Design and synthesis of bicyclic peptidomimetic scaffolds

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Preface (or life and how to live it)

I think it is impossible to separate the lessons I've learned from chemistry from those I have learned from life, and I think it is important to touch on this issue if not only for a brief moment. Chemistry is the science of life they say. Here are life lessons chemistry has taught me.

A mistake isn't a mistake unless you fail to learn anything from it. I don't regret any failed experiment in life or in chemistry. You should never be defined by your mistakes, you should, however, be judged by how you respond to them.

When chemistry and life aren't going well, don't sweat it too much. Sometimes all it takes is a little perspective to realize that, even if one experiment isn't going well, overall things are progressing. Life always takes missteps as well, but despite some meandering realize that, the path is getting you somewhere.

Speaking of paths, Pavement once said. "Between here and there is better than either here or there." Chemistry and life both will throw twists and turns at you, and even if it's not completely obvious where these twists will lead, it is often a good idea to take a chance on an idea, even if it doesn't direct you immediately to where you think you should be.

If something doesn't work three times in a row, try something else, hopefully something drastically different. And ask your friends for help when figuring that drastically different thing out. It is pretty easy to find yourself in a rut, it is really generally pretty hard to get out of it without a little help from your friends.

If it is currently over 30 degrees and humid, go play in the park, your not getting anything useful done anyways.

Don't completely trust anyone who is trying to sell you something, 99% pure yeah right . . .

Trust yourself, if you can't do that you're not going to get very far.

Mitch Huot, June 3rd 2010

Copyright statement

Abstract

Despite their promising biological activity, peptides have a number of unfavorable properties that hinder their ability to be drugs. Namely, peptides have poor bioavailability due to the proteases in the body that break them down. Also, peptides can often be substrates for numerous enzymes, therefore their selectivity can be quite poor. With this in mind, we aimed to design a series of constrained peptidomimetics designed to mimic dipeptide, while at the same time introducing conformational restraint in an attempt to improve selectivity, and they were designed without peptide bonds that could be cleaved by the body's proteases. In addition, these peptidomimetics were designed to be synthesized inexpensively and efficiently. The dipeptide-like linkages were designed to be introduced modularly and chemical handles were built into the design of molecule so that further functionalization would be simple. In this way, the molecule not only can act as a dipeptide mimetic but as a potental drug discovery platform for combinatorial chemistry. With this platform or scaffold, functional groups can easily be deployed in order to probe the geometric and electronic space of enzymes or receptors.

During the process of the synthesis of these drug scaffolds we discovered we could increase the diastereoselectivty of the venerable Diels-Alder reaction by running the reaction in less solvophobic solvents.

Resumé

Malgré leurs activités biologiques intéressantes, les peptides ont certaines propriétés peu favorables à leur conversion en médicaments. Pour exemple, les peptides sont rarement biodisponibles en raison des protéases présentes dans les milieux biologiques. Ces proteases les découpent en fragments plus petits qui peuvent a leur tour présenter diverses activités biologiques. De plus, les peptides peuvent se lier à diverses enzymes et récepteurs, réduisant ainsi leur sélectivité pour une protéine cible donnée.

Dans ce contexte, nous avons conçu une série de peptidomimétiques susceptibles de mimer des dipeptides naturels. L'incorporation de contraintes géométriques nous permet d'envisager une meilleure sélectivité pour une cible donnée alors que la réduction du nombre de liaisons amides devrait réduire leur protéolyse. La conception de ces molécules s'est également faite dans le contexte d'une accessibilité synthétique. La synthèse et la structure de ces molécules nous permettra une grande modularité alors que les groupements fonctionnels autour du cœur bicyclique pourront être utilisés comme autant de points d'ancrage pour l'introduction de diversité chimique et structurale.

Ainsi, ces molécules peuvent agir à titre de mimes de dipeptides mais aussi comme plateforme en synthèse combinatoire. Dans ce dernier cas, divers groupes fonctionnels peuvent être attachés sur les deux points d'ancrage.

Au cours du développement de la voie synthetique, nous avons mis a jour le lien entre la diastéréosélectivité de la réaction de cycloaddition intramoléculaire de Diels-Alder et la solvophobicité des solvants de réaction.

Acknowledgements

I would like to take a moment to thank the many people who helped make this thesis possible, some on purpose others mostly by accident.

First and foremost I would like to thank my parents Sheryl and Denis. They probably don't completely understand what I have done these last three years, but without their constant love and support I would not be here today. I would also like to thank my sister, grandparents, stepmother and the rest of my family for everything they have done for me over the years.

I would love to thank my supervisor, Professor Moitessier. He was always there to lend a helpful thought or to look over a manuscript at nearly any hour of the day. It goes without saying that none of this work would have been done without him, and I really do appreciate all that he has done.

Also I would like to thank all the lab mates I have had a privilege to work with over the years. It was truly a great experience and I feel like I have learned a lot from all of you. To Perrine Gissot who helped a lot one summer on the Knoevenagel reactions, thank you for your great work. When Perrine finally managed to reduce one of her products to an alcohol at the end of the summer, her excitement made me realize that in chemistry failure is to be expected, and success, always worth celebrating. I would also like to thank Janice Lawandi, who without her constant help, I don't know how I would have ever gotten along.

I would like to thank CIHR for giving me a scholarship so I could do much of this work, as well as McGill University for support along the way. I would also like to thank the administration, the secretarial staff, and the support staff for all their help along the way. Specifically, I would like to thank Dr. Fred Morin for all his help with the NMR services and Dr. Sayed for help with the mass spectroscopy.

I would like to thank all of my friends for their love and support. To Kylie, Pat, Chris and Jay, thanks for keeping me sane, between sports, drinks and Big Bumpin' you helped rejuvenate me whenever I needed a break from chemistry.

Contribution(s) of authors

Professor Nicolas Moitessier, as my supervisor, is a co-author of all articles presented.

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AAKT	Abboud-Abraham-Kamlet-Taft
Ac	Acetyl
aq.	Aqueous
Bn	Benzyl
Bzl	Benzoyl
BOC	*tert*-Butoxycarbonyl
Cbz	Carbobenzyloxy
CTAB	Cetyltrimethylammonium bromide
°C	Temperature in degrees Celcius
DEA	Diethyl amine
DIBAL	Diisobutylaluminum hydride
DMAB	Dimethylamine borane
DMAP	4-Dimethylamion pyridine
DMF	N,N'-Dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
h	Hour
IMDA	Intramolecular Diels-Alder reaction
*i*Pr	Isopropyl
IR	Infrared
Me	Methyl
MeOH	Methanol
MS	Molecular sieves
NMR	Nuclear magnetic resonance
Ph	Phenyl
PhMe	Toluene
POP	Prolyl oligo peptidase
Py	Pyridine
RT	Room temperature
SAR	Structure activity relationship
SOI	Secondary orbital interactions
t-Bu	*Tert*-Butyl
TEA	Triethyl amine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran

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Chapter 1 Scaffolds and peptidomimetics

1.1 *Introduction*

The growing emergence of crystal structures and NMR structures of proteins sometimes co-crystallized with their natural ligands or other binding molecules has led to a better understanding of these structures, their function and helped the design of synthetic binding molecules. Modern synthetic methodologies has allowed for the production of a wide range of peptides, many possessing impressive biological activity. Unfortunately, despite their biological activity, peptides have a number unfavorable pharmacological properties, including but not limited to, their poor selectivity and poor bioavailability. As peptides can often be the substrates of a variety of enzymes, the design of selective natural peptides as inhibitors can often be quite problematic. In addition peptides are generally unable to be administered orally because of the presence of proteases in the body, as well as biological barriers such as intestinal lumen and intestinal mucosa.

Despite these major obstacles, medicinal chemists have devised creative means to design peptide-like structures that are based on natural peptidic substrates without the limitations peptides possess. These pseudopeptides/ peptidomimetics can act as enzyme inhibitors or receptor agonists/antagonists while being orally available. These structures can often be designed in such away that they are more constrained than natural substrates thus providing a more selective potential inhibitor.

Not only do these non-peptidic mimics provide potential drug candidates, but having well designed, constrained peptidomimetics can also provide a platform for chemical diversity. These so-called drug scaffolds can be used to better understand enzymes or receptors by probing the geometric and electronic space of these enzymes or receptors.[1]

1.2 *Dipeptide Lactams*

Roger Freidinger is a true pioneer in the field of petidomimetics with his work at Merck beginning in the 1970's. Freidinger, while working on C3 symmetric cyclic hexapeptides, typified by *cyclo* (Ala-Sar)$_3$ studied for their effect on feed efficiency of ruminant animals. [2] Freidinger, in the course of a SAR study of the cyclic peptides, investigated whether conformational restricting the peptide backbone had a corresponding affect on activity. Freidinger modeled the system using the Merck Molecular Modeling System and used these models to synthesize molecules in the laboratory.

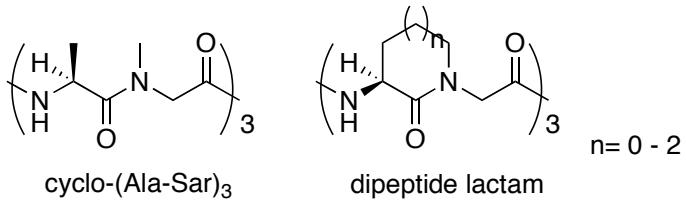
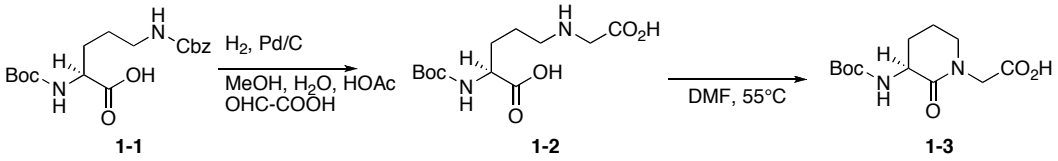


Figure 1.1 Freidinger's intial dipeptide lactam

From his modeling studies, Friedinger determined that the hexapeptide could be effectively constrained by bridging the α position of alanine to the nitrogen of sarconine. At the time, although innovative, the idea to use lactam rings was not wholly original, considering natural products contain lactam backbones, most notably, the β-lactam antibiotics including penicillin.



Scheme 1.1 Freidinger's synthesis of lactam amino acid

Freidinger designed his synthesis as shown in Scheme 1.1 starting from commercially available, chiral amino acids. In addition, these lactams were to be synthesized in a monoprotected form. Finally the lactam was to be easily incorporated into peptides under standard coupling conditions. Freidinger was quite successful in synthesizing his lactam under the goals that he had established.

The synthesis as shown in Scheme 1.1 began with **1-1** as starting material. Catalytic hydrogenolysis not only allowed for deprotection of the nitrogen but enabled the reductive amination of the newly formed amine in one pot. Cyclization occurred upon warming in DMF to afford the product in a 51% overall yied. This synthesized cyclic hexapeptide had similar activity to the parent *cyclo* $(Ala\text{-}Sar)_3$ in the ruminant fermentation assay.

1.3 *Azabicycloalkane amino acids*

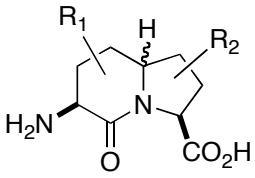
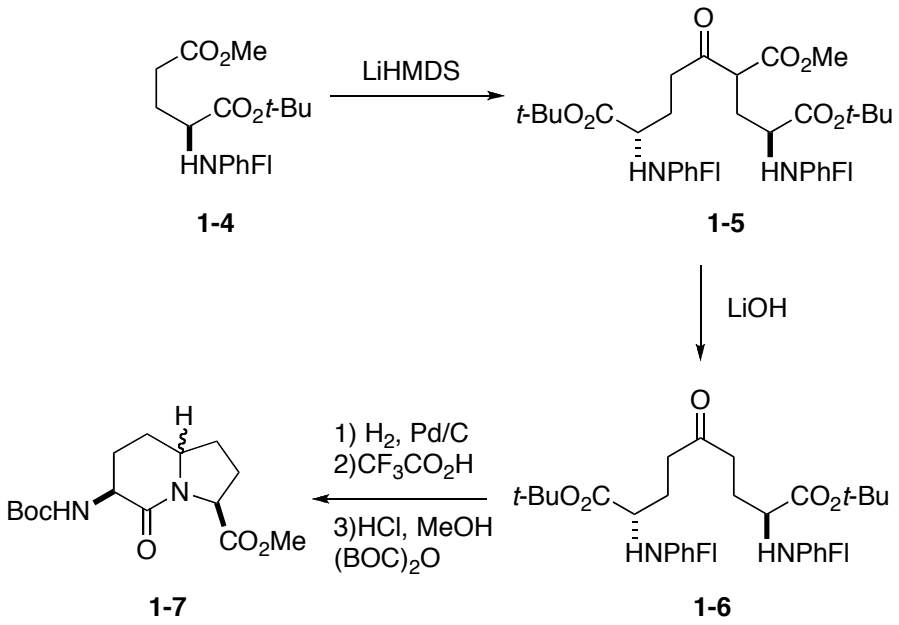


Figure 1.2 5,6-fused 1-2-oxobicycloalkane amino acids

Over the years, many examples of structures designed to mimic the secondary structure of natural peptides have been developed. One of the most widely studied of such structures is the azabicycloalkane amino acids.[1] The structure was designed to be an Ala-Pro type dipeptide and designed in order to mimic the β turn secondary structure of natural amino acids.



Scheme 1.2 Lombart et al. synthetic scheme for the synthesis of 5,6-fused 1-aza-2-oxobicycloalkane amino acid

Lombart et al. designed the first 5,6-fused 1-aza-2-oxobicycloalkane amino acid as a dipeptide mimetic.[3] This all carbon version of the general skeleton has an advantage over some of the other hetero atom analogues because it is stable to acid. Lombart's synthesis began as shown in Scheme 1.2 from fully protected glutamic acid. The initial and key step of the reaction is the Claisen condensation which is followed by saponification and decarboxylation. The final four steps allow for the formation of the diastereomeric indolizidinone ring in 25% overall yield.

Lombart manages to form the product in an 8-1 diastereomeric ratio, 99% enantiomeric purity and 25 % overall yield from the glutamate. However, the glutamate is not commercially available and must be prepared. The reaction also requires multiple protecting groups reducing the atomic economy of the reaction sequence. The molecular complexity is inherent in the starting material purchased, and is not generated in the reaction sequence. The molecule would also require a final deprotection step in order to couple to a peptide initially.

1.4 *Scaffold design*

In the current work, when designing peptidomimetics/ chemical platforms we envisioned a series of goals that we wanted to keep in mind:

- The scaffold should serve as a dipeptide surrogate.
- The scaffold should contain amide appendages at either end.
- The scaffold should mimic dipeptide secondary structures such as a β turn.
- The scaffold should conformationally constrain the dipeptide in the attempt to increase selectivity.
- The scaffold should be easily incorporated into peptide structures under standard conditions.

With these goals in mind, we developed the initial structure that we would attempt to synthesize. (Figure 1.3) Considering this general scaffold, a first series of dipeptide mimetics was envisioned following the Ala-XXX trend. (Figure 1.4) After this first series, the second series would change the first amino acid residue from alanine to other amino acids.

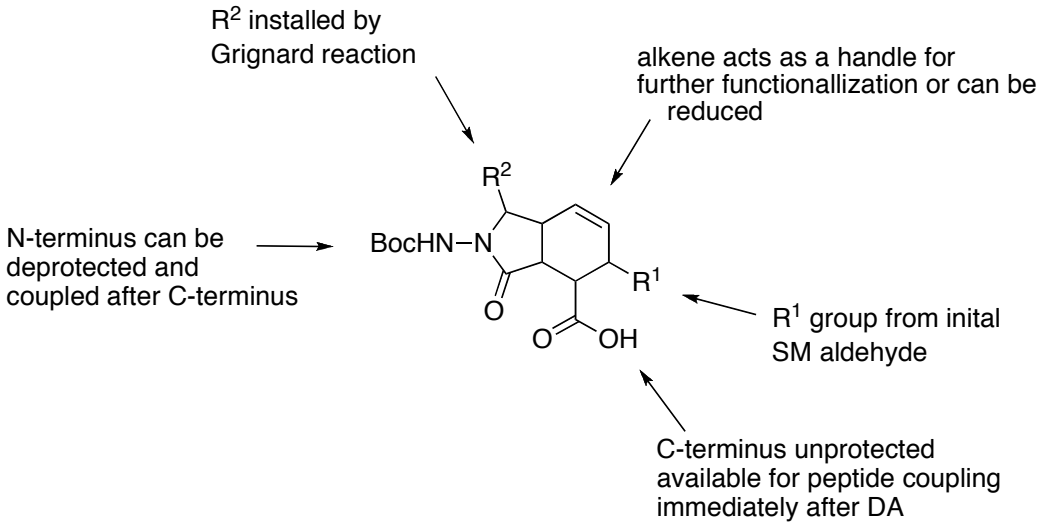


Figure 1.3 Core scaffold and possible points of functionalization

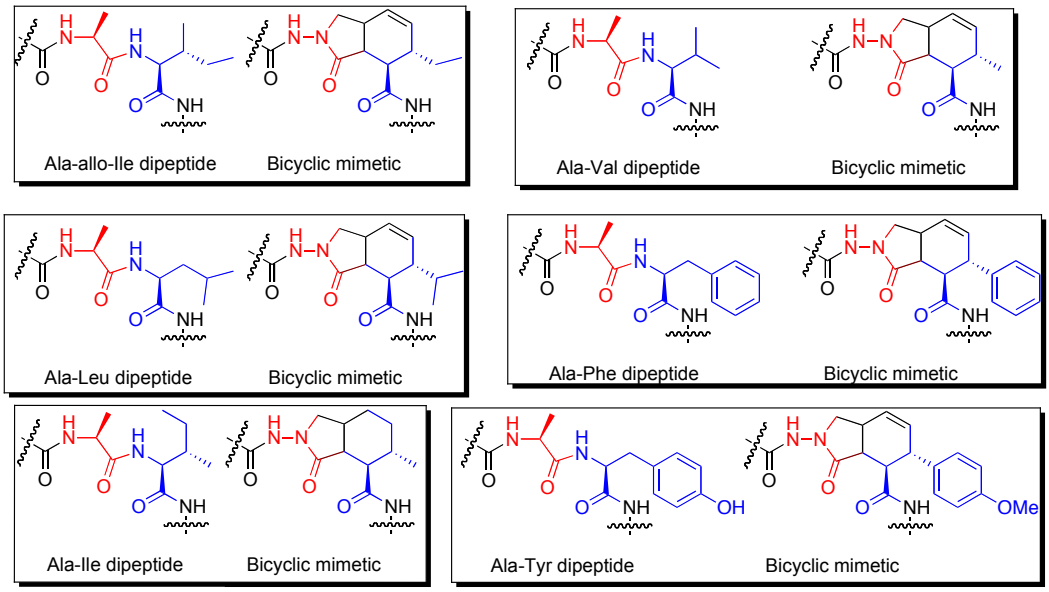


Figure 1.4 First series of dipeptide mimetics

1.5 *Synthetic goals*

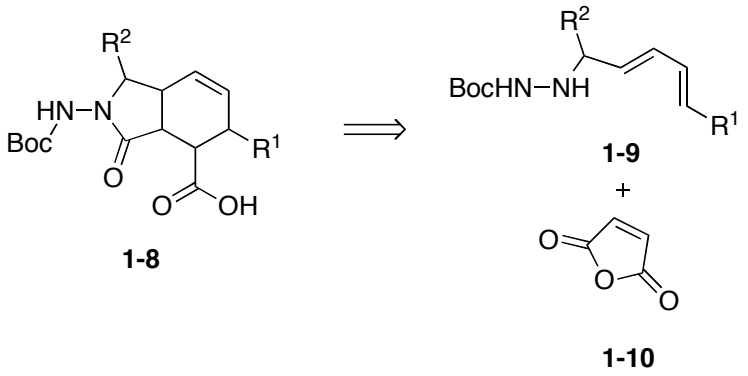
Considering the scaffold designed, we envisioned a series of additional goals that we attempted to follow in the design of a synthetic route.

- The synthesis should start from commercially available and inexpensive starting materials.

- The scaffold should be made in high yield with few synthetic steps and few isolation steps.
- Reactions with a high atom economy are paramount, building up the molecule through the synthetic scheme with little to no wasted side products.
- The synthesis should reduce or eliminate the need for protecting groups increasing the step economy of the reaction sequence.
- The synthesis should reduce or eliminate the need for environmentally harmful reagents and/or solvents.
- The scaffold should be synthesized in a protected form, enabling the modification of one terminus without disrupting the other.
- The synthesis should have good stereocontrol.
- The synthesis should be modular, enabling the key dipeptide structures to be easily incorporated into the final structure by judicious choice of starting material, without the need to change the synthetic scheme. Furthermore, this modular nature should allow for the introduction of not only amino acid like structures but permit the incorporation of many functional groups to enable the synthesis of "drug-like" molecules that can interact with the hydrophobic and hydrophilic regions of enzymes and proteins.
- Additional handles on the platform should be available for additional points of diversification allowing even greater control to synthesize probing molecules.

1.6 *Synthetic design*

With these several criteria in mind we strived forward with the design and synthesis of our scaffold. The retrosynthetic rational for the entire reaction sequence will be elaborated on in section 2.2. However, at this time we will focus on the key Diels-Alder reaction.



Scheme 1.3 Synthetic strategy

The R^1 and R^2 groups will establish which dipeptide will be mimicked originate from the diene hydrazine (synthesis will be documented in section 2.2). The Diels-Alder reaction between the diene and maleic anhydride will form the scaffold core, mono-protected at the N-terminus. This allows for the facile functionalization of the C-terminus. A deprotection step would then allow functionalization of the N-terminus. In the course of the Diels-Alder reaction, a double bond will of course remain. If the goal were merely the formation of peptide mimics this unsaturation can simply be reduced. However, if the molecule is to be used as a chemical platform, further functionalization of the molecule would result from manipulation of the double bond formed during the Diels-Alder cyclization. So on one hand, the R groups can be fixed in order to mimic dipeptides, or on the other hand, any series of R groups can be inserted rationally to investigate hydrophobic and hydrophilic pockets. Finally, the scaffold could also be used as a combinatorial platform, making as many combinations of R groups as possible in order to get structure activity relationships.

1.7 *Prolyl Oligopeptidase*

Prolyl oligopeptidase (POP) is a post-proline cleaving serine protease. It is an endopeptidase with a size of 80 kDa. POP is expressed in mammals, most widely in the brain, but it is also found in plants, bacteria and fungi. [4]

Much research has implicated POP with the central nervous system. Namely, POP has been shown to be important in neurodegenerative disorders

such as depression, amnesia and Alzheimer's disease. [5] In this regard, inhibitors of POP such as Cbz-Pro-prolinal have been developed, which, although showed in their preclinical trials promising results in the treatment of neurodegenerative disease, unfortunately, direct correlations between the disorder and POP could not be made. [6]

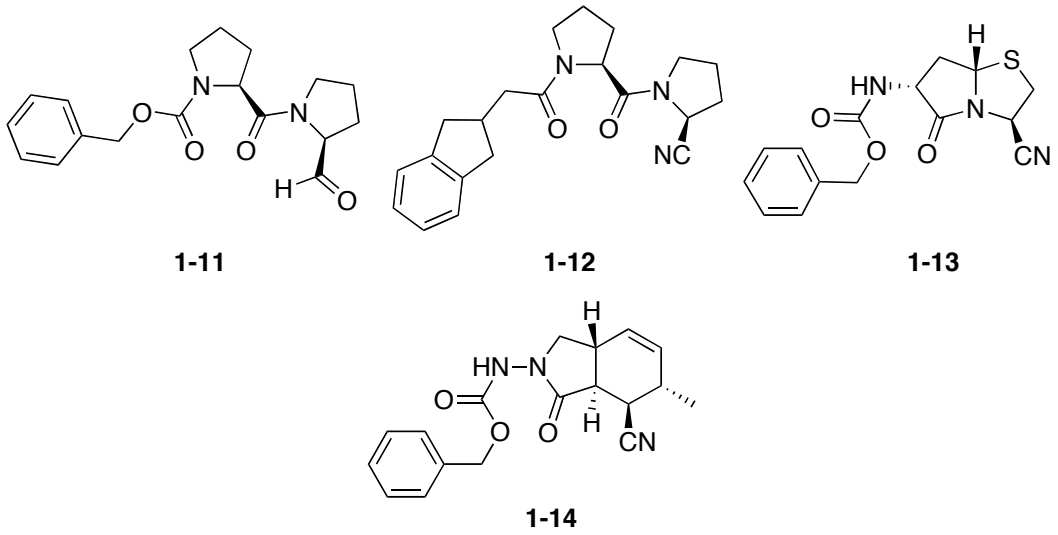


Figure 1.5 Known POP inhibitors **1-11, 1-12** and **1-13** and designed potential POP inhibitor **1-14**

In the development of potent POP inhibitors, a number of pseudopeptic and peptidomimetic inhibitors have been developed, of which three are shown in Figure 1.5. [6-8] From these three known inhibitors and many others, Lawandi et al. developed an important pharmacophore for the development of potential POP inhibitors. [4]

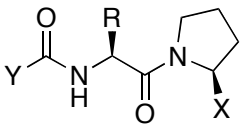


Figure 1.6 Pharmacaphore developed by Lawandi et al. for the inhibition of POP

When looking at our designed, potential POP inhibitor it is important to note that we maintain the important key features in the Y, R and X regions, in a relative stereochemistry that is close to the pharmacophore. The main point of

divergence is the six versus five membered ring of the molecule. Should this potential inhibitor not show activity, it very well could be likely that the enzymatic pocket cannot contain the extra ring size. The synthesis of the potential inhibitor is described in section 2.3.7.

1.8 *References*

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Chapter 2 Synthesis of *N*-amino-hexahydro-1*H* -isoindolones scaffolds

2.1 *Introduction*

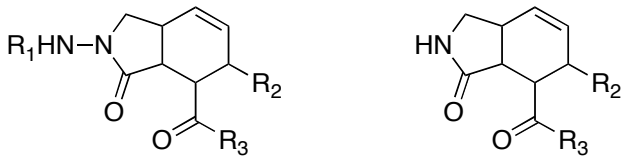


Figure 2.1 Schematic representation of a general *N*-amino-hexahydro-1*H* –isoindolone (left) and hexahydro-1*H* –isoindolone (right)

Despite intensive literature searches, no published reports of *N*-amino-hexahydro-1*H*-isoindolononones of the kind shown in Figure 2.1 have been reported in the literature. However, hexahydro-1*H*-isoindolones while by no means common in the literature, have been reported. More generally hydrosoindolones form the core structure of a series of natural products, the cytochalasins, whose synthesis has been undertaken by a number of groups.[9,10] Other groups have successfully synthesized the core via multi component cascade reactions.[11,12] Still others in the course of investigations of the Diels-Alder reaction itself, looked at the formation of isoindolones via an intermolecular[13,14] and via an intramolecular route.[15-20] In nearly all examples the key disconnection in the formation of the core is the Diels-Alder disconnection as shown in Figure 2.2.

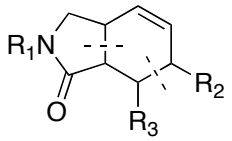
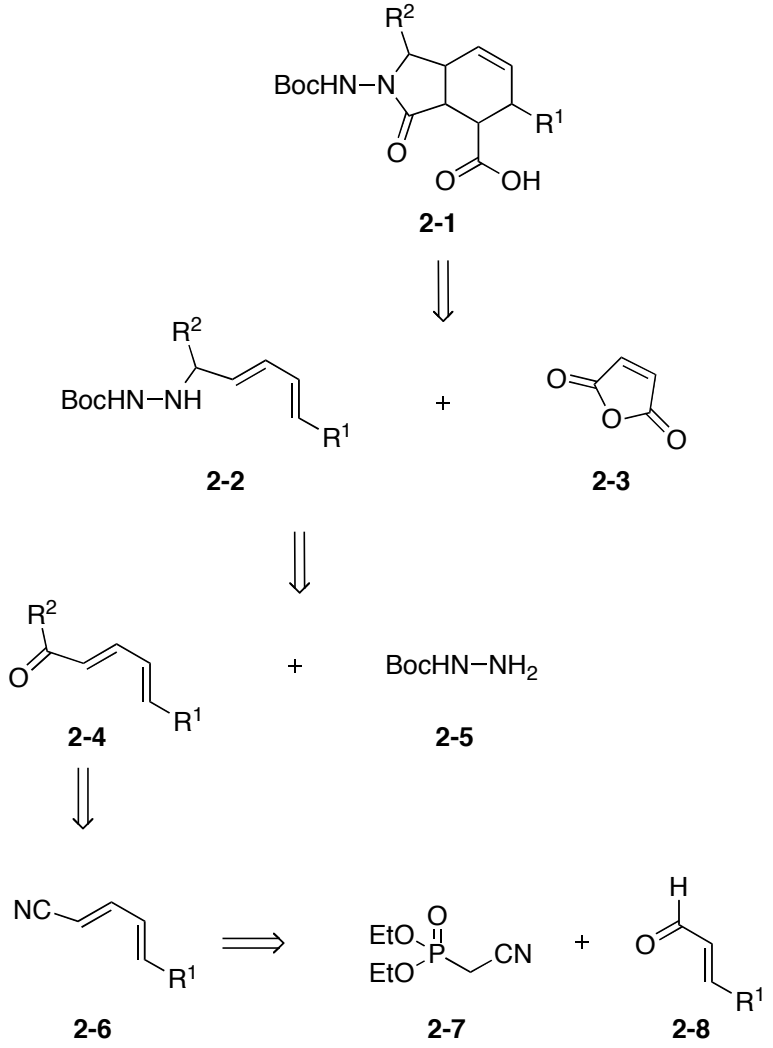


Figure 2.2 Common literature Diels-Alder disconnect

2.2 *Retrosynthetic analysis*

As shown in Scheme 2.1, the core of the *N*-amino-hexahydro-1*H* -isoindolone would form by the intramolecular Diels-Alder reaction of the triene formed between the functionalized hydrazide and commercially available maleic anhydride. The hydrazide would be built from a reductive amination between commercially available BOC hydrazide and the corresponding conjugated

aldehyde. These aldehydes, for some cases, are commercially available, otherwise they would be formed from the DIBAL reduction and subsequent hydrolysis of nitriles. The nitriles themselves would form from the two carbon homologation of commercially available α,β-unsaturated aldehydes. The homologation would come about by a Horner-Wadsworth-Emmons olefination with the cyano phosphonate, introducing mostly the *trans* double bond.



Scheme 2.1 Retrosynthetic analysis of *N*-amino-hexahydro-1*H*-isoindolone

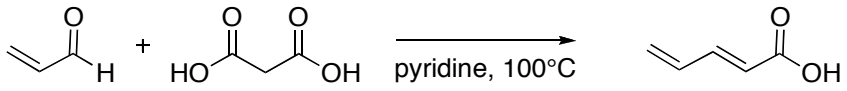
2.3 *Results and Discussion*

2.3.1 Dienal synthesis

Although not wholly uncommon, the synthesis of α,β,γ,δ-unsaturated aldehydes is not trivial. Only two such unsaturated aldehydes are readily

available from commercial sources such as Sigma Aldrich. There have been a number of techniques devised in order to form the conjugated system.[21-23] However, the most common method for the formation of these aldehydes is the two carbon homologation of the corresponding α,β-unsaturated aldehydes. This homologation is generally achieved through either a Knoevenagel condensation or a Horner-Wadsworth-Emmons olefination.

2.3.1.1 Knoevenagel condensation with Doebner modification for the formation of dienals

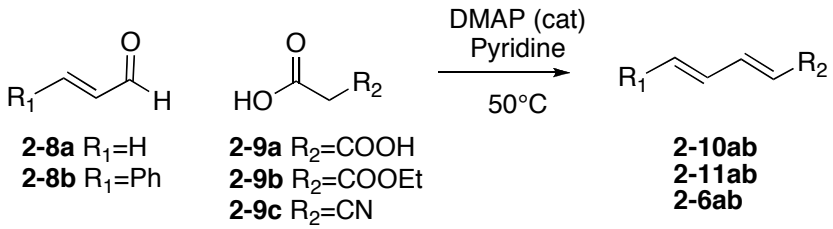


2-8a **2-9** **2-10a**

Scheme 2.2 Knoevenagel condensation with Doebner modification of malonic acid and acrolein.

The natural choice for the two carbon homologation would appear to be the Knoevenagel condensation with a Doebner modification. In the example in Scheme 2.2 the nucleophilic addition of commercially available malonic acid adds to commercially available acrolein. A dehydration and decarboxylation, subsequent to the addition, forms the desired unsaturated acid, which could be reduced in a myriad of fashions to afford the aldehyde. This reaction forms the *trans* double bond exclusively, and in the hands of others, is a very high yielding reaction forming a crystalline product. In our hands, the reaction was high yielding but difficult to crystallize. The resulting oil was insoluble in ethereal solvents proving difficult to reduce with LAH. Attempts to form the two carbon homologate of cinnamaldehyde by this method failed with only starting material remaining after reaction.

Table 2.1 Knoevenagel condensation between α,β-unsaturated aldehydes and various acids



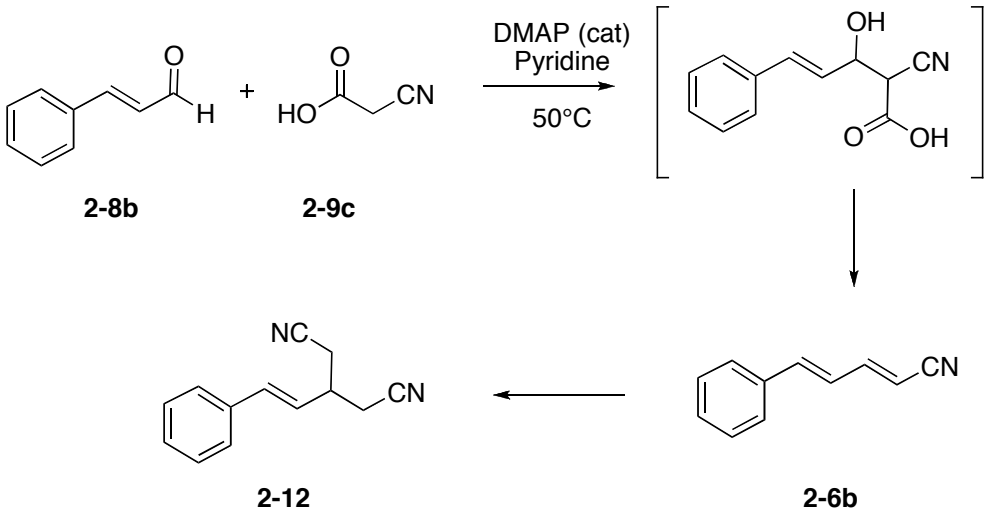
2-8a R_1=H
2-8b R_1=Ph

2-9a R_2=COOH
2-9b R_2=COOEt
2-9c R_2=CN

2-10ab
2-11ab
2-6ab

Compound	R_1	R_2	Yield %
2-10a	H	COOH	58-94
2-10b	Ph	COOH	NR
2-11a	H	COOEt	94
2-11b	Ph	COOEt	38
2-6a	H	CN	trace
2-6b	Ph	CN	20

Having difficulty reducing the acid formed between acrolein and malonic acid, and considering no reaction occurred between cinnamaldehyde and malonic acid, other Knoevenagel reactions were attempted in an effort to find a general protocol. Rodriguez and Waegell had shown success in the Knoevenagel reaction between α,β-unsaturated aldehydes and monoalkyl malonates.[24] Analogously, the Knoevenagel reaction with cyanoacetic acid was also attempted. (Table 2.1)[25]



Scheme 2.3 Formation of tandem Knoevenagel/ Micheal addition between cinnamaldehyde and cyanoacetic acid

As shown in Table 2.1, the Knoevenagel reaction with acrolein and malonic acid or monoethyl malonate was high yielding, however only trace amounts of product were formed with cyanoacetic acid, with a complicated mixture of products being formed. In the case of cinnamaldehyde, the results are disparaging; the reaction with monoethyl malonate and cyanoacetic acid does form some product, however, a major side reaction, a tandem Knoevenagel/ Michael addition (Scheme 2.3) prevents the reaction from being synthetically useful. Considering the number of sites for nucleophilic attack in the unsaturated system, it is unsurprising that formation of side products is observed.

2.3.1.2 Horner-Wadsworth-Emmons olefination for the sythesis of dienals

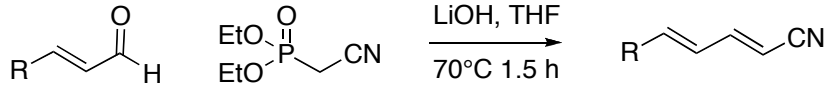
The next strategy attempted in the formation of the doubly unsaturated aldehydes was the Horner-Wadsworth-Emmons olefination. This reaction was desirable for a number of reasons. First, the double bond could be inserted with *E* stereochemistry predominantly. Second, the Wittig like reaction would prevent the chemoselectivity problems encountered with the Knoevenagel condensation.

The choice of phosphonate was pondered; a few criteria were established. First the reaction should insert a functional group that could be easily converted into an aldehyde. Second, reaction conditions should be mild. Third E-selectivity

is preferred, although some *Z* side product could be useful in the synthesis of other scaffolds. Fourth a high yielding reaction would be preferential. With these ideals established the Horner-Wadsworth-Emmons olefination with α-cyano phosphonate was attempted.[26]

Nitriles are a convenient functional group for a number of reasons. They are easily converted to various functional groups using well established chemistry. Most importantly, they can be reduced with DIBAL and immediately hydrolysed *in situ* to form aldehydes.[27] This reaction was exploited to great effect by Valla et al. in the synthesis of retinal.[28] Furthermore, the nitrile functional group is easily identifiable spectroscopically most notably by IR with a sharp, diagnostic peak at 2250 cm^{-1}. Another benefit of using α-cyano phosphonate is the mild conditions necessary for the deprotonation. With this reagent one can use LiOH as the base instead of using classical Horner-Wadsworth-Emmons strong bases such as LDA, LiHMDS or NaH.

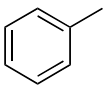
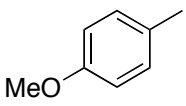
Table 2.2 LiOH promoted HWE olefination of α,β-unsaturated aldehydes with α-cyano phosphonate.



2-8a R=H
2-8b R=Ph
2-8c R=MeOPh
2-8d R=*i*-Pr

2-7

2-6a-d

Compound	R	Yield (%)	E/Z
2-6a	H	trace	70/30 (approx)
2-6b		72	80/20
2-6c		62	76/24
2-6d	*i*-Pr	51	77/23

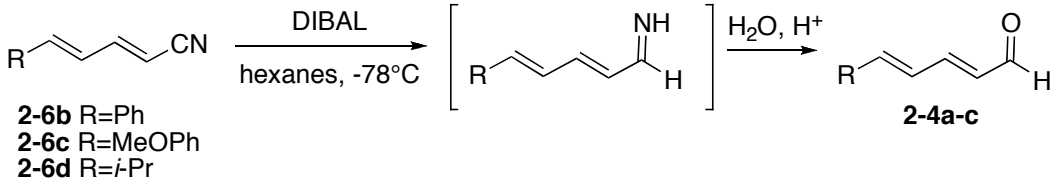
Lattanzi et al. demonstrated that α-cyano phosphonate, when reacted with cinnamaldehyde, can be relatively selective for the *E* isomer (75/25) with good

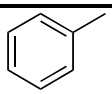
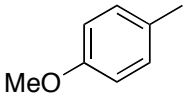
yields (72%). Our results (Table 2.2) agree with this assessment and other aldehydes showed fair to good yields and good selectivity. Acrolein, however, as was the case with the Knoevenagel reaction, failed to provide synthetically useful amounts of product.

2.3.2 Nitrile reduction and hydrolysis

With these results in hand, we proceded with the reduction and *in situ* hydrolysis of the nitriles. The nitriles were dissolved in toluene and 1.5 M DIBAL in hexanes was added at -78°C. After reduction to the imine, this intermediate is hydrolyzed with saturated ammonium chloride and then acidified with 10% H_2SO_4. All three nitriles were reduced in reasonable to good yields.

Table 2.3 Formation of dienals from corresponding nitriles via DIBAL reduction and hydrolysis



Compound	R	yield
2-4a		88%
2-4b		75%
2-4-c	*i*-Pr	63%

2.3.3 Hydrazide functionalization

General methodologies for the synthesis of alkyl hydrazines and hydrazides is of great importance. Hydrazines and hydrazides are crucial in fields as diverse as heterocycle synthesis,[29-32] carbene formation,[33] pseudopeptide synthesis,[34] aza-peptide synthesis,[35] natural product synthesis,[36] protecting group

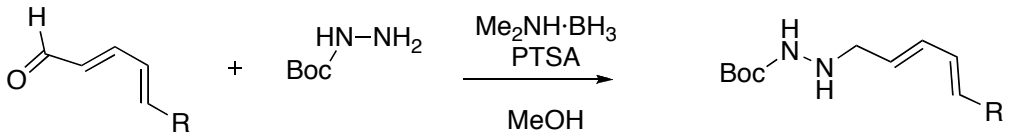
chemistry, chiral resolution and drug synthesis.[37] It is no coincidence that many strategies have been developed for the synthesis of a wide range of mono, di, tri and tetra substituted hydrazones and hydrazines. Ragnarsson has a review of the most important methods for the synthesis of such hydrazines up until 2001. Some more recent examples of hydrazine synthesis includes the use of Mitsunobu protocol,[38] palladium-catalyzed cross coupling,[39] elaborate protecting group manipulation,[40,41] nucleophilic substitution,[42] and reductive amination.[43,44]

2.3.3.1 Reductive amination of doubly unsaturated aldehydes with tert*-butyl carbazate*

Our synthetic strategy strives for good selectivity, high yields in few synthetic steps without lengthy purifications or isolations. We also strived for a reduction in the use of protecting steps and environmentally harmful reagents. With these criteria established reductive amination of commercially available BOC hydrazide with doubly unsaturated aldehydes was deemed to be the most appropriate choice of reaction.

The initial formation of the unsaturated hydrazone from the commercially available aldehydes and *tert*-butyl carbazate could be achieved by a ***solventless*** condensation, whereas the synthesized aldehyde required methanol as a solvent in order to react cleanly (Table 2.4).

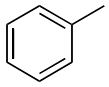
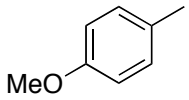
Table 2.4 Reductive amination of aldehydes with dimethyl amine borane complex



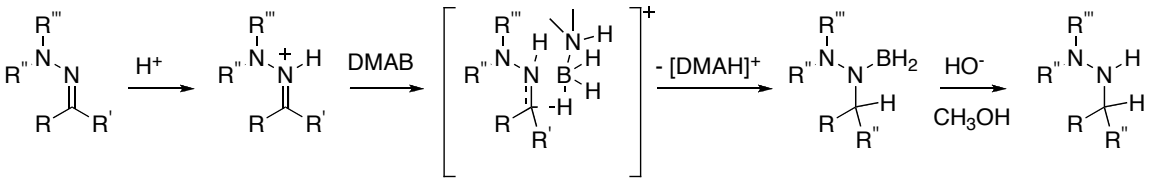
2-4a R=Ph
2-4b R=MeOPh
2-4c R=*i*-Pr
2-4d R=Me
2-4e R=Et

2-5a

2-2a-e

Compound	R	Condensation solvent	yield
2-2a		MeOH	64%
2-2b		MeOH	89%
2-2c	*i*-Pr	MeOH	61%
2-2d	Me	solventless	85%
2-2e	Et	solventless	92%

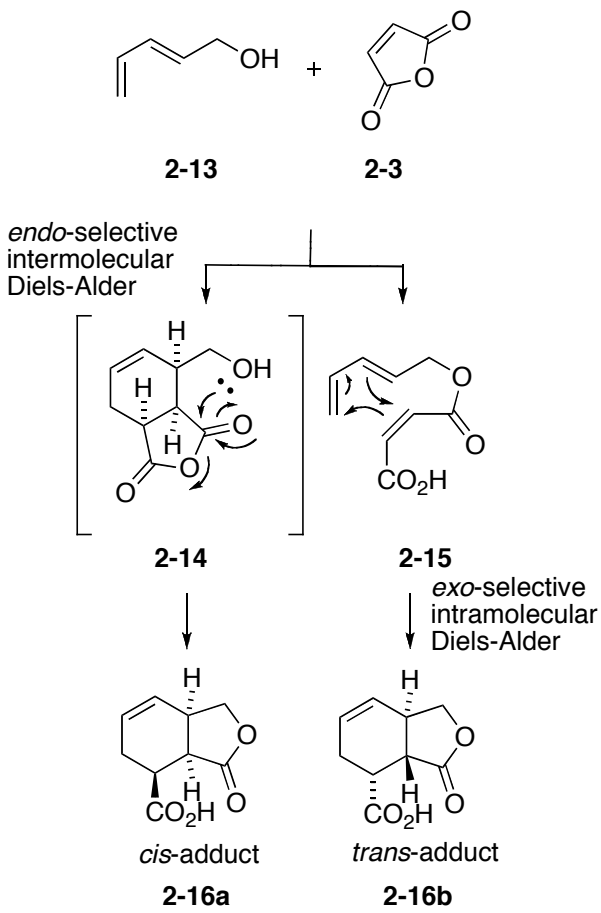
Initial attempts at the reductive amination of such a system with the standard reductant, sodium cyanoborohydride, proved fruitless. Considering the environmental hazard cyanides pose, no further attempts using this reducing agent were attempted. The literature was then searched to find a reducing agent that would perform the 1,2-reduction selectively. Fortunately Casarini et al. demonstrated they could perform the 1,2-reduction of α,β-unsaturated hydrazones selectively using dimethylamine-borane with PTSA. In the Casarini and coworkers' report, good yields and good selectivity were obtained for nearly all hydrazones reduced. Casarini et al. state that under acidic conditions, the Schiff base gets protonated. This in turn makes the iminium carbon vulnerable to hydride transfer from DMAB. (Scheme 2.4) The reaction ran smoothly with modest to good yields for all the aldehydes, (Table 2.4) also of note, no 1,4-addition was observed for any of the reductions.



Scheme 2.4 Casarini et al. proposed mechanism for the reduction of hydrazones with DMAB in acidic media

2.3.4 Scaffold synthesis via intramolecular Diels-Alder reaction

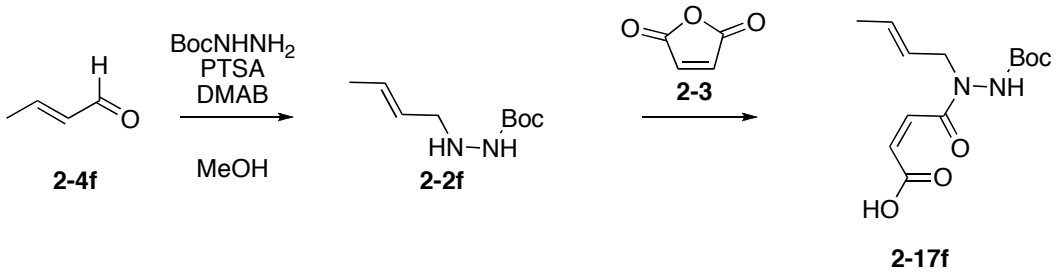
When considering the formation of the designed scaffolds it is important to consider the stereochemical outcome of the Diels-Alder reaction. As shown in Figure 1.4 it is important to note that the desired stereochemistry would be the *trans* fused ring. Considering this information, it was integral for us to find a set of conditions to form the scaffold with the *trans* fused ring selectively over the *cis* fused ring. Cayzer et al. showed in their work that they could form either the *cis* fused ring or the *trans* fused ring selectively during the course of the formation of their bicyclic lactone acids.[45] When performed in an intermolecular fashion, the reaction between 2,4-pentadien-1-ols with maleic anhydride, is almost completely *endo* selective forming the *cis* fused lactone acid. However, when performed intramolecularly with a pre-formed half ester, the *exo* selective Diels-Alder reaction predominates (Scheme 2.5).



Scheme 2.5 Cayzer et al. explanation for observed selectivity in Diels-Alder reactions

2.3.4.2 Feasibility of tandem reaction

With these results in mind, and considering the groups further work with nonatriene amides, [20] we attempted to find a way to form our analogous scaffolds, *exo* selectively in an attempt to form the *trans* fused ring. We decided coupling our diene hydrazide to maleic anhydride and performing a Diels-Alder reaction would furnish the desired cycloadduct with *exo* selectivity, forming the desired *trans* fused ring.

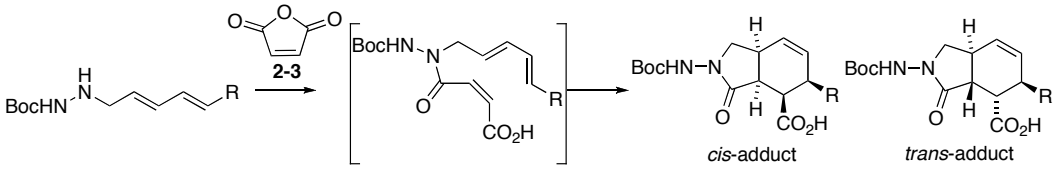


Scheme 2.6 Opening of maleic anhydride by a hydrazide

As a preliminary test to probe the feasibility of performing the tandem amide formation/ Diels-Alder reaction in one pot, we synthesized a hydrazide without a diene to test whether such a molecule could couple to maleic anhydride without the possibility of a further Diels-Alder reaction. Indeed the amide forms, opening the possibility to our tandem reaction sequence (Scheme 2.6).

2.3.4.3 Tandem amide formation/ Diels-Alder reaction

Table 2.5 Tandem amide formation/ Diels-Alder reaction



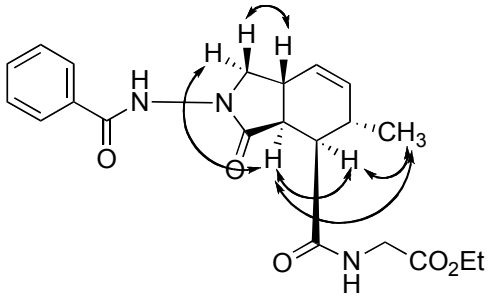
2-2a R=Ph
2-2b R=MeoPh
2-2c R=*i*-Pr
2-2d R=Me
2-2e R=Et

2-17a R=Ph
2-17b R=MeoPh
2-17c R=*i*-Pr
2-17d R=Me
2-17e R=Et

2-1a-j **2-1k-t**

Compound	R	yield	*exo*/ *endo* selectivity
2-1a,b,k,l	phenyl	80	1.4 to 3.9
2-1c,d,m,n	methoxy phenyl	68	3.0 to 5.6
2-1e,f,o,p	isopropyl	66	3.0
2-1g,h,q,r	methyl	71	1.0 to 3.3
2-1,i,j,s,t	ethyl	75	1.1 to 3.0

After this test reaction, we moved on to the tandem reaction between our diene hydrazides and maleic anhydride. As theorized, the bicyclic structures formed as a mixture of diastereomers with the desired *exo* Diels-Alder product, the *trans* fused ring forming in a majority (Table 2.5). (Note every enantiomer is labeled with its own letter but only one structure is shown.) The extent of this selectivity depended not only on the R group but also on the solvent system used. (Chapter 3) The relative stereoselectivity of the scaffolds was determined by 1D NOE and 2D NOESY experiments on the scaffolds and some derivatives. (Figure 2.3)



2-18ab

Figure 2.3 Selected NOE signals enabling structure assignment

2.3.5 Investigation into the feasibility of a one pot diene synthesis/ amide formation/ intramolecular Diels-Alder

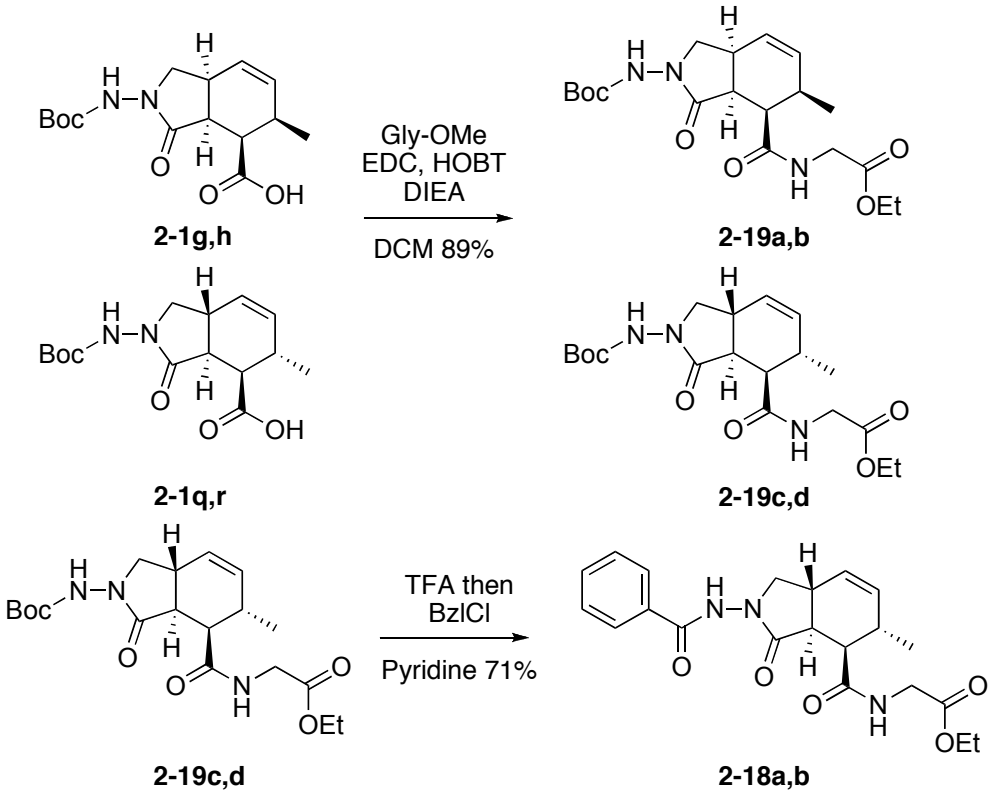
Initial studies were investigated in order to determine the feasibility of forming the diene and performing the Diels-Alder reaction in one pot. We thought this could be feasible considering the versatility of the Diels-Alder reaction. It can be performed under various conditions including a wide range of temperatures (0°C-100°C) as well as a diverse set of solvents including aqueous conditions (Table 3.1). An initial attempt to perform the reaction in one pot failed mainly due to the nucleophilic attack of hydrazine on maleic anhydride under acidic conditions.

Furthermore, attempting the reaction in two steps and one pot also failed. Under acidic conditions with methanol as the solvent, maleic anhydride alcoholysis competes with the formation of the Diels-Alder adduct. Attempts to

neutralize the base before the Diels-Alder reaction failed to yield satisfactory results.

2.3.6 Synthesis of peptide mimics

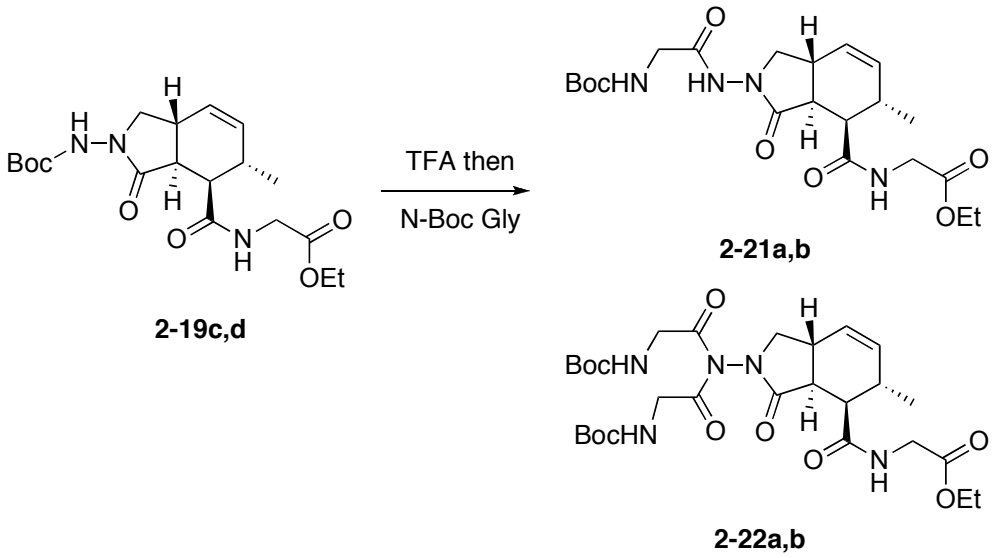
In order to determine the feasibility of using the scaffolds as potential peptide mimics, incorporating the structures into tetrapeptide mimics was probed. Coupling glycine ethyl ester to scaffold **2-1g,h** and **2-1q,r** under standard peptide coupling conditions provided the monoprotected tripeptide mimics **2-19a,b** and **2-19c,d** in good yields and also allowed for the separation of diastereomers. A one pot deprotection of the BOC protecting group along with coupling to benzoyl chloride allowed for the scaffold to be incorporated into a peptidomimetic structure **2-18a,b**. Attempts to couple the N terminus of the scaffold under more standard conditions caused the amino acid to couple twice to the hydrazide as a major side product. Multiple conditions were attempted however mono peptide coupling did not occur in a satisfactory yield as shown in Table 2.6. When acid chlorides were used the coupling was clean with a single product.



2-1g,h **2-19a,b** **2-1q,r** **2-19c,d** **2-19c,d** **2-18a,b**

Scheme 2.7 Formation of peptide like structures

Table 2.6 Attempts to peptide couple to *N*-terminus of scaffold



2-19c,d

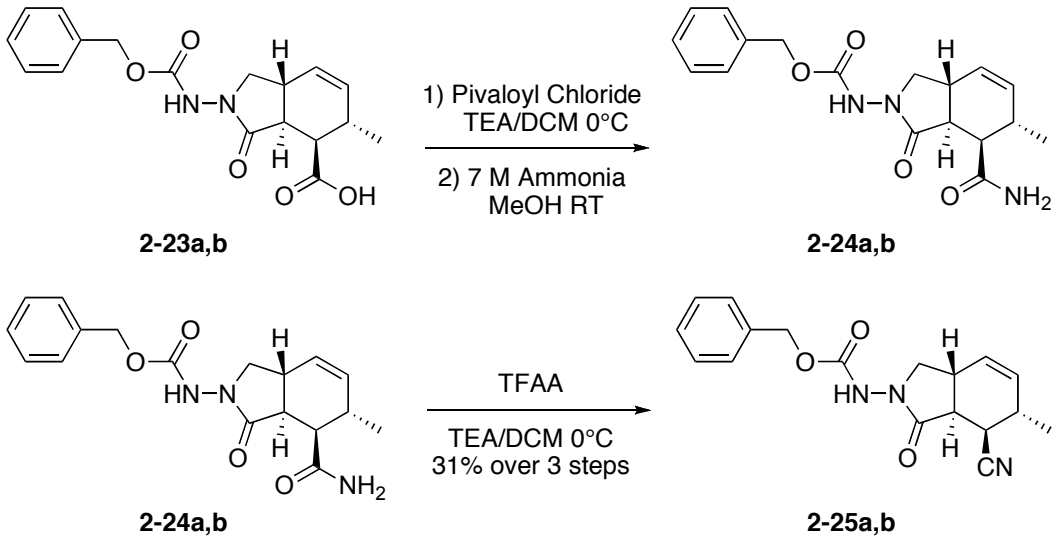
2-21a,b

2-22a,b

Deprotection conditions	Peptide coupling conditions	% yield mono coupled	% yield doubly coupled
HCl in Ether	EDC HOBt	18	25
TFA neat	EDC HOBt	7	28
TFA neat	HATU	minor	major

2.3.7 Synthesis of potential inhibitors

In order to probe the feasibility of using the scaffold in the preparation of potential inhibitors for POP, the synthesis of nitrile derivatives was probed. The carboxylic acid was first transformed into a mixed anhydride, which was then subjected to ammonia/ methanol to form the amide. This amide was then dehydrated with TFAA to furnish the nitrile.



2-23a,b **2-24a,b** **2-24a,b** **2-25a,b**

Scheme 2.8 Synthesis of potential inhibitors

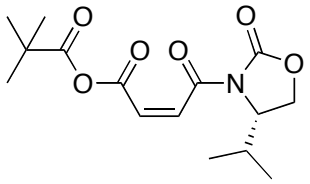
2.4 *Conclusions*

In conclusion we have shown an expedient means of synthesizing *N*-amino hexahydroisoindolones in a racemic fashion. The synthesis involves the modular synthesis of aldehyde dienes via a Horner-Wadsworth-Emmons olefination, and a reduction and hydrolysis of the resulting nitrile. We then, through reductive amination with dimethyl-amine borane complex, successfully coupled Boc hydrazide to the aldehydes selectively. Finally, the two part reaction, an amide formation/ intramolecular Diels-Alder reaction, furnished our products in good to moderate yield. We then showed that we could incorporate this scaffold into larger peptide structures and demonstrated that we could form potential POP inhibitors through well established chemistry.

2.5 *Future work*

2.5.1 Enantioselective Diels-Alder reaction

Forming the Diels-Alder product in an enantioselective fashion is of great interest. We believe that the best approach to accomplish this would be by introducing one of Evan's chiral auxiliaries to induce asymmetry, perform the Diels-Alder reaction, and finally removing the auxiliary. [46] The dienophile that would be used is shown in Figure 2.4.

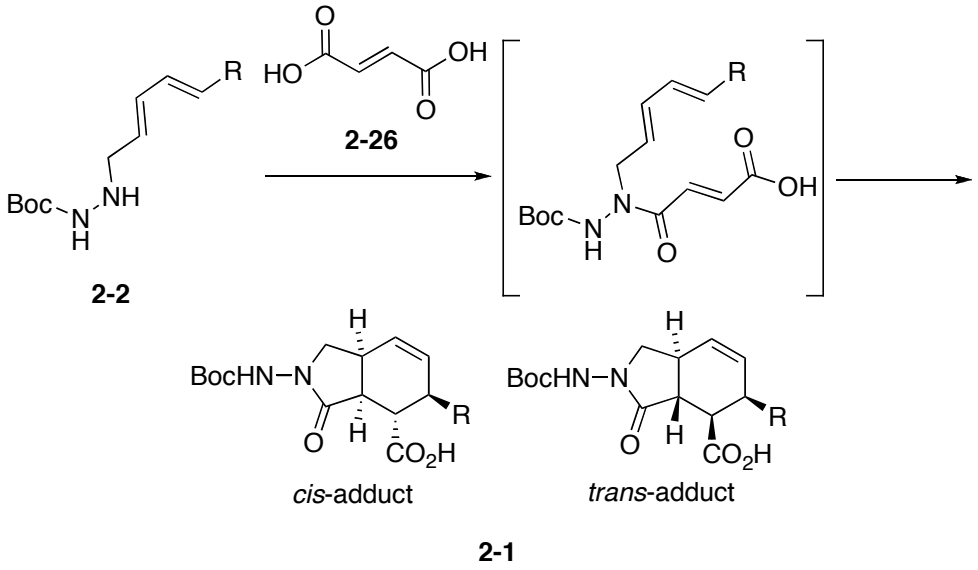


2-20

Figure 2.4 Dienophile coupled the Evan's chiral auxiliary for use in asymmetric Diels-Alder reaction

2.5.2 Diels-Alder reaction with *trans* dienophiles

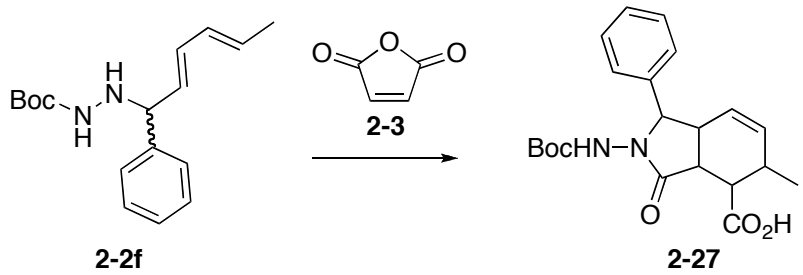
The next priority will be to perform the Diels-Alder reaction with a trans dienophile such as **2-26**. Not only will this allow us access to more scaffolds with differing stereochemistry, but it will also allow us to further investigate the stereo-outcome of the Diels-Alder reaction itself. Unfortunately, due to the nature of the *trans* double bond we believe it will be necessary to couple the diene first to the dienophile and then perform the intramolecular Diels-Alder reaction as shown in Scheme 2.9.



Scheme 2.9 Diels-Alder reaction with *trans* dienophile

2.5.3 Scope and synthesis of Phe-Val depeptide mimics

Finally, we would like to attempt the synthesis of a wider range of dipeptide mimics starting with a Phe-Val mimic. To accomplish this task, we will attempt use organometalic reagents to attack the hydrazones, and perform the Diels-Alder reaction once these functionalized dienes are formed. We will then carry out the Diels-Alder reaction with the goal of obtaining Phe-Val type mimics as shown in Scheme 2.10.



Scheme 2.10 Synthesis of Phe-Val mimic

2.6 *References*

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Chapter 3 Stereoselectivity of Diels- Alder reaction

3.1 *Introduction*

3.1.1 *Endo/ Exo* Selectivity

Almost immediately after Otto Diels and Kurt Alder first documented their discovery of the [4 + 2] cycloaddition between diene and dienophile (the reaction that now bears their names) much attention has been focused on the stereochemical outcome of the reaction.[47] Alder and Stein would formulate what would later be known as the "*endo* rule." [48,49] This rule based on the "maximum accumulation of double bonds" was used to rationalize the nearly ubiquitous formation of the *endo* product during the course of Diels-Alder reactions between substituted dienophiles to dienes. Woodward and Hoffman would later take a look themselves at the selectivity of the Diels-Alder reaction and would account for *endo* selectivity by the stabilizing effect of secondary orbital interactions on the *endo* transition state, interactions that are not present in the *exo* transition state as shown in Figure 3.1.[50]

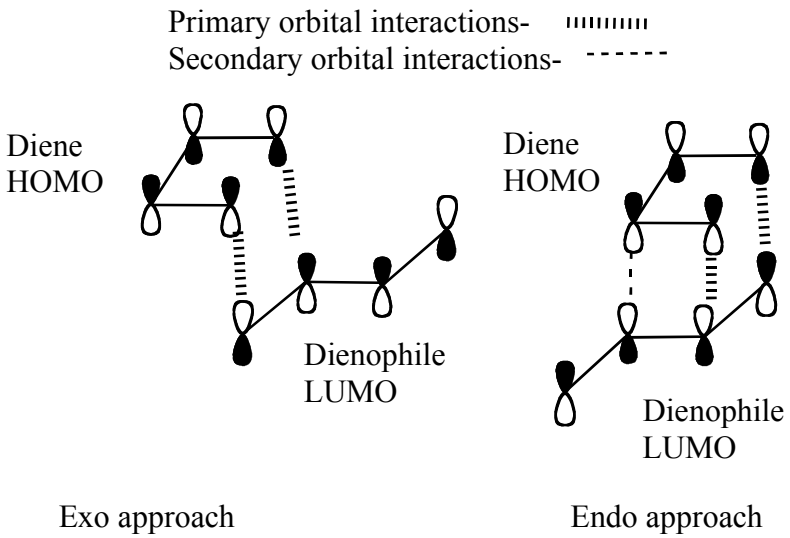


Figure 3.1 Woodward and Hoffman's proposed SOI (shown by dotted line) between diene and dienophile in the *endo* approach which is absent in the *exo* approach.

SOI's have, however, been met with some reservations by the academic community. Proponents of SOI such as Wannere et al. use density functional theory studies to confirm the phenomenon. [51] In comparison, Garcia et al.[52] suggest that invoking SOI's is not necessary when explaining *endo* selectivity in Diels-Alder reactions. In their paper, Garcia et al. claimed that what has been generally assumed to be SOI can instead be understood as a combination of steric interactions, hydrogen bonding, electrostatic forces and solvent effects. Herein we will focus mainly on the solvent effects on Diels-Alder reactions.

3.1.2 Solvent Effects

Traditional wisdom would suggest that since Diels-Alder reactions are generally thought of as completely pericyclic reactions with little to no development of charge, they should not succumb to solvent effects. Experimental evidence has, however, shown that solvent can have a varying effect on not only the kinetics of the reaction but also on the regio and stereochemistry of the resulting reactions.[53] Herein we will discuss the effect of solvent on the diastereoselectivity of the Diels-Alder reaction.

3.1.2.1 Solvent effects on exo/ endo selectivity of Diels-Alder reaction

Berson et al. pioneering work [54] on the stereoselectivity of Diels-Alder reactions essentially encouraged chemists to seriously consider solvent effects when looking at Diel-Alder reactions. Instead of looking at certain solvent parameters to try and find a correlation with *endo*/*exo* selectivity, Berson and coworkers instead looked at the Diels-Alder reaction between α,β-unsaturated esters with cyclopentadiene in 12 different solvents and introduced a new empirical solvent parameter Ω based on the *endo*/*exo* ratio obtained in the various solvents. This parameter Ω is said to be a measure of the solvent polarity. Berson explained his selectivity based on the dipole moments in the transition state of the intermediates of the Diels-Alder reaction. The *endo* transition state, having a greater dipole moment, is better stabilized in a more polar medium (Figure 3.2).

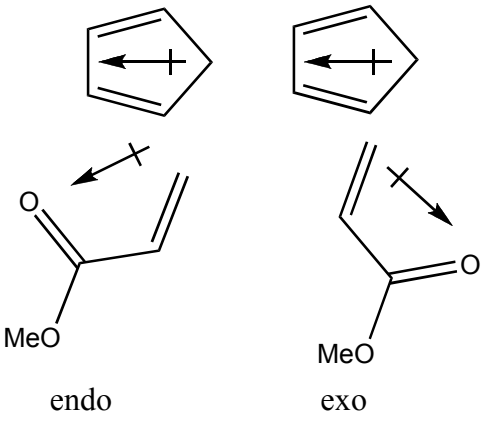
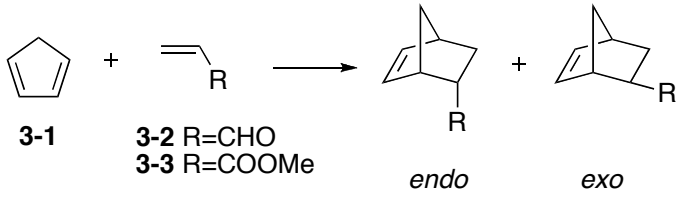


Figure 3.2 Berson's rational in the stabilizing effect polar solvent have on the endo transition state (left) over the exo (right)

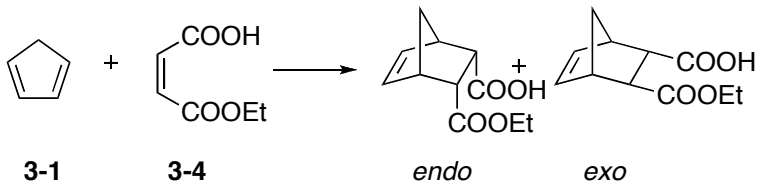
Due to detection limits at the time, the authors were unable to examine aqueous mixtures. However, having already demonstrated the importance of the hydrophobic effect on the rate acceleration of Diels-Alder reactions,[55] Breslow and coworkes investigated the solvent effect on Diels-Alder selectivity of the reaction in water between cyclopentadiene, butanone, and methyl acrylate amongst others.[55,56](Scheme 3.1) Breslow and coworkers showed that water can increase not only the rate of a Diels-Alder reaction but also raise the *endo* ratio of

the reaction. Breslow ascribes this increase to "the need to minimize trasition state surface area in water." Breslow goes on to show that this effect persists even with poorly soluble substrates.



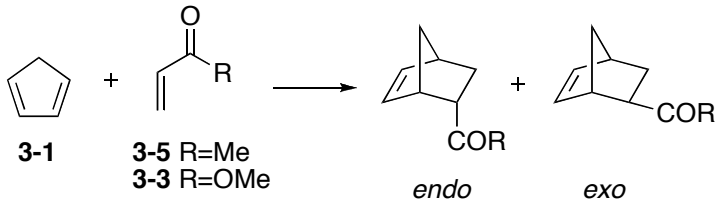
Scheme 3.1 Breslow's Diels-Alder reaction in aqueous solutions

In many ways expanding on the work of Breslow and others, Schneider et al. was the first to show an important correlation between Diels-Alder selectivity with the solvophobicity parameter S_p.[57] Breslow's work was important in showing the relationship between hydrophobicity and Diels-Alder steroselectivity. Schneider's work went beyond binary water mixtures and demonstrated the relationship of *endo/exo* selectivity with the solvent parameter S_p. Solvophobicity as defined by Michael H. Abraham is the "propensity of the solvent to provoke a hydrophobic effect on a given solute."[58,59] The S_p parameter is a quantitive measure of a solvent's solvophobic effect. Schneider considered two factors in the selectivity in the Diels-Alder reaction between cyclopentadiene and ethyl maleate, namely the solvophobicity of the solvent,[57] as represented by S_p, and the solvents polarity as represented by E_t. When ploting the log (*endo/exo*) against the S_p value for a series of 5 mixtures of methanol with water and 90% dioxane and hexane, Schneider showed that the *endo* selectivity increased with an increase in solvophobicity (Scheme 3.2). Schneider went on to show a poor correlation between E_t and selectivity, and when performing a multi parameter regression with both S_p and E_t included, Schneider showed the polarity, in fact, added very little weight to the equation.



Scheme 3.2 Schneider investigation into the correlation between solvent parameter S_p and the Diels-Alder reaction

Cativiela et al. also used multiple parameter regression models to compare log(*endo/exo*) for the reaction between cyclopentadiene and methyl vinyl ketone or methyl acrylate[53,60](Scheme 3.3) Cativiela and coworkers did an exhaustive study looking at 18 solvents and solvent mixtures and looked at a series of 5 parameters including the aforementioned S_p and E_t as well as the Kamlet and Taft solvatochromic parameters.[61] In addition to solvophobic effects, and polar effects, this allowed the authors to look at hydrogen bond donating, hydrogen bond accepting and polarizability parameters. Cativiela summarizes the results by showing that for both methyl vinyl ketone and methyl acrylate, hydrogen bond donating groups and S_p play an important role in selectivity, and for methyl acrylate, polarizability is also of statistical significance.



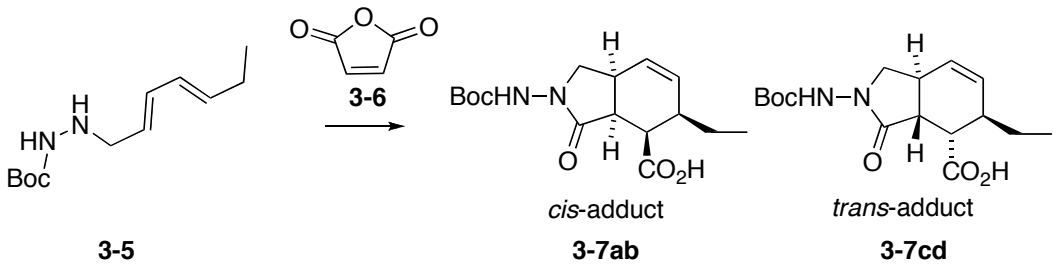
Scheme 3.3 Catievela's multiparameter investigation of the diastereoselectivity of Diels-Aldre reactions

Sustmann and Sicking took a theoretical approach when looking at the diastereoselectivity of the Diels-Alder reaction.[62] Using MNDO-PM3 calculations on the *endo* and *exo* transition states of the reaction between six membered dienes and acrylic acid and acrylamide, the authors found the selectivity was due in large part to dipole moment. The authors found that the polar character of the transition state determines the selectivity of the reaction. If the *endo* transition state has a higher dipole moment then it will be more stabilized in higher polarity solvents.

3.2 *Results and Discussion*

Considering the aforementioned examples in the literature studied, we found it imperative to establish which solvent parameters are important in our system; we first studied the reaction between **3-5** and **3-6** to form **3-7a,b** and **3-7c,d** with a set of 17 solvents as shown in Table 3.1. Following the examples above we decided to test the solvent parameters S_p, *Et* both individually and in a multiparameter approach as well as look the AAKT model.

Table 3.1 Solvent effects on the diastereomeric ratio on the reaction of **3-5**



	Solvent	E_t	S_p	π*	α	β	Log (*exo*/*endo*)
A	toluene	0.096	0	0.54	0.00	0.11	0.362
B	acetone	0.355	.1267	0.71	0.080	0.480	0.398
C	acetonitrile	0.472	0.2167	0.750	0.190	0.310	0.301
D	DCM	0.321	0	0.820	0.300	0.000	0.477
E	DMSO	0.441	0.2268	1	0.00	0.76	0.301
F	DMF	0.404	0.1384	0.88	0.00	0.69	0.462
G	1-propanol	0.617	0.1076	0.52	0.78	_	0.380
H	EtOH	0.654	0.1440	0.54	0.83	0.77	0.447
I	MeOH	0.765	0.1998	0.6	0.93	0.62	0.362
J	1-butanol	.602	.079	0.47	0.79	0.88	0.3979
K	*t*-butanol	0.407	_	0.41	0.68	1.01	0.462
L	chloroform	0.259	_	0.58	0.440	0	0.519
M	1-octanol	0.543	_	_	_	_	0.4771
N	2-butanol	.506	_	_	_	_	0.6434
O	30% EtOH in H_2O	_	0.7004	_	_	_	0.0414
P	50% EtOH in H_2O	_	0.4495	_	_	_	0.1139
Q	70% EtOH in H_2O	_	0.2799	_	_	_	0.2789

3.2.2 Solvent effects on the intramolecular Diels-Alder reaction of 3-5

Table 3.2 Results of the regression model of *endo/ exo* selectivities on the reaction of **3-5** with several solvent parameters

n	r^2	f	Intercept	E_t	S_p	π*	α	β
14	0.002	.019	0.44	-0.020 ±0.148	_	_	_	_
13	0.845	61.41	0.46	_	-0.625 ±0.080	_	_	_
10	0.422	2.56	.403	0.125 ±0.101	-0.591 ±0.261	_	_	_
11	0.165	0.460	0.472	_	_	0.472 ±0.151	-0.079 ±0.187	0.045 ±0.101
10	0.512	2.10	0.270	_	-0.639 ±0.261	0.230 ±0.164	0.105 ±0.069	_
10	0.352	1.90	0.431	_	-0.434 ±0.231	_	0.031 ±0.047	_

It is immediately apparent from Table 3.2 when comparing r^2 coefficients that the only reliable correlation occurs between log(*exo/endo*) and S_p, while there is likely no correlation with the other parameters. If we graph log(*exo/endo*) vs. E_t (Figure 3.3) and log(*exo/endo*) vs. S_p (Table 3.4) this becomes ever apparent. Cativiela et al. when describing their results of methyl acrylate reacting with cyclopentadiene attributes a diastereoselectivity with a significant E_t coeffecient as having a more asymmetrical or asynchronous transition state as compared to a reaction that only correlates with S_p.[53] The Diels-Alder reaction is still considered as a concerted cyclization however the developing internal bond is shorter in the transition state than the external developing bond, this phenomenon is known as asynchronousity (not to be confused with the album from The Police).[63] If a reaction only depends on S_p, Cativiela attributes this to the fact that the transition state has a greater difference in compactness between the *endo* and *exo* transition state. A density functional theory study on amide linked trienes done by Paddon-Row et al. shows that the transition state is indeed asynchronous.[20] Our

analogous system would presumably also be asynchronous and it is diffult to rationalize why the selectivity depends on only solvophobicity and not on polarity. Nonetheless, by Cativiela's logic, the solvent dependent selectivity we are observing could very well be caused by the compactness of the transition states. Since the *exo* transition state is less compact than the *endo* transition state, the *exo* is going to be favored in more solvophobic solvents.

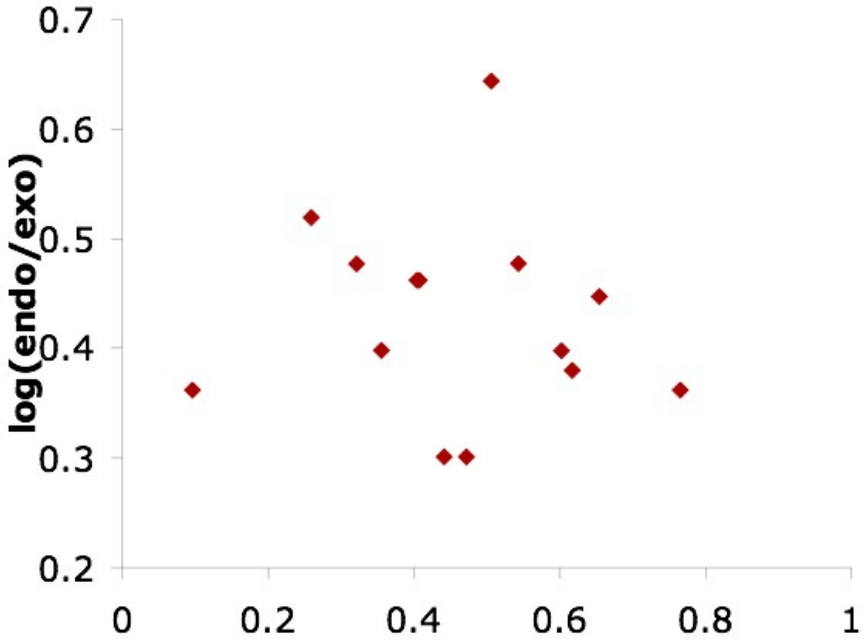


Figure 3.3 Diastereoselectivities log(*endo/exo*) vs. solvent polarity parameter E_t for the IMDA rection of **3-5**

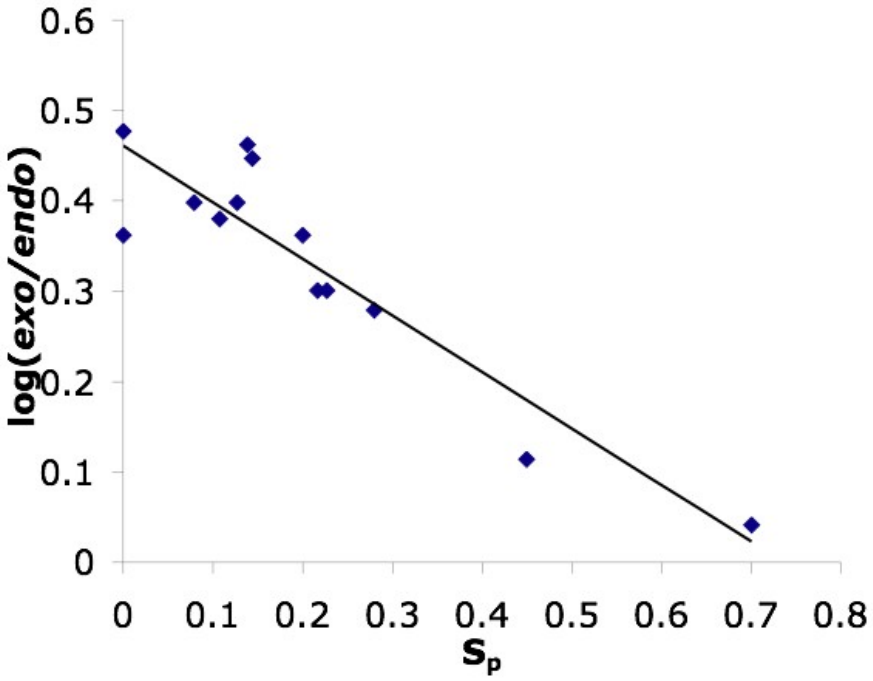
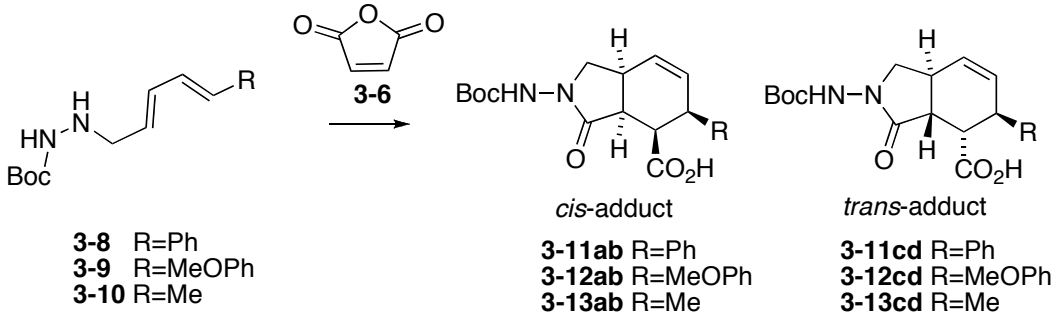


Figure 3.4 Diastereoselectivities log(*endo/exo*) vs. solvophobicity parameter S_p for the IMDA rection of **3-5**

3.2.3 Solvent effects on the diastereoselectivities of the reaction of diene hydrazides 3-8, 3-9 and 3-10 with maleic anhydride.

With the results of section 3.2.2 in hand we decided in Table 3.3 to see how changing the R group affects the solvent effect observed. Due to the fact that hydrazides **3-8** and **3-9** are synthetically more demanding to synthesize than the ethyl, we decided to look a smaller subset of solvents. Our objective was to look for general trends rather than to perform an exhaustive study. We decided to look at EtOH/ water mixtures as they account for a wide range of S_p values and because we enjoy ethanol water mixtures. We also chose to look at DCM since it showed good diastereoselectivity in the example of R= Et and with a S_p value of zero allows us to look at nearly the full range of S_p values [0-1].

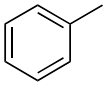
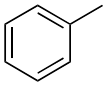
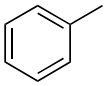
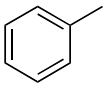
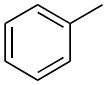
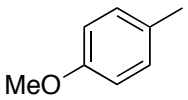
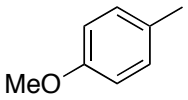
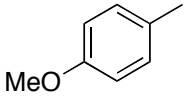
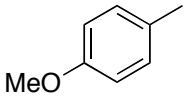
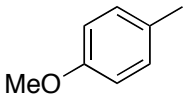
Table 3.3 Solvent effects on diastereoselectivity of the reaction between triene hydrazides and maleic anhydride



3-8 R=Ph
3-9 R=MeOPh
3-10 R=Me

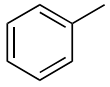
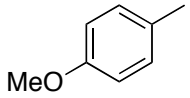
3-11ab R=Ph
3-12ab R=MeOPh
3-13ab R=Me

3-11cd R=Ph
3-12cd R=MeOPh
3-13cd R=Me

	Solvent	R	S_p	log(*exo/endo)*
D	DCM		0	0.556
O	30% EtOH in H_2O		0.7004	0.146
P	50% EtOH in H_2O		0.4495	0.279
Q	70% EtOH in H_2O		0.2799	0.398
H	EtOH		0.1440	0.591
D	DCM		0	.663
O	30% EtOH in H_2O		0.7004	0.477
P	50% EtOH in H_2O		0.4495	0.544
Q	70% EtOH in H_2O		0.2799	0.672
H	EtOH		0.1440	0.748
D	DCM	Me	0	0.415

O	30% EtOH in H_2O	Me	0.7004	0
P	50% EtOH in H_2O	Me	0.4495	0.080
Q	70% EtOH in H_2O	Me	0.2799	0.204
H	EtOH	Me	0.1440	0.398
L	Chloroform	Me	0	0.519
F	DMF	Me	0.1384	0.462

Table 3.4 Regression results of IMDA between triene hydrazides and maleic anhydride using solvent parameter S_p

R	n	r^2	Slope	intercept
Et	13	0.845	-0.625 ± 0.080	0.461 ± 0.022
	5	0.926	-0.661 ± 0.108	0.602 ± 0.043
Me	7	0.900	-0.750 ± 0.111	0.480 ± 0.038
	5	0.753	-0.342 ± 0.114	0.729 ± 0.046

The results tabulated in Table 3.3, Table 3.4, and graphed in Figure 3.5 revealed some interesting trends: First and foremost, for these types of hydrazide dienes reacting with maleic anhydride, a decrease in *exo* diastereoselectivity caused by an increase in solvent solvophobicity seems to be a general trend. Second, the slope for the case of R= Et and R= Ph are nearly identical and definitely within error of each other. With only two cases in hand it is hard to say whether this is merely coincidence or whether it is representative of a general phenomenom. For the case of methoxy phenyl, the difference in slope could be due to the more polar nature of the R group. Unfortunately E_t values could not be found for ethanol water mixtures otherwise a dual parameter correlation would have been investigated. Studying the system in MeOH water could shed some light on the situation as E_t values are available for these aqueous mixtures. Third,

the intrinsic diastereoselectivity of the three systems is of interest and worthy of further investigation.

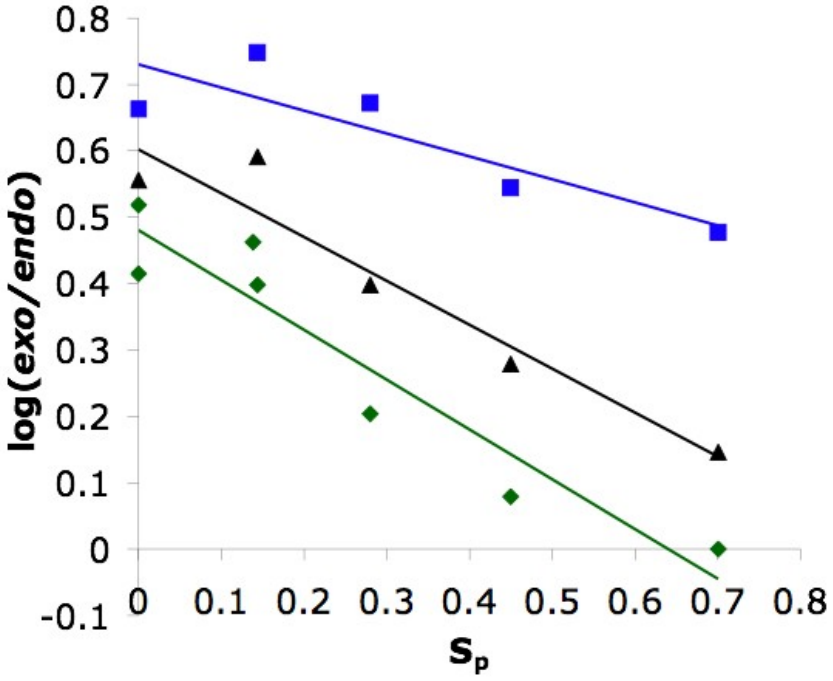


Figure 3.5 Diastereoselectivities log(*endo/exo*) vs. solvophobicity parameter S_p for the IMDA rection of **3-9** in blue, of **3-8** in black and of **3-10** in green

3.2.4 Effect of solvent additives on Diels-Alder reaction

During the course of the investigation into the diastereoselectivity observed for our Diels-Alder reactions we studied some solvents without defined S_p parameters and used solvent systems with additive and the preliminary results are tabulated for your benefit (Table 3.5). The chemical literature is rife with reports of additives having a diverse effect on the rate and selectivity of Diels-Alder reactions. The use of heterogeneneous catalysts has shown to increase rate with good diastereoselectivity.[64,65] The effect of salt additives was also investigated in great detail by a number of groups.[66,67] Finally the effects of ionic liquids,[68] micellar media[69] and surfactants[70,71] was also investigated

Table 3.5 Diastereoselectivity of Diels-Alder reation between **3-5** and **3-6** in solvent shown and with additivie added

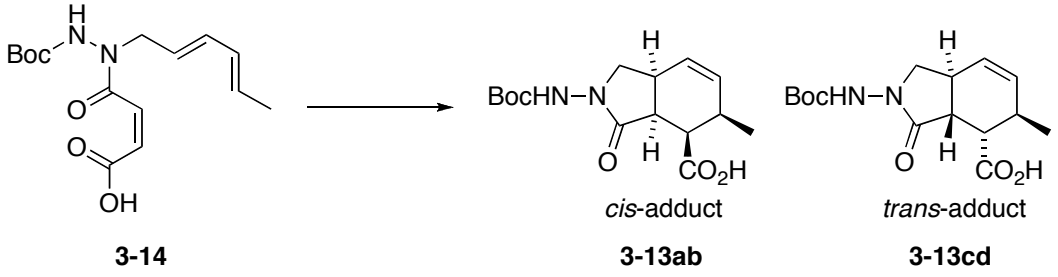
Solvent	Additive	Selectivity (*endo/exo*)
water	2M Guanidine	1.7
tert amyl alcohol		2.2
1% ethanol in hexanes		2.2
EtOH	SDS 0.02M	3.3
EtOH	C_{18} Alumina 1g	3.3
EtOH	Basic Alumina 1g	2.6
Chloroform	1 eq BF_3, -30° C	1.4

From Table 3.5, we can see that the Diels-Alder reaction is affected by the addition other solvents without corresponding solvent parameters such as tert-amyl alcohol, 2-hexanol and 1% ethanol in hexanes. We can also see the effects of adding various additives. The addition of guanidine does not significantly increase the diastereoselectivity of the Diels-Alder reaction in water. Also, the addition of a Lewis Acid such as BF_3 etherate allows the reaction to occur at -30°C, but it limits the diastereoselectivity of the Diels-Alder reaction in chloroform. Overall this data indicates that the diastereoselectivity of the Diels-

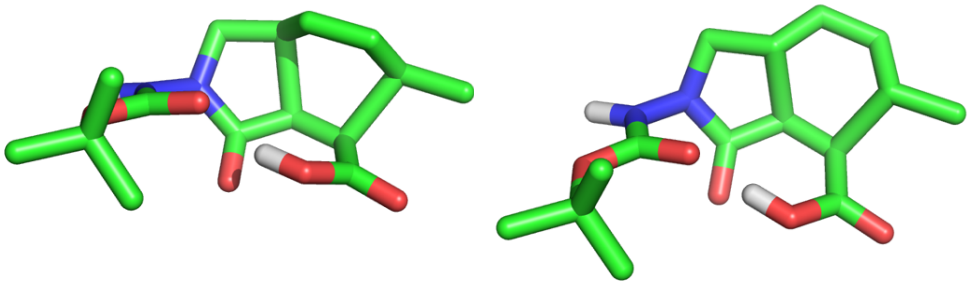
Alder reaction can be affected by non traditional solvents and solvent addititives. However, none of these solvents or addiditives significantly improve on the diasterstereoselectivity of the Diels-Alder reaction enough to warrant their use over more traditional low boiling solvents on their own.

3.2.5 Computational study of Diels-Alder reaction using ACE

Using our in house molecular mechanics based asymmetric catalysis transition state modeling software ACE, we modeled the Diels-Alder reaction of **3-14** and **3-15**. [72]

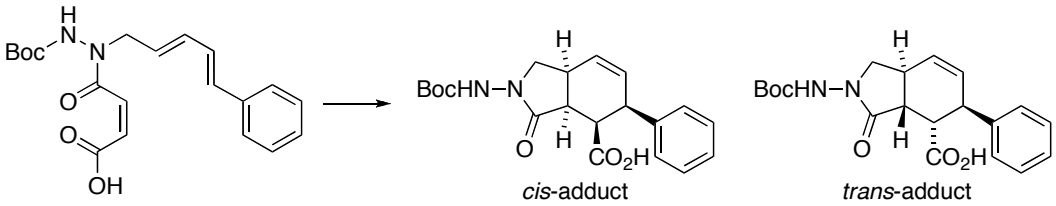


3-14 **3-13ab** **3-13cd**

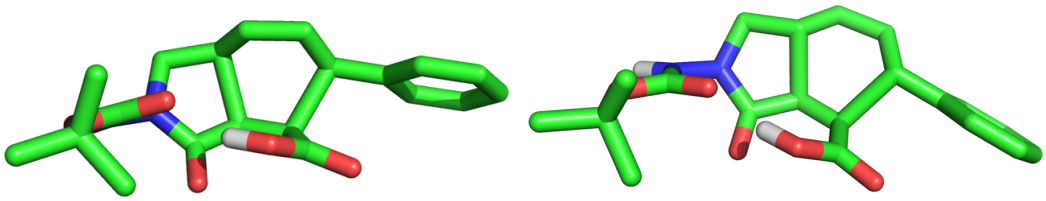


cis-adduct *trans*-adduct

Figure 3.6 Computational model of *cis* and *trans* transition states using ACE for the Diels-Alder reaction of **3-14**



3-15 **3-11ab** **3-11cd**



cis-adduct *trans*-adduct

Figure 3.7 Computational model of *cis* and *trans* transition states using ACE for the Diels-Alder reaction of **3-15**

It is important to note that due to the nature of the program being used, the developing bonds shown are of the same length. However, Paddon-Row and coworkers have shown by DFT on similar systems that the internal forming bond will be shorter than the external developing bond demonstrating that the Diels-Alder reaction for these types of trienes is asynchronous.[20]

In all four images it is important to note the important hydrogen bond network being developed between the carboxylic acid and the other two carbonyls.

Other results from the computational study unfortunately were unable to explain the experimental results. For both cases the model predicted the *cis* product to predominate. Also, the difference in solvent accessible surface area in both cases was negligible. This result does not allow us to explain the dependence of the stereoselectivity based on differing compactness of the transition state. The problems encountered could be due to the limitations of a molecular mechanics based system and other modeling programs based on density functional theory could be used to help us better understand the experimental results.

3.3 *Conclusions*

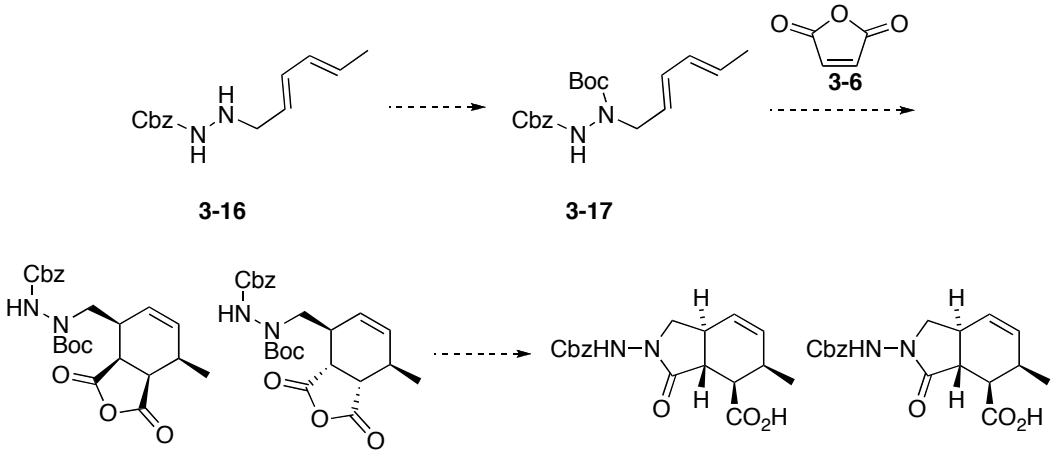
Our research has shown that the diastereoselectivity of the intramolecular Diels-Alder reaction of our hydrazine trienes is solvent dependent. Regression models have shown that this diastereoselectivity correlates well with Abraham's

solvophobicity parameter S_p. This effect does not correlate with solvent polarity as represented by E_t. Computational studies designed to help determine the source of such selectivity have in so far proved inconclusive.

3.4 *Future work*

First and foremost, we would like to look at a more in depth computational study of the intramolecular Diels-Alder reaction in order to determine possible sources of the solvent dependent diastereoselectivity of the reaction.

Secondly, we would like to look at a set of conditions that would reverse the selectivity of the Diels-Alder reaction. Considering the precedent set by Cayzer et al. we believe that if we can protect the hydrazine nitrogen so that it is unable to form an amide bond with maleic anhydride.[45] We can force the Diels-Alder reaction, to occur intermolecularly before the formation of the amide bond. In this case, the intermolecular Diels-Alder reaction should, if the above mentioned precedent applies to our system, form the *endo* product selectively.



Deprotection of the nitrogen should allow for the formation of the *cis* lactam.

Scheme 3.4 Hydrazine deprotection in an attempt to reverse selectivity of Diels-Alder reaction

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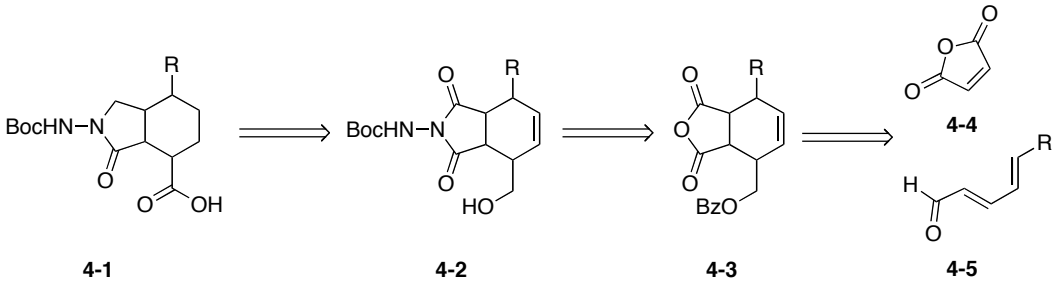
Chapter 4 Alternate routes and failed attempts

4.1 *Introduction*

In the course of the aforementioned investigation of *N*-amino-hexahydro-1*H*-isoindolone, alternate plans and routes were investigated and their viability determined. Two such alternate routes will be discussed and their merits and downfalls examined.

4.2 *Retrosynthetic analysis*



Scheme 4.1 Retrosynthetic analysis of scaffold with maleimide formation

The core scaffold will be formed by a selective reduction and deoxygenation of the maleimide. The maleimide will be formed by the nucleophilic opening and then reclosure of the anhydride. The anhydride will be formed from the Diels-Alder reaction between maleic anhydride and the dienals.

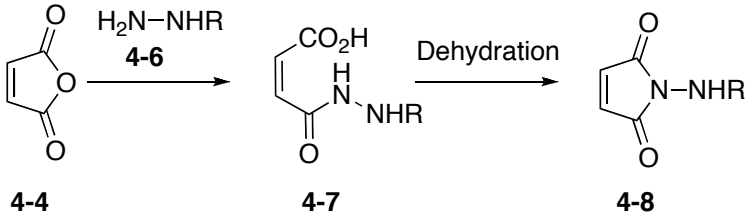
4.3 *Synthesis*

4.3.1 Formation of maleimide

Before the reaction scheme was started an initial investigation into the feasibility of opening maleic anhydride was investigated. Unfortunately, the literature is rather unclear as to if maleic anhydride can be opened with hyrazine to form *N*-amino maleimides.

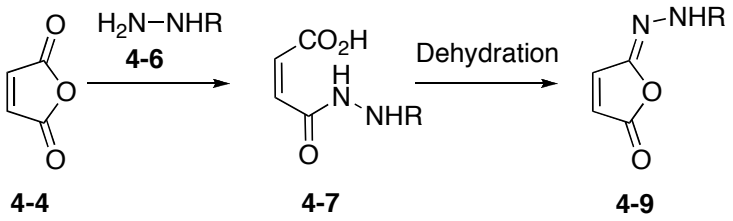
The main point of contention in the literature is how the hydrazine will attack maleic anhydride. Will hydrazine attack maleic anhydride, opening the ring and remain in the open form, will hydrazine attack maleic anhydride and

close back on itself to form a five membered ring, or will it close back on itself and form a six membered ring?



4-4 **4-7** **4-8**

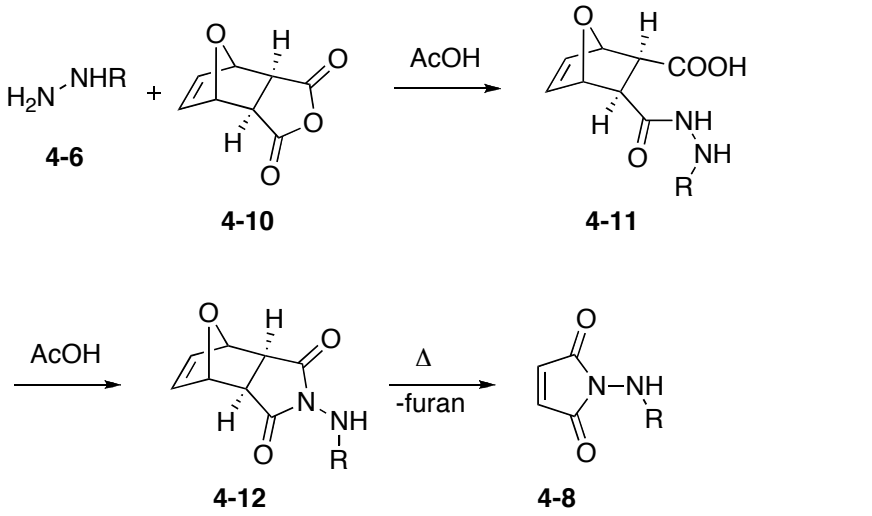
Scheme 4.2 Mischaracterized literature reports



4-4 **4-7** **4-9**

Scheme 4.3 Actual isoimide formed after attack of hydrazine and then dehydration

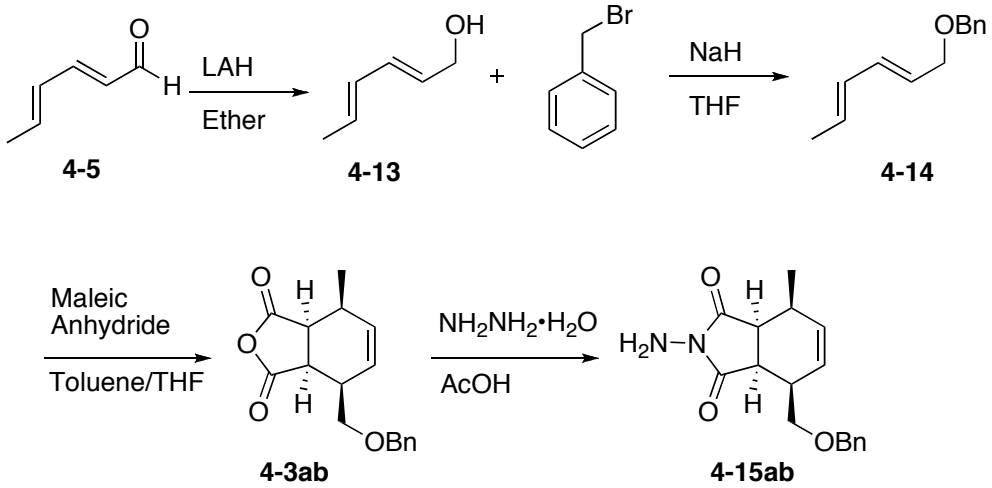
Initial reports from the literature demonstrate the attack of hydrazine on maleic anhydride and with subsequent dehydration, the formation of *N*-amino maleimides are reported.[73] This however, turned out to be a mischaracterization as proved by Harry Rubinstein and coworkers who showed that *N*-amino isomaleimides were in fact being formed.[74] Despite the report by Rubinstein et al. many groups claimed to have formed *N*-amino maleimides.[75,76] Furthermore, N. R. Conley and coworkers proved that in fact the *N*-amino isomaleimides were being formed under these conditions and devised a new route to authentic *N*-amino maleimides.[77]



Scheme 4.4 N. R. Conley and coworkers route to authentic N-amino maleimides

Considering the report by Conley, it was determined that perhaps the hydrazine moiety could be incorporated into the scaffold after the Diels-Alder reaction with maleic anhydride rather than before.

4.3.2 Diels-Alder reaction and hydrazide substitution



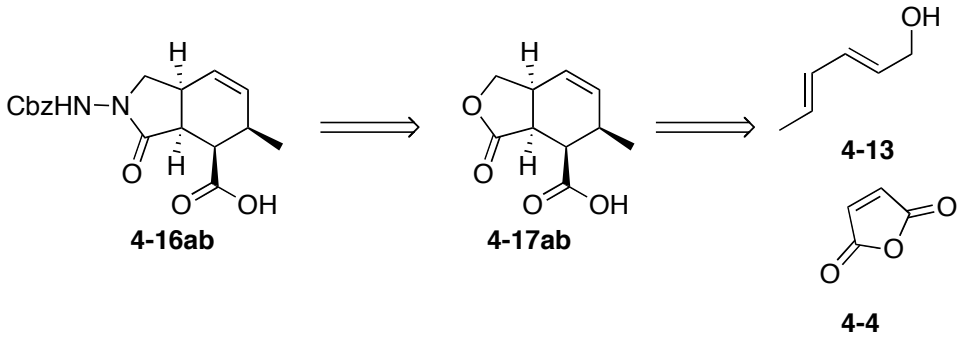
Scheme 4.5 Synthesis of *N*-amino scaffolds

The synthesis began with the LAH reduction of 2,4-hexadienal in ether to for the dienol. The dienol was then protected as a benzyl ether. The diene subsequently reacted in the Diels-Alder reaction with maleic anhydride to form the Diels-Alder adduct as essentially a single diastereomer, the *endo* product. Attack of hydrazine and *in situ* dehydration provided the *N*-amino maleimide.

Unfortunately, at this point, the likelihood of reducing the desired maleimide carbonyl while the other carbonyl remained intact was deemed unlikely to occur in an efficient manner, therefore an alternate route was devised.

4.4 *Second Route*

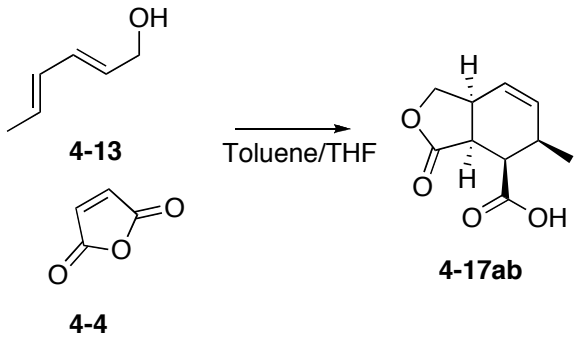
4.4.1 Retrosynthetic analysis



Scheme 4.6 Retrosynthetic analysis

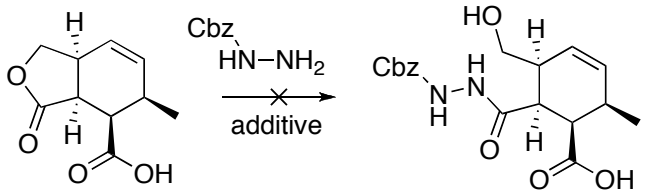
The desired scaffold could be obtained by opening the lactone with the hydrazine and then a dehydrative ring closing. The lactone would be formed by the intermolecular Diels-Alder reaction between the dienol and maleic anhydride and then an intramolecular lactonization.

4.4.2 Synthesis



Scheme 4.7 Diels-Alder reaction of dienol and maleic anhydride

Table 4.1 Attempted nucleophilic opening of lactone



4-17ab **4-18ab**

Additive	Temperature	Time	Yield
-	70°C	5 H	NR
-	110°C	24 H	NR
1/3 equiv AcOH	70°C	24 H	NR
In AcOH	rt - 80°C	7 H	NR
DCC	rt	24 H	NR

The synthesis began smoothly with the Diels-Alder reaction between 2,4-hexadienol and maleic anhydride forming nearly exclusively the cis fused adduct. However all attempts to open the lactone with hydrazine failed.

4.5 *References*

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Chapter 5 Experimental

5.1 *General remarks*

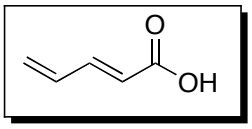
All commercially available reagents were used without further purification, unless otherwise stated. 4Å molecular sieves were dried at 100°C prior to use. FTIR spectra were recorded using a Perkin Elmer Spectrum One FT-IR. ^{1}H and ^{13}C NMR spectra were recorded on Varian mercury 400 MHz, 300 MHz or Unity 500 spectrometers. Chemical shifts are reported in ppm using the residual of chloroform as internal standard (7.26 ppm for ^{1}H and 77.160 ppm for ^{13}C respectively). Visualization was performed by UV or by development using $KMnO_4$, H_2SO_4/MeOH or Mo/Ce solutions. Chromatography was performed on silica gel 60 (230-40 mesh). Low resolution mass spectrometry was performed by ESI using a Thermoquest Finnigan LCQDuo. High resolution mass spectrometry was performed by EI Peak matching (70 eV) on a Kratos MS25 RFA Double focusing mass spectrometer or by ESI on a IonSpec 7.0 tesla FTMS at McGill University.

5.2 *Synthesis*

5.2.1 Knoevenagel condensation with Doebner modification

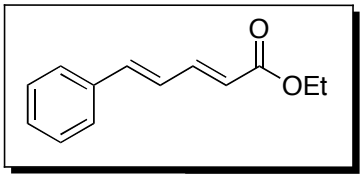
(*E*)-penta-2,4-dienoic acid (2-10a)

Synthesis previously described.[78]



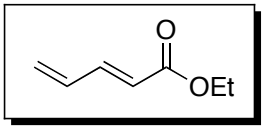
(2*E*,4*E*)-ethyl 5-phenylpenta-2,4-dienoate (2-11b)

Synthesis previously desribed. [24]



(*E*)-ethyl penta-2,4-dienoate (2-11a)

Synthesis previously desribed. [24]

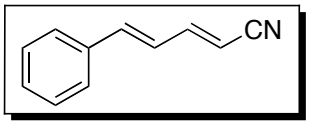


5.2.2 General procedure for Horner-Wadsworth-Emmons olefination

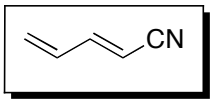
Modified from literature procedure.[26] LiOH (19.2 mmol) and diethyl cyanomethyl phosphonate (16.6 mmol) were added to THF (50 mL) and mixed under an inert atmosphere at 70° C for 30 min. When cooled to RT, aldehyde (8 mmol) was added dropwise and mixed for 2 h. Mixture diluted in ether (120 mL) washed with 1M HCl (40 mL) then brine (2 X 100 mL) and dried over sodium sulfate and concentrated under reduced pressure. Pruducts were purified by column chromatography.

(2*E*,4*E*)-5-phenylpenta-2,4-dienenitrile (2-6b)

Product characterized in the literature. [79]

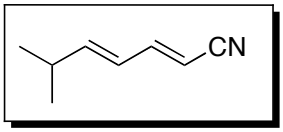


(E)-penta-2,4-dienenitrile (2-6a)



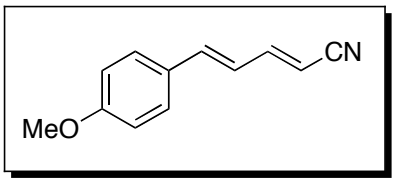
Trace product, full characterization not shown Rf=0.33 in 1-3 Hexanes/EtOAc UV. IR (film) ν max: 3450, 3064, 2924, 2854, 2213, 1735, 1623 cm^{-1};

(2E,4E)-6-methylhepta-2,4-dienenitrile (2-6d)



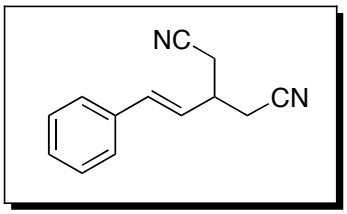
yield: 247 mg (51%). IR (film) ν max: 3449, 3066, 2971, 2936, 2878, 2222, 1720, 1638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 – 6.92 (m, 1H), 6.78 (t, J = 10.9, 0.3H), 6.58 – 6.42 (m, 0.3H), 6.23 – 5.97 (m, 2.3H), 5.25 (d, J = 15.6, 1H), 5.14 – 5.05 (m, 0.3H), 2.56 – 2.33 (m, 1.3H), 1.07 (d, J = 7.1, 0.9H), 1.04 (d, J = 6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 151.4, 151.0 150.3, 139.3, 125.3, 124.3, 105.2, 98.8, 96.7, 29.7, 29.6, 21.7, 18.9. Rf=0.33 in 5% EtOAc in Hexanes UV.

(2E,4E)-5-(4-methoxyphenyl)penta-2,4-dienenitrile (2-6c)



yield: 466 mg oil (62%). IR (film) ν max: 2935, 2839, 2209, 1623, 1602, 1587, 1509 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2.6H), 7.18 – 7.02 (m, 1.3H), 6.97 – 6.62 (m, 5.2H), 5.39 – 5.28 (m, 1H), 5.18 – 5.14 (m, 0.3H), 3.82 – 3.81 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 160.8, 150.7, 149.7, 141.4, 141.1, 129.2, 129.0, 128.0, 128.0, 123.3, 122.1, 118.8, 117.1, 114.4, 114.4, 96.6, 94.9, 55.4, 55.4. Rf= 0.2 in 7% EtOAc in Hexanes UV.

(E)-3-styrylpentanedinitrile (2-12)



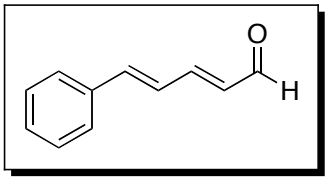
yield: 156 mg (31%). IR (film) ν max: 3060, 2925, 2223, 1712, 1634, 1600, 1494 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 4H), 7.24 – 7.21 (m, 1H), 6.64 (d, J = 15.8, 1H), 6.08 (dd, J = 8.3, 15.8, 1H), 3.02 – 2.95 (m, 1H), 2.66 (d, J = 6.5, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 134.4, 128.8, 128.6, 126.7, 125.5, 116.9, 36.4, 22.6. rf= 0.39 3-1 Hexanes/EtOAc UV.

5.2.3 General procedure for nitrile reduction and imine hydrolysis

To a solution of nitrile (0.50 mmol) in toluene (3 mL) at -78°C and under an inert atmosphere was added DIBAL (0.33 mL, 1.5 M in hexanes) and mixed for 1 h. A saturated solution of ammonium chloride (5 mL) was added and the solution mixed for 20 min and the solution warmed to RT. A solution of sulfuric acid (5mL, 10% v/v) was added and the solution mixed for 10 min. Organic layer extracted with DCM (3X 10 mL), dried with sodium sulfate and solvent removed under reduced pressure.

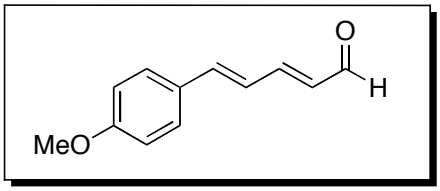
(2E,4E)-5-phenylpenta-2,4-dienal (2-4a)

Product characterized in the literature.[80]



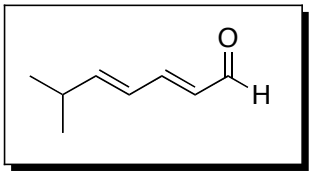
(2E,4E)-5-(4-methoxyphenyl)penta-2,4-dienal (2-4b)

Product characterized in the literature. [80]



(2E,4E)-6-methylhepta-2,4-diena (2-4c)

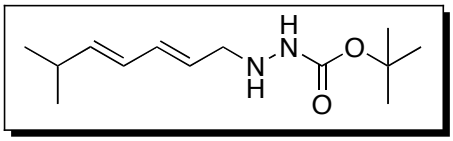
Product characterized in the literature. [81]



5.2.4 General procedure for reductive amination of aldehydes

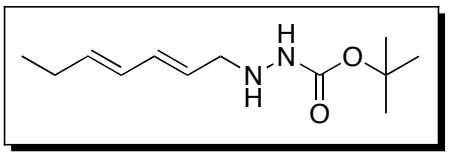
To melted Boc-hydrazide (1.19 g, 9.0 mmol) at 70ºC was added dienal (1.0 mL, 9.0 mmol) dropwise. The mixture was stirred for 15 minutes and cooled down to rt. The resulting solid was dissolved in MeOH (50 mL) and $Me_2NH{\cdot}BH_3$ (848 mg 14.4 mmol) was added slowly at 0°C followed by a solution of PTSA (10.3 g, 54.0 mmol) in MeOH (50 mL). After stirring for another 2 h, a solution of Na_2CO_3(aq) (120 mL, 10% w/v) was added and the mixture refluxed for 2 h then concentrated under reduced pressure, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated under reduced pressure to afford the product.

tert-butyl 2-((2E,4E)-6-methylhepta-2,4-dienyl)hydrazinecarboxylate (2-2c)



yield: 112 mg (61%). IR (film) ν max: 3328, 2967, 2931, 2870, 1701, 1458, 1366, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 – 5.90 (m, 2H), 5.70 – 5.51 (m, 2H), 3.46 (d, J = 6.8, 2H), 2.32 (m, 1H), 1.45 (s, 9H), 0.99 (d, J = 6.8, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 146.1, 142.2, 134.4, 126.7, 80.6, 53.9, 31.1, 28.4, 22.3. HRMS (ESI +) calcd for $C_{13}H_{24}N_2O_2Na$ 263.17300 found 263.17304.

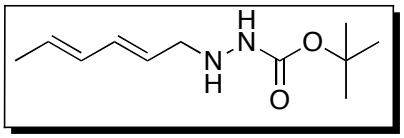
tert-butyl 2-((2E,4E)-hepta-2,4-dienyl)hydrazinecarboxylate (2-2e)



yield: 1.662 g (92%). IR (film) ν max: 3301, 2967, 2933, 2874, 1706, 1456, 1367, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.17 (dd, J = 10.4, 15.2, 1H), 6.02 (dd, J = 10.4, 15.1, 1H), 5.74 – 5.67 (m, 1H), 5.64 – 5.51 (m, 1H), 3.93 (bs, 1H), 3.46 (d, J = 6.8, 2H), 2.14 – 2.03 (m, 2H), 1.45 (s, 9H), 1.00 (t, J = 7.5

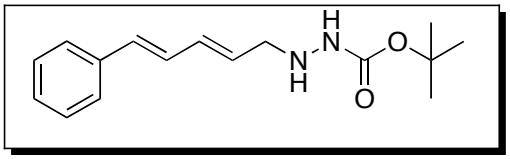
3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8, 136.8, 134.3, 128.8, 126.5, 80.6, 54.0, 28.5, 25.7, 13.6. HRMS (ESI +) calcd for $C_{12}H_{23}N_2O_2$ 227.17540 found 227.17546.

tert-butyl 2-((2E,4E)-hexa-2,4-dienyl)hydrazinecarboxylate (2-2d)



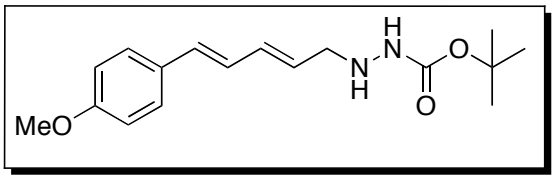
yield: yellow oil 1.620 g (85%). IR (film) ν max: 3308, 2978, 2933, 1704 cm^{-1}; ^{1}H NMR, 500 MHz, $CDCl_3$, (ppm): δ 6.73 (s, 1H), 6.02 (dd, J = 10.5, 15.1, 1H), 5.80-5.95 (m, 1H), 5.52 (td, J = 6.6, 13.5, 1H), 5.45 – 5.37 (m, 1H), 3.99 (s, 1H), 3.32 (d, J = 6.7, 2H), 1.60 (d, J = 6.8, 3H), 1.32 (s, 9H); ^{13}C NMR, 125 MHz, $CDCl_3$, (ppm): δ 156.6, 133.7, 130.9, 129.0, 126.1, 80.0, 28.2, 17.8; HRMS (ESI +) calcd for $C_{11}H_{20}N_2O_2Na$ 235.14170, found 235.14169.

tert-butyl 2-((2E,4E)-5-phenylpenta-2,4-dienyl)hydrazinecarboxylate (2-2a)



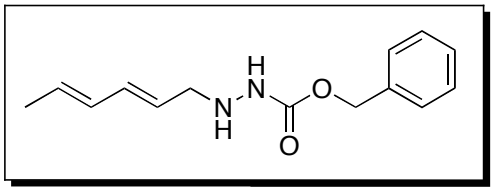
yield: 422 mg (64%). IR (film) ν max: 3286, 3026, 2978, 2929, 1708, 1450, 1367, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.15 (m, 5H), 6.75 (dd, J = 10.4, 15.6, 1H), 6.50 (d, J = 15.7, 1H), 6.35 (dd, J = 10.4, 15.1, 1H), 5.89 – 5.70 (m, 1H), 3.53 (d, J = 6.8, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 137.2, 133.9, 132.4, 129.7, 128.6, 128.4, 127.6, 126.4, 80.6, 53.8, 28.4.

tert-butyl 2-((2E,4E)-5-(4-methoxyphenyl)penta-2,4-dienyl)hydrazinecarboxylate (2-2b)



yield: 125 mg (89%). IR (film) ν max: 3334, 2977, 2932, 1702, 1604, 1510, 1157 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 6.87 – 6.75 (m, 2H), 6.61 (dd, J = 10.3, 15.5, 1H), 6.43 (d, J = 15.7, 1H), 6.31 (dd, J = 10.3, 15.1, 1H), 6.11 (bs, 1H), 5.83 – 5.64 (m, 1H), 3.77 (s, 3H), 3.51 (d, J = 6.7, 2H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 134.1, 132.0, 130.0, 128.5, 127.6, 126.4, 114.1, 80.5, 55.3, 44.5, 28.4.

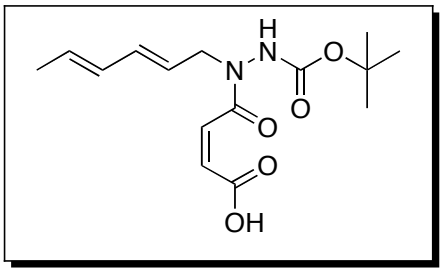
benzyl 2-((2E,4E)-hexa-2,4-dienyl)hydrazinecarboxylate



yield: 1.028g 94% ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 5H), 6.72 (bs, 1H), 6.06 (m, 2H), 5.64 (dq, J = 6.7, 13.5, 1H), 5.51 (dd, J = 7.1, 14.6, 1H), 5.10 (s, 2H), 4.25 (bs, 1H), 3.45 (d, J = 5.4, 2H), 1.72 (d, J = 6.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 136.2, 134.3, 130.9, 129.8, 128.6, 128.2, 128.2, 125.8, 67.0, 25.3, 18.1.

5.2.5 Reaction between hydrazides and maleic anhydride

(Z)-4-(2-(tert-butoxycarbonyl)-1-((2E,4E)-hexa-2,4-dienyl)hydrazinyl)-4-oxobut-2-enoic acid (2-17d)

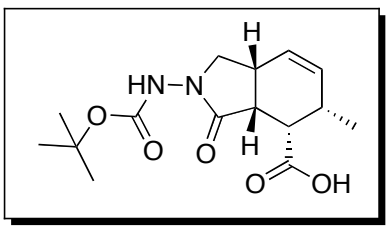


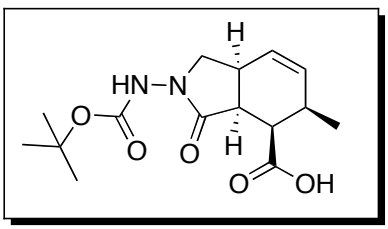
Crude NMR on unstable product, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 4H), 6.83 (d, J = 13.0, 1H), 6.37 (d, J = 13.0, 1H), 6.21 (dd, J = 10.5, 15.1, 1H), 6.11 – 6.01 (m, 1H), 5.78 (dd, J = 6.9, 15.0, 1H), 5.46 (dt, J = 7.3, 14.7, 1H), 1.77 (d, J = 6.8, 3H), 1.47 (d, J = 7.0, 9H).

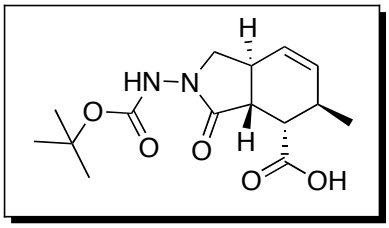
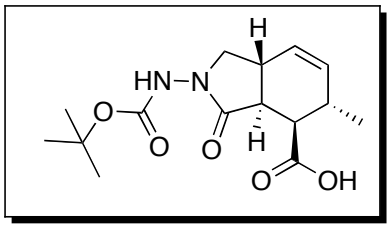
5.2.6 General procedure for Lactam formation/Diels-Alder reaction

Diene (54 mg, 0.25 mmol) was dissolved in $CHCl_3$ (1 mL.) To the solution was added maleic anhydride (25 mg, 0.25 mmol.) After stirring for 15 h, the solution was concentrated under reduced pressure and the residue purified by flash chromatography (EtOAc – Hexanes, 3:1) to afford the product.

(3aR,4S,5S,7aR)-2-(tert-butoxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1g and 3-13a) and (3aS,4R,5R,7aS)-2-(tert-butoxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1e and 3-13b) and (3aR,4S,5R,7aS)-2-(tert-butoxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1o and 3-13c) and (3aS,4R,5S,7aR)-2-(tert-butoxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1p and 3-13d)

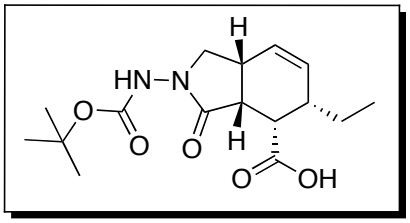
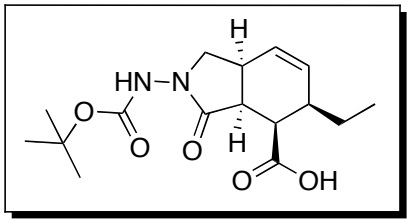


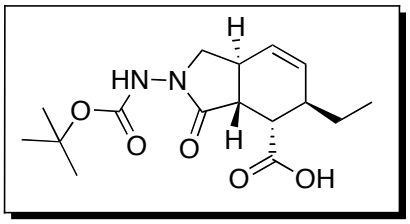
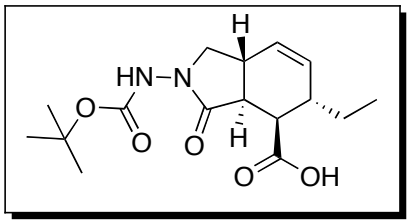


yield: brown oil, 56 mg (71%). The following data has been collected on a 2.3:1 mixture. IR (film) νmax: 3267, 2979, 2934, 2879, 2623, 1772, 1713, 1633. 1H NMR, 500 MHz, $CDCl_3$, (ppm): δ 9.87 – 8.58 (bs, 1H), 5.84 (s, 0.3H), 5.77 (d, J = 9.9, 0.7H), 5.59 (d, J = 9.9, 0.7H), 5.54 (d, J = 10.1, 0.3H), 3.90 (s, 0.3H), 3.56 (t, J = 7.4, 0.7H), 3.45 (s, 0.7H), 3.33 (d, J = 8.8, 0.3H), 3.22 (s, 0.3H), 3.15 (t, J = 5.2, 0.3H), 3.05 (s, 0.3H), 2.98 (d, J = 3.6, 0.7H), 2.93 (s, 1.4H), 2.70 (s, 0.3H), 2.39 (s, 0.3H), 1.45 (s, 9H), 1.15 (d, J = 7.3, 2.1H), 1.11 (d, J = 7.4, 0.9H). ^{13}C NMR, 125 MHz, CDCl3, (ppm): δ 175.8, 174.8, 174.4, 174.3, 154.7, 154.7, 134.1, 125.5, 124.5, 82.6, 82.1, 54.1, 52.5, 45.0, 43.0, 42.6, 38.7, 38.7, 33.4, 32.9, 30.9, 28.3, 28.3, 21.9, 18.0. HRMS (ESI +) calcd for $C_{15}H_{21}N_2O_5$ 309.14560, found 309.14504.

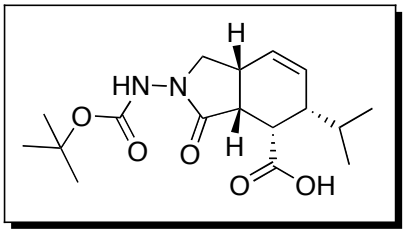
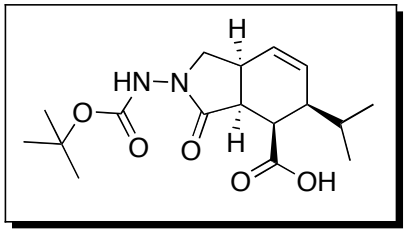
(3aR,4S,5S,7aR)-2-(tert-butoxycarbonylamino)-5-ethyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1i and 3-7a) and (3aS,4R,5R,7aS)-2-(tert-butoxycarbonylamino)-5-ethyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1j and 3-7b) and (3aR,4S,5R,7aS)-2-(tert-butoxycarbonylamino)-5-ethyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1s and 3-7c) and (3aS,4R,5S,7aR)-2-(tert-butoxycarbonylamino)-5-ethyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1 t and 3-7d)

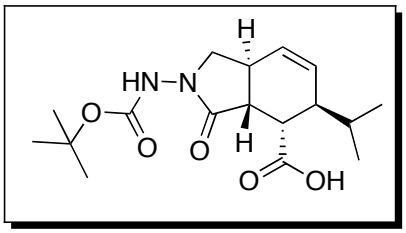
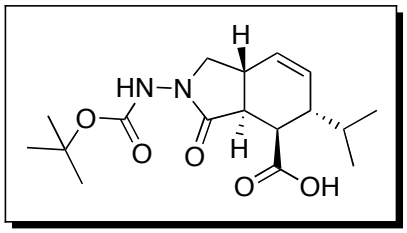



yield: 187 mg (75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (bs, 1H), 5.77 (s, 1H), 5.62 (s, 1H), 3.94 – 3.66 (m, 0.5H), 3.54 (s, 0.5H), 3.47 – 3.36 (m, 0.5H), 3.31 (s, 0.5H), 3.16 (s, 0.5H), 3.14 – 3.09 (m, 0.5H), 3.09 – 3.04 (m, 0.5H), 3.02 (s, 0.5H), 2.98 – 2.90 (m, 0.5H), 2.61 (s, 0.5H), 2.31 (s, 1H), 1.49 (s 2H) 1.41 (s, 9H), 0.97 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 176.2, 175.3, 166.8, 165.7, 154.7, 132.7, 131.5, 126.3, 125.1, 84.9, 82.1, 82.0, 53.8, 52.4, 43.1, 40.3, 40.2, 38.2, 32.9, 29.8, 28.8, 28.2, 27.9, 26.3, 12.3, 12.0. rf= 0.38 3-1 EtOAc/Hexanes. HRMS (ESI +) calcd for $C_{16}H_{25}N_2O_5$ 325.17580 found 325.17593.

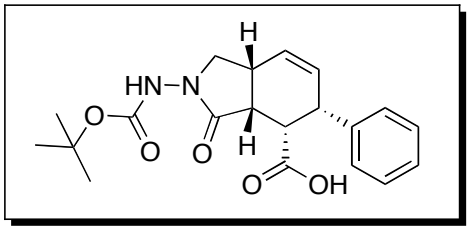
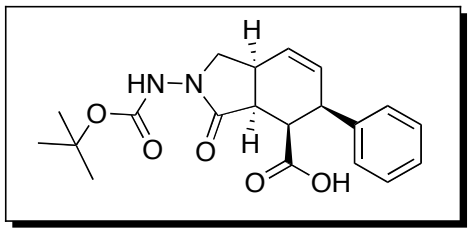
(3aR,4S,5S,7aR)-2-(tert-butoxycarbonylamino)-5-isopropyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1e) and (3aS,4R,5R,7aS)-2-(tert-butoxycarbonylamino)-5-isopropyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1f) and (3aR,4S,5R,7aS)-2-(tert-butoxycarbonylamino)-5-isopropyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1o) and (3aS,4R,5S,7aR)-2-(tert-butoxycarbonylamino)-5-isopropyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1p)

yield: 49 mg (66%). IR (film) ν max: 3252, 2964, 2934, 2873, 1779, 1714, 1369, 1249, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (d, J = 10.4, 0.6H), 5.86 – 5.75 (m, 0.4H), 5.67 (d, J = 10.2, 1H), 3.87 (bs, 1H) 3.59 (t, J = 7.5, 0.7H), 3.53 – 3.44 (m, 0.7H), 3.42 (s, 0.3H), 3.37 – 3.26 (m, 0.3H), 3.12 (d, J = 4.2, 1H), 3.06 – 2.97 (m, 0.7H), 2.97 – 2.89 (m, 0.3H), 2.61 (s, 0.7H), 2.35 – 2.24 (m, 0.3H), 1.88 – 1.78 (m, 1H), 1.45 (s, 9H), , 1.00 (d, J = 6.8, 3H), 0.94 (d, J = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 168.2, 165.1, 154.7, 133.9, 131.7, 131.0, 126.3, 83.6, 82.6, 53.9, 52.6, 44.3, 44.0, 38.2, 33.3, 32.9, 31.3, 29.8, 28.4, 28.31 28.3, 28.2, 28.1, 22.00, 21.4, 20.0, 19.9. rf= 0.20 7-3 Hexanes/EtOAc. HRMS (ESI +) calcd for $C_{17}H_{27}N_2O_5$ 339.19145 found 339.19187.

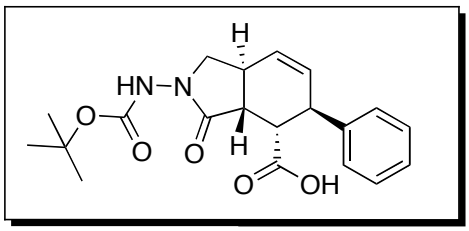
(3aR,4S,5S,7aR)-2-(tert-butoxycarbonylamino)-3-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1a and 3-11a) and (3aS,4R,5R,7aS)-2-(tert-butoxycarbonylamino)-3-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1b and 3-11b) and

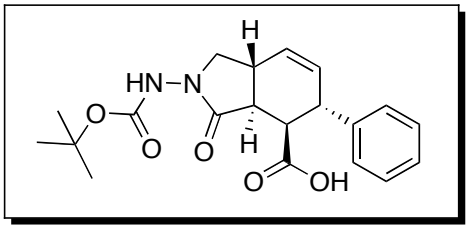



yield: 77 mg (80%) (both isomers). ^1H NMR (500 MHz, $CDCl_3$) δ 8.86 – 8.46 (m, 1H), 7.35 – 7.15 (m, 5H), 6.06 (s, 1H), 5.76 (s, 1H), 4.17 (s, 1H), 3.60 (s, 1H), 3.56 – 3.45 (m, 1H), 3.20 (s, 1H), 3.04 (s, 1H), 2.42 (s, 1H), 1.41 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 171.3, 154.6, 143.2, 130.0, 128.7, 127.9, 127.0, 126.7, 81.8, 52.3, 45.0, 43.5, 41.3, 32.6, 28.1. rf= 0.34 EtOAc/ Hexanes. HRMS (ESI +) calcd for $C_{20}H_{24}N_2O_5Na$ 395.15774 found 395.15846.

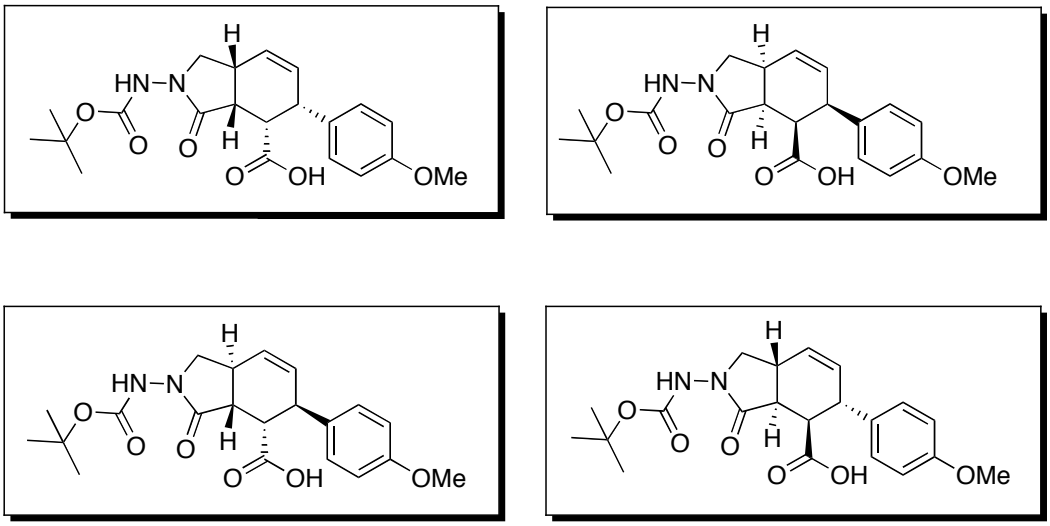
(3aR,4S,5R,7aS)-2-(tert-butoxycarbonylamino)-3-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1k and 3-11c) and (3aS,4R,5S,7aR)-2-(tert-butoxycarbonylamino)-3-oxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1l and 3-11d)





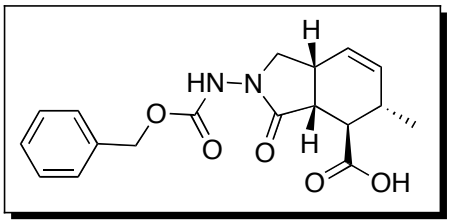
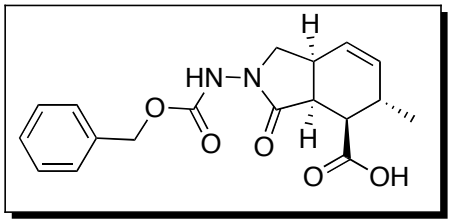
yield: 300 mg (80%) (both isomers). IR (film) ν max: 3229, 2981, 2927, 1714, 1631, 1247, 1156 cm^{-1} (mixture of diastereomers); ^1H NMR (300 MHz, $CDCl^3$) δ 7.35 – 7.15 (m, 5H), 6.06 (s, 1H), 5.92 (s, 1H) 3.95 (s, 1H), 3.92 – 3.83 (m, 1H), 3.58 (s, 1H), 3.44 (dd, J=4.9, 5.9, 1H) 3.24 – 3.08 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 165.3, 154.5, 135.2, 130.4, 129.0, 126.2, 114.1, 113.4, 83.1, 55.3, 45.2, 42.7, 41.3, 32.7, 28.1. rf= 0.22 6-1 EtOAc/Hexanes. HRMS (ESI +) calcd for $C_{20}H_{24}N_2O_5Na$ 395.15774 found 395.15789.

(3aR,4S,5S,7aR)-2-(tert-butoxycarbonylamino)-5-(4-methoxyphenyl)-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1c and 3-13a) and (3aS,4R,5R,7aS)-2-(tert-butoxycarbonylamino)-5-(4-methoxyphenyl)-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1 d and 3-12b) and (3aR,4S,5R,7aS)-2-(tert-butoxycarbonylamino)-5-(4-methoxyphenyl)-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1o and 3-12c) and (3aS,4R,5S,7aR)-2-(tert-butoxycarbonylamino)-5-(4-methoxyphenyl)-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-1 p and3-12d)

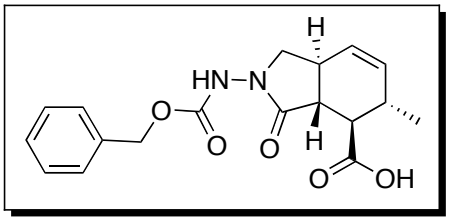
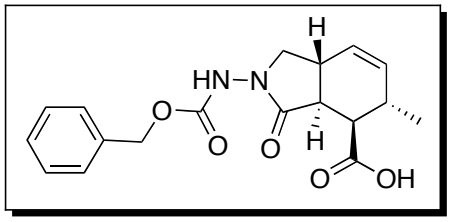


yield: 77 mg (68%). IR (film) ν max: 3225, 2977, 2925, 1724, 1633, 1611, 1511, 1249, 1157 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.7, 2H), 6.85 (d, J = 8.7, 2H), 6.07 (d, J = 9.9, 1H), 5.95 – 5.77 (m, 1H), 4.12 (bs, J = 7.1, 0.7H), 4.03 – 3.83 (m, 0.3H), 3.79 (s, 3H), 3.76 (d, J = 5.8, 1H), 3.61 (m, 0.7H), 3.55 – 3.46 (m, 0.3H), 3.44 – 3.38 (m, 0.3H), 3.13 (s, 0.7H), 3.09 – 2.97 (m, 0.7H), 2.69 (s, 1H), 2.48 – 2.37 (m, 0.3H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 174.3, 165.4, 159.1, 154.7, 136.2, 135.4, 130.9, 130.9, 130.6, 129.5, 129.2, 129.1, 127.7, 126.4, 114.3, 113.6, 83.3, 82.2, 55.5, 55.2, 52.5, 45.3, 42.8, 41.4, 32.9, 29.8, 28.3, 18.2, 28.0, 22.8. rf= 0.29 3-1 EtOAc/Hexanes. HRMS (ESI +) calcd for $C_{21}H_{27}N_2O_6$ 403.18636 found 403.18730.

(3aR,4R,5S,7aR)-2-(benzyloxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid and (3aS,4R,5S,7aS)-2-(benzyloxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid and (3aR,4R,5S,7aS)-2-(benzyloxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-23a) and (3aS,4R,5S,7aR)-2-(benzyloxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxylic acid (2-23b)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.40 – 7.30 (m, 5H), 5.77 – 7.65 (m, 1H), 5.62 – 5.50 (m, 1H), 5.23 – 5.03 (m, 2H), 3.90 (bs, 1H), 3.40 – 3.32 (m, 1H), 3.20 – 2.90 (m, 3H), 2.63 (bs, 1H), 1.09 (d, J = 6.5, 3H).

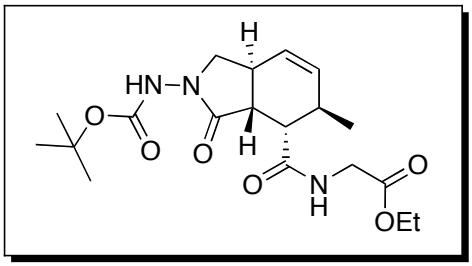
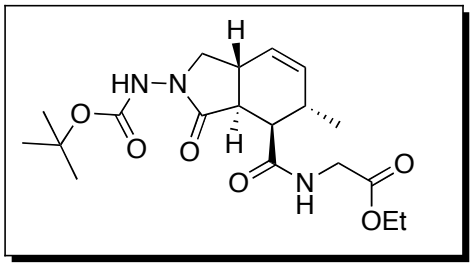
yield: 157 mg (94%) (for all isomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 7.40 – 7.30 (m, 5H), 5.74 (d, J = 9.7, 1H), 5.60 – 5.55 (m, 1H), 5.19 – 5.09 (m, 2H), 3.52 (t, J = 7.3, 1H), 3.49 – 3.40 (m, 1H), 3.00 – 2.86 (m, 3H), 2.39 (d, J = 10.7, 1H), 1.13 (d, J = 6.6, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 174.6, 155.5, 135.7, 134.1, 128.9, 128.7, 128.5, 124.4, 67.9, 42.9, 42.5, 33.3, 32.9, 21.8.

5.2.7 General procedure for the peptide coupling

2-1e,g,o,p (2.03 g, 6.5 mmol, 2:1 ratio) in CH_2Cl_2 (40 mL) was added HOBT (1.24 g, 9.1 mmol), Gly-OEt·HCl (1.28g, 9.1 mmol), DIEA (1.72 mL, 9.8 mmol) and EDC (1.76 g, 9.1 mmol). After stirring for 18h, the solution was diluted in EtOAc (150 mL), washed with citric acid (aqueous 20%), saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography separation (EtOAc – Hexanes, 3:1) afforded the product.

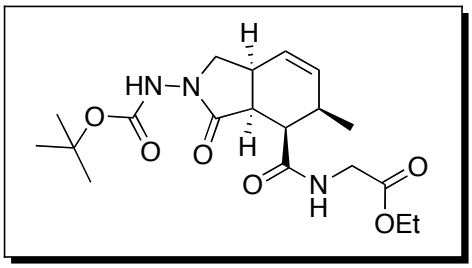
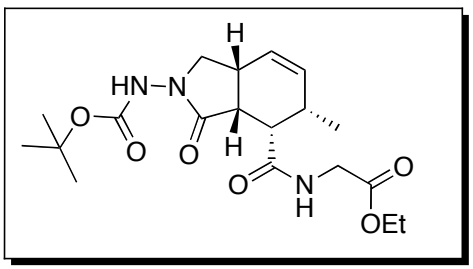
ethyl 2-((3aR,4S,5R,7aS)-2-(tert-butoxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-19c) and

ethyl 2-((3aS,4R,5S,7aR)-2-(tert-butoxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-19d)

IR (film) νmax: 3274, 3070, 2979, 2934 cm^{-1}; ^{1}H NMR, 500 MHz, $CDCl_3$, (ppm): δ 6.76 (s, 1H), 5.90 (d, J = 7.7, 1H), 5.53 (d, J = 10.0, 1H), 4.23 – 4.15 (m, 2H), 4.15 – 4.07 (m, 1H), 3.88 (d, J = 34.0, 2H), 3.29 (dd, J = 2.9, 8.6, 1H), 3.13 (s, 1H), 3.03 (s, 1H), 3.00 (t, J = 4.8, 1H), 2.70 (s, 1H), 1.47 (s, 9H), 1.30 – 1.22 (m, 4H), 1.10 (d, J = 7.4, 3H); ^{13}C NMR, 125 MHz, CDCl3, (ppm): δ 175.3, 173.4, 170.1, 154.2, 135.2, 125.2, 82.3, 61.4, 53.6, 46.6, 41.7, 31.7, 28.3, 21.2, 17.4, 14.3, 14.3; HRMS: calcd for $C_{19}H_{30}N_3O_6$ 396.21401, found 396.21313.

ethyl 2-((3aS,4R,5R,7aS)-2-(tert-butoxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-19a) and ethyl 2-((3aR,4S,5S,7aR)-2-(tert-butoxycarbonylamino)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-19b)

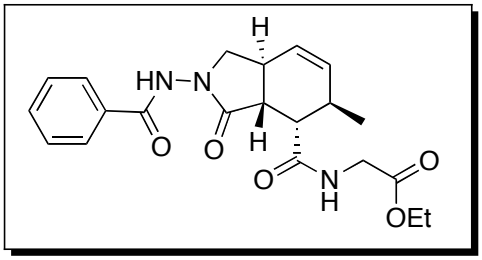
yield: brown oil 0.76g (89%) (all isomers). IR (film) νmax: 3302, 2979, 2933, 2873, 1734, 1711, 1689 $cm^{-}1$; ^{1}H NMR, 500 MHz, $CDCl_3$, (ppm): δ 6.78 (s, 1H), 6.61 (s, 1H) 5.73 (d, J = 9.9, 1H), 5.67 (d, J = 9.8, 1H), 4.14 (dd, J = 6.2, 13.4, 2H), 4.09 (dd, J = 7.0, 9.5, 1H), 3.75 (dd, J = 5.0, 17.9, 1H), 3.55 (t, J = 7.6, 1H), 3.51 – 3.45 (m, 1H), 2.98 (s, 1H), 2.93 (d, J = 3.6, 1H), 2.74 (d, J = 9.4, 1H), 2.57 (s, 1H), 1.46 (d, J = 7.8, 9H), 1.25 (td, J = 4.8, 7.1, 3H), 1.09 (d, J = 7.5, 3H);

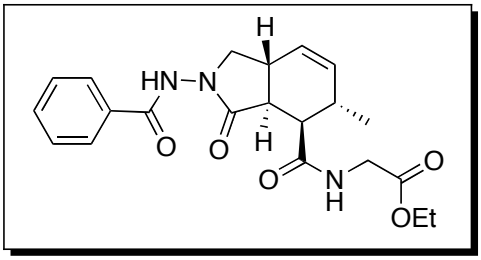
^{13}C NMR, 125 MHz, CDCl3, (ppm): δ 172.5, 171.3, 170.0, 154.3, 135.1, 123.50, 82.3, 61.4, 52.7, 43.6, 41.4, 33.4, 31.5, 28.3, 21.1, 14.3, 14.3; HRMS: calcd for $C_{19}H_{30}N_3O_6$ 396.21401, found 396.21316.

5.2.8 Nitrogen deprotection and benzoylation

2-19c,d (77 mg, 0.19 mmol) was mixed with TFA (2 mL) under an inert atmosphere at RT for 3 H then concentrated under reduced pressure. To the resulting residue immediately dissolved in pyridine (5 mL) at 0°C under an inert atmosphere was added benzoyl chloride (32 μL, 0.275 mmol). After stirring for another 30 minutes, the solution was concentrated under reduced pressure and the residue purified by flash chromatography (EtOAc – Hexanes, 3:1) to afford the product.

ethyl 2-((3aR,4S,5R,7aS)-2-benzamido-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-18a) and ethyl 2-((3aS,4R,5S,7aR)-2-benzamido-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-18b)

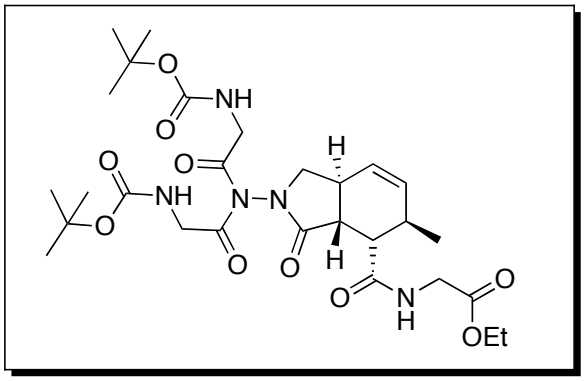


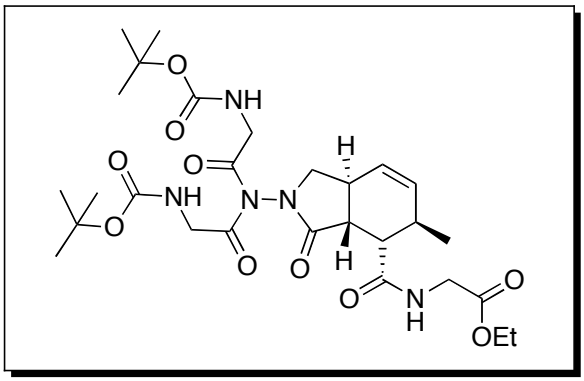


yield: brown oil 55mg (71%). IR (film) νmax: 3300, 2960, 1717, 1668, 1522, 1196 cm^{-}1; 1H NMR, 500 MHz, $CDCl_3$, (ppm): δ 8.69 (s, 1H), 7.79 (d, J = 7.5, 2H), 7.52 (t, J = 7.4, 1H), 7.41 (t, J = 7.7, 2H), 6.79 (t, J = 5.5, 1H), 5.74 (bd, J = 9.9, 1H), 5.71 – 5.65 (m, 1H), 4.14 (q, J = 7.1, 2H), 4.06 (dd, J = 6.1, 17.9, 1H), 3.83 (dd, J = 5.4, 18.0, 1H), 3.67 – 3.56 (m, 2H), 2.99 (bs, 1H), 2.94 (d, J = 3.5, 1H), 2.94 – 2.79 (bm, 1H), 2.69 (dd, J = 3.4, 13.1, 1H), 1.24 (t, J = 7.1, 3H), 1.12 (d, J = 7.4, 3H). ^{13}C NMR, 125 MHz, CDCl3, (ppm): δ 175.0, 172.3, 170.0, 166.0, 134.9, 132.4, 131.4, 128.6, 127.4, 123.4, 61.3, 52.4, 43.7, 43.5, 41.3, 33.5,

31.6, 21.0, 14.1. HRMS (ESI +) calcd for $C_{21}H_{26}N_3O_5$ 400.18779, found 400.18685.

ethyl 2-((3aR,4S,5R,7aS)-2-(2-(tert-butoxycarbonylamino)-N-(2-(tert-butoxycarbonylamino)acetyl)acetamido)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-22a) and ethyl 2-((3aR,4S,5R,7aS)-2-(2-(tert-butoxycarbonylamino)-N-(2-(tert-butoxycarbonylamino)acetyl)acetamido)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-22b)

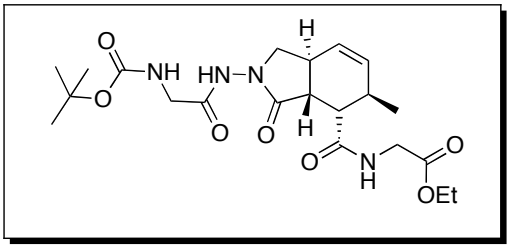


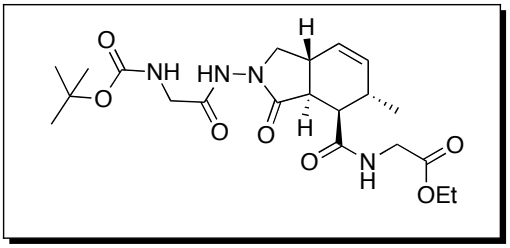


19c,d (553 mg 1.4 mmol) was mixed with TFA (2 mL) under an inert atmosphere at RT for 3 H then concentrated under reduced pressure. Without further purification a peptide coupling was performed under the same conditions as in 5.2.7 using *N*-BOC glycine. A second solution, a mixture of $ethanol_{(aq)}$ (100 mL, 40% (v/v), rye) and saccharose water (200 mL, coke) was promptly mixed at 0°C and drank without further purification. yield: 221 mg (25%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 – 8.61 (m, 1H), 6.78 (s, 1H), 5.70 (d, J = 9.8, 1H), 5.66 (s, 1H), 5.29 (s, 1H), 4.53 – 4.35 (m, 4H), 4.12 (dq, J = 7.1, 10.9, 2H, 3.50 (d, J = 7.7, 2H), 2.92 (d, J = 27.8, 2H), 2.74 (s, 1H), 2.57 (d, J = 13.1, 1H), 1.52 (s, 9H),

1.48 – 1.37 (m, 9H), 1.29 – 1.18 (m, 3H), 1.08 (d, J = 7.4, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 172.9, 172.5, 170.3, 167.1, 156.4, 151.7, 135.1, 123.4, 85.3, 80.1, 61.4, 52.3, 46.9, 45.8, 43.6, 43.5, 41.3, 33.6, 31.6, 28.5, 27.9, 21.0, 14.3. rf= 0.28 3-1 EtOAc/Hexanes.

ethyl 2-((3aR,4S,5R,7aS)-2-(2-(tert-butoxycarbonylamino)acetamido)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-21a) and ethyl 2-((3aS,4R,5S,7aR)-2-(2-(tert-butoxycarbonylamino)acetamido)-5-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-4-carboxamido)acetate (2-21b)

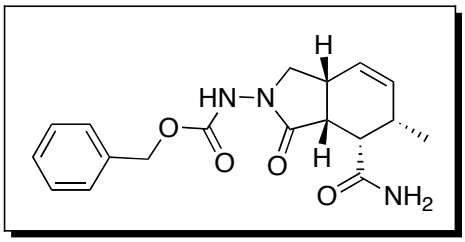
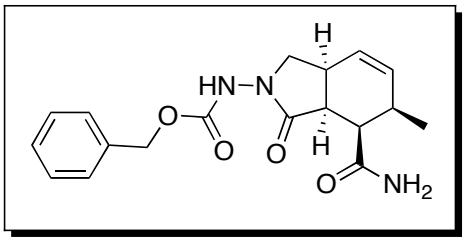




yield: 115mg (18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 5.86 (d, J = 8.0, 1H), 5.57 (d, J = 9.7, 1H), 5.32 – 5.24 (m, 2H), 4.23 – 4.08 (m, 4H), 3.99 – 3.76 (m, 5H), 3.27 (dd, J = 4.2, 8.3, 1H), 3.12 (s, 2H), 2.98 (t, J = 4.4, 1H), 2.65 (s, 1H), 1.76 (s, 3H), 1.44 (s, 12H), 1.26 (t, J = 7.2, 4H), 1.09 (d, J = 7.4, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 173.0, 170.4, 168.6, 156.2, 134.5, 125.0, 80.7, 61.5, 53.1, 50.7, 46.2, 43.1, 41.7, 40.0, 31.6, 29.8, 28.4, 17.6, 14.3. rf= 0.16 3-1EtOAc/Hexanes.

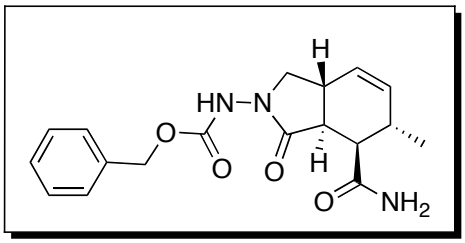
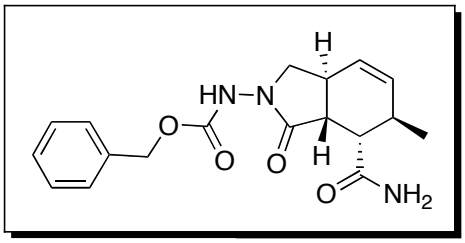
5.2.9 Synthesis of Cbz protected scaffolds

benzyl (3aR,6S,7S,7aR)-7-carbamoyl-6-methyl-1-oxo-3,3a-dihydro-1H-isoindol-2(6H,7H,7aH)-ylcarbamate and benzyl (3aS,6R,7R,7aS)-7-carbamoyl-6-methyl-1-oxo-3,3a-dihydro-1H-isoindol-2(6H,7H,7aH)-ylcarbamate

Modified from . Pivoyl chloride (46 μL, 0.37 mmol) was added dropwise to a solution of acid (129 mg, 0.37 mmol) in DCM (8 mL) at 0°C and under an inert atmosphere. TEA (56 μL, 0.47 mmol) was added dropwise. The mixture was stirred for 1 h and then ammonia methanol (1 mL, 7N) was added and the reaction stirred for 18 h. The organic layer was extracted with DCM (3X 20 mL). The organic phase was washed with a citric acid solution (20 mL, 30%), brine (20 mL) and saturated sodium bicarbonate (20 mL). Organic phase dried with magnesium sulfate and the solvent removed under reduced pressure. Moved on with crude.

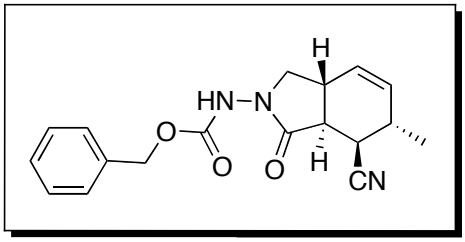
benzyl (3aR,6S,7R,7aS)-7-carbamoyl-6-methyl-1-oxo-3,3a-dihydro-1H-isoindol-2(6H,7H,7aH)-ylcarbamate (2-24a) and benzyl (3aS,6R,7S,7aR)-7-carbamoyl-6-methyl-1-oxo-3,3a-dihydro-1H-isoindol-2(6H,7H,7aH)-ylcarbamate (2-24b)

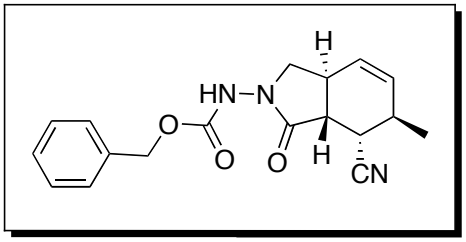



Did not isolate, moved on with crude

benzyl (3aR,6S,7R,7aS)-7-cyano-6-methyl-1-oxo-3,3a-dihydro-1H-isoindol-2(6H,7H,7aH)-ylcarbamate (2-25a) and benzyl (3aS,6R,7S,7aR)-7-

cyano-6-methyl-1-oxo-3,3a-dihydro-1H-isoindol-2(6H,7H,7aH)-ylcarbamate (2-25b)





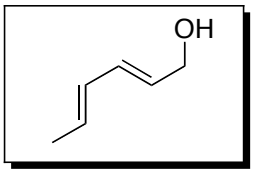
To the amide **2-24a,b** (296 mg 0.86 mmol) in DCM (25 mL) at 0°C and under and inert atmosphere was added TEA (0.538 mL, 3.87 mmol), and TFAA (0.240 mL 1.72 mmol) and mixed for 18 h. Organic layer extracted with DCM (3X 15 mL) dried over magnesium sulfate and the solvent removed under reduced pressure. Product recrystallized from DCM and Hexanes.

yield: 23 g (31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5H), 7.07 (bs, 1H), 5.87 (d, J = 10.0, 1H), 5.61 (dt, J = 3.2, 9.9, 1H), 5.28 – 5.05 (m, 2H), 3.63 (t, J = 7.6, 1H), 3.58 – 3.49 (m, 1H), 3.13 (d, J = 3.1, 1H), 3.10 – 3.97 (m, 1H), 3.85 – 3.75 (m, 1H), 2.44 (d, J = 10.,1 1H), 1.16 (d, J = 7.3, 3H). 13C NMR (75 MHz, $CDCl_3$) δ 171.7, 155.2, 135.5, 132.3, 128.7, 128.6, 128.3, 124.7, 119.4, 68.1, 51.9, 41.6, 35.6, 33.9, 30.0, 29.8, 21.3. rf= 0.2 7-3 Hexanes/EtOAc. HRMS (ESI +) calcd for $C_{17}H_{20}N_3O_6Na$ 3948.13186 found 348.13133.

5.2.10 Alternate scaffolds

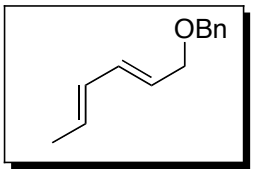
(2E,4E)-hexa-2,4-dien-1-ol (4-13)

Synthesis previously described.[82]



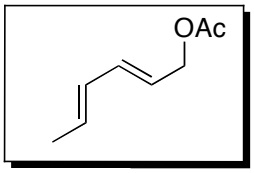
(((2E,4E)-hexa-2,4-dienyloxy)methyl)benzene (4-14)

Synthesis previously described.[83]

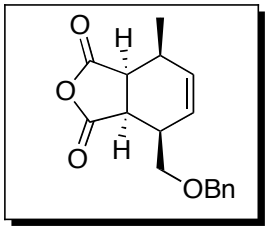


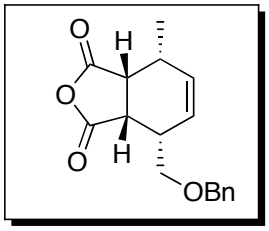
(2E,4E)-hexa-2,4-dienyl acetate

Synthesis previously reported. [84]



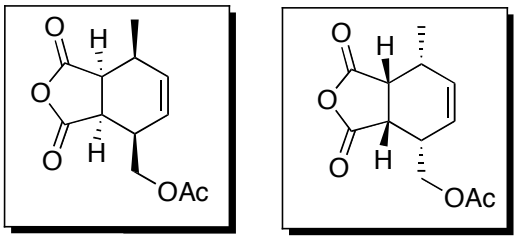
(3aR,4R,7S,7aS)-4-(benzyloxymethyl)-7-methyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (4-3a) and (3aS,4S,7R,7aR)-4-(benzyloxymethyl)-7-methyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (4-3b)





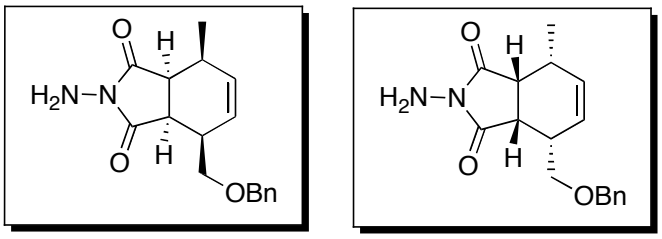
Protocol the same as in section 5.2.6. yield: 2.279g (95%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.30 (m, 5H), 5.86 – 5.76 (m, 2H), 4.64 (d, J = 11.6, 1H), 4.57 (d, J = 11.6, 1H), 4.02 (t, J = 8.9, 1H), 3.84 (dd, J = 7.0, 9.1, 1H), 3.63 (dd, J = 6.1, 9.4, 1H), 3.29 (dd, J = 7.2, 9.3, 1H), 2.63 (dd, J = 6.7, 14.2, 1H), 2.46 (dd, J = 7.1, 14.2, 1H), 1.43 (d, J = 7.4, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.4, 138.1, 135.1, 130.2, 128.6, 128.0, 128.0, 73.6, 69.5, 45.8, 43.1, 36.6, 30.8, 16.6. rf= 0.5 3-7 EtOAc/Hexanes.

((3aR,4R,7S,7aS)-7-methyl-1,3-dioxo-1,3,3a,4,7,7a-hexahydroisobenzofuran-4-yl)methyl acetate and ((3aS,4S,7R,7aR)-7-methyl-1,3-dioxo-1,3,3a,4,7,7a-hexahydroisobenzofuran-4-yl)methyl acetate



Protocol the same as in section 5.2.6. yield: 266 mg (55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 – 5.85 (m, 2H), 4.59 (dd, J = 8.0, 11.2, 1H), 4.50 (dd, J = 7.5, 11.2, 1H), 3.56 (dd, J = 5.9, 9.5, 1H), 3.34 (dd, J = 7.2, 9.5, 1H), 2.74 – 2.57 (m, 1H), 2.57 – 2.39 (m, 1H), 2.09 (s, 3H), 1.45 (d, J = 7.4, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 171.1, 171.0, 135.7, 129.4, 63.7, 45.7, 43.3, 35.2, 30.7, 21.0, 16.4. rf= 0.40 1-1 Hexanes EtOAc.

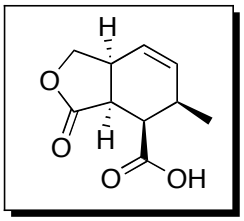
(3aR,4R,7S,7aS)-2-amino-4-(benzyloxymethyl)-7-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4-15a) and (3aS,4S,7R,7aR)-2-amino-4-(benzyloxymethyl)-7-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4-15b)

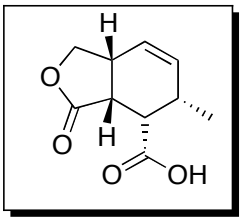


Hydrazine hydrate (0.5 mL) was added to anhydride **4-3a,b** (1.0 g 3.7 mmol) in acetic anhydride (15 mL) and stirred for 2 h. Solvent removed under reduced pressure. yield: 977 mg (93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 5.70 (t, J = 6.4, 2H), 4.65 (d, J = 11.8, 1H), 4.57 (d, J = 11.7, 1H), 4.06 (dd, J = 7.6, 9.1, 1H), 3.85 (dd, J = 8.0, 8.8, 1H), 3.27 (dd, J = 6.2, 8.4, 1H), 3.03 – 2.97 (m, 1H), 2.60 (d, J = 6.1, 1H), 2.42 (d, J = 7.3, 1H), 1.43 (d, J = 7.4, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 138.3, 134.7, 123.0, 128.5, 127.9, 127.8, 73.5, 70.2, 43.4, 40.9, 37.0, 31.3, 16.7. rf= 0.30 1-1 Hexanes –EtOAc stain $KMnO_4$.

(3aS,4R,5R,7aS)-5-methyl-3-oxo-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-carboxylic acid (4-17a) and (3aR,4S,5S,7aR)-5-methyl-3-oxo-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-carboxylic acid (4-17b)

Synthesis previously reported.[85,86]





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