Stereoselective Formation of All Carbon Quaternary Centers:

Synthesis of α,α-Disubstituted β-Amino Carbonyl Compounds via the Mannich Reaction

and

Total Synthesis of (-)-Puraquinonic Acid

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June 2011

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy

ABSTRACT

A bicyclic thioglycolate lactam chiral auxiliary was previously developed in our group for the asymmetric formation of quaternary carbon stereocenters via enolate alkylation. This method is notable for the stereocontrolled generation of α,α-disubstituted amide enolates, without reliance on the steric differences of the α-substituents. Coupled with excellent facial discrimination in electrophilic approach, this led to a general and practical method for enantioselective preparation of quaternary carbon centers via alkylation reactions. This thesis describes the extension of this methodology to the stereoselective formation of α,α-disubstituted β-amino carbonyl compounds via the Mannich reaction and also the application of the alkylation method to the total synthesis of (-)-puraquinonic acid.

α,α-Disubstituted lithium enolates, stereoselectively generated from α,α-disubstituted bicyclic thioglycolate lactams, undergo Mannich addition to benzenesulfonyl imines to form β-amino acid derivatives with high yield and diastereoselectivity. The reaction is general for a number of aromatic imines, including those with electron rich and electron poor substituents, heteroaromatic, and α,β-unsaturated imines. α-Substituents on the amide enolate can be varied to include methyl, ethyl, propyl, benzyl, and allyl groups. The addition occurs via a closed Zimmerman-Traxler transition state with *anti*/*syn* relationships controlled by enolate geometry. Methods for N-deprotection and removal of the auxiliary to afford β-amino acids and alcohols are described.

A concise synthesis of (-)-puraquinonic acid is accomplished using the bicyclic lactam chiral auxiliary to set the lone quaternary center at an early stage. A tandem ring-closing cross metathesis process followed by Diels-Alder cycloaddition generates a dihydroindene, which makes up the bicyclic system of puraquinonic acid. The central quinone is formed by a Curtius rearrangement/Fremy's salt oxidation sequence. Upon completion, the auxiliary is removed via acidic hydrolysis to give the required carboxylic acid functionality. The synthesis is completed in 14 steps from commercially available lactam in 21% overall yield, and represents a 24 step improvement over the previous asymmetric synthesis.

RÉSUMÉ

Un auxiliaire chiral de type lactame thioglycolate bicyclique permettant la formation de carbones asymétriques quaternaires via une alkylation d'énolates fut développé précédemment par notre groupe de recherche. Cette méthode est remarquable puisqu'elle permet la génération stéréocontrôlée d'énolates d'amide α,α-disubstitués, sans égard à la différence stérique entre les substituants α. Démontrant également une excellente discrimination faciale lors de l'approche de l'électrophile, ce protocole est maintenant devenu une méthode générale et pratique pour la préparation énantiosélective de carbones quaternaires par alkylation. Cette thèse rapporte l'application de cette méthode à la formation stéréosélective de composés β-amino carbonyles α,α-disubstitués via la réaction de Mannich, ainsi que son utilisation dans la synthèse totale de l'acide (-)-puraquinonique.

Les énolates α,α-disubstitués de lithium, générés de façon stéréosélective à partir de lactames thioglycolates bicycliques α,α-disubstituées, réagissent avec des imines benzènesulfoniques pour créer des acides β-aminés avec grande efficacité et diastéréosélectivité. La réaction est générale pour une panoplie d'imines aromatiques, incluant celles comportant des substituants pauvres en électrons, riches en électrons, hétéroaromatiques, ainsi que des imines α,β-insaturées. Les substituants α des énolates d'amides peuvent être des groupements méthyle, éthyle, propyle benzyle et allyle. L'addition emploie un état de transition de type Zimmerman-Traxler où la géométrie de l'énolate

contrôle le ratio d'addition *anti*/*syn*. Des méthodes de déprotection du groupe amino libérant des acides β-aminés et des alcools sont décrites.

Une courte synthèse de l'acide (-)-puraquinonique a été réalisée en utilisant l'auxiliaire chiral de type lactame thioglycolate bicyclique pour créer l'unique centre quaternaire présent tôt dans la séquence. Par la suite, un processus tandem fermeture de cycle par métathèse - cycloaddition de Diels-Alder produit un dihydroindene constituant le sytème bicyclique de l'acide puraquinonique. La quinone centrale est formée via une séquence comprenant un réarrangement de Curtius et une oxydation par le sel de Fremy. Lorsque la synthèse est complétée, l'auxiliaire est enlevé par une hydrolyse acide, révélant la fonctionnalité acide carboxylique nécessaire. La synthèse est complétée avec un rendement de 21 % à partir d'une lactame commercialement disponible, et ce, en 14 étapes. Cette synthèse représente donc une amélioration de 24 étapes par rapport à la synthèse asymétrique précédente.

ACKNOWLEDGEMENTS

I would like to express my appreciation for everyone who made the completion of this thesis possible. First of all, I owe my heartfelt thanks to my supervisor, Prof. James L. Gleason, for his patience, guidance, and support. His infectious enthusiasm for life and chemistry, insatiable curiosity for the unknown, and generosity in sharing his wealth of knowledge has shaped me as a scientist. I am grateful.

It was the dedication and enthusiasm of many science and chemistry teachers that set me on this path and for that I am sincerely grateful. In particular, I would like to thank Cikgu Hon for getting me interested in chemistry at the very beginning and Prof. Suzana K. Straus for believing.

For all their technical and spectroscopic assistance, I would like to acknowledge Fred Morin and Paul Xia (NMR), Nadim Saade and Alain Lesimple (MS), and Vincent Jazeron, Christopher Godbout, and Prof. D. Scott Bohle (X-ray). All HRMS analysis was performed by Nadim and Alain, and all X-ray crystal structures were solved by Vincent, Chris, and Prof. Bohle.

I would like to thank the administrative staff of the McGill chemistry department, Fay Nurse, Chantal Marotte, Alison McCaffrey, Karen Turner, and Sandra Aerssen, for all their help over the years. In particular, I would like to thank Chantal Marotte for keeping me on track, making sure all my paperwork was completed and all my deadlines were met, and above all, for being the champion every graduate student hopes to have.

For funding, I gratefully acknowledge the Natural Science and Engineering Research Council (NSERC), le Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT), and McGill University for postgraduate scholarships. In addition, I must acknowledge McGill University for an Alma Mater travel grant and graduate research enhancement awards.

Azelie Arpin and Jeffrey Manthorpe lay the foundation for my projects by developing the first and second generation chiral auxiliaries. For that, I am sincerely grateful. I would also like to thank Jeff for preparing enough DBB to last my entire Ph. D.

For their help in proofreading this manuscript, I would like to thank Joshua Fischer, Jonathan Hudon, Patricia MacLeod, and Janice Lawandi. In addition, I am grateful to Christian Drouin for the French translation of my abstract.

I am especially lucky to have had fantastic lab mates, past and present, who are a constant source of support, encouragement, advice, and camaraderie. My thanks to James, Tim, David, Chris, Azelie, Tan, Jonathan, Neenah, Lise, Joe, Jean-Manuel, Mallory, Marc, Stephan, Rodrigo, Boran, Daniel, Bin, Shuo, Josh, Laurie, Jeff, Marx, Rebecca, Dainis, Anne-Sophie, and Camille. I am especially grateful to David, Chris, Daniel, and Rodrigo not only for all the fun and entertainment, but for teaching me many, many important and serious things, and for being my rocks.

I am fortunate to have had plenty of love, laughter, and good times along this journey, thanks to some truly wonderful people I met along the way. The chem ladies, Rae, Carla, Patricia, Janice, Vishya, Eva, and Chantal, thank you for being my first line of support. *Les filles*, Letitia, Debra, Hannah, Laura, and Caro, thank you for all the (emergency) TKTs.

Finally, I would like to thank my family. My sisters, Jessica and Lee Ngo, and my brother, Aaron, thank you all for being my inspiration and for bringing out the best in me. My mom and dad, thank you for your unconditional love and unwavering support. None of this would have been possible without you. To you both, I dedicate this thesis.

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ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
aq.	aqueous
BINOL	1,1'-bi-2,2'-naphthol
Bn	benzyl
BOC	*tert*-butoxycarbonyl
BOX	bisoxazoline
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cy	cyclohexyl
d	doublet
DBB	4,4'-di-*tert*butylbiphenylide
DCM	dichloromethane
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*–dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
Dpp	diphenylphosphinoyl
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalents
er	enantiomeric ratio
Et	ethyl
Et_2O	diethyl ether

EtOAc	ethyl acetate
EWG	electron-withdrawing group
g	gram(s)
gen	generation
h	hour(s)
HBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
J	coupling constant
L	litre
LA	Lewis acid
LDA	lithium diisopropylamide
LICA	lithium cyclohexylisopropylamide
m	multiplet
M	moles per litre
m	*meta*
m/z	mass to charge ratio
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
min	minute(s)
mL	millilitre
mmol	millimole
mol	mole
MOM	methoxymethyl
MS	mass spectrometry
Ms	mesyl, methanesulfonyl

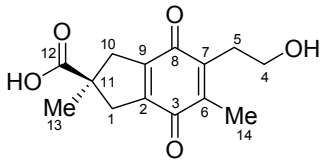
MW	molecular weight
N.D.	not determined
N.R.	no reaction
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance spectroscopy
PG	protecting group
pH	-log[H^+]
Ph	phenyl
PMP	*Para*-methoxyphenyl
Pr	propyl
RCM	ring closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
rt	room temperature
s	singlet
SALEN	*N,N′*-Ethylenebis(salicylimine)
SM	starting material
SMP	2-methoxymethylpyrrolidine
t	tertiary
t	triplet
TADDOL	(−)-2,3-*O*-Isopropylidene-1,1,4,4-tetraphenyl-L-threitol
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
tert	tertiary
Tf	triflyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhyride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TS	transition state

Ts	tosyl, *para*-toluene sulfonyl
Δ	heat

NOMENCLATURE

In discussion of enolates, the notations (*E*)-enolate and (*Z*)-enolate are used synonymously with *E*(*O*)-enolate and *Z*(*O*)-enolate. In this designation, the carbonyl oxygen is given higher priority regardless of the other substituent.

The numbering system for puraquinonic acid (**3**) is used as shown below. This numbering system was established by Becker *et. al.*[1] in their report documenting the isolation of puraquinonic acid.



3

[1] Becker, U.; Erkel, G.; Anke, T.; Sterner, O. *Nat. Prod.Lett.* **1997**, *9*, 229.

CHAPTER 1. INTRODUCTION

1.1 THE DEVELOPMENT OF A BICYCLIC THIOGLYCOLATE LACTAM CHIRAL AUXILIARY FOR THE ASYMMETRIC FORMATION OF QUATERNARY CARBON CENTERS VIA ENOLATE ADDITION

1.1.1 Importance of Quaternary Centers in Biologically Active Compounds

All carbon quaternary centers are present in a number of biologically relevant molecules, such as such Hamigeran B,[1] a highly potent antiviral, indacrinone,[2] a uricosuric drug, and puraquinonic acid,[3] an anti-leukemia compound (Figure 1.1). These compounds are attractive targets as the presence of quaternary centers confers additional stability and immunity to racemization.[4]

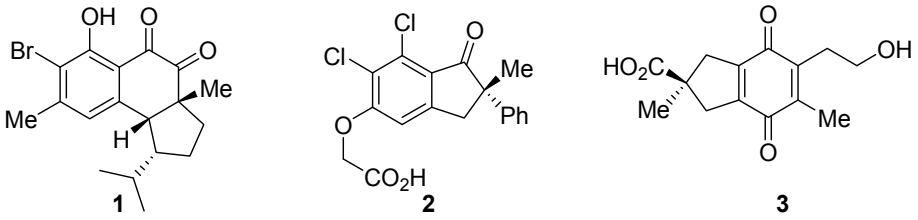
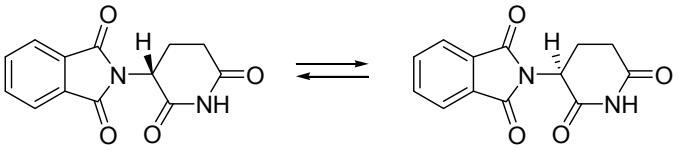


Figure 1.1 Natural products containing all carbon quaternary centers.

The importance of chiral quaternary centers is best exemplified by the infamous example of thalidomide where the (*R*)-enantiomer, **4**, alleviated morning sickness, while the (*S*)-enantiomer, **5**, caused birth deformities.[5] As the tertiary carbon center in thalidomide racemized readily (Scheme 1.1), use of the enantiopure drug would still result in unwanted side effects.[6] Although thalidomide was pulled from the market in 1961, there has recently been resurgent interest in thalidomide as a drug candidate due to its selective inhibition of tumour

necrosis factor-α.[7] To prevent the undesired racemization, one of the strategies employed was to alkylate the chiral center to form a quaternary center.[8]



4 **5**

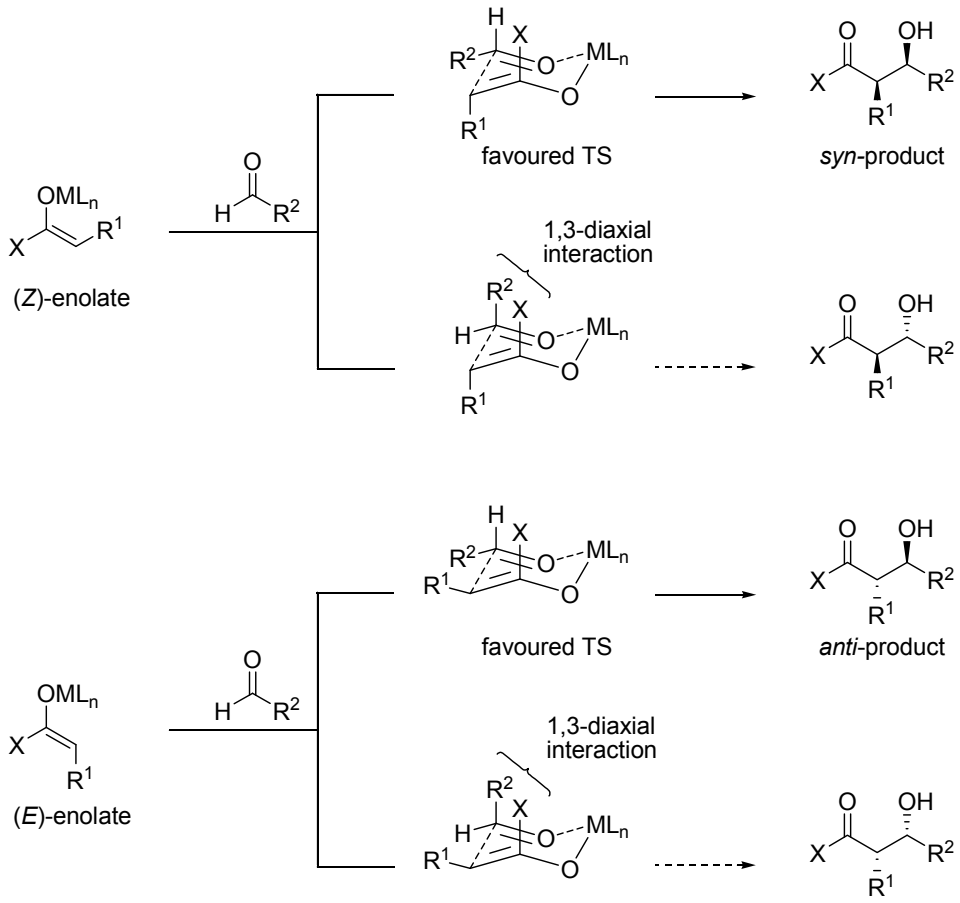
Scheme 1.1 Racemization of thalidomide.

1.1.2 Enolate Requirements in the Stereoselective Reactions

The formation of all carbon quaternary centers, especially in a stereoselective fashion, is a particularly challenging problem in synthetic organic chemistry. As a quaternary carbon center would have four bonds to carbons, any route to access it would therefore involve the construction of a C-C bond about a sterically crowded space.[9] Although there are a plethora of methods by which to form C-C bonds, the use of enolate chemistry is particularly attractive. Enolates can be formed from a large number of carbonyl compounds including esters, amides, ketones, thioesters, imides, and aldehydes. Additionally, enolate chemistry can be carried out with a large variety of electrophiles, such as alkyl halides, aldehydes (aldol reaction), and imines (Mannich reaction), thus generating a large array of structural motifs by C-C bond formation.

The stereochemical outcome in enolate reactions is often dependent on enolate geometry. This is best illustrated by the aldol reaction, where (*E*) and (*Z*)-enolates can add to aldehydes via a common Zimmerman-Traxler transition state

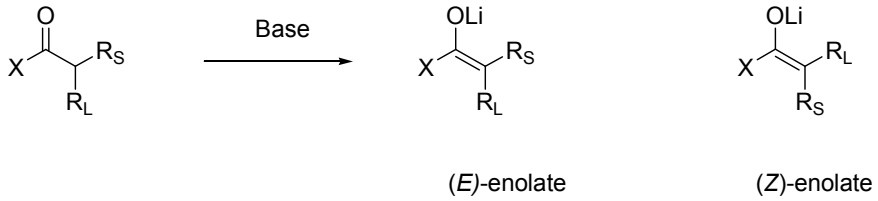
to produce diastereomeric products ((*E*)-enolates form *anti*-products, while (*Z*)-enolates form *syn* products) (Scheme 1.2).[10] In the preferred transition state, the 1,3-diaxial interactions are minimized.



Scheme 1.2 Zimmerman-Traxler transition state for aldol reactions.

However, it is important to note that there are two possible *syn* or *anti* enantiomers that can be formed. To control absolute stereochemistry, it is important to differentiate between the prochiral *(si* or *re*) faces of the enolate. This is usually achieved by incorporation of a stereodirecting element on one of the reactants (chiral auxiliary) or as a reagent (chiral catalyst), to block one face of the enolate towards electrophilic approach and thus promote the selective formation of one enantiomer.

In general, for asymmetric synthesis using enolate chemistry, both enolate geometry and facial selectivity must be simultaneously controlled. In the formation of tertiary carbon centers, good selectivity in enolate formation can often be obtained by taking advantage of the difference in size of the α-substituents (R_L=alkyl, R_S=H) (Scheme 1.3). However, this is not a practical solution in the formation of quaternary carbon centers where the α-substituents are much closer in size (R_L=alkyl, R_S=alkyl). The use of chiral auxiliaries as the stereodirecting element therefore becomes very important in this case, as the auxiliary can often help in enolate stereocontrol (*vide infra*).



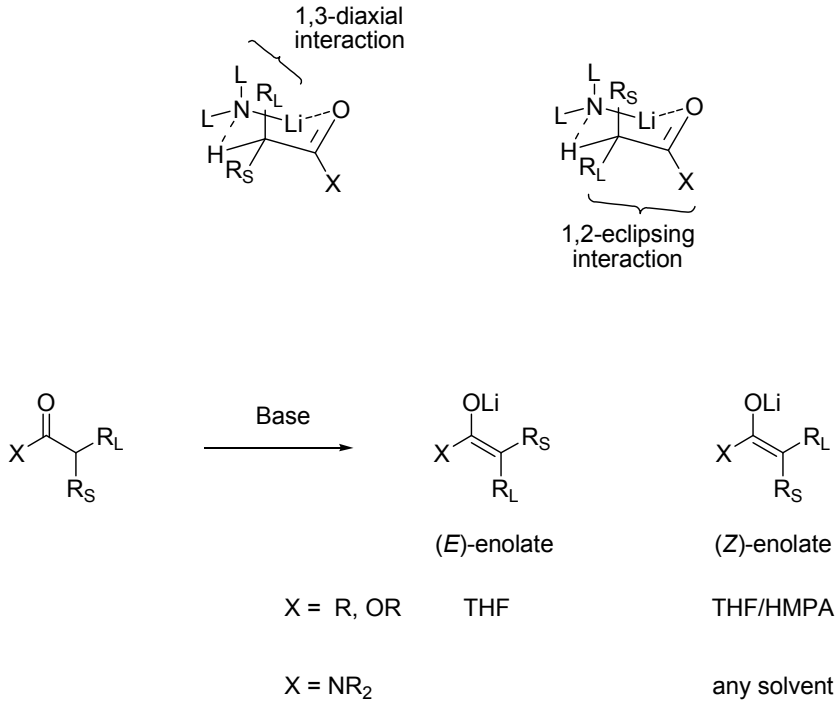
Scheme 1.3 Formation of (*E*)- and (*Z*)-enolates.

1.1.3 Methods for Enolate Stereocontrol

1.1.3.1 Ireland Model

Control of *E*/*Z* enolate formation in acyclic systems can be rationalized with the use of the Ireland model,[11] where deprotonation of a carbonyl compound using an amide base is depicted in a chair-like transition state (Scheme 1.4). (*E*)- versus (*Z*)-enolate formation is then governed by the minimization of either the 1,3-diaxial interaction between the α-substituent on the enolate and the amide base or the 1,2-eclipsing interaction between the α-substituent and the X group as

shown in Scheme 1.4. For ketones and esters (X=R or OR), reaction in tetrahydrofuran (THF) leads to predominant formation of the (*E*)-enolate to minimize 1,3-diaxial interactions across the 6-membered ring. However, addition of a polar co-solvent such as hexamethylphosphoramide (HMPA) results in the loosening of the transition state, thus 1,2-eclipsing interactions becomes important and the (Z)-enolate forms preferentially. For amides ($X=NR_2$), 1,3-interactions between the α-substituents and *N*-substituents results in the formation of (Z)-enolate regardless of solvent choice (Figure 1.2).



Scheme 1.4 Ireland model for enolate formation.

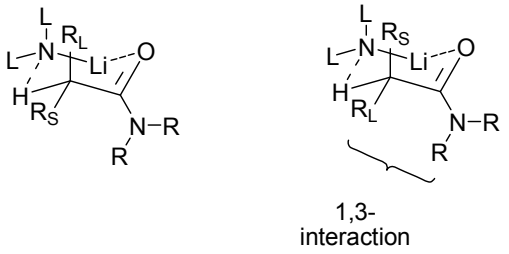
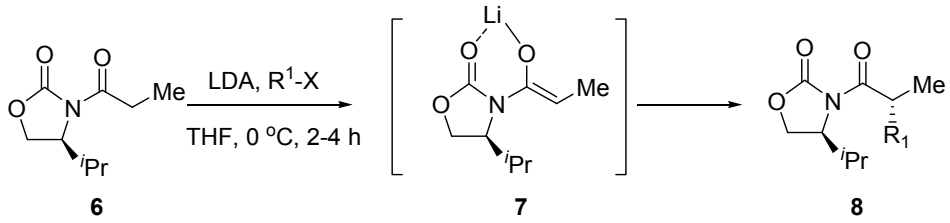


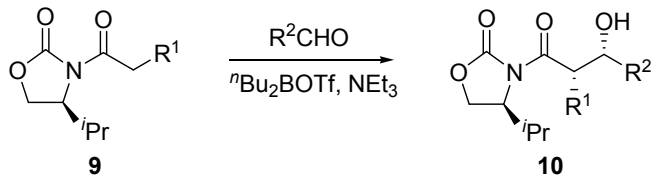
Figure 1.2 Deprotonation of amides.

Deprotonation based on the Ireland model has been used successfully in the formation of tertiary carbon centers. For example, use of Evans' chiral oxazolidinones[12] resulted in deprotonation to form the (*Z*)-enolate selectively (Scheme 1.5). The electrophile approached from the back face to avoid interactions with the substituent on the oxazolidinone ring, resulting in good diastereoselectivity in alkylation reactions.



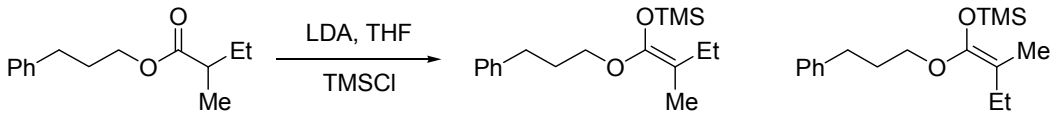
Scheme 1.5 Evans' auxiliary in enolate alkylation.

The same auxiliary was also successfully used in aldol reactions using (*Z*)-boron enolates (Scheme 1.6).[13] The reaction proceeded via a Zimmerman-Traxler transition state to give the *syn*-product with a high level selectivity as the short B-O bond length resulted in a tight transition state.



Scheme 1.6 Evans' auxiliary in aldol reactions.

As predicted by the Ireland model, the formation of disubstituted enolates is more challenging. As both substituents at the α-position are alkyl groups, both 1,3-diaxial and 1,2-eclipsing interactions compete, resulting in decreased *E*/*Z* selectivity. For example, deprotonation of α,α-disubstituted ester **11** and trapping of the resultant enolate using trimethylsilane, showed that the enolate formation occurred with extremely low selectivity with only ~2:1 preference for the (*Z*)-isomer observed (Scheme 1.7).[14]



11 (*Z*)-isomer (*E*)-isomer

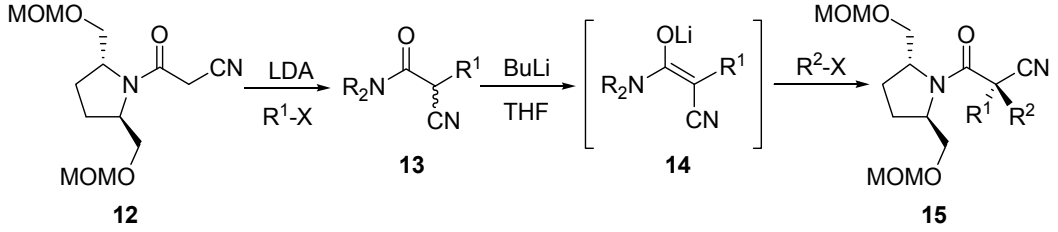
67:33

Scheme 1.7 Low *E*/*Z* selectivity in enolate formation for α,α-disubstituted esters.

Furthermore, in the deprotonation of amides, the increased steric crowding about the α-proton and increased 1,2-eclipsing interaction often lead to difficulties in deprotonation. This can result in no deprotonation using amide bases (LDA)[15,16] or the use of much harsher conditions (*s*-BuLi).[17]

One solution for controlling the geometry of α,α-disubstituted enolates is to use sterically diminutive alkyl groups[18,19] to enable differentiation of the α-substituents based on size. An example of this approach was reported by Yamaguchi, where a small nitrile group was incorporated as an α-substituent (Scheme 1.8).[16,20] The decreased interaction between the nitrile group and the pyrolidine ring allowed for the formation of enolate **14**. The C_2-symmetry of the auxiliary directed electrophilic approach from the back face despite any rotation

about the C-N bond. Although the reaction proceeded with excellent yields and stereoselectivities, the lengthy synthesis of the auxiliary limited its applicability.

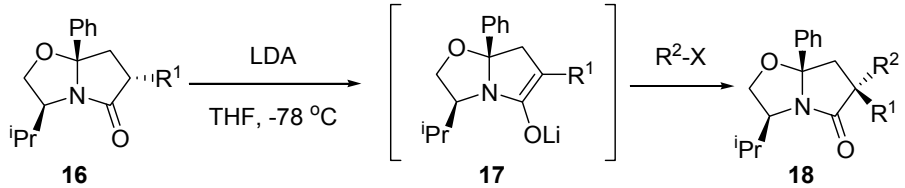


12 13 14 15

Scheme 1.8 Use of Yamaguchi's C_2-symmetric pyrolidine auxiliary.

1.1.3.2 Cyclic Enolates

In general, other models are employed to control enolate geometry to avoid the difficulty in differentiating between two similar α-substituents by size. One method that has found practical application is the formation of endocyclic enolates, where enolate geometry is governed by incorporation within a ring. [21] This strategy was successfully employed by Meyers using a bicyclic lactam chiral auxiliary (Scheme 1.9).[22] Formation of enolate **17**, followed by alkylation from the *endo* face of the bicyclic system, resulted in the formation of quaternary centers with excellent diastereoselectivity. However, upon cleavage of the auxiliary, residual functionality is left at the γ-position.

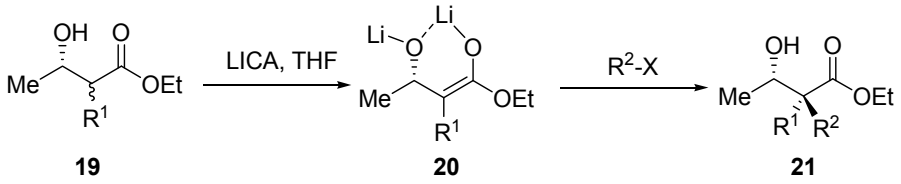


16 17 18

Scheme 1.9 Use of Meyer's bicyclic lactam chiral auxiliary.

1.1.3.3 Chelation Control

An alternate method for stereoselective enolate formation is by chelation control. Here, the presence of another Lewis basic site on the substrate allows for bidentate coordination to the metal cation, forming a temporary ring to control enolate geometry. This is exemplified by Frater's use of β-hydroxy esters in the formation of quaternary carbon centers (Scheme 1.10).[23] The β-hydroxy stereocenter was installed by reduction of the corresponding ketone using Baker's yeast. Chelation of the lithium cation to the carbonyl and hydroxide oxygen atoms led to the selective formation of enolate **20**. Electrophilic approach from the opposite face of the hydroxy group gave α,α-disubstituted β-hydroxy carbonyl compounds **21** upon alkylation.



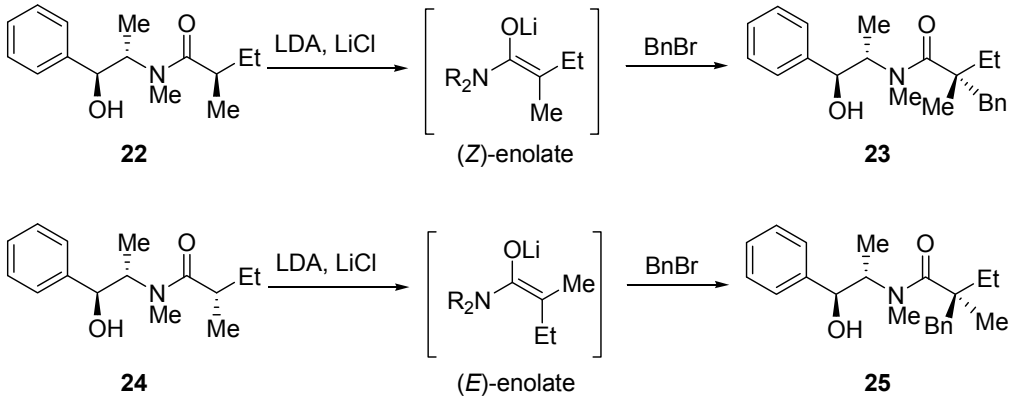
19 **20** **21**

Scheme 1.10 Chelation control in the alkylation of β-hydroxy esters.

1.1.3.4 Stereospecific Deprotonation

A method that does not rely on the presence of cyclic systems, temporary or otherwise, is stereospecific deprotonation based on a pre-existing stereocenter. Myers recently developed an approach using pseudoephedrine, which was previously shown to be a practical auxiliary for the formation of tertiary carbon centers.[24] Deprotonation of the diastereomeric α,α-disubstituted amides **22** and

24, which were formed by stereoselective alkylation of the monosubstituted enolate, gave the (*Z*)- and (*E*)-enolate respectively (Scheme 1.11). [25] In the pre-transition state assembly, the base approaches from the opposite face of the alkoxide with the α-H aligned at approximately 90° to the carbonyl plan. Alkylation of the (*Z*)-enolate proceeded with a high level of stereoselectivity, but decreased for the (*E*)-enolate.



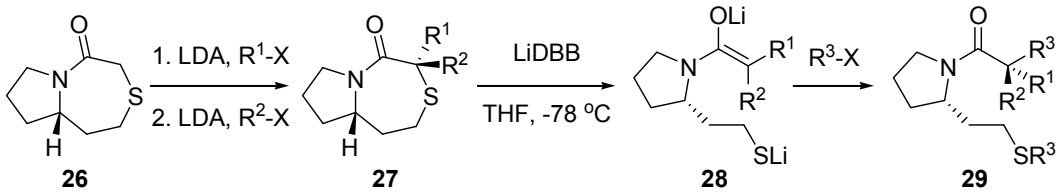
Scheme 1.11 Use of pseudoephedrine as a chiral auxiliary.

1.1.4 Development of a General Method for the Stereoselective Formation of Quaternary Carbon Centers

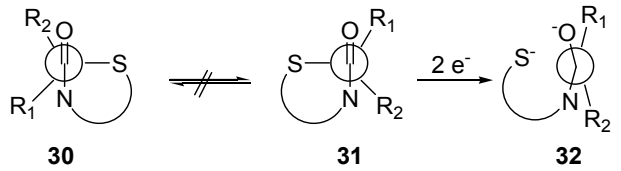
Although there are a number of documented solutions for the stereoselective formation of disubstituted enolates, most of these methods suffer from one or more shortcomings. In particular, they result in the formation of residue functionality, do not allow access to both enolate isomers, or do not show the same level of selectivity for both (*E*)- and (*Z*)- enolates. Consequently, there is a need for the development of a general method that addresses all of these issues.

The bicyclic thioglycolate lactam chiral auxiliaries developed in our lab sought to fill this position. The first generation chiral auxiliary (**26**) featured a 5,7-bicyclic thioglycolate lactam synthesized from L-proline (Scheme 1.12).[26] Successive alkylations installed R^1 and R^2 at the α-position with good yields and diastereoselectivity with the electrophile approaching from the *exo* face of the bicycle.

Formation of enolate proceeded with good E/Z selectivity via two-electron reduction of the C-S bond using lithium 4,4'-di-*tert*butylbiphenylide (LiDBB). In our working model, the α-substituents are constrained to one face of the carbonyl plane by the rigid bicycle, while the O-C-C-S dihedral angle is as close as possible to 90° (Scheme 1.13). Via the least motion principle, the relative positions of R^1 and R^2 are maintained during enolate formation so that E/Z selectivity depends solely on the initial order of alkylation. Significantly, the size of R^1 and R^2 does not affect the enolate formation, with the differentiation between propyl and allyl possible.

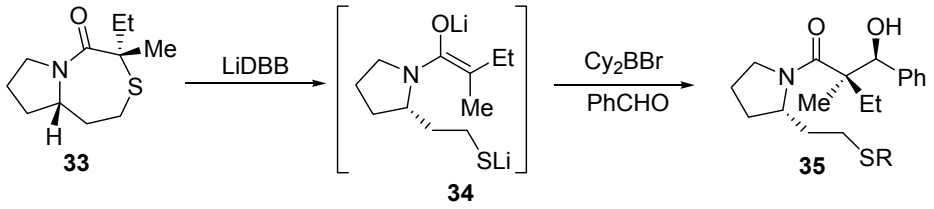


Scheme 1.12 Alkylation of first generation bicyclic thioglycolate lactam auxiliary.



Scheme 1.13 Reductive enolization of the first generation auxiliary.

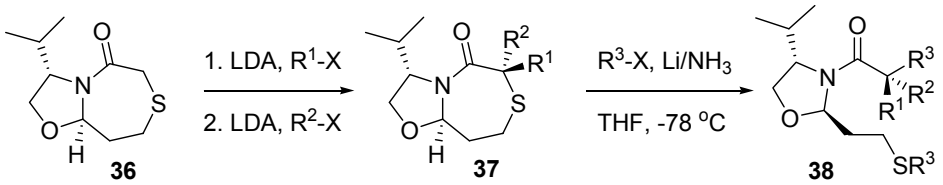
The enolate could then be used in alkylations[27] to form α-quaternary carbon centers with good yields and diastereoselectivity (Scheme 1.12). Removal of the auxiliary via reduction with lithium amido borohydride gave the corresponding alcohol. This method of enolate generation was also amendable to the aldol reaction.[28] Transmetallation of the (*Z*)-enolates to form boron enolates, followed by addition to aromatic and α,β-unsaturated aldehydes gave the *syn*-product with good selectivity (Scheme 1.14).



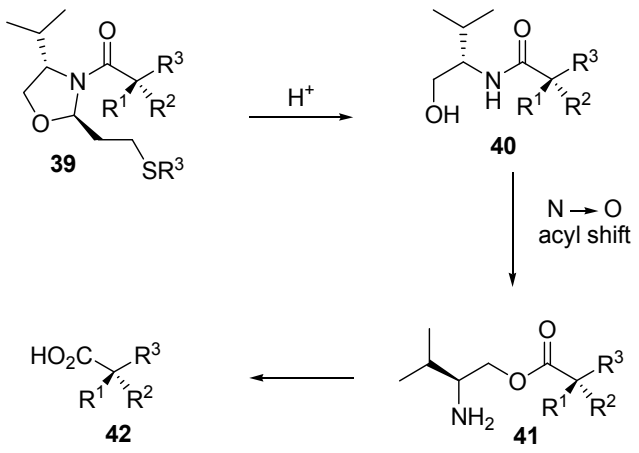
Scheme 1.14 Use of the first generation chiral auxiliary in the aldol reaction.

While this first generation auxiliary represented a general method for the formation of quaternary carbon centers via enolate chemistry, it suffered from a number of practical limitations. Specifically, (i) its synthesis was quite lengthy, (ii) the alkylation of (*E*)-enolates proceeded with poor selectivity; although, in practice, the opposite enantiomer could be accessed by inverting the order of the alkylations, and (iii) the auxiliary could not be removed via simple hydrolysis. A second generation auxiliary was therefore developed to address these issues.

The second generation bicyclic thioglycolate lactam **36** was developed using L-valine as the chiral source and could be used in the formation of α-quaternary carbon centers with excellent yield and selectivity (Scheme 1.15).[29] The synthesis of **36** was completed in three steps from commercially available materials and once again featured a 5,7-bicycle, which controlled the facial approach of the first two alkylations. Similar to the first generation auxiliary, reductive enolization of the C-S bond resulted in selective E/Z enolate formation. However, in this case, a pseudo C_2-symmetric auxiliary was liberated. This was key in the highly selective alkylation of both (*E*)- and (*Z*)-enolates, as electrophilic approach was directed from the same face despite any rotation about the C-N bond. Finally, due to the use of an oxazolidine ring as opposed to a pyrrolidine ring, the auxiliary could be hydrolyzed directly to the corresponding carboxylic acid (Scheme 1.16). Under acidic conditions, the aminal was hydrolyzed and the liberated alcohol underwent N to O acyl transfer. The resultant ester was then easily hydrolyzed to the acid.



Scheme 1.15 Alkylation of second generation chiral auxiliary.



Scheme 1.16 Acidic hydrolysis of second generation auxliary.

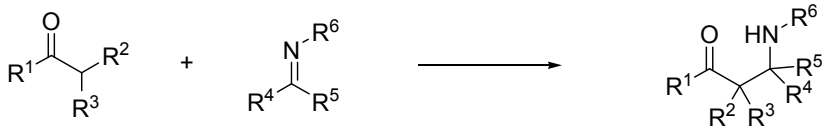
The use of this second generation bicyclic lactam chiral auxiliary represented a general method for the asymmetric formation of quaternary carbon centers via enolate alkylation. Both (*E*)- and (Z)-enolates could be accessed and alkylated with excellent selectivity. In addition, no residual stereodirecting functionality was left behind.

To illustrate the applicability of the second generation bicyclic lactam auxiliary in the formation of quaternary carbon centers via other enolate reactions, it was employed in the additions to imines (Mannich reaction) to form α,α-disubstituted β-amino carbonyl compounds (Chapter 2). The utility of the chiral auxiliary in the total synthesis of natural products was also examined in the synthesis of (-)-puraquinonic acid (Chapter 3).

1.2 STEREOSELECTIVE FORMATION OF α-QUATERNARY STEREOCENTERS VIA THE MANNICH REACTION

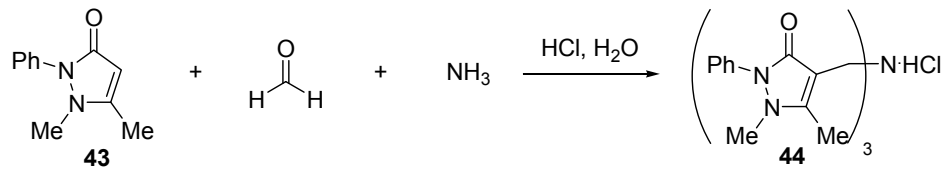
1.2.1 The Mannich Reaction

The Mannich reaction[30] between an enolate (typically of an aldehyde, ketone, or ester) and an imine is a highly convenient and convergent method of accessing β-amino carbonyl compounds (Scheme 1.17). These Mannich adducts are important in the formation of β-amino alcohols and β-amino acid derivatives such as β-lactams and β-peptides. [31] As such, this highly versatile reaction has seen much use in synthetic and medicinal chemistry.

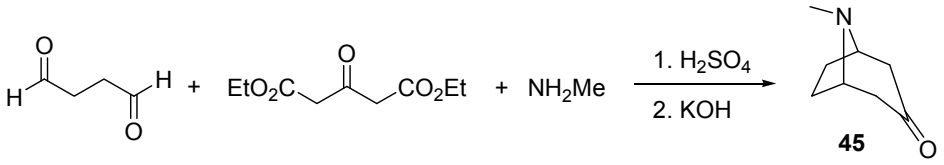


Scheme 1.17 The Mannich reaction.

The origins of the Mannich reaction can be traced back to 1912, when Mannich formed tertiary amine **44** in the reaction between **43**, formaldehyde, and ammonia (Scheme 1.18).[32] As a reflection of its importance in natural product synthesis, the Mannich reaction was used shortly thereafter in Robinson's classical synthesis of tropinone (Scheme 1.19).[33] In this expedient synthesis, succinaldehyde, ethyl acetonedicarboxylate, and methylamine were condensed in one pot to form tropinone (**45**).

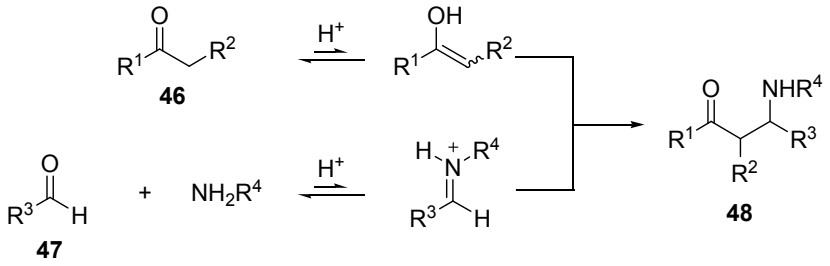


Scheme 1.18 The first Mannich reaction.



Scheme 1.19 Robinson's synthesis of tropinone.

A general mechanism for the Mannich reaction is depicted in Scheme 1.20. The acidic conditions promote the enolization of **46** and the iminium formation of the amine with a non-enolizable carbonyl compound (**47**). The resultant enol adds to the iminium species to form β-amino carbonyl **48**.



Scheme 1.20 Mechanism of the Mannich reaction.

This three component Mannich reaction suffered from a number of limitations.[30b] Specifically, long reaction times and harsh conditions were often required. In addition, carboxylic acid derivatives such as esters and amides were unreactive, therefore only aldehydes and ketones could be used as the nucleophile, with use of ketones resulting in regioselectivity issues. The use of primary amines or ammonia often resulted in the formation of multiple products, as the Mannich adducts formed could undergo further condensation reactions to form reactive iminium species. Therefore, for selective formation of one product, secondary amines were often used. To overcome these limitations, subsequent development of the Mannich reaction therefore focused on the use of preformed

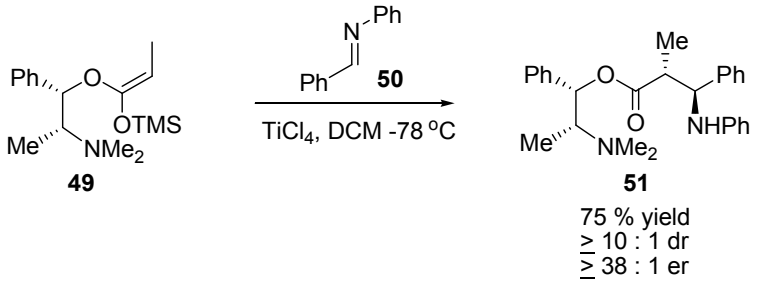
nucleophiles (enolates, enol ethers, enamines) and electrophiles (imines or iminium salts). This led to more facile reactions with lower reaction times and temperatures due to the higher concentration of reactive species. Protic solvents were not required with the use of preformed components, and thus more nucleophilic species, such as enolates, could be used. In addition, the use of chiral stereodirecting elements could be easily incorporated thus allowing the stereoselective synthesis of Mannich adducts.

1.2.2 Asymmetric Synthesis α-Monosubstituted β-Amino Carbonyl Compounds via the Mannich Reaction.

The stereoselective formation of β-amino carbonyl compounds that are either unsubstituted or contain a single alkyl group at the α-position is well documented. Similar to the aldol reaction discussed in Section 1.1.2, the Mannich reaction often proceed through a highly ordered Zimmerman-Traxler type transition state. Thus, control over enolate geometry often results in good diastereoselectivity in a stereospecific fashion. Mannich reactions can also proceed via open transition states, where the *syn*/*anti* selectivity is not dependent on enolate geometry, but on other factors such as the size of the α-substituent or Lewis acid.[34] In addition to the diastereoselectivity, enantioselectivity must be controlled as well. This can be achieved by the use of chiral auxiliaries, chiral Brønsted or Lewis acid activation of the imine, or organocatalytic activation of the nucleophile.

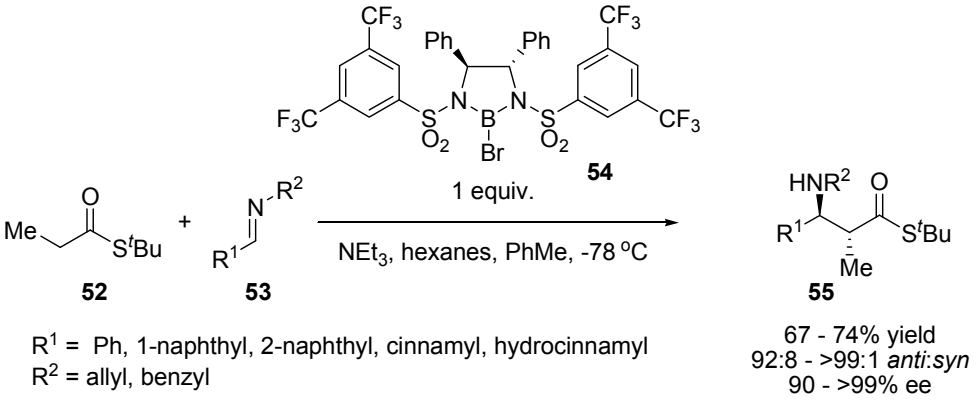
1.2.2.1 Use of Chiral Auxiliaries

Use of chiral auxiliaries[35] on either the enolate or imine species can allow excellent stereocontrol of the Mannich addition. One of the earliest examples of chiral auxiliary controlled Mannich reaction employed readily available ephedrine as the chiral source (Scheme 1.21).[36] Titanium promoted addition of ketene silyl acetal **49** to *N*-phenylbenzaldimine **50** gave β-amino ester **51** in 75% yield with good diastereo- and enantioselectivity for the *anti*-product. The auxiliary could be removed using LiHMDS to form the β-lactam in 79% yield without loss of optical purity.



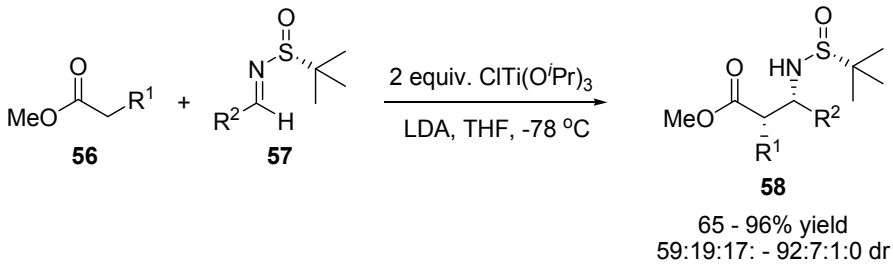
Scheme 1.21 Use of ephedrine based chiral auxiliary.

The *in situ* formation of a chiral auxiliary using a chiral boron complex was demonstrated by Corey in 1991 (Scheme 1.22).[37] *S*-*tert*-Butyl thiopropionate added to *N*-allyl or *N*-benzyl imine with good yields and excellent diastereo- and enantioselectivity. The (*E*)-boron enolate formed added to the imine component via a 6-membered ring transition state, with boron coordinating to both the enolate and imine components, to give the *anti*-product. Treatment of the resultant β-amino ester with *tert*-butyl magnesium chloride formed the corresponding β-lactam.



Scheme 1.22 Asymmetric induction using chiral borolidine.

In an example of a chiral auxiliary on the imine component, Ellman demonstrated the addition of titanium enolates to chiral sulfinyl aldimines and ketimines. Condensation of enantiomerically pure *tert*-butanesulfinamide, which can be obtained on large scale (*ca.* 1 mol),[38] with aldehydes or ketones formed chiral *tert*-butanesulfinyl imines. The *N*-sulfinyl group activated the imine and directed nucleophilic approach of the enolate to give β-amino ester compounds with good *syn*-selectivity (Scheme 1.23).[39] The auxiliary was easily removed under acidic conditions without epimerization. Chiral arylsulfinyl imines have also been used in asymmetric Mannich reactions.[40]

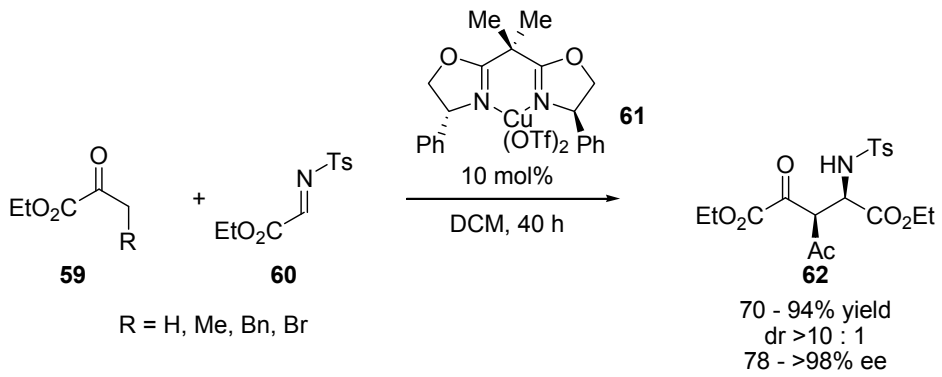


Scheme 1.23 Use of chiral sulfinyl imines.

1.2.2.2 Chiral Lewis Acid Catalysis

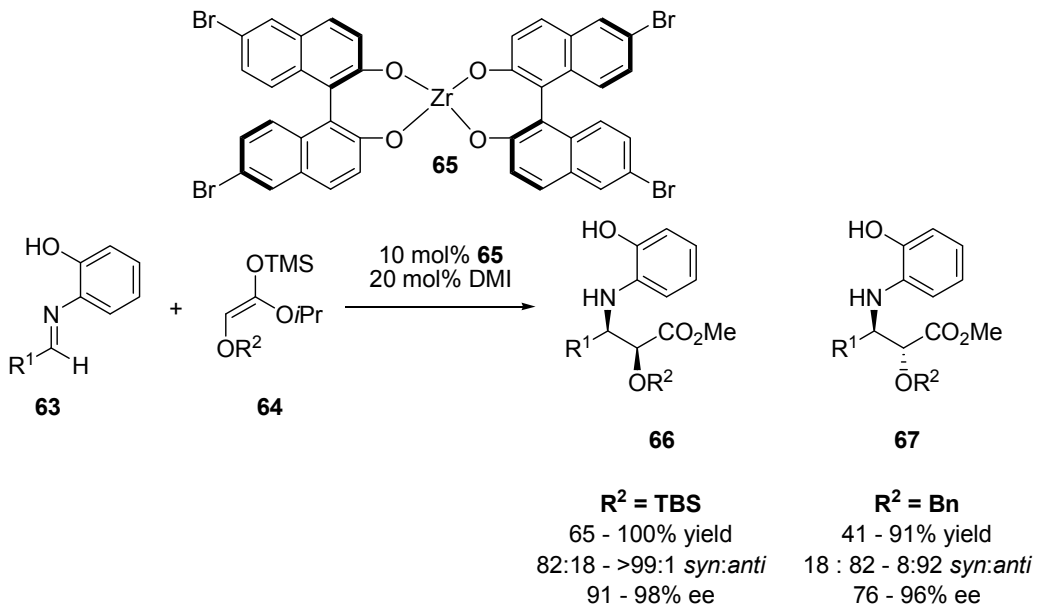
Chiral Lewis acid[41] catalyzed Mannich reactions have emerged as a practical way to generate β-amino carbonyl compounds. The advantage of this mode of activation is that substoichiometric quantities of chiral material is required and can often be recovered and reused. Conversely, the challenge here is the development of Lewis acids that will activate the imine without being deactivated by the Lewis basic Mannich adducts. Deactivation of the Lewis acid would ultimately result in undesirably high catalyst loadings. Lewis acids can also activate the carbonyl component towards *in situ* enol formation, thus removing the need for pre-activation.

Jørgensen demonstrated the use of Ph-BOX-Cu(OTf)$_2$ **61**, as a chiral Lewis acid catalyst in the reaction between pyruvate **59** and *N*-tosyl-α-imino ester **60**.[42] The pyruvates are activated carbonyl species, which readily enolized *in situ* to form the (*E*)-enol ether. The reaction, which was proposed to proceed through a 6-membered transition state with both enol and imine components coordinating to Cu (II) in a bidentate fashion, proceeded with good yields and *syn*-selectivity and high enantioselectivity. This substrate scope was later expanded to enable access to α,β-diamino esters.[43]



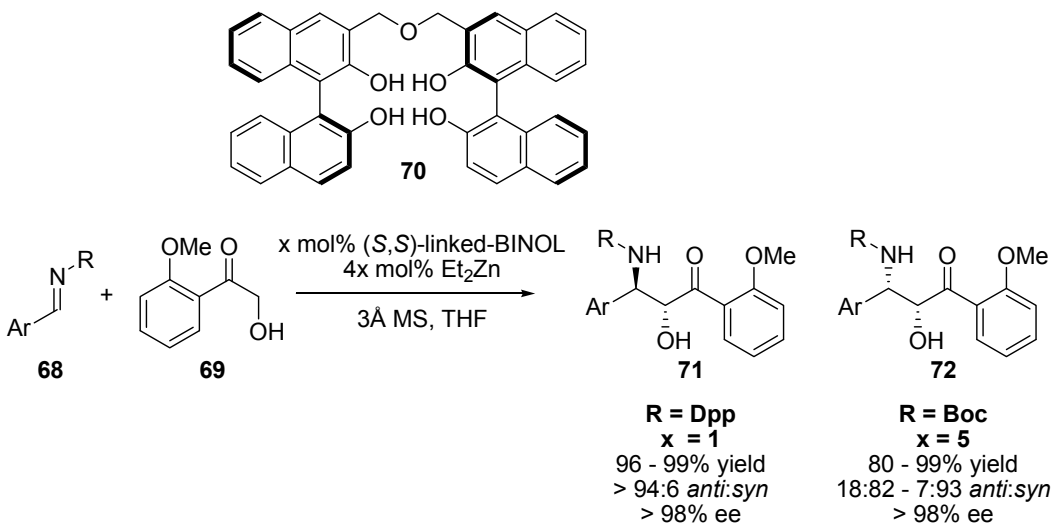
Scheme 1.24 Jørgensen's chiral copper complex.

Kobayashi employed chiral zirconium complex **65** in the reaction between α-alkoxy ketene silyl acetal **64** and aldimines **63** (Scheme 1.25).[44] Addition of 1,2-dimethylimidazole was required to break up oligomeric zirconium species into active monomeric species. Use of hydroxyphenol in aldimine **63** was crucial for selectivity (almost no chiral induction was observed with phenyl or methoxyphenyl). Although initially the chiral zirconium species was formed *in situ* using zirconium (IV) *tert*-butoxide and (*R*)-6,6'-dibromo-BINOL, it was later found that the catalyst was stable to air and moisture, and thus could be prepared and stored under air at room temperature for extended periods.[45] The reaction gave *syn*- or *anti*-products depending on the nature of the alkoxy group; α-silyloxy substitution gave the *syn*-isomer, while a benzyloxy group gave the *anti*-isomer. This selectivity is not dependent on the initial geometry of the ketene silyl acetal that is used and is consistent with an open transition state.



Scheme 1.25 Kobayashi's chiral zirconium catalyst.

Shibasaki developed an *anti*-selective catalytic asymmetric Mannich reaction between α-hydroxy ketones **69** and *N*-diphenylphosphinoyl (Dpp) imines **68** (R=Dpp) using a chiral zinc complex (Scheme 1.26).[46] Use of Dpp allowed for easy deprotection of the amino group by acidic hydrolysis. The reaction proceeded with excellent yields, diastereo- and enantioselectivity. Although initially limited to aromatic imines, the substrate scope was later expanded to include enolizable aliphatic imines.[47] Using the same catalytic system with *N*-Boc protected imines switched the diastereoselectivity of the reaction to favour the *syn*-isomer (Scheme 1.26).[48] The *syn*-Mannich adduct was observed with similar yield and enantioselectivity; however, the diastereoselectivity was slightly eroded. Importantly, this reaction proceeds with the use of unmodified ketones, with no preactivation of the carbonyl species. The catalyst acts as a base and a Lewis acid.



Scheme 1.26 Shibasaki's chiral zinc catalyst.

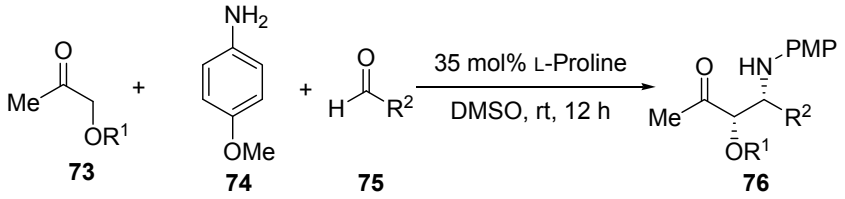
Trost reported the same selectivity pattern using a chiral dinuclear zinc catalyst in the reaction between α-hydroxy ketones and enolizable imines to give *anti*- or *syn*-amino alcohols depending on the *N*-protecting group used.[49,50] Once again, use of Dpp-protected imines gave *anti*-adducts, while use of Boc-protected imines gave *syn*-adducts.

1.2.2.3 Organocatalysis

The use of organocatalysts[51] allows for metal-free and often less stringent reaction conditions, as organocatalysts are generally air and water stable. One of the main appeals of organocatalysis is that it allows for three component reactions where the imine is formed *in situ* from an amine and an aldehyde.

The first example of an organocatalytic Mannich reaction was reported by List using L-proline as a catalyst in a three component, asymmetric reaction between propanone, *p*-anisidine, and an aldehyde.[52] Subsequently, he showed that

α-hydroxy ketones could be employed to form α-hydroxy β-amino ketones **76** (Scheme 1.27). [53] No prefunctionalization of the ketone was required, as use of proline as a catalyst resulted in the formation of a more nucleophilic enamine species. The reaction proceeded regioselectively, with good *syn*-selectivity and from moderate to good yields and enantioselectivities. Both aliphatic and aromatic aldehydes could be used to form amines with *p*-anisidine *in situ*.

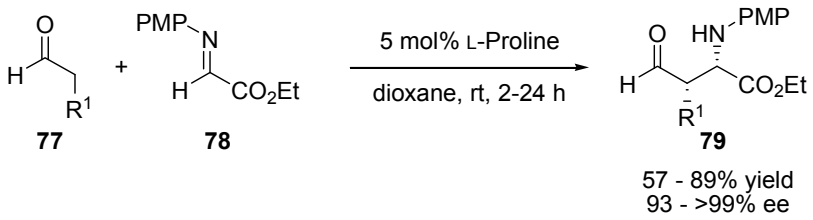


R^1 = H , R^2 = ^{i}Pr 57% yield, 17:1 dr, 65% ee
R^1 = Me, R^2 = *p*-NO_2Ph 93% yield, >20:1 dr, 98% ee

Scheme 1.27 Organocatalytic Mannich using L-proline.

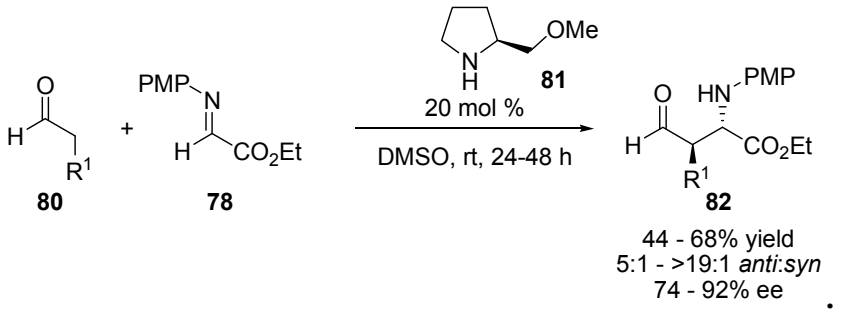
In 2002, the first use of unmodified aldehydes in asymmetric Mannich reactions was documented by Barbas (Scheme 1.28).[54] The reaction of aliphatic aldehydes with α-imino ester **78**, catalyzed by proline, proceeded with good yields and excellent enantioselectivities. Although the crude product showed good diastereoselectivity (in general >19:1 *syn*:*anti*), epimerization during purification resulted in a decrease of the diastereomeric ratio in the purified products. Diastereoselectivity also decreased when less sterically demanding substituents were used on the aldehyde (R^1 = Me or Et). Reduction of the aldehyde *in situ* to the corresponding alcohol using sodium borohydride could be used to overcome the epimerization problem.[55] The three-component variant using aldehydes was later published,[55,56,57] where aliphatic aldehydes were used as the nucleophilic component, while aromatic and heteroaromatic aldehydes or ethyl glyoxylate

made up the electrophilic component upon imine formation with *p*-anisidine. Homo-coupling reations with one aliphatic aldehyde playing both roles was also possible, although diastereo- and enantioselectivity were generally lower.



Scheme 1.28 Use of aldehydes in the Mannich reaction.

An *anti*-selective organocatalytic Mannich reaction between unmodified aliphatic aldehydes and α-imino ethyl glyoxylate catalyzed by 2-methoxymethylpyrrolidine (SMP) was reported by Barbas (Scheme 1.29).[58] The reaction gave moderate yields, but good diastereomeric and enantiomeric ratios, although the reaction products were again prone to racemization. Increase in diastereoselectivity was observed with increasing the bulk of the aldehyde substituent. The *anti*-selective Mannich was later improved upon by a number of different groups. Jørgensen implemented a chiral TMS protected α,α-diarylprolinol catalyst,[59] Maruoka a chiral amino sulfonamide catalyst prepared from L-tartaric acid,[60] and Barbas a 5-methyl-3-pyrrolidinecarboxylic acid designed in collaboration with Houk and Tanaka. [61]



Scheme 1.29 *Anti*-selective organocatalytic Mannich.

Many of the organocatalytic Mannich reactions yielded *N*-PMP protected β-amino carbonyl compounds, which required oxidative conditions for deprotection. There are some examples of the use of *N*-Boc protected imines,[62,63,64] which allow more practical N-deprotection. However these reactions are not as well documented as the imines must be preformed and only aromatic imines can be used.

Chiral phosphoric acids[65] are attractive Brønsted acids, which have been utilized in the activation of imines in a number of organic transformations including reductive amination, Friedel-Crafts additions, aza-Darzens, and Pictet-Spengler reactions.[66] The tetradentate phosphorus (V) allows incorporation of a cyclic structure to prevent rotation of the chiral groups (Figure 1.3).[67, 68]

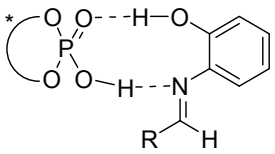
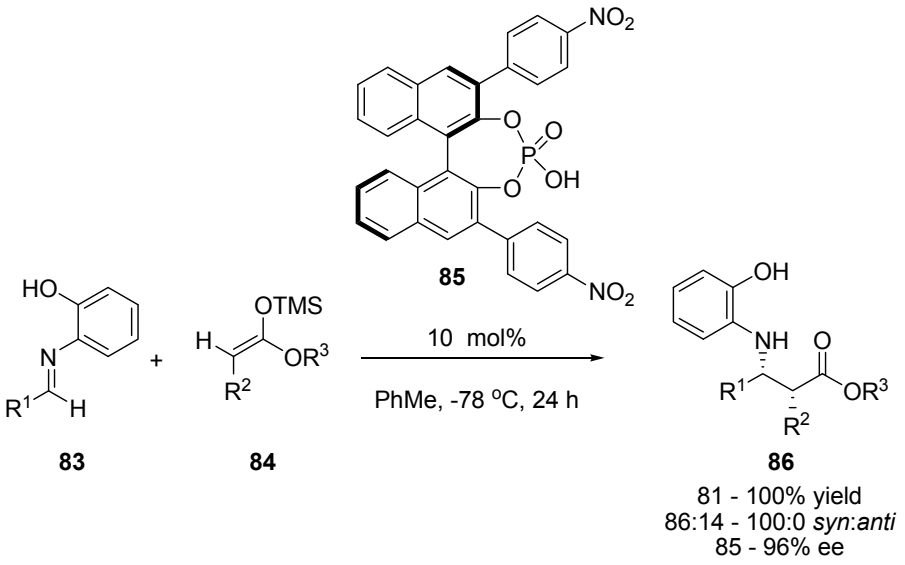


Figure 1.3 Phosphoric acid as bifunctional catalyst.

Cyclic phosphoric acid diester **85** constructed from (*R*)-BINOL proved to be an excellent Brønsted acid catalyst (Scheme 1.30).[68,69] The Mannich reaction between ketene silyl acetal **84** and aromatic, heteroaromatic, and cinnamyl

aldimines proceeded with good *syn*-selectivity and enantioselectivity. Additionally, this reaction tolerated α-silyloxy substitution. The 2-hydroxyphenyl protecting group was required on the imine, as the use of phenyl, 4-hydroxyphenyl, or 2-methoxyphenyl resulted in greatly diminished yields and enantioselectivities. TADDOL scaffolds synthesized from (+)-diethyl tartrate have also been used in chiral phosphoric acid catalysis.[70]

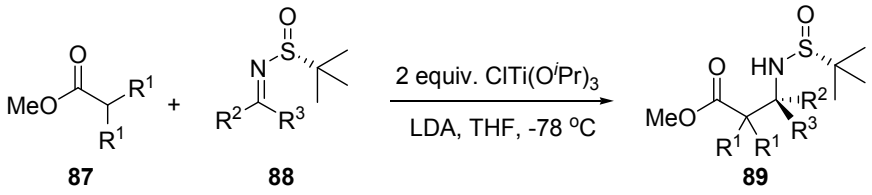


Scheme 1.30 Use of chiral phosphoric acid in Brønsted acid catalyzed Mannich.

1.2.3 Asymmetric Synthesis of α,α-Disubstituted β-Amino Carbonyl Compounds

In contrast to the numerous methods for the asymmetric synthesis of α-monosubstituted β-amino carbonyl compounds, there are only limited examples of the formation of β-amino carbonyl compounds bearing non-equivalent α,α-disubstitution. This can be traced to the difficulty in controlling enolate *E*/*Z*

stereochemistry, which often results in variable *syn*/*anti*-selectivity. Some of the stereoselective methods described above can be carried out on substrates with α,α-disubstitution,[71,72] but because of the difficulty in *E/Z* stereocontrol, equivalent substituents were used. For example, Ellman's addition of titanium enolates to chiral sulfinyl aldimines and ketimines, allows access to mono-, di-, tri-, and tetra-substituted β-amino esters.[39] Although excellent diastereoselectivities can be obtained for compounds with asymmetric β,β-disubstitution, only substrates with equivalent α-groups were reported (Scheme 1.31).



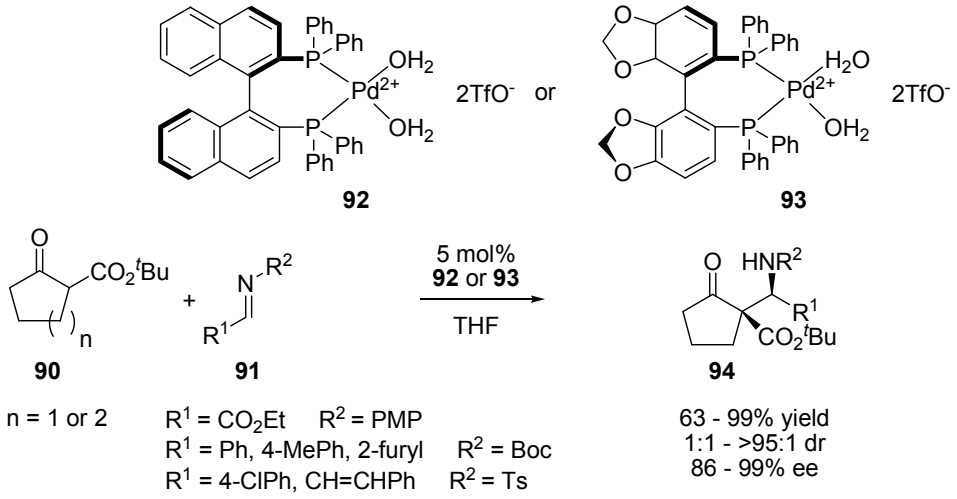
87 **88** **89**

Scheme 1.31 Use of chiral tert-butane sulfinyl imines.

1.2.3.1 Cyclic Enolates

As described in the alkylation chemistry in Section 1.1.3.2, one method to circumvent *E*/*Z* stereocontrol issues is by the use of cyclic enolates. In an example by Sodeoka, 5- and 6-membered cyclic β-keto esters were added to a number of different imines, including α-imino esters, and *N*-Boc and *N*-tosyl imines derived from simple aldehydes (Scheme 1.32).[73] Palladium complexes with either (*R*)-BINAP (**92**) or (*R*)-SEGPHOS (**93**) backbone were employed. In general, the reactions proceeded with good yields and enantioselectivities but the

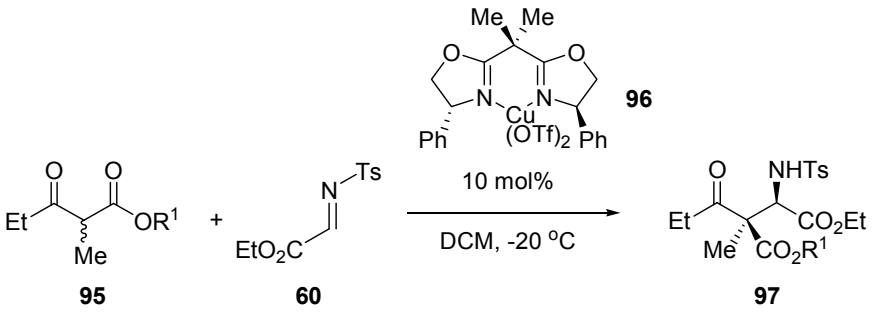
diastereoselectivities were variable. Cyclic enolates have also been used in organocatalytic systems to form α,α-disubstituted β-amino carbonyl compounds.[74,75]



Scheme 1.32 Use of cyclic enolates in asymmetric Mannich.

1.2.3.2 Chelation Control

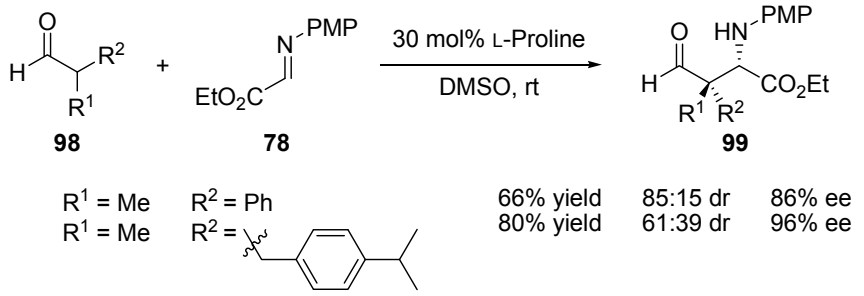
Chelation control has also been used in Mannich reactions to control *E*/*Z* enolate geometry with good results. Jørgensen showed that use of acyclic β-ketoesters allowed for temporary formation of a 6-membered ring via coordination of the two carbonyl groups to Cu (II), thus enabling control over enolate geometry.[76] The Mannich reaction with *N*-tosyl α-imino ester **60** proceeded with good yields and diastereoselectivities, but with moderate enantioselectivities (Scheme 1.33). The diastereo- and enantioselection typically increased with increasing steric bulk of the ester moiety.



Scheme 1.33 Use of acyclic β-ketoesters in the Mannich reaction.

1.2.3.3 Steric Difference in α-Substituents

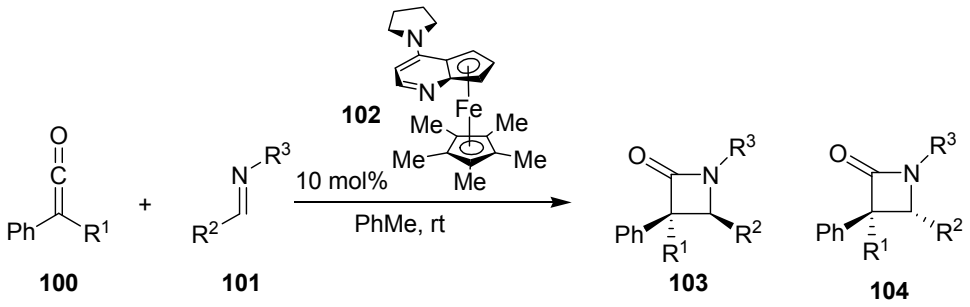
The use of cyclic enolates or chelating functionalities leaves residual structural features, which must be transformed; therefore, selective *E*/*Z* enolate formation without reliance on these features is highly desirable. Unfortunately, there have been limited successful applications of acyclic disubstituted enolates in the formation of Mannich adducts. In one example by Barbas, addition of α,α-disubstituted aldehyde **98** to *N*-PMP protected α-imino esters **78** catalyzed by L-proline proceeded with good yields, diastereo- and enantioselectivities (Scheme 1.34).[77] However in all of the examples shown, the α-substituents vary greatly in size (often methyl versus aromatic) to allow for *E*/*Z* selectivity in enolate formation. For instance, in the reaction using 2-phenylpropanal (**98**, R^1=Me, R^2=Ph), a diastereomeric ratio of 85:15 was obtained. However, when the phenyl group was substituted for a cymenyl group, the diastereomeric ratio dropped to 61:39.



Scheme 1.34 Proline catalyzed Mannich reaction of α,α-disubstituted aldehydes.

Fu developed a chiral catalyst based on 4-dimethylaminopyridine (DMAP) that could be used in a stereoselective Staudinger reaction between a ketene and an imine to form β-lactams (Scheme 1.35).[78,79] Interestingly, diastereoselectivity of the lactam formation could be controlled by the choice of imine protecting group. Use of *N*-triflyl (Tf) imines resulted in the selective formation of **104**, while *N*-tosyl (Ts) imines resulted in **103**. It was proposed that the reaction proceeded via two different pathways; with the use of *N*-triflyl imines, the catalytic cycle was initiated by the addition of the chiral DMAP to the imine component, while in the *N*-tosyl imine case, the catalyst first added to the ketene component. While the reaction proceeded with good yields and stereoselectivities, again there was a need for large steric differences in the α-substituents to enable good diastereoselectivity. In the ketene component, one of the substituents was always phenyl and the other one an alkyl group. For example, in the addition of isobutylphenylketene (**100**, R^1=^{i}Bu) to *N*-tosyl furaldimine (**101**, R^1=2-furyl R^3=Ts), β-lactam **103** (R^1=^{i}Bu, R^2=2-furyl, R^3=Ts) was selectively formed in a diastereomeric ratio of 11:1. However, despite the steric differences of the α-substituents in the ketene component, some variability in selectivity was

observed. In the addition of phenylmethylketene (**100**, R^1=Me) to *N*-tosyl furaldimine (**101**, R^2=furyl, R^3=Ts), a diastereomeric ratio of only to 2:1 was obtained.



Scheme 1.35 Chiral DMAP catalyst in the Staudinger reaction.

1.2.4 Stereoselective Formation of α-Quaternary Stereocenters via the Mannich Reaction

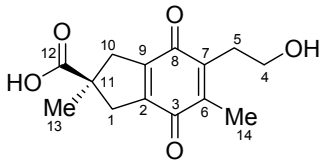
As there is a lack of a general method for the asymmetric synthesis of α,α-disubstituted β-amino carbonyl compounds, we were interested in constructing these compounds using our chiral bicyclic lactam **36** in the Mannich reaction. Our group has previously demonstrated the use of our bicyclic thioglycolate lactam chiral auxiliary in stereocontrolled enolate formation where both (*E*)- and (*Z*)-enolates may be obtained without reliance on steric differences between the two α-substituents (Section 1.1.4). In addition, the auxiliary efficiently blocked one face of the enolate towards electrophilic approach in alkylation reactions. Thus, by utilizing enolates formed in such a manner as

nucleophiles in the Mannich reaction, we sought to generate α,α-disubstituted β-amino carbonyl compounds in a selective fashion. This work is documented in Chapter 2.

1.3 (-)-PURAQUINONIC ACID

1.3.1 Isolation

Puraquinonic acid is an intriguing fungal metabolite isolated from mycelial cultures of the basidiomycete *Mycena pura*.[80] It was shown to induce differentiation of human promyelocytic leukemia cells (HL-60), making it a potential lead compound in leukemia drug design. During its initial isolation in 1997, its structure was established by MS and NMR. Soon thereafter, the absolute stereochemistry of puraquinonic acid was determined by its enantioselective synthesis (*vide infra*).[81,82]



3

Figure 1.4 (-)-Puraquinonic acid.

1.3.2 Derivatives

Puraquinonic acid is a norilludalane sesquiterpene. Other examples of norilludalane sesquiterpenes include russujaponol L (**105**),[83] deliquinone (**106**),[84]

and epoxydeliquinone (**107**)[84] (Figure 1.5). Russujaponol L was isolated from the fruit bodies of *Russula japonica*,[83] while deliquinone and epoxydeliquinone were produced in the injured fruit bodies of *Russula delica*.[84] The biological activity of these three compounds is unknown. Intriguingly, deliquinone and epoxydeliquinone were not observed in healthy fruit bodies suggesting that they may be part of the fungi's defence mechanism against parasitic invasion.

The structures of these norilludalanes were determined by NMR and MS; however their absolute stereochemistry has not been established. For epoxydeliquinone, the relative stereochemistry is unknown as well. Of the three, only deliquinone has been synthesized, albeit in racemic fashion.[85,86]

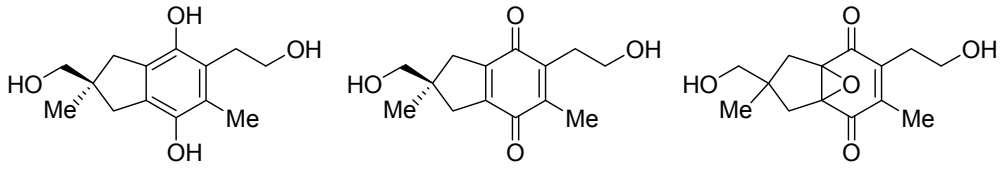


Figure 1.5 Derivatives of puraquinonic acid.

1.3.3 Biosynthesis

Basidiomycetes are known to produce sesquiterpenes such as protoilludalanes, illudanes, illudalanes, and norilludanes with carbon skeletons as shown in Figure 1.6.[87] They are thought to be part of the fungi's defence mechanism against bacterial infection. Protoilludalanes, illudanes, and illudalanes, originate from a common protoilludyl cation **109**, which in turn is obtained from the cyclization of humulene (**108**) (Scheme 1.36).[88] The

norilludanes are believed to have been derived in a similar manner, although it is unclear how they are formed as they are one carbon deficient.[84,89]

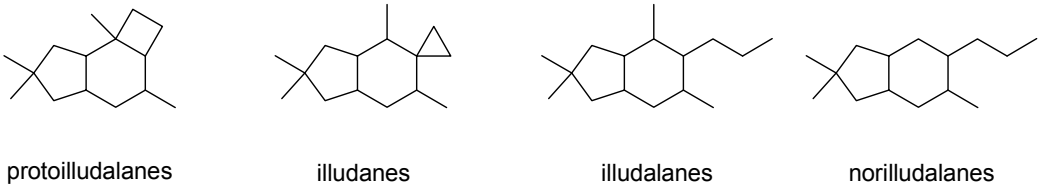
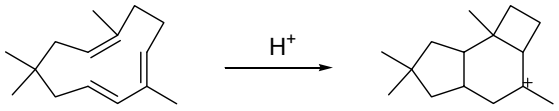


Figure 1.6 Carbon skeleton of protoilludalanes, illudanes, illudalanes, and norilludalanes.



Scheme 1.36 Formation of protoilludyl cation.

1.3.4 Previous Syntheses of Puraquinonic Acid

The deceptively simple architecture of puraquinonic acid presents an interesting stereochemical challenge. There is considerable distance between the lone quaternary stereocenter and its stereo-differentiating elements (ethyl hydroxy at C-7 and methyl at C-6) on the distal side of the quinone ring making it difficult to construct stereoselectively using conventional methods. The 5,6-bicycle forms the core of the molecule and its construction can greatly influence the efficiency of the synthesis. However, in addition to having the quaternary center on this 5,6-ring system, the 6-membered ring is fully substituted as well. In addition, puraquinonic acid possesses a number of oxygenated functionalities in multiple oxidation states (alcohol, ketone, and carboxylic acid). The quinone functionality

is particularly prone to addition and must be installed at a late stage. All of these elements contribute to making the asymmetric synthesis of puraquinonic acid quite challenging.

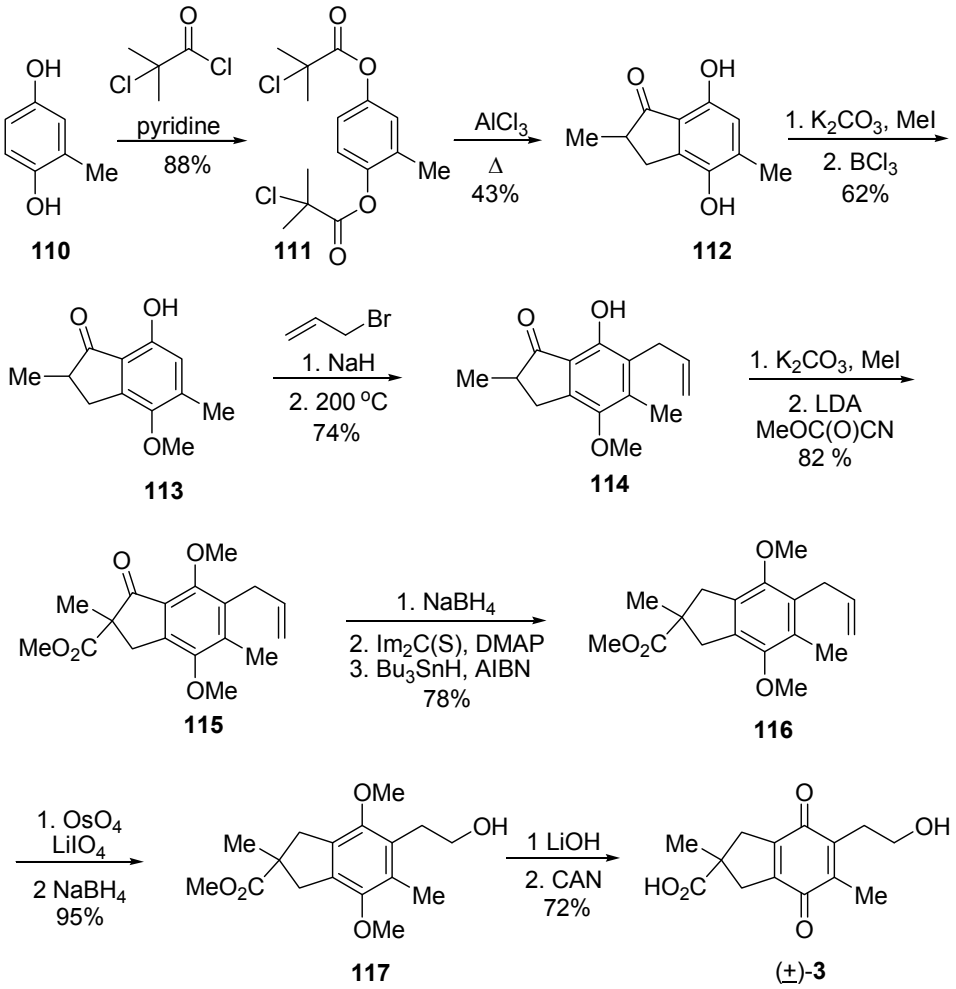
While concise racemic syntheses of puraquinonic acid have been published,[86,90,91] the only enantioselective synthesis requires more than 30 discrete steps.[81,82] This is due in large part to the difficulty in accessing the quaternary carbon center.

1.3.4.1 Racemic Syntheses of (±)-Puraquinonic Acid

The synthesis of racemic puraquinonic acid was first completed in 2001 by Clive and coworkers.[90] The synthesis was almost 30 steps long starting from 2,5-dimethoxybenzoic acid. Shortly thereafter, Clive released another paper documenting an alternate synthesis of puraquinonic acid in approximately half the steps.[91] The second synthesis bore a high degree of similarity to the first, but by judicious choice of starting material and by changing the strategy for installing the side chains, a significant decrease in the number of steps was reported.

In the second synthesis (Scheme 1.37), 2-methylbenzene-1,4-diol was acylated to give diester **111**. To form the 5-membered ring, **111** was subjected to Fries rearrangement followed by Nazarov cyclization to give indanone **112**. Dimethylation followed by ketone directed deprotection gave *p*-methoxyphenol **113**. Subsequently, allylation of **113** allowed for a Claisen rearrangement to put in a handle for the installation of the ethyl hydroxy side chain at a later stage.

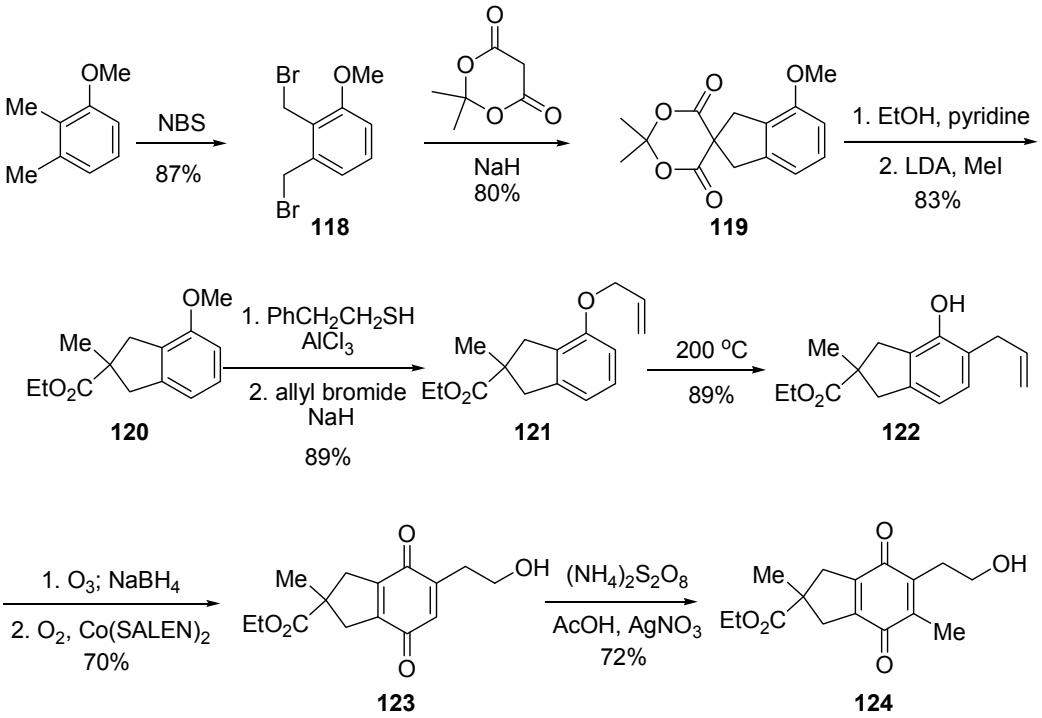
Enolization of the ketone, which was then quenched with Mander's reagent, delivered the quaternary center in **115**. Reduction of the ketone to the alcohol and Barton-McCombie deoxygenation gave **116**. To install the ethyl hydroxy side chain, the olefin was oxidatively cleaved then reduced to alcohol **117**. Saponification of the methyl ester and ceric ammonium nitrate (CAN) oxidation to the quinone completed the synthesis of (±)-puraquinonic acid. This route to puraquinonic acid was 15 steps long, with an 8% overall yield.



Scheme 1.37 Clive's synthesis of (±)-puraquinonic acid.

Kraus developed an expedient route to racemic puraquinonic acid ethyl ester **124** in 2002.[86] Bromination of 2,3-dimethylanisole using *N*-

bromosuccinimide (NBS) gave dibromide **118**, which was then displaced with Meldrum's acid to give the spirocyclic dilactone **119** (Scheme 1.38). Under basic conditions, ester formation and decarboxylation occurred to give the ethyl ester, which was methylated to form the lone quaternary center in the molecule. Deprotection of the phenol, followed by allylation formed **121**, which enabled a thermal Claisen rearrangement. The resultant alkene **122** was subjected to ozonolysis then worked up using sodium borohydride to furnish the hydroxy ethyl group on the right hand side of the molecule. Oxidation of the phenol gave the quinone **123**. Finally, a methyl group was installed by addition of a methyl radical formed from ammonium persulfate, silver nitrate, and acetic acid in a unique reaction, which maintained the oxidation state of the quinone. In this remarkably efficient route to puraquinonic acid, within the first four steps, both the 5,6-bicycle and the quaternary carbon center were installed. The synthesis was completed in 10 steps from commercially available 2,3-dimethyl anisole, with an impressive 23% overall yield.

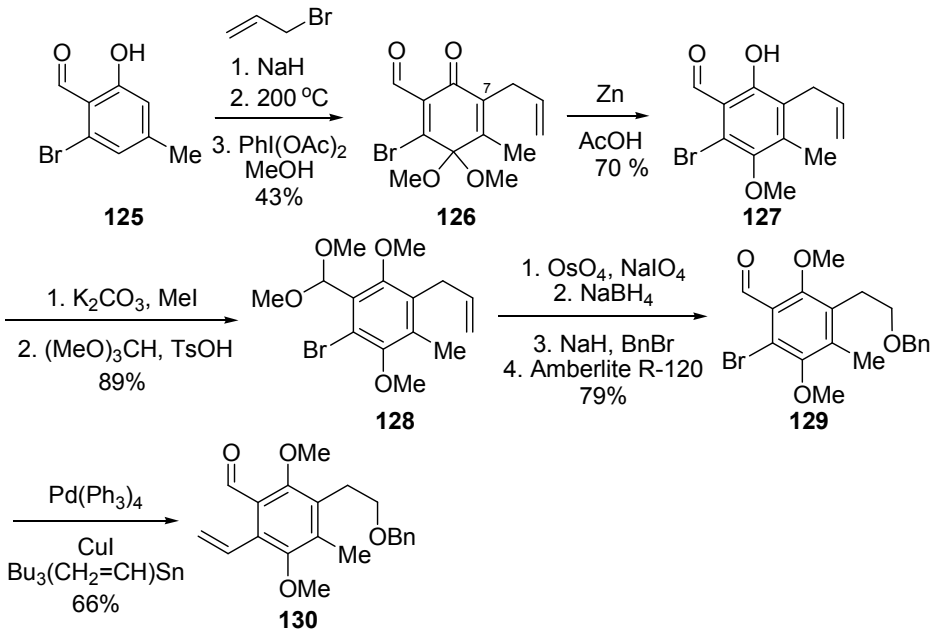


Scheme 1.38 Kraus' racemic synthesis of puraquinonic acid ethyl ester.

1.3.4.2 Asymmetric Synthesis of Puraquinonic Acid

Clive's synthesis of (+)-puraquinonic acid was the only published enantioselective route to puraquinonic acid at the outset of our studies.[81,82] As shown in Scheme 1.39, the synthesis commenced from known starting material **125**. Allylation followed by thermal [3,3]-sigmatropic rearrangement installed the allyl group at C-7, which would later form the ethyl hydroxy side chain of puraquinonic acid. Oxidation using diacetoxy iodobenzene in methanol followed by zinc reduction of the resultant acetal gave *p*-methoxyphenol **127**. After a series of protection reactions, Lemieux-Johnson oxidation of the terminal olefin and reduction of the resultant aldehyde installed the desired ethyl hydroxy side chain. At this stage however, it was necessary to protect the alcohol and this was

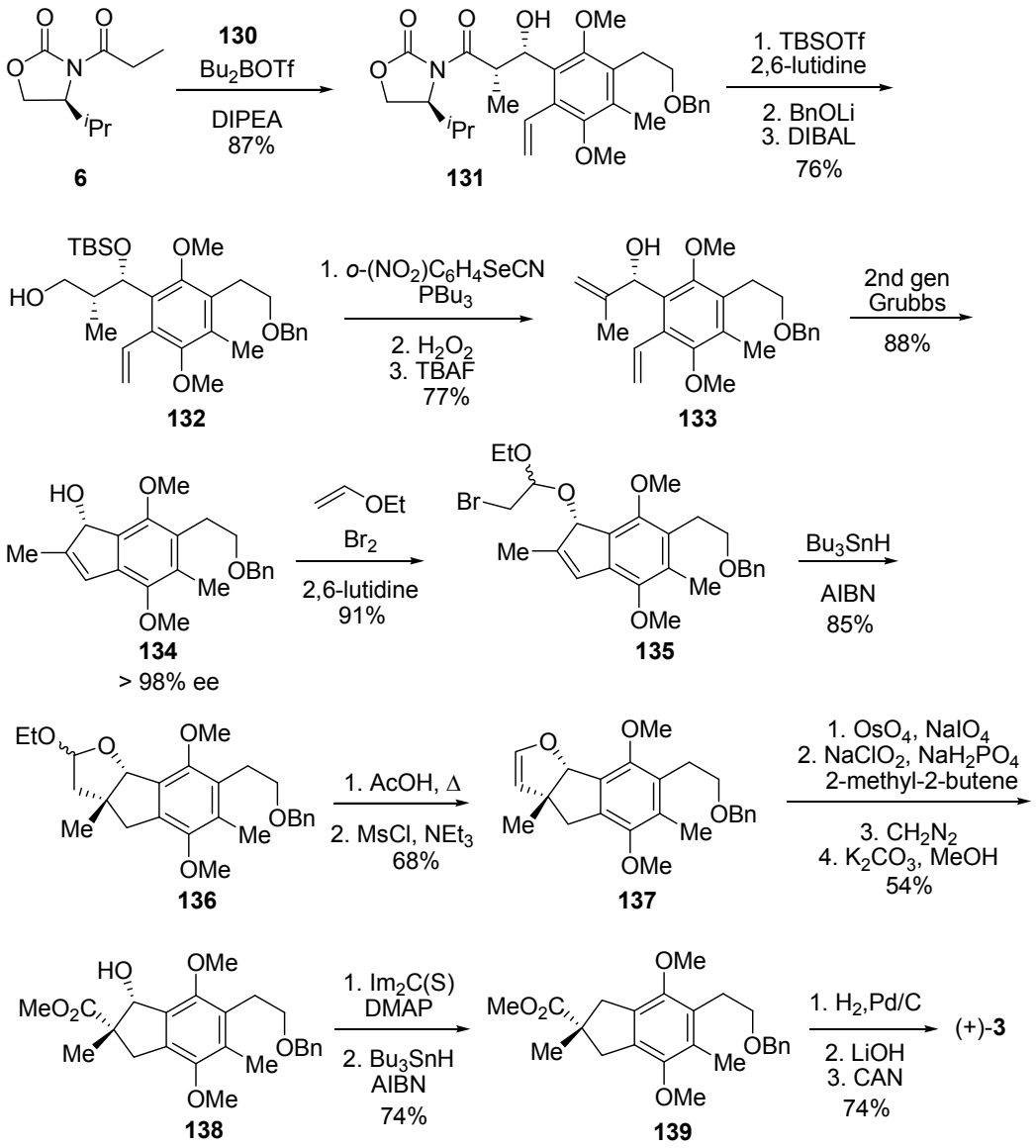
accomplished by benzylation. Deprotection of the aldehyde using an acidic cation exchange resin and subsequent palladium catalyzed cross-coupling of aryl bromide **129** with tributylvinylstannane gave aldehyde **130**.



Scheme 1.39 Installation of the side chains in (+)-puraquinonic acid.

Aldehyde **130** was then used in a diastereoselective aldol using Evans' oxazolidinone to obtain the *syn*-product (**131**) (Scheme 1.40). *tert*-Butyldimethylsilyl (TBS) protection followed by auxiliary removal gave a benzyl ester, which was reduced to alcohol **132**. Grieco elimination of **132** and TBS deprotection formed diene **133**, which was subjected to metathesis to form the required 5-membered ring. At this point, it was determined by HPLC comparison to racemic material that alcohol **134** had > 98% ee. To enable radical cyclization to form the quaternary stereocenter, bromo acetal **135** was prepared from the opening of an ethoxy bromonium by alcohol **134**. Using 2,2'-azobis(2-methylpropionitrile) (AIBN) and tributyltin hydride, the *cis*-5,5-bicycle was formed by radical cyclization, thus enabling the stereoselective installation of the

quaternary carbon center. Hydrolysis of to the hemiacetal followed by elimination gave dihydrofuran **137**. A four step sequence beginning with Lemieux-Johnson oxidation of the alkene, followed by oxidation of the resultant aldehyde to a carboxylic acid, methylation, and finally cleavage of the formyl ester, gave β-hydroxy ester **138**. Using manipulations highly similar to the racemic synthesis (Scheme 1.37), the hydroxy group was removed by Barton-McCombie deoxygenation. Thereupon, the ethyl hydroxy group and carboxylic acid moieties were unveiled by hydrogenation and saponification respectively. Lastly, oxidative demethylation using ceric ammonium nitrate (CAN) installed the quinone, thus affording (+)-puraquinonic acid, which was determined to have opposite specific rotation to that of natural puraquinonic acid, thus establishing the (*R*)-configuration of the lone stereocenter of (-)-puraquinonic acid.



Scheme 1.40 Asymmetric synthesis of (+)-puraquinonic acid.

This synthesis was accomplished in 32 steps from known starting material or 38 steps from commercially available starting material. The overall yield of this synthesis from previously synthesized phenol **125** was 1%. The inefficiency of this synthesis was largely due to the formation of the 5-membered ring containing the quaternary stereocenter. In this synthesis, asymmetry was introduced using an Evans' aldol to obtain β-hydroxy ester **131**. The hydroxy

group was used to direct the formation of the quaternary stereocenter on the adjacent carbon in a radical cyclization process, before being removed via Barton-McCombie deoxygenation. Both the stereocenters installed using Evans' aldol were eventually destroyed. In addition, the aldol reaction represented a three carbon homologation to the molecule, one of which was ultimately removed. Similarly, the radical cyclization to install the quaternary stereocenter added two extra carbons and only one was kept. The substantial length of this synthesis illustrates the challenge in the construction of the quaternary stereocenter in puraquinonic acid. However, it was through this synthesis that the absolute stereochemistry of (-)-puraquinonic acid was determined.

1.3.5 Development of a Concise Synthesis of (-)-Puraquinonic Acid

We were interested in developing an expedient synthesis of (-)-puraquinonic acid. By using the second generation bicyclic thioglycolate lactam auxiliary developed in our lab (Section 1.1.4), the problematic quaternary stereocenter could be constructed at an early stage. Judicious choice of substituents on the quaternary center would enable rapid assembly of both the 5- and 6-membered rings. Our synthetic route is documented in Chapter 3.

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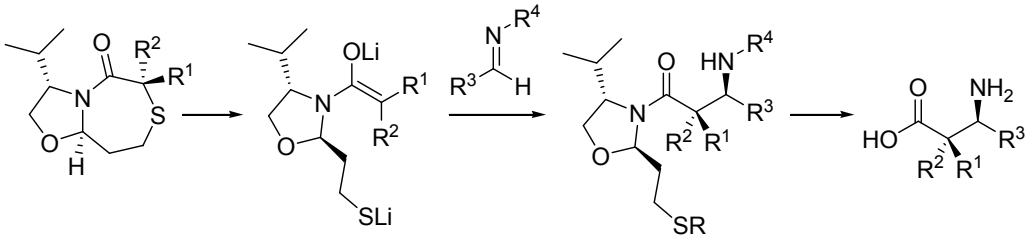
CHAPTER 2. STEREOSELECTIVE FORMATION OF α-QUATERNARY STEREOCENTERS VIA THE MANNICH REACTION

2.1 OVERVIEW OF PROJECT

The use of our bicyclic thioglycolate lactam chiral auxiliary **36** allows for stereocontrolled enolate formation (Section 1.1.4). Both (*E*)- and (*Z*)-enolates can be obtained depending on the initial order of alkylation and independent of steric differences between the two α-substituents. The liberated auxiliary is pseudo C_2-symmetric and will direct the approach of the electrophile from the same face despite any rotation about the C-N bond. This system has been used successfully in enolate alkylations (Section 1.1.4), and thus we were interested in expanding the use of this system to include other, more complex electrophiles.

The use of an earlier, first generation bicyclic thioglycolate lactam auxiliary in the addition to the aldehydes led to stereoselective aldol reactions via transmetallation to dicyclohexylboron bromide.[1] The substitution of imines for aldehydes as the electrophilic component would allow for the development of a route to α,α-disubstituted β-amino carbonyl compounds via Mannich additions (Scheme 2.1).[2] It was anticipated that stereocontrol in the Mannich reaction would follow the precedent in the aldol, although the need for transmetallation was not clear. This would represent the only method for stereoselective synthesis of α,α-dialkylated Mannich products, where the two α-substituents are not greatly

different in size. Removal of the auxiliary and N-deprotection would give access to useful α,α-disubstituted β-amino carbonyl compounds such as β-amino acids, which are important precursors to β-lactams and β-peptides.[3]

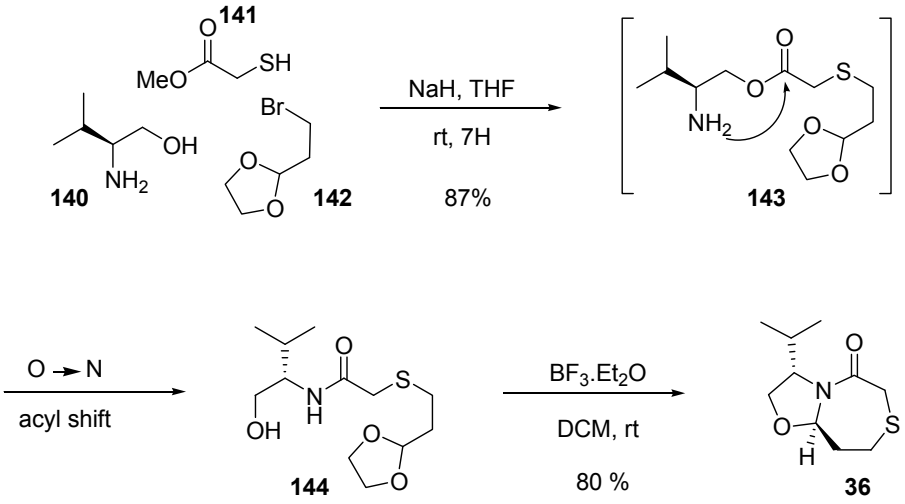


Scheme 2.1 Mannich reaction using our bicyclic lactam chiral auxiliary.

2.2 SYNTHESIS OF THE BICYCLIC THIOGLYCOLATE LACTAM CHIRAL AUXILIARY

The bicyclic thioglycolate lactam chiral auxiliary **36** was originally prepared via the published three step protocol.[4] Addition of methyl thioglycolate (**141**) to bromodioxolane **142** gave a methyl ester, which could be transesterified with valinol to give **143**. Under basic conditions, O to N acyl transfer resulted in the formation of amide **144**, which could be cyclized to the chiral auxiliary (**36**) using borontrifluoride. However, it was subsequently discovered that the sequence could be shortened to two steps without compromise of reaction yields (Scheme 2.2). The transesterification of methyl thioglycolate (**141**) with valinol followed by S-alkylation using bromodioxolane **142** could be performed in one pot to give aminoester **143**. Under these basic conditions, the aminoester undergoes an O to N acyl transfer, resulting in isolation of hydroxyamide **144** in

87% yield. Lewis acid mediated cyclization to the 5,7-bicyclic thioglycolate lactam was accomplished using borontrifluoride to give **36** in 80% yield.



Scheme 2.2 Preparation of bicyclic thioglycolate lactam chiral auxiliary 36.

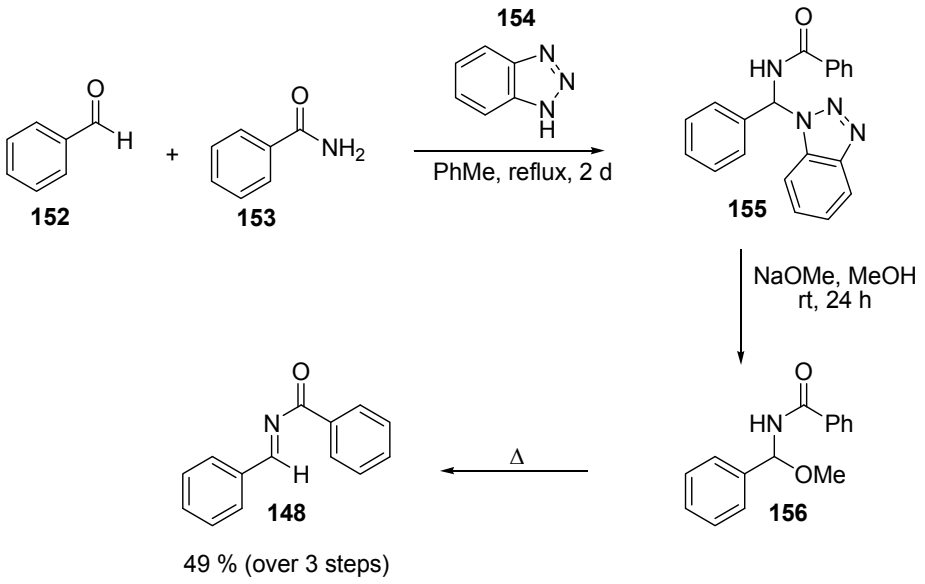
2.3 SYNTHESIS OF IMINES

Free primary aldimines (e.g. RCH=NH) are not stable and thus one must usually incorporate a protecting group on the nitrogen if a primary amine is desired from the Mannich reaction. Importantly, the nature of the protecting group can greatly influence both the reactivity and selectivity of the imines (Section 1.2.2).

In order to screen for an appropriate *N*-protecting group on the imine component, a number of benzaldimines, with varying N-substitution, were synthesized according to literature protocols.[5,6,7] In general, condensation of benzaldehyde with the appropriate primary amine in the presence of a drying agent and/or acid catalyst led to the formation of the desired imines (Table 2.1).

Simple imines with *N*-alkyl protecting group were relatively easy to synthesize. *N*-Phenyl and *N*-benzyl benzaldimines were obtained by mixing benzaldehyde with aniline and benzylamine respectively and stirring at room temperature for 1 hour without the need for the addition of an acid catalyst or removal of water (Table 2.1, entries 1 and 2). *o*-Methoxyphenyl benzaldimine (**147**) was formed by mixing benzaldehyde with *o*-anisidine in the presence of magnesium sulfate as a dehydrating agent (Table 2.1, entry 3).

The formation of imines with electron-withdrawing *N*-substituents was more involved as the decreased nucleophilicity of the amines made them less prone to condensation with benzaldehyde. For example, direct addition of acetamide or benzamide to benzaldehyde gave no reaction. *N*-Benzoylbenzaldimine was synthesized according to Katritzky's method,[6] by refluxing benzaldehyde, benzamide, and benzotriazole over 2 days to give triazole adduct **155** (Scheme 2.3Scheme 2.1). Displacement of benzotriazole using sodium methoxide[8] gave *N*,*O*-acetal **156**, which could be distilled to give *N*-benzoylbenzaldimine with loss of MeOH.[9,10] This reaction proceeded with a yield of 49% over 3 steps (Table 2.1, entry 4).

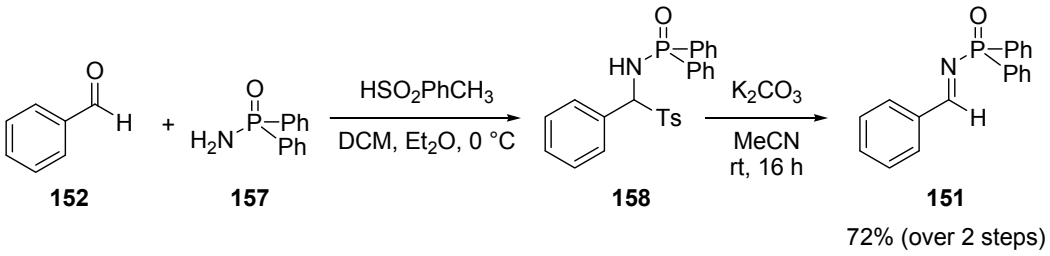


Scheme 2.3 Synthesis of *N*-benzoylbenzaldimine.

N-tosyl and *N*-benzenesulfonyl benzaldimines could be obtained by mixing benzaldehyde with toluenesulfonamide and benzenesulfonamide respectively (Table 2.1, entries 5 and 6). However, this condensation reaction now required more forcing conditions. The reaction was performed in refluxing toluene for an extended period of time with a Dean-Stark trap to remove water and an acid catalyst. The reaction still only proceeded with modest yields of 48% and 49% for *N*-tosyl and *N*-benzenesulfonyl benzaldimines respectively. Use of an acid cation resin and molecular sieves in refluxing toluene for 24 hours gave the *N*-tosyl imine in lower yields.

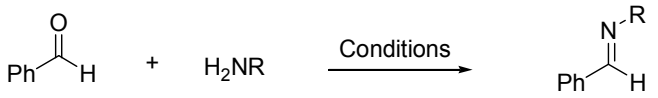
The synthesis of *N*-phosphinoyl imine was initially attempted by the addition of *P*,*P*-diphenylphosphinamide to benzaldehyde in the presence of triethylamine and catalytic titanium tetrachloride.[11] The reaction yields proved to be low and inconsistent, especially on larger scales. We thus turned to the use of a more recent protocol by Charette,[7] where the addition of *P*,*P*-

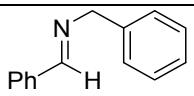
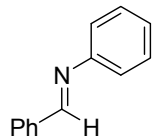
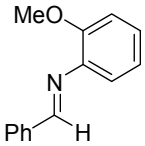
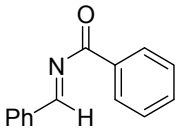
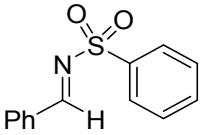
diphenylphosphinamide and *p*-toluenesulfinic acid to benzaldehyde gave sulfinyl adduct **158** (Scheme 2.4). Base promoted elimination of the sulfinyl group gave *N*-phosphinoyl benzaldimine (**151**) in 72% yield over 2 steps (Table 2.1, entry 7).

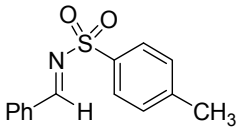
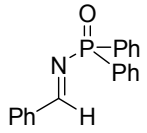


Scheme 2.4 Synthesis of *N*-phosphinoyl imines.

Table 2.1 Synthesis of imines.



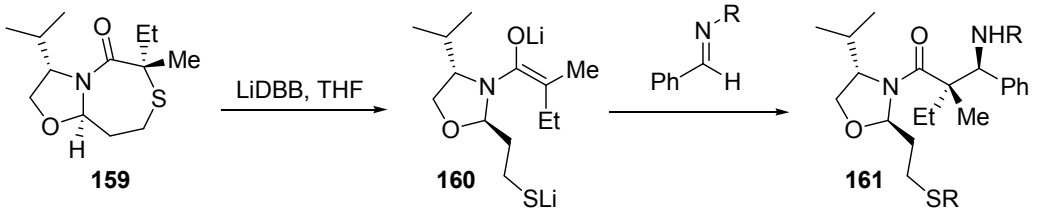
Entry	R	Product	Conditions	Yield (%)[a]
1		**145**	1 h, rt	96
2		**146**	1 h, rt	44
3		**147**	$MgSO_4$, Et_2O, rt, 4 d	27
4		**148**	1. benzotriazole, PhMe, reflux, 2 d 2. NaOMe, MeOH, rt, 24 h 3. Δ	49
5		**149**	Dean-Stark trap, TsOH PhMe, reflux, 24 h	48

6		**150**	Dean-Stark trap, TsOH PhMe, reflux, 2 d	49
7		**151**	1. HSO_2PhCH_3, DCM, Et_2O, 0 °C 2. K_2CO_3, MeCN, rt, 16 h	72

[a] Yields are unoptimized.

The benzaldimines prepared above were then screened in the Mannich reaction to identify the optimal *N*-protecting group to use in the development of our methodology. Me,Et-dialkylated auxiliary **159** was reductively enolized using lithium di-*tert*-butylbiphenylide (LiDBB) to give the (*E*)-enolate **160**, which was then subjected to the Mannich addition with *N*-tosyl and *N*-phenyl benzaldimines. Disappointingly, the reaction of **160** with *N*-tosylbenzaldimine, using 2.5 or 4 equivalents of the imine component at −78 °C for 3 h, gave no sign of Mannich base formation (Table 2.2, entries 1 and 2). The reaction of (*E*)-enolate **160** and *N*-phenylbenzaldimine was warmed up to room temperature and left for an extended period of time to no avail (Table 2.2, entry 3).

Table 2.2 Mannich reaction using Et,Me-dialkylated auxiliary.



Entry	R	Equiv. Imine	Temp	Time (h)	Product
1	Ts	2.5	−78 °C	3	N.R.
2	Ts	4	−78 °C	3	N.R
3	Ph	2.5	rt	30	N.R

2.4 PYRROLIDINE MODEL SYSTEM

At this point, it was decided that an achiral model system would be employed to explore this Mannich reaction. This would enable conservation of the chiral starting material while simplifying the analysis of the Mannich adducts. In addition, it would allow us to determine whether the lack of reactivity was due to the enolate or imine component. Pyrrolidine amide **162** was thus synthesized from the addition of pyrrolidine to propionyl chloride to serve as the model system. Pyrrolidine was chosen as it was a cyclic, tertiary amide with a high degree of similarity to the liberated auxiliary in our method. In essence it was a simplified system with no stereodirecting group. Deprotonation forms an α-monosubstituted enolate and thus there is less steric hindrance about the reaction site. The lack of the reactive oxazolidine ring and thiol group makes this a more robust system compared to our chiral auxiliary.

Pyrrolidine amide **162** was deprotonated using lithium diisopropylamide (LDA) then subjected to addition with the previously synthesized imines (Table 2.3). It was discovered that the reaction with *N*-phenylbenzaldimine proceeded sluggishly at −78 °C with mostly starting material after 5 hours (Table 2.3, entry 1). The reaction improved with increasing temperature (Table 2.3, entries 2 and 3) but remained a slow reaction even at room temperature. This difference in reactivity compared to the use of the bicyclic lactam system where no reaction was observed at all after 30 hours at room temperature (Table 2.2, entry 3), is likely due to the added steric interference in the bicyclic lactam system. The imine is not activated and thus even with the model substrate the reaction was quite slow

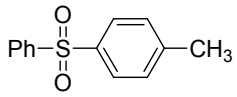
at room temperature. In our system, the enolate is disubstituted as is the 5-membered ring, thus contributing to the steric hindrance at the enolate reaction site making it less reactive than the model pyrrolidine amide. Here, the use of the pyrrolidine model showed that simple *N*-phenyl imines are not activated enough to be used with our bicyclic lactam auxiliary.

A similar reactivity trend was noted in the use of the 2-methoxylphenyl protecting group. In this case, the imine is further deactivated by the electron-donating substituent on the phenyl group, and no reaction was observed at −78 °C (Table 2.3, entry 4). Once again, the reaction could be accelerated by increasing the reaction temperature, but remained a slow reaction (Table 2.3, entry 5).

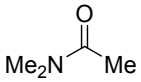
When more activated imines were used, an increase in conversion was clearly observed. When *N*-benzoylbenzaldimine was used as the electrophile at −78 °C the ratio of product to starting material improved to 1.5:1 (Table 2.3, entry 6). Increasing the temperature further improved the ratio to 1.8:1 (Table 2.3, entry 7).

Consistent with the results obtained using our bicyclic lactam derived enolate, the reaction of pyrrolidine amide **162** with *N*-tosylbenzaldimine gave no reaction even when the temperature was raised to room temperature (Table 2.3, entries 8-10). However when *N*-benzenesulfonyl imine was used instead, the reaction proceed at −78 °C to give a 1.8:1 ratio of product to starting material making this the most facile reaction of all the imines screened (Table 2.3, entry 11). Again the reaction rate increased when the temperature was increased (Table

2.3, entry 12). The huge disparity between the reaction with *N*-toluene and *N*-benzenesulfonyl imine was surprising, as electronically the two imines are virtually identical. We suspect that the acidity of the methyl group in the toluene sulfonamide might quench the enolate prior to Mannich reaction. A literature search did not turn up the pK_a value of the methyl group in toluene sulfonamide. However, the pK_a of tolyl phenyl sulfone[12] in DMSO is 29.8, while the pK_a of *N*,*N*-dimethylacetamide[13] in DMSO is 35 (Figure 2.1). It is likely then, that in our system, the enolate is being quenched by the acidic proton in *N*-tosylbenzaldimine.



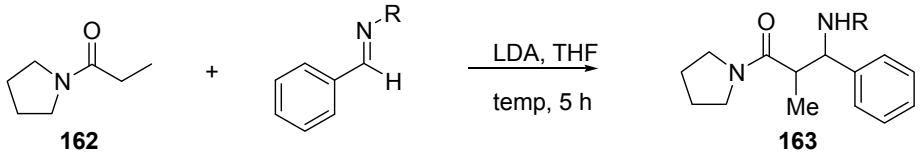
pKa (in DMSO) = 29.8



pKa (in DMSO) = 35

Figure 2.1 Comparison of pKa values.

Table 2.3 Mannich reaction using pyrrolidine amide.



162 **163**

Entry	R	Temp	Prod:SM
1	Ph	−78 °C	1:1.8
2	Ph	0 °C	1:1
3	Ph	rt	1.3:1
4	*o*-MeOPh	−78 °C	N. R.
5	*o*-MeOPh	0 °C to rt	1.2:1
6	Bz	−78 °C	1.5:1
7	Bz	0 °C to rt	1.8:1
8	Ts	−78 °C	N. R.
9	Ts	0 °C	N. R.
10	Ts	rt	N. R.
11	SO_2Ph	−78 °C	1.8:1
12	SO_2Ph	0 °C to rt	3.2:1

2.5 SELECTION OF N-PROTECTING GROUP

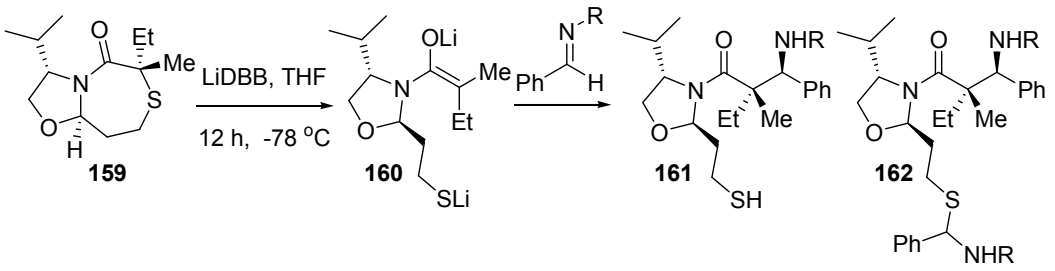
Through the use of the pyrrolidine model system, we established that the Mannich reaction could be feasible with the dialkylated auxiliary **159** using an activated imine, provided that the electron-withdrawing group did not contain an acidic proton. As such, we then went back and examined the Mannich addition of Me,Et-dialkylated auxiliary **159**, with the imines that had been previously synthesized in Table 2.1.

As anticipated, reductive enolization followed by addition to simple, unactivated *N*-benzyl and *N*-phenyl benzaldimines gave no reaction (Table 2.4, entries 1 and 2). However contrary to the results expected based on the pyrrolidine model system where the *o*-methoxy group further deactivated the imine, here the use of 2-methoxyphenyl benzaldimine proceeded to give Mannich adduct **161** (R=2-MeOPh) in 44% yield (Table 2.4, entry 3). This difference is presumably due to metal coordination of the methoxy group, which may activate the imine and bring it in closer proximity to the enolate by bidentate metal coordination to the imine and enolate components. As a similar effect was not observed in the pyrolidine system, the liberated thiolate likely participated in the coordination of the of the enolate and imine components.

In the activated imine series, addition to *N*-tosylbenzaldimine gave no reaction as previously shown (Table 2.4, entry 4). Gratifyingly, addition to *N*-benzenesulfonyl imine gave the Mannich adduct in 83% yield (Table 2.4, entry 5). The product was obtained as a mixture of **161** (R=SO_2Ph) and **162** (R= SO_2Ph),

where in the case of **162** (R=Ts), the intermediate lithium sulfide was quenched by another equivalent of the imine. Addition to *N*-phosphinoyl benzaldimine gave a 1:1.3 mixture of the **161** (R=$P(O)Ph_2$) and **162** (R= $P(O)Ph_2$) in 33% yield (Table 2.4, entry 6). Finally, use of *N*-benzoyl benzaldimine gave **161** (R=Bz) and **162** (R=Bz) in quantitative yield in a 9.4:1 ratio (Table 2.4, entry 7).

Table 2.4 Imine N-protecting group selection.



Entry	R	Yield (%)[a]	161:162
1	Bn	N. R.	N. R.
2	Ph	N. R.	N. R.
3	2-MeOPh	44	1:0
4	SO_2PhMe	N. R.	N. R.
5	SO_2Ph	83	1:4
6	$P(O)Ph_2$	33	1:1.3
7	Bz	100	9.4 :1

[a] N. R. No reaction

Although the benzoyl imine gave the highest yield of all imines studied, subsequent hydrolysis of the protecting group was expected to be difficult. Thus, it was decided to proceed using *N*-benzenesulfonyl as the nitrogen protecting group as a compromise between good reaction yields and ease of deprotection. In addition, the ease of synthesis of *N*-benzenesulfonyl imines made them a more attractive substrate than *N*-benzoylimines, which are prepared via a three step procedure.

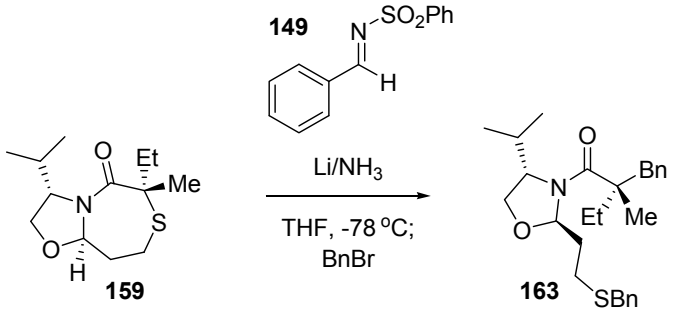
2.6 USE OF LITHIUM IN AMMONIA AS THE ELECTRON SOURCE

In the alkylation reactions of the disubstituted auxiliary, the reaction was cleaner, afforded higher yields, and could be carried out on larger scale using lithium in ammonia (Li/NH_3) as the electron source.[4] In addition, Li/NH_3 could be prepared the same day, while lithium di-*tert*-butylbiphenylide (LiDBB) must be preformed 24 hours in advance. Li/NH_3 was therefore studied as the electron source to determine if it was beneficial to Mannich additions.

In the reaction between Me,Et-dialkylated lactam **159** and *N*-benzenesulfonyl benzaldimine, use of Li/NH_3 as the electron source yielded no discernible Mannich adduct. In practice, use of Li/NH_3 requires the formation of excess reagent, whilst with the use of LiDBB, there is minimal excess reagent in the reaction flask. LiDBB is pre-made as a solution in tetrahydrofuran (THF) and stored for several weeks.[14] Enolization is then carried out by titration until a green colour persists, so there is minimal excess reagent in the reaction flask.

With the use of Li/NH_3 in the Mannich reaction, the excess reagent may have decomposed the imine by cleavage of the sulfonyl group or the excess ammonia in the system may have deactivated the imine by addition to the carbon center. To test this hypothesis, Me,Et-dialkylated auxiliary **159** was reductively enolized using Li/NH_3 and added to imine **149**. After stirring for 2 h at −78 °C, the reaction was quenched with benzyl bromide (Scheme 2.5). Upon work up, only alkylated product **163** was obtained, thus showing that the enolate is still

active under these conditions. Therefore, the problem with the use of Li/NH_3 likely lies with the deactivation of the imine component.



Scheme 2.5 Use of Li/NH_3 as the electron source.

2.7 DETERMINATION OF STEREOSELECTIVITY

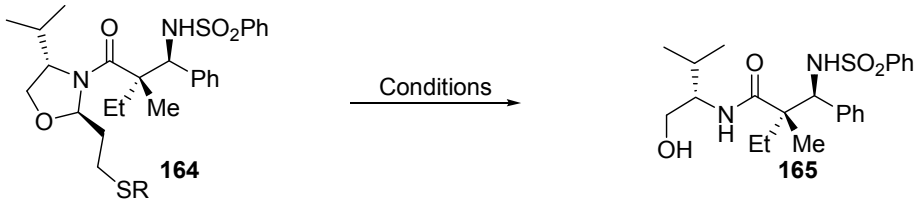
2.7.1 Partial Hydrolysis of Amide

Analysis of the selectivity of the Mannich reaction proved to be difficult by both ^1H NMR and GC. As shown in Table 2.4, there are eight possible products for each reaction (four stereoisomers each for free thiol **161** and *S*,*N*-acetal **162**). Furthermore, the presence of rotamers and the thermal instability of these products complicated the analysis. It was finally decided that the auxiliary should be partially hydrolyzed by cleaving the aminal to give hydroxy amide **165** to allow for simpler product identification. Accordingly, the Mannich adducts **161** ($R=SO_2Ph$) and **162** ($R=SO_2Ph$) synthesized above were subjected to various hydrolytic conditions.

Hydrolysis of Mannich base **164** using a variety of acidic conditions gave the stable valinol amide **165** (Table 2.5). Initial examination of hydrochloric acid (HCl), sulphuric acid (H_2SO_4), nitric acid (HNO_3), *p*-toluenesulfonic acid (TsOH),

and acetic acid (AcOH) for this hydrolysis (Table 2.5, entries 1 to 5) showed that the use of HCl or TsOH for 3.5 hours in dioxane gave the best results (50% and 56% yield respectively). Increasing the concentration of TsOH to 2.5M and decreasing reaction time gave an improved yield of 82% (Table 2.5, entry 6). However, when this reaction was followed by ^{1}H NMR, it was observed that after 1 hour, side products started to form and after 22 hours the yield had dropped to 76% (Table 2.5, entry 7). Using 0.3 M HCl, 84% yield of the desired alcohol **165** was obtained after 7 hours at room temperature (Table 2.5, entry 8). Increasing the reaction time increased the yield until optimal conditions were reached at 12 hours when the alcohol was obtained in quantitative yield (Table 2.5, entry 9).

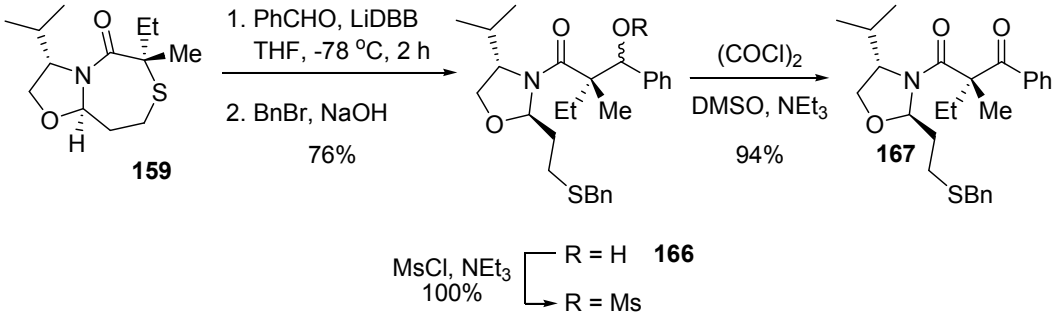
Table 2.5 Conditions for partial hydrolysis of chiral auxiliary.



Entry	Acid	Solvent	Time (h)	Yield (%)
1	1.0 M HCl	dioxane	3.5	50
2	1.5 M H_2SO_4	dioxane	3.5	16
3	1.5 M HNO_3	dioxane	3.5	39
4	1.0 M TsOH	dioxane	3.5	56
5	1.5 M AcOH	dioxane	3.5	48
6	2.5 M TsOH	dioxane	1	82
7	2.5 M TsOH	dioxane	22	76
8	0.3 M HCl	dioxane	7	84
9	0.3 M HCl	dioxane	12	100

2.7.2 Synthesis of Authentic Standard

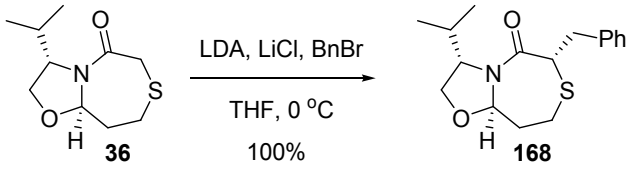
Because valinol amide **165** is not a known compound, an authentic mixture of all four possible isomers was needed to enable the analysis of the reaction diastereoselectivity. Initially we sought to access **165** via an aldol strategy. Me,Et-dialkylated auxiliary **159** was reductively enolized then added to benzaldehyde to obtain aldol product **166** in 76% yield, after benzylation of the free thiol (Scheme 2.6).[15] The benzylic alcohol was then oxidized under Swern oxidation[16] conditions to give β-ketoamide **167** in 94% yield. Numerous attempts at reductive amination[17] of the ketone resulted only in recovery of the starting material, and thus an alternative approach was pursued. The alcohol **166** was mesylated, in quantitative yield, with the intention of displacing it with an azide. The azide would later be converted to the corresponding amine via a Staudinger reduction.[18] All attempts at displacement led only to the recovery of starting material. Evidently, the steric hindrance at this neopentyl location precludes any manipulation involving nucleophilic addition to the benzylic center.



Scheme 2.6 Synthesis of authentic standard via the aldol reaction.

Therefore, to avoid manipulations at the benzylic position, we attempted to aminate the benzylic position prior to formation of the adjacent quaternary

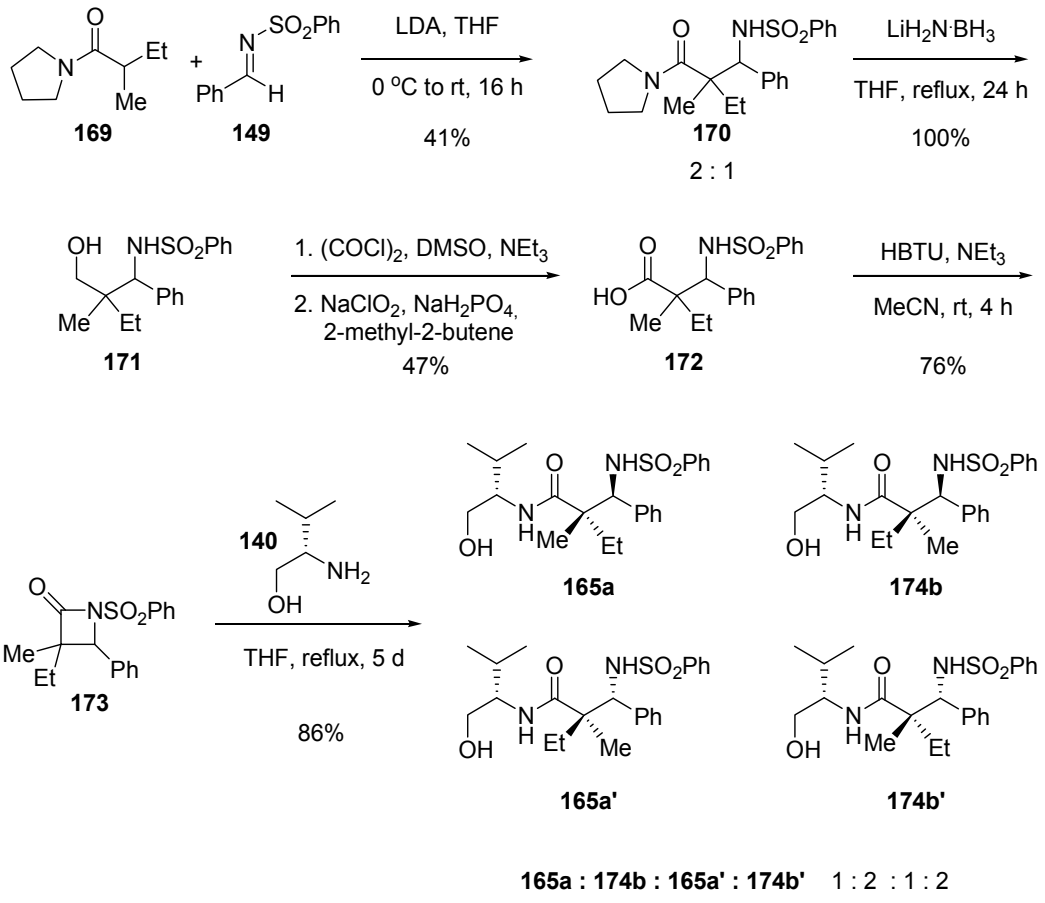
center. The bicyclic thioglycolate lactam was thus benzylated to give **168** in quantitative yield (Scheme 2.7). However, oxidative nucleophilic substitution using DDQ and trimethylsilyl azide[19] gave only recovery of the starting material.



Scheme 2.7 Benzylation of bicyclic thioglycolate amide 36.

After several synthetic attempts at accessing the desired β-amino carbonyl compounds, including the Staudinger cycloaddition[20] of ketenes and imines to form β-lactams and the Mannich reaction using benzyl ester enolates, proved to be unsuccessful and low yielding respectively, an alternative strategy was employed using α,α-dialkylated pyrrolidine amide **169** (Scheme 2.8). Deprotonation of **169** followed by addition to *N*-benzenesulfonyl benzaldimine **149** gave Mannich adduct **170** in 41% yield and a 2:1 diastereomeric ratio. Reduction of amide **170** using lithium amidoborohydride[21] gave alcohol **171** in quantitative yield. Swern oxidation[16] of the primary alcohol to the corresponding aldehyde, followed by oxidation of the aldehyde using sodium chlorite[22] gave carboxylic acid **172** in 47% yield over two steps. Treatment with HBTU converted the β-amino acid **172** to β-lactam **173** in 67% yield. All attempts at direct coupling of valinol to the carboxylic acid resulted in the formation of β-lactam only. However, the α,α-dialkylated β-lactam could be easily opened with valinol by refluxing in THF for five days to give an authentic sample of the four required β-amino amides in 86% yield. The reaction time could be decreased to 16 hours by the addition of catalytic amounts of DMAP. Overall, this six step

reaction sequence yielded the authentic standard in 13% without optimization. The stereochemistry of these standards was initially not known, but was eventually identified through comparisons with the Mannich addition product using the α,α-disubstituted auxiliary.



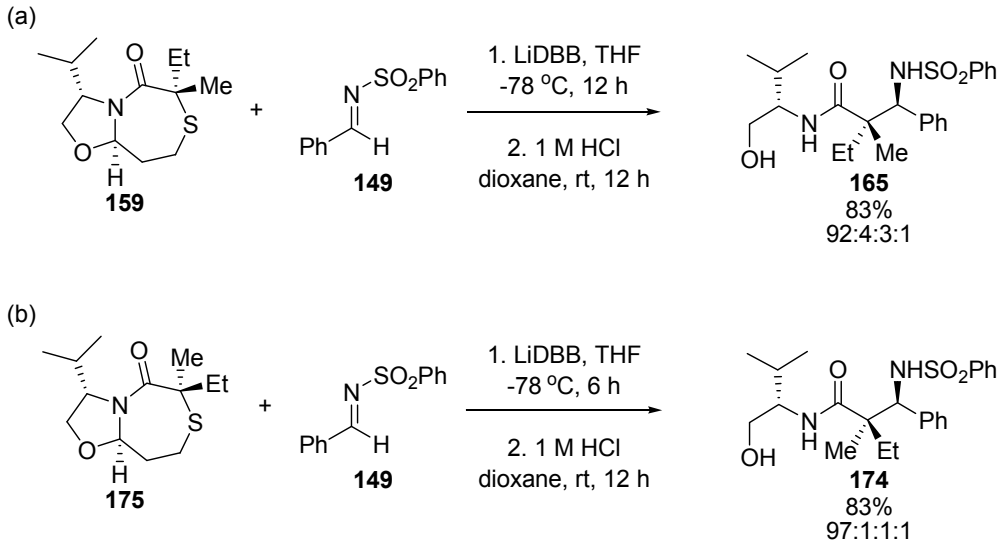
Scheme 2.8 Synthesis of authentic standard.

2.7.3 Determination of Diastereoselectivity

Using normal phase HPLC conditions, on a Phenomenex Luna 3μ silica column, it was possible to separate all four stereoisomers from the authentic standard. Subsequent HPLC analysis of the Mannich addition product of bicyclic

lactam **159** against the prepared standard showed that the reaction proceeded with excellent diastereoselectivity (92:4:3:1) (Scheme 2.9a). (see Appendix for sample HPLC analysis).

The first insight into the stereoselection of the reaction came from the reduction and Mannich addition of lactam **175** (Scheme 2.9b), which proceeded with good yield and excellent diastereoselectivity. From prior studies, it was known that **175** should form the (*Z*)-enolate, in contrast to the (*E*)-enolate obtained from **159**.[4] By comparison of the HPLC traces of **165**, **174** and the authentic standard, with **174** matching a major component and **165** matching a minor component of the standard, it was clear that the relative stereochemistry at the quaternary carbon and amine stereocenter in the Mannich adduct were different. This would be consistent with a common transition state (e.g. a Zimmerman-Traxler transition state) between the two enolate stereoisomers.



Scheme 2.9 Selectivity of the Mannich reaction.

Moreover, it was now possible to assign all four isomers to the peaks in the HPLC trace of the authentic standard. The four stereoisomers in the authentic

standard were formed in a 2:2:1:1 ratio. Amide enolates are known to form (*Z*)-enolates preferentially (Section 1.1.3.1).[23] As there is no bias in facial approach of the electrophile, the 2:1 ratio of diastereomeric products reflects the ratio of *Z*/*E* enolate. One of the major peaks in the HPLC trace of the authentic standard corresponded to **174**, which is a Mannich product of a (*Z*)-enolate. The other major peak therefore corresponds to the product of the (*Z*)-enolate with opposite facial approach of the electrophile. By the same reasoning, one of the minor peaks of the authentic standard corresponded to **165**, which is the Mannich adduct of the (*E*)-enolate. The other minor peak of the standard would therefore be the product of the (*E*)-enolate with the electrophile approaching from the opposite face. Hence, for **165** (Scheme 2.9a) all four peaks in the HPLC trace can be assigned and it was determined that the minor isomers formed in 4% and 3% were from the formation of a small amount of the (*Z*)-enolate and opposite facial approach of the enolate on the (*E*)-enolate respectively.

The excellent diastereoselectivity obtained with the α,α-disubstituted bicyclic lactams is particularly noteworthy. Use of Me,Et-dialkylated pyrrolidine amide **169** in the synthesis of the standard mixture (Scheme 2.8), showed a 2:1 *Z*:*E* enolate ratio obtained based on steric differences between the methyl and ethyl group alone. The excellent diastereoselectivities of these Mannich reactions using the auxiliary showed that both (*E*)- and (*Z*)-enolates could be selectively formed with no dependence on steric differences of the α-substituents.

While the diastereoselectivity of the reaction could be determined by comparison with the authentic standard, it did not identify the absolute

stereochemistry of the major products. Fortunately, both **165** and **174** could be recrystallized from methanol or methanol/water, to give crystals viable for structural determination by x-ray crystallography (Figure 2.2). The X-ray structure allowed us to establish the relative stereochemistry of **165** and **174**. Since the isopropyl stereocenter was derived from L-valine, the absolute stereochemistry could also be established.

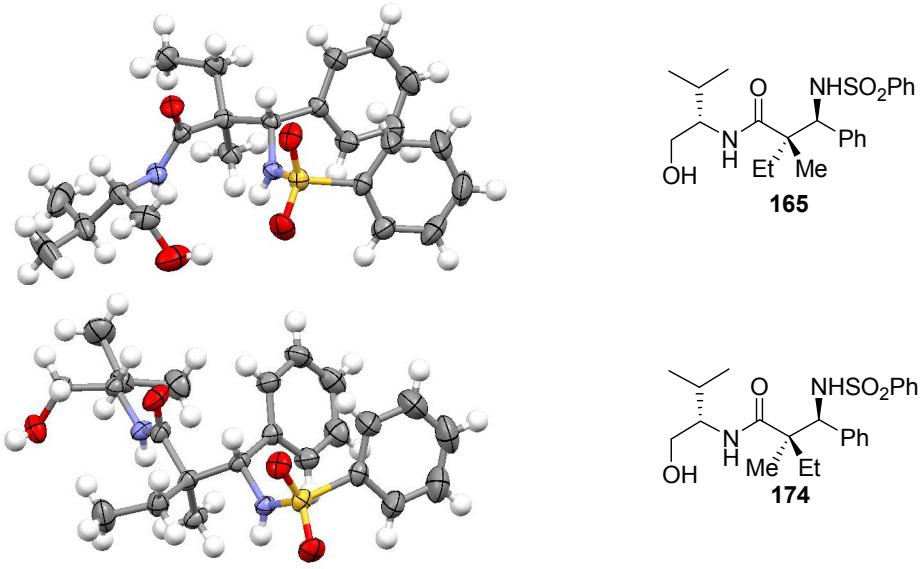
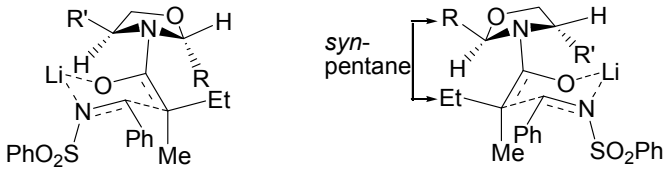


Figure 2.2 X-ray crystal structures of 165 and 174.

Based on the stereochemistry of the products obtained, the addition most likely proceeds via a closed 6-membered ring Zimmerman-Traxler transition state,[24] with approach of the imine from the back face of the enolate. The enolate facial selectivity is consistent with that observed in alkylation reactions (Section 1.1.4). In the proposed transition state, the amide nitrogen is pyramidalized to enable the twisting of the oxazolidine ring away from the enolate plane, thus minimizing the $A^{1,3}$-strain between the ring and the α-substituents on the enolate (Figure 2.3).[25] The imine then approaches from the back face (**176**) to avoid the

development of *syn*-pentane interactions between the substituents at the α-position of the enolate and the substituents on the oxazolidine ring (**177**).



176
Favoured

177
Disfavoured

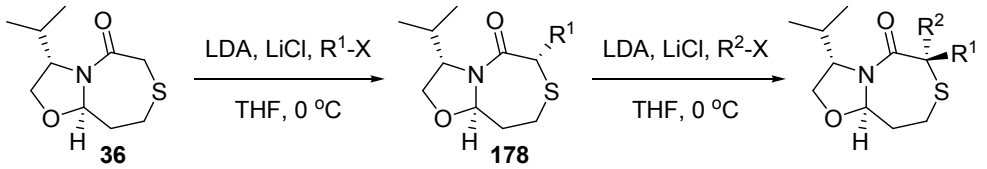
Figure 2.3 Proposed transition state.

2.8 REACTION SCOPE

As we have established that the bicyclic thioglycolate lactam **36** can be used in the stereoselective formation of α,α-disubstituted Mannich bases with good yields and selectivity without need for transmetallation, we went on to elucidate the scope of the reaction by varying the substitution on both the enolate and imine components.

Bicyclic lactam **36** was sequentially alkylated to obtain a number of dialkylated compounds as single stereoisomers (Table 2.6). These compounds prepared were chosen so that we could access (*E*)- and (*Z*)-enolate pairs.

Table 2.6 Alkylation of chiral auxiliary.



36 178

Entry	R^1-X	Yield (%)	R^2-X	Product	Yield (%)
1	EtI	N.P.[a]	MeI	**174**	85[b]
2	MeI	93	EtI	**165**	73
3	^{n}PrI	N.P.[a]	MeI	**179**	89[b]
4	MeI	93	*n*PrI	**180**	92
5	allyl bromide	95	MeI	**181**	62
6	MeI	93	allyl bromide	**182**	96
7	BnBr	100	MeI	**183**	69
8	MeI	93	BnBr	**184**	87

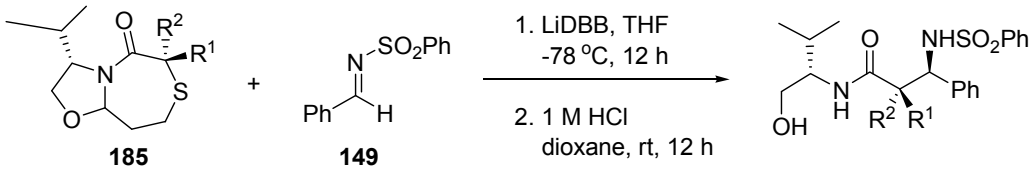
[a] N.P. Not purified.
[b] Yield over 2 steps.

The Mannich reaction was conducted with the series of lactams prepared in Table 2.6 and the diastereomeric ratio of each reaction was determined by cleavage of the aminal in the Mannich adduct to give valinol amides. The crude reaction mixture was passed thru a silica plug to remove excess 4,4'-di-*tert*butylbiphenylide (DBB) which would otherwise dominate the HPLC spectrum, but otherwise no purification was performed. An authentic standard of the four possible isomers of each reaction was prepared according to the procedure outlined in Scheme 2.8 and the HPLC trace of each reaction in Table 2.7 was compared to that of the authentic standard.

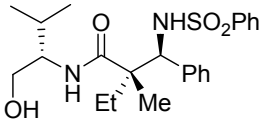
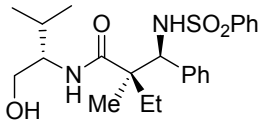
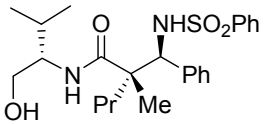
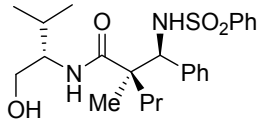
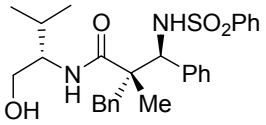
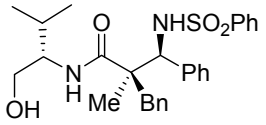
The Mannich reaction proceeded with good to excellent yields and selectivities for a variety of α-substituents including propyl, benzyl, and allyl (Table 2.7). By comparing the reaction of each (*E*)- and (*Z*)-enolate pairs, it could be seen that both (*E*)- and (*Z*)-enolates gave high levels of selectivity. In addition,

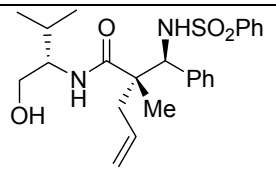
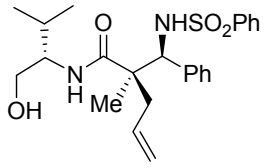
reaction selectivity did not depend on steric differences of the α-substituent as both Me,Et-enolates and Me,Bn-enolates (Table 2.7, entries 1 and 5) reacted with similar levels of selectivity.

Table 2.7 Substrate scope – Varying α-substitution.



185 + **149**

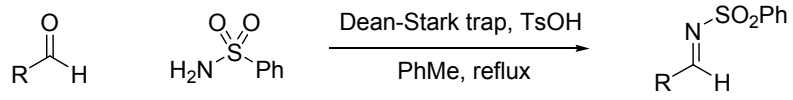
Entry	Product[a]	Yield (%)	ds
1	 **165**	83	92:4:3:1
2	 **174**	83[b]	97:1:1:1
3	 **186**	100	87:10:2:1
4	 **187**	100	95:3:2:0
5	 **188**	72	98:1:1:0
6	 **189**	76	95:3:2:0

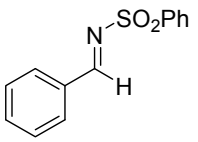
7	 **190**	86	94:4:2:0
8	 **191**	98	92:5:2:0

[a] Relative stereochemistry of **186-191** were assigned by analogy to **165** and **174**.
[b] Reaction was complete in 6 hours.

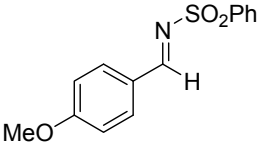
The substrate scope of the imine component in this Mannich reaction was also elucidated with the series of imines shown in Table 2.8.[26,27] High yields and selectivities were obtained upon addition of Et,Me-dialkylated lactam **175** to *N*-benzenesulfonyl imines, bearing both electron rich and electron poor aromatic substitution (Table 2.9, entries 2 and 3), heteroaromatic substitution (Table 2.9, entry 4), and α,β-unsaturated imines (Table 2.9, entry 5). This reaction however, did not tolerate aliphatic imines, as no Mannich adducts could be discerned from the crude reaction mixtures. Although aliphatic imines were not viable substrates for the Mannich, these compounds can in theory be accessed through hydrogenation of the α,β-unsaturated imine products.

Table 2.8 Varying substitution on the imine component.

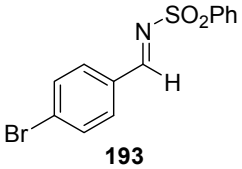




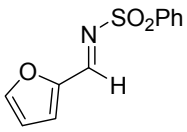
149
48%



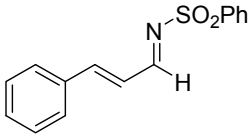
192
54%



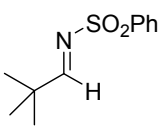
193
40%



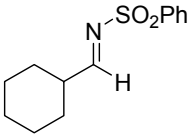
194
64%



195
79%



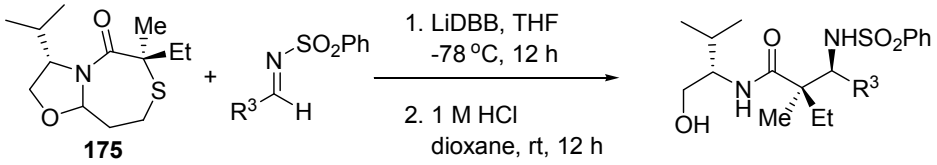
196
66%[a]



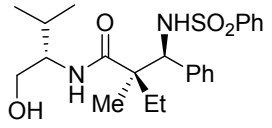
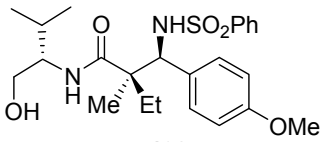
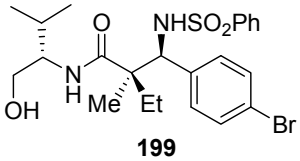
197
74%[b]

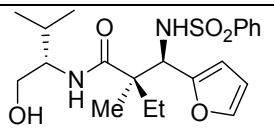
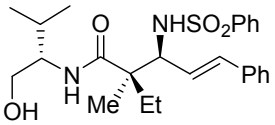
[a] Reaction conditions: $TiCl_4$, NEt_3, DCM, 0 °C
[b] Reaction conditions: $PhSO_2Na$, CHO_2H, H_2O, rt

Table 2.9 Substrate scope – Varying imine substitution.



175

Entry	Product	Yield (%)	ds
1	 **175**	83[a]	97:1:1:1
2	 **198**	93[a]	99:1:0:0
3	 **199**	80	97:2:1:0

4	 **200**	86[a]	92:5:2:1
5	 **201**	76	85:12:2:1

[a] Reaction was complete in 6 hours.

2.9 DEPROTECTION OF MANNICH ADDUCTS

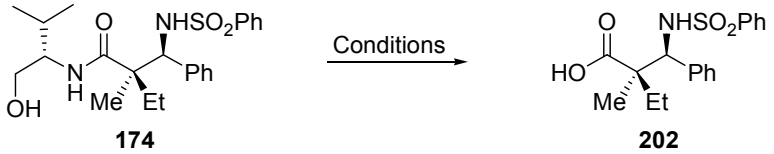
2.9.1 Removal of the Auxiliary

For this methodology to be practical, the auxiliary should be easily removed after the desired Mannich reaction has been achieved. In previous work on the formation of quaternary carbon centers via enolate alkylations, the auxiliary could be removed using refluxing aqueous sulphuric acid, to give the corresponding carboxylic acid (Section 1.1.4).[4] It was therefore anticipated that a similar cleavage could be effected here. Hence, Mannich adduct **174** was subjected to a range to acidic hydrolytic conditions as shown in Table 2.10.

Hydroxyamide **174** was impervious to reaction with a number of acids, including hydrochloric acid (HCl), sulphuric acid (H_2SO_4), and acetic acid (AcOH) at room temperature (Table 2.10, entries 1-3). When the reactions were heated in refluxing dioxane, use of HCl resulted in recovery of starting material while use of H_2SO_4 gave decomposition products (Table 2.10, entries 4 and 5).

However, a change to alcoholic solvents gave promising results. Hydrolysis using H_2SO_4 in refluxing methanol resulted in the formation of aminoester **203** and oxazoline **204** (Table 2.10, entry 6), while use of alcohols with higher boiling points such as isopropanol, butanol, and 2-methoxy ethanol gave exclusive formation of amino ester **203** (Table 2.10, entries 7-9).

Table 2.10 Hydrolysis of amide to β-amino acid.

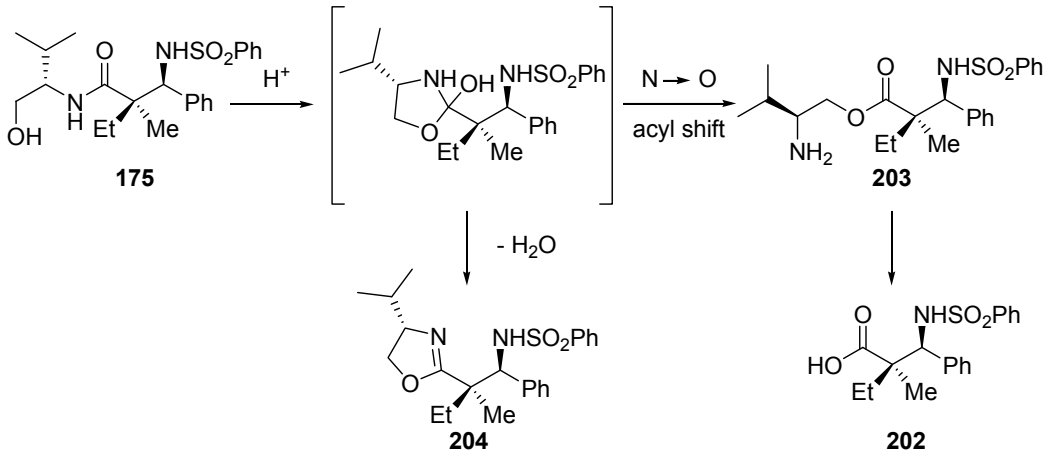


174 **202**

Entry	Acid	Solvent	Time	Temp	Product
1	1.5 M HCl	dioxane/H_2O	5 d	rt	SM
2	13 M AcOH	H_2O	5 d	rt	SM
3	1.5 M H_2SO_4	dioxane/H_2O	5 d	rt	SM
4	0.33 M HCl	dioxane/H_2O	16 h	reflux	SM
5	1.5 M H_2SO_4	dioxane/H_2O	16 h	reflux	decomposition
6	1.8 M H_2SO_4	MeOH/H_2O	12 h	reflux	SM + aminoester[b] + oxazoline[a]
7	2.7 M H_2SO_4	*i*PrOH/ H_2O	4 h	reflux	aminoester[b]
8	2.7 M H_2SO_4	*n*BuOH/ H_2O	23 h	reflux	aminoester[b]
9	2.7 M H_2SO_4	2-methoxy ethanol/H_2O	3 days	reflux	aminoester[b]

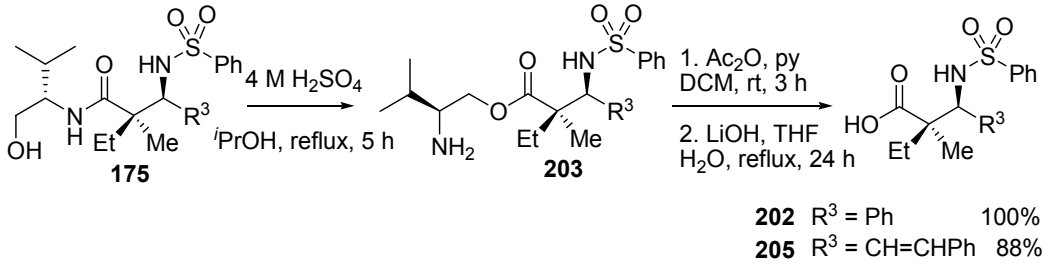
[a] see structure **204** in Scheme 2.10.
[b] see structure **203** in Scheme 2.10.

Under acidic conditions, the hydrolysis was expected to proceed via the formation of an intermediate oxazolidine (Scheme 2.10). N to O acyl transfer would give aminoester **203**, which could be hydrolyzed to carboxylic acid **202**. However, dehydration of the oxazolidine would result in the formation of oxazoline **204** as a side product as was observed in Table 2.10 (entry 6).[28]



Scheme 2.10 Mechanism of auxiliary cleavage under hydrolytic conditions.

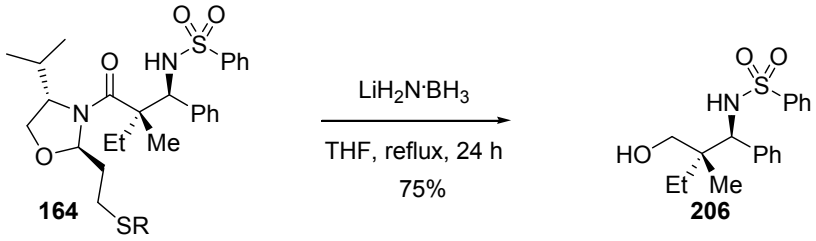
From our investigation of acid hydrolysis of **175**, we found that the aminoester **203** could be obtained cleanly but could not be directly hydrolyzed to the carboxylic acid. It was therefore decided that basic saponification should be used instead. Aminoester **203** was acetylated to prevent O to N acyl transfer under basic conditions (Scheme 2.11).[29] Saponification using lithium hydroxide gave carboxylic acid **202** in quantitative yield. This three-step hydrolytic sequence was also performed on Mannich base **201** (R^3 = cinnamyl) to obtain carboxylic acid **205** in 88% yield over three steps.



Scheme 2.11 Cleavage of auxiliary by hydrolysis.

Alternatively, the auxiliary could be removed by reduction using lithium amidoborohydride,[21] which had been successfully employed with the alkylation products of the first and second generation chiral bicyclic lactam auxiliaries

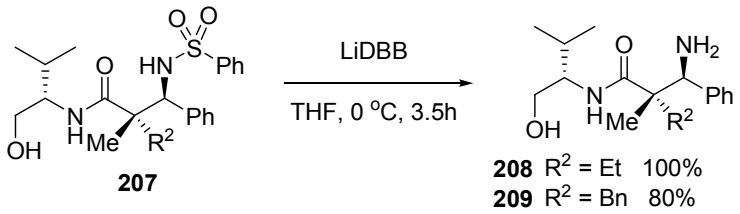
(Section 1.1.4).[4,30] When oxazolidine amide **164** was reduced using lithium amidoborohydride, primary alcohol **206** was obtained in 75% yield (Scheme 2.12). The partially hydrolyzed valinol amide **175** could not be directly reduced as deprotonation of the secondary amide rendered the carbonyl center much less electrophilic.



Scheme 2.12 Cleavage of auxiliary by reduction.

2.9.2 N-Deprotection

N-deprotection should be facile to enable practical application of this methodology. Here, the sulfonyl group was removed reductively[31] to obtain the free amine in good yields for a number of Mannich adducts as shown in Scheme 2.13. The reaction is operationally simple and proceeds by titration using LiDBB until the deep green colour persists.



Scheme 2.13 Removal of *N*-protecting group.

2.10 CONCLUSIONS

We have developed a highly stereoselective route for the formation of α,α-disubstituted β-amino carbonyl compounds using our bicyclic thioglycolate lactam chiral auxiliary in the Mannich reaction. A variety of α-substituents were tolerated on the amide enolate including methyl, ethyl, propyl, benzyl, and allyl groups. Both (*Z*) and (*E*)-enolates underwent additions with similar yields and selectivities. On the imine component, both electron rich and electron poor aromatic substitution were tolerated, along with heteroaromatic and α,β-unsaturated groups. Based on the diastereoselectivity of the product, the reaction is presumed to proceed via a closed Zimmerman-Traxler type transition state.

Upon completion the auxiliary could be removed by reduction to give the corresponding primary alcohol, or by a three-step hydrolytic sequence to give the carboxylic acid. The β-amino moiety was deprotected by removal of the sulfonyl group using reducing conditions.

To the best of our knowledge, this methodology represents the first example in the literature where non-equivalent α,α-disubstituted β-amino carbonyl compounds can be obtained in a stereoselective manner without dependence on the steric differences of the α-substituents or by the use of cyclic enolates. Because the *E*/*Z* selectivity of enolate formation is predetermined by the initial order of enolate alkylation, there is no reliance on the steric differences of the α-substituents.

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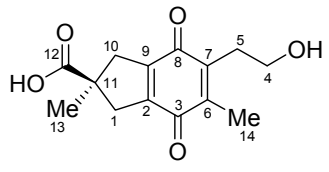
CHAPTER 3. TOTAL SYNTHESIS OF (-)-PURAQUINONIC ACID

3.1 OVERVIEW OF PROJECT

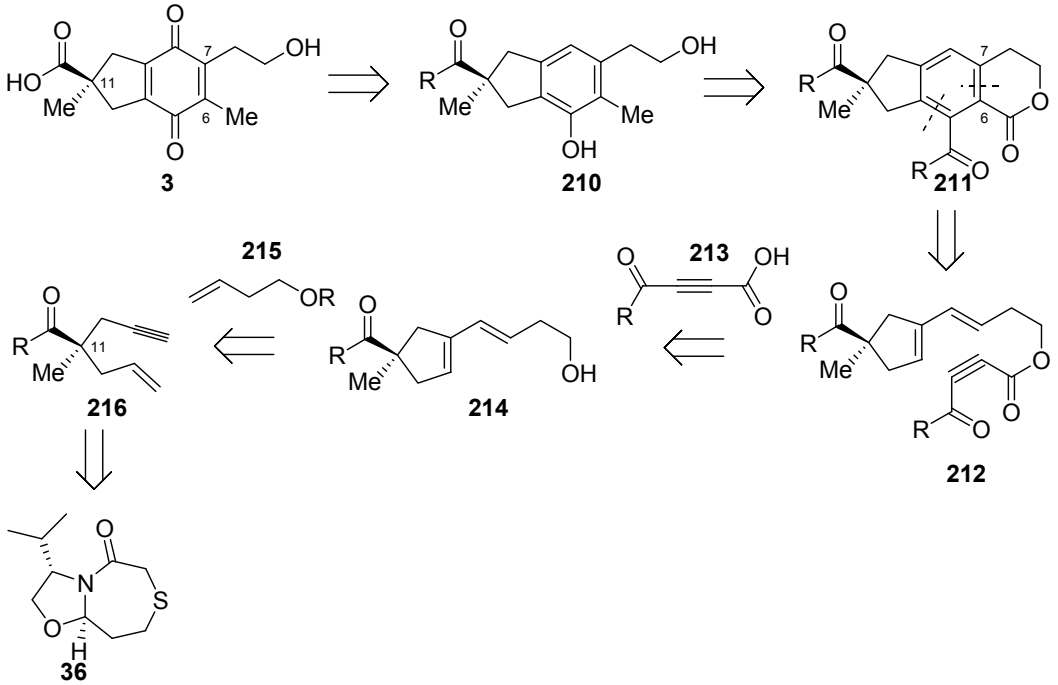
(-)-Puraquinonic acid, **3**, [1] (Figure 3.1) was isolated from mycelial cultures of *Mycena pura* in 1997 and showed potential as a lead compound in leukemia drug design. A number of racemic syntheses of puraquinonic acid have been published,[2,3,4] including a highly expedient route[2] to its ethyl ester (CO_2Et in place of CO_2H at C-11) in 10 steps (Section 1.3.4.1). However, despite having only one stereocenter and seemingly simple architecture, there has only been one published asymmetric synthesis of puraquinonic acid and it is over 30 steps long (Section 1.3.4.2).[5,6] This is largely due to the synthetic challenge in forming the quaternary carbon stereocenter at C-11. It is well removed from its stereo-differentiating elements, ethyl hydroxy group at C-7 and methyl group at C-6, making it difficult to access via traditional means. To us, this made puraquinonic acid an ideal substrate for examining the utility of our bicyclic thioglycolate lactam auxiliary **36** (Section 1.1.4) in the synthesis of natural products. We anticipated that **36** could be used to construct the lone stereocenter at C-11 and thus key an efficient and concise asymmetric synthesis of (-)-puraquinonic.



3

Figure 3.1 Structure of (-)-puraquinonic acid.

Our goal was to develop a short route, of approximately 10 steps, to puraquinonic acid. Retrosynthetically, it was envisioned that the quinone moiety of puraquinonic acid would be obtained from the oxidation of phenol **210** (Scheme 3.1), which might evolve from a Baeyer-Villiger oxidation of ketone **211**. The 6-membered ring could be obtained from a Diels-Alder cycloaddition of **212**, with the ketone activating the dienophile. Additionally, the substituents at C-7 and C-6 (ethyl hydroxy and methyl) would be masked as a lactone in **211**, which would arise if the Diels-Alder was intramolecular. The diene component for the Diels-Alder cycloaddition could be constructed from a tandem ring-closing/cross metathesis on enyne **216**, which would also form the 5-membered ring of puraquinonic acid. Chiral enyne **216** could be constructed at an early stage using the bicyclic lactam **36**.



Scheme 3.1 Retrosynthetic analysis for (-)-puraquinonic acid.

3.2 MODEL SYSTEM FOR PURAQUINONIC ACID

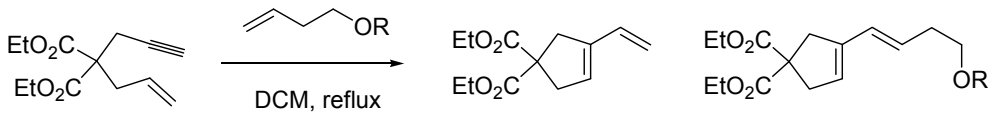
We expected enynes such as **216** to be readily prepared. However, their synthesis would be a minimum of five steps (two steps for the auxiliary synthesis plus three alkylation steps). Thus we opted for a simple model using diethyl malonate, which could be alkylated in 80% yield over two steps to afford **217** (Scheme 3.2).[7,8]

A tandem ring-closing/cross metathesis[9,10,11] of enyne **217** with 3-buten-1-ol was required to produce diene **219** (R=H) for the subsequent Diels-Alder cycloaddition (Table 3.1). The hydroxy group would serve as a handle for appending the dienophile, thus enabling an intramolecular Diels-Alder reaction. A literature search uncovered a tandem enyne ring-closing/cross metathesis reaction of **217** with but-3-enyl benzoate **223**.[11b] The reaction with unprotected 3-butenol or use of any other protecting group was not discussed. Nevertheless, we decided to perform the metathesis reaction using unprotected 3-butenol, as this would eliminate the need for an addition deprotection step.

To our dismay, the metathesis of enyne **217** with 3-butenol gave only the ring closing metathesis product **218** using the first generation Grubbs' catalyst (Table 3.1, entry 1). [12] The use of the second generation Grubbs' catalyst,[13] which is more active while displaying greater stability towards air and moisture, afforded only the ring closing metathesis product **218** as well (Table 3.1, entry 2). We then explored *tert*-butyldimethylsilyl (TBS) a protecting group as it is easily installed and removed. As the desired enyne ring-closing/cross metathesis

reaction was known to proceed using allyltrimethylsilane as the alkene partner,[11b] we anticipated that the reaction would tolerate the presence of a silyl protecting group. However, only the ring closing metathesis product **218** was obtained (Table 3.1, entry 3). We therefore turned to the use of but-3-enyl benzoate **223** where, as expected, the metathesis reaction proceeded smoothly to give the ring-closing/cross metathesis product **220** in 86% yield under optimized conditions (Table 3.1, entries 4-6).

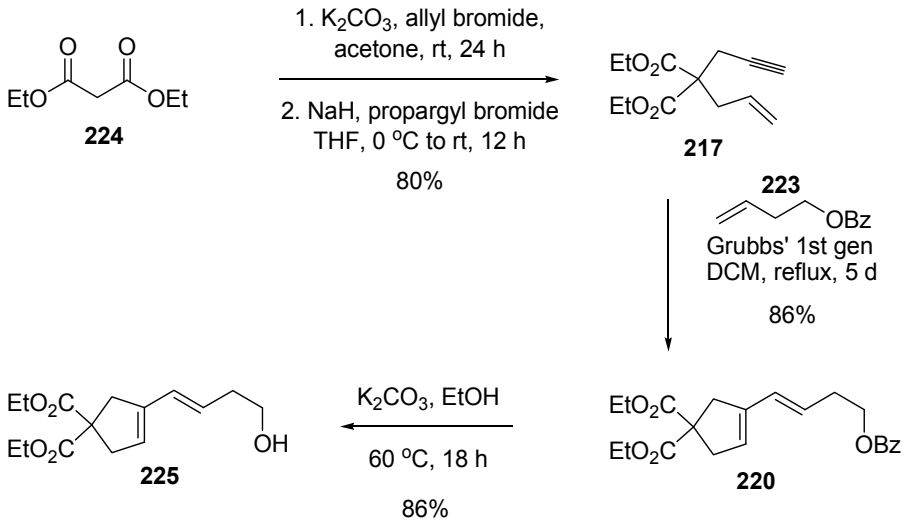
Table 3.1 Optimization of ring-closing/cross metathesis conditions.



217 **218** **219**

Entry	R	Alkene	Catalyst	Time	Product	Yield (%)
1	H	**221**	Grubbs' 1st gen	16 h	**218**	78
2	H	**221**	Grubbs' 2nd gen	16 h	**218**	N. D.[a]
3	TBS	**222**	Grubbs' 1st gen	16 h	**218**	79
4	Bz	**223**	Grubbs' 2nd gen	16 h	**219**	54
5	Bz	**223**	Grubbs' 1st gen	4 d	**219**	75
6	Bz	**223**	Grubbs' 1st gen	5 d	**219**	86

[a] N. D. Not determined.

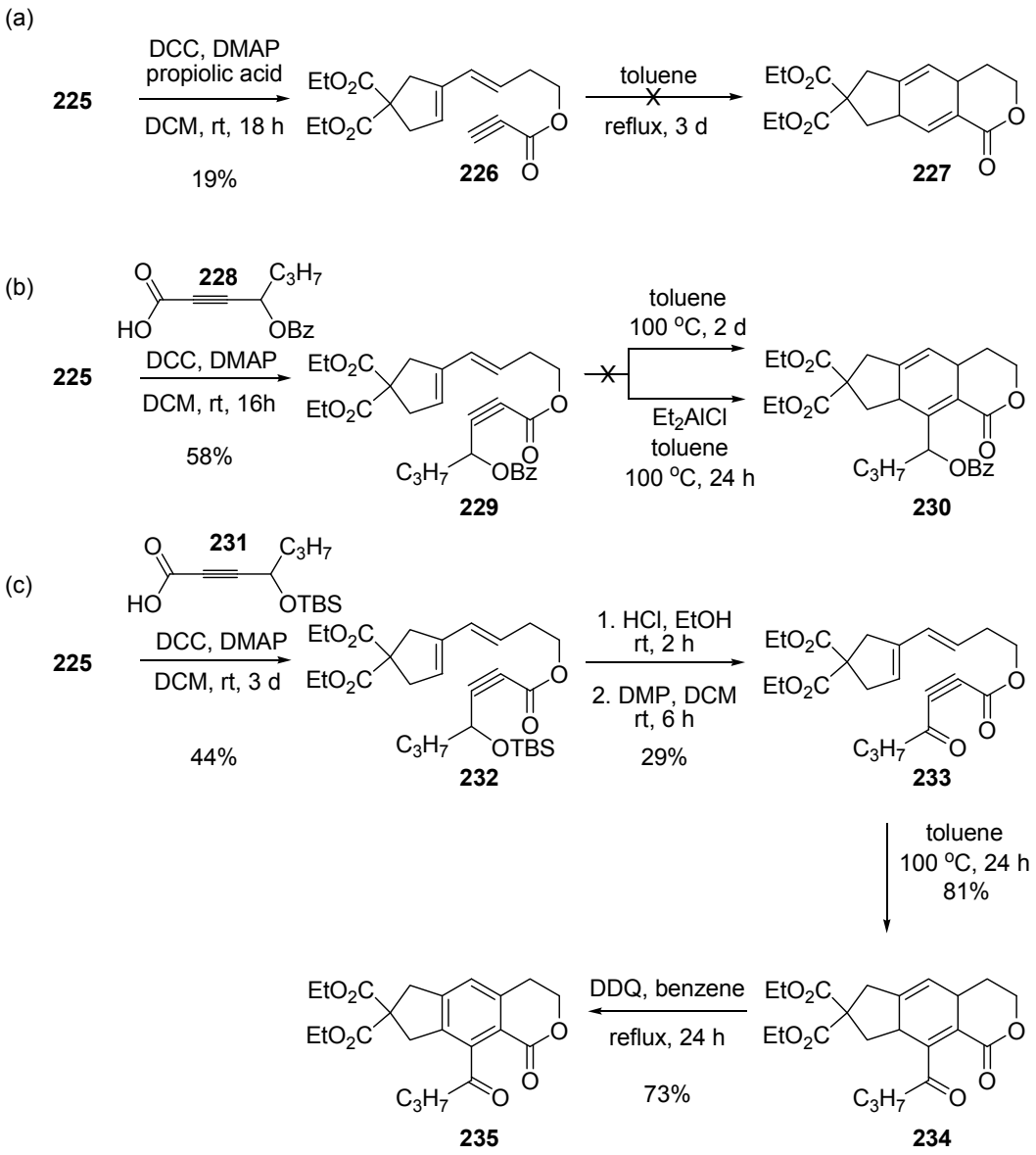


Scheme 3.2 Model system for the synthesis of puraquinonic acid.

To set the stage for studies on the Diels-Alder cycloaddition, the benzoyl group was removed using potassium ethoxide to reveal the alcohol (**225**) (Scheme 3.2). The intramolecular Diels-Alder was preferred as it circumvents regioselectivity issues that would be present in the intermolecular version. Thus, alcohol **225** was coupled[14,15,16] to a number of different alkynes to form dienynes, which could undergo intramolecular cycloadditions.

Reaction of **225** with propiolic acid gave the terminal alkyne **226**, which was subjected to refluxing toluene for three days (Scheme 3.3a). While it was disappointing that only starting material was recovered, this system did not meet all the requirements of the Diels-Alder precursor outlined in our retrosynthesis (*vide supra*). The terminal alkyne needed to be furnished with an additional carbonyl group to provide a handle for the required Baeyer-Villiger reaction. Accordingly, two other model substrates were where synthesized by coupling alcohol **225** to 4-benzoyloxyheptynoic acid and 4-silyloxyheptynoic acid to form **229** and **232** respectively. The presence of the protected propargylic alcohol

would allow for oxidation to a ketone either before or after cycloaddition. Attempted cycloaddition of internal alkyne **229** by heating to 100 °C in toluene only gave starting material, while addition of Lewis acids such as Et_2AlCl lead to decomposition products (Scheme 3.3b). Alkyne **232** was therefore deprotected and oxidized to give dienyne **233** (Scheme 3.3c). In this case, the dienophile is activated by the additional carbonyl group and gratifyingly, when heated to 100 °C for 24 hours in toluene, underwent a [4+2] cycloaddition to give **234** in 81% yield. The cycloadduct **234** was aromatized using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[17] in refluxing benzene,[18] to form **235** with a 73% yield.



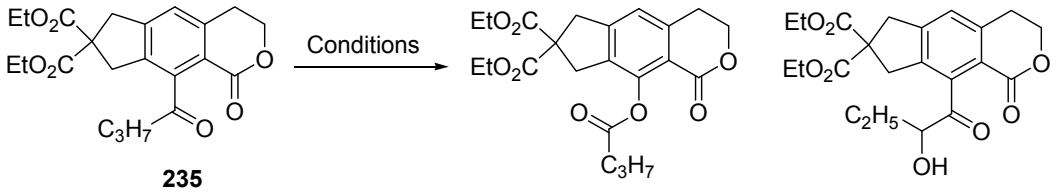
Scheme 3.3 Diels-Alder cycloaddition using terminal and internal alkynes.

At this point, it was necessary to install a heteroatom on the aromatic ring to facilitate the oxidation to a quinone (Table 3.2). It was anticipated that Baeyer-Villiger oxidation[19] of ketone **235** would give ester **236** upon preferential migration of the phenyl group, thus incorporating an oxygen atom on the central aromatic ring. Although Baeyer-Villiger reaction of such a highly substituted ketone is undocumented, we remained optimistic since there are numerous

examples where the corresponding Dakin oxidation[20] of pentasubstituted benzaldehydes could be performed.[21,22,23]

Unfortunately, treatment of **235** with *meta*-chloroperbenzoic acid (*m*-CPBA) under both basic[24] and acidic[25,26] conditions gave no reaction even when the reaction was heated to reflux in dichloromethane (Table 3.2, entries 1-3). Suspecting that the *di*-ortho substitution would contribute to significant steric hindrance at the reaction site, smaller peroxides were then employed. However, oxidation using sodium perborate[27] (Table 3.2, entry 5) or sodium percarbonate[28] (Table 3.2, entry 6) resulted in recovery of the starting material, while use of basic hydrogen peroxide[29] (Table 3.2, entry 7) resulted in decomposition. Meanwhile, use of trifluoroperacetic acid[30] (Table 3.2 entries 8-9) or prolonged reaction using *m*-CPBA (Table 3.2 entry 4), resulted in formation of the Rubottom oxidation[31] product **237**, which would arise from oxidation of an equilibrium quantity of enol. The lack of reactivity of ketone **235** towards Baeyer-Villiger oxidation, when the closely related Dakin oxidation of aldehydes is so well-documented, is most probably due to a combination of the steric crowding about the carbonyl moiety and the decreased reactivity of ketones towards nucleophilic addition compared to aldehydes. At this juncture, with all our attempts at the Bayer-Villiger oxidation of **235** unsuccessful, an alternative approach for installing a heteroatom on the aromatic ring was sought.

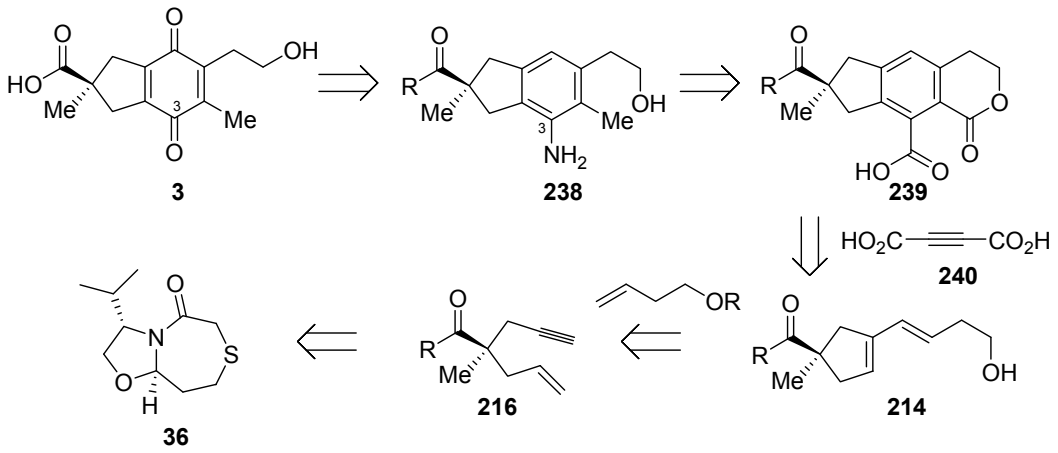
Table 3.2 Conditions for Baeyer-Villiger oxidation.



235 **236** **237**

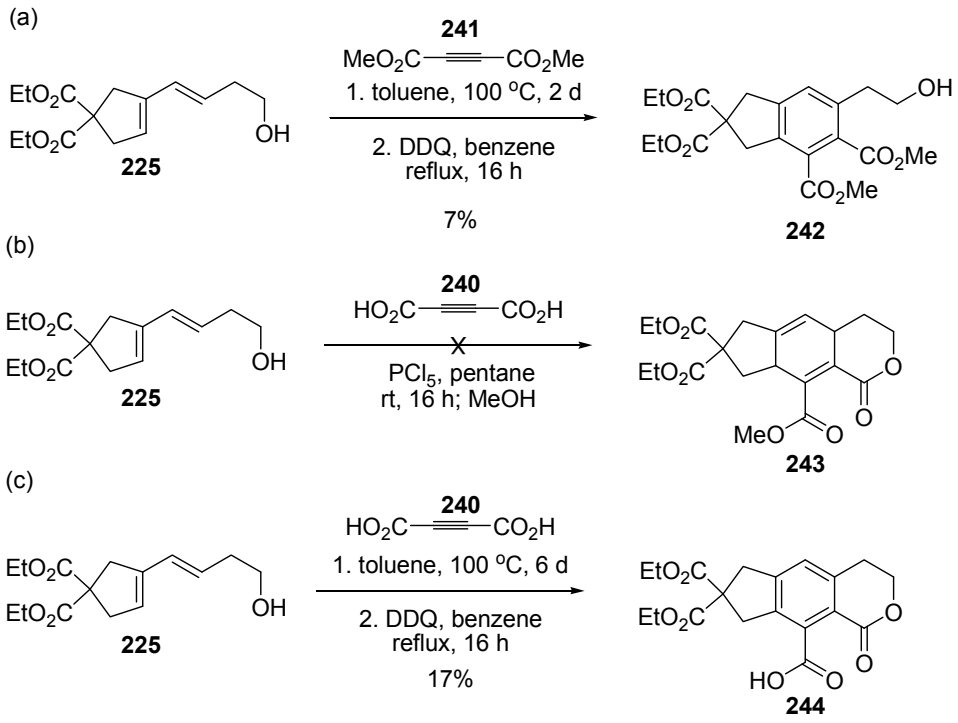
Entry	Reagent	Solvent	Temp	Time	Product	Yield (%)
1	*m*-CPBA, $NaHCO_3$	DCM	rt	14 d	SM	--
2	*m*-CPBA, TsOH	DCM	reflux	4 d	SM	--
3	*m*-CPBA, TFA	DCM	rt	16 h	SM	--
4	*m*-CPBA, TFA	DCM	rt	14 d	**237**	--
5	$NaBO_3 \cdot 4H_2O$, TFA	TFA	rt	16 h	SM	--
6	$Na_2CO_3 \cdot 1.5H_2O$, TFA	TFA	rt	16 h	SM	--
7	H_2O_2, NaOH	MeOH	rt	3 d	decomposition	--
8	TFAA, H_2O_2	DCM	rt	2 d	**237**	89
9	TFAA, H_2O_2	DCM	40 °C	16 h	**237**	78

Our inspiration came from the commercial production of benzoquinone. One method for the large scale production of benzoquinone is by oxidation of aniline using manganese dioxide or sodium dichromate in sulphuric acid.[32] To apply this to our synthesis, the required aniline **235** could be obtained from the Curtius rearrangement of an acyl azide derived from carboxylic acid **239** (Scheme 3.4). The Diels-Alder cycloaddition would remain a key step in this new sequence. Taking into consideration the requirement for two electron withdrawing groups on the dienophile, the same diene **214** would now be added to an acetylene dicarboxylic acid synthon.



Scheme 3.4 Modified retrosynthesis of (-)-puraquinonic acid.

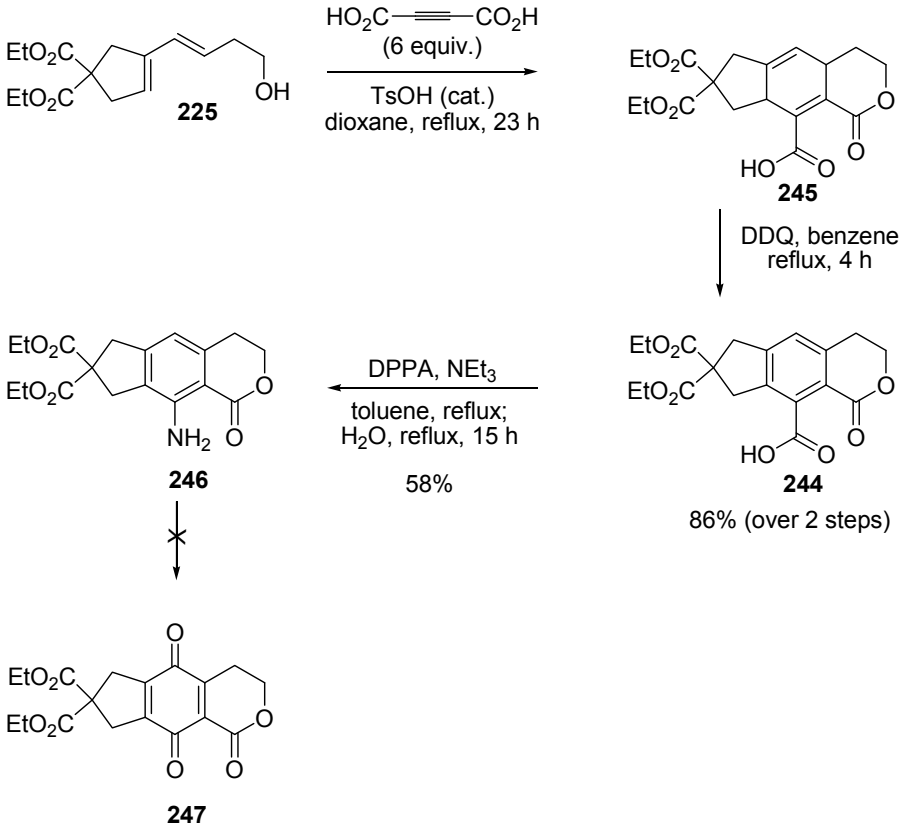
The previously synthesized dienol was examined in Diels-Alder reactions with both dimethyl acetylenedicarboxylate (DMAD) and acetylene dicarboxylic acid (Scheme 3.5). Symmetrical alkynes were employed to avoid the formation of regioisomers in the intermolecular Diels-Alder cycloadditions. When the reaction of **225** with dimethyl acetylenedicarboxylate was heated to 100 °C in toluene for 2 days, and then aromatized using DDQ, phthalate **242** was obtained in an unoptimized 7% yield (Scheme 3.5a). The cycloaddition of acetylenedicarboxylic acid with **225** in the presence of phosphorus pentachloride was expected to proceed via an intermediate diacyl dichloride (Scheme 3.5b).[33] Addition of alcohol **225** to the intermediate acyl chloride would enable an intramolecular Diels-Alder. However, under these conditions, no Diels-Alder adduct was observed. Direct cycloaddition with acetylenedicarboxylic acid under thermal conditions was more promising, occurring with concomitant lactonization to give the desired carboxylic acid **244** in 17% yield after aromatization (Scheme 3.5c).



Scheme 3.5 Diels-Alder cycloaddition with acetylene dicarboxylic acid equivalents.

The cycloaddition with acetylene dicarboxylic acid, which was preferred as the required carboxylic acid functionality is directly installed, was further optimized. The reaction proceeded more efficiently using dioxane as a solvent as it allowed for increased solubility of acetylene dicarboxylic acid.[34,35] Furthermore, addition of catalytic amounts of *p*-toluenesulfonic acid increased the rate of cyclization presumably by promoting Fischer esterification to form an intermediate dienyne, which can undergo intramolecular cycloaddition. Under these optimized condition, the cycloaddition yielded carboxylic acid **244** in 86% yield after aromatization (Scheme 3.6). The desired Curtius rearrangement[36] could be effected by treating carboxylic acid **244** with diphenylphosphoryl azide (DPPA) in refluxing toluene to give an isocyanate, which underwent hydrolysis in water to give aniline **246** in 58% yield.[37]

All attempts at oxidization of aniline **246** using a variety of oxidants including Fremy's salt (potassium nitrosodisulfonate),[38] sodium dichromate, and iodobenzene diacetate[6] led to the either the recovery of starting material or decomposition products (Scheme 3.6). A search of the literature revealed that nearly all oxidations of anilines to quinone occur on electron rich aromatics.[39]

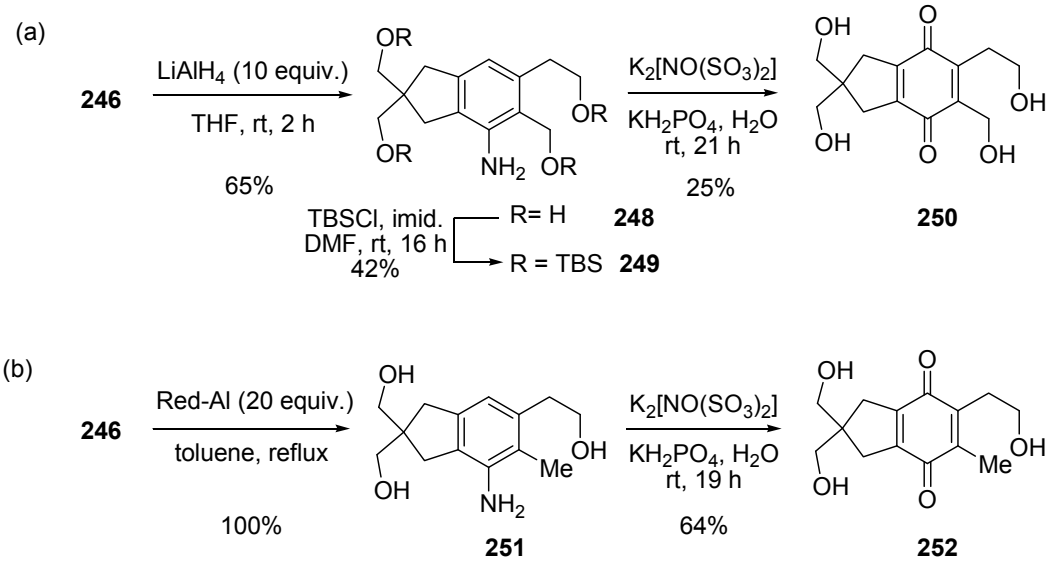


Scheme 3.6 Modified route to puraquinonic acid.

The electron withdrawing lactone was therefore removed by reduction to determine if this would enable aniline oxidation to the quinone. Reduction of lactone **246** using lithium aluminum hydride or Red-Al at room temperature led to the formation of tetraol **248** (Scheme 3.7a). We initially silylated tetraol **248** to facilitate purification and handling. Unfortunately the tetrasiloxy compound **249** could not be oxidized under any condition. However, the tetraol oxidized readily

with Fremy's salt to give quinone **250** (Scheme 3.7a). This difference in reactivity could be attributed to substrate solubility.

Although the oxidation to the quinone was now possible, this route would still require us to differentiate the hydroxy ethyl and hydroxy methyl groups on the quinone ring. A fortuitous solution was identified in that reduction of lactone **246** using Red-Al in refluxing toluene, led to the formation of triol **251** (Scheme 3.7b),[40] which possesses the required side chains on the right side of the molecule (methyl and ethyl hydroxy). Oxidation of triol **251** proceeded as for **248** to afford quinone **252** in 64% yield. This now completed the model system for puraquinonic acid, with all the required functionalities incorporated aside from the chiral quaternary center, which will be installed using our bicyclic lactam chiral auxiliary in the asymmetric version of the synthesis.



Scheme 3.7 Completed synthesis of model system.

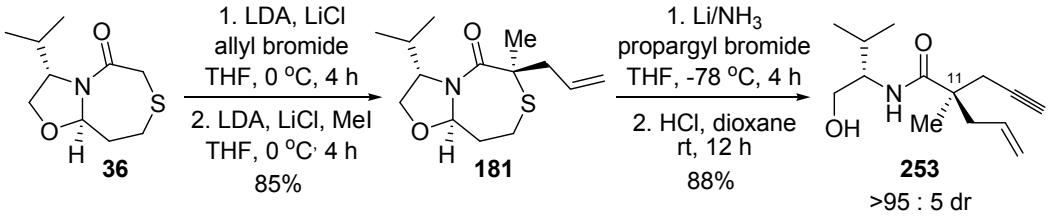
In summary, the synthesis of the 5,6-bicyle in puraquinonic acid was keyed by the use of metathesis and Diels-Alder reactions. The side chains (ethyl

hydroxy and methy) were obtained from lactone reduction, while the quinone ring was constructed from a facile oxidation of aniline. Importantly, several criteria were established to direct our subsequent work on the synthesis of the natural product. In the tandem ring-closing/cross metathesis, 3-buten-1-ol must be protected as an ester as hydroxy and silyloxy groups are not tolerated. The Diels-Alder cycloaddition requires that the dienophile be activated by two carbonyl groups, while oxidation of the aniline to the quinone only proceeds in the absence of electron withdrawing functionality on the aromatic ring.

3.3 SYNTHESIS OF (-)-PURAQUINONIC ACID

The diethyl malonate model system allowed us a study of all the structural elements necessary in puraquinonic acid aside from the quaternary stereocenter at C-11. Our asymmetric synthesis of puraquinonic acid therefore commenced with the assembly of the quaternary stereocenter using the previously developed bicyclic thioglycolate lactam[41,42,43] (Section1.1.4). Auxiliary **36** was first allylated, and then methylated to give dialkylated auxiliary **181** in 85% yield as a single diastereomer (Scheme 3.8). Reductive enolization of **181** using lithium in ammonia followed by addition to propargyl bromide and hydrolysis of the aminal formed the quaternary stereocenter in 88% yield and > 95:5 dr. Partial removal of the auxiliary by aminal hydrolysis was performed because the presence of amide rotamers and the thermal instability of the aminal complicated product analysis. Moreover, subsequent steps in the synthesis involved use of thermal and acidic

conditions, which would cleave the aminal and may result in unwanted side reactions. In proceeding, we elected to maintain the amide instead of hydrolyzing to the carboxylic acid, which is present at C-11 of puraquinonic acid, as the acid is incompatible with subsequent steps in the synthesis. In addition, the stability of the amide functionality allows it to be carried through to the end of the synthesis, while being differentiated from other acyl groups. The resultant alcohol in **253** would be protected with an acid labile group, so that it can be deprotected using the same acidic conditions required for carboxylic acid formation at a late stage of the synthesis.



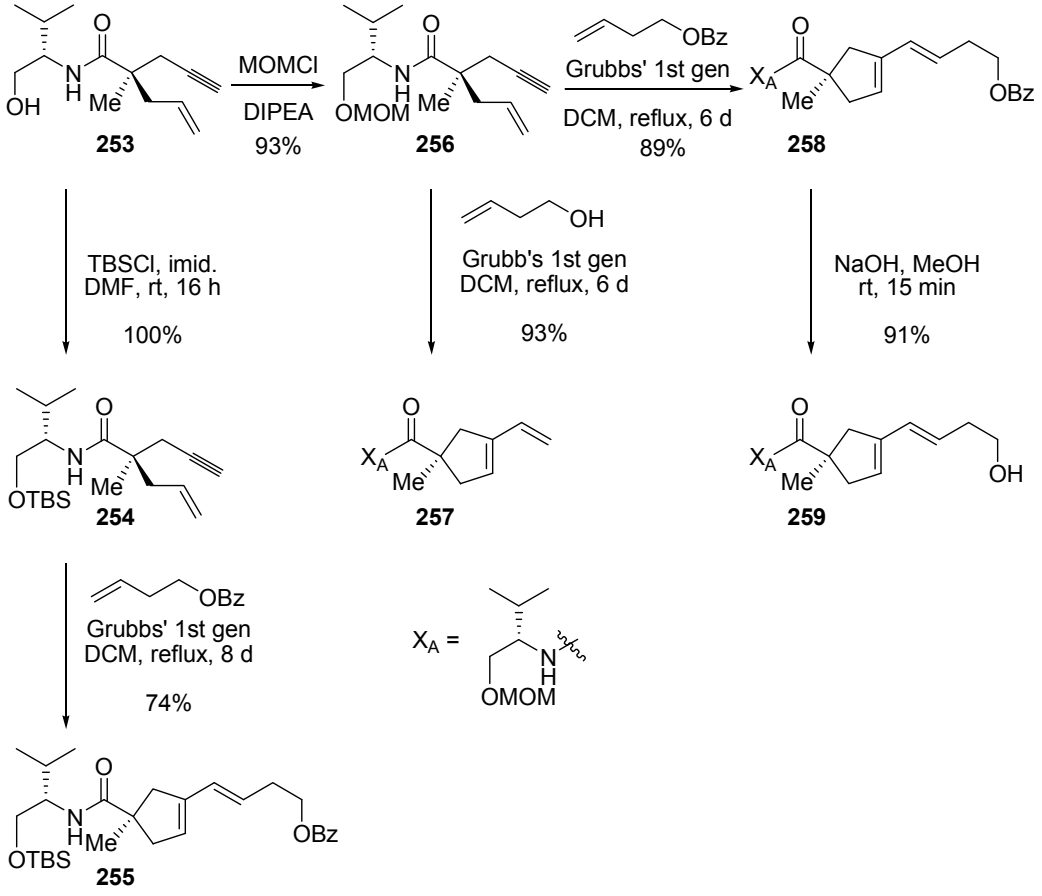
36 **181** **253**

>95 : 5 dr

Scheme 3.8 Formation of quaternary carbon center in (-)-puraquinonic acid.

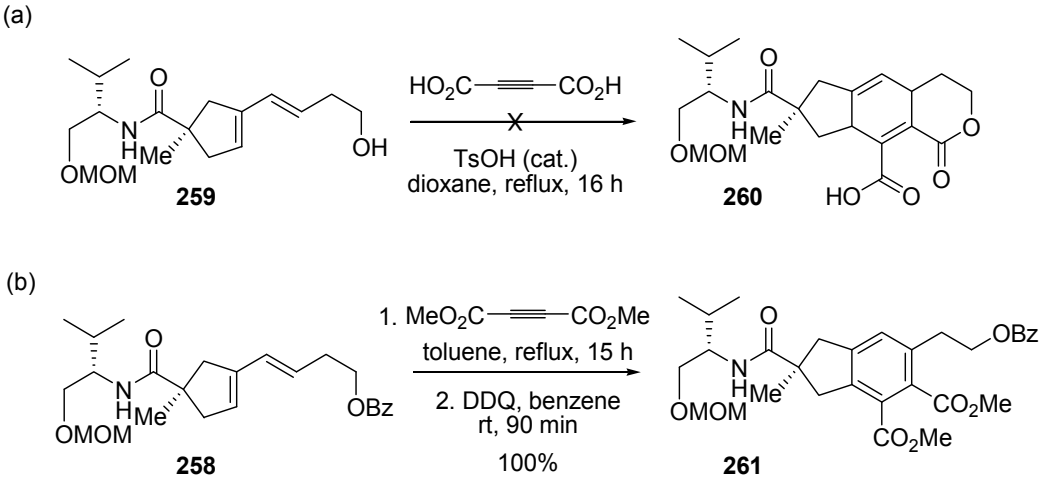
To set up for the tandem ring-closing/cross metathesis reaction, primary alcohol **253** was then silylated to give **254** in quantitative yield (Scheme 3.9). While the model system did not tolerate *tert*-butyldimethylsilyl (TBS) protected 3-buten-1-ol as a dienophile in the ring-closing/cross metathesis reaction, silylation of the diene component was well tolerated and the reaction gave diene **255** in 74% yield. We were concerned with the long term stability of the primary *tert*-butyldimethylsilyl protected alcohol, thus for a more acid stable protecting group, alcohol **253** was protected as a methoxy methyl ether (**256**), then subjected to the previously developed metathesis conditions. Similar to the model system, it was found that metathesis with unprotected butenol gave only the ring-closing

enyne metathesis product **257** (93% yield), while use of the equivalent benzoate ester gave the ring-closing/cross metathesis product **258** in 89% yield after 6 days. Attempts at speeding up the reaction by using toluene or 1,2-dichloroethane (DCE) as the solvent conversely decreased the rate of the cross metathesis reaction, while use of second generation Grubbs' catalyst had no effect on the reaction rate. The reaction could only be sped up by increasing the amount of catalyst. Using double the amount of catalyst (20 mol%), the reaction was completed in 2 days, however a slight erosion in yield was observed (78% yield). To prepare for the Diels-Alder cycloaddition, benzoate ester **258** was saponified using sodium hydroxide to reveal the alcohol in 91% yield.



Scheme 3.9 Ring closing – cross metathesis to form the diene.

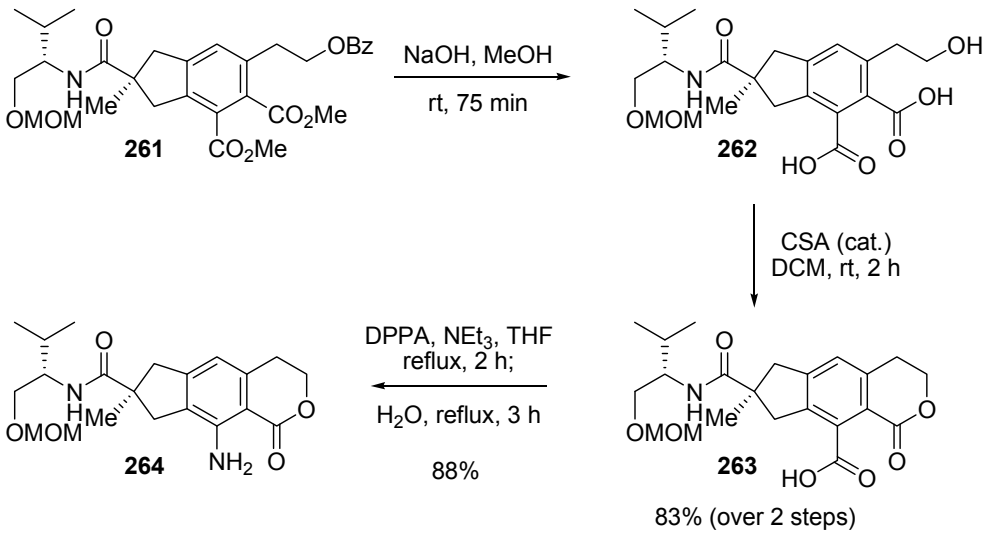
Diels-Alder cycloaddition of diene **259** with acetylenedicarboxylic acid under conditions previously optimized for the model system resulted only in decomposition (Scheme 3.10a). An NMR experiment performed by dissolving the diene in deuterated toluene and heating at to 100 °C showed that within an hour approximately half the material had decomposed. Addition of *p*-toluenesulfonic acid accelerated the decomposition process. It was not clear why the change from diester to amide in the 5-membered ring resulted in this different stability. In sharp contrast, the cycloaddition of benzoyl protected amide **258** with dimethyl acetylenedicarboxylate, which had proceeded in low yields in the model system, proved to be a facile reaction when minimal solvent was used (Scheme 3.10b). Under optimized conditions, it was found that reaction of two equivalents of dimethyl acetylenedicarboxylate with a 0.7 M solution of **258** in refluxing toluene for 15 h, led to formation of **261** in quantitative yield after aromatization using DDQ.



Scheme 3.10 Diels-Alder cycloaddition to form the 6-membered ring.

Global saponification of all three esters gave dicarboxylic acid **262**, which was subjected to acid promoted lactone formation (Scheme 3.11). The lactone

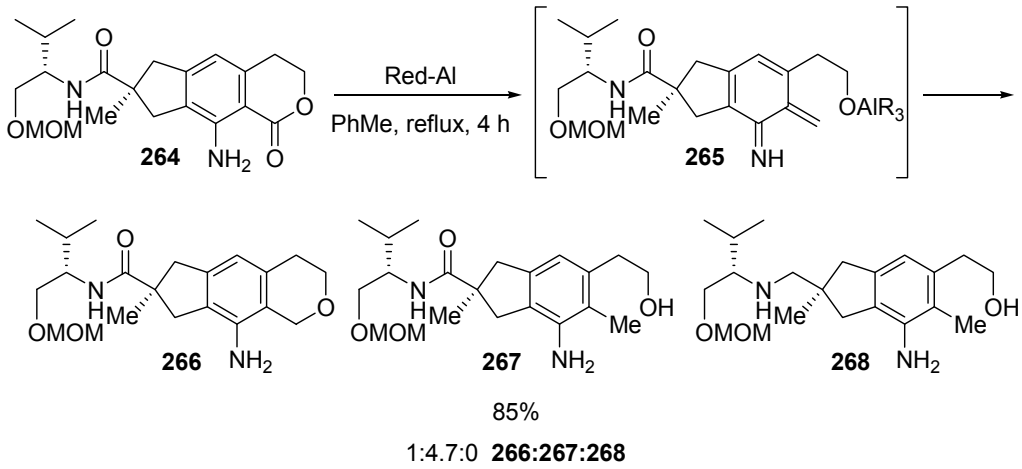
formation was necessary to enable differentiation of the two carboxylic acids and to protect the hydroxy group. Although lactonization is typically carried out in benzene, it proved to be a poor solvent in this case due to the insolubility of diacid **262**, prompting the choice of dichloromethane as a solvent. *p*-Toluenesulfonic acid could be used to promote lactonization on a small scale, but the yields decreased on a larger scale. Meanwhile, use of hydrochloric acid and acetic acid gave low yields and no reaction respectively. Camphor sulfonic acid was found to be the superior catalyst for lactonization, affording carboxylic acid **263** in 83% yield over 2 steps. As in the model system, reaction of carboxylic acid **263** with diphenylphosphoryl azide formed the acyl azide, which underwent a Curtius degradation to the amine **264** in 88% yield.



Scheme 3.11 Installation of the aniline moiety.

With the amine in hand, reduction of the lactone was now explored. In contrast to the model system, we required a selective reduction of the lactone, ideally to a methyl group, without concomitant reduction of the secondary amide. When lactone **264** was subjected to reduction using four equivalents of Red-Al in

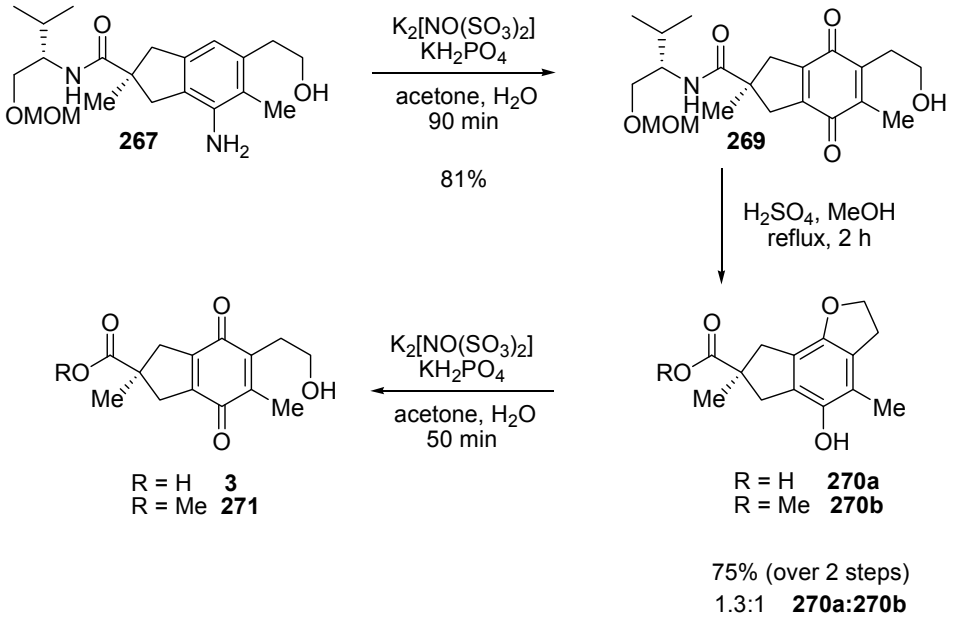
refluxing toluene, a 4.7:1 mixture of the desired alcohol **267** along with ether **266** was obtained in 85% yield (Scheme 3.12). The ether proved to be inert to further reduction when resubjected to Red-Al but can be easily removed via column chromatography. The lack of reduction of ether **266** suggests that the reduction to the methyl group likely proceeds via intermediate **265**, where the unwanted ether **266** is formed by intramolecular addition of the alcohol to the imine. Attempts to suppress the formation of the ether by-product by changing the solvent, reductant, and reaction time were unsuccessful. In fact, when the reductant was added slowly, in a dropwise fashion, a higher ratio of ether **266** was observed. Although this translated to an isolated yield of 70% for the alcohol **267**, this is a noteworthy reaction, as two side chains (methyl and ethyl hydroxy) are installed in one step. In addition, the benzylic carbonyl group is reduced to the methyl group while the amide carbonyl is left untouched. This selectivity is due to the assistance of the *o*-amine in the reduction and the steric hindrance about the amide moiety. Increasing the amount of Red-Al will lead to reduction of the amide to give amine **268**. The formation of the amine was noted when 4.2 equiv Red-Al was used (80% yield, 1:13.6:1.4 **266**:**267**:**268**).[44] Use of a large excess of Red-Al (10 equiv) led to the formation of amine **268** as the major product.



Scheme 3.12 Formation of the side chains via lactone reduction.

To our satisfaction, oxidation of the aniline **267** using Fremy's salt as an oxidant gave quinone **269** in 81% yield (Scheme 3.13). At this stage, all that would be left to complete the synthesis would be amide hydrolysis. Under acidic conditions, it was expected that the methoxy methyl ether would be cleaved, and the resultant alcohol would undergo N to O acyl transfer to give an ester that could be hydrolyze to give (-)-puraquinonic acid. However, when subjected to aqueous sulphuric acid in refluxing methanol, dihydrofuran **270a** and **270b** were obtained. The ester **270b** was obtained from transesterification of the intermediate ester with methanol, and indeed use of a non-alcoholic solvent such as dioxane suppressed the ester formation but still resulted in the formation of dihydrofuran **270a**. Both of these reactions require reduction of the benzoquinone ring system and it is unclear what serves the role of the reductant in the reaction. Initially, we suspected reduced sulfur species in the sulphuric acid. However, changing the acid to hydrochloric acid still resulted in dihydrofuran formation, albeit with a lower yield. **270a** and **270b** could be reoxidized to give (-)-puraquinonic acid and (-)-puraquinonic methyl ester in 75% yield over 2 steps in a 1.3:1 ratio. However,

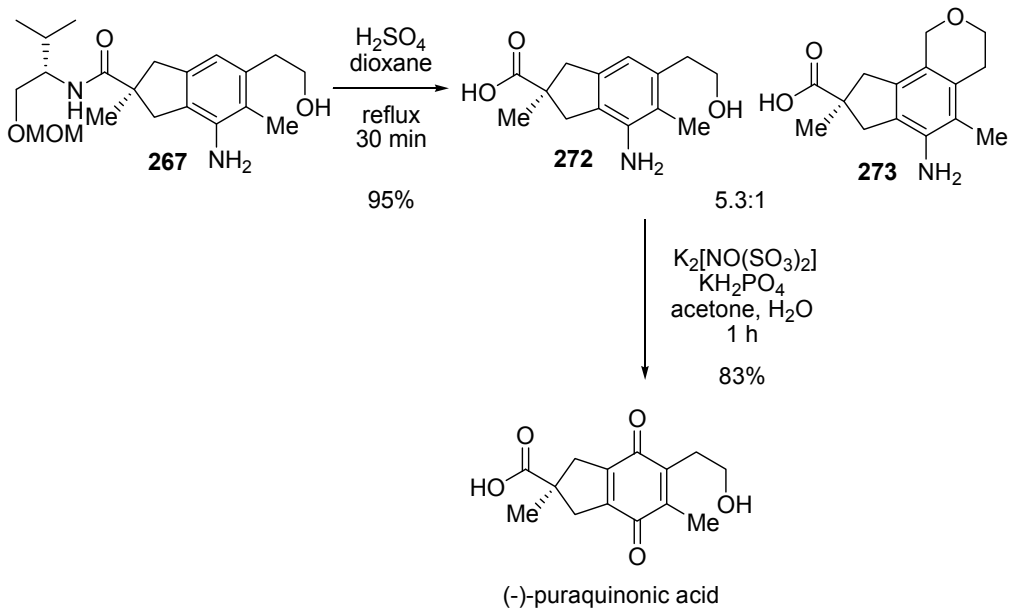
the redundancy of performing the oxidation of the aromatic ring twice prompted a revision of the final steps of the reaction sequence.



Scheme 3.13 Formation of dihydrofuran side product during auxiliary cleavage.

To avoid two oxidation reactions to form the quinone, we investigated the possibility of conducting the amide hydrolysis first. There was some concern with this approach as we had previously found that hydrolysis of β-amino amides was quite challenging (Section 2.9.1). We were delighted to find that when the aniline **267** was subjected directly to acidic hydrolysis using 4 M sulphuric acid in refluxing dioxane, the desired amino acid **272** was formed in 80% yield (Scheme 3.14). However a dihydropyran side product **273** was also observed (15% yield). The dihydropyran ring formation occurs via the addition to formaldehyde given off from methoxy methyl ether deprotection. Longer reflux times led to decreases in yield, while increasing the formation of the side product. Use of 1 M sulphuric acid gave almost complete formation of the undesired dihydropyran product,

while increasing the molarity of the acid to 6 M gave 1:1 mixture of both products in quantitative yield. No condition could be found to give only the desired acid **272**, but the 80% yield with 4 M acid was sufficient for our needs.



Scheme 3.14 Total synthesis of (-)-puraquinonic acid.

Finally, the oxidation of the aniline to the quinone proceeded smoothly using Fremy's salt to give (-)-puraquinonic acid in 83% yield. The characterization data of our synthetic (-)-puraquinonic acid was in good agreement with literature values (Table 3.3). Hence, the overall synthesis of (-)-puraquinonic acid was accomplished in 14 steps with an overall 21% yield.

Table 3.3 Comparison of characterization data for synthetic (-)-puraquinonic acid with literature values.

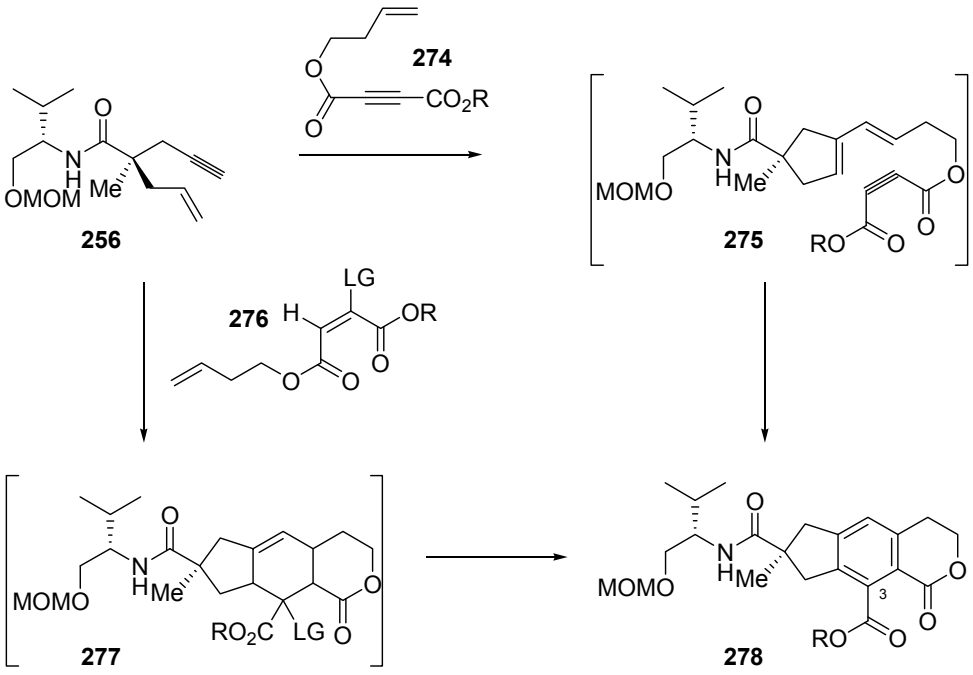
	Experimental Value	Literature Value
^{1}H NMR (500 MHz, $CDCl_3$)	3.76, 2H, t, 6.5 Hz	3.75,2H, t, 6.5Hz
	3.36, 2H, m	3.37, 2H, m
	2.78, 2H, t, 6.5 Hz	2.78, 2H, t, 6.5 Hz
	2.73, 2H, m	2.74, 2H, m
	2.07, 3H, s	2.07, 3H, s
	1.41, 3H, s	1.41, 3H, s
^{13}C NMR (125 MHz, $CDCl_3$)	186.2	186.2
	185.7	185.7
	181.9	181.5
	145.7	145.7
	145.3	145.4
	142.8	142.8
	141.3	141.4
	61.4	61.4
	46.9	46.9
	42.3	42.3
	42.2	42.3
	29.8	29.9
	25.7	25.7
	12.2	12.1
IR (KBr)	3450	3450
	2964	2965
	1705	1705
	1647	1650
	1462	1460
	1430	1425
	1376	1375
	1333	1330
	1285	1285
	1210	1210
	1040	1045
	719	720
MS (EI) *m/z*	MNa^+ 287.09008	M^+ 264.0999
[α]$_D^{25}$	+1.5 ° (c 0.3, $CHCl_3$)	+1 ° (c 1.0 $CHCl_3$)
Physical appearance	Yellowish oil	Yellowish oil

3.4 FUTURE DIRECTION

Although, the synthesis of puraquinonic acid was completed with very satisfactory yields and number of steps, we sought to further improve our synthetic route if possible. Carboxylic acid **263**, which was required for a Curtius rearrangement to install a heteroatom at C-3, was synthesized in five steps from chiral enyne **256**. However, the 5,6-bicycle of puraquinonic acid was completed within the first two steps. The subsequent 3 steps were functional group manipulations to access the desired substrate for a Curtius rearrangement while protecting all other reactive functionality. In particular, the ethyl hydroxy side chain at C-7 was protected as a benzyl ester in order to perform the enyne ring-closing/cross metathesis. It was then deprotected by saponification, before being reprotected as a lactone. We envisioned that if we designed the alkene component in the metathesis reaction with the dienophile component required for the Diels-Alder cycloaddition already incorporated, we could perform a one-pot tandem ring-closing/cross metathesis/Diels-Alder/aromatization sequence,[45] in essence combining the metathesis, cycloaddition, aromatization, deprotection, and lactone formation into one step.

Knowing that the enyne ring-closing/cross metathesis reaction tolerates the presence of esters, we thus used an ester linkage between the alkene component required for metathesis and the alkyne component required for the Diels-Alder cycloaddition as depicted in **274** (Scheme 3.15). The other end of the alkyne would incorporate the required carboxylic acid, likely masked as an ester. It would also serve as the extra activating group required for the Diels-Alder

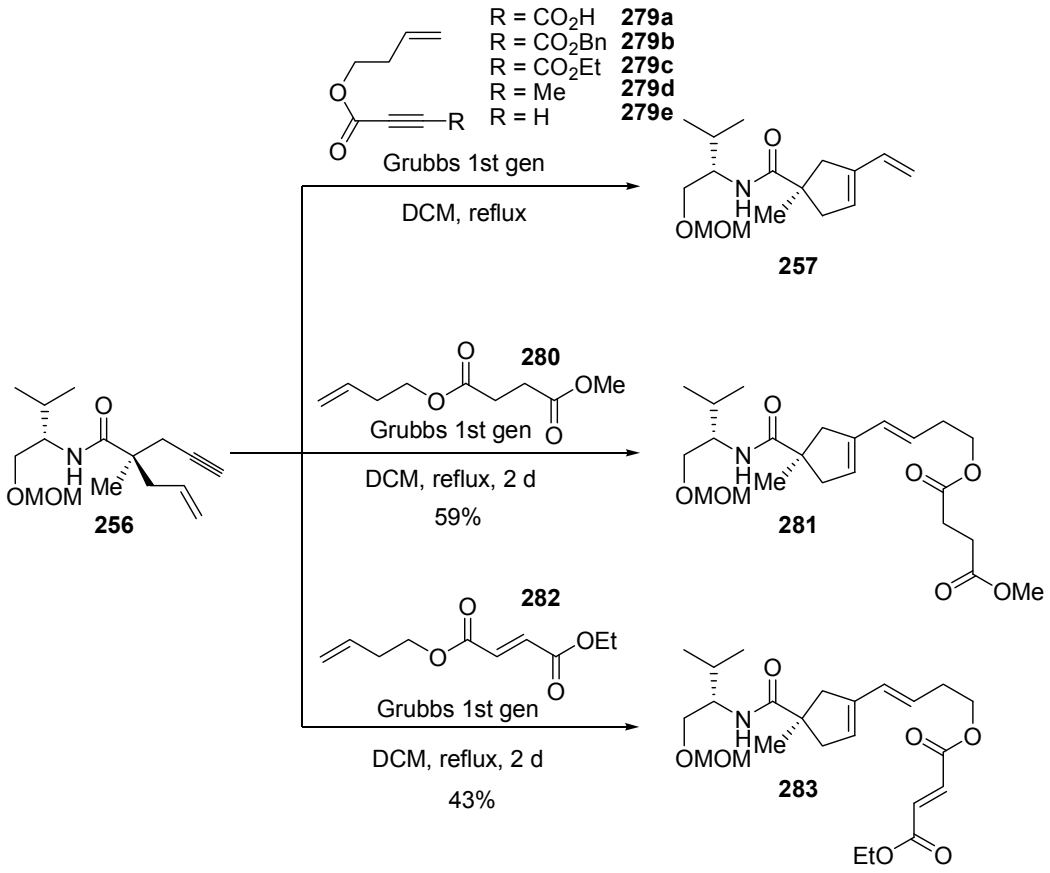
reaction. Alkynes with electron withdrawing groups attached are known to be sluggish to metathesis,[11a] and thus were not expected to interfere with the metathesis reaction. Upon ring-closing/cross metathesis, dienyne **275** would be formed, which could undergo an intramolecular Diels-Alder cycloaddition to give **278** after aromatization by ruthenium catalyzed transfer hydrogenation, which can be performed with the same catalyst used for metathesis.[46] Thus, by building complexity into the alkene component, a more convergent synthesis could be performed, allowing for a shorter linear sequence overall. Additionally, this would create a novel tandem reaction sequence to efficiently generate a 5,6,6-tricyclic structures in natural product synthesis.



Scheme 3.15 Tandem metathesis/Diels-Alder sequence.

To explore the plausibility of our proposed tandem reaction sequence, enyne **279a** was synthesized (Scheme 3.16). However, when subjected to the previously developed conditions for metathesis, only enyne ring-closing

metathesis product **257** was observed. Since carboxylic acids are not known to be compatible with metathesis reactions, we suspected that it may be interfering with the desired reaction. Thus, diesters **279b** and **279c** were synthesized. The benzyl ester **279b** would allow for selective deprotection by hydrogenation in the final product, without opening the lactone. However, its synthesis from the addition of but-3-enyl propiolate (**279e**) to benzyl chloroformate resulted in contamination by dibenzyl carbonate. Thus diester **279c** was also synthesized as it could be obtained cleanly. Unfortunately, metathesis reaction with both **279b** and **279c** gave only the ring closing product **257**. Reaction with second generation Grubbs' catalyst and well as first generation Hoveyda-Grubbs' catalyst[47] resulted in **257** as the major product as well. Speculating that the second ester group might be interfering with the reaction, enyne **279d** and **279e** were subjected to metathesis, but to no avail. It seemed likely then, that the alkyne component was deactivating the alkene towards metathesis. This was verified by the reaction of enyne **256** with diester **280**, which lacks the alkyne group. Tandem ring-closing/cross metathesis proceeded readily to give diene **281** in 59 % yield.



Scheme 3.16 Studies towards a tandem metathesis/Diels-Alder sequence.

Our inability to carry out the desired ring-closing/cross metathesis sequence therefore prompted a change in our reaction scheme. Instead of an alkyne, a masked acetylene in the form of **276**, with an alkene component bearing a leaving group, would be employed (Scheme 3.15). Metathesis followed by Diels-Alder cycloaddition would give **277**. Elimination of the leaving group would form a diene, which can be aromatized. We postulated that a sulfinyl group would be an appropriate group as vinyl sulfoxides are known to undergo Diels-Alder cycloadditions.[48] In addition, elimination of the sulfinyl group will proceed under thermal conditions.

Preliminary investigation of the ring-closing/cross metathesis of enyne **256** with diene **282**, showed the formation in triene **283** in 43% yield **(**Scheme 3.16**)**. That the desired metathesis reaction proceeds with the presence of the alkene is promising. Future work will focus the use of vinyl sulfoxides as acetylene masking group in the tandem ring-closing cross metathesis.

3.5 CONCLUSIONS

An efficient and concise route to (-)-puraquinonic acid was developed. This synthesis featured the use of bicyclic thioglycolate lactam **36** to install the quaternary center stereoselectively from the start. The resultant enyne could be use in a sequential ring-closing cross metathesis followed by Diels-Alder cycloaddition to rapidly assemble the 5- and 6- membered rings. A Curtius rearrangement resulted in the formation of an aniline, which was oxidized to the quinone using Fremy's salt. The ethyl hydroxy and methyl side chains were installed via a selective lactone reduction, while the carboxylic acid functionality was installed by acidic hydrolysis of the chiral auxiliary. The overall synthesis was performed in 14 steps from lactam[49] **36** and in 21% overall yield.

This route represents a significant improvement over the previous asymmetric synthesis[5,6] as (-)-puraquinonic acid was synthesized in less than half the steps. The previous asymmetric synthesis was done in 32 steps from known starting material (or 38 steps from commercially available starting materials) and in 1% overall yield (Section 1.3.4.2). In fact, our asymmetric synthesis of

puraquinonic acid is comparable to the shortest racemic synthesis,[50] which was 10 steps to puraquinonic acid ethyl ester with an overall yield of 23% (Section 1.3.4.1). This exemplifies the utility of the bicyclic thioglycolate lactam **36** in the synthesis of natural products.

The rapid access to the norilludalane skeleton could be applied to the enantioselective synthesis of other members of the family such as russujaponol L (**105**),[51] deliquinone (**106**),[52] and epoxydeliquinone (**107**)[52] with minor modifications to the synthetic sequence. All these compounds have unknown absolute stereochemistry, which can be easily verified via synthesis.

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CONTRIBUTIONS TO KNOWLEDGE

1. An expedient, 2 step synthesis of chiral bicyclic thioglycolate lactam **36** was achieved.

2. Using chiral auxiliary **36**, a general method for the asymmetric synthesis of quaternary carbon centers via the Mannich reaction was developed. The reaction tolerates a variety of substituents at both the α- and β-positions to give α,α-disubstituted β-amino carbonyl compounds with good diastereoselectivity.

3. Hydrolytic cleavage and amide reduction were established as methods to remove the chiral auxiliary, and access β-amino acid and alcohol respectively. Reductive cleavage of the N-S bond was performed to isolate the free amine from the Mannich adducts.

4. Chiral auxiliary **36** was successfully employed in a concise synthesis of (-)-puraquinonic acid. The synthesis was completed in 14 steps and represents a significant improvement over the only other published asymmetric synthesis.

5. The 5,6-bicyclic core of (-)-puraquinonic acid was efficiently assembled using a tandem ring-closing metathesis followed by a Diels-Alder cycloaddition. Conditions for the installation of the ethyl hydroxy and methyl side chains of (-)-puraquinonic acid by selective reduction of a lactone over an amide were developed. Conditions for acidic hydrolysis of the chiral auxiliary to install the desired carboxylic acid functionality were established.

CHAPTER 4. EXPERIMENTAL PROCEDURES

General Experimental

All commercial reagents were used without further purification with the following exceptions: Tetrahydrofuran was distilled from sodium benzophenone ketyl. Diisopropylamine, dichloromethane, and triethylamine were distilled from calcium hydride. *n*-Butyllithium was titrated with *sec*-butanol in toluene using 2,2'-dipyridyl as an indicator. Chiral auxiliary **36** can be purchased from Aldrich or prepared as published.[1] Alkylation and imine addition substrates were dried via azeotropic removal of water using dry toluene. Alkyl halides were passed through basic alumina prior to use. All reaction flasks and lithium chloride were flame-dried under vacuum. All reactions were conducted under argon. Chromatography was conducted using 200-400 mesh silica gel. NMR spectra were recorded at 400 or 500 MHz for ^{1}H and 67.5, 75, or 100 MHz for ^{13}C. Coupling constants are reported in Hz. HPLC analyses were conducted on a Phenomenex Luna 3μ silica column. High resolution mass spectrometry was performed by Nadim Saade and Alain Lesimple at McGill University.

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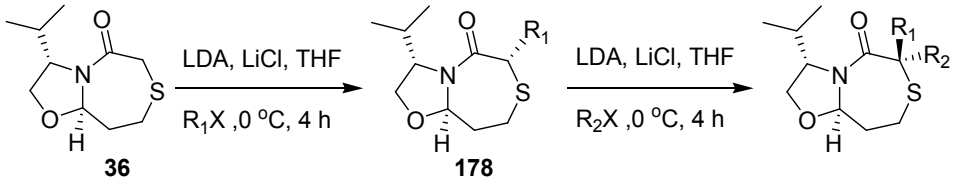
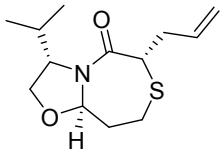
4.1 STEREOSELECTIVE FORMATION OF α-QUATERNARY STEREOCENTERS VIA THE MANNICH REACTION

Sample procedure for alkylation with alkyl halides.



36 **178**

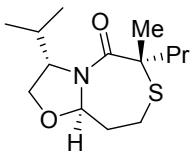
Synthesis of (3*S*,7*R*,10*S*)-1-Aza-10-isopropyl-3-allyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (178, R=allyl).



A solution of *n*-butyllithium in hexanes (2.63 M; 1.18 mL; 3.10 mmol; 1.10 equiv.) was added to a slurry of diisopropylamine (473 μL, 3.38 mmol; 1.20 equiv.) and lithium chloride (596 mg; 14.07 mmol; 5.0 equiv.) in tetrahydrofuran (35 mL) at 0 °C. After 15 minutes, a solution of (7*R*,10*S*)-1-Aza-10-isopropyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone **36** (606 mg; 2.81 mmol; 1.0 equiv.) in tetrahydrofuran (15 mL) was added via cannula. The resulting mixture was stirred for 15 minutes, whereupon allyl bromide (502 μL; 5.63 mmol; 2.0 equiv.) was added dropwise. After stirring for 4 h at 0 °C, a solution of saturated aqueous ammonium chloride (10 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel eluting 20% ethyl acetate in hexanes to afford 681 mg of **178** (R=allyl) as a white solid (95% yield). ^{1}H NMR ($CDCl_3$)

δ 5.78 (1H, m), 5.35 (1H, d, *J* = 10.0 Hz), 5.16 (1H, d, *J* = 17.0 Hz), 5.09 (1H, d, *J* = 10.5 Hz), 4.25 (1H, m), 3.90 (1H, t, *J* = 7.5 Hz), 3.81 (1H, dd, *J* = 8.5, 3.0 Hz), 3.48 (1H, t, *J* = 7.5 Hz), 2.87 (1H, m), 2.80 (1H, m), 2.71 (1H, dt, *J* = 14.0, 4.0 Hz), 2.62 (1H, m), 2.35 (2H, m), 2.01 (1H, m), 0.85 (3H, d, *J* = 7.0 Hz), 0.81 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 169.5, 134.1, 118.0, 88.6, 64.3, 62.6, 47.0, 34.8, 34.7, 27.8, 23.8, 19.2, 16.0; IR (film) ν 2956, 2875, 1616, 1431, 1415, 1193, 1169, 952. HRMS calc. for ($C_{13}H_{22}NO_2S^+$): 256.13680. Found: 256.13658. mp 78-80 °C.

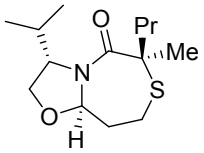
Synthesis of (3*S*,7*R*,10*S*)-1-Aza-3-propyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (180).



A solution of *n*-butyllithium in hexanes (2.15 M; 752 μL; 1.62 mmol; 1.10 equiv.) was added to a slurry of diisopropylamine (237 μL, 1.69 mmol; 1.15 equiv.) and lithium chloride (312 mg; 7.35 mmol; 5.0 equiv.) in tetrahydrofuran (15 mL) at 0 °C. After 15 minutes, a solution of (3*S*,7*R*,10*S*)-1-Aza-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (337 mg; 1.47 mmol; 1.0 equiv.) in tetrahydrofuran (5 mL) was added via cannula. The resulting mixture was stirred for 15 minutes, whereupon propyl iodide (187 μL; 2.94 mmol; 2.0 equiv.) was added dropwise. After stirring for 4 h at 0 °C, a solution of saturated aqueous ammonium chloride (10 mL) was added and the resulting mixture was warmed to 23 °C and extracted with ethyl acetate (3 x 15 mL). The combined organic layers

were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel eluting 20% ethyl acetate in hexanes to afford 365 mg of (3*S*,7*R*,10*S*)-1-Aza-3-propyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (**180**) as a white solid (92% yield). ^{1}H NMR ($CDCl_3$) δ 5.57 (1H, dd, *J* = 10.0, 2.0 Hz), 4.30 (1H, m), 3.87 (2H, m), 2.95 (1H, m), 2.69 (1H, dt, *J* = 15.0, 5.0 Hz), 2.38 (1H, m), 2.25 (1H, dt, *J* = 14.0, 2.0 Hz), 1.95 (2H, m), 1.80 (1H, dt, *J* = 12.5, 4.5 Hz), 1.49 (3H, s), 1.43 (1H, m), 1.31 (1H, m), 0.94 (3H, t, *J* = 7.0 Hz), 0.87 (3H, d, *J* = 7.0 Hz), 0.83 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.1, 89.0, 63.7, 63.3, 51.1, 41.2, 35.1, 27.5, 26.2, 23.9, 19.5, 18.0, 15.9, 14.6; IR (film) ν 2954, 2871, 1615, 1393, 1371, 1192, 1154, 1093, 957, 752 cm^{-1}. HRMS calc. for ($C_{14}H_{26}NO_2S^+$): 272.16788. Found: 272.16773. mp 87-88 °C.

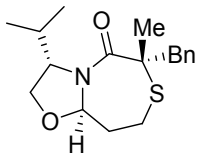
Synthesis of (3*R*,7*R*,10*S*)-1-Aza-3-propyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (179).



The alkylation was carried out following the general procedure above using 1.3 equiv. of methyl iodide. The residue was purified by chromatography on silica gel eluting 25% ethyl acetate in hexanes to afford 506 mg of (3*R*,7*R*,10*S*)-1-Aza-3-propyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (**179**) as a clear oil (89% yield). ^{1}H NMR ($CDCl_3$) δ 5.62 (1H, d, *J* = 9.5 Hz), 4.26 (1H, m), 3.89 (1H, m), 3.83 (1H, m), 2.82 (1H, m), 2.68 (1H, m), 2.37 (1H, m), 2.25

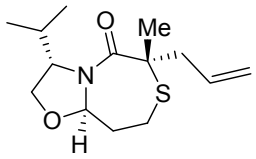
(1H, m), 1.94 (1H, m), 1.79 (2H, t, *J* = 9.0 Hz), 1.50 (3H, s), 1.49 (2H, m), 0.94 (3H, t, *J* = 7.0 Hz), 0.85 (3H, d, *J* = 7.5 Hz), 0.81 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.5, 88.8, 64.1, 62.8, 52.0, 42.8, 34.4, 27.5, 24.5, 19.2, 18.0, 16.0, 14.6; IR (film) ν 2959, 2872, 1630, 1461, 1421, 1387, 1353, 1309, 1190, 1149, 989 cm^{-1}. HRMS calc. for ($C_{14}H_{26}NO_3S^+$): 288.16279. Found: 288.16277.

Synthesis of (3*S*,7*R*,10*S*)-1-Aza-3-benzyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (184).



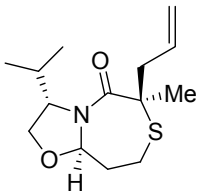
The alkylation was carried out following the general procedure above using 1.3 equiv. of benzyl bromide. The residue was purified by chromatography on silica gel eluting 20% ethyl acetate in hexanes to afford 432 mg of (3*S*,7*R*,10*S*)-1-Aza-3-benzyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (**184**) as a white solid in 87% yield. ^{1}H NMR ($CDCl_3$) δ 7.24 (5H, m), 5.51 (1H, dd, *J* = 10.0, 1.6 Hz), 4.30 (1H, m), 3.89 (1H, dd, *J* = 9.2, 7.2 Hz), 3.76 (1H, dd, *J* = 8.8, 4.4 Hz), 3.38 (1H, d, *J* = 13.6 Hz), 3.09 (1H, d, *J* = 14.0 Hz), 2.82 (2H, m), 2.34 (2H, m), 2.01 (1H, m), 1.56 (3H, s), 0.84 (3H, d, *J* = 7.2 Hz), 0.62 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.2, 136.1, 130.7, 128.1, 127.0, 89.0, 63.7, 63.3, 52.4, 46.2, 34.4, 27.3, 27.0, 23.4, 19.4, 15.6; IR (film) ν 2959, 2874, 1626, 1454, 1385, 1357, 1086, 988, 739, 699 cm^{-1}. HRMS calc. for ($C_{18}H_{26}NO_2S^+$): 320.16788. Found: 320.16755. mp 57-59 °C.

Synthesis of (3*S*,7*R*,10*S*)-1-Aza-3-allyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (182)



The alkylation was carried out following the general procedure above at 0°C over 4h using 2.0 equiv. of allyl bromide. The residue was purified by chromatography on silica gel eluting 20% ethyl acetate in hexanes to afford 550 mg of (3*S*,7*R*,10*S*)-1-Aza-3-allyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (**182**) as a white solid (96% yield). ^{1}H NMR ($CDCl_3$) δ 5.74 (1H, m), 5.56 (1H, d, *J* = 9.5 Hz), 5.14 (2H, m), 4.30 (1H, m), 3.90 (1H, m), 3.83 (1H, m), 2.92 (1H, m), 2.73 (1H, dt, *J* = 14.5, 4.5 Hz), 2.67 (2H, d, *J* = 7.0 Hz), 2.37 (1H, m), 2.29 (1H, m), 1.99 (1H, m), 1.51 (3H, s), 0.87 (3H, d, *J* = 7.0 Hz), 0.83 (3H, d, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 171.8, 132.4, 119.2, 89.0, 63.9, 63.4, 50.7, 43.6, 34.9, 27.5, 26.2, 23.8, 19.5, 16.0; IR (film) ν 2953, 2872, 1614, 1398, 1193, 956, 937 cm^{-1}. HRMS calc. for ($C_{14}H_{24}NO_2S^+$): 270.15223. Found: 270.15211. mp 76-77 °C.

Synthesis of (3*R*,7*R*,10*S*)-1-Aza-3-allyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (181).

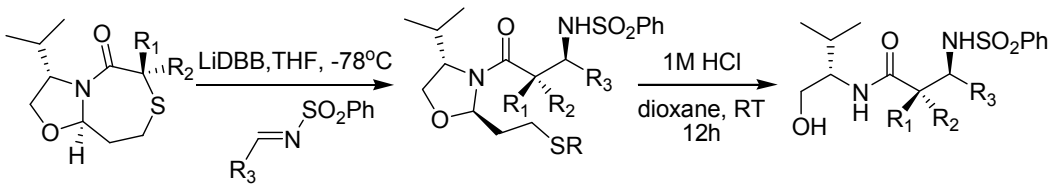


The alkylation was carried out following the general procedure above 1.3 equiv. of methyl iodide. The residue was purified by chromatography on silica gel eluting 20% ethyl acetate in hexanes to afford 446 mg of (3*R*,7*R*,10*S*)-1-Aza-3-allyl-10-isopropyl-3-methyl-8-oxa-4-thiabicyclo[5.3.0]-2-decanone (**181**) as a white solid (62% yield). ^{1}H NMR ($CDCl_3$) δ 5.97 (1H, m), 5.63 (1H, dd, *J* = 10.0, 2.0 Hz), 5.15 (2H, m), 4.28 (1H, m), 3.90 (1H, dd, *J* = 9.2, 6.8 Hz), 3.84 (1H, dd, *J* = 8.8, 3.6 Hz), 2.86 (1H, m), 2.75-2.56 (3H, m), 2.38 (1H, m), 2.27 (1H, m), 1.96 (1H, m), 1.52 (3H, s), 0.87 (3H, d, *J* = 7.2 Hz), 0.82 (3H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.1, 134.3, 118.7, 88.9, 64.2, 62.9, 50.9, 44.7, 34.8, 27.6, 24.5, 19.3, 16.1; IR (film) ν 2960, 2874, 1629, 1423, 1389, 1355, 1191, 991, 917 cm^{-1}. HRMS calc. for ($C_{14}H_{24}NO_2S^+$): 270.15223. Found: 270.15218. mp 35-36 °C.

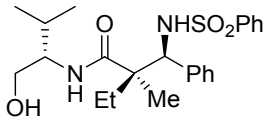
Preparation of Lithium di-*tert*-butylbiphenylide (LiDBB)

Lithium (121 mg, 17.5 mmol, 1.2 eq) was pressed into thin sheets, rinsed with hexanes, methanol, hexanes, then THF before added to a solution of 4,4'-di-*tert*-butylbiphenyl (3.87 g, 14.5 mmol, 1.0 eq) in THF (20 mL) at 0 °C. The resulting solution was stirred at 0 °C for 5 h before use. Excess reagent was stored at 0 °C for up to a week.

Sample procedure for imine addition:



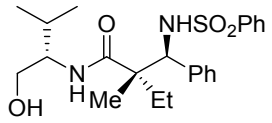
Synthesis of (R)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-((S)-phenyl(phenylsulfonamido) methyl)butanamide (174).



A solution of lithium di-*tert*-butylbiphenylide (LiDBB) in tetrahydrofuran was added dropwise via a glass syringe to a solution of lactam **175** (16.1 mg, 1.0 mmol, 1.0 equiv.) in tetrahydrofuran (10 ml) in a round bottom flask at –78 °C until the green colour of LiDBB persists. After 15 minutes at –78 °C, imine **149** (38.4 mg, 2.5 mmol; 2.5 equiv.) was added via cannula (10 mL) and the resulting mixture was stirred for 6 h at –78 °C, at which point a solution of saturated ammonium chloride (10 mL) was added to quench the reaction. The product was extracted using ethyl acetate (3 x 10 mL) and the combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was dissolved in minimum dichloromethane and applied onto a short pad of silica. The plug was rinsed with 250 mL of hexanes to remove DBB followed by 400 mL of ethyl acetate and concentrated to recover the product. HCl (1M, 8 mL) was added dropwise to a solution of the crude product in 1,4-dioxane (16 ml) to enable hydrolysis of the aminal. After stirring for 12 h, 1M NaOH was added to neutralize the solution. The product was extracted with ethyl acetate (3 x 10 mL), washed with brine (8 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 22.4 mg of **174** as a white solid (83% yield). The product was determined to have 97:1:1:1 ds as determined by HPLC by elution of iPrOH/Hexanes. ^{1}H NMR ($CDCl_3$) δ 7.49 (2H,

1, *J* = 7.0 Hz), 7.48-7.02 (6H, m), 6.97 (2H, d, *J* = 6.5 Hz), 6.76 (1H, d, *J* = 8.5 Hz), 5.58 (1H, d, *J* = 8.5 Hz), 4.44 (1H, d, *J* = 8.5 Hz), 3.62 (1H, m), 3.53 (2H, d, *J* = 4.5 Hz), 1.74 (1H, m), 1.57 (1H, m), 1.43 (1H, m), 1.30 (3H, s), 1.97 (3H, t, *J* = 7.5 Hz), 0.83 (3H, d, *J* = 7.0 Hz), 0.75 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 176.0, 140.9, 137.4, 131.9, 128.5, 128.1, 128.0, 127.8, 126.9, 63.6, 63.4, 57.1, 49.8, 29.1, 28.0, 20.2, 19.6, 18.9, 8.8; IR (film) ν 3428, 2958, 1635, 1517, 1459, 1308, 1155, 1085, 1051, 685, 589, 551 cm^{-1}. HRMS calc. for ($C_{23}H_{32}N_2O_4SNa^+$): 455.19750. Found: 455.1966. mp 198-199 °C.

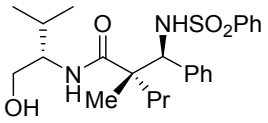
Synthesis of (S)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-((S)-phenyl(phenylsulfonamide) methyl)butanamide (165).



The Mannich reaction was carried out according to the general procedure outlined above over 16 h at –78 °C. The reaction was purified by chromatography on silica gel eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 1.77g of **165** as a white solid (83% yield). The product was determined to have 92:4:3:1 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.42 (2H, d, *J* = 7.2 Hz), 7.38 (1H, d, *J* = 8.4 Hz), 7.26 (1H, m), 7.11 (2H, t, *J* = 8.0 Hz), 7.06 (1H, d, *J* = 6.8 Hz), 7.00 (2H, t, *J* = 7.2 Hz), 6.93 (2H, d, *J* = 6.8 Hz), 5.53 (1H, d, *J* = 8.0 Hz), 4.30 (1H, d, *J* = 8.8 Hz), 3.64 (1H, m), 3.50 (2H, m), 2.12 (1H, m), 1.76 (1H, m), 1.68 (2H, m), 0.99 (3H, s), 0.93 (3H, t, *J* = 7.2 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 0.82 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 176.3, 141.4, 137.6, 131.6, 128.4, 128.2, 128.0, 127.8, 126.7, 64.4, 63.0, 57.0, 49.4, 31.0, 28.9, 19.7, 19.0, 18.9, 8.8; IR

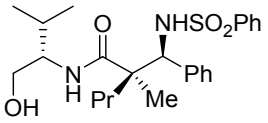
(film) ν 3408, 3247, 2961, 2928, 1628, 1526, 1457, 1323, 1158, 1065, 724, 608 cm^{-1}. HRMS calc. for ($C_{23}H_{33}O_4N_2S^+$): 433.21556. Found: 455.49685. mp 208-210 °C.

Synthesis of (S)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-((S)-phenyl(phenylsulfonamido) methyl)pentanamide (186).



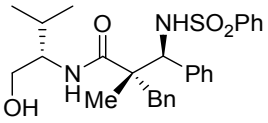
The Mannich reaction was carried out according to the general procedure outlined above over 16 h at –78 °C. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 56.1 mg of **186** as a white solid in 100% yield. The product was determined to have 87:10:2:1 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.44 (1H, d, *J* = 7.5 Hz), 7.38 (1H, d, *J* = 8.5 Hz), 7.27 (1H, m), 7.13 (2H, t, *J* = 8.0 Hz), 7.07 (1H, t, *J* = 7.5 Hz), 7.01 (2H, t, *J* = 8.0 Hz), 6.94 (2H, d, *J* = 7.0 Hz), 5.50 (1H, d, *J* = 7.5 Hz), 4.28 (1H, d, *J* = 8.5 Hz), 3.62 (1H, m), 3.48 (2H, m), 2.11 (1H, dt, *J* = 4.0, 13.0 Hz), 1.75 (1H, m), 1.51 (1H, dt, *J* = 4.5, 13.5 Hz), 1.41 (1H, m), 1.14 (1H, m), 1.00 (3H, s), 0.92 (3H, t, *J* = 7.0 Hz), 0.86 (3H, d, *J* = 6.5 Hz), 0.81 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 176.3, 141.5, 137.7, 131.6, 128.4, 128.2, 128.0, 127.8, 126.7, 64.7, 63.0, 57.1, 49.1, 40.4, 28.9, 19.6, 19.5, 19.0, 17.7, 14.6; IR (film) ν 3403, 3241, 2957, 2927, 1624, 1525, 1458, 1320, 1159, 1091, 1066, 722, 605 cm^{-1}. HRMS calc. for ($C_{24}H_{35}N_2O_4S^+$): 447.23212. Found: 447.23020. mp 132-133 °C.

Synthesis of (R)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-((S)-phenyl(phenylsulfonamido)methyl)pentanamide (187).



The Mannich reaction was carried out according to the general procedure outlined above over 16 h at –78 °C. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 75.3 mg of **187** as a white solid in 100% yield. The product was determined to have 95:3:2:0 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.48 (2H, m), 7.18-7.03 (6H, m), 6.96 (2H, m), 6.81 (1H, d, *J* = 7.5 Hz), 5.58 (1H, d, *J* = 9.0 Hz), 4.44 (1H, d, *J* = 8.5 Hz), 3.61 (1H, m), 3.54 (2H, m), 1.74 (1H, m), 1.47 (4H, m), 1.30 (3H, s), 0.89 (3H, m), 0.83 (3H, d, *J* = 6.5 Hz), 0.75 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 176.1, 140.9, 137.4, 131.9, 128.5, 128.1, 128.0, 127.9, 127.8, 126.9, 114.0, 63.6, 63.4, 57.1, 49.5, 37.5, 29..9, 29.1, 19.6, 18.9, 17.6, 14.8; IR (film) ν 3418, 2959, 2925, 1510, 1458, 1241, 1162, 1088, 1043, HRMS calc. for ($C_{24}H_{34}N_2O_4SNa^+$): 469.21315. Found: 469.21329. mp 138-139 °C.

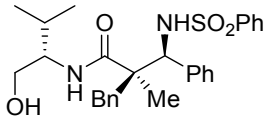
Synthesis of (2S,3S)-2-benzyl-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-3-phenyl-3-(phenyl sulfonamido)propanamide (188).



The Mannich reaction was carried out according to the general procedure outlined above over 16 h at –78 °C. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to

afford 13.4 mg of **188** as a white solid (72% yield). The product was determined to have 98:1:1:0 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.57 (1H, d, *J* = 8.4 Hz), 7.44 (2H, d, *J* = 8.0 Hz), 7.28-7.05 (9H, m), 7.00 (2H, t, *J* = 8.0 Hz), 6.94 (2H, d, *J* = 8.4 Hz), 5.20 (1H, d, *J* = 6.8 Hz), 4.39 (1H, d, *J* = 8.4 Hz), 3.78 (1H, d, *J* = 13.2 Hz), 3.45 (3H, m), 2.69 (1H, d, *J* = 13.2 Hz), 1.87 (1H, m), 0.92 (3H, s), 0.69 (3H, d, *J* = 6.8 Hz), 0.53 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 175.6, 141.4, 137.3, 136.8, 131.7, 130.7, 128.4, 128.3, 128.1, 127.9, 126.9, 126.7, 65.6, 62.9, 57.8, 50.1, 44.1, 29.9, 28.7, 19.7, 19.3, 18.9; IR (film) ν 3400, 3280, 2959, 2925, 1630, 1523, 1496, 1455, 1391, 1323, 1161, 1091, 1057, 912, 722, 702, 590, 560 cm^{-1}. HRMS calc. for ($C_{28}H_{34}N_2O_4SNa^+$): 517.21315. Found: 517.21254. mp 138-139 °C.

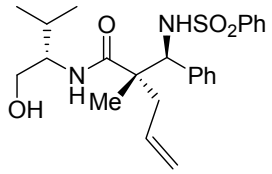
Synthesis of (2R,3S)-2-benzyl-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-3-phenyl-3-(phenylsulfonamido)propanamide (189).



The Mannich reaction was carried out according to the general procedure outlined above over 16 h at –78 °C. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 29.2 mg of **189** as a white solid (76% yield). The product was determined to have 93:5:2:0 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.60 (2H, d, *J* = 7.5 Hz), 7.34 (2H, t, *J* = 7.5 Hz), 7.22 (5H, m), 7.15 (2H, d, *J* = 7.0 Hz), 7.06 (3H, d, *J* = 6.0 Hz), 7.00 (1H, d), 5.92 (1H, d, *J* = 8.5 Hz), 5.14 (1H, d, *J* = 7.5 Hz), 4.72 (1H, d, *J* = 9.0 Hz), 3.33-3.28 (4H, m), 2.84 (1H, d, *J* = 13.0 Hz), 1.46 (1H,

m), 1.10 (3H, s), 0.59 (3H, d, J = 6.5 Hz), 0.35 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 174.0, 139.7, 136.8, 132.4, 130.8, 128.7, 128.5, 128.3, 128.0, 127.7, 127.3, 126.9, 64.1, 62.7, 57.4, 52.3, 42.8, 29.8, 28.5, 19.3, 18.7; IR (film) ν 3286, 2925, 1631, 1524, 1457,1323, 1163, 1089, 1054, 722, 703, 587, 550 cm^{-1}. HRMS calc. for ($C_{28}H_{35}N_2O_4S^+$): 495.23121. Found: 495.23058. mp 133-134 °C.

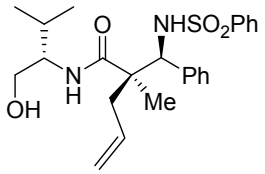
Synthesis of (S)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-((S)-phenyl(phenylsulfonamido) methyl)pent-4-enamide (190).



The Mannich reaction was carried out according to the general procedure outlined above over 16 h at –78 °C. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 25.1 mg of **190** as a white solid (86% yield). The product was determined to have 94:4:2:0 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.41 (2H, m), 7.26 (2H, m), 7.09 (3H, m), 7.00 (2H, t, J = 8.0 Hz), 6.92 (2H, d, J = 8.8 Hz), 5.76 (1H, m), 5.49 (1H, d, J = 8.0 Hz), 5.18 (2H, m), 4.31 (1H, d, J = 9.2 Hz), 3.61 (1H, m), 3.48 (0.2H, m), 2.92 (1H, dd, J = 13.2, 7.2 Hz), 2.38 (1H, dd, J = 13.2, 8.4 Hz), 1.75 (1H, m), 0.99 (3H, s), 0.89 (3H, d, J = 6.4 Hz), 0.80 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 175.7, 141.4, 137.2, 132.8, 131.6, 128.4, 128.2, 128.0, 127.8, 126.7, 120.0, 64.5, 63.1, 57.1, 48.9, 42.6, 29.9, 28.9, 19.6, 19.0; IR (film) ν 3398, 2950, 2924, 2854, 1634, 1526, 1460, 1324, 1161, 1091, 1063, 915, 722,

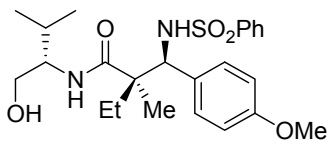
705, 688, 587, 557 cm^{-1}. HRMS calc. for ($C_{24}H_{32}N_2O_4SNa^+$): 467.19750. Found: 467.19704. mp 163-164 °C.

Synthesis of (R)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-((S)-phenyl(phenylsulfonamido) methyl)pent-4-enamide (191).



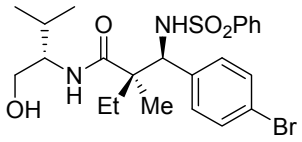
The Mannich reaction was carried out according to the general procedure outlined above over 16 h at –78 °C. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 21.8 mg of **191** as a white solid (98% yield). The product was determined to have 93:5:2:0 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.46 (2H, d, J = 7.5 Hz), 7.30-6.94 (8H, m), 5.86 (1H, m), 5.78 (1H, d, J = 8.0 Hz), 5.19 (1H, d, J = 10.5 Hz), 5.13 (1H, d, J = 17.0 Hz), 2.27 (1H, m), 2.18 (1H, m), 1.72 (1H, m), 1.40 (3H, s), 0.83 (6.5H, d), 0.75 (7H, d); ^{13}C NMR ($CDCl_3$) δ 176.0, 140.9, 137.2, 133.4, 131.9, 128.5, 128.3, 128.1, 127.9, 126.9, 120.0, 64.8, 63.5, 57.3, 49.1, 40.4, 29.8, 29.0, 21.3, 19.5, 18.8; IR (film) ν 3245, 2956, 2923, 2853, 1633, 1524, 1459, 1323, 1161, 1089, 1055, 917, 723, 705, 688, 586, 552 cm^{-1}. HRMS calc. for ($C_{24}H_{33}N_2O_4S^+$): 445.21556. Found: 445.21471. mp 192-193 °C.

Synthesis of (R)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-((S)-(4-methoxyphenyl)(phenyl sulfonamide)methyl) -2-methylbutanamide (198).



The Mannich reaction was carried out according to the general procedure outlined above over 6 h at –78 °C. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 28.5 mg of **198** as a white solid (93% yield). The product was determined to have 99:1:0:0 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.49 (2H, dd, *J* = 8.0, 1.0 Hz), 7.31 (1H, t, *J* = 7.5 Hz), 7.19 (2H, t, *J* = 7.5 Hz), 6.89 (2H, d, *J* = 8.5 Hz), 6.74 (1H, d, *J* = 9.0 Hz), 6.56 (2H, d, *J* = 9.0 Hz), 5.62 (1H, d, *J* = 8.5 Hz), 4.39 (1H, d, *J* = 8.5 Hz), 3.70 (3H, s), 3.62 (1H, m), 3.56 (2H, d, *J* = 4.0 Hz), 1.75 (1H, m), 1.57 (1H, m), 1.39 (1H, m), 1.28 (3H, s), 0.95 (3H, t, *J* = 7.0 Hz), 0.84 (3H, d, *J* = 6.5 Hz), 0.77 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 176.2, 159.1, 141.0, 131.8, 129.5, 129.3, 128.5, 127.0, 113.4, 63.5, 63.2, 55.4, 55.4, 49.9, 29.1, 28.0, 19.6, 18.9, 8.7; IR (film) ν 3402, 3272, 2962, 1630, 1514, 1449, 1380, 1320, 1248, 1160, 1032, 726, 597, 553 cm^{-1}. HRMS calc. for ($C_{24}H_{35}N_2O_5S^+$): 463.22612. Found: 463.22563.

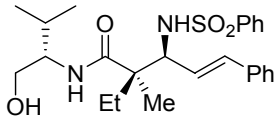
Synthesis of (R)-2-((S)-(4-bromophenyl)(phenylsulfonamido)methyl)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methylbutanamide (199).



The Mannich reaction was carried out according to the general procedure outlined above over 16 h at –78 °C. The reaction was purified by preparative chromatography on silica gel eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 75 mg of **199** as a white solid (80% yield). The product was determined to have 97:2:1:0 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.48

(2H, d, J = 10.0 Hz), 7.37 (1H, t, J = 9.0 Hz), 7.21 (2H, t, J = 10.0 Hz), 7.15 (2H, d, J = 10.0 Hz), 6.86 (2H, d, J = 10.5 Hz), 5.68 (1H, d, J = 10.5 Hz), 4.38 (1H, d, J = 10.0 Hz), 3.65-3.55 (3H, m), 1.76 (1H, m), 1.54 (1H, m), 1.35 (1H, m), 1.28 (3H, s), 0.95 (3H, t, J = 9.5 Hz), 0.85 (3H, d, J = 8.0 Hz), 0.77 (3H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 175.9, 140.8, 136.6, 132.0, 131.1, 130.0, 128.7, 126.9, 121.8, 63.5, 63.2, 57.1, 49.5, 29.1, 27.9, 20.3, 19.6, 18.9, 8.7; IR (film) ν 3281, 2962, 2928, 1630, 1525, 1448, 1326, 1161, 1073, 1010, 925, 724, 687, 591, 551 cm^{-1}. HRMS calc. for ($C_{23}H_{32}N_2O_4SBr^+$): 511.12607. Found: 511.12585. mp 163-165 °C.

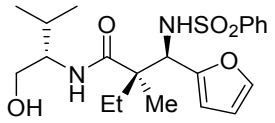
Synthesis of (2R,3S,E)-2-ethyl-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-5-phenyl-3-(phenylsulfonamide)pent-4-enamide (201).



The Mannich reaction was carried out according to the general procedure outlined above over 16 h at –78 °C. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 30.3 mg of **201** as a white solid (76% yield). The product was determined to have 85:12:2:1 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.78 (2H, d, J = 8.0 Hz), 7.31 (3H, m), 7.20 (3H, m), 7.03 (2H, d, J = 6.5 Hz), 6.06 (1H, d, J = 16.0 Hz), 5.92 (1H, t, J = 9.0 Hz), 5.88 (1H, d, J = 8.0 Hz), 3.92 (1H, t, J = 9.0 Hz), 3.75-3.59 (3H, m), 1.85 (1H, m), 1.71 (1H, m), 1.52 (1H, m), 1.29 (3H, s), 0.94 (6H, m), 0.89 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 176.3, 141.3, 136.1, 132.3, 128.9, 128.5, 128.0, 127.3, 126.5, 125.4, 64.0, 62.9, 57.1, 50.1, 29.1, 29.0,

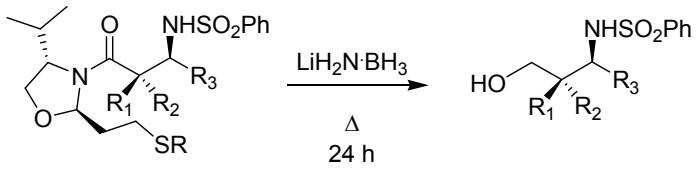
19.8, 19.7, 19.1, 8.6; IR (film) ν 3390, 2964, 1633, 1524, 1448, 1324, 1160, 1090, 1071, 969, 913, 725, 690, 590 cm^{-1} .HRMS calc. for ($C_{25}H_{35}N_2O_4S^+$): 459.23121. Found: 459.23192. mp 84-85 °C.

Synthesis of (R)-2-((R)-furan-2-yl(phenylsulfonamido)methyl)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methylbutanamide (200).

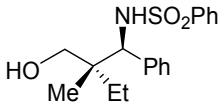


The Mannich reaction was carried out according to the general procedure outlined above over 6 h at –78 °C. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes + 5% acetic acid to afford 22.6 mg of **200** as a white solid (86% yield). The product was determined to have 92:4:3:1 ds as determined by HPLC. ^{1}H NMR ($CDCl_3$) δ 7.62 (2H, d, *J* = 7.0 Hz), 7.39 (1H, t, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 7.05 (1H, d, *J* = 1.0 Hz), 6.30 (1H, d, *J* = 10.0 Hz), 6.00 (1H, m), 5.83 (2H, m), 4.56 (1H, d, *J* = 10.0 Hz), 3.68 (2H, m), 3.58 (1H, m), 1.78 (1H, m), 1.65 (1H, m), 1.54 (1H, m), 1.25 (3H, s), 0.92 (3H, t, *J* = 7.0 Hz), 0.88 (3H, d, *J* = 6.5 Hz), 0.82 (3H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 175.7, 151.0, 141.7, 140.5, 132.2, 128.7, 126.9, 110.4, 109.0, 64.0, 57.7, 57.2, 50.7, 29.9, 29.0, 28.9, 19.7, 19.2, 18.9, 8.7; IR (film) ν 3395, 2961, 2924, 1635, 1525, 1449, 1389, 1327, 1161, 1091, 1014, 913, 722, 600, 587 cm^{-1}. HRMS calc. for ($C_{21}H_{30}N_2O_5SNa^+$): 445.17677. Found: 445.17697. mp 206-207 °C.

Sample procedure for reduction using lithium amidoborohydride:



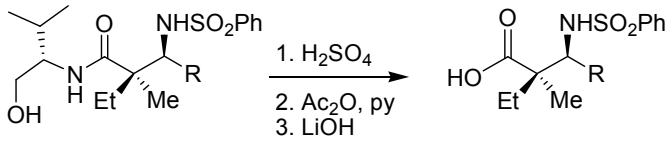
Synthesis of N-((1S,2S)-2-(hydroxymethyl)-2-methyl-1-phenylbutyl)benzenesulfonamide (206).



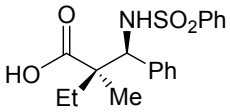
A solution of *n*-butyllithium in hexanes (1.59 mL 2.46 M, 3.9 equiv.) was slowly added to a stirred solution of diisopropylamine (575 μL, 2.61 mmol, 4.1 equiv.) in 10 mL tetrahydrofuran at 0 ^{o}C. After stirring for 10 minutes, borane-ammonia complex (137 mg, 2.55 mmol, 4.0 equiv.) was added in one portion under high pressure of argon. After stirring at 0 ^{o}C for 15 minutes, the mixture was warmed to room temperature and a solution of **164** in tetrahydrofuran (10 mL) was added via cannula. The resulting mixture was heated to reflux for 24 h, then cooled to 0^{o}C and quenched with aqueous hydrochloric acid (7 mL, 3 M). The solution was warmed to room temperature and stirred for 30 minutes, whereupon aqueous sodium hydroxide was added (3 M, 14 mL). The mixture was stirred for 30 minutes, and extracted with diethyl ether (3 x 15 mL). The combine organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue obtained was purified by chromatography on silica gel eluting 20% ethyl acetate/hexanes to afford 132 mg of **206** in 75% yield. ^{1}H NMR ($CDCl_3$) δ 7.48 (2H, d, J = 8.0 Hz), 7.29 (1H, t, J = 7.5 Hz), 7.15 (2H, t, J = 7.5 Hz), 7.05

(2H, d, J = 6.5 Hz), 6.98 (2H, d, J = 6.0 Hz), 6.32 (1H, d, J = 9.5 Hz), 4.34 (1H, d, J = 9.0 Hz), 3.59 (1H, d, J = 11.0 Hz), 3.30 (1H, d, J = 11.0 Hz), 1.11 (2H, m), 1.04 (3H, d), 0.84 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 140.6, 137.7, 131.9, 128.5, 128.4, 127.8, 127.2, 126.9, 67.9, 64.4, 41.6, 26.5, 19.2, 7.9; IR (film) ν 3510, 3290, 2966, 2882, 1448, 1321, 1158, 1090, 1061, 1003, 917, 719, 687, 590, 554 cm^{-1}. HRMS calc. for ($C_{18}H_{24}NO_3S^+$): 34.14714. Found: 334.14692. mp 92-93 °C.

Sample procedure for hydrolysis:



Synthesis of (R)-2-methyl-2-((S)-phenyl(phenylsulfonamido)methyl)butanoic acid (202).



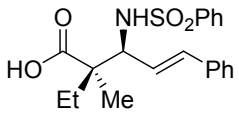
A freshly made H_2SO_4 (3.86 M, 7 mL) was added to a solution of **174** (27mg, 0.063 mmol, 1.0 equiv.) in 3 mL isopropanol. The mixture was brought to reflux for 5 h, whereupon it was cooled to room temperature, diluted with water (8 mL), and extracted with dichloromethane (4 x 10 mL). The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated.

Pyridine (24 μL, 0.29 mmol, 3.0 equiv.) was then added to a solution of the ester prepared above in 3 mL dichloromethane, followed by acetic anhydride

(11 μL, 0.12 mmol, 1.2 equiv.). The reaction mixture was stirred for 3 h, upon which it was concentrated *in vacuo*.

$LiOH{\cdot}H_2O$ (74 mg, 1.76 mmol, 20 equiv.) was added to a solution of the protected amine prepared above in tetrahydrofuran (6 mL), methanol (2 mL) , and water (2 mL) and heated to reflux for 24 h. The reaction mixture was cooled to room temperature, acidified with HCl (10 mL, 1M), and extracted with dichloromethane (4 x 10 mL). The combine organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes to afford 22.9 mg of **202** (100% yield). ^{1}H NMR ($CDCl_3$) δ 7.51 (2H, dd, *J* = 8.5, 1.0 Hz), 7.30 (1H, t, *J* = 7.5 Hz), 7.16 (2H, t, *J* = 8.0 Hz), 7.02 (3H, m), 6.95 (2H, d, *J* = 7.0 Hz), 6.00 (1H, s), 4.50 (1H, s), 1.78 (1H, m), 1.49 (1H, m), 1.28 (3H, s), 0.89 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 178.8, 140.3, 136.8, 132.2, 128.6, 128.0, 127.8, 127.1, 127.0, 63.7, 51.4, 28.7, 18.7, 8.9; IR (film) ν 1704, 1458, 1323, 1161, 1088, 914, 723, 703, 687, 587, 552 cm^{-1} HRMS calc. for ($C_{18}H_{21}NO_4SNa^+$): 370.10835. Found: 370.10792. mp 87-89 °C.

Synthesis of (2R,3S,E)-2-ethyl-2-methyl-5-phenyl-3-(phenylsulfonamido)pent-4-enoic acid (205).

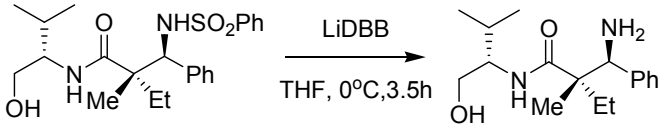


The hydrolysis was carried out according to the general procedure outlined to afford 30 mg of **205** as a white solid (88% yield). ^{1}H NMR ($CDCl_3$) δ 7.82 (2H, m), 7.29 (3H, m), 7.20 (3H, m), 7.01 (2H, m), 6.12 (1H, d, *J* = 15.5 Hz), 6.08 (1H,

d, J = 10.0 Hz), 5.74 (1H, m), 3.97 (1H, m), 1.94 (1H, m), 1.73 (1H, m), 1.54 (3H, s), 0.99 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 181.1, 180.9, 141.2, 140.8, 136.1, 136.0, 134.7, 134.0, 132.9, 132.5, 132.4, 129.3, 129.0, 128.9, 128.6, 128.4, 128.0, 127.4, 127.3, 126.6, 126.5, 124.7, 124.5, 62.5, 62.0, 50.7, 50.1, 30.4, 29.8, 29.5, 29.1, 29.0, 23.4, 19.5, 19.0, 18.5, 8.4, 8.3; IR (film) ν 3267, 2973, 1703, 1448, 1325, 1161, 1093, 911, 732, 690, 593 cm^{-1} HRMS calc. for ($C_{20}H_{23}NO_4SNa^+$): 396.12400. Found: 396.12394.

Sample procedure for N-deprotection:

N-deprotection to form (S)-2-((S)-amino(phenyl)methyl)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methylbutanamide (208).

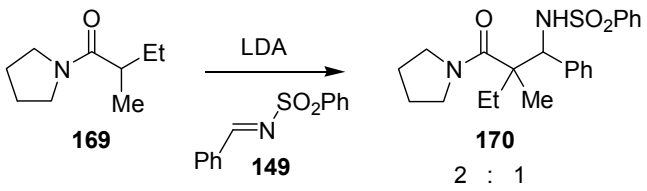


165 **208**

LiDBB was dropwise to a solution of **165** (16.6 mg, 0.038 mmol, 1.0 equiv.) in 5 mL tetrahydrofuran until the green colour persists for 3.5 h. Distilled water (5 mL) was added and the mixture was acidified using 1M HCl. The aqueous was washed with diethyl ether (3 x 5 mL) whereupon the aqueous layer was basified to pH 14 using 1M NaOH. The aqueous was extracted with dichloromethane (6 x 10 mL). The combined organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated to afford 11.8 mg of **208** as a white solid (100% yield). ^{1}H NMR ($CDCl_3$) δ 7.28 (5H, m), 6.75 (1H, d, J = 7.6 Hz), 4.13 (1H, s), 3.84 (1H, dq, J = 8.0, 3.6 Hz), 3.78 (1H, dd, J = 11.2, 3.6 Hz), 3.56 (1H, dd, J = 11.6, 7.6 Hz), 2.53 (2H, br s), 1.95 (1H, m), 1.87 (1H, m), 1.09

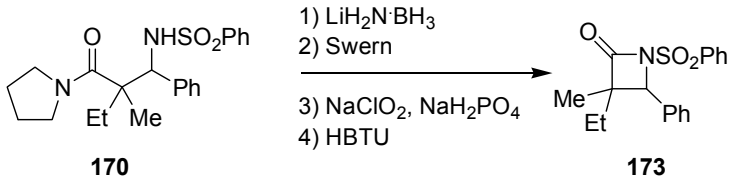
(1H, m), 1.04 (3H, s), 0.99 (3H, d, J = 6.8 Hz), 0.96 (3H, d, J = 7.2 Hz), 0.82 (3H, t, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 175.6, 141.4, 137.3, 136.8, 131.7, 130.7, 128.4, 128.3, 128.1, 127.9, 126.9, 126.7, 65.6, 62.9, 57.8, 50.1, 44.1, 29.9, 28.7, 19.7, 19.3, 18.9; IR (film) ν 3351, 2963, 2928, 2876, 1634, 1526, 1462, 1385, 703 cm^{-1}. HRMS calc. for ($C_{17}H_{29}N_2O_2^+$): 293.22235. Found: 293.22202. mp 64-65 °C.

Synthesis of the authentic standard N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-(phenyl(phenylsulfonamido)methyl)butanamide (165a, 165a', 174b, 174b').



A solution of *n*-butyllithium in hexanes (5.15 mL, 2.53 M, 1.10 equiv.) was added to a solution of diisopropylamine (1.92 mL, 13.7 mmol, 1.15 equiv.) in tetrahydrofuran (10 mL) at 0 °C. After 10 minutes a solution of **169** (1.84 g; 11.9 mmol; 1.0 equiv.) in tetrahydrofuran (10 mL) was added via cannula. The resulting mixture was stirred for 15 minutes, whereupon **149** (5.83g; 23.8 mmol; 2.0 equiv.) was added. Stirring was continued for 1.5 h before the reaction was allowed to come to room temperature over 16 h. Saturated aqueous ammonium chloride (10 ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by chromatography on silica gel eluting 25% ethyl acetate/hexanes to afford 1.93 g

of **170** as a white solid (41% yield). ^{1}H NMR ($CDCl_3$) δ 7.53 (5H, dd, *J* = 8.8, 1.2 Hz), 7.44 (2H, d, *J* = 7.6 Hz), 7.34-6.94 (29H, m), 6.44 (2.5H, d, *J* = 7.6 Hz), 4.36 (2.5H, d, *J* = 8.0 Hz), 4.26 (1H, d, *J* = 8.4 Hz), 3.40 (7H, m), 3.23 (1H, m), 3.07 (3H, m), 2.67 (2.5H, m), 2.50 (1H, m), 2.27 (1H, m), 1.90 (2.5H, m), 1.60 (13.5H, m), 1.48 (3.5H, m), 1.32 (7.5H, s), 1.16 (3H, s), 0.92 (3H, t, *J* = 7.2 Hz), 0.75 (7.5H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 174.2, 173.1, 141.6, 141.0, 138.1, 138.0, 131.9, 131.5, 128.6, 128.5, 128.3, 127.8, 127.6, 127.5, 127.0, 126.7, 65.0, 64.6, 52.1, 51.3, 49.0, 47.5, 47.0, 32.3, 29.0, 27.1, 22.9, 21.9, 21.0, 9.6, 8.9; IR (film) ν 3202, 2970, 2878, 1589, 1457, 1410, 1325, 1162, 1090, 1061, 916, 722, 586, 554 cm^{-1}. HRMS calc. for ($C_{22}H_{28}N_2O_3SNa^+$): 423.17129. Found: 423.17189. mp 160 °C.



170 **173**

A solution of *n*-butyllithium in hexanes (3.85 mL, 2.53 M, 5.7 equiv) was slowly added to a stirred solution of diisopropylamine (1.44 mL, 10.25 mmol, 6.0 equiv.) in 5 mL tetrahydrofuran at 0 °C. After stirring for 10 minutes, borane-ammonia complex (343 mg, 10.0 mmol, 5.8 equiv.) was added in one portion under high pressure of argon. After stirring at 0 °C for 15 minutes, the mixture was warmed to room temperature and a solution of **170** (689 mg; 1.72 mmol; 1.0 equiv) in tetrahydrofuran (10 mL) was added via cannula. The resulting mixture was heated to reflux for 24 h, then cooled to 0 °C and quenched with aqueous hydrochloric acid (10 mL, 3 M). The solution was warmed to room temperature

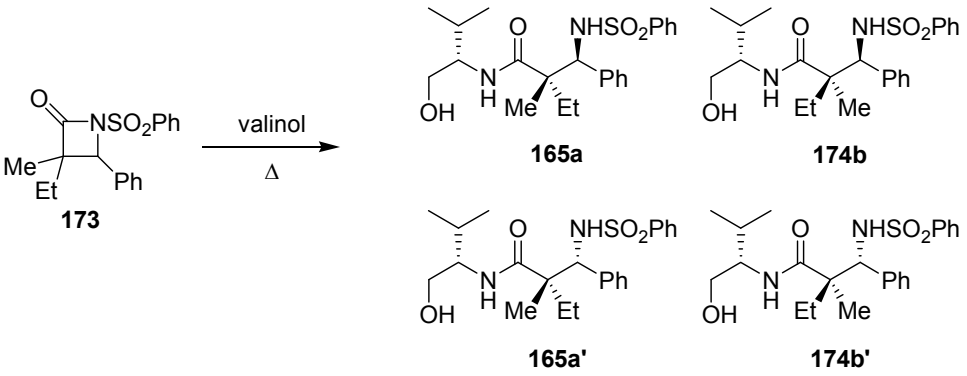
and stirred for 30 minutes, whereupon aqueous sodium hydroxide was added (20 mL, 3 M). The mixture was stirred for 30 minutes, and extracted with diethyl ether (3 x 20 mL). The combine organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated.

Dimethyl sulfoxide (321 μL, 4.83 mol, 3.0 equiv.) in dichloromethane (2 mL) was added to a stirred solution of oxalyl chloride (286 μL, 3.22 mol, 2.0 equiv.) in dichloromethane (2 mL) at –78 °C. After 20 minutes, a solution of the alcohol prepared above in dichloromethane (5 mL) was added via cannula. After stiring for 20 minutes, triethylamine (898 μL, 6.44 mol, 4.0 equiv.) was added and the reaction was allowed to warm to room temperature. The mixture was diluted with ethyl acetate (10 mL) and washed with hydrochloric acid (5mL, 1M) and distilled water (5 mL). The organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated.

Sodium chlorite (259 mg, 2.29 mmol, 3.4 equiv) and sodium dihydrogen phosphate monohydrate (158 mg, 1.15 mmol, 1.7 equiv.) were added to a solution of the aldehyde prepared above in 12 mL 5:1 tert-butanol : water. 2-methyl-2-butene (2.33 mL, 2M, 6.9 equiv.) was added via syringe whereupon the mixture was stirred for 1 h and concentrated. The residue was taken up in ethyl acetate (15 mL) and washed with distilled water (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated.

Triethylamine (658 μL, 4.72 mol, 3.0 equiv) and HBTU (656 mg, 1.73 mmol, 1.1 equiv.) were added consecutively to a solution the carboxylic acid

prepared above in acetonitrile (20 mL). Stirring was continued for 1 h, whereupon the reaction mixture was diluted with distilled water (8 mL), and extracted with ethyl acetate (3 x 15 mL). The organic phase was washed with $KHSO_4$ (8 mL, 1M), then dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography eluting 25% ethyl acetate in hexanes to afford 396mg of **173** in an overall 36% yield over four steps. ^{1}H NMR ($CDCl_3$) δ 7.96 (4H, m), 7.68 (2H, m), 7.56 (5H, m), 7.31 (7H, m), 7.18 (5H, m), 4.84 (1H, s), 4.71 (2H, s), 1.64 (2H, m), 1.38 (2H, m), 1.25 (5H, s), 1.04 (2H, m), 0.85 (3H, t, J = 7.5 Hz), 0.76 (3H, s), 0.64 (5H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 171.1, 171.0, 138.7, 138.4, 134.7, 134.4, 134.3, 129.4, 128.7, 128.6, 128.5, 127.7, 127.0, 126.8, 69.2, 66.4, 60.9, 60.2, 28.9, 24.6, 18.9, 15.6, 8.6, 8.2; IR (film) ν 2972, 1792, 1451, 1365, 1171, 1089, 771, 687, 599, 568 cm^{-1}. HRMS calc. for ($C_{18}H_{19}NO_3SNa^+$): 352.09779. Found: 352.09784.

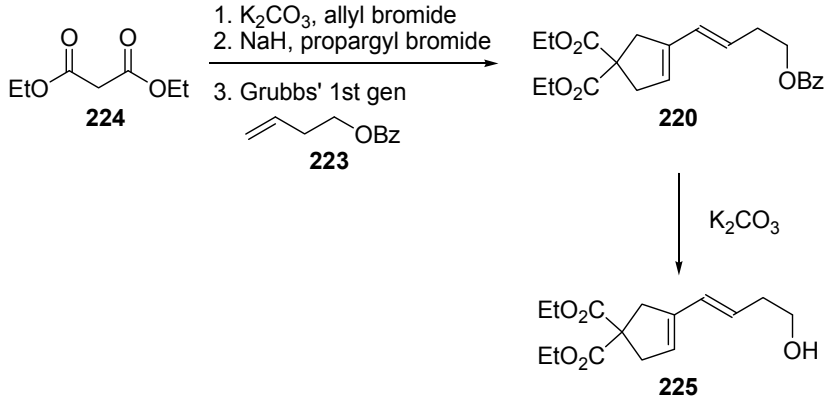


A solution of β-lactam **173** (200 mg, 0.61 mmol, 1.0 equiv.) in tetrahydrofuran (10 mL) was added to a solution of valinol (125 mg, 122 mmol, 2.0 equiv.) in tetrahydrofuran (10 mL) via cannula. The solution was brought to reflux for 7 days, whereupon it was cooled to room temperature and concentrated

in vacuo. The crude product was purified by column chromatography eluting 10% acetonitrile in chloroform to yield 226 mg of all four diastereomers of N-((S)-1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-phenyl(phenylsulfonamido)methyl)butanamide in a 1:1:2:2 mixture (86% yield). ^{1}H NMR ($CDCl_3$) δ 7.48 (6H, t, *J* = 8.0 Hz), 7.43-6.91 (51H, m), 6.76 (2H, d, *J* = 8.5 Hz), 6.64 (2H, d, *J* = 8.0 Hz), 5.63 (2H, d, *J* = 7.0 Hz), 5.58 (2H, d, *J* = 8.5 Hz), 5.53 (2H, d, *J* = 6.5 Hz), 4.44 (2H, d, *J* = 8.5 Hz), 4.37 (2H, d, *J* = 8.5 Hz), 4.23 (2H, m), 3.66-3.48 (m), 2.22 (m), 1.75-1.55 (m), 1.42 (m), 1.33-1.20 (m), 0.99-0.69 (m); ^{13}C NMR ($CDCl_3$) δ 176.7, 176.3, 176.0, 175.3, 141.5, 141.4, 140.9, 140.6, 137.6, 137.5, 137.4, 137.1, 132.0, 131.9, 131.6, 129.3, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.0, 126.9, 126.7, 126.6, 64.7, 64.5, 64.4, 63.9, 63.7, 63.6, 63.4, 63.1, 57.5, 57.1, 57.0, 49.8, 49.6, 49.5, 31.3, 31.0, 29.8, 29.1, 28.9, 28.7, 28.4, 28.0, 20.1, 19.7, 19.6, 19.0, 18.9, 8.9, 8.8, 8.6; IR (film) ν 3393, 3287, 2964, 2878, 1633, 1523, 1459, 1389, 1323, 1160, 1089, 1061, 915, 752, 723, 668, 587, 553 cm^{-1}. HRMS calc. for ($C_{23}H_{32}N_2O_4SNa^+$): 455.19750. Found: 455.19714.

4.2 TOTAL SYNTHESIS OF (-)-PURAQUINONIC ACID

Synthesis of (E)-diethyl 3-(4-hydroxybut-1-enyl)cyclopent-3-ene-1,1-dicarboxylate (225).



Diethyl malonate (10.0 mL, 66.0 mmol, 1.5 equiv) and allyl bromide (3.78 mL, 43.7 mmol, 1.0 equiv.) were added consecutively to a solution the potassium carbonate (27.0 g, 195.4 mmol, 4.5 equiv.) in acetone (300 mL). Stirring was continued for 24 h, whereupon the reaction mixture was quenched with saturated ammonium chloride (200 mL) and extracted with dichloromethane (3 x 250 mL). The combined organic phase was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate, filtered, and concentrated.

Diethyl 2-allylmalonate prepared above was dissolved in tetrahydrofuran (10 mL) and added dropwise over 5 min to a suspension of sodium hydride (2.79 g, 69.8 mmol, 1.6 equiv) in tetrahydrofuran (50 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred until the evolution of hydrogen gas subsided, whereupon it was cooled back to 0 °C and propargyl bromide (7.76 mL, 69.7 mmol, 1.6 equiv.) was added via syringe. The reaction was warmed to room temperature and stirring was continued for 12 h, then cooled to 0 °C, diluted with

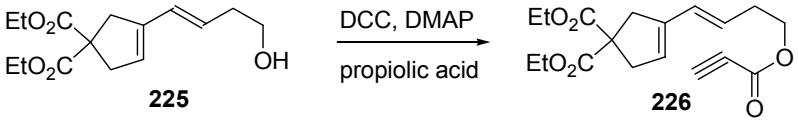
water (50 mL) and extracted with diethyl ether (3 x 75 mL). The combined organic phase was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography eluting 5% ethyl acetate in hexanes to yield 8.32 g of 2-allyl-2-(prop-2-ynyl)malonate (**217**, 80% yield).

A solution Grubbs' 1st generation catalyst (219 mg, 0.27 mmol, 0.10 equiv.) in dichloromethane (10 mL) was added to a solution of but-3-enyl benzoate (**223**, 2.35 g, 13.4 mmol, 5.0 equiv.) and diethyl 2-allyl-2-(prop-2-ynyl)malonate prepared above (**217**, 635 mg, 2.66 mmol, 1.0 equiv.) in dichloromethane (10 mL) via cannula. The solution was brought to reflux for 6 days; w whereupon it was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 4% ethyl acetate in hexanes to yield 881 mg of (E)-diethyl 3-(4-(benzoyloxy)but-1-enyl)cyclopent-3-ene-1,1-dicarboxylate (**220**, 86% yield).

Potassium carbonate (5.02 g, 36.3 mmol, 10.0 equiv) was added in one portion to a solution of diene **220** (1.40 g, 3.63 mmol, 1.0 equiv.) in anhydrous ethanol (10 mL) and heated to 60 °C. After 18 h, the reaction was quenched with saturated ammonium chloride (50 mL), and extracted with ethyl acetate (3 x 100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography eluting 28% to 32% gradient of ethyl acetate in hexanes to afford 881 mg of the title compound **225** (86% yield). ^{1}H NMR ($CDCl_3$) δ 6.28 (1H, d, J = 15.5 Hz), 5.55 (1H, dt, J = 15.5, 7.5 Hz), 5.48 (1H, m), 4.19 (4H, q, J = 7.0 Hz), 3.68 (2H, m),

3.08 (4H, m), 2.37 (2H, td, J = 6.5, 6.0 Hz), 1.25 (6H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.1, 139.2, 128.8, 127.6, 125.3, 62.0, 61.6, 58.8, 40.7, 39.6, 36.2, 14.0; IR (film) ν 3424, 2982, 1731, 1446, 1367, 1251, 1183, 1160, 1097, 1055, 1016, 967, 861 cm^{-1}. HRMS calc. for ($C_{15}H_{22}O_5Na^+$): 305.13594. Found: 305.13580.

Synthesis of (E)-diethyl 3-(4-(propioloyloxy)but-1-enyl)cyclopent-3-ene-1,1-dicarboxylate (226).

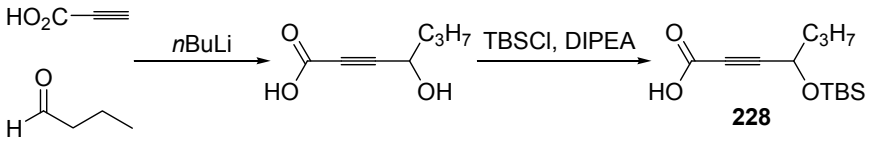


225 **226**

A solution of *N*,*N*'-dicyclohexylcarbodiimide (63 mg, 0.31 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (3 mg, 0.02 mmol, 0.10 equiv.) in dichloromethane (10 mL) was added slowly to a solution of propiolic acid (19 μL, 0.3 mmol, 1.1 equiv) and alcohol **225** (76 mg, 0.27 mmol, 1.0 equiv.) in dichloromethane (5 mL) at 0 °C over 1 h using a syringe pump. The reaction mixture was warm to room temperature and stirred for 18 h, whereupon the reaction mixture was filtered through Celite, washed with diethyl ether, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 30% ethyl acetate in hexanes to afford 17 mg of the title compound **226** (19% yield). ^{1}H NMR ($CDCl_3$) δ 6.27 (1H, d, J = 16.0 Hz), 5.55-5.49 (2H, m), 4.24-4.18 (6H, m), 3.08 (4H, m), 2.88 (1H, s), 2.48 (2H, dt, J = 7.0, 6.5 Hz), 1.25 (6H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.0, 152.6, 139.1, 128.8, 125.9, 125.8, 74.7, 74.6, 65.4, 61.6, 58.8, 40.7, 39.6, 31.8, 14.0; IR (film) ν 3256,

2983, 1718, 1447, 1367, 1233, 1183, 1071, 968, 756 cm^{-1}. HRMS calc. for ($C_{18}H_{22}O_6Na^+$): 357.13086. Found: 357.13135.

Synthesis of 4-(tert-butyldimethylsilyloxy)hept-2-ynoic acid (228).

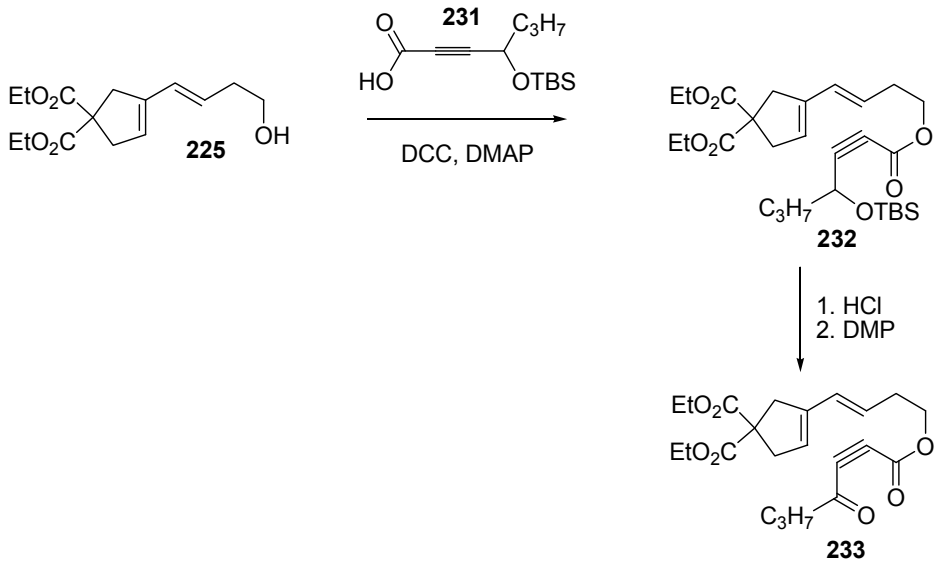


n-Butyl lithium (2.44M, 26.8 mL, 65.3 mmol, 2.1 equiv.) was added dropwise using a pressure-equalized dropping funnel to a solution of propiolic acid (2 mL, 31.1 mmol, 1.0 equiv.) in tetrahydrofuran (50 mL) at −78 °C. The reaction was warmed to room temperature and stirred for 1 hour whereupon it was cooled back down to −78°C and butanal (3.08 mL, 34.2 mmol, 1.1 equiv.) was added dropwise. The reaction was warmed up to room temperature and stirred overnight, then diluted with water. The aqueous phase was basified to pH 14 using NaOH (1M) and extracted with dichloromethane. The aqueous layer was than acidified to pH 1 using HCl (1 M) and extracted with ethyl acetate (3 x 200 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting a gradient of 4% ethyl acetate in hexanes + 5% acetic acid to 8% ethyl acetate in hexanes + 5% acetic acid to afford 1.75 g of the alcohol (39% yield).

TBSCl (959 mg, 6.4 mmol, 1.1 equiv.) was added to a solution of the alcohol prepared above (822 mg, 5.8 mmol, 1.0 equiv.) and imidazole (1.97 g, 28.9 mmol, 5.0 equiv.) in dichloromethane (20 mL) at room temperature. The reaction was stirred overnight then diluted with water (50 mL), acidified to pH 2

with HCl (1 M), and extracted with diethyl ether (4 x 80 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 24% ethyl acetate in hexanes + 1% acetic acid to yield 650 mg of the title compound **228** (44% yield) and 242 mg of the starting alcohol (29% yield). ^{1}H NMR ($CDCl_3$) δ 4.48 (1H, t, *J* = 6.5 Hz), 1.71 (2H, m), 1.46 (2H, m), 0.93 (3H, t, *J* = 7.0 Hz), 0.90 (9H, s), 0.15 (3H, s), 0.11 (3H, s); ^{13}C NMR ($CDCl_3$) δ 157.8, 91.7, 62.4, 39.7, 25.7, 18.3, 18.1, 13.6, -4.7, -5.2; IR (film) ν 2959, 2932, 2859, 2240, 1691, 1464, 1407, 1362, 1340, 1256, 1115, 1088, 1040, 1006, 973, 939, 894, 836, 812, 778, 730, 670 cm^{-1}. HRMS calc. for ($C_{13}H_{24}O_3SiNa^+$): 279.13869. Found: 279.14037.

Synthesis of (E)-diethyl 3-(4-(4-oxohept-2-ynoyloxy)but-1-enyl)cyclopent-3-ene-1,1-dicarboxylate (233).



N,*N*'-dicyclohexylcarbodiimide (641 mg, 3.1 mmol, 3.1 equiv.) was added in one portion to a solution of 4-dimethylaminopyridine (25 mg, 0.2 mmol, 0.20

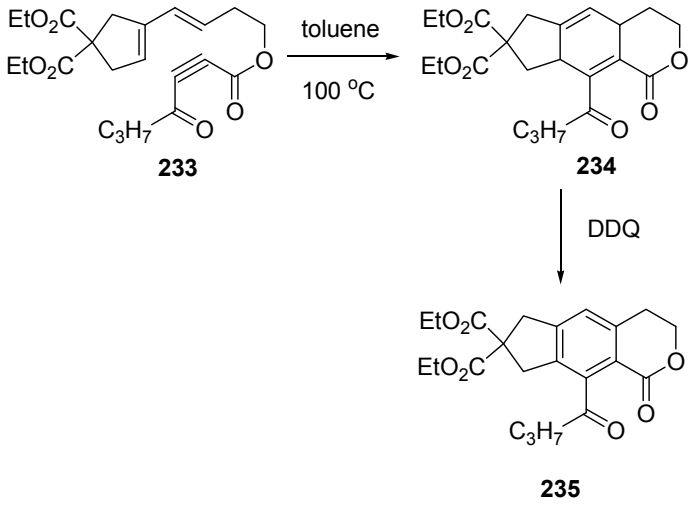
equiv.), carboxylic acid **231** (495 mg, 1.9 mmol, 1.9 equiv.), and alcohol **225** (292 mg, 1.0 mmol, 1.0 equiv.) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred warmed to room temperature and stirred for 3 days, whereupon the reaction mixture was filtered through Celite, washed with ethyl acetate, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 4% to 8% gradient of ethyl acetate in hexanes to afford 234 mg of the dienyne **232** (44% yield).

HCl (conc., 2.5 mL) was added dropwise to a solution of dienyne **232** (234 mg, 0.45 mmol, 1.0 equiv.) in ethanol (10 mL) and stirred at room temperature for 2 hours. The solvent was removed *in vacuo*. The residue was redissolved in ethanol and the solvent removed *in vacuo* to give 185 mg of the alcohol.

Dess Martin periodinane (389 mg, 0.9 mmol, 1.4 equiv.) was added in one portion to a solution of the alcohol prepared above in dichloromethane (10 mL). After 6 hours, the reaction was quenched with saturated sodium bicarbonate, and excess saturated sodium thiosulfate was added. The solution was stirred until the solids dissolved, whereupon the aqueous phase was extracted with dichloromethane (4 x 40 mL). The combined organic phase was washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to give 184 mg of the title compound in quantitative yield over two steps. ^{1}H NMR ($CDCl_3$) δ 6.27 (1H, d, J = 16.0 Hz), 5.51 (2H, m), 4.27 (2H, t, J = 6.5 Hz), 4.20 (4H, q, J = 7.5 Hz), 3.08 (4H, m), 2.62 (2H, td, J = 7.5, 2.0 Hz), 2.49 (2H, q, J = 7.0 Hz), 1.72 (2H, m), 1.25 (6H, t, J = 7.5 Hz), 0.96 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 186.0, 172.0, 152.2, 139.0, 129.0, 126.0, 125.6, 80.9, 77.9, 66.0,

61.6, 58.8, 47.1, 40.7, 39.6, 31.7, 17.0, 14.0, 13.4; IR (film) ν 2968, 1725, 1690, 1465, 1367, 1247, 1183, 1071, 969, 861, 748 cm^{-1}. HRMS calc. for ($C_{22}H_{28}O_7Na^+$): 427.17272. Found: 427.17404.

Synthesis of diethyl 9-butyryl-1-oxo-3,4-dihydrocyclopenta[γ]isochromene-7,7(1H,6H,8H)-dicarboxylate (235).

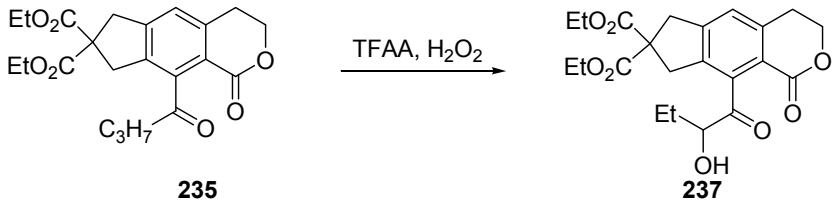


Dienyne **233** (9.7 mg, 0.02 mmol, 1.0 e quiv.) was dissolved in toluene (3 mL) and heated to 100 °C for 24 h. The solvent was removed *in vacuo*, and the crude product was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes to afford 7.9 mg of diene **234** (81% yield).

2,3-Dichloro-5,6-dicyanobenzoquinone (4 mg, 0.02 mmol, 1.02 equiv.) was added in one portion to a solution of diene **234** (6.3 mg, 0.016 mmol, 1.0 equiv.) in benzene (5 mL). The reaction was brought to reflux. After 24 hours, the reaction was filtered through Celite, washed with diethyl ether (2 x5 mL), and concentrated *in vacuo*. The crude product was product was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes to afford 4.6 mg

of the title compound **235** (73% yield). ^{1}H NMR ($CDCl_3$) δ 7.13 (1H, s), 4.50 (2H, t, *J* = 6.0 Hz), 4.20 (4H, q, *J* = 7.2 Hz), 3.60 (2H, s), 3.46 (2H, s), 3.02 (2H, t, *J* = 6.0 Hz), 2.72 (2H, t, *J* = 7.6 Hz), 1.79 (2H, m), 1.25 (6H, t, *J* = 6.8 Hz), 1.00 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 206.3, 170.8, 164.0, 147.4, 141.7, 139.6, 136.4, 123.5, 120.8, 67.0, 62.1, 60.2, 45.4, 40.4, 38.3, 28.2, 17.1, 14.0, 13.7; IR (film) ν 2965, 1728, 1287, 1251, 1191, 1149, 1068 cm^{-1}. HRMS calc. for ($C_{22}H_{26}O_7Na^+$): 425.15707. Found: 425.15706.

Synthesis of diethyl 9-(2-hydroxybutanoyl)-1-oxo-3,4-dihydrocyclopenta[γ]isochromene-7,7(1H,6H,8H)-dicarboxylate (237).

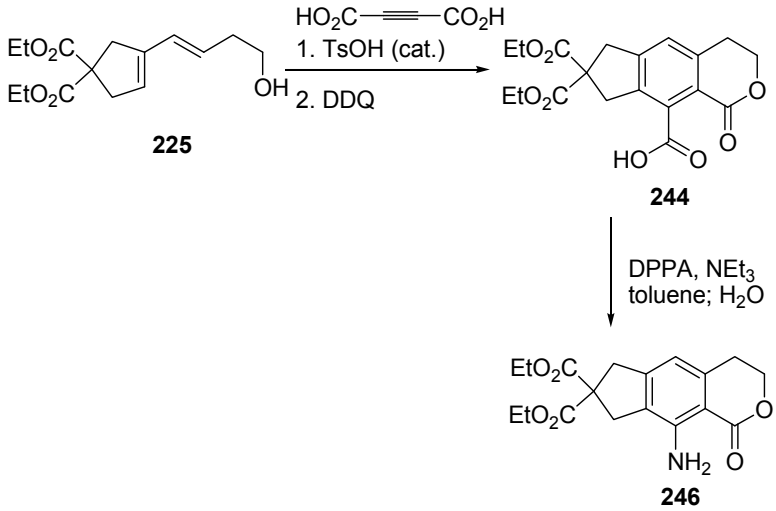


235 **237**

Ketone **235** (10 mg, 0.025 mmol, 1.0 equiv.) was dissolved in dichloromethane (1 mL) and added to a solution of H_2O_2 (30% v/v, 0.2 mL) and trifluoroacetic anhydride (1.12 mL) in dichloromethane (1.5 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 48 hours. Reaction mixture was poured into a solution of K_2CO_3 (2% w/v, 5 mL) and extracted with dichloromethane (4x 10 mL). The combine organic phase was washed with water (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The reaction was purified by preparative thin layer chromatography eluting 40% ethyl acetate in hexanes to afford 9.3 mg of **237** (89% yield). ^{1}H NMR ($CDCl_3$) δ 7.20 (1H, s), 4.59 (1H, dd, *J* = 9.5, 3.5 Hz), 4.54 (2H, m), 4.19 (4H, m), 3.63 (4H, m), 3.14 (1H, m), 2.97 (1H, td, *J* = 16.5, 4.0 Hz), 2.33 (1H, m), 2.05 (1H, m),

1.26 (3H, t, J = 7.5 Hz), 1.23 (3H, t, J = 7.5 Hz), 1.13 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 198.5, 170.9, 170.7, 164.7, 148.0, 139.6, 139.4, 138.4, 124.5, 121.1, 67.2, 65.1, 62.1, 62.0, 60.2, 40.5, 39.1, 28.0, 26.0, 14.0, 14.0, 10.7; IR (film) ν 2979.22, 2933.98, 1730.96, 1705.63, 1605.23, 1445.34, 1392.37, 1367.19, 1284.47, 1250.77, 1191.41, 1154.29, 1133.63, 1067.6, 1007.2, 968.75, 930.5, 906.14, 860.14, 803.14, 749.81, 713.15 cm^{-1}. HRMS calc. for ($C_{22}H_{26}O_8Na^+$): 441.15199. Found: 441.15344.

Synthesis of diethyl 9-amino-1-oxo-3,4-dihydrocyclopenta[γ]isochromene-7,7(1H,6H,8H)-dicarboxylate (246).



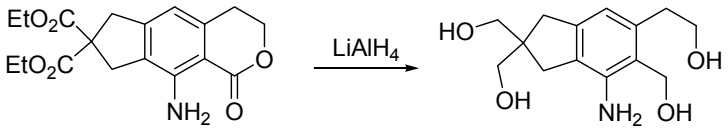
p-Toluenesulfonic acid (106 mg, 0.6 mmol, 0.5 equiv.) was added in one portion to a solution of acetylene dicarboxylic acid (804 mg, 6.7 mmol, 6.0 equiv) and alcohol **225** (315 mg, 1.1 mmol, 1.0 equiv.) in dioxane (10 mL), whereupon the reaction mixture was brought to reflux. After 21 hours, the reaction was cooled to room temperature and the solvent was removed *in vacuo*.

2,3-dichloro-5,6-dicyanobenzoquinone (736 mg, 3.2 mmol, 2.9 equiv.) was added to a solution of the diene prepared above in benzene (20 mL). The reaction was brought to reflux and after 4 h, concentrated *in vacuo* to give the crude product, which was purified by column chromatography eluting 0.5% methanol in dichloromethane + 0.5% acetic acid 1.0% methanol in dichloromethane + 1.0% acetic acid gradient to give 359 mg carboxylic acid **244** (86% yield). ^{1}H NMR ($CDCl_3$) δ 7.19 (1H, s), 4.50 (2H, t, *J* = 6.0 Hz), 4.21 (4H, q, *J* = 7.0 Hz), 3.72 (2H, s), 3.62 (2H, s), 3.02 (2H, t, *J* = 6.0 Hz), 1.26 (26H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 171.1, 170.9, 163.7, 147.3, 139.7, 138.7, 131.8, 124.4, 121.7, 67.0, 62.1, 60.0, 40.5, 38.9, 28.4, 14.0; IR (film) ν 2984, 1723, 1609, 1448, 1392, 1368, 1252, 1189, 1138, 1072, 1056, 1009, 859, 750, 735 cm^{-1}. HRMS calc. for ($C_{19}H_{19}O_8^-$): 375.10744. Found: 375.10973.

Diphenylphosphoryl azide (826 μL, 3.7 mmol, 10.0 equiv.) was added via syringe to a solution of triethylamine (570 μL, 4.1 mmol, 11.0 equiv.) and carboxylic acid **244** in toluene (20 mL). The reaction mixture was brought to reflux. After 3 h, H_2O (10 mL) was added and reflux continued for 15 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. The residue was treated with 5% w/w K_2CO_3 (20 mL) then extracted with ethyl acetate (3 x 40 mL). The combine organic extracts was washed with brine then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 28% to 32% gradient of ethyl acetate in hexanes to afford 70 mg of the title compound **246** (54% yield). ^{1}H NMR ($CDCl_3$) δ 6.34 (1H, s), 5.93 (2H, br s), 4.37 (2H, t, *J* = 6.0 Hz), 4.19 (4H,

q, J = 7.5 Hz), 3.51 (2H, s), 3.35 (2H, s), 2.88 (2H, t, J = 6.0 Hz), 1.23 (6H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 171.3, 167.4, 147.5, 146.8, 140.4, 123.4, 110.9, 104.9, 67.0, 61.9, 59.6, 41.3, 37.1, 28.9, 14.0; IR (film) ν 3468, 3359, 2982, 1729, 1685, 1614, 1441, 1259, 1190, 1109, 1057 cm^{-1}. HRMS calc. for ($C_{18}H_{21}NO_6Na^+$): 370.12611. Found: 370.12677.

Synthesis of 2-(7-amino-2,2,6-tris(hydroxymethyl)-2,3-dihydro-1H-inden-5-yl)ethanol (248).

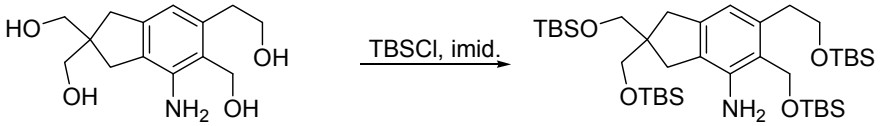


246 **248**

A solution of lactone **246** (49 mg, 0.14 mmol, 1.0 equiv.) in tetrahydrofuran (4 mL) was added dropwise over 5 mins to a solution of lithium aluminum hydride (56 mg, 1.4 mmol, 10 equiv.) in THF (2 mL) at 0 °C. The reaction was warmed up to room temperature and stirred for 2 h, whereupon it was quenched by the Fieser work up. Water (56 μL) was added, followed by NaOH (15% w/v, 56 μL), and water (168 μL). After 3 hours, anhydrous sodium sulfate was added and stirred for 15 mins, whereupon the mixture was filtered through Celite and washed with methanol and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography eluting 15% methanol in dichloromethane to afford 23.5 mg of tetraol **248** (65% yield). ^{1}H NMR ($CDCl_3$) δ 6.47 (1H, s), 4.65 (2H, s), 3.64 (2H, t, J = 7.0 Hz), 3.56 (4H, s), 2.84 (2H, t, J = 7.0 Hz), 2.72 (2H, s), 2.57 (2H, s); ^{13}C NMR ($CDCl_3$) δ 142.7, 142.4, 136.2, 125.8, 121.4, 116.3, 65.4, 63.0, 56.8, 49.4, 37.8, 36.4, 34.4; IR

(film) ν 3348, 2924, 1630, 1582, 1437, 1033, 826 cm^{-1}. HRMS calc. for ($C_{14}H_{21}NO_4Na^+$): 290.13628. Found: 290.13717.

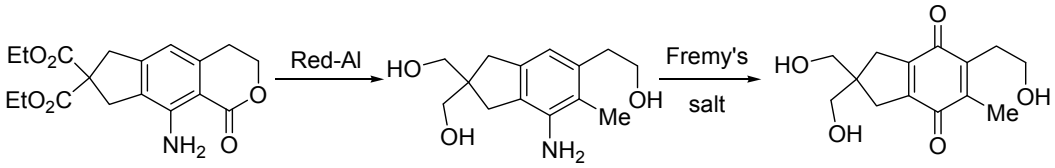
Synthesis of 6-(2-(tert-butyldimethylsilyloxy)ethyl)-2,2,5-tris((tert-butyldimethylsilyloxy)methyl)-2,3-dihydro-1H-inden-4-amine (249).



248 **249**

tert-Butyldimethylsilyl chloride (117.5 mg, 0.8 mmol, 4.2 equiv.) was added to a solution of tetraol **248** (47 mg, 0.2 mmol, 1.0 equiv.) and imidazole (126 mg, 1.9 mmol, 10.0 equiv.) in dimethylformamide (10 mL). The reaction was stirred at room temperature overnight whereupon it was quenched with saturated sodium bicarbonate (5 mL) then extracted with methyl *tert*-butyl ether (3 x 15 mL). The combined organic phase was washed with brine, then dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 12% ethyl acetate in hexanes to afford 56 mg of the title compound **249** (42% yield). ^{1}H NMR ($CDCl_3$) δ 6.45 (1H, s), 4.75 (2H, s), 3.68 (2H, t, *J* = 7.5 Hz), 3.54 (4H, s), 2.82 (2H, t, *J* = 7.5 Hz), 2.67 (2H, s), 2.50 (2H, s), 0.92-0.88 (36H, m), 0.12-0.01 (24H, m); ^{13}C NMR ($CDCl_3$) δ 143.3, 142.8, 135.2, 125.9, 120.9, 116.7, 65.3, 65.0, 59.5, 50.1, 38.5, 37.4, 34.6, 26.0, 25.9, 25.9, 18.4, 18.3, 18.3, -5.2, -5.3, -5.4; IR (film) ν 3375, 2954, 2929, 2897, 2857, 1619, 1584, 1471, 1439, 1388, 1361, 1252, 1147, 1095, 1039, 1005, 939, 909, 833, 814, 773, 734, 667 cm^{-1}. HRMS calc. for ($C_{38}H_{77}NO_4Si_4Na^+$): 746.48219. Found: 746.48428.

Synthesis of 6-(2-hydroxyethyl)-2,2-bis(hydroxymethyl)-5-methyl-1,2-dihydro-1H-indene-4,7-dione (252).



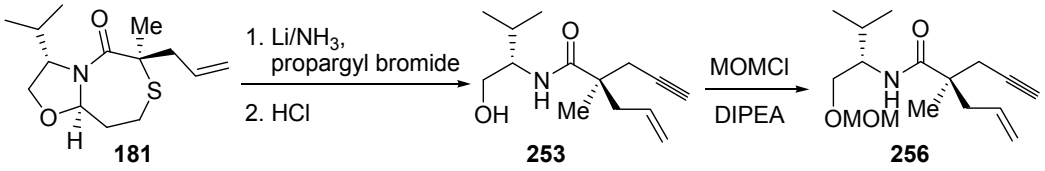
246 **251** **252**

Red-Al (667 μL, 2.2 mmol, 20.0 equiv., 65% w/w in toluene) was added dropwise via syringe to a solution of aniline **246** (38 mg, 0.1 mml, 1.0 equiv.), whereupon the reaction mixture was brought to reflux. After 19 h, the reaction was cooled to 0 °C and "wet" silica (150 μL in 500 mg silica) was added. The slurry was stirred for 30 min then filtered through Celite and washed with methanol. The filtrate was concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography eluting 5% methanol in dichloromethane to afford 32 mg of triol **251** (100% yield). ^{1}H NMR (CD_3OD) δ 6.45 (1H, s), 3.61 (2H, t, J = 7.6 Hz), 3.56 (4H, s), 2.78 (2H, t, J = 7.6 Hz), 2.69 (2H, s), 2.57 (2H, s), 2.08 (3H, s); ^{13}C NMR (CD_3OD) δ 141.0, 139.6, 135.3, 125.2, 118.2, 116.5, 65.4, 62.4, 37.7, 37.2, 34.7, 11.2; IR (film) ν 3344, 2876, 1627, 1584, 1438, 1276, 1261, 1082, 1028, 750 cm^{-1}. HRMS calc. for ($C_{14}H_{20}NO_3^-$): 250.14377. Found: 250.14499.

Fremy's salt (282 mg, 1.1 mmol, 8.0 equiv.) was added to a rapidly stirred solution of potassium dihydrogen phosphate (143 mg, 1.0 mmol, 8.0 equiv.) in water (6 mL). The resulting purple solution was added dropwise to a solution of potassium dihydrogen phosphate (143 mg, 1.0 mmol, 8.0 equiv.) and aniline **251** (33 mg, 0.1 mmol, 1.0 equiv.) in water (1.5 mL). The reaction mixture was stirred

at room temperature for 19 h then diluted with ethyl acetate (3 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography eluting 15% methanol in dichloromethane to afford 19 mg of title compound **252** (64% yield). ^{1}H NMR (CD_3OD) δ 3.61 (2H, t, *J* = 7.0 Hz), 3.52 (4H, s), 2.74 (2H, t, *J* = 6.5 Hz), 2.64 (4H, s), 2.04 (3H, s); ^{13}C NMR (CD_3OD) δ 186.2, 185.9, 146.5, 146.5, 142.3, 141.0, 65.3, 60.2, 47.6, 35.6, 29.5, 10.8; IR (film) ν 3361, 2926, 1645, 1607, 1431, 1374, 1335, 1209, 1078, 1030, 717 cm^{-1}. HRMS calc. for ($C_{14}H_{17}O_5^-$): 265.10705. Found: 265.10819.

Synthesis of (R)-N-((S)-1-(methoxymethoxy)-3-methylbutan-2-yl)-2-methyl-2-(prop-2-ynyl)pent-4-enamide (256).



Lithium wire (207 mg, 29.8 mmol, 4.0 equiv.) was cut and pressed, rinsed in hexanes, tetrahydrofuran, methanol, and tetrahydrofuran, then added to liquid ammonia (50 mL) at −78 °C. After 1 hour of stirring at −78 °C, dialkylated lactam **181** (2.01 g, 1.94 mmol, 1.0 equiv.) in tetrahydrofuran (50 mL) was added to the lithium-ammonia solution via cannula. The resulting mixture was stirred for 20 minutes, whereupon benzyl bromide (3.32 mL, 29.8 mmol, 4.0 equiv.) was added via syringe. After stirring for 4 h at −78 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL) warmed to 23 °C and

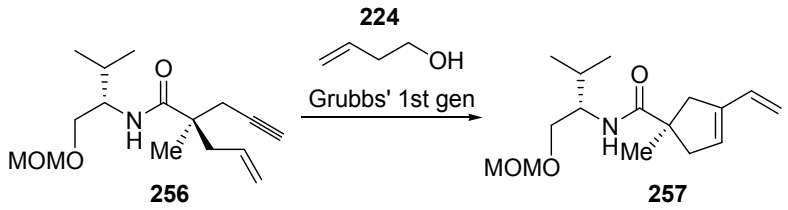
extracted with ethyl acetate (3 x 120 mL). The combined organic layers was dried over anhydrous sodium sulfate, filtered and concentrated.

HCl (1M, 50 mL) was added slowly to a solution of the crude product above in 1,4-dioxane (100 ml). After stirring for 12 h at room temperature, the reaction mixture was diluted with water (20 mL), then extracted with ethyl acetate (3 x 100 mL), washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography eluting 44% to 52% gradient of ethyl acetate in hexanes to afford 1.55 g of alcohol **253** (88% yield). ^{1}H NMR ($CDCl_3$) δ 6.10 (1H, d, *J* = 8.0 Hz), 5.72 (1H, m), 5.09 (2H, m), 3.73 (1H, m), 3.62 (2H, m), 3.09 (1H, br s), 2.50 (1H, dd, *J* = 16.8, 2.4 Hz), 2.44 (1H, dd, *J* = 14.0, 7.2 Hz), 2.36 (1H, dd, *J* = 16.8, 2.4 Hz), 2.26 (1H, dd, *J* = 14.0, 7.2 Hz), 2.06 (1H, t, *J* = 2.8 Hz), 1.88 (1H, m), 1.26 (3H, s), 0.93 (3H, d, *J* = 6.8 Hz), 0.90 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 176.1, 133.4, 118.9, 118.9, 81.3, 71.4, 64.3, 57.3, 45.3, 42.9, 42.8, 29.0, 28.2, 21.8, 21.7, 19.6, 18.7, 18.7; IR (film) ν 3362, 3309, 2963, 2876, 1640, 1526, 1465, 1076, 920, 636 cm^{-1}. HRMS calc. for ($C_{14}H_{24}NO_2^+$): 238.18016. Found: 238.18054.

Methyl chloromethyl ether (744 μL, 9.8 mmol, 1.5 equiv.) was added via syringe to a solution of alcohol **253** (1.47 g, 6.5 mmol, 1.0 equiv.) and *N,N*-Diisopropylethylamine (5.70 mL, 32.7 mmol, 5.0 equiv.) in THF (50 mL) at 0 °C. The reaction was brought to reflux. After 19 h, the reaction was cooled to room temperature and quenched with saturate ammonium chloride (40 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and

concentrated. The crude product was purified by column chromatography eluting 36% ethyl acetate in hexanes to afford 1.36 g of the title compound **256** (93% yield). ^{1}H NMR ($CDCl_3$) δ 6.12 (1H, d, *J* = 7.5 Hz), 5.74 (1H, m), 5.10 (2H, m), 4.61 (2H, s), 3.89 (1H, m), 3.71 (1H, dd, *J* = 10.0, 3.5 Hz), 3.44 (1H, dd, *J* = 10.0, 3.5 Hz), 3.67 (3H, s), 2.55 (1H, dd, *J* = 16.5, 2.5 Hz), 2.48 (1H, dd, *J* = 13.5, 7.5 Hz), 2.37 (1H, dd, *J* = 16.5, 2.5 Hz), 2.27 (1H, dd, *J* = 13.5, 7.5 Hz), 2.04 (1H, t, *J* = 2.5 Hz), 1.90 (1H, m), 1.27 (3H, s), 0.96 (3H, d, *J* = 7.0 Hz), 0.93 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 174.6, 133.6, 118.6, 96.9, 81.3, 71.1, 68.5, 55.4, 54.0, 45.1, 42.8, 29.3, 28.2, 21.7, 19.6, 18.9; IR (film) ν 3349, 2961, 2932, 1639, 1530, 1112, 1040, 918 cm^{-1}. HRMS calc. for ($C_{16}H_{28}NO_3^+$): 282.20637. Found: 282.20642.

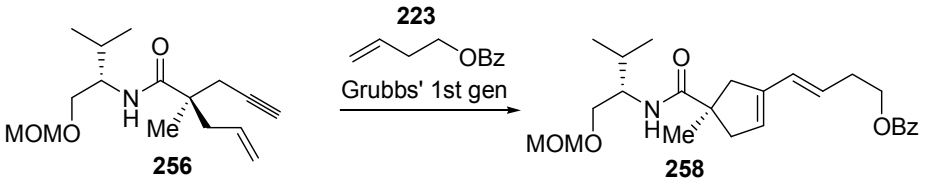
Synthesis of (R)-N-((S)-1-(methoxymethoxy)-3-methylbutan-2-yl)-1-methyl-3-vinylcyclopent-3-enecarboxamide (257).



A solution Grubbs' 1st generation catalyst (18 mg, 0.02 mmol, 0.10 equiv.) in dichloromethane (5 mL) was added to a solution of but-3-en-1-ol (96 μL, 1.2 mmol, 5.0 equiv.) and enyne **256** (61 mg, 0.22 mmol, 1.0 equiv.) in dichloromethane (5 mL) via cannula. The reaction was brought to reflux. After 5 days, the reaction was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 24% to 32% gradient of acetonitrile in chloroform to yield 57 mg of the title compound **257**

(93% yield). ^{1}H NMR ($CDCl_3$) δ 6.52 (1H, dd, *J* = 17.5, 11.5 Hz), 5.85 (1H, d, *J* = 8.5 Hz), 5.64 (1H, m), 5.06 (2H, m), 4.59 (2H, s), 3.87 (1H, m), 3.71 (1H, dd, *J* = 10.5, 3.5 Hz), 3.46 (1H, dd, *J* = 10.5, 4.0 Hz), 3.35 (3H, s), 2.93 (2H, m), 2.35 (2H, m), 1.90 (1H, m), 1.34 (3H, s), 0.96 (3H, d, *J* = 6.5 Hz), 0.92 (3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 177.7, 141.2, 133.2, 128.3, 114.5, 96.9, 68.4, 55.4, 53.8, 48.5, 44.9, 43.0, 29.5, 26.7, 19.6, 19.0; IR (film) ν 3345, 2959, 2927, 1638, 1526, 1465, 1151, 1112, 1039, 919 cm^{-1}. HRMS calc. for ($C_{16}H_{27}NO_3Na^{+}$): 304.18831. Found: 304.18859.

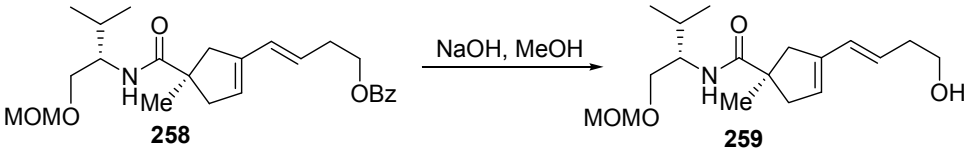
Synthesis of (E)-4-((R)-4-(((S)-1-(methoxymethoxy)-3-methylbutan-2-yl)carbamoyl)-4-methylcyclopent-1-enyl)but-3-enyl benzoate (258).



A solution Grubbs' 1st generation catalyst (231 mg, 0.28 mmol, 0.10 equiv.) in dichloromethane (30 mL) was added to a solution of but-3-enyl benzoate (**223**, 2.47 g, 14.0 mmol, 5.0 equiv.) and enyne **256** (789 mg, 2.8 mmol, 1.0 equiv.) in dichloromethane (30 mL) via cannula. The reaction was brought to reflux. After 6 days; it was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 32% ethyl acetate in hexanes to yield 1.07 g of the title compound **258** (89% yield). ^{1}H NMR ($CDCl_3$) δ 8.03 (2H, dd, *J* = 8.4, 1.2 Hz), 7.56 (1H, m), 7.44 (2H, t, *J* = 8.0 Hz), 6.35 (1H, d, *J* = 15.6 Hz), 5.85 (1H, d, *J* = 8.8 Hz), 5.59 (2H, m), 4.58 (2H, s), 4.36 (2H, t, *J* = 6.8 Hz), 3.86 (1H, m), 3.71 (1H, dd, *J* = 10.0, 3.6 Hz), 3.46 (1H,

dd, J = 10.0, 3.6 Hz), 2.92 (2H, m), 2.57 (2H, q, J = 6.8 Hz), 2.33 (2H, m), 1.89 (1H, m), 1.33 (3H, s), 0.96 (3H, d, J = 6.8 Hz), 0.91 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 177.7, 166.5, 140.4, 132.9, 129.6, 129.2, 128.3, 126.7, 126.3, 96.9, 68.4, 64.2, 55.4, 53.8, 48.6, 44.8, 43.5, 32.2, 29.5, 26.7, 19.6, 19.0; IR (film) ν 3349, 2958, 2927, 1720, 1648, 1522, 1275, 1114, 1040, 713 cm^{-1}. HRMS calc. for ($C_{25}H_{36}NO_5^+$): 430.25990. Found: 430.26020.

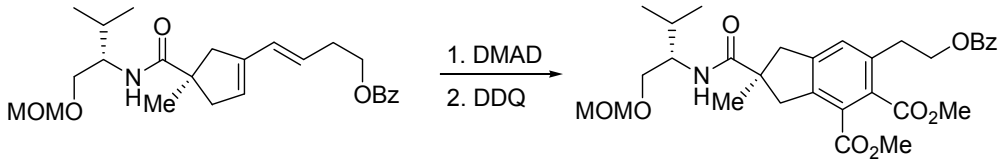
Synthesis of (R)-3-((E)-4-hydroxybut-1-enyl)-N-((S)-1-(methoxymethoxy)-3-methylbutan-2-yl)-1-methylcyclopent-3-enecarboxamide (259).



Sodium hydroxide (488 mg, 12.2 mmol, 7.0 equiv.) dissolved in anhydrous methanol (10 mL) and added to benzoate **258** (731 mg, 1.7 mmol, 1.0 equiv.). After 15 mins, the solvent was removed *in vacuo*. The residue was treated with water (20 mL) and extracted with ethyl acetate (3 x 60 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography eluting 24% ethyl acetate in hexanes to afford 503 mg of the title compound **259** (91% yield). ^{1}H NMR ($CDCl_3$) δ 6.31 (1H, d, J = 16.0 Hz), 5.85 (1H, d, J = 9.5 Hz), 5.52 (2H, m), 4.58 (2H, s), 3.86 (1H, m), 3.69 (3H, m), 3.46 (1H, dd, J = 10.0, 3.5 Hz), 3.34 (3H, s), 2.91 (2H, m), 2.34 (4H, m), 1.89 (1H, m), 1.61 (1H, br s), 1.32 (3H, s), 95.00 (3H, d, J = 7.0 Hz), 0.91 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 177.7, 140.4, 129.5, 127.2, 126.6, 96.9, 68.4, 62.0, 55.4,

53.8, 48.5, 44.9, 43.6, 36.2, 29.5, 26.7, 19.6, 19.0; IR (film) ν 3345, 2959, 2928, 1640, 1528, 1466, 1388, 1293, 1214, 1151, 1112, 1041, 964, 920 cm^{-1}. HRMS calc. for ($C_{18}H_{31}NO_4Na^+$): 348.21453. Found: 348.21457.

Synthesis of (S)-dimethyl 2-(((S)-1-(methoxymethoxy)-3-methylbutan-2-yl)carbamoyl)-6-(2-(benzoyloxy)ethyl)-2-methyl-2,3-dihydro-1H-indene-4,5-dicarboxylate (261)



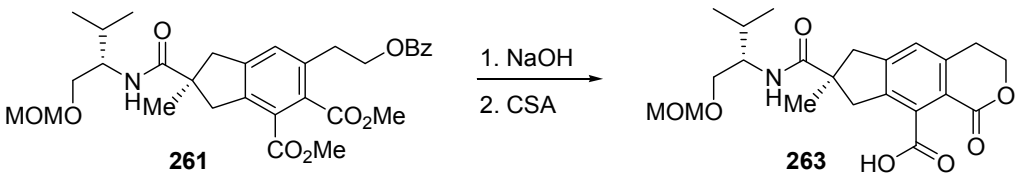
258 **261**

Dimethyl acetylenedicarboxylate (2.43 mL, 19.8 mmol, 2.0 equiv.) was added in one portion to a solution of diene **258** (4.86 g, 9.9 mmol, 1.0 equiv) in toluene (15 mL), whereupon the reaction mixture was brought to reflux. After 15 hours, the reaction was cooled to room temperature and the solvent was removed *in vacuo*.

2,3-dichloro-5,6-dicyanobenzoquinone (2.30 g, 9.9 mmol, 1.0 equiv.) was added to a solution of the diene prepared above in benzene (60 mL). The reaction was stirred at room temperature for 90 min, filtered through Celite, and concentrated *in vacuo* to give the crude product, which was purified by column chromatography eluting 50% ethyl acetate in hexanes to yield 5.63 g of the title compound **261** (100% yield). ^{1}H NMR ($CDCl_3$) δ 7.99 (2H, dd, *J* = 7.8, 1.2 Hz), 7.54 (1H, t, *J* = 8.0 Hz), 7.42 (2H, t, *J* = 8.0 Hz), 7.34 (1H, s), 5.97 (1H, d, *J* = 9.2 Hz), 4.59 (2H, s), 4.50 (2H, t, *J* = 6.8 Hz), 3.90 (3H, s), 3.86 (3H, s), 3.74 (1H, dd, *J* = 10.0, 3.2 Hz), 3.58-3.44 (3H, m), 3.56 (3H, s), 3.14-3.04 (3H, m), 2.80 (1H, d,

J = 16.4 Hz), 1.90 (1H, m), 1.32 (3H, s), 0.96 (3H, d, J = 7.2 Hz), 0.91 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 176.3, 169.4, 167.1, 166.4, 144.9, 141.5, 134.9, 133.0, 132.9, 130.1, 130.1, 129.6, 128.4, 126.4, 96.9, 68.5, 64.9, 55.4, 54.1, 52.6, 52.4, 50.1, 44.6, 43.7, 32.7, 29.5, 25.7, 19.6, 19.1; IR (film) ν 3353, 2956, 1724, 1652, 1525, 1442, 1274, 1206, 1113, 1040, 714 cm^{-1}. HRMS calc. for ($C_{31}H_{40}NO_9^+$): 570.26976. Found: 570.27151.

Synthesis of (S)-7-(((S)-1-(methoxymethoxy)-3-methylbutan-2-yl)carbamoyl)-7-methyl-1-oxo-1,3,4,6,7,8-hexahydrocyclopenta[g]isochromene-9-carboxylic acid (263)

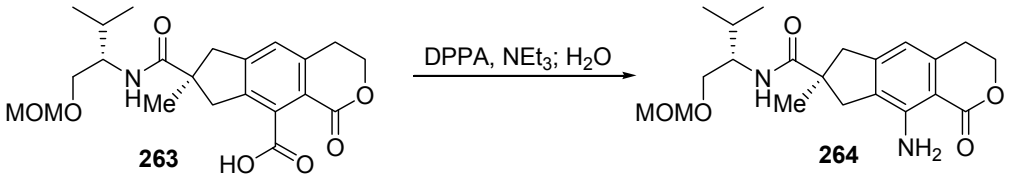


A solution of sodium hydroxide (320 mg, 8.3 mmol, 10.0 equiv.) in methanol (10 mL) was added to triester **261** (468 mg, 0.82 mmol, 1.0 equiv.). The reaction was stirred at room temperature for 75 min, at which point the solvent as removed *in vacuo*. The residue was treated with HCl (15 mL, 1 M) and extracted with ethyl acetate (3 x 40 mL). The combine organic extracts was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*.

Camphorsulfonic acid (38 mg, 0.2 mmol, 0.2 equiv.) was added to a solution of the crude diacid prepared above in dichloromethane (10 mL). The reaction was stirred at room temperature for 2 h, then quenched with water (10 mL) and acidified with HCl (1M) to pH 1. The acidic solution was then extracted with ethyl acetate (3 x 40 mL). The combined organic phase was dried over

anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude lactone was purified by column chromatography eluting 100% ethyl acetate to 100% ethyl acetate + 0.5% acetic acid gradient to yield 286 mg of the title compound **263** (83% yield). ^{1}H NMR ($CDCl_3$) δ 7.19 (1H, s), 6.56 (1H, d, *J* = 9.2 Hz), 4.62 (2H, m), 4.50 (2H, t, *J* = 5.6 Hz), 3.93 (1H, m), 3.82 (1H, dd, *J* = 10.4, 4.0 Hz), 3.66 (1H, d, *J* = 17.2 Hz), 3.57 (1H, dd, *J* = 10.8, 3.2 Hz), 3.43 (1H, d, *J* = 16.0 Hz), 3.36 (3H, s), 3.07 (1H, d, *J* = 16.4 Hz), 3.02 (2H, t, *J* = 6.0 Hz), 2.85 (1H, d, *J* = 16.8 Hz), 1.96 (1H, m), 1.41 (3H, s), 0.98 (3H, d, *J* = 6.8 Hz), 0.94 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 176.6, 171.1, 163.8, 149.3, 139.3, 139.3, 132.8, 124.7, 120.8, 96.7, 68.4, 67.0, 55.6, 54.4, 50.7, 43.8, 42.1, 29.4, 28.4, 25.7, 19.5, 19.2; IR (film) ν 3350, 2962, 1721, 1637, 1538, 1265, 1192, 1139, 1037, 915, 732 cm^{-1}. HRMS calc. for ($C_{22}H_{30}NO_7^+$): 420.20168. Found: 420.20296.

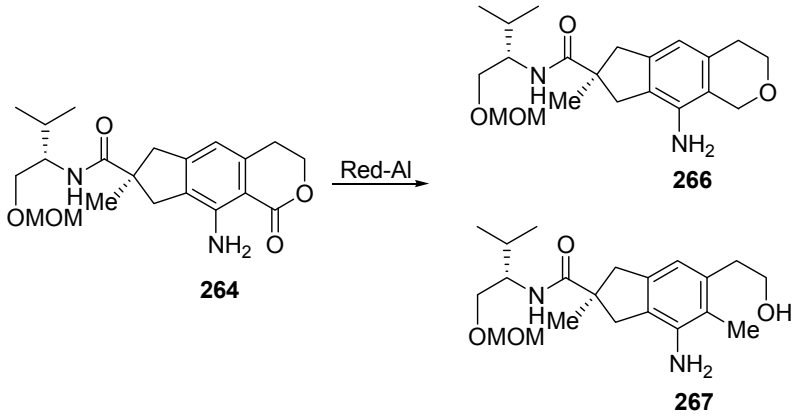
Synthesis of (S)-9-amino-N-((S)-1-(methoxymethoxy)-3-methylbutan-2-yl)-7-methyl-1-oxo-1,3,4,6,7,8-hexahydrocyclopenta[g]isochromene-7-carboxamide (264).



Diphenylphosphoryl azide (2.0 mL, 8.6 mmol, 5.0 equiv.) was added via syringe to a solution of triethylamine (2.3 mL, 16.7 mmol, 10.0 equiv.) and carboxylic acid **263** in THF (20 mL). The reaction mixture was brought to reflux. After 2 h, H_2O (4 mL) was added and reflux continued for 3 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. The residue was

treated with saturated K_2CO_3 (6 mL) and diluted with water (30 mL) then extracted with ethyl acetate (4 x 60 mL). The combine organic extracts was washed with brine then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 16% acetonitrile in chloroform to afford 574 mg of the title compound **264** (88% yield). ^{1}H NMR ($CDCl_3$) δ 6.37 (1H, s), 5.95 (1H, d, *J* = 9.2 Hz), 5.89 (2H, br s), 4.59 (2H, s), 4.42 (2H, t, *J* = 6.0 Hz), 3.87 (1H, m), 3.74 (1H, dd, *J* = 10.4, 3.6 Hz), 3.46 (1H, dd, *J* = 10.4, 3.6 Hz), 3.41 (1H, d, *J* = 16.4 Hz), 3.35 (3H, s), 3.20 (1H, d, *J* = 15.2 Hz), 2.92 (2H, t, *J* = 6.0 Hz), 2.77 (1H, d, *J* = 16.4 Hz), 2.60 (1H, d, *J* = 15.2 Hz), 1.89 (1H, m), 1.38 (3H, s), 0.95 (3H, d, *J* = 6.4 Hz), 0.90 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 176.5, 167.5, 148.3, 147.9, 140.0, 124.6, 111.6, 104.8, 96.9, 68.5, 67.1, 55.5, 54.1, 49.9, 45.2, 40.7, 29.5, 28.9, 26.3, 19.6, 19.0; IR (film) ν 3450, 3352, 2959, 1679, 1613, 1529, 1440, 1272, 1242, 1110, 1039 cm^{-1}. HRMS calc. for ($C_{21}H_{31}N_2O_5^+$): 391.22275. Found: 391.22351.

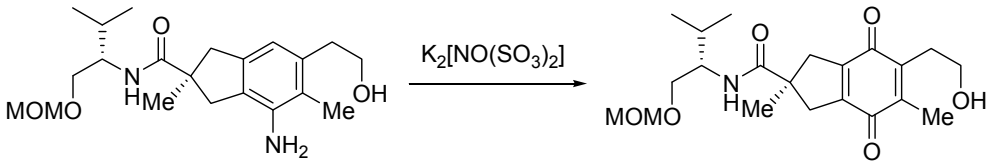
Synthesis of (S)-4-amino-6-(2-hydroxyethyl)-N-((S)-1-(methoxymethoxy)-3-methylbutan-2-yl)-2,5-dimethyl-2,3-dihydro-1H-indene-2-carboxamide (267).



Red-Al (903 μL, 3.0 mmol, 4.0 equiv., 65% w/w in toluene) was added dropwise via syringe to a solution of aniline **264** (289 mg, 0.7 mmol, 1.0 equiv.) in toluene (10 mL), whereupon the reaction mixture was brought to reflux. After 4 h, the reaction was cooled to 0 °C and "wet" silica (300 μL in 1g silica) was added. The slurry was stirred for 30 min then filtered through Celite and washed with methanol. The filtrate was concentrated *in vacuo* and the crude product purified by column chromatography eluting 2% to 4% gradient of methanol in dichloromethane to afford 192 mg of the desired aminol **267** (69% yield) and 43 mg of the DHP side product **266** (15%). **267**: ^{1}H NMR ($CDCl_3$) δ 6.53 (1H, s), 5.89 (1H, d, *J* = 9.2 Hz), 4.57 (2H, s), 3.86 (1H, m), 3.76 (2H, t, *J* = 6.8 Hz), 3.70 (1H, dd, *J* = 10.4, 4.0 Hz), 3.45 (1H, dd, *J* = 10.4, 4.0 Hz), 3.34 (3H, s), 3.31 (1H, d, *J* = 15.2 Hz), 3.21 (1H, d, *J* = 15.6 Hz), 2.86 (2H, m), 2.79 (1H, d, *J* = 15.6 Hz), 2.63 (1H, d, *J* = 15.2 Hz), 2.09 (3H, s), 1.87 (1H, m), 1.37 (3H, s), 0.92 (3H, d, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 177.3, 141.2, 139.4, 135.8, 124.3, 118.4, 116.5, 96.9, 68.4, 63.0, 55.4, 53.9, 50.2, 44.5, 41.3, 37.4,

29.4, 26.1, 19.5, 18.8, 12.5; IR (film) ν 3359, 2959, 2878, 1640, 1524, 1440, 1111, 1040 cm^{-1}. HRMS calc. for ($C_{21}H_{35}N_2O_4^+$): 379.25913. Found: 379.25966. **266**: ^1H NMR ($CDCl_3$) δ 6.48 (1H, s), 5.88 (1H, d, *J* = 9.0 Hz), 4.62 (2H, s), 4.59 (2H, s), 3.92-3.86 (3H, m), 3.71 (1H, dd, *J* = 10.5, 4.0 Hz), 3.46 (1H, dd, *J* = 10.5, 4.0 Hz), 3.37-3.31 (4H, m), 3.20 (1H, d, *J* = 15.5 Hz), 2.80 (3H, m), 2.64 (1H, d, *J* = 15.0 Hz), 1.88 (1H, m), 1.38 (3H, s), 0.94 (3H, d, *J* = 6.5 Hz), 0.87 (3H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 177.1, 140.3, 138.0, 133.0, 123.6, 117.6, 115.3, 96.9, 68.4, 64.9, 64.8, 55.4, 53.9, 50.1, 44.4, 40.7, 29.4, 28.8, 26.1, 19.6, 18.8; IR (film) ν 3361, 2959, 2928, 1641, 1521, 1442, 1107, 1039 cm^{-1}. HRMS calc. for ($C_{21}H_{32}N_2O_4Na^+$): 399.22543. Found: 399.22517.

Synthesis of (R)-5-(2-hydroxyethyl)-N-((S)-1-(methoxymethoxy)-3-methylbutan-2-yl)-2,6-dimethyl-4,7-dioxo-2,3,4,7-tetrahydro-1H-indene-2-carboxamide (269).

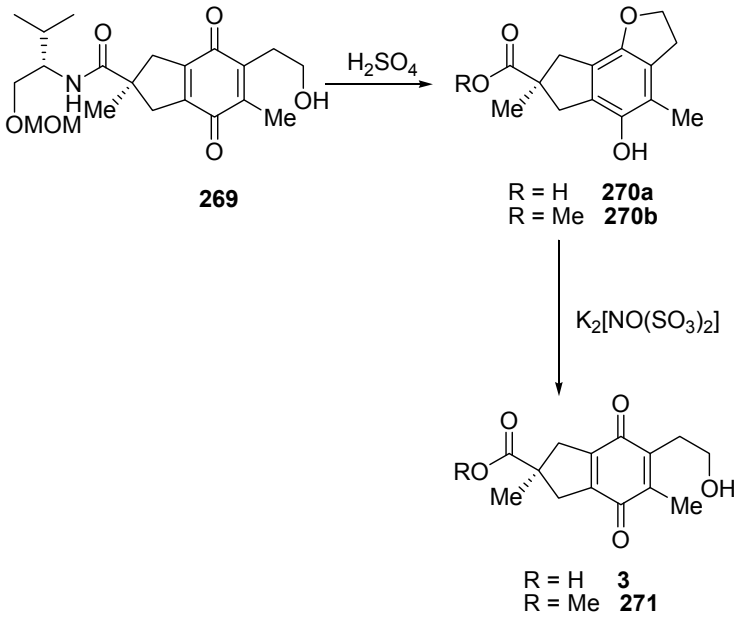


267 **269**

KH_2PO_4 (416 mg, 3.1 mmol, 4.5 equiv.) was dissolved in water (30 mL) and added to a solution of aniline **267** (257 mg, 0.7 mmol, 1.0 equiv.) in acetone (10 mL). Fremy's salt ($K_2[NO(SO_3)_2]$, 2.19 g, 8.2 mmol, 12.0 equiv.) was added with rapid stirring to a solution of KH_2PO_4 (1.11 g, 8.2 mmol, 12.0 equiv.) in water (120 mL). The resultant purple solution was added dropwise to the starting material. After 90 minutes, a change in colour from purple to yellow was observed. The reaction was diluted with ethyl acetate (50 mL) then extracted with

ethyl acetate (3 x 150 mL). The combine organic extracts was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 4% to 8% gradient of methanol in dichloromethane to afford 217 mg of quinone **269** (81% yield). ^{1}H NMR ($CDCl_3$) δ 5.97 (1H, d, *J* = 9.2 Hz), 4.60 (2H, m), 3.85 (1H, m), 3.78-3.72 (3H, m), 3.47 (1H, dd, *J* = 10.4, 3.6 Hz), 3.37 (3H, s), 3.36 (1H, m), 3.32 (1H, m), 2.78 (2H, t, *J* = 6.4 Hz), 2.73 (1H, d, *J* = 3.6 Hz), 2.68 (1H, d, *J* = 4.0 Hz), 2.07 (3H, s), 1.90 (1H, m), 1.37 (3H, s), 0.97 (3H, d, *J* = 6.4 Hz), 0.92 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 186.4, 185.9, 175.8, 145.9, 145.5, 142.7, 141.4, 97.0, 68.5, 61.5, 55.5, 54.3, 47.8, 42.7, 42.6, 29.9, 29.5, 26.5, 19.5, 19.2, 12.2; IR (film) ν 3347, 2960, 1649, 1529, 1290, 1111, 1039 cm^{-1}. HRMS calc. for ($C_{21}H_{32}NO_6^+$): 394.22241. Found: 394.22358.

Synthesis of (-)-puraquinonic acid (3).



269

R = H **270a**
R = Me **270b**

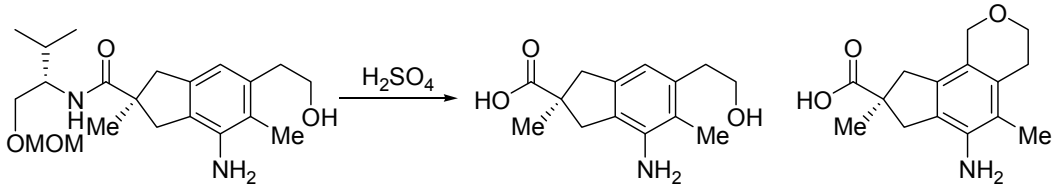
R = H **3**
R = Me **271**

H_2SO_4 (3.9 M, 7 mL) was added slowly to a solution of quinone **269** (30 mg, 0.08 mmol, 1.0 equiv) in methanol (3 mL), whereupon the reaction was brought to reflux. After 2 h, the reaction was cooled to room temperature, diluted with water (5 mL), and extracted with dichloromethane (4 x 15 mL). The combined organic extracts was dried over anhydrous sodium sulfate, filtered, and concentrated. **270a**: ^{1}H NMR ($CDCl_3$) δ 4.55 (2H, t, *J* = 8.5 Hz), 3.38 (2H, m), 3.08 (2H, t, *J* = 8.5 Hz), 2.76 (2H, m), 2.13 (3H, s), 1.42 (3H, s); ^{13}C NMR ($CDCl_3$) δ 183.0, 149.2, 143.7, 126.7, 125.8, 119.5, 119.2, 71.4, 50.1, 40.4, 40.4, 29.4, 25.2, 12.6; IR (film) ν 3432, 2924, 2854, 1701, 1459, 1260, 1228, 734 cm^{-1}. HRMS calc. for ($C_{14}H_{16}O_4Na^+$): 271.09408. Found: 271.09350.

KH_2PO_4 (50 mg, 0.4 mmol, 4.5 equiv.) was dissolved in water (3 mL) and added to a solution the crude product above in acetone (1 mL). Fremy's salt ($K_2[NO(SO_3)_2]$, 133 g, 1.0 mmol, 12.0 equiv.) was added with rapid stirring to a solution of KH_2PO_4 (133 g, 1.0 mmol, 12.0 equiv.) in water (12 mL). The resultant purple solution was added dropwise to the starting material. After 50 minutes, the brown reaction mixture was diluted with ethyl acetate (10 mL) then extracted with ethyl acetate (3 x 30 mL). The combine organic extracts was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 0% to 10% gradient of methanol in dichloromethane to afford 6.9 mg (-)-puraquinonic acid, (**3**) (32% yield) and 9.8 mg (-)-puraquinonic acid methyl ester (**271**) (43% yield). **3**: $[\alpha]_D^{22}$ +1.5 ° (c 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 3.76 (2H, t, *J* = 6.5 Hz), 3.36 (2H, m), 2.78 (2H, t, *J* = 6.5 Hz), 2.73 (2H, m), 2.07 (3H, s), 1.14 (3H, s); ^{13}C NMR

($CDCl_3$) δ 186.2, 185.7, 181.9, 145.7, 145.3, 142.8, 141.3, 61.4, 46.9, 42.3, 42.2, 29.8, 25.7, 12.2; IR (film) ν 3450, 2964, 1705, 1647, 1462, 1430, 1376, 1333, 1285, 1210, 1040, 719 cm^{-1}. HRMS calc. for ($C_{14}H_{16}O_5Na^+$): 287.08899. Found: 287.09008. **271**: ^1H NMR ($CDCl_3$) δ 3.75 (2H, t, *J* = 6.0 Hz), 3.72 (3H, s), 3.35 (2H, m), 2.78 (2H, t, *J* = 6.0 Hz), 2.72 (2H, m), 2.07 (3H, s), 1.38 (3H, s); ^{13}C NMR ($CDCl_3$) δ 186.3, 185.8, 176.9, 145.8, 145.4, 142.7, 141.4, 61.5, 52.4, 47.0, 42.4, 42.4, 29.9, 25.9, 12.2; IR (film) ν 3482, 2953, 1732, 1649, 1433, 1332, 1271, 1209, 1115, 1043 cm^{-1}. HRMS calc. for ($C_{15}H_{18}O_6Na^+$): 301.10464. Found: 301.10540.

Synthesis of (S)-4-amino-6-(2-hydroxyethyl)-2,5-dimethyl-2,3-dihydro-1H-indene-2-carboxylic acid (272).

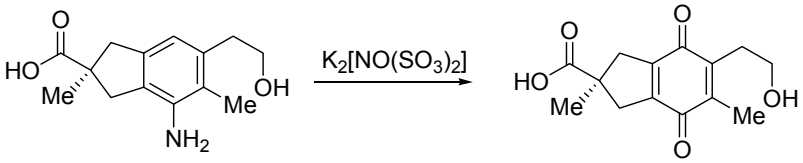


267 **272** **273**

H_2SO_4 (4 M, 6 mL) was added slowly to a solution of aniline **267** (56 mg, 0.15 mmol, 1.0 equiv) in dioxane (3 mL), whereupon the reaction was brought to reflux. After 30 min, the reaction was cooled to room temperature then 0 °C. NaOH (5 M) was added until the solution reached pH of 3-4, whereupon it was extracted with ethyl acetate (4 x 20 mL). The combined organic extracts was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 0% to 40% gradient of methanol in dichloromethane to afford 28.4 mg amino acid **272** (80% yield) and

5.7 mg dihydropyran **273** (15% yield). **272**: ^{1}H NMR ($CDCl_3$) δ 6.55 (1H, s), 3.79 (2H, t, *J* = 7.0 Hz), 3.47 (1H, d, *J* = 16.0 Hz), 3.33 (1H, d, *J* = 15.0 Hz), 2.88 (2H, td, *J* = 6.5, 2.0 Hz), 2.81 (1H, d, *J* = 16.0 Hz), 3.65 (1H, d, *J* = 15.5 Hz), 2.11 (3H, s), 1.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 182.2, 141.0, 139.3, 135.7, 124.1, 118.4, 116.5, 63.0, 49.2, 44.1, 40.9, 37.3, 25.5, 12.6; IR (film) ν 3374, 2925, 1701, 1624, 1438, 1308, 1219, 1040, 730 cm^{-1}. HRMS calc. for ($C_{14}H_{19}NO_3Na^+$): 272.12571. Found: 272.12585. **273**: ^{1}H NMR ($CDCl_3$) δ 4.63 (1H, d, *J* = 14.0 Hz), 4.59 (1H, d, *J* = 14.5 Hz), 3.97 (2H, m), 3.34 (1H, d, *J* = 15.5 Hz), 3.29 (1H, d, *J* = 16.5 Hz), 2.72-2.66 (3H, m), 2.63 (1H, d, *J* = 16.0 Hz), 2.03 (3H, s), 1.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 182.9, 138.8, 134.4, 130.7, 123.7, 121.4, 118.4, 66.5, 65.5, 49.3, 41.6, 40.8, 27.0, 25.9, 11.7; IR (film) ν 2961, 2926, 1700, 1625, 1462, 1384, 1294, 1266, 1233, 1131, 1100, 984, 902, 851, 735, 702 cm^{-1}. HRMS calc. for ($C_{15}H_{20}NO_3^+$): 262.14377. Found: 262.14356.

Synthesis of (-)-puraquinonic acid (3).

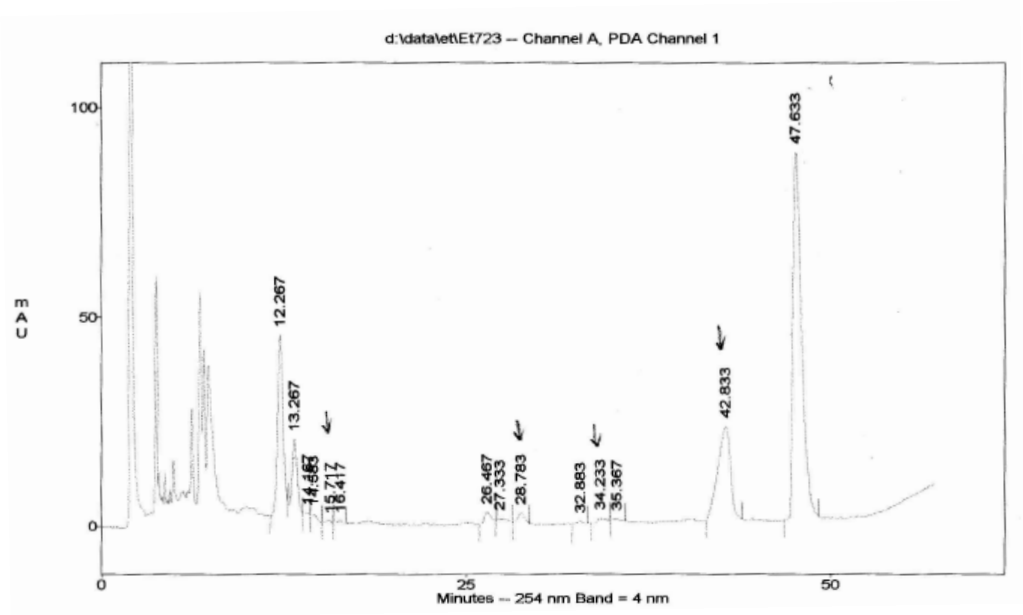


272 **3**

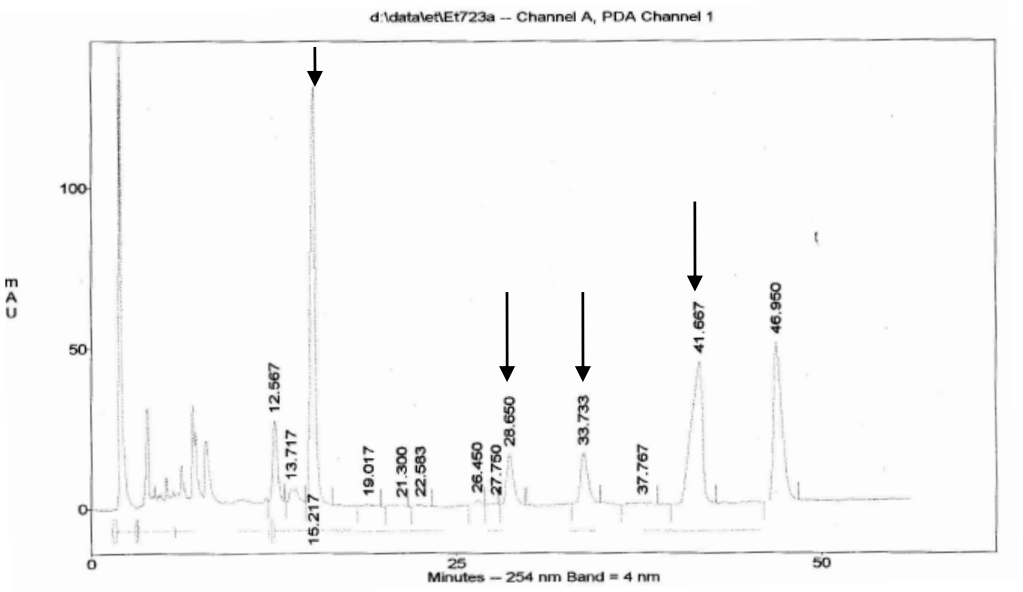
KH_2PO_4 (30 mg, 0.22 mmol, 1.5 equiv.) was dissolved in water (2 mL) and added to amino acid **272** (36 mg, 0.15 mmol, 1.0 equiv.). Fremy's salt ($K_2[NO(SO_3)_2]$, 159 mg, 0.6 mmol, 4.0 equiv.) was added with rapid stirring to a solution of KH_2PO_4 (81 g, 0.6 mmol, 4.0 equiv.) in water (9 mL). The resultant purple solution was added dropwise to the starting material. After 1 h, the brown reaction mixture was diluted with ethyl acetate (5 mL) then extracted with ethyl

acetate (3 x 20 mL). The combine organic extracts was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography eluting 0% to 10% gradient of methanol in dichloromethane to afford 32.2 mg (-)-puraquinonic acid **3** (83% yield).: $[\alpha]_D^{22}$ +1.5 ° (c 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 3.76 (2H, t, *J* = 6.5 Hz), 3.36 (2H, m), 2.78 (2H, t, *J* = 6.5 Hz), 2.73 (2H, m), 2.07 (3H, s), 1.14 (3H, s); ^{13}C NMR ($CDCl_3$) δ 186.2, 185.7, 181.9, 145.7, 145.3, 142.8, 141.3, 61.4, 46.9, 42.3, 42.2, 29.8, 25.7, 12.2; IR (film) ν 3450, 2964, 1705, 1647, 1462, 1430, 1376, 1333, 1285, 1210, 1040, 719 cm^{-1}. HRMS calc. for ($C_{14}H_{16}O_5Na^+$): 287.08899. Found: 287.09008.

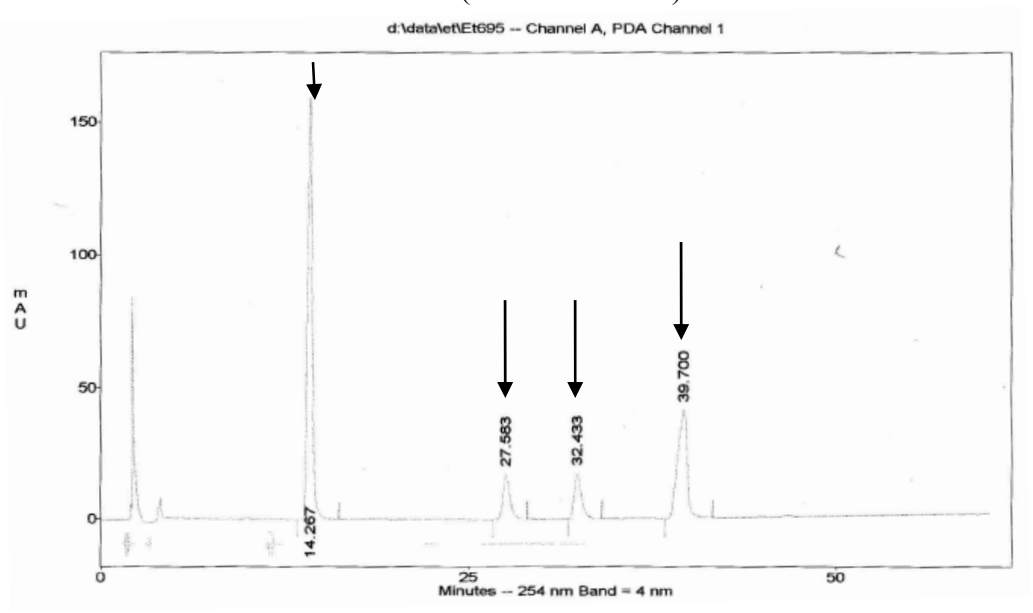
Compound **189**
HPLC conditions: 1.5% *i*PrOH:Hexanes to 3.5% for 20 mins then 1.5% to 3.5% *i*PrOH:Hexanes over 40 mins.



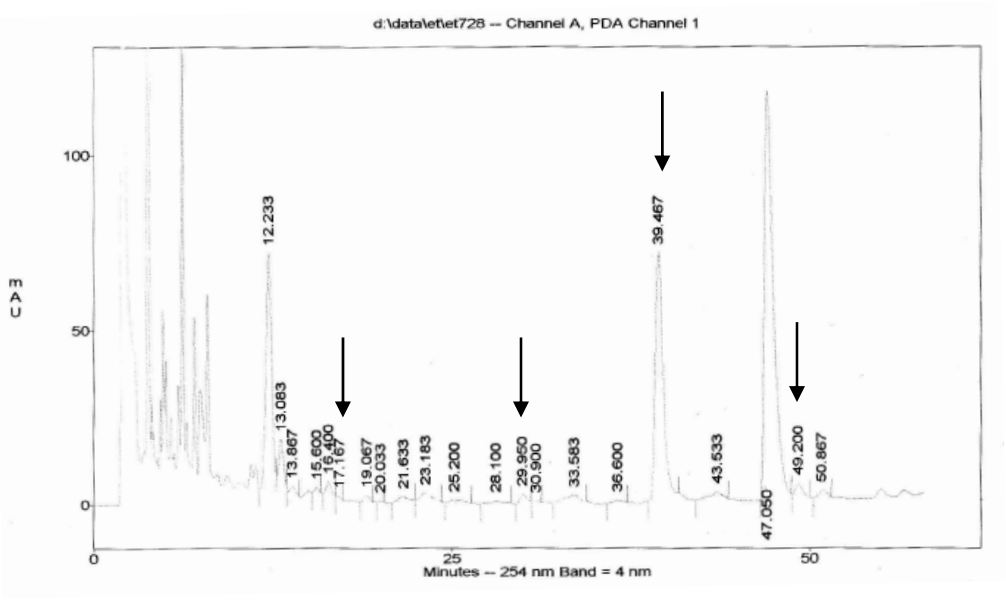
Compound **189** spiked with authentic standard mixture of 4 diastereomers.



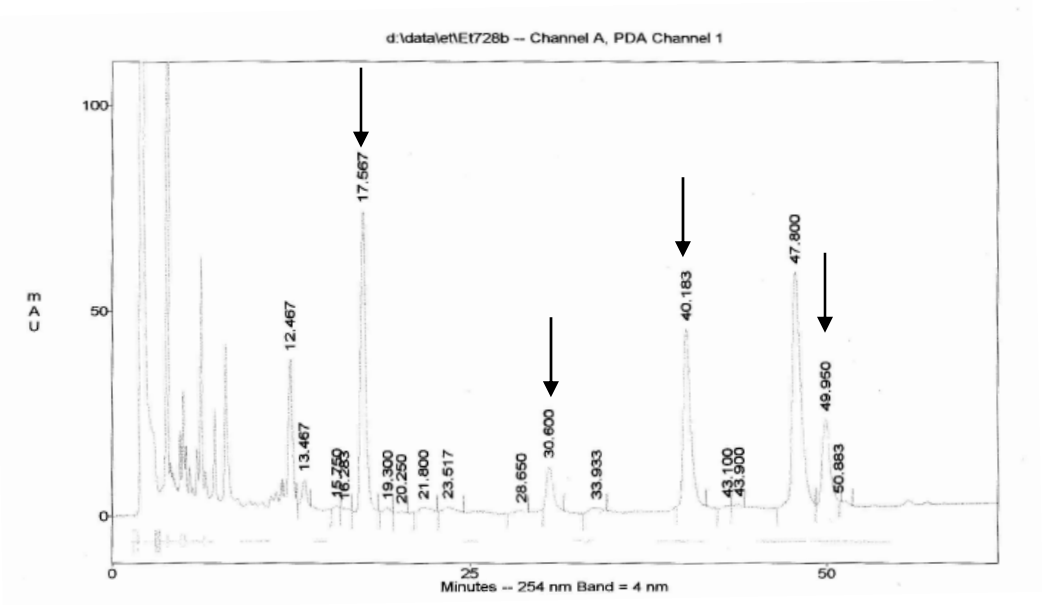
Authentic standard mixture for **189** (4 diastereomers).



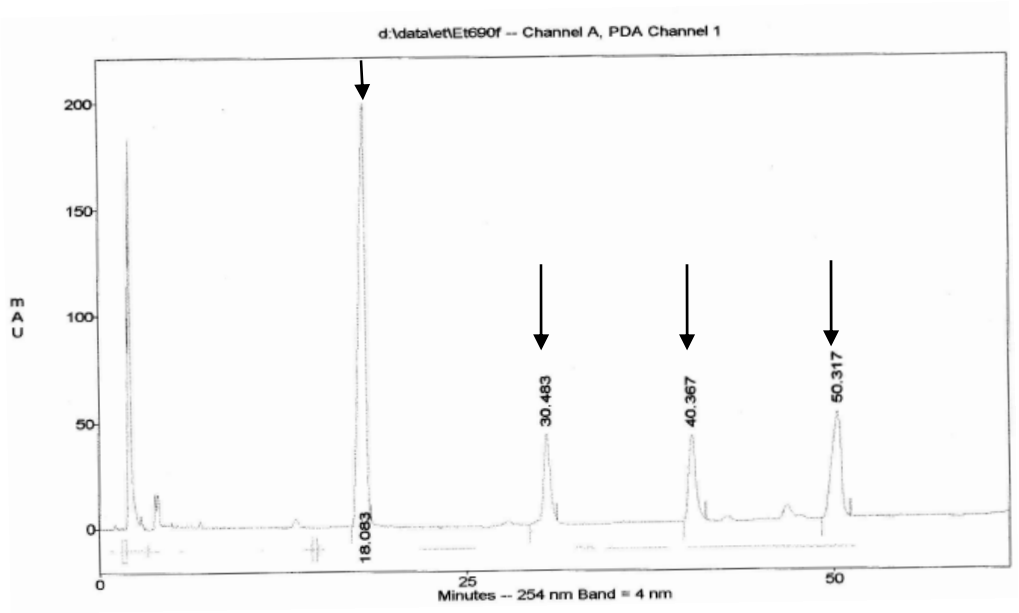
Compound **190**
HPLC conditions: 1.5% *i*PrOH:Hexanes to 3.5% for 20 mins then 1.5% to 3.5% *i*PrOH:Hexanes over 40 mins.



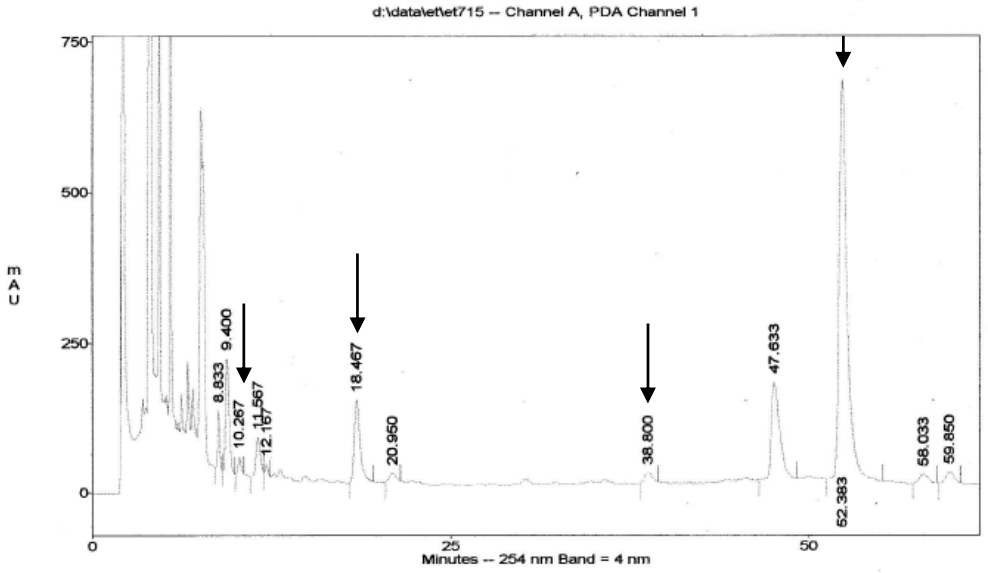
Compound **190** spiked with authentic standard mixture of 4 diastereomers.



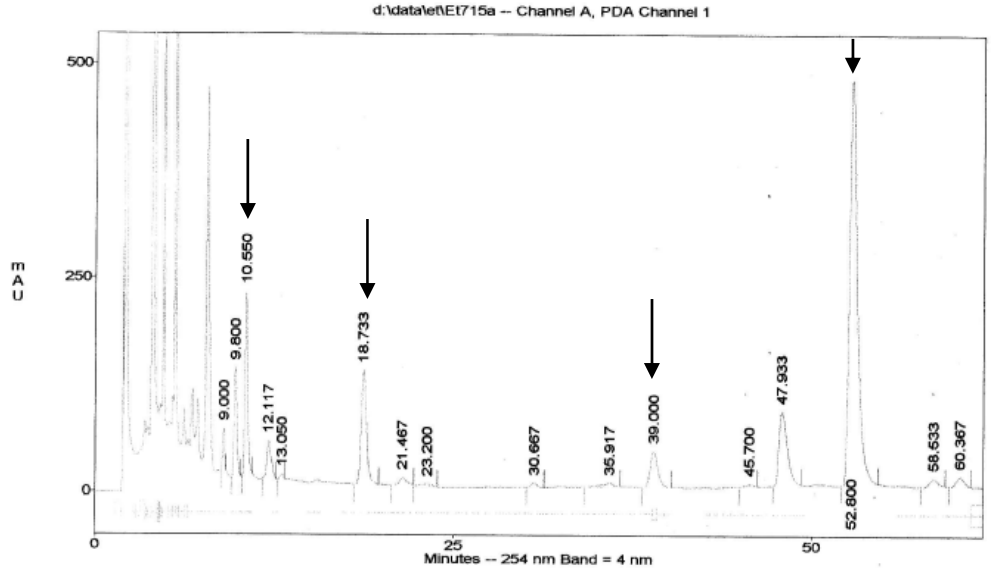
Authentic standard mixture for **190** (4 diastereomers).



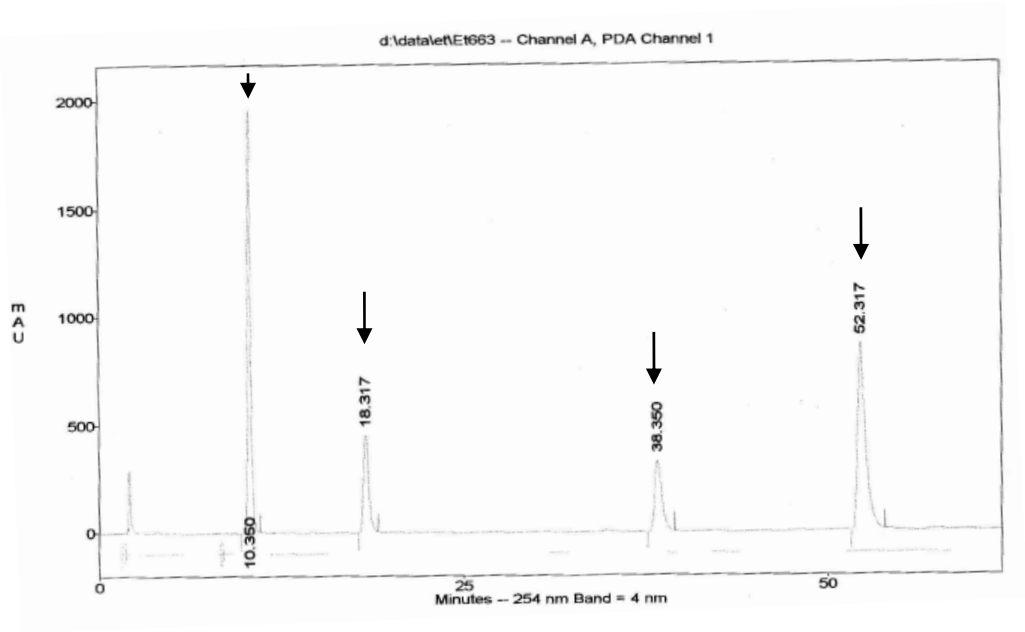
Compound **201**
HPLC conditions: 1.5% *i*PrOH:Hexanes to 3.5% for 20 mins then 1.5% to 3.5% *i*PrOH:Hexanes over 40 mins.



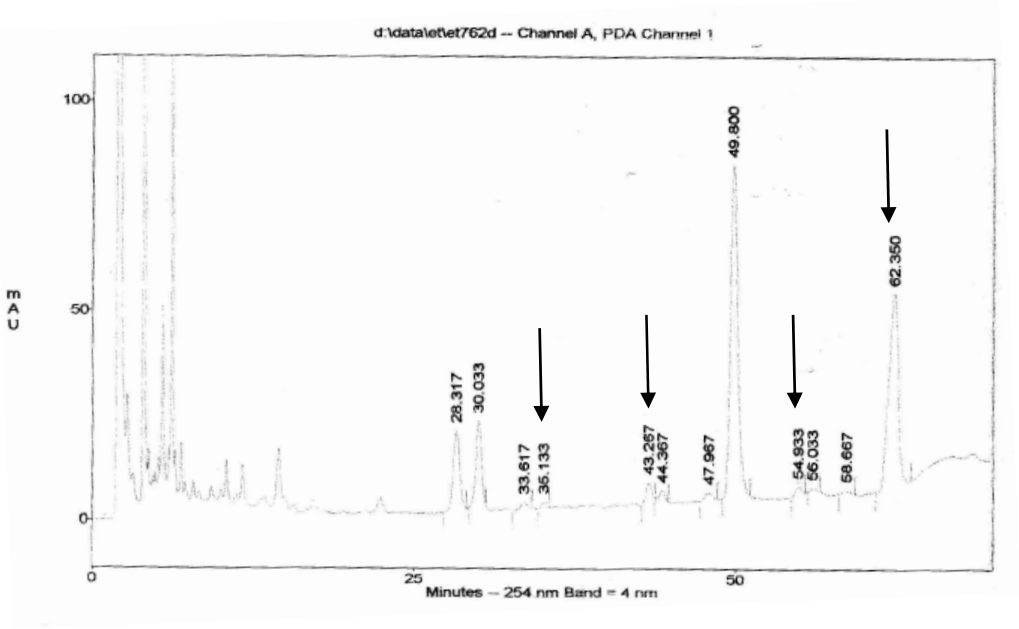
Compound **201** spiked with authentic standard mixture of 4 diastereomers.



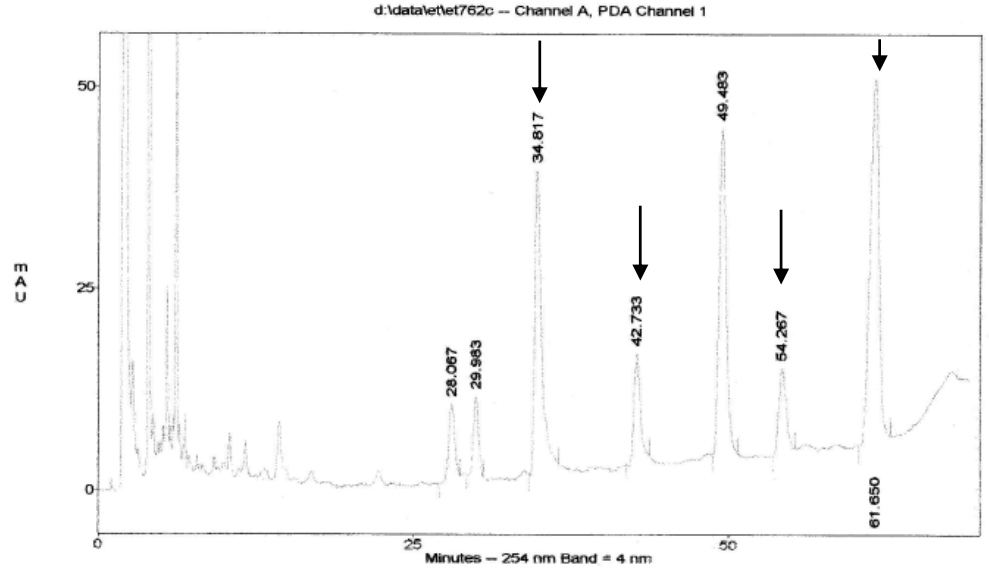
Authentic standard mixture for **201** (4 diastereomers).



Compound **200**
HPLC conditions: 1.5% *i*PrOH:Hexanes to 3.5% for 22 mins then 1.5% to 3.5% *i*PrOH: Hexanes over 38 mins.



Compound **200** spiked with authentic standard mixture of 4 diastereomers.



Authentic standard mixture for **200** (4 diastereomers).