.4 Hz), 45.6, 31.4, 16.3 (d, *J* = 5.9 Hz), 12.5 ppm ; **HRMS** calcd for $C_{16}H_{27}FN_2O_5SNa$ $[M+Na^+]$: 401.1517, found: 401.1527 (2.45 ppm).

(–)-1-((1*S*,2*R*,3*R*,4*S*)-1-(tert-butylthio)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)-3-methylpentyl)pyrimidine-2,4(1H,3H)-dione (5-81)

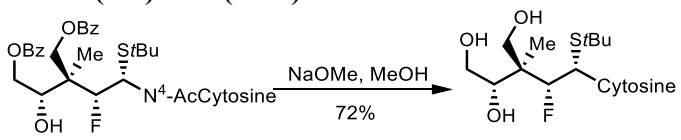


5-28 **5-81**

To a solution of **5-28** (90 mg, 0.16 mmol, 1.0 eq.) in MeOH (1.2 ml, 0.13 M) at 0 °C was added NaOMe (20 µl, 0.08 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 °C. A 1 N HCl solution (~ 10 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (DCM/Isopropanol, 80:20), provided **5-81** (37 mg, 64%): $\mathbf{R_f}$ = 0.59 (DCM/Isopropanol, 80:20); **$[\alpha]^{25}_D$** –64 (*c* 0.8, CD_3OD) ; **Formula** : $C_{15}H_{25}FN_2O_5S$; **MW** : 364.4328 g/mol ; **IR** (neat) ν_{max} 3382, 2958, 1691 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 8.00 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.47 (appd, *J* = 31.0 Hz, 1H), 5.78 (d, *J* = 8.1 Hz, 1H), 4.89 (appd, *J* = 71.9 Hz, 1H), 3.86 (d, *J* = 11.1 Hz, 1H), 3.78 (dd, *J* = 8.1, 2.2 Hz, 1H), 3.71 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.65 (d, *J* = 11.1 Hz, 1H), 3.51 (ddd, *J* = 11.0, 8.2, 2.4 Hz, 1H), 1.33 (s, 9H), 1.11 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in*

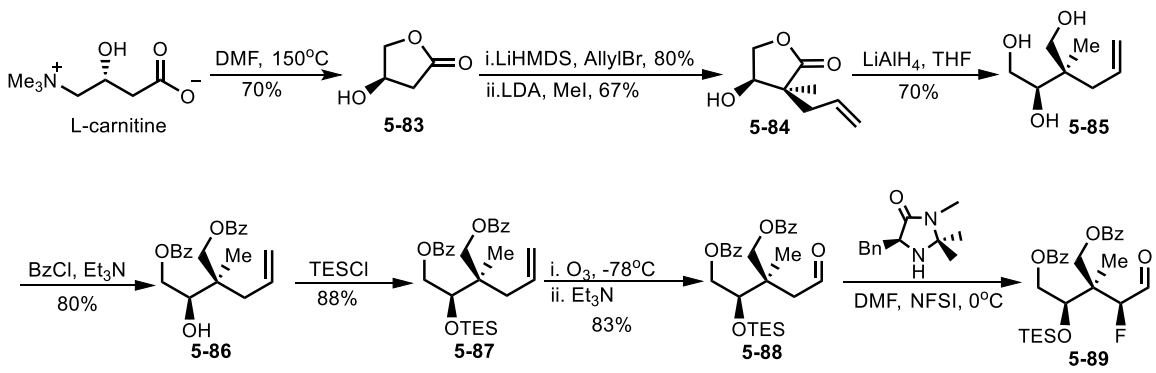
CD_3OD ; **^{13}C NMR** (125 MHz, CD_3OD) δ 166.0, 152.2, 144.5 (d, *J* = 3.5 Hz), 103.0, 100.4 (d, *J* = 182.1 Hz), 77.4, 65.1 (d, *J* = 6.3 Hz), 64.1 (d, *J* = 5.5 Hz), 60.5 (d, *J* = 19.9 Hz), 47.0 (d, *J* = 17.3 Hz), 45.7, 31.3, 16.2 (d, *J* = 6.1 Hz) ppm ; **HRMS** calcd for $C_{15}H_{25}FN_2O_5SNa$ $[M+Na^+]$: 387.1360, found: 387.1359 (-0.32 ppm).

(–)-4-amino-1-((1*S*,2*R*,3*R*,4*S*)-1-(tert-butylthio)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)-3-methylpentyl)pyrimidin-2(1H)-one (5-82)

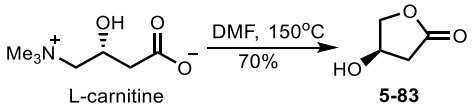


5-36 **5-82**

To a solution of **5-36** (0.11 g, 0.18 mmol, 1.0 eq.) in MeOH (1.4 ml, 0.13 M) at 0 °C was added NaOMe (20 µl, 0.09 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 °C. A 1 N HCl solution (~ 10 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (DCM/Isopropanol, 60:40), provided **5-82** (46 mg, 72%): $\mathbf{R_f}$ = 0.21 (DCM/Isopropanol, 60:40); $\mathbf{[\alpha]^{25}_D}$ –80 (*c* 0.9, CD_3OD) ; **Formula** : $C_{15}H_{26}FN_3O_4S$; **MW** : 363.4480 g/mol ; **IR** (neat) ν_{max} 3339, 2963, 1648 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 8.03 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.50 (appd, *J* = 31.7 Hz, 1H), 5.96 (d, *J* = 7.5 Hz, 1H), 4.85 (appd, *J* = 46.9 Hz, 1H), 3.87 (d, *J* = 11.2 Hz, 1H), 3.83 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.72 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.66 (d, *J* = 11.1 Hz, 1H), 3.55 – 3.49 (m, 1H), 1.30 (s, 9H), 1.12 (s, 3H) ppm *OH and NH_2 signals missing possibly due to exchange in* CD_3OD ; **^{13}C NMR** (125 MHz, CD_3OD) δ 167.5, 158.1, 145.0 (d, *J* = 3.0 Hz), 100.5 (d, *J* = 182.0 Hz), 96.3, 77.2, 65.0 (d, *J* = 6.2 Hz), 64.2 (d, *J* = 6.0 Hz), 60.9 (d, *J* = 19.8 Hz), 47.1 (d, *J* = 17.3 Hz), 45.6, 31.4, 16.2 (d, *J* = 5.9 Hz) ppm ; **HRMS** calcd for $C_{15}H_{26}FN_3O_4SNa$ $[M+Na^+]$: 386.1520, found: 386.1519 (-0.43 ppm).



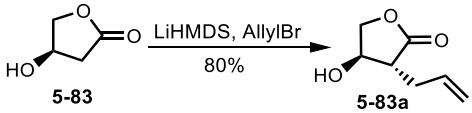
(+)-(*R*)-4-hydroxydihydrofuran-2(3H)-one (5-83)



Following a slightly modified literature procedure,[28] a solution of L-carnitine (9.5 g, 59.1 mmol, 1.0 eq.) in DMF (95 ml, 0.62 M) was heated to 150 °C for 16 hours and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 0:100) provided the known compound **5-83** (4.2 g, 70%). Characterization data correlate with the previously reported data.[28]

5-83: $\mathbf{R_f}$ = 0.28 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ +79 (*c* = 0.9, MeOH); **Formula** : $C_4H_6O_3$; **MW** : 102.0886 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.70 – 4.66 (m, 1H), 4.42 (dd, *J* = 10.3, 4.5 Hz, 1H), 4.30 (appd, *J* = 10.3 Hz, 1H), 2.86 (d, *J* = 3.8 Hz, 1H), 2.75 (dd, *J* = 17.9, 6.1 Hz, 1H), 2.52 (dd, *J* = 18.0, 1.0 Hz, 1H) ppm.

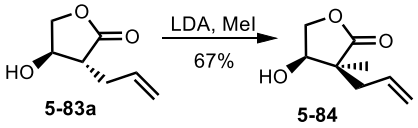
(+)-(3*R*,4*R*)-3-allyl-4-hydroxydihydrofuran-2(3H)-one (5-83a)



To LiHMDS (70 ml, 69 mmol, 2.4 eq., 1 M THF) at –78 °C was added a solution of **5-83** (2.95 g, 29 mmol, 1.0 eq.) in anhydrous THF (47 ml, 0.61 M). Stirring was maintained for 1 hour at –40°C. AllylBr (3.3 ml, 38 mmol, 1.3 eq.) and DMI (7.0 ml, 64 mmol, 2.2 eq.) were added as a

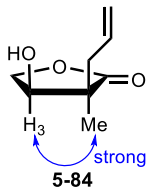
solution in anhydrous THF (16 ml, 2.4 M) and stirred for 2 hours at –40°C. The reaction mixture was quenched with 1 N HCl (20 ml) and concentrated. The aqueous layer was extracted with isopropyl acetate (4 × 50 ml) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 20:80) provided **5-83a** (3.3 g, 80%): $\mathbf{R_f}$ = 0.52 (Hexanes/EtOAc, 20:80); $\mathbf{[\alpha]^{25}_D}$ +29 (*c* = 1.4, $CDCl_3$) ; **Formula** : $C_7H_{10}O_3$; **MW** : 142.1525 g/mol ; **IR** (neat) ν_{max} 3442, 2911, 1759 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.90 – 5.78 (m, 1H), 5.20 (appd, *J* = 17.0 Hz, 1H), 5.16 (appd, *J* = 10.3 Hz, 1H), 4.46 – 4.37 (m, 2H), 4.08 (dd, *J* = 8.5, 3.8 Hz, 1H), 2.67 – 2.56 (m, 2H), 2.40 – 2.25 (m, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.1, 134.0, 118.7, 72.8, 71.9, 48.1, 32.6 ppm ; **HRMS** calcd for $C_7H_{10}O_3Na$ [M+Na^+] : 165.0522, found: 165.0523 (0.47 ppm).

(+)-(3*S*,4*R*)-3-allyl-4-hydroxy-3-methyldihydrofuran-2(3H)-one (5-84)



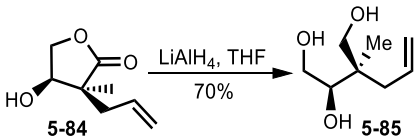
To a solution of DIPA (13.5 ml, 94.9 mmol, 2.5 eq.) in anhydrous THF (95 ml, 1.0 M) at –78 °C was added *n*-BuLi (38 ml, 94.9 mmol, 2.5 eq., 2.5 M solution in Hexanes). The reaction mixture was stirred at –40 °C for 1 hour. **5-83a** (5.4 g, 38 mmol, 1.0 eq.) as a solution in anhydrous THF (76 ml, 0.5 M) was added and stirred for 2 hours at –40 °C. A solution of MeI (3.8 ml, 61 mmol, 1.6 eq.) and DMI (9.2 ml, 84 mmol, 2.2 eq.) in anhydrous THF (76 ml, 0.80 M) was added and stirred for 3 hours at –35 °C. The reaction mixture was quenched with 6N HCl (20 ml) and concentrated. The aqueous layer was extracted with isopropyl acetate (4 × 20 ml) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/Et_2O, 30:70), provided **5-84** (3.97 g, 67%): $\mathbf{R_f}$ = 0.26 (Hexanes/Et_2O, 30:70); $\mathbf{[\alpha]^{25}_D}$ +47 (*c* = 1.3, $CDCl_3$) ; **Formula** : $C_8H_{12}O_3$; **MW** : 156.1810

g/mol ; **IR** (neat) ν_{max} 3447, 2978, 2928, 1752 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.98 – 5.85 (m, 1H), 5.27 – 5.17 (m, 2H), 4.43 (dd, *J* = 10.2, 4.5 Hz, 1H), 4.22 (apps, 1H), 4.18 (dd, *J* = 10.2, 2.0 Hz, 1H), 2.54 (dd, *J* = 14.3, 7.6 Hz, 1H), 2.42 (dd, *J* = 14.3, 7.0 Hz, 1H), 2.23 (d, *J* = 3.6 Hz, 1H), 1.23 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 180.0, 133.4, 119.4, 75.6, 72.4, 46.7, 35.9, 20.2 ppm ; **HRMS** calcd for $C_8H_{12}O_3Na$ [M+Na^+] : 179.0679, found: 179.0680 (0.97 ppm). A strong coupling between H3 and the C2-Me group was confirmed by NOESY.



5-84

(–)-(2*R*,3*R*)-3-allyl-3-methylbutane-1,2,4-triol (5-85)

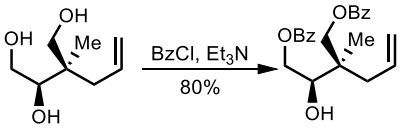


5-84 **5-85**

To a solution of **5-84** (6.1 g, 39 mmol, 1.0 eq.) in anhydrous THF (130 ml, 0.30 M) at 0 °C was added $LiAlH_4$ (30 ml, 58.7 mmol, 1.5 eq., 1M solution in THF). The reaction was stirred for 4 hours at 10 °C, quenched with Na_2SO_4•$10H_2O$ (30 g) and stirred for an additional 1.5 hours at 25 °C. After dilution with EtOAc, the mixture was dried over Na_2SO_4, washed with THF (3 × 50 ml), filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-85** (4.4 g, 70%): $\mathbf{R_f}$ = 0.33 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ –11 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_8H_{16}O_3$; **MW** : 160.2108 g/mol ; **IR** (neat) ν_{max} 3328, 2931, 2888, 1638 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.92 – 5.80 (m, 1H), 5.13 (dd, *J* = 3.7, 2.9 Hz, 1H), 5.10 (apps, 1H), 3.78 – 3.66 (m, 2H), 3.60 (dd, *J* = 6.8, 3.4 Hz, 1H), 3.56 (d, *J* = 11.1 Hz, 1H), 3.53 (d, *J* = 11.4 Hz, 1H), 2.24 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.14 (dd, *J* = 13.7, 7.5 Hz, 1H), 0.85 (s, 3H)

ppm *OH signals missing possibly due to exchange in $CDCl_3$* ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.0, 118.5, 77.1, 68.2, 62.7, 40.8, 40.3, 17.9 ppm; **HRMS** calcd for $C_8H_{16}O_3Na$ [M+Na^+] : 183.0992, found: 183.0992 (0.23 ppm).

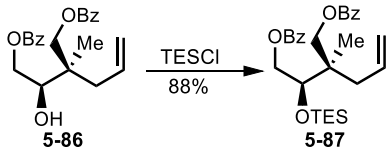
(–)-(2*R*,3*R*)-2-allyl-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-86)



5-85 **5-86**

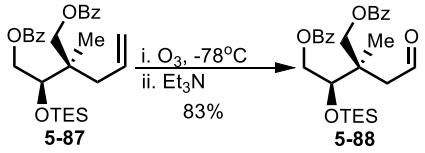
To a solution of **5-85** (1.9 g, 12.1 mmol, 1.0 eq.) in anhydrous DCM (15 ml, 0.80 M) at –40 ^oC was added NEt_3 (13.5 ml, 96.6 mmol, 8.0 eq.) followed by stirring for 30 minutes. BzCl (3.1 ml, 26.6 mmol, 2.2 eq.) was added and the reaction mixture was placed at –20 ^oC for 16 hours. The reaction was quenched with 1 N HCl solution (10 ml) and the aqueous layer was extracted with dichloromethane (3 × 15 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-86** (3.6 g, 80%): $\mathbf{R_f}$ = 0.48 (Hexanes/EtOAc, , 70:30); $\mathbf{[\alpha]^{25}_D}$ –8 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{22}H_{24}O_5$; **MW** : 368.4290 g/mol ; **IR** (neat) ν_{max} 3505, 3065, 2973, 1718 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 – 8.03 (m, 4H), 7.60 – 7.55 (m, 2H), 7.45 (dt, *J* = 14.1, 7.7 Hz, 4H), 5.96 – 5.86 (m, 1H), 5.18 (appd, *J* = 3.7 Hz, 1H), 5.15 (apps, 1H), 4.66 (dd, *J* = 11.5, 2.3 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.40 (dd, *J* = 11.5, 8.7 Hz, 1H), 4.19 (d, *J* = 11.3 Hz, 1H), 3.95 (appd, *J* = 8.6 Hz, 1H), 2.70 (d, *J* = 3.5 Hz, 1H), 2.35 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.29 (dd, *J* = 13.7, 7.6 Hz, 1H), 1.09 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 166.8, 133.5, 133.4, 133.3, 130.1, 130.0, 129.82, 129.77, 128.7, 128.6, 119.2, 73.3, 67.8, 66.7, 41.1, 39.5, 17.3 ppm ; **HRMS** calcd for : $C_{22}H_{24}O_5Na$ [M+Na^+] : 391.1516, found: 391.1516 (0.02 ppm).

(–)-(2*R*,3*R*)-2-allyl-2-methyl-3-((triethylsilyl)oxy)butane-1,4-diyl dibenzoate (5-87)



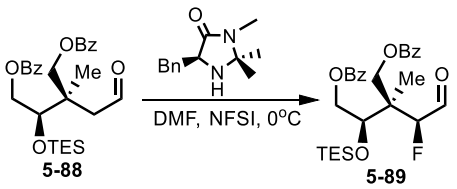
To a solution of **5-86** (0.60 g, 1.63 mmol, 1.0 eq.) in anhydrous DCM (8.2 ml, 0.20 M) at 0 ^{o}C was added imidazole (0.28 g, 4.1 mmol, 2.5 eq.) and TESCl (0.40 ml, 2.1 mmol, 1.3 eq.) The reaction mixture was stirred at 25 ^{o}C for 16 hours. A saturated solution of NH_4Cl (5 ml) was added and the aqueous layer was extracted with diethyl ether (3 × 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-87** (0.69 g, 88%): $\mathbf{R_f}$ = 0.43 (Hexanes/EtOAc, 90:10); $\mathbf{[\alpha]^{25}_D}$ –17 (*c* 1.3, $CDCl_3$) ; **Formula** : $C_{28}H_{38}O_5Si$; **MW** : 482.6920 g/mol ; **IR** (neat) ν_{max} 2958, 2877, 1717 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 – 8.02 (m, 4H), 7.60 – 7.54 (m, 2H), 7.45 (td, *J* = 7.8, 3.4 Hz, 4H), 5.92 – 5.81 (m, 1H), 5.12 – 5.05 (m, 2H), 4.66 (dd, *J* = 11.7, 2.9 Hz, 1H), 4.32 (dd, *J* = 11.7, 6.7 Hz, 1H), 4.26 (d, *J* = 11.1 Hz, 1H), 4.22 (d, *J* = 11.1 Hz, 1H), 4.11 (dd, *J* = 6.6, 2.8 Hz, 1H), 2.36 – 2.26 (m, 2H), 1.08 (s, 3H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.67 – 0.57 (m, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.9, 166.5, 133.6, 133.2, 133.1, 130.4, 130.2, 129.8, 129.7, 128.57, 128.55, 118.8, 74.4, 68.0, 67.7, 41.7, 39.2, 17.7, 7.1, 5.4 ppm ; **HRMS** calcd for : $C_{28}H_{38}O_5SiNa$ [M+Na$^+$] : 505.2381, found: 505.2378 (-0.55 ppm).

(–)-(2*R*,3*R*)-2-methyl-2-(2-oxoethyl)-3-((triethylsilyl)oxy)butane-1,4-diyl dibenzoate (5-88)



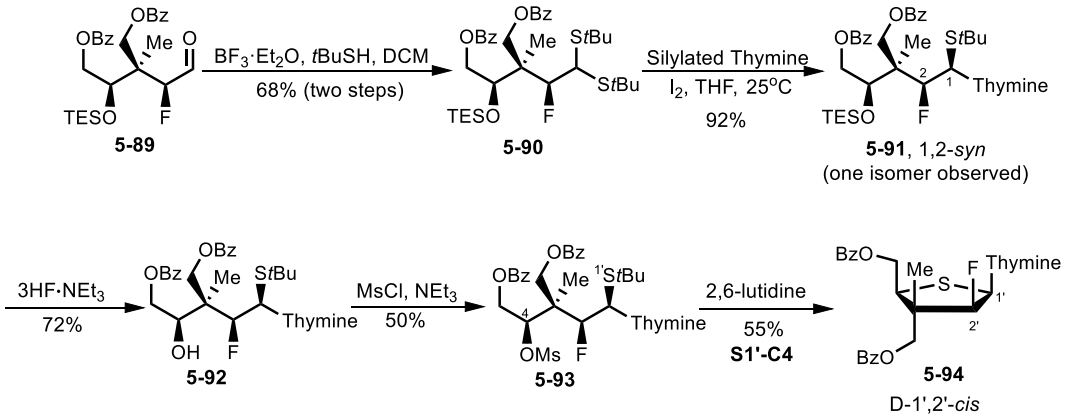
To a solution of **5-87** (0.69 g, 1.4 mmol, 1.0 eq.) in DCM (50 ml, 0.03 M) at –78 °C was bubbled O_3 under vacuum until the solution turned pale blue (about 25 minutes). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (1.2 ml, 8.6 mmol, 6.0 eq.), the reaction was warmed to 25 °C for 1 hour and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **5-88** (0.58 g, 83%): $\mathbf{R_f}$ = 0.33 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ –17 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{27}H_{36}O_6Si$; **MW** : 484.6566 g/mol ; **IR** (neat) ν_{max} 2952, 2872, 1719 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.91 (t, *J* = 2.5 Hz, 1H), 8.05 – 7.97 (m, 4H), 7.59 – 7.54 (m, 2H), 7.46 – 7.42 (m, 4H), 4.61 (dd, *J* = 11.9, 4.0 Hz, 1H), 4.45 – 4.33 (m, 3H), 4.18 (dd, *J* = 5.4, 4.1 Hz, 1H), 2.70 (dd, *J* = 15.5, 2.8 Hz, 1H), 2.53 (dd, *J* = 15.5, 2.4 Hz, 1H), 1.32 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.69 – 0.60 (m, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.9, 166.6, 166.3, 133.35, 133.31, 129.9, 129.9, 129.8, 129.7, 128.7, 128.6, 74.6, 68.6, 66.8, 48.4, 42.5, 19.8, 7.0, 5.2 ppm ; **HRMS** calcd for : $C_{27}H_{36}O_6SiNa$ $[M+Na^+]$: 507.2173, found: 507.2182 (1.80 ppm).

(–)-(2*R*,3*R*)-2-((*S*)-1-fluoro-2-oxoethyl)-2-methyl-3-((triethylsilyl)oxy)butane-1,4-diyl dibenzoate (5-89)

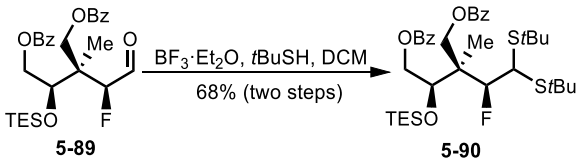


To the (*S*)-imidazolidinone catalyst (68 mg, 0.31 mmol, 1.3 eq.) at -40 °C, was added **5-88** (0.12 g, 0.24 mmol, 1.0 eq.) as a solution in anhydrous DMF (0.25 ml, 1.0 M). After stirring for 10 minutes, NFSI (84 mg, 0.25 mmol, 1.05 eq.) was added. Once homogeneous, it was left at –20 °C for 72 hours. The reaction mixture was diluted with Et_2O and water (1.0 ml) and treated with Me_2S (40 µl, 0.48 mmol, 2.0 eq.). The aqueous layer was extracted with Et_2O (3 × 1 ml) and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution

of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR spectroscopic analysis of the unpurified C2-F aldehyde indicated ~17:1 diastereomeric ratio for the fluorination. Some of the C2-F aldehyde was isolated and characterized: **5-89**: $\mathbf{R_f}$ = 0.44 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ –31.3 (*c* 1.42, $CDCl_3$) ; **Formula** : $C_{27}H_{35}FO_6Si$; **MW** : 502.6544 g/mol ; **IR** (neat) ν_{max} 2958, 2877, 1723 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.81 (dd, *J* = 7.5, 0.9 Hz, 1H), 8.00 (ddd, *J* = 19.8, 9.9, 5.7 Hz, 4H), 7.61 – 7.55 (m, 2H), 7.46 (dd, *J* = 16.2, 8.2 Hz, 4H), 4.97 (d, *J* = 48.0 Hz, 1H), 4.63 (dd, *J* = 12.1, 3.9 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.48 (dd, *J* = 11.5, 2.2 Hz, 1H), 4.40 (dd, *J* = 12.7, 4.9 Hz, 1H), 4.26 – 4.22 (m, 1H), 1.30 (s, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.68 (q, *J* = 7.9 Hz, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.2 (d, *J* = 35.8 Hz), 166.6, 166.2, 133.6, 133.5, 129.9, 129.85, 129.83, 129.78, 128.82, 128.79, 95.5 (d, *J* = 181.3 Hz), 73.0, 66.7 (d, *J* = 3.1 Hz), 65.1 (d, *J* = 5.0 Hz), 48.1 (d, *J* = 17.9 Hz), 16.0 (d, *J* = 5.5 Hz), 7.0, 5.2 ppm ; **HRMS** calcd for : $C_{27}H_{35}FO_6SiNa$ [M+Na^+] : 525.2079, found: 525.2079 (-0.09 ppm).

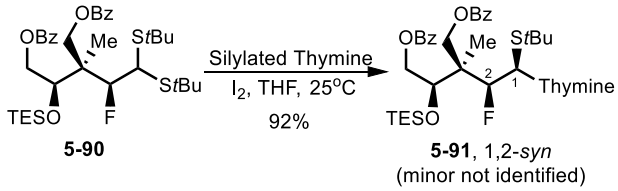


(+)-(2*R*,3*R*)-2-((*S*)-2,2-bis(tert-butylthio)-1-fluoroethyl)-2-methyl-3-((triethylsilyl)oxy)butane-1,4-diyl dibenzoate (5-90)



To the crude C2-F aldehyde **5-89** in anhydrous DCM (2.4 ml, 0.10 M) at –70 °C was added *t*BuSH (100 µl, 0.97 mmol, 4.0 eq.) and BF_3•OEt_2 (80 µl, 0.60 mmol, 2.5 eq.). The reaction was stirred at -60 °C for 3 hours. Upon addition of NEt_3 (0.14 ml, 0.97 mmol, 4.0 eq.) stirring was maintained at -50 °C for 15 minutes. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane (3 × 5 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **5-90** (108 mg, 68% for two steps): $\mathbf{R_f}$ = 0.52 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +5 (*c* 1.3, $CDCl_3$) ; **Formula** : $C_{35}H_{53}FO_5S_2Si$; **MW** : 665.0074 g/mol ; **IR** (neat) ν_{max} 2963, 2877, 1723 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 4H), 7.54 – 7.49 (m, 2H), 7.37 (dd, *J* = 16.1, 8.3 Hz, 4H), 5.37 (d, *J* = 43.9 Hz, 1H), 5.15 (d, *J* = 11.9 Hz, 1H), 4.71 – 4.65 (m, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.48 – 4.41 (m, 2H), 4.29 (dd, *J* = 29.3, 0.9 Hz, 1H), 1.45 (s, 9H), 1.42 (s, 9H), 1.28 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.70 – 0.60 (m, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.5, 166.4, 133.0, 132.95, 130.4, 130.2, 129.71, 129.65, 128.43, 128.40, 97.9 (d, *J* = 180.7 Hz), 74.1, 67.6 (d, *J* = 8.9 Hz), 66.2 (d, *J* = 7.3 Hz), 47.1 (d, *J* = 17.8 Hz), 46.9 (d, *J* = 2.5 Hz), 46.0, 44.8, 32.0, 31.7, 19.1 (d, *J* = 6.5 Hz), 7.0, 5.2 ppm ; **HRMS** calcd for : $C_{35}H_{53}FO_5S_2SiNa$ [M+Na^+] : 687.2980, found: 687.2990 (1.44 ppm).

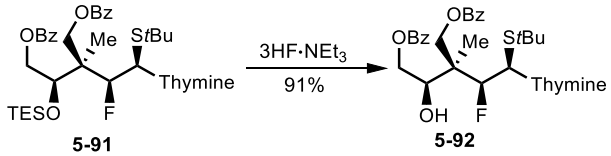
(+)-(2*R*,3*R*)-2-((1*S*,2*R*)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methyl-3-((triethylsilyl)oxy)butane-1,4-diyl dibenzoate (5-91)



5-90 **5-91**, 1,2-*syn* (minor not identified)

Following general procedure 5-A, silylated thymine (0.8 ml, 0.52 mmol, 3.0 eq. of a 0.67 M solution in THF), and I_2 (88 mg, 0.35 mmol, 2.0 eq.) were added to a solution of **5-90** (0.11 g, 0.17 mmol, 1.0 eq.) in anhydrous THF (1.8 ml, 0.10 M) and stirred at 25 °C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 80:20) provided **5-91** (0.11 g, 92%): $\mathbf{R_f}$ = 0.23 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +45 (*c* 1.0, $CDCl_3$) ; **Formula** : $C_{36}H_{49}FN_2O_7SSi$; **MW** : 700.9384 g/mol ; **IR** (neat) ν_{max} 3188, 2958, 2877, 1717, 1675 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.96 (ddd, *J* = 24.7, 8.3, 1.0 Hz, 4H), 7.67 (s, 1H), 7.57 – 7.51 (m, 2H), 7.39 (dt, *J* = 22.5, 7.8 Hz, 4H), 6.15 (appd, *J* = 31.4 Hz, 1H), 5.02 (appd, *J* = 46.4 Hz, 1H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.59 – 4.53 (m, 2H), 4.48 (dd, *J* = 5.9, 4.3 Hz, 1H), 4.40 (ddd, *J* = 11.7, 6.1, 2.6 Hz, 1H), 1.96 (s, 3H), 1.30 (s, 12H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.68 – 0.59 (m, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.5, 166.3, 163.4, 150.1, 138.0 (d, *J* = 2.9 Hz), 133.2, 133.1, 130.2, 130.0, 129.7, 129.6, 128.52, 128.48, 111.3, 99.5 (d, *J* = 184.8 Hz), 72.7, 67.0 (d, *J* = 6.6 Hz), 65.6 (d, *J* = 4.8 Hz), 58.7 (d, *J* = 20.0 Hz), 45.8 (d, *J* = 16.8 Hz), 45.2, 31.0, 17.5 (d, *J* = 6.1 Hz), 12.8, 7.0, 5.3 ppm ; **HRMS** calcd for : $C_{36}H_{49}FN_2O_7SSiNa$ $[M+Na^+]$: 723.2906, found: 723.2927 (2.9 ppm).

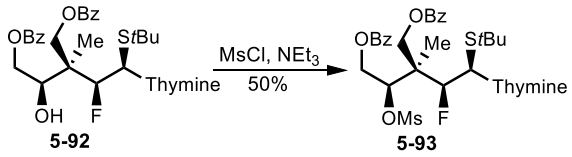
(+)-(2*R*,3*R*)-2-((1*S*,2*R*)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-3-hydroxy-2-methylbutane-1,4-diyl dibenzoate (5-92)



To a solution of **5-91** (1.77 g, 2.53 mmol, 1.0 eq.) in anhydrous THF (25.0 ml, 0.10 M) in a plastic vial at 0 °C was added 3HF•NEt_3 (1.24 ml, 7.59 mmol, 3.0 eq.). The reaction was stirred for 16 hours at 25 °C. A saturated solution (10 ml) of $NaHCO_3$ was added and the aqueous layer

was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-92** (1.4 g, 91%): $\mathbf{R_f}$ = 0.27 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +15 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{30}H_{35}FN_2O_7S$; **MW** : 586.6754 g/mol ; **IR** (neat) ν_{max} 3446, 3188, 2963, 1680 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.12 – 7.98 (m, 4H), 7.69 (s, 1H), 7.59 – 7.53 (m, 2H), 7.43 (dt, *J* = 19.3, 7.8 Hz, 4H), 6.35 (appd, *J* = 29.8 Hz, 1H), 5.00 (appd, *J* = 47.3 Hz, 1H), 4.74 (dd, *J* = 11.6, 2.3 Hz, 1H), 4.63 (d, *J* = 11.8 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.49 (dd, *J* = 11.6, 8.3 Hz, 1H), 4.36 – 4.32 (m, 1H), 3.52 (d, *J* = 4.0 Hz, 1H), 1.96 (s, 3H), 1.35 (s, 3H), 1.33 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 166.4, 163.5, 150.9, 137.7 (d, *J* = 2.1 Hz), 133.4, 133.3, 130.0, 129.89, 129.88, 129.83, 128.7, 128.5, 112.1, 99.1 (d, *J* = 185.0 Hz), 73.0 (d, *J* = 3.3 Hz), 66.9 (d, *J* = 4.0 Hz), 65.3 (d, *J* = 4.3 Hz), 58.5 (d, *J* = 19.8 Hz), 45.2292, 45.2291 (d, *J* = 17.3 Hz), 31.1, 16.1 (d, *J* = 4.7 Hz), 12.8 ppm ; **HRMS** calcd for $C_{30}H_{35}FN_2O_7SNa$ $[M+Na^+]$: 609.2041, found: 609.2058 (2.84 ppm).

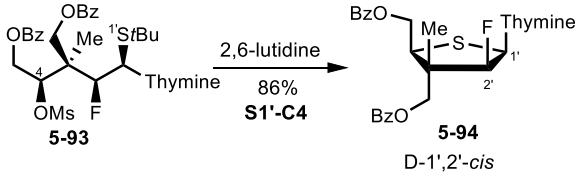
(+)-(2*R*,3*R*)-2-((1*S*,2*R*)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl dibenzoate (5-93)



To a solution of **5-92** (36 mg, 0.06 mmol, 1.0 eq.) in anhydrous DCM (0.20 ml, 0.30 M) at 0 °C was added triethylamine (40 µl, 0.24 mmol, 4.0 eq.) and methanesulfonyl chloride (14 µl, 0.18 mmol, 3.0 eq). The reaction was stirred for 16 hours at 25 °C. A 1.0 N solution (0.20 ml) of HCl was added and the aqueous layer was extracted with dichloromethane (3 × 1 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$,

filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-93** (20 mg, 50%): $\mathbf{R_f}$ = 0.17 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +34 (*c* 0.7, $CDCl_3$) ; **Formula** : $C_{31}H_{37}FN_2O_9S_2$; **MW** : 664.7619 g/mol ; **IR** (neat) ν_{max} 3183, 2963, 1717, 1685 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.05 (t, *J* = 7.6 Hz, 4H), 7.67 (s, 1H), 7.57 (t, *J* = 7.4 Hz, 2H), 7.47 – 7.41 (m, 4H), 6.25 (appd, *J* = 31.6 Hz, 1H), 5.56 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.88 (appd, *J* = 46.7 Hz, 1H), 4.87 (dd, *J* = 12.8, 1.8 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.62 – 4.55 (m, 2H), 3.07 (s, 3H), 1.97 (s, 3H), 1.43 (s, 3H), 1.32 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 166.1, 163.2, 150.2, 137.5 (d, *J* = 2.3 Hz), 133.6, 133.5, 129.90, 129.88, 129.7, 129.4, 128.74, 128.69, 111.7, 99.7 (d, *J* = 186.3 Hz), 82.1, 65.5 (d, *J* = 4.7 Hz), 64.3 (d, *J* = 8.1 Hz), 58.3 (d, *J* = 20.2 Hz), 45.7, 45.2 (d, *J* = 17.4 Hz), 39.4, 31.1, 17.6 (d, *J* = 6.2 Hz), 12.8 ppm ; **HRMS** calcd for $C_{31}H_{37}FN_2O_9S_2Na$ $[M+Na^+]$: 687.1817, found: 687.1842 (3.8 ppm).

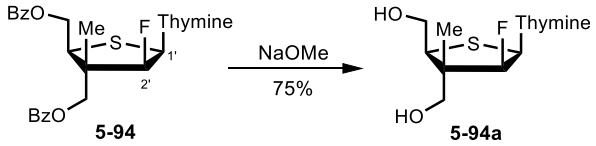
(+)-((2*S*,3*S*,4*S*,5*R*)-4-fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)yl)tetrahydrothiophene-2,3-diyl)bis(methylene) dibenzoate (5-94)



A solution of **5-93** (0.584 g, 0.88 mmol, 1.0 eq.) in 2,6-lutidine (9.0 ml, 0.10 M) was refluxed for 4 hours at 160 °C. Upon cooling to 25 °C, the reaction mixture was concentrated. Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-94** (0.39 g, 86%): $\mathbf{R_f}$ = 0.28 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ +106 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{26}H_{25}FN_2O_6S$; **MW** : 512.5499 g/mol ; **IR** (neat) ν_{max} 3215, 2979, 1717, 1685 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.10 – 8.02 (m, 4H), 7.79 (s, 1H), 7.60 (t, *J* = 7.4 Hz, 2H), 7.47 (td, *J* = 7.8, 3.2 Hz,

4H), 6.65 (dd, *J* = 25.7, 4.0 Hz, 1H), 5.04 (dd, *J* = 51.5, 4.0 Hz, 1H), 4.80 (appt, *J* = 10.2 Hz, 1H), 4.63 (dd, *J* = 11.3, 5.7 Hz, 1H), 4.43 (apps, 2H), 3.72 (dd, *J* = 9.0, 5.7 Hz, 1H), 1.95 (s, 3H), 1.48 (d, *J* = 1.4 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.3, 166.1, 163.3 (d, *J* = 1.1 Hz), 150.9, 138.7 (d, *J* = 4.5 Hz), 133.8, 133.6, 129.88, 129.86, 129.7, 129.3, 128.8, 128.7, 110.6, 98.5 (d, *J* = 190.9 Hz), 68.0 (d, *J* = 9.5 Hz), 65.9 (d, *J* = 4.6 Hz), 62.3 (d, *J* = 17.0 Hz), 52.54, 52.51 (d, *J* = 17.8 Hz), 15.2 (d, *J* = 7.1 Hz), 12.7 ppm ; **HRMS** calcd for : $C_{26}H_{25}FN_2O_6SNa$ [M+Na^+] : 535.1310, found: 535.1334 (4.6 ppm).

(+)-1-((2*R*,3*S*,4*S*,5*S*)-3-fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (5-94a)

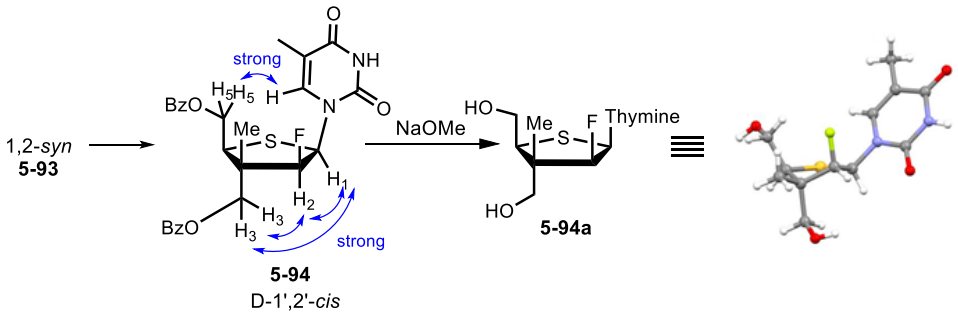


To a solution of **5-94** (0.39 g, 0.88 mmol, 1.0 eq.) in MeOH (5.8 ml, 0.13 M) at 0 °C was added NaOMe (86 µl, 0.38 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 16 hours at 25 °C. Formic acid (~ 2 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (Isopropanol/DCM, 5:95), provided **5-94a** (0.17 g, 75%): **R_f** = 0.10 (Isopropanol/DCM, 5:95); **$[\alpha]^{25}_D$** +139 (*c* 1.1, $CDCl_3$) ; **Formula** : $C_{12}H_{17}FN_2O_4S$; **MW** : 304.3364 g/mol ; **IR** (neat) ν_{max} 3398, 2884, 2811, 1686 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.96 (s, 1H), 6.47 (dd, *J* = 25.3, 4.0 Hz, 1H), 4.89 (dd, *J* = 52.5, 4.1 Hz, 1H), 3.90 (ddd, *J* = 11.1, 4.8, 0.8 Hz, 1H), 3.74 – 3.68 (m, 1H), 3.62 (d, *J* = 11.2 Hz, 1H), 3.52 (dd, *J* = 11.2, 2.3 Hz, 1H), 3.29 (dd, *J* = 10.2, 4.8 Hz, 1H), 1.91 (d, *J* = 1.2 Hz, 3H), 1.23 (d, *J* = 1.7 Hz, 3H) ppm *OH and NH signals missing possibly due to exchange in CD_3OD*; **^{13}C NMR**

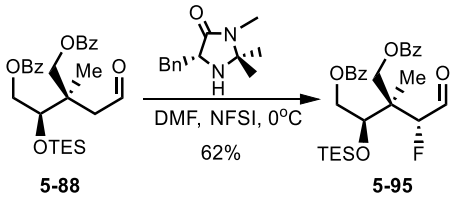
(125 MHz, Acetone-d_6) δ 164.1, 151.9, 139.6 (d, J = 5.2 Hz), 109.8, 100.1 (d, J = 187.4 Hz), 67.8 (d, J = 9.7 Hz), 64.9 (d, J = 3.5 Hz), 62.2 (d, J = 16.8 Hz), 57.6, 54.2 (d, J = 15.9 Hz), 14.6 (d, J = 7.7 Hz), 12.7 ppm ; **HRMS** calcd for : $C_{12}H_{17}FN_2O_4SNa$ [M+Na$^+$] : 327.0785, found: 327.0778 (-2.34 ppm).

Stereochemical Proofs

The peaks in the ^{1}H NMR spectra were assigned using ^{1}H/^{1}H COSY experiments, chemical shifts, and coupling constants. Proof of structure for the C1'-C2' relative stereochemistry were provided by NOESY experiments. The X-ray of **5-94a** confirms its structure.

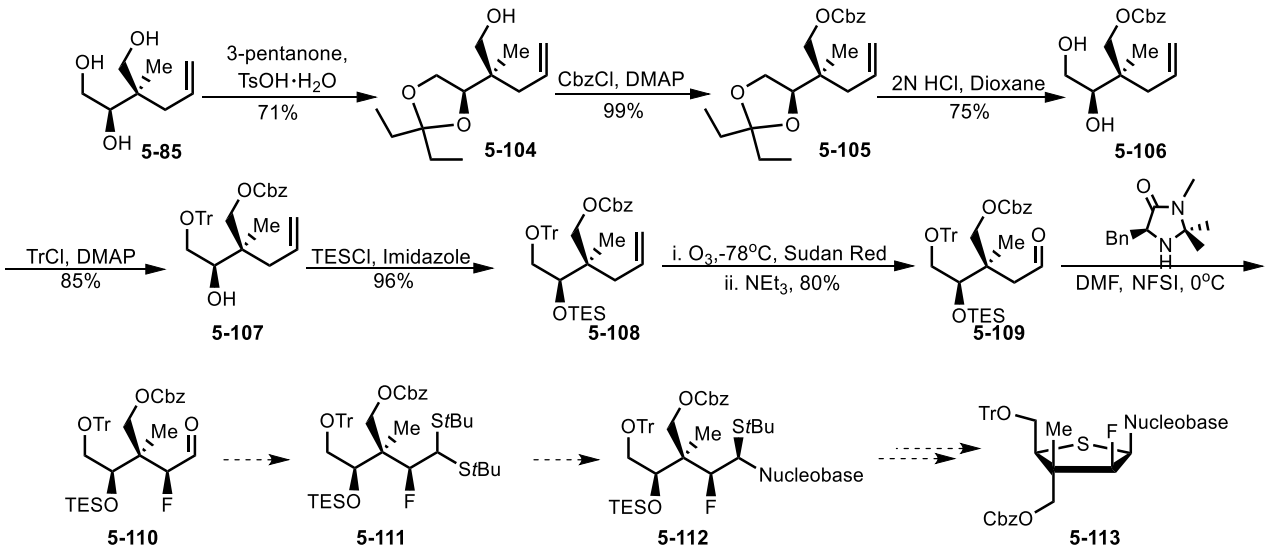


(+)-(2*R*,3*R*)-2-((*R*)-1-fluoro-2-oxoethyl)-2-methyl-3-((triethylsilyl)oxy)butane-1,4-diyl dibenzoate (5-95)

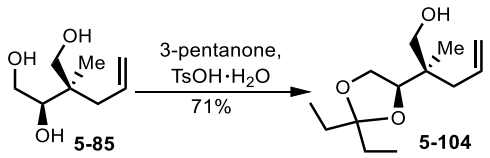


To the (*R*)-imidazolidinone catalyst (0.14 g, 0.64 mmol, 1.2 eq.) at –40 °C, was added **5-88** (0.25 g, 0.52 mmol, 1.0 eq.) as a solution in anhydrous DMF (0.6 ml, 1.0 M). After stirring for 10 minutes, NFSI (0.17 g, 0.55 mmol, 1.05 eq.) was added. Once homogeneous, it was left at –20 °C for 72 hours. The reaction mixture was diluted with Et_2O and water (1.0 ml) and treated with Me_2S (80 µl, 1.04 mmol, 2.0 eq.). The aqueous layer was extracted with Et_2O (3 × 1 ml) and the

combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR spectroscopic analysis of the unpurified C2-F aldehyde indicated ~17:1 diastereomeric ratio for the fluorination. Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-95** (0.16 g, 62%): $\mathbf{R_f}$ = 0.23 (Hexanes/EtOAc, 90:10); $\mathbf{[\alpha]^{25}_D}$ +2.4 (*c* 1.1, $CDCl_3$); **Formula** : $C_{27}H_{35}FO_6Si$; **MW** : 502.6471 g/mol; **IR** (neat) ν_{max} 2958, 2877, 1721 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.80 (d, *J* = 6.5 Hz, 1H), 8.01 (dd, *J* = 23.4, 8.0 Hz, 4H), 7.60 – 7.54 (m, 2H), 7.49 – 7.41 (m, 4H), 4.81 (d, *J* = 48.3 Hz, 1H), 4.68 (dd, *J* = 12.0, 3.9 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.50 – 4.45 (m, 2H), 4.22 (dd, *J* = 6.2, 4.1 Hz, 1H), 1.27 (d, *J* = 15.0 Hz, 3H), 0.96 – 0.88 (m, 9H), 0.71 – 0.56 (m, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.6 (d, *J* = 36.4 Hz), 166.5, 166.1, 133.44, 133.35, 129.9, 129.8, 129.73, 129.70, 128.7, 128.6, 95.9 (d, *J* = 184.4 Hz), 73.4, 67.2 (d, *J* = 6.2 Hz), 65.2 (d, *J* = 5.0 Hz), 48.5 (d, *J* = 17.9 Hz), 16.6 (d, *J* = 6.0 Hz), 6.9, 5.1 ppm ; **HRMS** calcd for : $C_{27}H_{35}FO_6SiNa$ [M+Na^+] : 525.2079, found: 525.2099 (3.74 ppm).

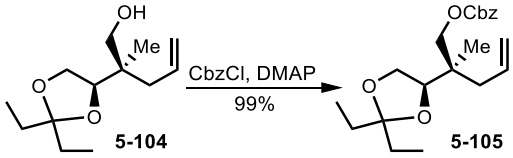


(*R*)-2-((*R*)-2,2-diethyl-1,3-dioxolan-4-yl)-2-methylpent-4-en-1-ol (5-104)



To a solution of **5-85** (1.42 g, 8.9 mmol, 1.0 eq.) in 3-pentanone (9.0 ml, 1.0 M) were added 4 Å molecular sieves (1.1 g) and TsOH•H_2O (0.10 mg, 0.44 mmol, 0.05 eq.). After stirring at 25 ^oC for 16 hours, additional molecular sieves and TsOH•H_2O were added and stirring was maintained for 2 hours. A saturated solution (10 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-104** (1.4 g, 71%) as an oil : $\mathbf{R_f}$ = 0.44 (Hexanes/EtOAc, 70:30); **Formula** : $C_{13}H_{24}O_3$; **MW** : 228.3279 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.87 – 5.75 (m, 1H), 5.14 – 5.04 (m, 2H), 4.03 (dd, *J* = 9.0, 6.2 Hz, 1H), 3.93 (dd, *J* = 8.0, 6.2 Hz, 1H), 3.72 (appt, *J* = 8.5 Hz, 1H), 3.59 (d, *J* = 11.2 Hz, 1H), 3.49 (d, *J* = 11.2 Hz, 1H), 2.61 (s, 1H), 2.15 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.06 (dd, *J* = 13.9, 7.8 Hz, 1H), 1.73 – 1.53 (m, 4H), 0.97 – 0.81 (m, 9H) ppm.

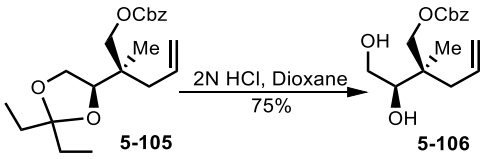
Benzyl ((*R*)-2-((*R*)-2,2-diethyl-1,3-dioxolan-4-yl)-2-methylpent-4-en-1-yl) carbonate (5-105)



To a solution of **5-104**(1.4 g, 6.3 mmol, 1.0 eq.) in anhydrous DCM (21 ml, 0.30 M) at 0 ^oC were added DMAP (2.3 g, 18.8 mmol, 3.0 eq.) followed by CbzCl (1.9 ml, 12.5 mmol, 2.0 eq.). After stirring 16 hour at 25 ^oC, the reaction mixture was concentrated. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-105** (2.3 g, 99%): $\mathbf{R_f}$ = 0.58

(Hexanes/EtOAc, 70:30); **Formula** : $C_{21}H_{30}O_5$; **MW** : 362.4660 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 5H), 5.81 – 5.71 (m, 1H), 5.16 (s, 2H), 5.10 – 5.02 (m, 2H), 4.09 (d, *J* = 2.0 Hz, 2H), 4.00 (dd, *J* = 8.7, 6.4 Hz, 1H), 3.89 (dd, *J* = 7.8, 6.5 Hz, 1H), 3.70 (t, *J* = 8.4 Hz, 1H), 2.15 – 2.01 (m, 2H), 1.70 – 1.52 (m, 4H), 0.95 – 0.82 (m, 9H) ppm.

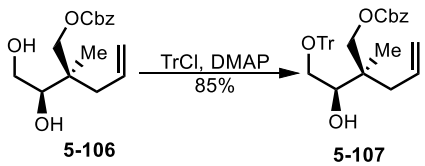
Benzyl ((*R*)-2-((*R*)-1,2-dihydroxyethyl)-2-methylpent-4-en-1-yl) carbonate (5-106)



5-105 **5-106**

To a solution of **5-105** (2.3 g, 6.2 mmol, 1.0 eq.) in dioxane (16 ml, 0.40 M) was added 2 N HCl (16 ml) and stirried for 6 hours at 45 ^oC. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc (20 ml). The aqueous layer was extracted with ethyl acetate (3 × 10 ml) and the combined organic layers were washed with a saturated $NaHCO_3$ solution (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (DCM/Acetone, 90:10), provided **5-106** (1.4 g, 75%): $\mathbf{R_f}$ = 0.28 (DCM/Acetone, 90:10); **Formula** : $C_{16}H_{22}O_5$; **MW** : 294.3470 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 5H), 5.84 – 5.74 (m, 1H), 5.16 (s, 2H), 5.14 – 5.06 (m, 2H), 4.20 (dd, *J* = 10.9, 8.5 Hz, 1H), 3.96 (dd, *J* = 11.0, 1.1 Hz, 1H), 3.74 – 3.68 (m, 1H), 3.62 – 3.52 (m, 2H), 2.11 (d, *J* = 7.4 Hz, 2H), 0.87 (s, 3H) ppm; *OH signals missing possibly due to exchange in* $CDCl_3$.

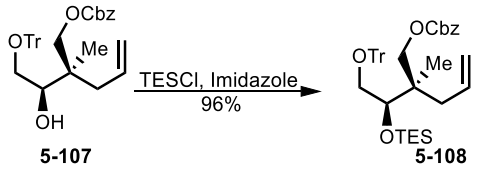
Benzyl ((*R*)-2-((*R*)-1-hydroxy-2-(trityloxy)ethyl)-2-methylpent-4-en-1-yl) carbonate (5-107)



5-106 **5-107**

To a solution of **5-106** (1.34 g, 4.6 mmol, 1.0 eq.) in pyridine (23 ml, 0.20 M) was added DMAP (56 mg, 0.46 mmol, 0.10 eq.) and TrCl (1.9 g, 6.9 mmol, 1.5 eq.). The reaction mixture was stirred for 16 hours at 50 °C and quenched with MeOH. Dilution with Et_2O followed by filtration on silica and concentration provided the crude product. Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-107** (2.1 g, 85%): $\mathbf{R_f}$ = 0.19 (Hexanes/EtOAc, 90:10); **Formula** : $C_{35}H_{36}O_5$; **MW** : 536.6680 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.20 (m, 20H), 5.74 – 5.63 (m, 1H), 5.13 (s, 2H), 5.03 – 4.90 (m, 2H), 4.10 (d, *J* = 10.6 Hz, 1H), 3.94 (d, *J* = 10.6 Hz, 1H), 3.72 (dd, *J* = 5.7, 2.9 Hz, 1H), 3.33 (dd, *J* = 9.5, 2.7 Hz, 1H), 3.14 (appt, *J* = 9.1 Hz, 1H), 2.57 (d, *J* = 3.1 Hz, 1H), 1.97 (ddd, *J* = 31.9, 13.7, 7.6 Hz, 2H), 0.74 (s, 3H) ppm.

Benzyl ((*R*)-2-methyl-2-((*R*)-1-((triethylsilyl)oxy)-2-(trityloxy)ethyl)pent-4-en-1-yl) carbonate (5-108)

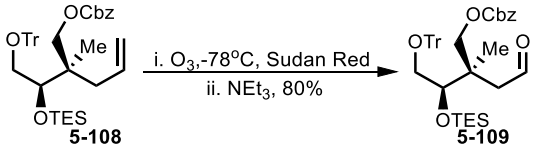


5-107 **5-108**

To a solution of **5-107** (1.0 g, 1.9 mmol, 1.0 eq.) in anhydrous DCM (9.3 ml, 0.20 M) at 0 °C were added imidazole (0.32 g, 4.7 mmol, 2.5 eq.) and TESCl (0.4 ml, 2.4 mmol, 1.3 eq.). The reaction mixture was stirred for 16 hours at 25 °C. A saturated solution of NH_4Cl solution (9.0 ml) was added and the aqueous layer was extracted with diethyl ether (3 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-108** (1.16 g, 96%): $\mathbf{R_f}$ = 0.42 (Hexanes/EtOAc, 90:10); **Formula** : $C_{41}H_{50}O_5Si$; **MW** : 650.9310 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 – 7.22 (m, 20H), 5.82 – 5.69 (m, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 5.06 – 4.95 (m, 2H), 4.03 (d, *J* = 10.4 Hz, 1H), 3.99 – 3.96 (m, 1H), 3.94

(d, *J* = 10.4 Hz, 1H), 3.36 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.04 (dd, *J* = 10.1, 5.6 Hz, 1H), 2.10 (dd, *J* = 12.8, 8.9 Hz, 2H), 0.96 – 0.88 (m, 9H), 0.77 (s, 3H), 0.67 – 0.58 (m, 6H) ppm.

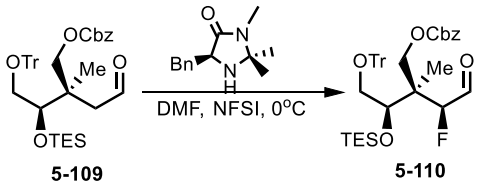
Benzyl ((2*R*,3*S*)-2-methyl-5-oxo-2-(2-oxoethyl)-5,5,5-triphenyl-3-((triethylsilyl)oxy)-5l6-pentyl) carbonate (5-109)



5-108 **5-109**

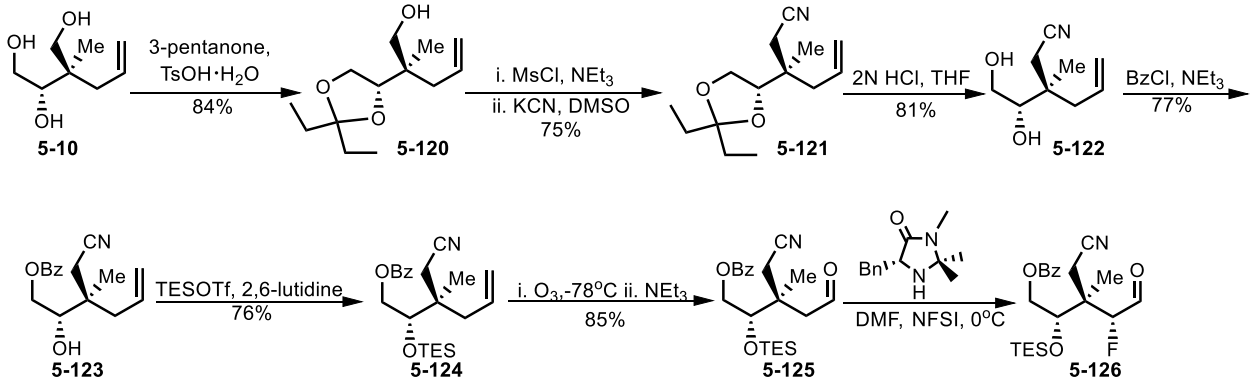
To a solution of **5-108** (0.50 g, 0.76 mmol, 1.0 eq.) in DCM (15 ml, 0.05 M) containing Sudan Red (0.3 mg) at –78 °C was bubbled O_3 under vacuum until the solution turned from red to pale orange (about 5 minutes). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (0.45 ml, 3.0 mmol, 4.0 eq.), the reaction was warmed to 25 °C for 30 minutes and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-109** (0.40 g, 80%): $\mathbf{R_f}$ = 0.22 (Hexanes/EtOAc, 90:10); **Formula** : $C_{40}H_{48}O_6Si$; **MW** : 652.9050 g/mol ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.4 Hz, 1H), 7.49 – 7.20 (m, 20H), 5.18 – 5.12 (m, 2H), 4.18 (d, *J* = 10.6 Hz, 1H), 4.05 (d, *J* = 10.6 Hz, 1H), 4.01 (t, *J* = 5.2 Hz, 1H), 3.27 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.11 (dd, *J* = 10.3, 4.7 Hz, 1H), 2.42 (dd, *J* = 15.7, 2.7 Hz, 1H), 2.34 (dd, *J* = 15.7, 2.3 Hz, 1H), 1.02 (s, 3H), 0.93 – 0.83 (m, 9H), 0.55 (q, *J* = 7.8 Hz, 6H) ppm.

Benzyl ((2*R*,3*S*)-3-fluoro-2-methyl-4-oxo-2-((*R*)-1-((triethylsilyl)oxy)-2-(trityloxy)ethyl)butyl) carbonate (5-110)

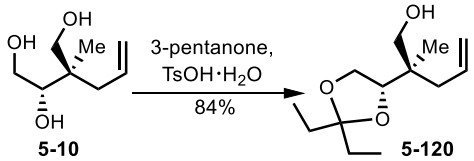


5-109 **5-110**

To the (*S*)-imidazolidinone catalyst (32 mg, 0.18 mmol, 1.15 eq.) at -40 °C, was added **5-109** (82 mg, 0.13 mmol, 1.0 eq.) as a solution in anhydrous DMF (0.20 ml, 1.0 M). After stirring for 10 minutes, NFSI (42 mg, 0.13 mmol, 1.05 eq.) was added. Once homogeneous, it was left at 0 °C for 48 hours. The reaction mixture was diluted with Et_2O and water (0.20 ml) and treated with Me_2S (20 µl, 0.25 mmol, 2.0 eq.). The aqueous layer was extracted with Et_2O (3 × 1 ml) and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was used as a crude reaction mixture. **5-110** (crude): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.69 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.22 (m, 20H), 5.16 (s, 2H), 4.91 (d, *J* = 47.5 Hz, 1H), 4.32 (d, *J* = 10.9 Hz, 1H), 4.13 – 4.06 (m, 2H), 3.34 (dd, *J* = 10.5, 5.9 Hz, 1H), 3.17 (dd, *J* = 10.4, 4.6 Hz, 1H), 1.03 (s, 3H), 0.93 – 0.83 (m, 9H), 0.63 – 0.52 (m, 6H) ppm.



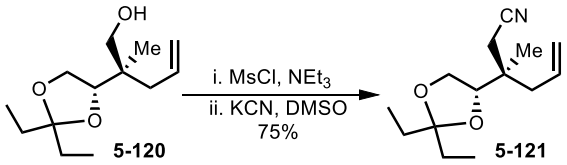
(+)-(*R*)-2-((S)-2,2-diethyl-1,3-dioxolan-4-yl)-2-methylpent-4-en-1-ol (5-120)



To a solution of **5-10** (0.57 g, 3.6 mmol, 1.0 eq.) in 3-pentanone (3.6 ml, 1.0 M) were added 4 Å molecular sieves (0.26 g) and TsOH·H_2O (34 mg, 0.18 mmol, 0.05 eq.). After stirring at 25 °C

for 16 hours, additional molecular sieves (0.26 g) and TsOH•H_2O (34 mg, 0.18 mmol, 0.05 eq.) were added and stirring was maintained for 5 hours. A saturated solution (2.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-120** (0.69 g, 84%) as an oil : $\mathbf{R_f}$ = 0.46 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +1.7 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{13}H_{24}O_3$; **MW** : 228.3279 g/mol ; **IR** (neat) ν_{max} 3465, 2973, 2940, 2882 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.91 – 5.80 (m, 1H), 5.13 – 5.06 (m, 2H), 4.02 (dd, *J* = 8.7, 6.3 Hz, 1H), 3.94 (dd, *J* = 8.0, 6.3 Hz, 1H), 3.76 (appt, *J* = 8.4 Hz, 1H), 3.53 (dd, *J* = 11.2, 7.0 Hz, 1H), 3.42 (dd, *J* = 11.2, 4.5 Hz, 1H), 2.52 – 2.47 (m, 1H), 2.34 (dd, *J* = 13.7, 7.1 Hz, 1H), 1.96 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.74 – 1.57 (m, 4H), 0.94 – 0.86 (m, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.2, 118.3, 112.8, 82.9, 69.1, 65.6, 39.7, 37.1, 29.7, 28.9, 18.6, 8.5, 8.3 ppm ; **HRMS** calcd for : $C_{13}H_{25}O_3$ $[M+H^+]$: 229.1798, found: 229.1795 (-1.47 ppm).

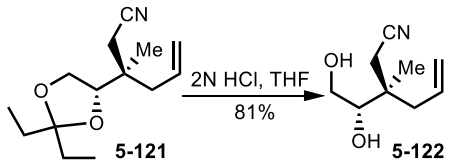
(+)-(*R*)-3-((S)-2,2-diethyl-1,3-dioxolan-4-yl)-3-methylhex-5-enenitrile (5-121)



To a solution of **5-120** (0.89 g, 3.9 mmol, 1.0 eq.) in anhydrous DCM (20 ml, 0.20 M) at 0 °C were added NEt_3 (1.1 ml, 7.8 mmol, 2.0 eq.) and MsCl (0.40 ml, 5.1 mmol, 1.3 eq.). After stirring 1 hour at 0 °C, the reaction mixture was quenched with 1N HCl (5 ml) and extracted with diethyl ether (3 x 20ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* To the crude mesylated olefin in anhydrous DMSO (18.0 ml, 0.22 M) were added KCN (0.77 g, 11.7 mmol, 3.0 eq.) and DMAP (0.24 g, 1.95 mmol, 0.5 eq.). The reaction mixture was stirred at 150°C for 16 hours. Upon cooling to 25 °C, water (10 ml) was

added and the reaction mixture extracted with ethyl acetate (3 × 20 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **5-121** (0.69 g, 75% two steps): $\mathbf{R_f}$ = 0.51 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +0.26 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{14}H_{23}NO_2$; **MW** : 237.3379 g/mol ; **IR** (neat) ν_{max} 2968, 2941, 2888 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.86 – 5.72 (m, 1H), 5.19 – 5.12 (m, 2H), 4.03 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.95 (dd, *J* = 8.0, 6.5 Hz, 1H), 3.70 (appt, *J* = 8.2 Hz, 1H), 2.41 (d, *J* = 16.7 Hz, 1H), 2.33 – 2.26 (m, 2H), 2.15 (dd, *J* = 13.9, 7.4 Hz, 1H), 1.73 – 1.58 (m, 4H), 1.10 (s, 3H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 132.7, 119.9, 118.2, 113.0, 80.4, 64.9, 40.3, 38.0, 29.5, 28.7, 25.0, 21.1, 8.4, 8.2 ppm ; **HRMS** calcd for : $C_{14}H_{24}NO_2$ [M+H$^+$] : 238.1802, found: 238.1796 (-2.16 ppm).

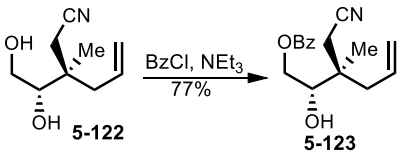
(+)-(*R*)-3-((S)-1,2-dihydroxyethyl)-3-methylhex-5-enenitrile (5-122)



To a solution of **5-121** (97 mg, 0.41 mmol, 1.0 eq.) in anhydrous THF (1.0 ml, 0.50 M) was added 2 N HCl (1.0 ml) and stirred for 16 hour at 25 ^oC. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with diethyl ether (3 × 1 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **5-122** (56 mg, 81%): $\mathbf{R_f}$ = 0.43 (Hexanes/EtOAc, 80:20); $\mathbf{[\alpha]^{25}_D}$ +21 (*c* 0.98, $CDCl_3$) ; **Formula** : $C_9H_{15}NO_2$; **MW** : 169.2209 g/mol ; **IR** (neat) ν_{max} 3398, 2973, 2882, 2238 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.86 – 5.75 (m, 1H), 5.20 – 5.12 (m, 2H), 3.80 (ddd, *J* = 10.3, 5.3, 2.4 Hz, 1H), 3.69 – 3.65 (m, 1H), 3.65 – 3.58 (m, 1H), 2.70 (d, *J* = 3.7 Hz, 1H), 2.51 (d, *J* = 16.7 Hz, 1H), 2.36 – 2.28 (m, 2H), 2.13 (dd, *J*

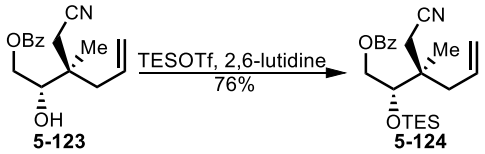
= 14.0, 7.3 Hz, 1H), 1.98 (t, *J* = 5.2 Hz, 1H), 1.10 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 132.9, 119.7, 118.6, 76.3, 62.6, 40.0, 39.2, 25.4, 21.6 ppm ; **HRMS** calcd for : $C_9H_{15}NO_2Na$ [M+Na^+] : 192.0995, found: 192.0994 (-0.37 ppm).

(+)-(2*S*,3*R*)-3-(cyanomethyl)-2-hydroxy-3-methylhex-5-en-1-yl benzoate (5-123)



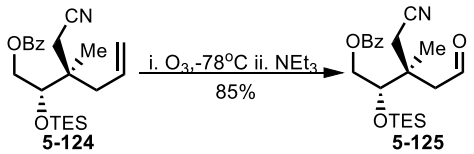
To a solution of **5-122** (47 mg, 0.28 mmol, 1.0 eq.) in anhydrous DCM (0.40 ml, 0.80 M) at –40 °C was added NEt_3 (0.16 ml, 1.1 mmol, 4.0 eq.) with stirring for 30 minutes. BzCl (40 µl, 0.31 mmol, 1.1 eq.) was added and stirring was maintained for 4.5 hour at -40 °C. A 1 N HCl solution (0.5 ml) was added. The aqueous layer was extracted with DCM (3 × 1 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 80:20), provided **5-123** (59 mg,77%): **R_f** = 0.23 (Hexanes/EtOAc, 80:20); **[α]$^{25}_D$** +11 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{16}H_{19}NO_3$; **MW** : 273.3270 g/mol ; **IR** (neat) ν_{max} 3482, 2968, 2243, 1719 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 5.89 – 5.79 (m, 1H), 5.22 – 5.16 (m, 2H), 4.55 (dd, *J* = 11.5, 2.4 Hz, 1H), 4.35 (dd, *J* = 11.5, 8.5 Hz, 1H), 3.97 (appd, *J* = 8.1 Hz, 1H), 2.61 (d, *J* = 16.6 Hz, 1H), 2.56 (s, 1H), 2.44 – 2.34 (m, 2H), 2.21 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.20 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 133.6, 132.7, 129.8, 129.6, 128.7, 120.0, 118.3, 74.7, 66.3, 39.7, 39.6, 25.6, 21.6 ppm ; **HRMS** calcd for : $C_{16}H_{19}NO_3Na$ [M+Na^+] : 296.1257, found: 296.1262 (1.66 ppm).

(+)-(2*S*,3*R*)-3-(cyanomethyl)-3-methyl-2-((triethylsilyl)oxy)hex-5-en-1-yl benzoate (5-124)



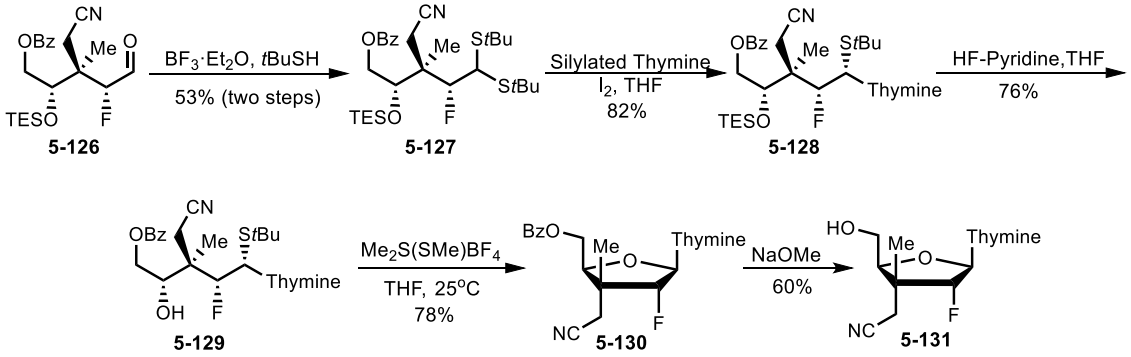
To a solution of **5-123** (50 mg, 0.18 mmol, 1.0 eq.) in anhydrous THF (0.50 ml, 0.50 M) at –50 ^{o}C were added 2,6-lutidine (40 µl, 0.37 mmol, 2.0 eq.) and TESOTf (60 µl, 0.24 mmol, 1.3 eq.). Stirring was maintained for 2 hour at –50 ^{o}C. A saturated solution of NH_4Cl solution (0.5 ml) was added and the aqueous layer was extracted with ethyl acetate (3 × 1 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-124** (54 mg,76%): $\mathbf{R_f}$ = 0.33 (Hexanes/EtOAc, 90:10); $\mathbf{[\alpha]^{25}_D}$ +20 (*c* 1.4, $CDCl_3$) ; **Formula** : $C_{22}H_{33}NO_3Si$; **MW** : 387.5950 g/mol ; **IR** (neat) ν_{max} 2963, 2877, 2249, 1717 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.61 – 7.57 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 5.88 – 5.79 (m, 1H), 5.20 – 5.12 (m, 2H), 4.53 (dd, *J* = 11.8, 3.5 Hz, 1H), 4.27 (dd, *J* = 11.8, 6.0 Hz, 1H), 3.99 (dd, *J* = 6.0, 3.5 Hz, 1H), 2.53 (d, *J* = 16.6 Hz, 1H), 2.41 – 2.31 (m, 2H), 2.22 (dd, *J* = 14.0, 7.4 Hz, 1H), 1.17 (s, 3H), 0.94 (m, 9H), 0.66 (m, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 133.4, 133.0, 129.9, 129.8, 128.7, 119.6, 118.5, 75.5, 66.7, 40.7, 40.1, 25.5, 21.7, 7.0, 5.3 ppm ; **HRMS** calcd for : $C_{22}H_{33}NO_3SiNa$ [M+Na^+] : 410.2122, found: 410.2125 (0.85 ppm).

(+)-(2*S*,3*S*)-3-(cyanomethyl)-3-methyl-5-oxo-2-((triethylsilyl)oxy)pentyl benzoate (5-125)

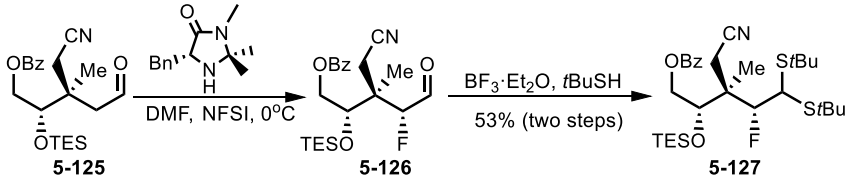


To a solution of **5-124** (0.63 g, 1.63 mmol, 1.0 eq.) in DCM (30 ml, 0.05 M) at –78 ^{o}C was bubbled O_3 under vacuum until the solution turned pale blue (about 45 minutes). The reaction

was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (0.68 ml, 4.9 mmol, 3.0 eq.), the reaction was warmed to 25 °C for 30 minutes and concentrated. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-125** (0.54 g, 85%): $\mathbf{R_f}$ = 0.41 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +9 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{21}H_{31}NO_4Si$; **MW** : 389.5606 g/mol ; **IR** (neat) ν_{max} 2957, 2877, 2238, 1717 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.83 (t, *J* = 2.1 Hz, 1H), 8.05 – 8.02 (m, 2H), 7.62 – 7.58 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 4.52 (dd, *J* = 12.0, 4.1 Hz, 1H), 4.31 (dd, *J* = 12.1, 5.2 Hz, 1H), 4.10 – 4.05 (m, 1H), 2.78 (dd, *J* = 16.2, 2.2 Hz, 1H), 2.72 (apps, 2H), 2.48 (dd, *J* = 16.2, 1.9 Hz, 1H), 1.31 (s, 3H), 0.98 – 0.92 (m, 9H), 0.66 (m, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.7, 166.5, 133.6, 129.8, 129.6, 128.7, 117.8, 75.1, 66.1, 48.8, 41.3, 26.2, 22.3, 7.0, 5.1 ppm ; **HRMS** calcd for : $C_{21}H_{31}NO_4SiNa$ [M+Na^+] : 412.1915, found: 412.1911 (-0.97 ppm).



(–)-(2*S*,3*R*,4*R*)-5,5-bis(tert-butylthio)-3-(cyanomethyl)-4-fluoro-3-methyl-2-((triethylsilyl)oxy)pentyl benzoate (5-127)

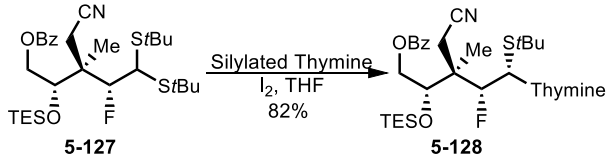


To the (*R*)-imidazolidinone catalyst (83 mg, 0.38 mmol, 1.15 eq.) at –40 °C, was added **5-125** (0.13 g, 0.33 mmol, 1.0 eq.) as a solution in anhydrous DMF (0.33 ml, 1.0 M). After stirring for 10 minutes, NFSI (0.11 g, 0.35 mmol, 1.05 eq.) was added. Once homogeneous, it was left at –20 °C for 72 hours. The reaction mixture was diluted with Et_2O and water (0.50 ml) and treated with Me_2S (50 µl, 0.66 mmol, 2.0 eq.). The aqueous layer was extracted with Et_2O (3 x 1 ml) and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR spectroscopic analysis of the unpurified C2-F aldehyde indicated ~17:1 diastereomeric ratio for the fluorination. To the crude C2-F aldehyde **5-126** in anhydrous DCM (3.3 ml, 0.10 M) at –50 °C was added *t*BuSH (0.15 ml, 1.32 mmol, 4.0 eq.) and $BF_3{\cdot}OEt_2$ (0.10 ml, 0.82 mmol, 2.5 eq.). The reaction was stirred at –50 °C for 5 hours. Upon addition of NEt_3 (0.92 ml, 6.6 mmol, 20 eq.) stirring at –50 °C was maintained for 15 minutes. A saturated solution (2 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane (3 × 4 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 90:10), provided **5-127** (99 mg, 53% for two steps): $\mathbf{R_f}$ = 0.33 (Hexanes/EtOAc, 90:10); $\mathbf{[\alpha]^{25}_D}$ –5.6 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{29}H_{48}FNO_3S_2Si$; **MW** : 569.9102 g/mol ; **IR** (neat) ν_{max} 2963, 2882, 2249, 1723 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 5.17 (dd, *J* = 44.6, 1.8 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.29 – 4.17 (m, 3H), 2.99 (d, *J* = 16.0 Hz, 1H), 2.68 (d, *J* = 16.0 Hz, 1H), 1.47 (s, 3H), 1.44 (s, 9H), 1.42 (s, 9H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.68 (q, *J* = 8.0 Hz, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 133.3, 130.1, 129.8, 128.6, 117.8 (d, *J* = 1.5 Hz), 95.6 (d, *J* = 185.0 Hz), 76.0, 67.7 (d, *J* = 9.3 Hz), 47.3 (d, *J* = 23.5 Hz), 46.3, 45.9 (d, *J* = 21.4 Hz), 45.8, 31.8, 31.7, 24.1 (d, *J* = 7.6 Hz), 19.0 (d, *J* = 7.2 Hz),

7.1, 5.2 ppm ; **HRMS** calcd for : $C_{29}H_{48}FNO_3S_2SiNa$ [M+Na^+] : 592.2721, found: 592.2729 (1.37 ppm).

5-126 (crude): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.76 (d, *J* = 8.2 Hz, 1H), 8.01 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 4.86 (appd, *J* = 47.5 Hz, 1H), 4.59 (dd, *J* = 12.4, 3.7 Hz, 1H), 4.34 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.17 – 4.12 (m, 1H), 2.68 (apps, 2H), 1.37 (d, *J* = 1.2 Hz, 3H), 0.98 – 0.91 (m, 9H), 0.68 (qd, *J* = 8.0, 3.8 Hz, 6H) ppm.

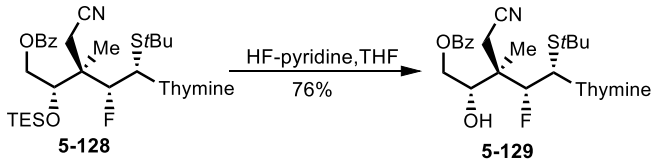
(–)-(2*S*,3*R*,4*R*,5*S*)-5-(tert-butylthio)-3-(cyanomethyl)-4-fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-((triethylsilyl)oxy)pentyl benzoate (5-128)



Following general procedure 5-A, silylated thymine (1.3 ml, 0.89 mmol, 3.0 eq. of a 0.71 M solution in DCM), and I_2 (0.19 g, 0.74 mmol, 2.0 eq.) were added to a solution of **5-127** (0.17 g, 0.30 mmol, 1.0 eq.) in anhydrous THF (3.0 ml, 0.10 M) and stirred at 25 °C for 16 hours. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (Hexanes/EtOAc, 70:30) provided **5-128** (0.15 g, 82%) as a white foam: $\mathbf{R_f}$ = 0.33 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ –33 (*c* 1.2, $CDCl_3$) ; **Formula** : $C_{30}H_{44}FN_3O_5SSi$; **MW** : 605.8364 g/mol ; **IR** (neat) ν_{max} 3199, 2959, 2877, 2248, 1691 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 2H), 7.65 (s, 1H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 6.10 (appd, *J* = 31.1 Hz, 1H), 4.82 (appd, *J* = 46.3 Hz, 1H), 4.61 (d, *J* = 10.9 Hz, 1H), 4.27 (appdd, *J* = 20.2, 6.3 Hz, 2H), 2.97 (d, *J* = 16.3 Hz, 1H), 2.62 (d, *J* = 15.9 Hz, 1H), 1.97 (s, 3H), 1.43 (s, 3H), 1.31 (s, 9H), 0.95 (t, *J* = 7.7 Hz, 9H), 0.70 (appdd, *J* = 15.3, 7.5 Hz, 6H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.5, 163.3, 150.3,

137.6 (d, *J* = 3.2 Hz), 133.4, 129.9, 129.7, 128.7, 117.3, 111.7, 98.6 (d, *J* = 186.7 Hz), 75.0, 67.0 (d, *J* = 6.9 Hz), 58.3 (d, *J* = 20.1 Hz), 45.5, 44.8 (d, *J* = 19.2 Hz), 31.2, 22.9 (d, *J* = 6.9 Hz), 19.6 (d, *J* = 5.9 Hz), 12.8, 7.0, 5.2 ppm ; **HRMS** calcd for : $C_{30}H_{44}FN_3O_5SSiNa$ [M+Na$^+$] : 628.2647, found: 628.2670 (3.58 ppm).

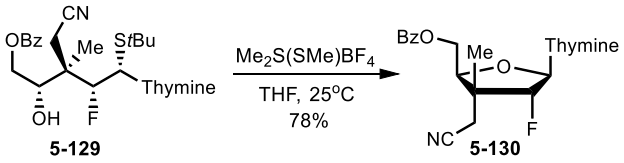
(–)-(2*S*,3*R*,4*R*,5*S*)-5-(tert-butylthio)-3-(cyanomethyl)-4-fluoro-2-hydroxy-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)pentyl benzoate (5-129)



To a solution of **5-128** (0.14 g, 0.23 mmol, 1.0 eq.) in anhydrous THF (2.4 ml, 0.10 M) in a plastic vial at 0 ^oC was added HF-pyridine (0.50 ml, 2ml/mmol, ~70% HF). The reaction was stirred for 16 hours at 25 ^oC. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 3 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 50:50), provided **5-129** (87 mg, 76%): $\mathbf{R_f}$ = 0.23 (Hexanes/EtOAc, 50:50); $\mathbf{[\alpha]^{25}_D}$ –22 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{24}H_{30}FN_3O_5S$; **MW** : 491.5755 g/mol ; **IR** (neat) ν_{max} 3435, 3183, 2968, 2254, 1685 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.66 (s, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 6.43 (appd, *J* = 32.1 Hz, 1H), 4.77 (appd, *J* = 45.6 Hz, 1H), 4.61 (dd, *J* = 11.7, 2.1 Hz, 1H), 4.50 (dd, *J* = 11.6, 8.4 Hz, 1H), 4.19 (appd, *J* = 8.2 Hz, 1H), 3.51 (s, 1H), 3.22 (d, *J* = 16.6 Hz, 1H), 2.72 (d, *J* = 16.6 Hz, 1H), 1.94 (s, 3H), 1.39 (s, 3H), 1.32 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.0, 163.4, 150.8, 137.6 (d, *J* = 2.6 Hz), 133.7, 129.9, 129.5, 128.7, 117.5, 112.0, 99.6 (d, *J* = 186.1 Hz), 74.2 (d, *J* = 3.1 Hz), 66.2 (d, *J* = 3.3 Hz), 58.9 (d, *J* = 19.9

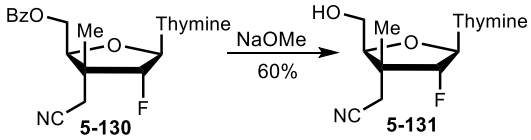
Hz), 45.7, 43.5 (d, *J* = 18.4 Hz), 31.1, 22.9 (d, *J* = 4.5 Hz), 19.7 (d, *J* = 5.4 Hz), 12.8 ppm ; **HRMS** calcd for $C_{24}H_{30}FN_3O_5SNa$ [M+Na^+] : 514.1782, found: 514.1785 (0.56 ppm).

(+)-((2*S*,3*R*,4*R*,5*R*)-3-(cyanomethyl)-4-fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl benzoate (5-130)

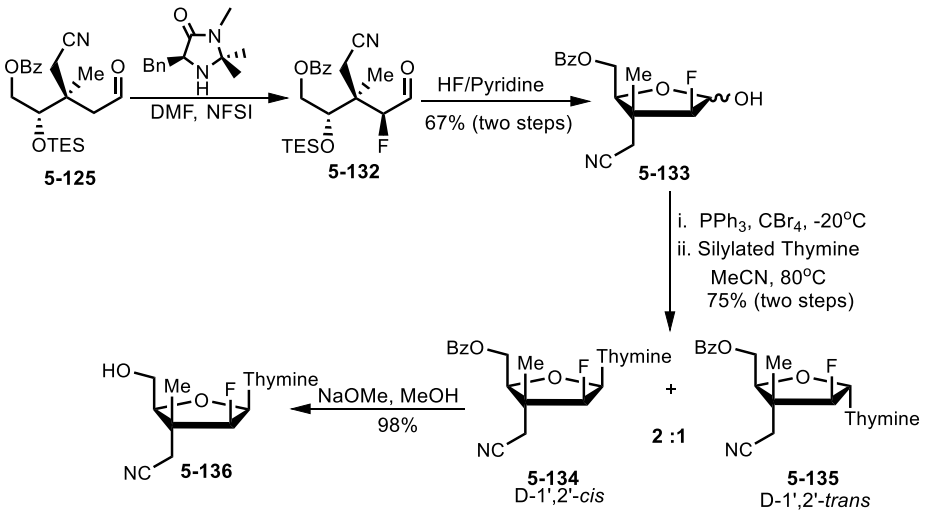


To a solution of **5-129** (0.106 g, 0.22 mmol, 1.0 eq.) in anhydrous THF (2.2 ml, 0.10 M) was added $Me_2S(SMe)BF_4$ (84 mg, 0.43 mmol, 2.0 eq.). The reaction was stirred for 5 hours at 25 °C. A saturated solution (1.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 × 3 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (Hexanes/EtOAc, 30:70), provided **5-130** (67 mg, 78%): $\mathbf{R_f}$ = 0.26 (Hexanes/EtOAc, 30:70); $\mathbf{[\alpha]^{25}_D}$ +64 (*c* 0.9, $CDCl_3$) ; **Formula** : $C_{20}H_{20}FN_3O_5$; **MW** : 401.3883 g/mol ; **IR** (neat) ν_{max} 3183, 3038, 2254, 1691 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.04 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 1.2 Hz, 1H), 5.79 (dd, *J* = 19.8, 2.3 Hz, 1H), 5.03 (dd, *J* = 51.8, 2.2 Hz, 1H), 4.65 (dd, *J* = 12.3, 4.2 Hz, 1H), 4.60 (dd, *J* = 12.3, 6.3 Hz, 1H), 4.41 (dd, *J* = 6.0, 4.3 Hz, 1H), 2.74 (d, *J* = 17.0 Hz, 1H), 2.66 (dd, *J* = 16.7, 3.2 Hz, 1H), 1.85 (s, 3H), 1.34 (d, *J* = 1.3 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.1, 163.3, 150.1, 134.5, 133.9, 129.8, 129.2, 128.9, 116.4, 111.8, 99.9 (d, *J* = 193.1 Hz), 90.1 (d, *J* = 38.4 Hz), 82.5, 62.5, 44.7 (d, *J* = 16.5 Hz), 22.6 (d, *J* = 13.0 Hz), 17.8 (d, *J* = 4.1 Hz), 12.7 ppm ; **HRMS** calcd for $C_{20}H_{20}FN_3O_5Na$ [M+Na^+] : 424.1279, found: 424.1278 (-0.29 ppm).

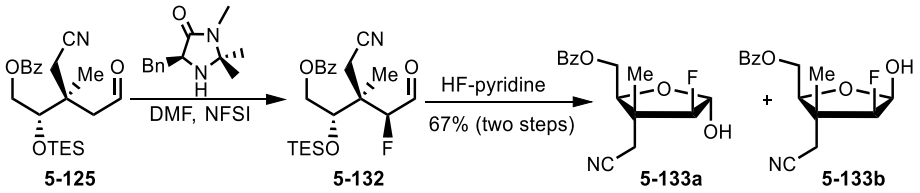
(+)-2-((2*S*,3*R*,4*R*,5*R*)-4-fluoro-2-(hydroxymethyl)-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl)acetonitrile (5-131)



To a solution of **5-130** (21 mg, 0.052 mmol, 1.0 eq.) in MeOH (0.4 ml, 0.13 M) at 0 ^{o}C was added NaOMe (6 µl, 0.03 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 1 hour at 25 ^{o}C. Formic acid (~ 2 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-131** (9.2 mg, 60%): $\mathbf{R_f}$ = 0.27 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ +15 (*c* 0.9, CD_3OD) ; **Formula** : $C_{13}H_{16}FN_3O_4$; **MW** : 297.2822 g/mol ; **IR** (neat) ν_{max} 3430, 2936, 2238,1691 cm^{-1} ; ^{1}**H NMR** (500 MHz, CD_3OD) δ 7.81 (d, *J* = 1.0 Hz, 1H), 5.95 (dd, *J* = 18.7, 3.5 Hz, 1H), 5.04 (dd, *J* = 52.7, 3.5 Hz, 1H), 4.10 (appt, *J* = 4.6 Hz, 1H), 3.86 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.81 (dd, *J* = 12.0, 4.9 Hz, 1H), 2.84 (dd, *J* = 17.0, 2.4 Hz, 1H), 2.79 (dd, *J* = 17.0, 1.2 Hz, 1H), 1.90 (d, *J* = 0.9 Hz, 3H), 1.29 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in* CD_3OD; ^{13}**C NMR** (125 MHz, CD_3OD) δ 166.3, 152.4, 137.3, 118.7, 111.8, 101.0 (d, *J* = 191.5 Hz), 89.6 (d, *J* = 36.6 Hz), 86.2, 61.5, 45.5 (d, *J* = 16.2 Hz), 23.2 (d, *J* = 12.8 Hz), 17.8, 12.5 ppm; **HRMS** calcd for $C_{13}H_{17}FN_3O_4$ $[M+H^+]$: 298.1198, found: 298.1193 (-1.39 ppm).



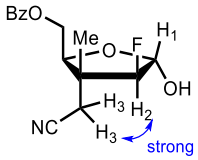
(+)-((2*S*,3*R*,4*S*)-3-(cyanomethyl)-4-fluoro-5-hydroxy-3-methyltetrahydrofuran-2-yl)methyl benzoate (5-133)



To the (*S*)-imidazolidinone catalyst (0.71 g, 3.25 mmol, 1.3 eq.) at –40 °C, was added **5-125** (0.97 g, 2.50 mmol, 1.0 eq.) as a solution in anhydrous DMF (2.5 ml, 1.0 M). After stirring for 10 minutes, NFSI (0.84 g, 2.7 mmol, 1.07 eq.) was added. Once homogeneous, it was left at –20 °C for 72 hours. The reaction mixture was diluted with Et_2O and water (2.0 ml) and treated with Me_2S (0.4 ml, 4.9 mmol, 2.0 eq.). The aqueous layer was extracted with Et_2O (3 × 4 ml) and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR spectroscopic analysis of the unpurified C2-F aldehyde indicated ~17:1 diastereomeric ratio for the fluorination. To the crude C2-F aldehyde **5-132** in anhydrous THF (25 ml, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (5.0 ml, 2ml/mmol, ~70% HF). The reaction was stirred for 4

hours at 25 °C. A saturated solution (2.0 ml) of $NaHCO_3$ was added and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified lactol indicated ~8:1 diastereomeric ratio in favor of the α-anomer **5-133a**. Purification by flash chromatography (Hexanes/EtOAc, 70:30), provided **5-133a** and **5-133b** (0.49 g, 67% two steps): $\mathbf{R_f}$ = 0.41 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +44 (*c* 1.0, $CDCl_3$) ; **Formula** : $C_{15}H_{16}FNO_4$; **MW** : 293.2902 g/mol ; **IR** (neat) ν_{max} 3441, 2963, 2249, 1719 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 – 8.03 (m, 2H), 7.61 – 7.56 (m, 1H), 7.48 – 7.43 (m, 2H), 5.62 (dd, *J* = 12.5, 2.5 Hz, 1H, α-anomer), 5.56 – 5.50 (m, 1H, β-anomer), 4.71 (d, *J* = 52.2 Hz, 1H, β-anomer), 4.71 (d, *J* = 51.4 Hz, 1H, α-anomer), 4.49 – 4.34 (m, 3H, α-anomer), 4.15 (dd, *J* = 7.7, 5.0 Hz, 1H, β-anomer), 3.56 – 3.49 (m, 1H, β-anomer), 3.04 (s, 1H, α-anomer), 2.83 (d, *J* = 16.9 Hz, 1H, α-anomer), 2.76 (d, *J* = 16.8 Hz, 1H, α-anomer), 2.56 (q, *J* = 17.3 Hz, 2H, β-anomer), 1.41 (d, *J* = 3.0 Hz, 3H, β-anomer), 1.37 (d, *J* = 3.6 Hz, 3H, α-anomer) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6 (β-anomer), 166.3 (α-anomer), 133.6 (β-anomer), 133.5 (α-anomer), 129.9 (α-anomer), 129.7 (α-anomer), 128.69 (β-anomer), 128.65 (α-anomer), 117.0 (α-anomer), 116.3 (β-anomer), 100.8 (d, *J* = 33.9 Hz, α-anomer), 99.9 (d, *J* = 118.8 Hz, α-anomer), 96.5 (d, *J* = 17.1 Hz, β-anomer), 94.4 (d, *J* = 195.2 Hz, β-anomer), 82.9 (α-anomer), 80.8 (β-anomer), 64.4 (d, *J* = 2.1 Hz, β-anomer), 64.2 (d, *J* = 1.1 Hz, α-anomer), 45.9 (d, *J* = 19.7 Hz, β-anomer), 45.4 (d, *J* = 19.8 Hz, α-anomer), 27.4 (d, *J* = 4.8 Hz, β-anomer), 27.3 (d, *J* = 6.5 Hz, α-anomer), 14.6 (d, *J* = 9.5 Hz, β-anomer), 14.3 (d, *J* = 12.2 Hz, α-anomer) ppm ; **HRMS** calcd for $C_{15}H_{16}FNO_4Na$ [M+Na^+] : 316.0956, found: 316.0959 (1.11 ppm).

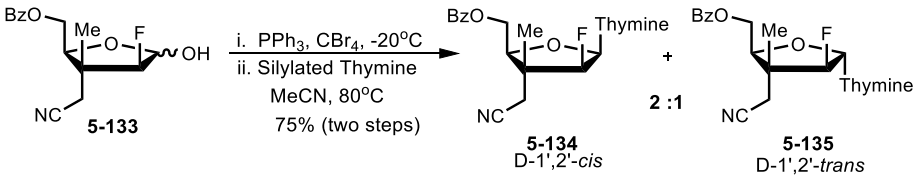
NOESY experiment shows a strong correlation between H2 and H3 but no coupling between H1 and H2 suggesting that the major isomer is the α-anomer.



5-133a

5-132 (crude): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.74 (dd, *J* = 5.0, 1.8 Hz, 1H), 8.07 – 7.98 (m, 2H), 7.62 – 7.56 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 4.74 (dd, *J* = 12.2, 2.9 Hz, 1H), 4.50 (dd, *J* = 47.6, 1.7 Hz, 1H), 4.38 – 4.28 (m, 1H), 4.05 (dd, *J* = 6.9, 2.8 Hz, 1H), 2.68 – 2.56 (m, 2H), 1.44 (s, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.70 – 0.60 (m, 6H) ppm.

(+)-((2*S*,3*R*,4*S*,5*R*)-3-(cyanomethyl)-4-fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl benzoate (5-134) & (+)-((2*S*,3*R*,4*S*,5*S*)-3-(cyanomethyl)-4-fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl benzoate (5-135)



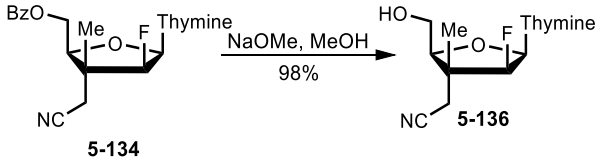
To a solution of PPh_3 (0.61 g, 2.3 mmol, 1.4 eq.) in anhydrous DCM (15 ml, 0.15 M) at –20 °C were added a solution of **5-133** (0.48 g, 1.65 mmol, 1.0 eq.) in anhydrous DCM (7.2 ml, 0.25 M) and CBr_4 (0.82 g, 2.5 mmol, 1.5 eq.) After stirring for 16 hours at –20 °C, silica gel (1.3 g) was added followed by filtration and concentration. ^{1}H NMR spectroscopic analysis of the crude product indicated a >20:1 diastereomeric ratio for the bromination. To the crude bromo-sugar in anhydrous MeCN (16 ml, 0.10 M) was added silylated thymine (4.5 ml, 3.3 mmol, 2.0 eq. of a 0.74 M solution in DCM). The reaction mixture was heated for 6 hours at 80 °C. Upon cooling to 25 °C, MeOH (2.0 ml) was added and the mixture was passed through a pad of silica gel. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1.7:1 mixture of the 1',2'-*cis* **5-134** and 1',2'-*trans* **5-135** diastereomers. Purification by flash chromatography

(Hexanes/EtOAc, 70:30) provided **5-134** (0.20 g)**,** a mix of **5-134** and **5-135** (0.16 g) and **5-135** (0.12 g) for a total yield of 75%.

5-134: $\mathbf{R_f}$ = 0.24 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +86 (*c* 0.8, $CDCl_3$) ; **Formula** : $C_{20}H_{20}FN_3O_5$; **MW** : 401.3883 g/mol ; **IR** (neat) ν_{max} 3199,3076, 2249, 1701 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.09 – 8.06 (m, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.38 (s, 1H), 6.22 (dd, *J* = 20.8, 3.1 Hz, 1H), 4.95 (dd, *J* = 52.1, 3.1 Hz, 1H), 4.60 (dd, *J* = 12.3, 7.5 Hz, 1H), 4.52 (dd, *J* = 12.3, 4.0 Hz, 1H), 4.38 (dd, *J* = 7.3, 4.0 Hz, 1H), 2.68 (d, *J* = 16.9 Hz, 1H), 2.62 (d, *J* = 16.9 Hz, 1H), 1.79 (d, *J* = 0.9 Hz, 3H), 1.48 (d, *J* = 3.0 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 163.3, 150.2, 135.8 (d, *J* = 2.7 Hz), 133.9, 129.9, 129.3, 128.8, 115.8, 110.7, 94.8 (d, *J* = 198.3 Hz), 85.3 (d, *J* = 16.5 Hz), 82.9, 63.6 (d, *J* = 2.2 Hz), 46.8 (d, *J* = 19.7 Hz), 27.8 (d, *J* = 7.9 Hz), 14.9 (d, *J* = 10.4 Hz), 12.5 ppm ; **HRMS** calcd for : $C_{20}H_{20}FN_3O_5Na$ [M+Na^+] : 424.1279, found: 424.1282 (0.62 ppm).

5-135: $\mathbf{R_f}$ = 0.28 (Hexanes/EtOAc, 70:30); $\mathbf{[\alpha]^{25}_D}$ +71 (*c* 0.7, $CDCl_3$) ; **Formula** : $C_{20}H_{20}FN_3O_5$; **MW** : 401.3883 g/mol ; **IR** (neat) ν_{max} 3183, 3059, 2254, 1691 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.05 – 8.01 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 1.1 Hz, 1H), 5.64 (dd, *J* = 69.2, 4.6 Hz, 1H), 5.57 (dd, *J* = 32.5, 4.6 Hz, 1H), 4.75 (appt, *J* = 5.8 Hz, 1H), 4.54 – 4.46 (m, 2H), 2.81 (d, *J* = 17.0 Hz, 1H), 2.76 (d, *J* = 17.0 Hz, 1H), 1.94 (d, *J* = 0.9 Hz, 3H), 1.35 (d, *J* = 4.1 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 163.5, 150.5, 138.9, 133.7, 129.9, 129.4, 128.7, 116.4, 112.0, 97.1 (d, *J* = 195.5 Hz), 93.8 (d, *J* = 35.6 Hz), 83.5 (d, *J* = 2.6 Hz), 62.9, 45.9 (d, *J* = 18.6 Hz), 25.6, 13.7 (d, *J* = 12.3 Hz), 12.5 ppm ; **HRMS** calcd for : $C_{20}H_{20}FN_3O_5Na$ [M+Na^+] : 424.1279, found: 424.1280 (0.16 ppm).

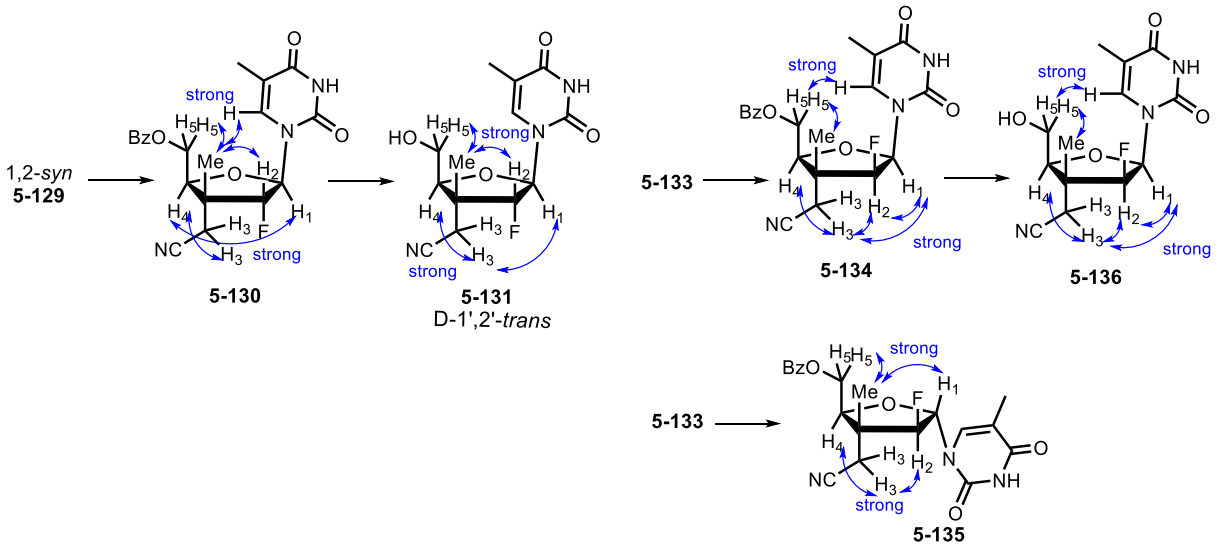
(+)-2-((2*S*,3*R*,4*S*,5*R*)-4-fluoro-2-(hydroxymethyl)-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl)acetonitrile (5-136)



To a solution of **5-134** (0.13 g, 0.31 mmol, 1.0 eq.) in MeOH (2.5 ml, 0.13 M) at 0 ^{o}C was added NaOMe (40 µl, 0.16 mmol, 0.5 eq., 25 wt% solution in MeOH). The reaction was stirred for 2 hour at 25 ^{o}C. Formic acid (~ 4 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (Hexanes/EtOAc, 0:100), provided **5-136** (90 mg, 98%): $\mathbf{R_f}$ = 0.52 (Hexanes/EtOAc, 0:100); $\mathbf{[\alpha]^{25}_D}$ +100 (*c* 0.5, CD_3OD) ; **Formula** : $C_{13}H_{16}FN_3O_4$; **MW** : 297.2822 g/mol ; **IR** (neat) ν_{max} 3446, 2952, 2254,1694 cm^{-1} ; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.67 (s, 1H), 6.18 (dd, *J* = 19.4, 3.6 Hz, 1H), 4.96 (dd, *J* = 52.8, 3.6 Hz, 1H), 4.02 (dd, *J* = 7.5, 4.7 Hz, 1H), 3.79 – 3.70 (m, 2H), 2.86 (d, *J* = 17.2 Hz, 1H), 2.81 (d, *J* = 17.1 Hz, 1H), 1.90 (d, *J* = 0.9 Hz, 3H), 1.29 (d, *J* = 3.6 Hz, 3H) ppm *OH and NH signals missing possibly due to exchange in* CD_3OD; **^{13}C NMR** (125 MHz, CD_3OD) δ 166.4, 152.0, 138.2 (d, *J* = 5.6 Hz), 118.3, 110.6, 96.6 (d, *J* = 196.8 Hz), 86.61 (d, *J* = 16.7 Hz), 86.58 , 62.4, 47.1 (d, *J* = 19.3 Hz), 27.2 (d, *J* = 7.0 Hz), 14.2 (d, *J* = 11.8 Hz), 12.4 ppm; **HRMS** calcd for $C_{13}H_{17}FN_3O_4$ $[M+H^+]$: 298.1198, found: 298.1196 (-0.42 ppm).

Stereochemical Proofs

The peaks in the ^{1}H NMR spectra were assigned using ^{1}H/^{1}H COSY experiments, chemical shifts, and coupling constants. Proof of structure for the C1'-C2' relative stereochemistry were provided by NOESY experiments.



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