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Christopher J. MacNevin Date

Part 1: Stereoselective Synthesis of Quaternary Center Bearing Azetines and β-Amino Acid Derivatives

Part 2: Natural and Enantiomeric Progesterone Analogues for the Treatment of Traumatic Brain Injury

By

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Doctor of Philosophy

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Date

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An abstract of
A dissertation submitted to the Faculty of the Graduate School of Emory University
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in Chemistry
2008

Abstract

Part 1: Stereoselective Synthesis of Quaternary Center Bearing Azetines and β-Amino Acid Derivatives. Part 2: Natural and Enantiomeric Progesterone Analogues for the Treatment of Traumatic Brain Injury.

By Christopher J. MacNevin

Part 1: A novel method for the synthesis of highly substituted β-amino acid derivatives has been developed. The synthetic method described herein involves the use of a stable, four-membered azetine heterocycle that is generated from the reaction of a chlorotitanium enolate with an *N*-acyl imidazolidinone. The azetine has been shown to serve as a useful template for the introduction of an electrophile in order to form a quaternary center with complete diastereoselectivity. Treatment of the substituted azetine with benzoyl chloride and cleavage of its tethered chiral auxiliary afforded $\beta^{2,2,3}$-amino acid derivatives in good yield.

Part 2: Pre-clinical and clinical research findings have revealed that the hormone progesterone, when acutely administered, can dramatically reduce cerebral edema, inflammation, tissue necrosis, and programmed cell death following traumatic brain injury (TBI). The use of progesterone as a therapeutic suffers however from a number of practical limitations, including its poor solubility and the instability of its formulation. Several chemically novel analogues of progesterone, its enantiomer, and its natural metabolite allopregnanolone have been synthesized and screened using both an *in vitro* assay and a whole animal model of TBI. All new derivatives demonstrated greatly improved solubility relative to progesterone and select compounds have shown equivalent effectiveness to progesterone in reducing cerebral edema after TBI.

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I began my studies at Emory with the idea of working with Dennis Liotta. After I had a chance to get to know him, there was no doubt that this was the guy I wanted as an advisor. His unbounded generosity, knowledge, confidence, and good nature will serve as traits I will hope to aspire to for the rest of my days. I can't imagine having worked for a better "boss" these last five years. Thanks Doc, for making it such a pleasure.

I would like to thank my thoughtful committee members for their insight and patience over the years. Without them, I would not have had such a clear idea of just how little I truly knew before beginning this journey. Professor Frank McDonald I thank as I feel I have greatly benefited from his consistent excellence and the demands he places on his advisees to reach their own. Professor Lanny Liebeskind I thank for his kind redirection in the face of my sometimes less than well thought through ideas, as well as his seemingly bottomless well of good advice.

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Most importantly, I thank Itta Bluhn-Chertudi, for the joy she constantly brings to my life and for giving me the will and the reason to keep on going.

Table of Contents

Part 1: Stereoselective Synthesis of Quaternary Center Bearing Azetines and β-Amino Acid Derivatives

List of Figures

List of Schemes

List of Tables

Part 2: Natural and Enantiomeric Progesterone Analogues for the Treatment of Traumatic Brain Injury

List of Figures

List of Schemes

List of Tables

Part 1: Stereoselective Synthesis of Quaternary Center Bearing Azetines and β-Amino Acid Derivatives

1. Introduction and Background

1.1 β-Amino Acids in Nature and Medicine

β-amino acids have attracted increased attention from the scientific community in recent years due to their unique structural and pharmacological characteristics. Contrary to the α-amino acids, which are the fundamental building blocks of proteins and are thus ubiquitous and essential to life, the β-amino acids, differing from their better known cousins by the simple incorporation of an additional carbon into their chemical structure, are much less common and can only be found either in free form or as constituents of select natural products. Although little is known regarding the original function of these compounds, it is hypothesized that lower organisms have generated β-amino acid containing metabolites as a form of protective adaptation.[1]

It is not surprising then that once isolated and screened in biological assays, β-amino acid containing compounds often show potent activity and they are thus becoming an important class of potential lead structures for the development of new therapeutics.[2] Compounds containing such moieties have been found to exhibit such diverse properties as HIV protease inhibition,[3] angiotensin-converting enzyme inhibition,[4] antifungal activity,[5] antibiotic activity (both in peptidic form[6] and as precursors to the β-lactam antibiotics[7]), and cytotoxic activity, as seen in the highly potent compounds cryptophycin,[8] and paclitaxel (Taxol, Figure 1).[9]

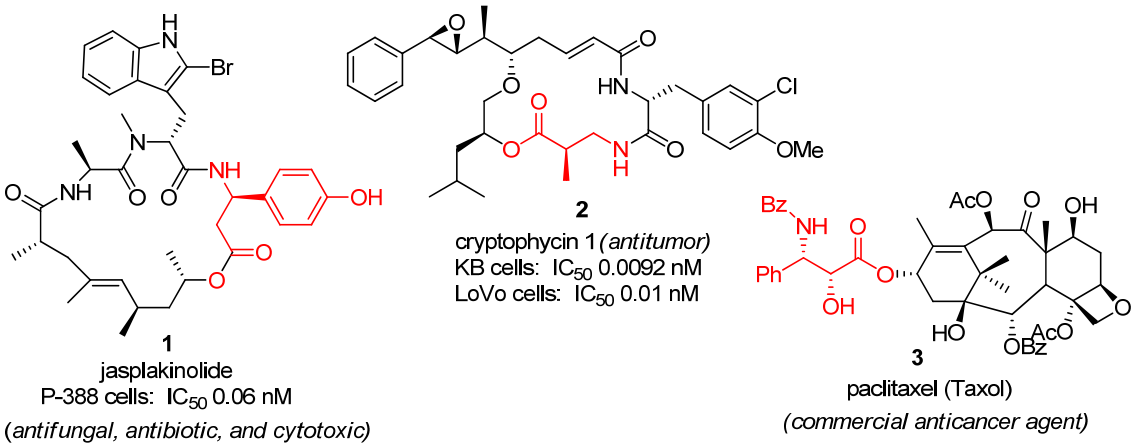
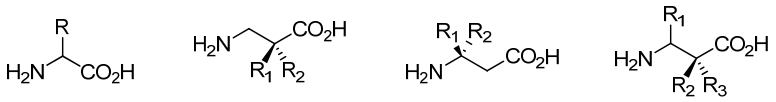


Figure 1. Pharmacologically active β-amino acid containing natural products.

Oligomers of the β-amino acids, the β-peptides, have been shown to form unusually stable secondary structures and may serve as useful tools in facilitating the design of synthetic biopolymers with novel biological and catalytic properties.[10] The preferred conformation of β-peptides is highly dependent on the substitution pattern of the individual β-amino acid constituents implemented. Elements of conformational preference such as the direction and number of residues per complete helical rotation, as well as the presence or lack of β-peptidic pleated sheets and/or hairpin turns may be controlled through the use of specific β-amino acids.[11] The β-peptides show increased stability to enzyme catalyzed degradation relative to that of α-peptides.[12] In addition, peptidomimetics that incorporate a β-amino acid at the scissile site of an α-peptide are useful tools for exploring enzyme binding features and facilitate the design of targeted enzyme inhibitors as therapeutic agents.[13]

1.2 Asymmetric Synthesis of β-Amino Carbonyl Derivatives

Seebach is credited for having established the widely accepted system of nomenclature for β-amino acids that designates the carbon adjacent to the acid carbonyl carbon as the β^2 position and the next carbon of the chain, adjacent to the amino group, as β^3. For compounds with more than one substituent at either of these positions, the superscript is simply repeated for that carbon (**5**,**6**, and **7**, Figure 2). While a wide array of methods are available for synthesizing β-amino acids, relatively few exist which allow for the stereoselective preparation of geminally disubstituted species, as this requires the synthetically challenging formation of a quaternary center.



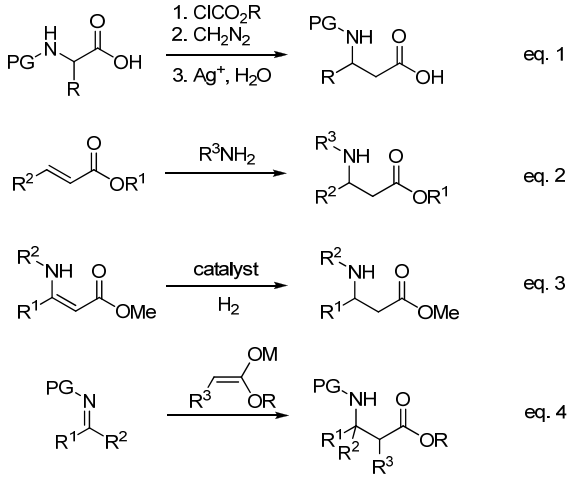
4 **5** **6** **7**

α- $\beta^{2,2}$- $\beta^{3,3}$- $\beta^{2,2,3}$-

Figure 2. Designation of representative amino acids.

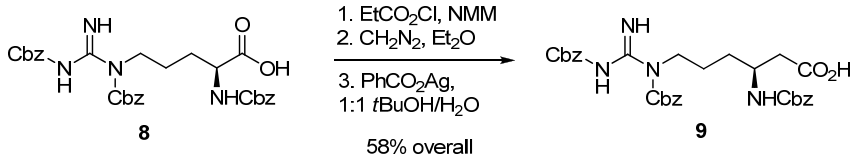
1.2.1 General approaches

In the most general sense, the asymmetric synthesis of β-amino acids commonly relies upon one of the following approaches: 1) Arndt-Eistert homologation of α-amino acids (Scheme 1, eq. 1), 2) conjugate additions of amine equivalents to acrylate derivatives (eq. 2), 3) hydrogenations of amino acrylates (eq. 3), and 4) enolate additions to imine derivatives (eq. 4). Several recent comprehensive reviews are available which describe traditional methods for β-amino acid synthesis.[14] Selected examples are provided here in order to illustrate each of the above stated main strategies.



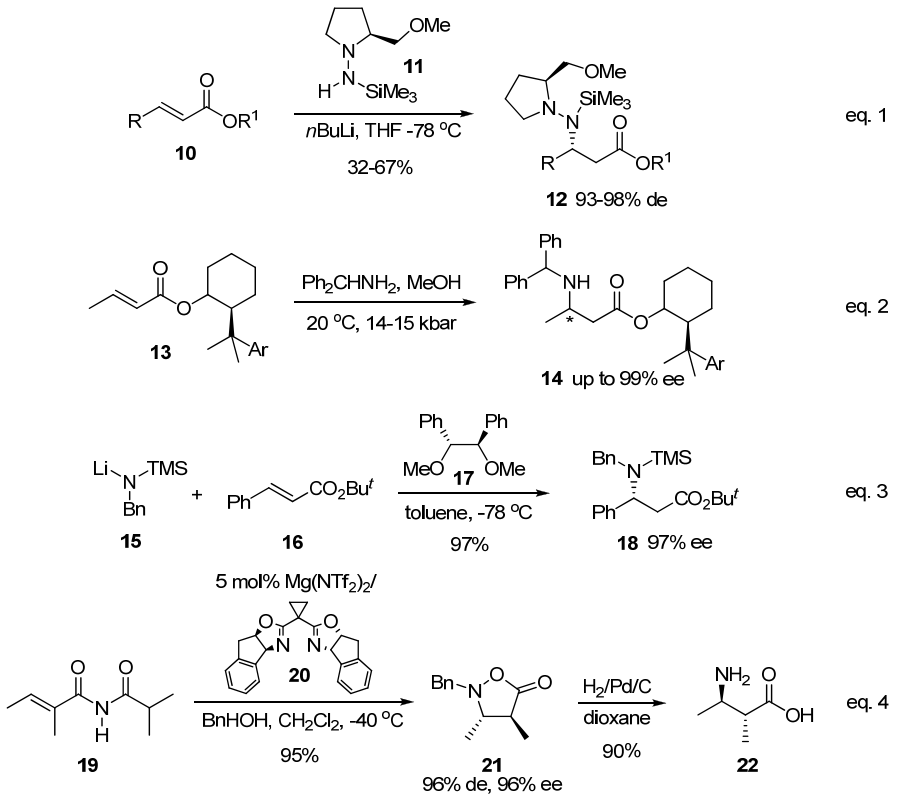
Scheme 1. General approaches to β-amino acid synthesis.

The Arndt-Eistert reaction is considered to be one of the best methods available for one carbon chain elongation of a carboxylic acid.[15] Naturally occurring, enantiomerically pure α-amino acids serve as useful starting materials for the synthesis of the corresponding β-amino acids. The method was successfully applied by Yuan and Williams, for example, in the total synthesis of the antibiotic agents TAN-1057 A-D.[16] Tri-*N*-CBz-L-arginine (**8**, Scheme 2) was first prepared as a mixed anhydride and allowed to react with diazomethane to give the diazoketone. The unintended cleavage of a CBz group resulting from a Wolff rearrangement/ LiOH saponification protocol was avoided by applying a modified Arndt-Eistert procedure using a 1:1 mixture of *tert*-butyl alcohol and water as the solvent system. The desired β^3-amino acid derivative **9** was obtained in 58% overall yield.



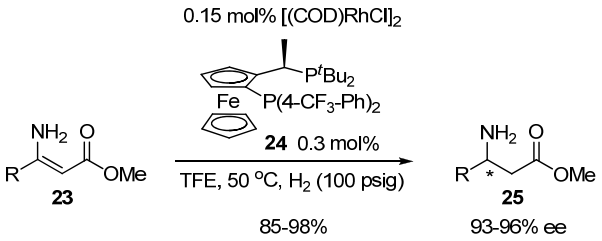
Scheme 2. Yuan and Williams application of Arndt-Eistert reaction.

The asymmetric conjugate addition of an amine to an acrylate has been carried out using several different methods of chiral induction. Enders, Wahl, and Bettray reported a highly selective method for β^3-amino acid synthesis using the chiral amine (*S*)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP, **11**, eq. 1, Scheme 3).[17] A chiral ester auxiliary strategy was employed by Dumas, Mezrhab, and d'Angelo, which resulted in very high diastereoselectivities when the reaction was run under high pressure conditions (eq. 2).[18] Chiral ligands can also be used, such as the dimethyl ether **17**, as demonstrated by Tomioka and co-workers (eq. 3).[19] Also, asymmetric conjugate additions have been achieved using chiral Lewis acids. Sibi and co-workers utilized a magnesium triflimide complexed with the chiral ligand **20** to generate $\beta^{2,3}$-amino acids after hydrogenolysis of the intermediate isoxazolidinone **21**.[20]



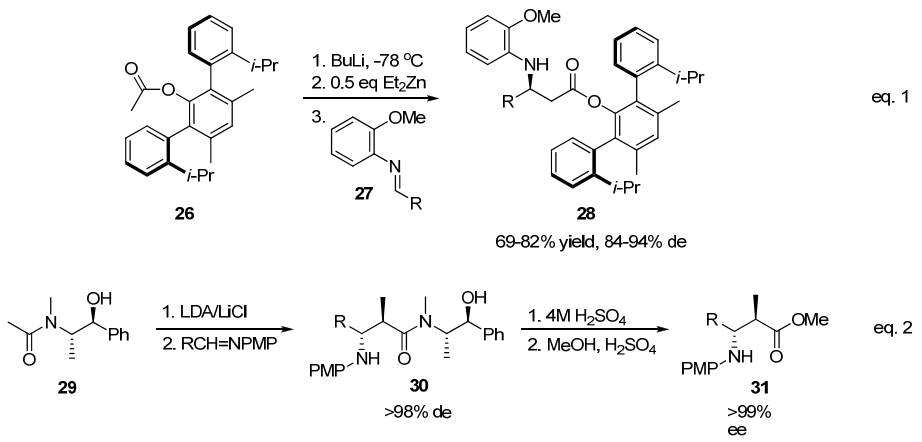
Scheme 3. Asymmetric conjugate addition reactions of amines and acrylates.

Asymmetric catalytic reductions of β-amino acrylates have also been explored.[21] For example, Hsiao and co-workers were able to generate β^3-amino esters via the reduction of unprotected enamine esters in the presence of an Rh-ferrocenophophine complex (Scheme 4).[22] Good yields and enantioselectivities were reported across a number of different enamine esters with as low as 0.3 mol % catalyst loading.



Scheme 4. Catalytic asymmetric reduction of enamine esters.

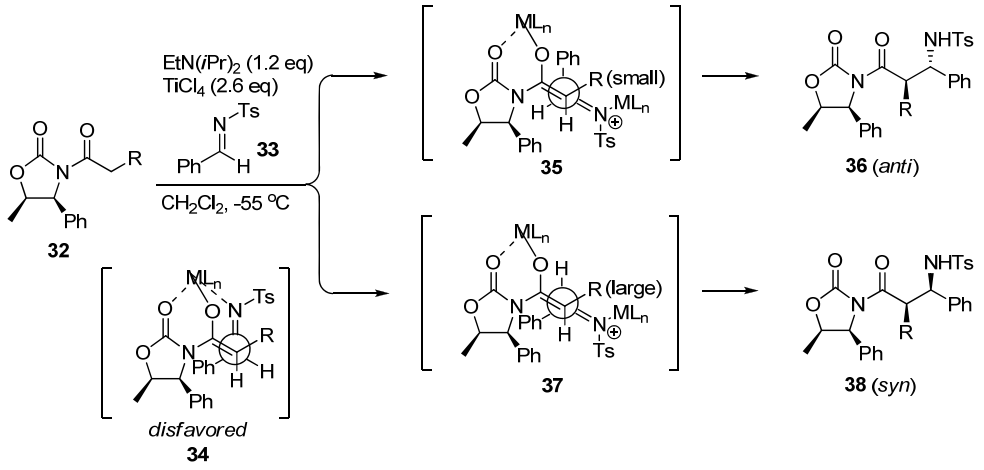
β-amino acid synthesis via condensation of an imine and an ester enolate or equivalent is another strategy that has been investigated extensively.[23] Many such methods make use of a chiral enolate component in order to direct the selectivity of addition. Yamamoto and co-workers for example utilize the lithium enolate of chiral acetate **26** (Scheme 5, eq. 1) for directed addition of diethylzinc activated imines.[24] The reactions proceeded to give β^3-amino carbonyl adducts in good yield and with high diastereoselectivity across a range of *o*-anisidine aldimines. Badia and co-workers demonstrated the use of (*S,S)*-(+)-pseudoephedrine chiral auxiliary **29** (Scheme 5, eq 2) for the diastereoselective addition of an enolate to *p*-methoxyphenyl substituted imines.[25] Excellent selectivities were observed and the auxiliary was removed without racemization through hydrolysis/esterification to give the amino esters in good yield.



Scheme 5. Chiral auxiliary mediated diastereoselective imine/enolate condensations.

The oxazolidinone chiral auxiliary, originally developed by Evans for diastereoselective aldol reactions,[26] has also been effectively applied in imine enolate additions by several groups.[27] In an early example, Wyatt and co-workers showed that the addition of titanium enolates of *N*-acyloxazolidinones to aldimines proceeded with moderate to good yield and selectivity but that reaction outcomes were substrate specific (Scheme 6).[28] Given that the presence of excess Lewis acid was necessary to achieve acceptable yields, the authors reasoned that the reaction was most likely proceeding through an open transition state (**35**). A Zimmerman-Traxler, closed six-membered transition state (**34**) would be disfavored by several factors, including 1,3-diaxial interactions of the tosyl and R groups, dipole-dipole repulsions between the C=C and C=N bonds, and steric interactions between the phenyl group of the imine and the oxazolidinone ring. It was also reasonably proposed that when the enolate R was a larger group, such as phenyl, preferential *syn* adducts would arise from transition state **37**. The reversal of selectivity could be attributed to approach of the imine as mediated by the favorable reduction in gauche steric interactions between the imine and enolate phenyl

groups. If the R group is smaller, as with a methyl or ethyl group, this gauche interaction does not play a significant role in determining the preferred transition state conformation.

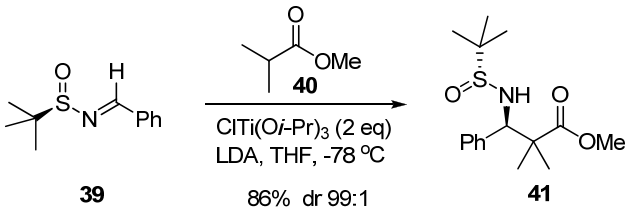


Scheme 6. Wyatt addition of imine to chlorotitanium enolate of oxazolidinone.

1.2.2 Stereoselective synthesis of $\beta^{2,2,3}$-amino acid derivatives

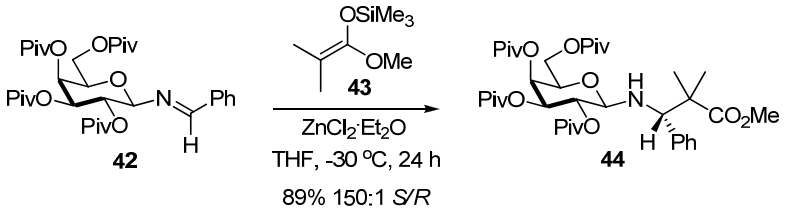
Asymmetric Mannich-type reactions

The limited number of effective strategies available for the stereoselective synthesis of $\beta^{2,2,3}$-amino acid derivatives predominantly make use of variations to already existing methods for the preparation of mono-substituted or $\beta^{2,3}$ substrates as described above. Ellman and co-workers for example reported the asymmetric addition reaction of ester enolates to *tert*-butanesufinyl imines to generate a range of differentially substituted β-amino acids (Scheme 7). The imines were readily prepared from Lewis acid mediated condensation of a given aldehyde or ketone with *tert*-butanesufinamide. The reaction gave $\beta^{2,2,3}$-derivatives with good yield and excellent diastereoselectivity but no cases were reported that used an ester enolate with differential β^2 substituents.



Scheme 7. Ellman addition of ester enolate to *tert*-butanesulfinyl imine.

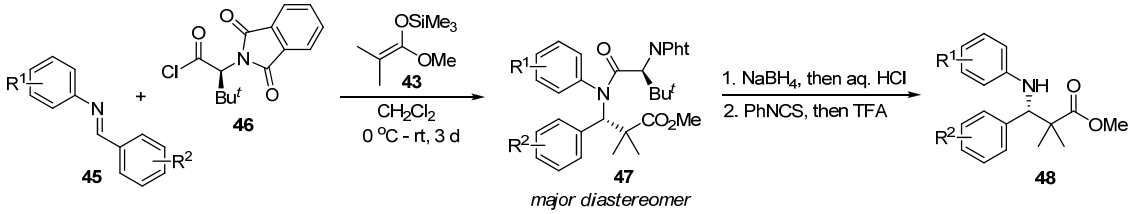
The zinc chloride catalyzed Mannich reaction of 2,2-disubstituted silyl ketene acetals with *N*-galactosylaldimines was shown to provide $\beta^{2,2,3}$-amino acid derivatives with good yield and diastereoselectivity, as described by Kunz and co-workers (Scheme 8).[29] The carbohydrate 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine serves as a chiral auxiliary once it is condensed with an aldehyde or ketone in the presence of molecular sieves and silica gel and may be removed following addition reaction by treatment with mild acid.[30] Only examples with 2,2-dimethyl silyl ketene acetals were provided so relative effectiveness of this strategy for achieving stereoselectivity at the β^2 position cannot be accurately assessed.



Scheme 8. Kunz Mannich reaction with carbohydrate derived aldimine.

Waldmann has reported a similar Mannich-type reaction using *N,N*-phthaloylamino acids as removable chiral auxiliary groups.[31] Schiff bases (**45**) are first treated with *N,N*-phthaloyl-protected amino acid chlorides to generate an acyliminium intermediate species

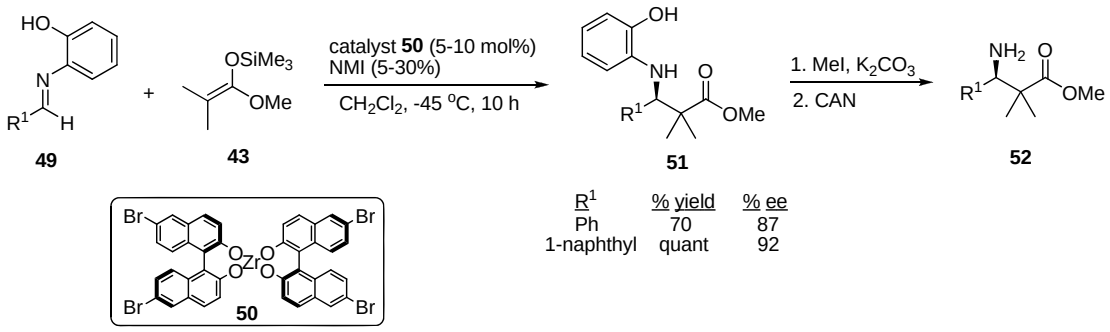
in situ and then the ketene silyl acetal is added (Scheme 9). Yields for the addition products ranged from moderate to good, depending on the substituent groups present on the aryl groups connected to the imine nitrogen and C=N bond carbon of the Schiff base. Reactions were run at room temperature but required 3 days to reach completion. The auxiliary must be removed through a two step sequence involving initial phthaloyl group cleavage with $NaBH_4$ and subsequent Edman degradation[32] to give the N-arylated $\beta^{2,2,3}$ amino acid ester. The authors also report that if an alkoxy substituted N-aryl group is employed, it may be removed in a separate step through treatment with cerium ammonium nitrate (CAN) to afford the N-deprotected $\beta^{2,2,3}$ amino acid ester.[33]



Scheme 9. Waldmann's use of *N,N*-phthaloylamino acids as chiral auxiliaries.

Kobayashi and co-workers reported the first catalytic enantioselective Mannich-type reaction of aldimines with silyl enolates using a novel chiral zirconium catalyst to give $\beta^{2,2,3}$-amino ester derivatives (Scheme 10).[34] The catalyst was formed *in situ* through treatment of two equivalents (*M*)-6,6′-dibromo-1,1′-bi-2-naphthol with $Zr(OtBu)_4$. When used in combination with an *N*-methylimidazole additive, the system was found to achieve >90% *ee* at as low as 5 mol% catalyst loading. An *o*-phenol substituent on the imine nitrogen was found to be critical to the success of this reaction due to its role in establishing favorable coordination with the catalyst. The group may be removed

through a two step sequence requiring initial methylation of the phenolic OH followed by deprotection using CAN. As with the other Mannich-type strategies described above, only 2,2-dimethyl derivatives were prepared and no examples with distinct β^2 substituents have yet been reported.

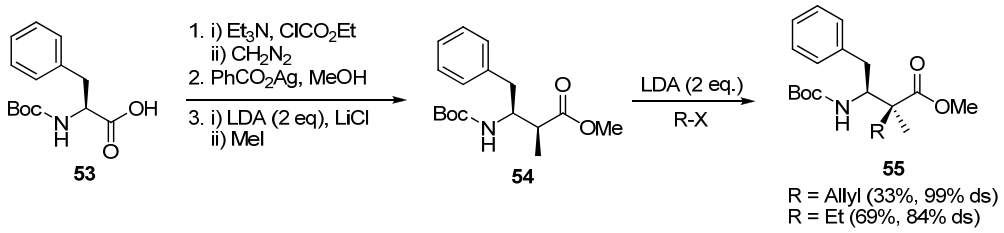


Scheme 10. Kobayashi catalytic enantioselective Mannich-type reaction.

Alkylations of $\beta^{2,2,3}$-amino acid precursors

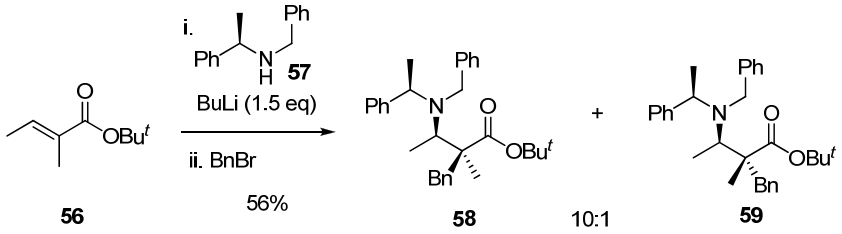
A second primary strategy taken to access $\beta^{2,2,3}$-amino acid derivatives has been through the alkylation of $\beta^{2,3}$ precursors. In contrast to the Mannich based methods described above, alkylation strategies have demonstrated successful formation of a chiral quaternary center at the β^2 position. One such example can be found in the work of Seebach and Podlech (Scheme 11).[35] The α-methyl-β^3-homophenylalanine substrate **54** was prepared by first subjecting natural phenylalanine to the Arndt-Eistert reaction, which requires a three step process involving use of toxic diazomethane. This was followed by application of Seebach's previously developed method for α-alkylation of β-aminoalkanoates to achieve the methylation.[36] In a separate step, the chiral quaternary center is formed under the same alkylation conditions as for the methylation (2 equiv

LDA, LiCl, then addition of electrophile). Yields were moderate but additions proceeded with good diastereoselectivity for the two examples given.



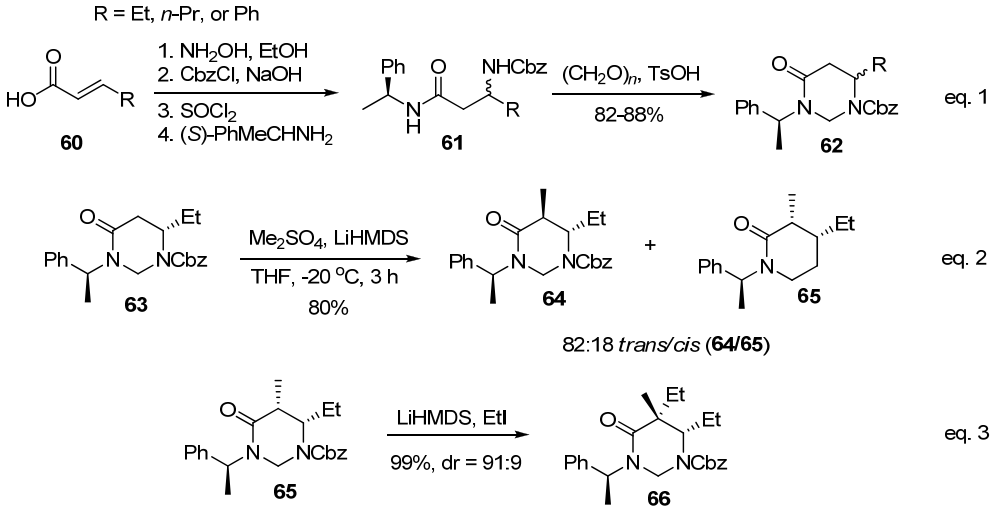
Scheme 11. Seebach and Podlech alkylation of α-methyl-β^3-homophenylalanine.

Davies and co-workers developed conditions to carry out the conjugate addition of *N*-benzyl-*N*-α-methylbenzylamide to simple α,β-unsaturated esters with high *syn* selectivity.[37] The reaction was extended through the implementation of a tandem addition-alkylation sequence (Scheme 12) to provide $\beta^{2,2,3}$-amino acid derivatives. Quenching with benzylbromide achieved stereoselective alkylation in 56% yield and with an *anti:syn* ratio of 10:1. The reaction was not proven to be particularly robust however as ethyliodide failed to react under the same conditions.



Scheme 12. Davies' tandem conjugate addition-alkylation sequence.

Stereoselective alkylation of a perhydropyrimidin-4-one heterocyclic template is described by Cardillo, Tomasini, and co-workers (Scheme 13).[38] Addition of hydroxylamine to an alk-2-enoic acid generated a racemic mixture of β^3-amino acids. The adducts were then transformed into (*S*)-phenylethylamido derivatives (**61**) that were subsequently cyclized through treatment with paraformaldehyde to give a 1:1 mixture of perhydropyrimidinone diastereomers (**62**). Separation of the isomers at this point was a point of difficulty. Methylation of perhydropyrimidinone **63** gave a 4:1 mixture of diastereomers. Iodoethane alkylations using the *trans* isomer **64** proceeded in low yield but it was discovered that the minor *cis* isomer **65** could be alkylated in high yield and with good diastereoselectivity. Although not demonstrated for compound **66**, the perhydropyrimidinone can be opened through acidic hydrolysis to provide the free β-amino acid derivative.

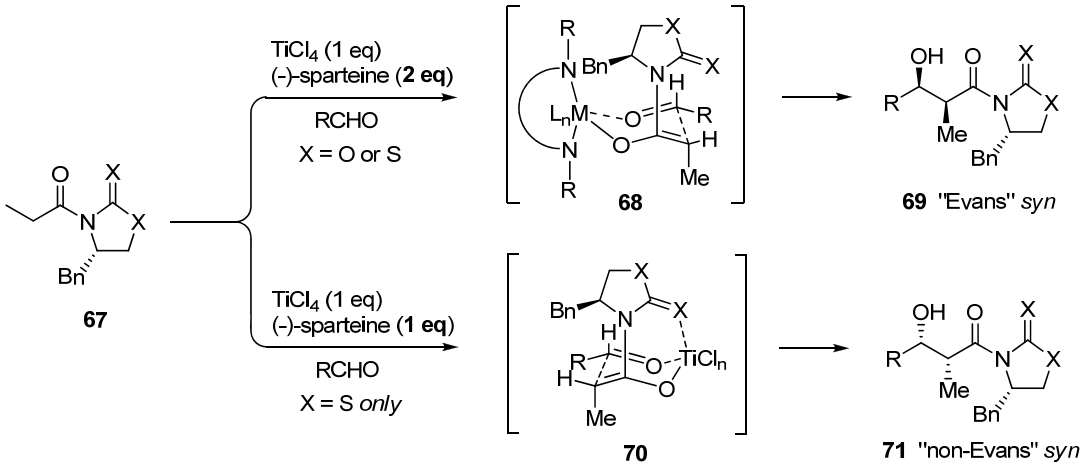


Scheme 13. Cardillo ethylation of perhydropyrimidin-4-one.

1.3 A New Route to β[2,2,3]-Amino Acids from Azetines

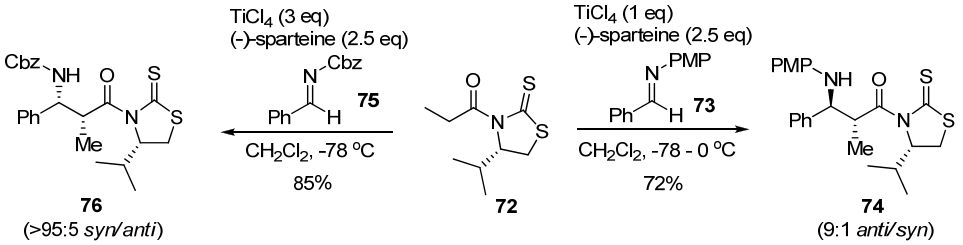
1.3.1 Addition of chlorotitanium enolates to aldimines

The Crimmins group has extensively investigated the diastereoselective addition of chlorotitanium enolates to aldehydes.[39] Their work has highlighted the frequent importance of subtle factors on the selectivity of such reactions. Depending on the type of auxiliary and the stoichiometry of the base, they found that either the "Evans" *syn* or "non-Evans" *syn* conformation may be accessed selectively (Scheme 14). The authors propose that the non-chelated transition state **68** is favored when an additional equivalent of (-)-sparteine is used. Coordination of the second equivalent of diamine to the metal center prevents coordination of the imide or thioimide carbonyl of the auxiliary to the metal. When a single equivalent of (-)-sparteine is used, the "non-Evans" *syn* adduct is favored, but only for the thiazolidinethione auxiliary. This is argued to be due to the greater nucleophilicity of the thiazolidinethionethione thionyl, relative to the carbonyls of either the oxazolidinone or oxazolidinethione,[40] which results in the highly ordered, chelated transition state **70**.



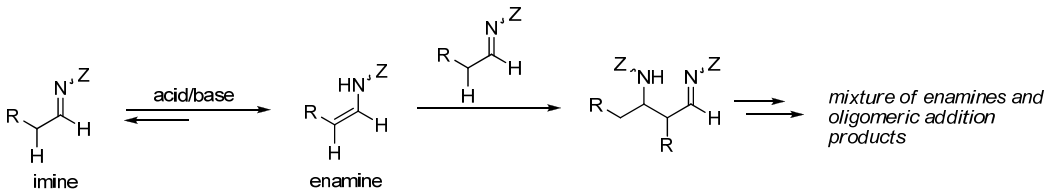
Scheme 14. Crimmins' asymmetric aldol additions with chlorotitanium enolates.

The Liotta group sought to extend upon this work by exploring similar reaction conditions for the addition of enolates to aldimines.[41] The thiazoldinethione auxiliary (**72**, Scheme 15) was employed because of its ease of preparation, the facile visualization of its addition products during silica gel column chromatography, its ability to be easily cleaved from the addition products, and its recoverability for reuse. It was found that the imine protecting group played an important role in determining the diastereoselectivity of the addition. The *p*-methoxyphenyl (PMP) substituted aryl imine led to the non-Evans *anti* adduct **74**, while use of an *N*-carbobenzyloxy (Cbz) imine gave preferential non-Evans *syn* products (**76**). The difference in reaction outcomes was attributed to the effect on the preferred transition state resulting from the availability of metal coordination through the carbamoyl oxygen of the CBz bearing imines. Such an interaction is not possible in the case of PMP substituted imines.



Scheme 15. Effect of imine substituent on diastereoselectivity of enolate addition.

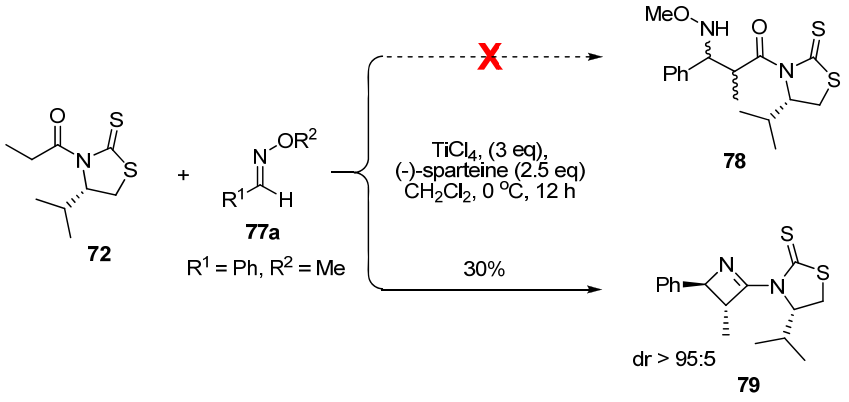
The reaction conditions were applied successfully across several aryl substituted imine substrates but enolizable imines were found to be incompatible and failed to produce the desired addition products. In the presence of acid or base, enolizable imines are known to readily undergo tautomerization, leading to oligomerization and subsequent loss of reactivity (Scheme 16). A more stable imine alternative was therefore sought.



Scheme 16. Imine/enamine tautomerization and oligomerization.

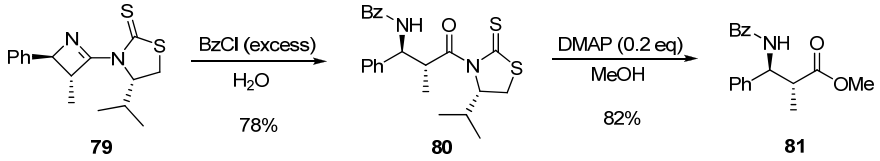
1.3.2 The unexpected discovery of azetines

The lack or reactivity among enolizable imines was addressed through the use of oxime ethers as imine equivalents. The electron donating character of the nitrogen substituent in the case of *O*-alkyl oximes was thought to strongly disfavor equilibration to the enamine tautomer and therefore allow reactivity of enolizable substrates. A single major product was isolated in 30% yield from the reaction of *N*-acylthiazolidinethione **72** with *O*-methyl oxime **77a** in the presence of 3.0 equivalents titanium tetrachloride and 2.5 equivalents of (-)-sparteine (Scheme 17). However, the compound isolated was not the β-amino acid addition product **78** as intended but was instead a *trans* substituted four-membered azetine ring (**79**). The reaction was later optimized with a total of 4 equivalents of $TiCl_4$ to improve the yield of **79** to 65% at the 1 millimole (mmol) scale.



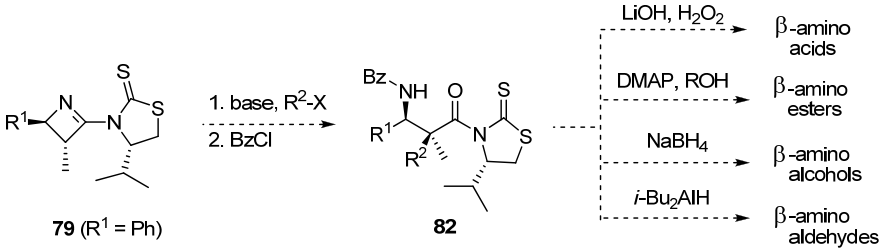
Scheme 17. Addition of oxime ether to chlorotitanium enolate gives an azetine.

The azetine products were later found to be easily opened to the corresponding β-amino carbonyl derivative when treated with benzoyl chloride in air (Scheme 18).[42] Cleavage of the thiazolidinethione auxiliary with methanol and catalytic dimethylamino pyridine (DMAP) provided β-amino methyl esters with retention of the absolute configuration.



Scheme 18. Hydrolytic ring opening of azetine and cleavage of auxiliary.

It was hypothesized that an azetine substrate such as **79**, with auxiliary still intact, had further potential to serve as a useful template for stereoselective functionalization of its enolate, thereby creating a quaternary center at what would become the β^2 position of the ring opened, β-amino carbonyl derivative (**82**, Scheme 19). This strategy, if proved to be feasible in practice, would then constitute a novel and practical entry into the stereoselective synthesis of $\beta^{2,2,3}$-amino acids and related compounds.

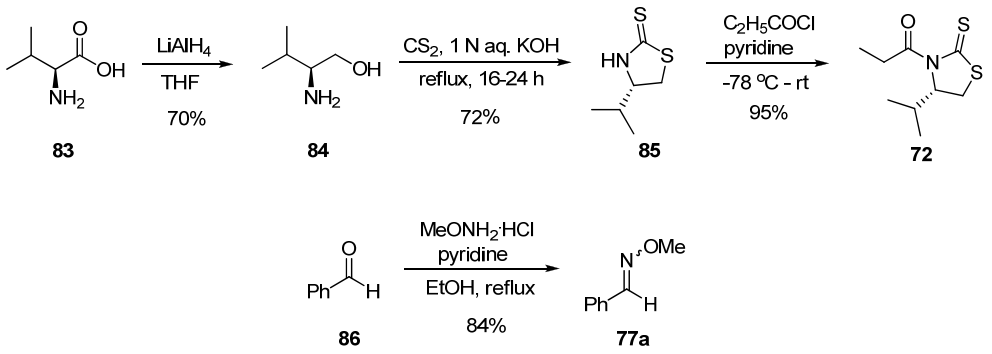


Scheme 19. Hypothesized route to $\beta^{2,2,3}$-amino acids and related compounds.

2. Results and Discussion

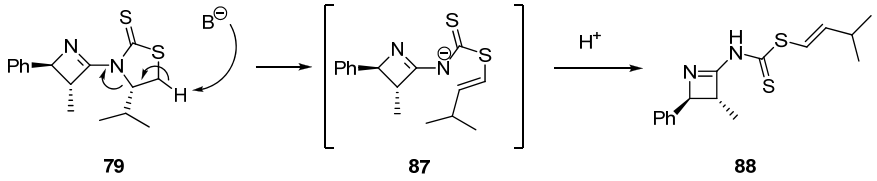
2.1 Azetine Alkylation Reactions with Traditional Auxiliaries

Initial investigations into the methodology as envisioned utilized the thiazolidinethione auxiliary **72**. The auxiliary was prepared from L-valinol, as accessed through reduction of L-valine, followed by cyclization with carbon disulfide under basic conditions and subsequent acylation with propionyl chloride.[43] The *O*-methyl oxime **77a** was derived from the condensation of benzaldehyde with methoxylamine hydrochloride. Distillation of the crude oxime product mixture gave **77a** in 84% yield as a 25:1 mixture of *E/Z* isomers.



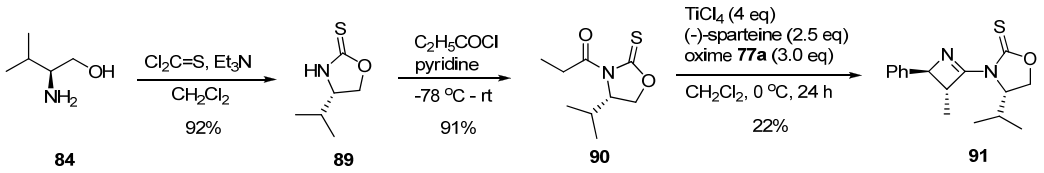
Scheme 20. Synthesis of thiazolidinethione auxiliary **72** and oxime ether **77a**.

Initial efforts to alkylate *trans* substituted azetine **79** with methyliodide using 1.1 equivalent lithium tetramethylpiperidine (LTMP) in THF at -78 °C resulted in complete consumption of the starting material but no desired product. Analysis of the product mixture indicated that, rather than formation of the aza-enolate, a deprotonation at C-5 of the thiazolidinethione ring was occurring. This deprotonation was then leading to ring opening of the auxiliary and formation of an (*E*)-alkene (**88,** Scheme 21).



Scheme 21. Thiazolidinine-2-thione ring opening under strongly basic conditions.

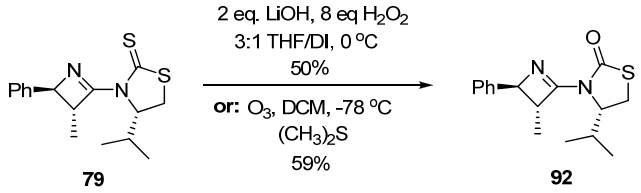
The oxazolidinethione auxiliary was prepared from L-valinol and thiophosgene according to the procedure reported by Crimmins, King, Tabet, and Chaudhary.[44] Acylation with propionyl chloride proceeded without difficulty. The *trans* substituted azetine **91** was obtained as a white solid in 22% yield via addition of oxime ether **77a**. Analysis of reaction mixtures following attempted alkylations indicated that the reactions were proceeding in a similar fashion as had been observed in the thiazolidinethione series. However, unlike the thiazolidinethione azetine reactions in which the starting material was completely consumed, the oxazolidinethione azetine was recoverable in 20% yield. The isolated major product from these reactions was not fully characterized but it was clearly determined to not be the desired alkyl addition product and further investigations utilizing azetine **91** as a substrate for alkylation were not pursued.



Scheme 22. Synthesis of oxazolidinethione auxiliary **90** and azetine **91**.

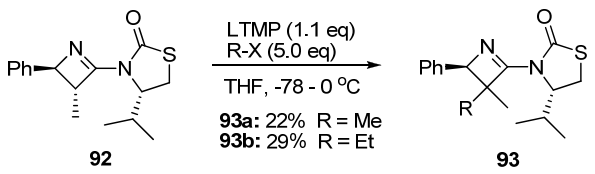
During the course of previous work towards the development of methodology for the direct conversion of chiral auxiliary substituted azetines to the corresponding β-

lactams, it was discovered that the thiazolidinethione auxiliary could be oxidized to the thiazolidinone **92** without disruption of the azetine nucleus. This outcome was originally noted following treatment of the azetine with excess hydrogen peroxide and LiOH but it was later found to be achievable in greater yield through ozonolysis and reductive workup with dimethylsulfide.



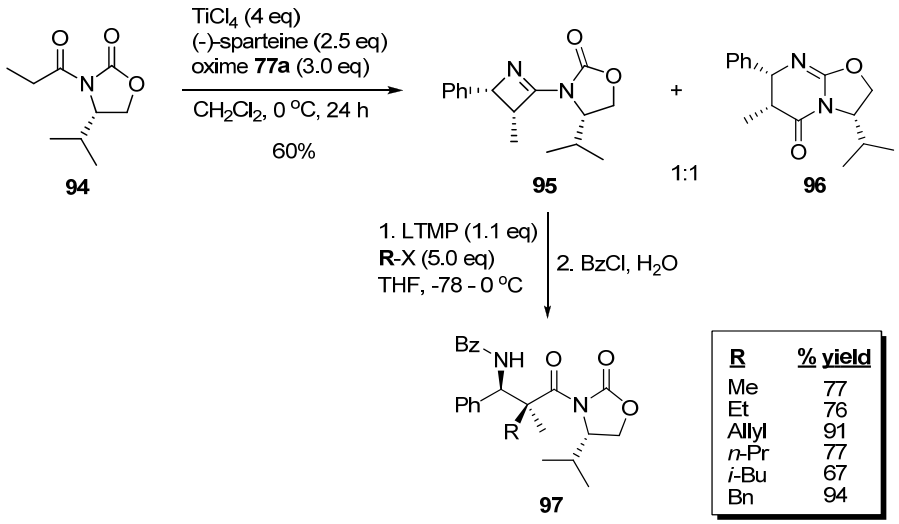
Scheme 23. Synthesis of thiazolidinone auxiliary **92**.

The first successful azetine alkylation resulted from the reaction of compound **92** with methyliodide in the presence of LTMP following the procedure as previously used among the other azetine series (Scheme 24). No significant degradation of the starting material was observed following base addition. The 3,3-dimethyl azetine **93a** was isolable in 22% yield. Starting thiazolidinone azetine was also recoverable. No significant change in product distribution was noted to arise from attempts to optimize the reaction conditions. The reaction was extended to alkylation with ethyliodide. The 3-ethyl-3-methyl azetine adduct **93b** was obtained in 29% yield. The proton NMR spectrum indicated the formation of a single diastereomer, although the absolute configuration was not determined.



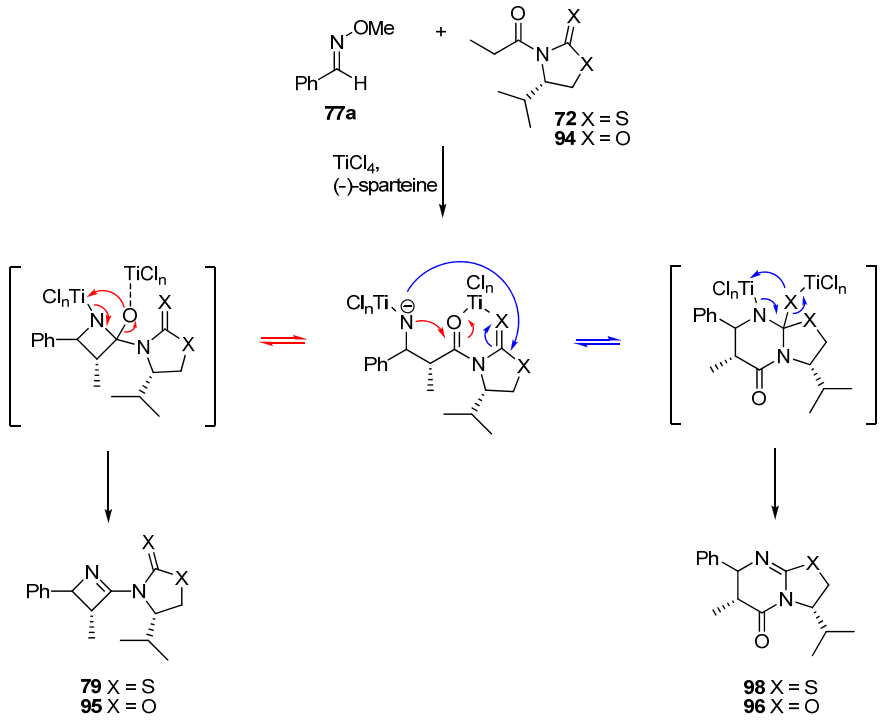
Scheme 24. First azetine alkylation reactions with thiazolidinone auxiliary.

Reaction of oxime **77a** with the oxazolidinone auxiliary **94** leads to the *cis* azetine addition product **95** (Scheme 25). Although isolable yields of the oxazolidinone derived azetine **95** was low, it did serve as a useful substrate for the alkylation/ring opening sequence, giving adducts with complete diastereoselectivity and in good yields across a range of electrophiles.[45]



Scheme 25. Synthesis and alkylation of oxazolidinone azetine.

The methodology as demonstrated was limited however by low isolable yields at gram scale of the azetine substrates themselves (Table 1). The azetine is recovered in as much as a 1:1 ratio with a pyrimidinone side product (**96** and **98,** Scheme 26), depending on the type of auxiliary employed. The pyrimidinone is the result of a competitive cyclization pathway thought to involve nucleophilic attack of the transient nitrogen anion to the auxiliary, rather than acyl, carbonyl. Pyrimidinone formation was observed to be increasingly favored with increasing reaction scale in the case of the thiazoldinethione auxiliary. The origins of this trend are not fully understood.



Scheme 26. Competitive reaction pathways to either azetine or pyrimidinone.

Table 1. Azetine/pyrimidinone product distribution and yield relative to auxiliary type.

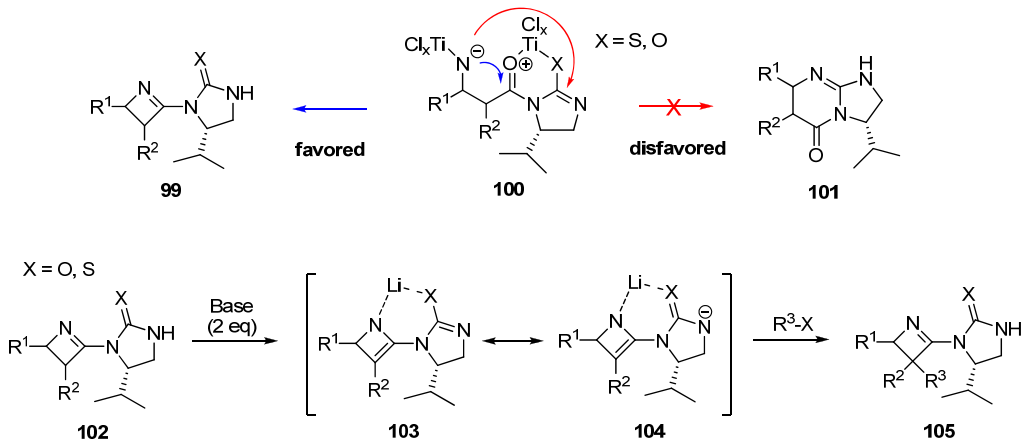
entry	auxiliary: X (name)	azetine	azetine substitution	ratio azetine:pyrimidinone[a]	isolated azetine yield (%)
1	**72**: S (thiazolidinethione)	**79**	*trans*	2:1	20-25
2	**94**: O (oxazolidinone)	**95**	*cis*	1:1	20-25

[a] Ratios based on isolated product yields obtained at gram scale.

One factor believed to be play an important role in the observed product distributions was the relative electrophilicity of the thionyl and carbonyl groups of the auxiliaries, with the more electrophilic carbonyl of the oxazolidinone giving a greater proportion of pyrimidinone. It was therefore believed that a more significant reduction in the electrophilicity of the auxiliary carbon would lead to a corresponding reduction in the

appearance of the side product, thereby favoring the reaction pathway leading to the desired azetine substrate. This was thought to be achievable through the use of an imidizolidinone based chiral auxiliary.

Deprotonation of the free N-H of an imidazolidinone would render the adjacent carbonyl carbon much less electrophilic, thereby strongly disfavoring formation of the pyrimidinone side product (Scheme 27). Use of such a substrate would also highly disfavor deprotonation at C-5 of the auxiliary, as seen with the thiazolidinethione auxiliary. Due to the success in execution of the alkylation strategy using the *cis* substituted, oxazolidinone bearing azetine, an auxiliary that could generate a *cis* substituted azetine preferentially was also desired.

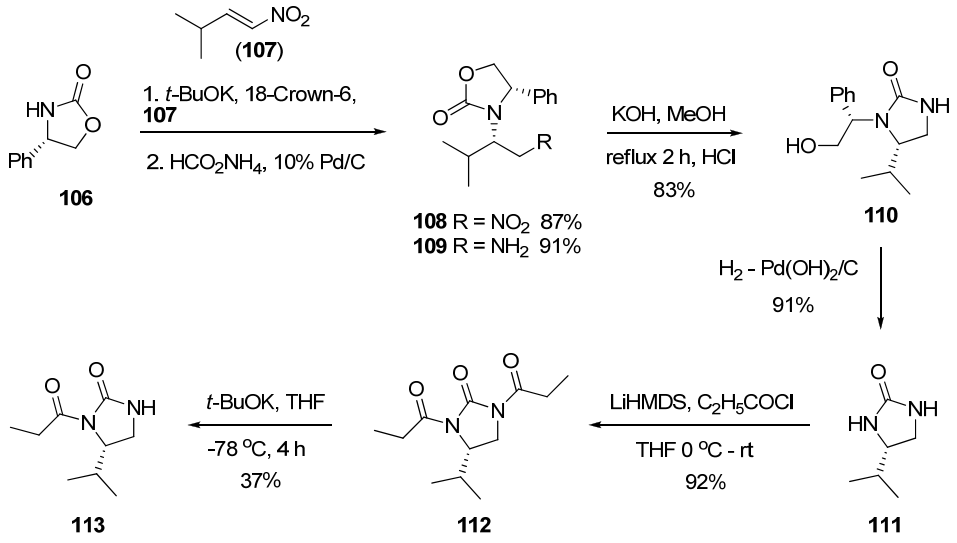


Scheme 27. Hypothesized advantages of imidazolidinone based chiral auxiliary.

2.2 Imidazolidinone Based Auxiliaries

2.2.1 Free N-H Auxiliaries

Imidazolidin-2-one based chiral auxiliaries are not as widely used as their oxazolidinone or thiazolidinethione counterparts but they have nevertheless been shown to exhibit high selectivity over a range of asymmetric synthesis applications.[46] There are also distinct advantages present among the imidazolidinones, including their crystallinity, N-bifunctionality,[47] and resistance to nucleophilic ring opening.[48] We believed that an auxiliary, such as (*S*)-5-isopropyl-1-propionyl-imidazolidin-2-one (**113**, Scheme 28), could be particularly useful for our desired application.

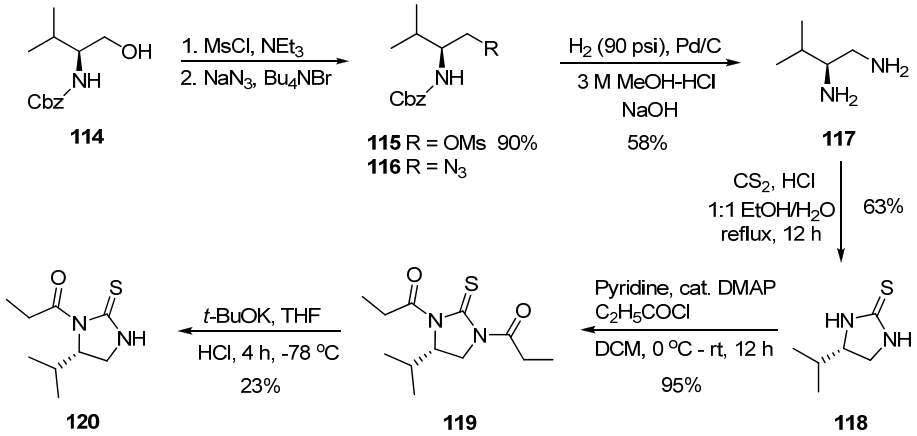


Scheme 28. Synthesis of imidazolidinone auxiliary **113**.

Preparation of substrate **113** proved to be challenging due to difficulties associated with both diamine synthesis and regioselective acylation. Initial access was afforded through the Michael addition of (*S*)-4-phenyl-oxazolidin-2-one **106** to 3-methyl-1-nitrobutene **107**, followed by reduction, cyclization, and benzylic cleavage to the free

imidazolidinone **111**.[49] Di-acylation and finally regioselective de-acylation with potassium *t*-butoxide provided **113** in an overall yield of 21% (6 steps). Once in hand, reaction of **113** with benzaldehyde *O*-methyl oxime **77a** under our standard azetine forming conditions (4 equiv. $TiCl_4$, (-)-sparteine, CH_2Cl_2, 0 °C, 12 h) with an additional equivalent of base for deprotonation of the free N-H afforded no desired azetine product. The main isolated materials were either the starting auxiliary or its deacylated parent compound. Alteration of reaction variables, including the use of lithium amide bases, different solvents, and higher temperatures, did not achieve any improvement.

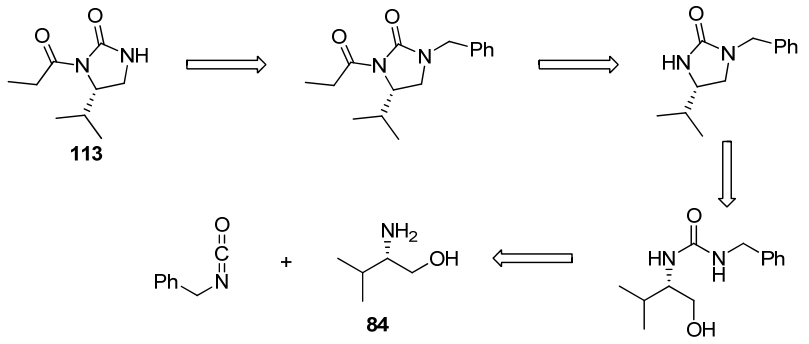
A parallel synthetic strategy afforded access to the imidazolidinethione auxiliary **120** through diamine **117**, which was prepared from *N*-Cbz-L-valinol (**114**) as described by Hegedus and co-workers (Scheme 29).[50] The free imidazolidinethione **118**, prepared through refluxing **117** with carbon disulfide, was diacylated,[51] and subjected to the same regioselective de-acylation conditions as developed for the imidazolidinone auxiliary **113**. Auxiliary **120** however behaved similarly to **113** and did not prove useful for azetine synthesis.



Scheme 29. Synthesis of imidazolidinethione auxiliary **120**.

2.2.2 Substituted Imidazolidinones

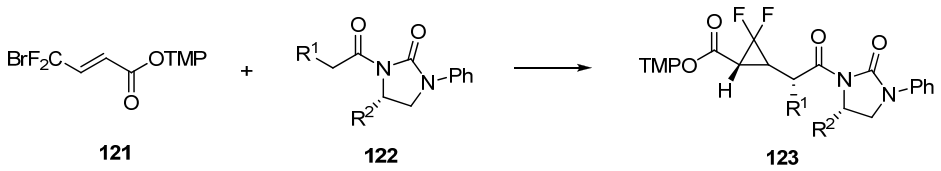
Several additional synthetic routes were concurrently under development for the preparation of the free N-H imidazolidinone auxiliary before the substrate had finally been accessed and evaluated as to its potential utility for azetine synthesis. One of these routes sought to avoid the need for the low-yielding di-acylation/regioselective de-acylation process through the use of an appropriately substituted isocyanate.[52] A benzyl substituted isocyante for example could be allowed to react with amino alcohol **84** to give an intermediate urea addition product that could be cyclized and then acylated without concerns regarding regioselectivity of acylation. The benzyl group could then be removed through hydrogenolysis in a following step to give the free N-H auxiliary **113**.



Scheme 30. Retrosynthetic approach to imidazolidinone auxiliaries from isocyanates.

At this point in time it was noted from the literature that Taguchi and co-workers had utilized an *N*-phenyl substituted imidazolidinone (**122**, Scheme 31) for the intended purpose of reducing the likelihood of cyclization to the auxiliary carbonyl in a Michael addition reaction with difluorocrotonate **121**.[53] None of the undesired cyclization adduct was observed and the reaction proceeded as planned. Based on this precedent, we next

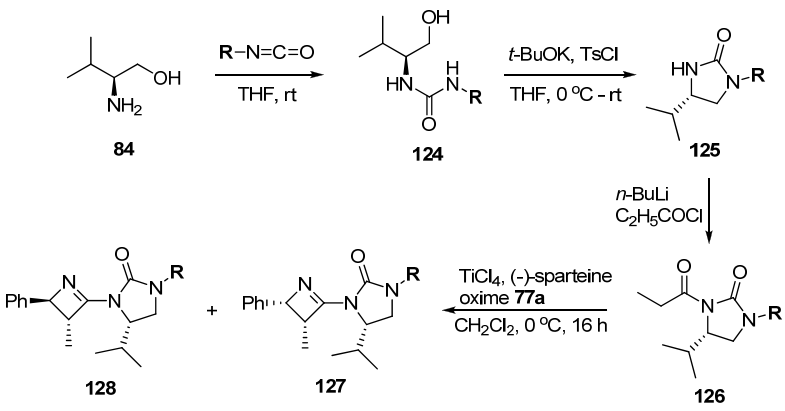
considered the possibility that deprotonation of the free N-H may not be necessary in order to deactivate the auxiliary carbonyl towards nucleophilic attack if in fact the resonance delocalization provided by a substituted nitrogen lone pair, relative to that of sulfur or oxygen, was sufficiently enhanced. The above outlined synthetic scheme was therefore not carried fully through to give the free N-H auxiliary, but instead was stopped at the penultimate step with the *N*-benzyl substituent still intact.



Scheme 31. Taguchi's Michael addition of substituted imidazolidinone.

The *N*-benzyl substituted imidazolidinone auxiliary **126a** (Table 2) was thus submitted to the developed azetine forming reaction conditions (4 eq $TiCl_4$, 2.5 eq (-)-sparteine, 3 eq oxime **77a**, CH_2Cl_2, 0 °C, 16 h). Unfortunately, none of the expected azetine product was isolated from the reaction mixture. A minor product was recovered in ~10% yield that appeared to be a mixture of diastereomers and was not identified at the time.

The phenyl substituted auxiliary **126b** was prepared and allowed to react with benzaldehyde *O*-methyl oxime **77a** under the same standard conditions (Scheme 32). This reaction proved to give a very different result from that obtained using auxiliary **126a**. The major products were found to be a combination of *cis* and *trans* azetines (**127b** and **128b**, Figure 3), separable by conventional chromatography and isolated in 61% total yield in a 1:1.7 (*cis*:*trans*) diastereomeric ratio. Most notably, *no pyrimidinone product was evident in the product mixture*.



Scheme 32. Isocyanate route to imidazolidin-2-one auxiliaries.

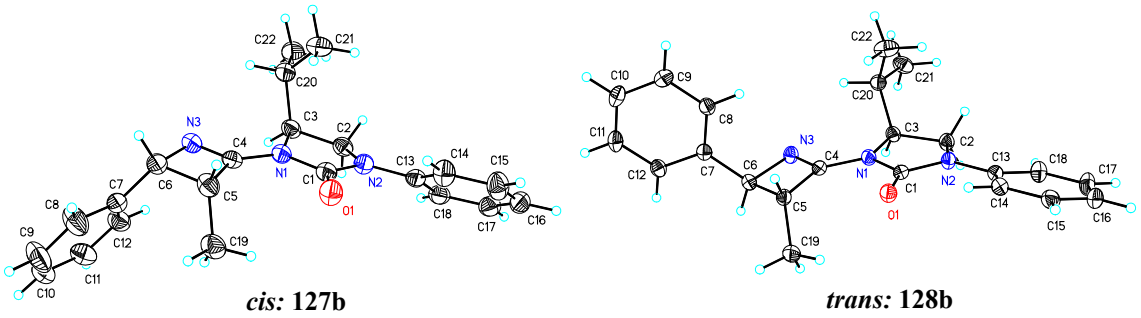


Figure 3. ORTEP structures for *cis* and *trans* azetines **127b** and **128b** derived from *N*-phenyl substituted imidazolidinone chiral auxiliary **126b**.

Given the difference in reactivity observed between the *N*-phenyl and *N*-benzyl substituted auxiliaries, the degree to which the *N*-substituent itself might influence azetine yield and/or *cis/trans* selectivity was unknown. Therefore, several differentially substituted imidazolidinones were prepared in order to investigate the potential effect of the *N*-substituent on yield and diastereomeric ratio (Table 2). Urea formation among the substrates proceeded rapidly in all cases, generating solid products that were recrystallized or simply filtered, washed, and carried on to the next step without additional purification. Cyclization yields were found to be highly substrate dependent and varied from a high of 90% for the *N*-benzyl **125a** to a low of 19% for the *N*-phenyl

imidazolidinone **125b**. Only the *N*-phenyl (**126b)**, *N*-*p*-tolyl (**126c**), and *N*-4-chlorophenyl (**126d**) isocyanate derived auxiliaries were successfully carried forward to generate azetines. Total azetine yields were uniformly improved relative to that obtained from either the thiazolidinethione or oxazolidinone auxiliaries.

Table 2. Azetine yield and selectivity data for variably substituted imidazolidinones.

entry	**R**–N=C=O	product: yield %			total azetine yield %	*cis:trans* **127:128**
1	Bn	**124a**: 75	**125a**: 90	**126a**: 51	ni[b]	-
2	Ph	**124b**: 79	**125b**: 19	**126b**: 87	61	1:1.7 **127b:128b**
3	*p*-Tol	**124c**: 99[a]	**125c**: 23	**126c**: 84	66	1:1.9 **127c:128c**
4	*p*-Cl-Ph	**124d**: 91	**125d**: 39	**126d**: 98	45	1:1.1 **127c:128c**
5	*p*-MeOPh	**124e**: 90	**125e**: 60	**126e**: 40	ni	-
6	*p*-NO_2-Ph	**124f**: 67	**125f**: 56	**126f**: 60	ni	-
7	*t*-Bu	**124g**: 99[a]	**125g**: 38	**126g**: 41	ni	-
8	Et	**124h**: 72	**125h**: 88	**126h**: 46	ni	-

[a] product carried forward without recrystallization. [b] ni = not isolated

A general increase in yield is seen with increasing electron donating character of the substituent (Figure 4). This apparent trend may be due to an increase in the reactivity of the enolate through enhancing its nucleophilicity. It was thought that the *p*-methoxyphenyl substituted auxiliary **126e** might show a further increase in yield, however no azetine products were recovered from the reaction mixture. The observed lack of reactivity in the case of auxiliary **126e**, as well as for the *p*-nitrophenyl substituted auxiliary **126f**, is thought to be the result of an unexpected interaction between the substituent group and the titanium Lewis acid.

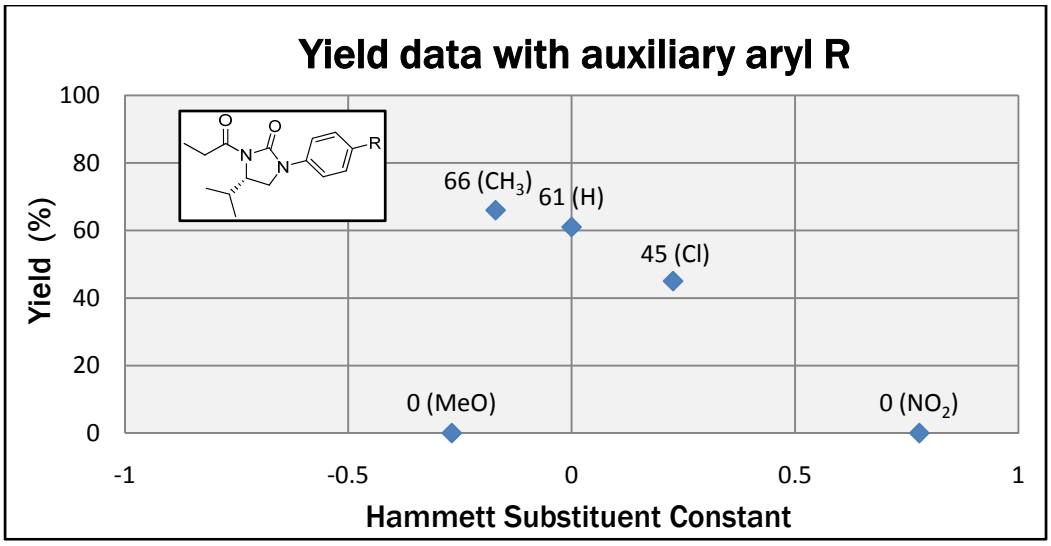


Figure 4. Yield data for different imidazolidinone auxiliary aryl R groups.

The sterically demanding *t*-butyl substituted auxiliary **126g** gave no azetine products. The auxiliary **126h** was prepared with an ethyl N-substituent in order to provide a comparative example of an auxiliary with a substituent of relatively low steric demand. While auxiliary **126h** also did not provide azetine products, it was noted that the main product isolated (~10% yield) bore some similarity to the main product isolated from the reaction of the benzyl substituted auxiliary **126a** with respect to its proton spectrum. Mass spectrometry analysis of the samples indicated that the products had incorporated a molecule of HCl into what would either be a typical azetine or pyrimidinone product. Given any transient activation of the azetine as an iminium species, addition of chloride anion would be a facile process. Although the HCl addition product was only recovered from the **126a** (N-benzyl) and **126h** (N-ethyl) auxiliary reaction mixtures, speculation as to why these particular auxiliaries may have facilitated the addition will not be made as the species may have in fact been present in other cases but not isolated due to either low yields or a focus on azetine products.

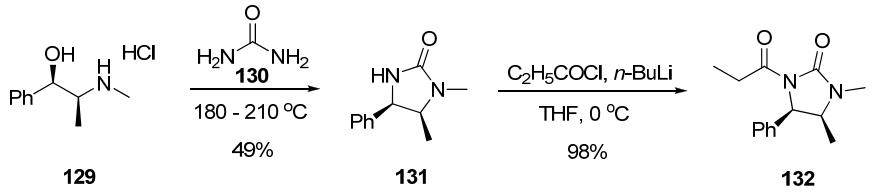
Another factor that was examined for its effect on diastereoselectivity and yield was the choice of Lewis acid (Table 3). The screen consisted predominantly of titanium based Lewis acids with variable stoichiometries of either chloride, cyclopentadienyl, and/or isopropyl ligands in the coordination sphere. Addition of one equivalent trichloro(cyclopentadienyl)titanium(IV) with three equivalents titanium (IV) tetrachloride showed a shift in diastereoselectivity to favor formation of the *cis* substituted azetine over the *trans*, though the selectivity, at 1.4:1 *cis/trans*, was still not very high. The yield in this case was also dramatically reduced. The only other Lewis acid screened that resulted in an isolable yield of azetine product was zirconium (IV) chloride. The *cis* azetine was recovered exclusively, though in just 6% yield. All other titanium complexes, including those complexed with BINOL as well as the bulky pentamethylcyclopentadienyltitanium trichloride ligand, proved ineffective for azetine formation. The greater strength of the titanium tetrachloride Lewis acid appeared to be essential for the reaction.

Table 3. Effect of Lewis acid on yield and diastereoselectivity of azetine reaction with auxiliary **126a**.

entry	Lewis acid	azetine ratio (*cis:trans*)	total azetine yield %
1	$TiCl_4$	1:1.8	61
2	1 Cl_3TiCp: 3 $TiCl_4$	1.4:1	26
3	$ZrCl_4$	1:0	6
4	$Sn(OTf)_2$	-	-
5	$ClTi(OiPr)_3$	-	-
6	Cl_2TiCp_2	-	-
7	$ClTi(OiPr)_3$	-	-
8	$Cl_3Ti(Cp(CH_3)_5)$	-	-
9	$Cl_2Ti(OiPr)_2$	-	-
10	$Cl_3TiOiPr$	-	-
11	3 $Cl_3TiOiPr$: 1 $TiCl_4$	-	-
12	1 $Cl_2TiBINOL$: 3 $TiCl_4$	-	-

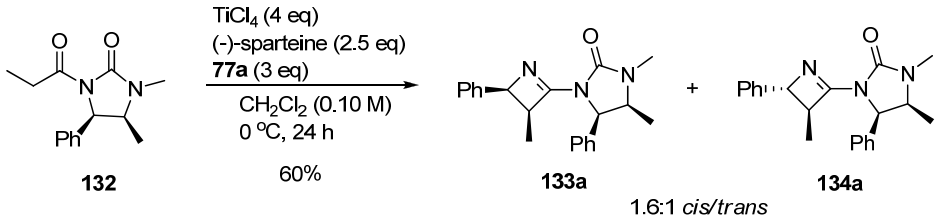
2.2.3 Ephedrine Derived Auxiliaries

Ephedrine derived imidazolidinone auxiliaries were thought to provide a number of potential benefits, including their ease of preparation, low cost, and the availability of either enantiomer.[54] The fusion cyclization of (1*R*,2*S*)-(-)-ephedrine hydrochloride (**129**) with urea (**130)** provided solid (4*R*,5*S*)-1,5-dimethyl-4-phenyl-imidazolidin-2-one **131** that could be crystallized in large quantity and subsequently acylated in high yield (**132**, Scheme 33).[55]



Scheme 33. Synthesis of ephedrine derived chiral auxiliary **132**.

Benzaldehyde *O*-methyl oxime **77a** was again chosen as the test substrate and allowed to react with the acylated auxiliary **132** under standard azetine reaction conditions (Scheme 34). Initial experiments at the 1 mmol scale returned a 1.6:1 separable mixture of *cis* and *trans* azetines (**133a:134a**) in 60% total yield.



Scheme 34. Azetine formation using ephedrine derived auxiliary **132**.

The reaction was subsequently optimized for both yield and diastereoselectivity responses utilizing a design of experiments approach. A randomized 3 factor, 2 level

design evaluating possible time, temperature, and concentration effects was used which required a total of 8 experimental runs (Table 4). Yield and selectivity response data points were derived from the isolated samples following column chromatography of the reaction mixture at the 0.5 mmol scale.

Table 4. Experimental design and raw data for optimization study.

run #	A: concentration (M) +/- = 0.10/0.01	B: temperature (^{o}C) +/- = 23/0	C: time (h) +/- = 24/1	total azetine yield (%)	diastereomeric ratio (*cis/trans*)
1	+	+	+	35	1.8
2	+	-	+	38	1.8
3	-	+	-	38	2.7
4	+	+	-	23	1.7
5	-	-	-	23	4.6
6	-	-	+	50	2.0
7	-	+	+	65	1.9
8	+	-	-	18	1.7

None of the selected factors were shown to affect diastereomeric ratio, but both time and concentration proved to be significant with respect to overall yield (Figure 5).[56] These results translated to an experimentally manageable concentration of 0.03 M and an increased reaction time of at least 24 h. The favorable effect of a lowered concentration on yield may arise from minimizing the heterogeneity of the reaction mixture, which would in turn increase the reactive surface area of the chlorotitanium enolate complex. Another notable outcome of this study was that the reaction mixtures were now allowed to warm to ambient temperature after initial oxime addition, thus eliminating the need for prolonged temperature management.

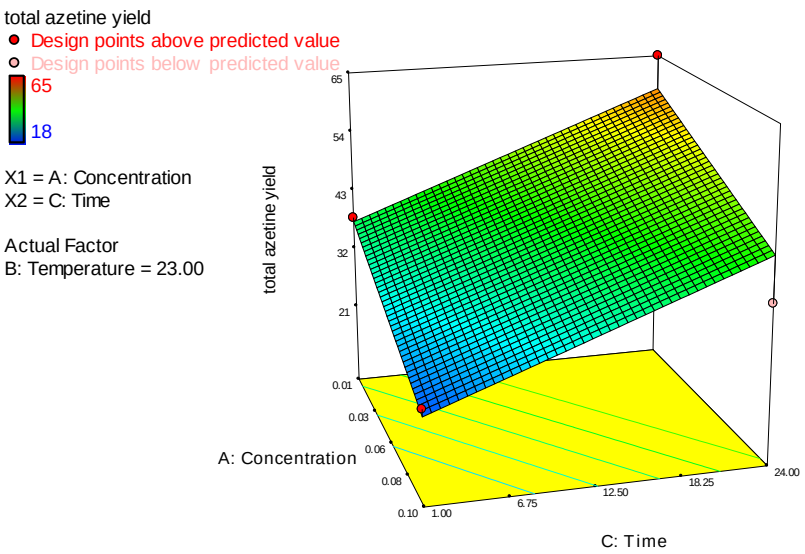
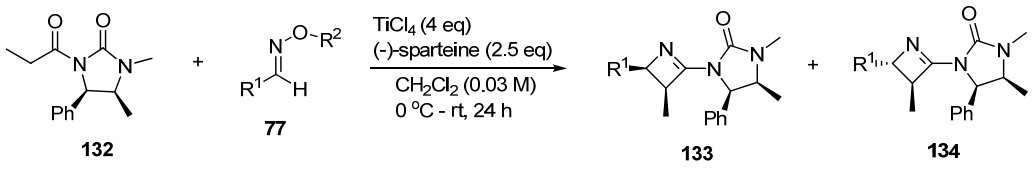


Figure 5. Randomized 3 factor/2 level optimization study results: response surface plot for total azetine yield.

These conditions were applied at gram scale across a range of both enolizable and non-enolizable oximes to afford azetine products in good yields (Scheme 35). Oximes were prepared as either the *O*-methyl or *O*-benzyl derivative, depending on the stability of the substrate. Azetine yields were generally improved by 10-25% when compared to those obtained with the unoptimized conditions and were in all cases greater than those achievable using any of the previously tested auxiliaries (Table 5).



Scheme 35. Preparation of azetines from auxiliary **132** under optimized conditions.

Table 5. Gram scale additions of oxime **77** to ephedrine derived auxiliary **132**.

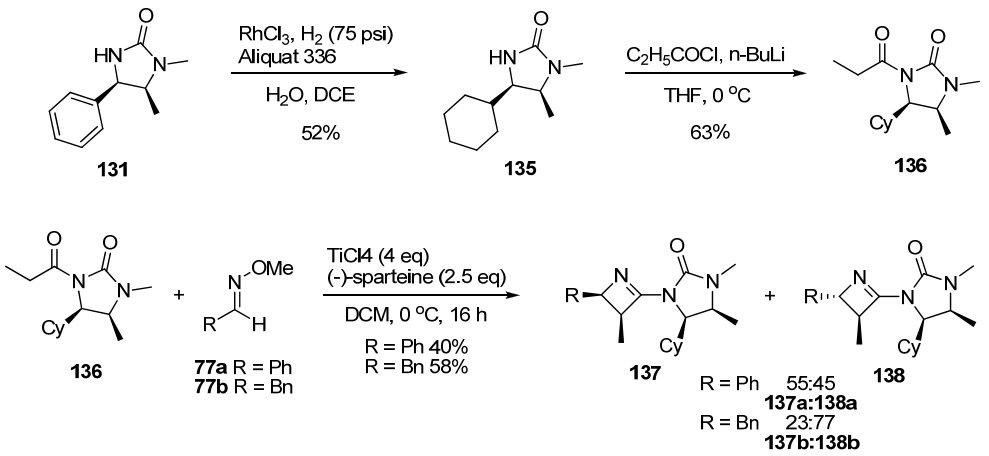
entry	oxime (R^1, R^2)	yield % **77**	total azetine yield % ***initial***	total azetine yield % ***optimized***	dr[a] *cis:trans* **133:134**
1	**77a** (Ph, Me)	84	61	69	64:36 **133a:134a**
2	**77b** (Bn, Me)	62	70	77	29:71 **133b:134b**
3	**77c** (*c*-Hex, Bn)	82	57	72	36:64 **133c:134c**
4	**77d** ( , Bn)	86	n/a	61	43:57 **133d:134d**
5	**77e** ( , Bn)	86	20	64	54:46 **133e:134e**
6	**77f** ( , Bn)	86	n/a	62	38:62 **133f:134f**

[a] Diastereomeric ratios determined from ^{1}H NMR spectra for crude reaction mixtures

We were however surprised to find a mixture of *cis*:*trans* selectivity among the different cases. The *E/Z* ratio of the oxime mixture was not shown to have any influence on selectivity as the isomers of oxime **77a** that were completely separated by careful preparative HPLC both produced the same reaction outcome. No trend appears to exist between the *E/Z* ratio of a given oxime with the resulting *cis/trans* azetine product ratio from that oxime mixture either. The choice of *O*-alkyl group also did not appear to play a role in selectivity as both *O*-Me and *O*-Bn oxime derivatives prepared from benzaldehyde

and reacted with auxiliary **132** gave equivalent results with respect to yield and *cis/trans* azetine ratio.

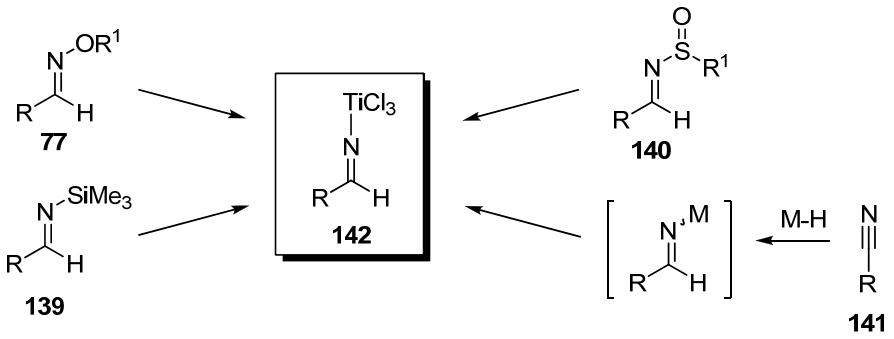
The ephedrine derived imidazolidinone substrate **131** was hydrogenated to afford the more hindered cyclohexyl derivative **135** that was then acylated to give auxiliary **136** (Scheme 36).[57] Reaction outcomes followed similar trends as with auxiliary **132**, with the phenyl oxime **77a** giving *cis* preferential azetine products and the benzyl oxime **77b** favoring the *trans* azetine. No significant improvement in selectivity was observed due to the more bulky directing group however, and yields were also reduced.



Scheme 36. Synthesis and azetine reactions of cyclohexyl auxiliary **136**.

The generation of azetines has been shown to arise from the reaction of chlorotitanium enolates with various other substrates in addition to oximes, such as silylimines[58] and sulfinimines.[59] Silylimines (**139**, Scheme 37) have been demonstrated to readily convert to the titanium imine in the presence of $TiCl_4$. In the case of sulfinimines (**140**), the chirality of the sulfininimine was shown to have no effect on the stereochemical outcome of the reaction. Taken together with the reactivity trends observed among the oximes, the

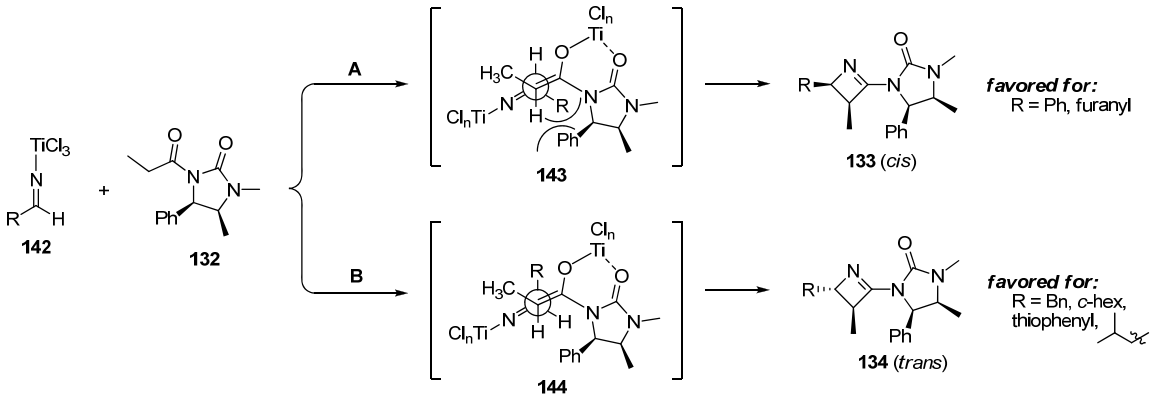
results imply the likely role of a common intermediate such as the titanium imine species **142**. This hypothesis was further substantiated by the successful synthesis of azetines utilizing an imine equivalent as prepared by the hydrometallation of a nitrile (**141**) and subsequent transmetallation with $TiCl_4$.[60]



Scheme 37. Titanium imine **142** as a common intermediate for azetine synthesis.

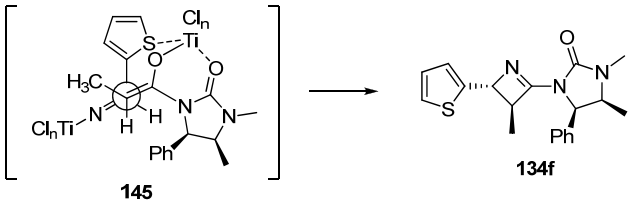
The existence of two or more competing transition states is implied by the fact that even as the observed *cis/trans* azetine ratios were consistent across experimental runs with each oxime, none of the diastereomeric ratios was particularly high (Scheme 38). The generation of a *Z*-enolate under the given conditions is assumed due to extensive literature precedents to that effect.[61] An open transition state can be postulated to exist given the presence of an excess of titanium tetrachloride in the reaction mixture.[28] An open conformation, as depicted in structures **143** and **144**, also minimizes dipole-dipole repulsions between the enolate C=C and imine C=N bonds. Oximes with smaller substituents, such as a phenyl group, may favor transition state **143** leading to the *cis* azetine **133** in order to minimize gauche interactions between the imine substituent and the methyl group of the enolate. Conversely, oximes bearing relatively larger

substituents, such as a benzyl, cyclohexyl, or 2-methylpropanyl group, are generally biased towards the formation of *trans* azetines. In these cases, a transition state such as **144**, where the oxime R group is oriented in order to minimize interactions with the imidazolidinone ring, may be favored.



Scheme 38. Hypothesized open transition states leading to azetines **133** and **134**.

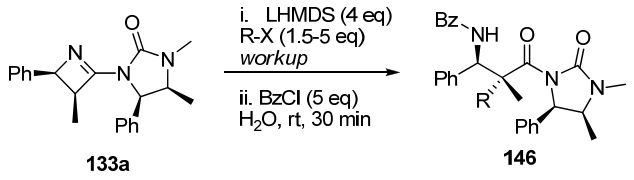
The difference in favored selectivity observed for the similarly sized furanyl (*cis/trans* = 54:46) and thiophenyl (*cis/trans* = 38:62) groups may be rationized by considering the potential interaction of the heteroatom of the substituent heterocycle with titanium. Fowles has reported that 1,4-thioxane preferentially coordinates with titanium tetrachloride through sulfur, rather than oxygen.[62] If operating through transition state **145 (**Scheme 39), the thiophenyl ring would conceivably be in a position to coordinate to titanium through its sulfur atom, which would lead to the *trans* substituted azetine. It should again be noted however that the modest diastereoselectivity observed in this case and others implies that a number of energetically similar transition states are likely operating simultaneously.



Scheme 39. Hypothesized transition state leading to *trans* thiophenyl azetine **134f**.

2.3 Azetine Alkylation Reactions with Imidazolidinone Auxiliary

It remained to be shown whether the imidazolidinone auxiliary bearing azetines could be successfully functionalized as originally intended. Initial alkylation experiments using *cis* substituted azetine **133a** revealed lithium hexamethyldisilazide to be the optimum base for azetine enolate formation (Scheme 40). Reactions were carried out in THF at 0 °C with 1.5-5 equivalents of alkyl halide and quenched with aqueous 1 N HCl after 1 h. Although the reactions appeared to be nearing completion as determined by TLC, isolated yields were lower than expected following chromatographic purification. The crude product from the alkylation step was therefore carried on to subsequent hydrolytic ring opening of the azetine without intermediate purification. Treatment with excess benzoyl chloride, followed by aqueous work-up, afforded access to a number of geminally disubstituted $\beta^{2,2,3}$-amino carbonyl derivatives in good yield (Table 6). Based on analysis of the ^{1}H NMR spectra, *all products were determined to have been formed as a single diastereomer.*



Scheme 40. Alkylation/ring opening of **133a** to give $\beta^{2,2,3}$-amino carbonyl derivatives.

Table 6. Alkylation of α-substituted azetines and hydrolysis to β-amino acid derivatives.

entry	R-X	product	**146** yield % (two steps)	diastereomeric ratio
1	benzyl bromide	**146a**	69	> 95:5
2	iodoethane	**146b**	63	> 95:5
3	iodopropane	**146c**	70	> 95:5
4	iodobutane	**146d**	51	> 95:5
5	allyl iodide	**146e**	71	> 95:5
6	1-iodo-2-methylpropane	**146f**	66	> 95:5

The absolute configuration at the quaternary center of addition product **146f** was determined from its X-ray crystal structure (Figure 6). Given the uniform isolation of a single diastereomer across products **146a** – **146f**, it is assumed that the same absolute configuration is formed for all β[2,2,3]-amino carbonyl derivatives.

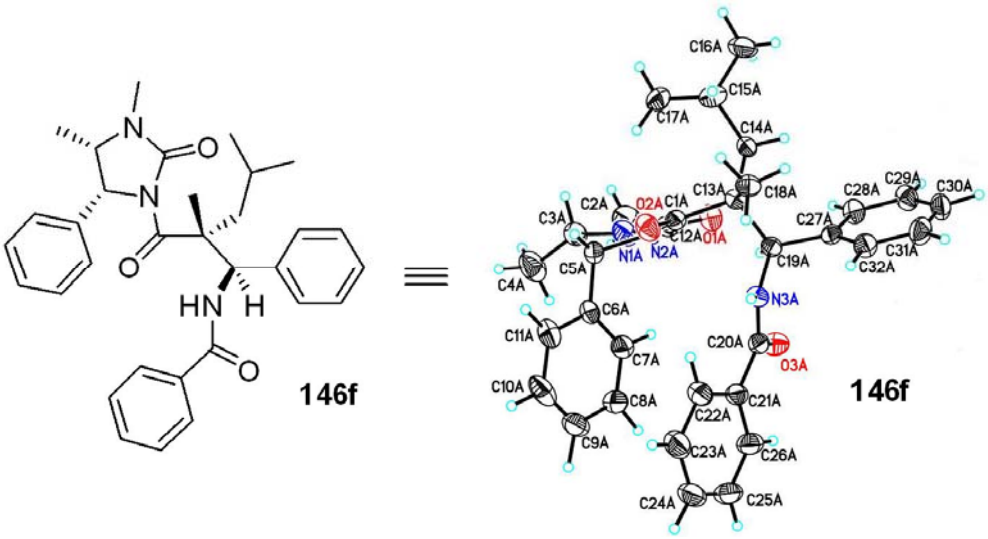


Figure 6. Crystal structure for alkylation addition product **146f.**

The observed stereochemistry is consistent with attack of the electrophile as directed by the mutually reinforcing orientation of azetine phenyl and auxiliary phenyl groups assumed to exist within a chelated transition state (Figure 7).

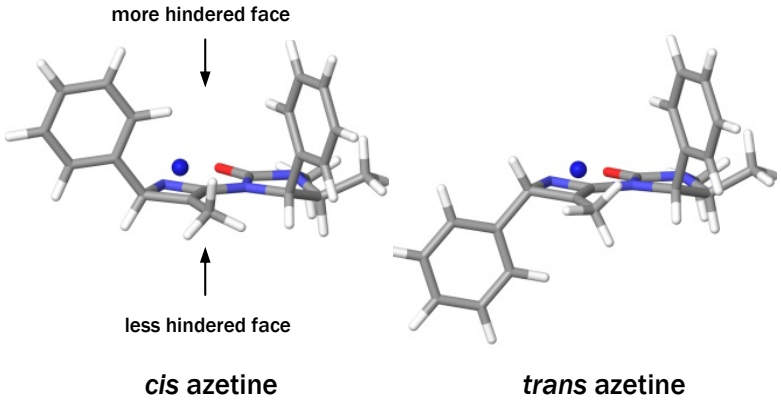
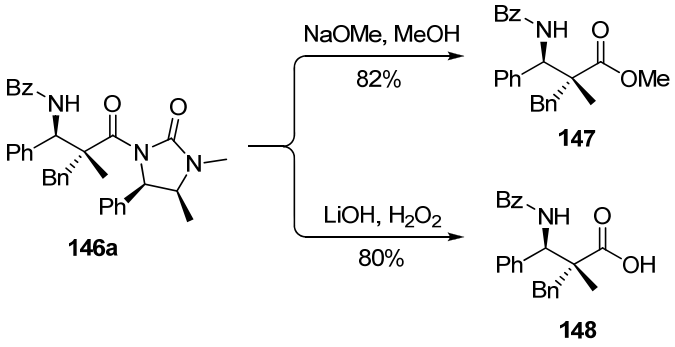


Figure 7. Substituent directed approach of electrophile to hypothesized azetine transition state.

The developed alkylation/ring opening conditions were also applied to the *trans* substituted azetine **134a** but the reaction proceeded with only modest yield and selectivity (28%, dr 2:1 for the benzyl bromide adduct). This result may be attributable to the now mutually opposing phenyl directing groups present within the hypothesized transition state.

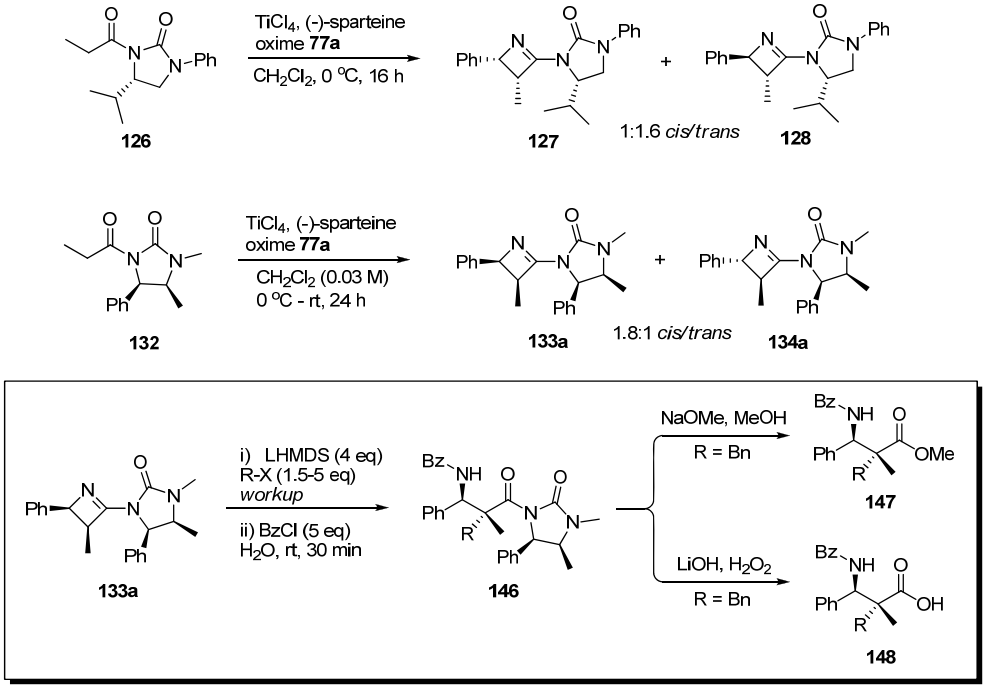
Finally, removal of the chiral auxiliary was demonstrated for compound **146a**, from which both the methyl ester **147** and acid **148** were obtained in good yield (Scheme 41).



Scheme 41. Auxiliary cleavage to access $\beta^{2,2,3}$-amino acid and ester derivatives.

3. Conclusion

In summary, imidazolidinone based chiral auxiliaries have been found to be effective in eliminating the appearance of the pyrimidinone side product as encountered under previously reported conditions for azetine formation. Imidazolidinone auxiliaries allow access to all four possible azetine diastereomers in better yield than has been possible using other traditional auxiliaries. Specific use of the ephedrine derived imidazolidinone auxiliary **132**, in combination with optimized reaction conditions, resulted in improved accessibility to the azetine substrates at gram scale. The further utility of *cis* substituted azetine **133a** as a substrate for stereoselective alkylation demonstrates what we believe to be a uniquely practical method for the diastereoselective synthesis of $\beta^{2,2,3}$-amino acid derivatives with potentially wide ranging scope and application.



Scheme 42. Imidazolidinone auxiliaries for the synthesis of azetines and $\beta^{2,2,3}$-amino acid derivatives.

Part 2: Natural and Enantiomeric Progesterone Analogues for the Treatment of Traumatic Brain Injury

1. Introduction and Background

1.1 Traumatic Brain Injury: Incidence and Approaches to Treatment

Traumatic brain injury (TBI) is a significant public health problem that affects nearly 1.5 million Americans each year, resulting in approximately 235,000 hospitalizations, 80,000 cases of long term disability, and 50,000 deaths.[63] An estimated 5.3 million Americans currently require long-term assistance in performing basic activities of daily living as the result of having suffered a TBI.[64] Care related costs for the treatment of TBI patients has been estimated to total nearly $60 billion annually in the United States.[65] In addition, a recent comprehensive study of Iraq and Afghanistan war veterans reports that 19% of those surveyed had suffered a TBI, making it one of the so-called "signature injuries" found among soldiers returning from duty.[66]

Despite several decades of effort from the scientific community, no single pharmacological agent or treatment protocol has been found that results in consistently improved outcomes following TBI.[67] A recent meta-analysis of studies evaluating the effectiveness of five experimental treatments for TBI (hyperventilation, mannitol, CSF drainage, barbiturates, and corticosteroids) showed that none of the interventions reliably reduced death or disability (Figure 1).[68] The Corticosteroids After Significant Head Injury (CRASH) trial, which originally sought to utilize a population group of 20,000, was terminated at just over 10,000 subjects as it became clear that the treatment group (0.4 g methylprednisolone per h for 48 h) had a higher mortality rate than that of the control group.[69] Continuous infusions of magnesium were also not shown to achieve

neuroprotection following moderate or severe TBI.[70] Hypothermia has shown some favorable effects among brain injured patients.[71] However, clinical results using hypothermia have been variable and the treatment is thought to be potentially harmful to patients over the age of 45.[72] The current Guidelines for the Treatment of Severe Traumatic Brain Injury issued from the Brain Trauma Foundation recommend little beyond medical stabilization of peripheral injuries, surgical intervention if necessary, maintenance of adequate oxygen supply and blood flow, and controlling blood pressure.[73]

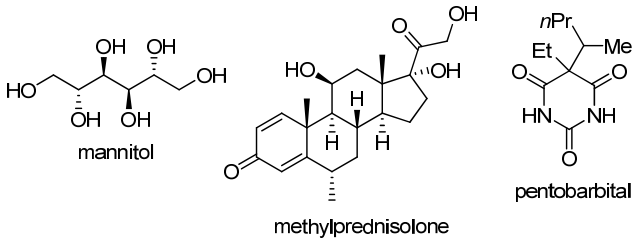


Figure 1. Clinically studied compounds with negligible effects for the treatment of TBI.

1.2 Progesterone as Neuroprotectant

1.2.1 Pre-Clinical Evidence

A growing body of evidence indicates that progesterone may be a promising alternative therapeutic candidate for the treatment of traumatic brain injury. It was first observed by Stein and co-workers that female rats appeared to recover more quickly than males following injury to the brain.[74] In order to more closely investigate the nature of this association, a study was designed using three groups of rats: males, females in proestrus (when estrogen levels are high but progesterone is at its lowest level), and pseudopregnant females (progesterone levels at their most elevated).[75] After injury to the frontal cortex, brain samples were excised from both injured and non-injured sections of

the brains and wet to dry weights were compared to measure relative cerebral edema levels. As it is known that the increased intracranial pressure from cerebral edema can cause neuronal cell death, this assay was used as a predictive model of therapeutic outcome. The study found that proestrus females had somewhat less edema than males, but most notably, the pseudopregnant females, the group with the highest level of progesterone, developed almost no post-injury cerebral edema (Figure 2).

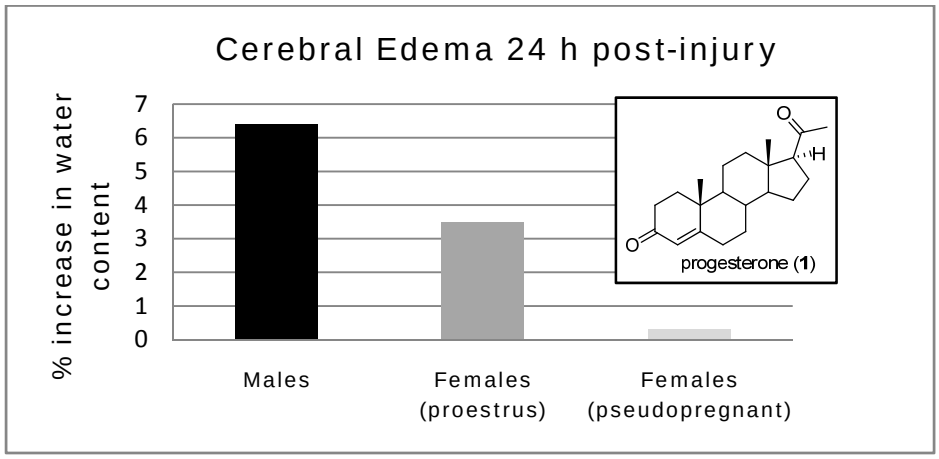


Figure 2. Initial findings correlate progesterone levels to reduction in cerebral edema.

Additional animal studies have shown that exogenous treatment with progesterone is also effective in reducing cerebral edema after injury, regardless of sex.[76] When animals were dosed (4 mg/kg) with progesterone at 1, 6, 24, and 48 hours following injury, it was found that both male and female treatment animals had significantly reduced levels of cerebral edema relative to controls. The treated animals also showed significantly smaller brain lesions and less secondary neuronal loss in the thalamus.[77]

In order to determine how quickly cerebral edema develops and the time frame necessary to provide therapeutic intervention, another study was run which monitored

edema levels of injured rats over the course of one week.[78] Edema was found to develop in rats within 2 h of injury, reaching its peak levels at 24 h, and decreasing gradually over 7 days. The most significant reductions in edema were achieved when treatment was initiated within 2 h of injury. Progesterone given 1 h following injury reduced edema levels at 3 days post injury to what would normally be observed in untreated animals at 7 days post injury. It was also shown that reduction of edema could be achieved with even up to a 24 hour treatment delay.

A direct correlation between serum progesterone levels and reduction in cerebral edema was established by Wright and co-workers using male rats.[79] Further investigation into the appropriate therapeutic window revealed an inverse U-shaped dose-response curve to exist, with an 8-16 mg/kg dosing level (7 injections over 5 days) providing the most benefit, as determined by behavioral functioning measures such as performance on the Morris water maze test.[80] It was also found that a tapered reduction in progesterone dosing following injury provided greater benefit than acute withdrawal.[81] Abrupt withdrawal from progesterone was associated with greater levels of anxiety and higher levels of inflammatory factors and tissue markers of apoptosis such as tumor necrosis factor alpha (TNFα) and nuclear factor kappa B (NFκB).

1.2.2 Neuroprotective Mechanisms of Progesterone

Progesterone is an endogenous steroid produced by the adrenal glands and the corpus luteum, as well as by neurons and glial cells within the central and peripheral nervous systems.[82] It is normally present in both men and women in small amounts but is up-regulated during pregnancy in order to support the growing fetus. Just as progesterone

has been associated with a variety of protective roles during gestation, it has also been linked to several different but mutually supportive modes of neuroprotection following traumatic brain injury. These roles can be separated into the following general mechanisms:

Attenuation of cerebral edema

Brain swelling is thought to account for a substantial proportion of the loss in function and/or death resulting from TBI.[83] There are two primary types of cerebral edema. Vasogenic edema is characterized by a disruption of the blood brain barrier (BBB) which allows plasma fluid to enter the brain parenchyma, leading to increased intracranial pressure and neuronal cell death. Cytotoxic edema refers to the accumulation of fluid inside neurons. This type of edema causes cells to release toxic agents into the brain parenchyma, which then initiates a cycle of secondary cell death.[84]

Progesterone has been shown to reduce vasogenic edema through stabilization of the BBB.[85] Such stabilization may be achieved through a number of mechanisms, including the minimization of lipid peroxidation and free radical generation, as well as anti-inflammatory effects, both of which will be discussed separately in following sections.

The mechanism of water removal by progesterone, which is important to both vasogenic and cytotoxic edema, is not fully understood but one study has examined the membrane progesterone binding protein 25-Dx, which is abundant in regions of the brain proximal to cerebrospinal fluid, including in areas of the hypothalamus associated with osmoregulation.[86] Following TBI, it was found that 25-Dx expression is increased in

these areas. The investigators also noted that 25-Dx is co-expressed with vasopressin, an important regulator of water permeability at the cellular level.

An interaction between progesterone and aquaporins (AQP), a class of channel membrane proteins associated with water retention, has also been discovered.[87] AQP-4 is located in astrocytes and microglia and can act as an osmosensor to control water drainage into the ventricles of the brain. Knock-out mice deficient in AQP-4 were shown to have much greater survival than wild-type mice in a model of cerebral edema caused by water intoxication.[88] Following cortical TBI, progesterone treated rats were found to have lowered expression of AQP-4 around the site of injury when compared to control group animals, as well as significantly decreased levels of edema.

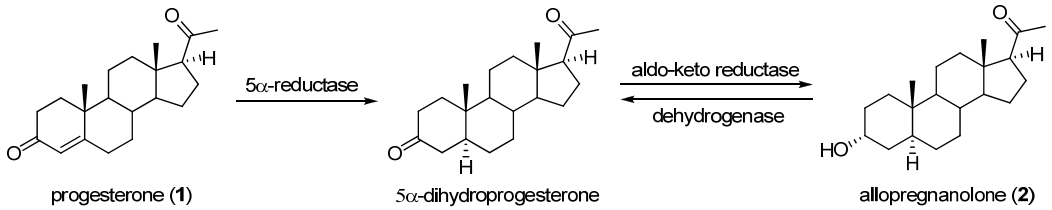
Reduction of lipid peroxidation and oxidative stress

Several studies have shown that progesterone is effective in reducing free radical damage. Lipid peroxidation, the process by which lipids are oxidatively degraded by free radicals, has been shown to be reduced in an *in vitro* system through treatment with progesterone in a dose-dependent manner,[89] as well as following traumatic brain injury in a whole animal rat study.[90] Administration of progesterone appears to achieve reductions in oxidative stress through a number of complementary actions, such as increasing levels of mitochondrial glutathione, a critical free radical scavenger,[91] down-regulating injury-induced increases in manganese superoxide dismutase,[92] and decreasing the amounts of nitrite, superoxide, and hydrogen peroxide generated by macrophages in response to cytokines.[93] In addition, lowered levels of 8-isoprostane, a vasoconstrictive free radical

generated prostaglandin, were found among rats given progesterone following cortical contusion relative to untreated controls.[94]

Anti-inflammatory effects

Cytokines are a category of signaling proteins that act as potent initiators of the inflammatory process. TBI is known to produce a significant inflammatory response resulting in heavy gliosis proximal to the area of injury.[95] Glial scarring of this type is believed to be another significant contributor to lowered functional outcomes following severe TBI. Progesterone treatment was shown to significantly reduce levels of the inflammatory factors C3 complement and NFκB in frontal cortex contused male rats.[96] Both progesterone and its natural metabolite allopregnanolone (**2**, Scheme 1) have been found to reduce expression of the pro-inflammatory cytokines interleukin 1beta (IL-1β) and TNFα.[97] Disruption of the BBB and subsequent increases in vasogenic edema have been associated with increased cerebral concentration of both IL-1β[98] and TNFα.[99] Progesterone and allopregnanolone have also been reported to enhance expression of the cell surface protein CD55, which is involved in the inhibition of the inflammatory cascade.[100]



Scheme 1. Enzymatic conversion of progesterone (**1**) to allopregnanolone (**2**).

Reduction of cellular apoptosis

Both progesterone and allopregnanolone reduced expression of the pro-apoptotic proteins caspase-3 and Bax, as well as the level of apoptotic DNA fragmentation, within one day of treatment following bilateral contusions of the frontal cortex in male rats.[101] Progesterone treatment was also correlated with up-regulation of the *anti*-apoptotic proteins bcl-2 and ERK.[102] Bcl-2 is believed to play a role in preventing the release of cytochrome c from mitochondria. An increase in bcl-2 expression would therefore result in the prevention of cytochrome c from binding to and subsequently activating caspase-3, a pathway known to lead to apoptosis and neuronal cell death.

Inhibition of excitotoxicity

Several reports have illustrated the role of progesterone in up-regulating gamma aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.[103] An increase in circulating GABA can in turn decrease injury-induced excitotoxicity caused by the release of excitatory neurotransmitters such as glutamate.[104]

Assisting in myelin repair

The production of myelin, a protective insulator of neuronal axons, is disturbed by injury. Demyelination is a significant component of several neurodegenerative diseases, including multiple sclerosis, that are characterized by the disruption of proper neuronal signaling. Progesterone was shown to accelerate the formation of myelin sheaths in co-cultures of neurons and myelin generating Schwann cells, though the nature of this interaction is yet to clarified.[105] Progesterone has also been shown to promote

myelination by oligodendrocytes in the central nervous system.[106] Separate studies demonstrated the role of progesterone in increasing both the number[107] and degree of branching of cultured oligodendrocytes.[108] Remyelination by oligodendrocytes was found to be promoted by progesterone administration after toxin-induced demyelination in 9-month old rats.[109] This result was considered to be especially significant as rats at this age are known to have greatly reduced capacity to regenerate myelin sheaths.[110]

1.2.3 Clinical Evidence

In light of the promising pre-clinical evidence illustrating the neuroprotective benefits of progesterone, a phase II, randomized, placebo-controlled human clinical trial was initiated in order to evaluate the safety and potential efficacy of intravenous progesterone administration for the treatment of acute traumatic brain injury.[111] The ProTECT (Progesterone for Traumatic brain injury – Experimental Clinical Treatment) trial was conducted at Grady Memorial Hospital in Atlanta, Georgia. The study was limited to 100 adult blunt trauma victims who reached the hospital for evaluation and achieved either personal or proxy consent for participation within 11 hours of initial injury. Patients were separated into two primary groups, either "severe" or "moderate", based on their initial functional assessment using the Glasgow Coma Scale.[112] Treatment group patients were given 0.71 mg/kg/h progesterone for the first hour, followed by 0.5 mg/kg/h for the next 11 hours. Five additional 1 h treatments of 0.5 mg/kg/h at 12 h time intervals over the next 60 h were given, for a total treatment period of 3 days.

Several outcome measures were collected, including duration of coma, duration of post-traumatic amnesia, and mortality within 30 days of injury. In addition, each

surviving participant was evaluated at 30 days post-injury for their functional status, using two different highly validated scoring tools.[113] The study concluded that progesterone administration to brain-injured patients was safe, based on the findings that no "serious adverse events" were noted and that the rates of "adverse events" among treatment and placebo groups were similar. The most significant result from the study however was that *the rate of mortality among severely injured patients treated with progesterone was reduced by over 60% relative to the placebo group* (Table 1).

outcome variables	**initial functional assessment**	**progesterone group** (mean value)	**placebo group** (mean value)
mortality (%)	severe	13.2*	40.0
	moderate	16.7	14.3
amnesia (days)	severe	18.6	12.8
	moderate	10.7	18.3
coma (days)	severe	10.1*	3.9
	moderate	4.1	6.1
disability (score)	severe	10.7*	4.4
	moderate	5.0*	12.7

* denotes statistically significant difference between progesterone and placebo groups.

Table 1. Major findings from Phase II clinical trial of progesterone treatment for TBI.

No significant differences in duration of amnesia were found between groups. The number of days spent in coma and the overall disability ratings among severely injured patients were both found to be significantly higher in the treatment group than the control group. This was reasonably hypothesized to be due to the fact that a greater number of more seriously disabled patients survived among the treatment group relative to the placebo group. The moderately injured patients that received progesterone treatment did show a significant improvement relative to controls in functional ability at 30 days post-

injury. The overall favorable results found from this trial prompted the authors to recommend a larger follow-up study across multiple clinical sites with the suggested implementation of a more rapid initiation of treatment following injury if possible.

1.3 Progesterone as a Drug Candidate

1.3.1 Limitations of Natural Progesterone

Despite the encouraging patient outcomes observed in the clinical trial, the eventual use of progesterone as a therapeutic may be limited due to its poor aqueous solubility. For use in the clinical trial, progesterone had to be solubilized in the carrier Intralipid under temperature controlled conditions through a time consuming process. The resulting formulation is not stable at room temperature for long periods of time and therefore had to be used quickly following its preparation. As the most potentially beneficial administration of progesterone appears to be immediately after injury in what would typically be an emergency situation, a lengthy preparation time for the treatment would be unacceptable.

1.3.2 Novel Progesterone Analogues

Access to a more highly water soluble progesterone analogue that would be amenable to pre-formulation and long-term storage was therefore desired. The target compound would also have to maintain at least the same levels of clinical efficacy as natural progesterone. An approach to the development of novel progesterone derived compounds was designed in order to explore structure-activity relationships (SAR) potentially arising from several different sources (Figure 3).

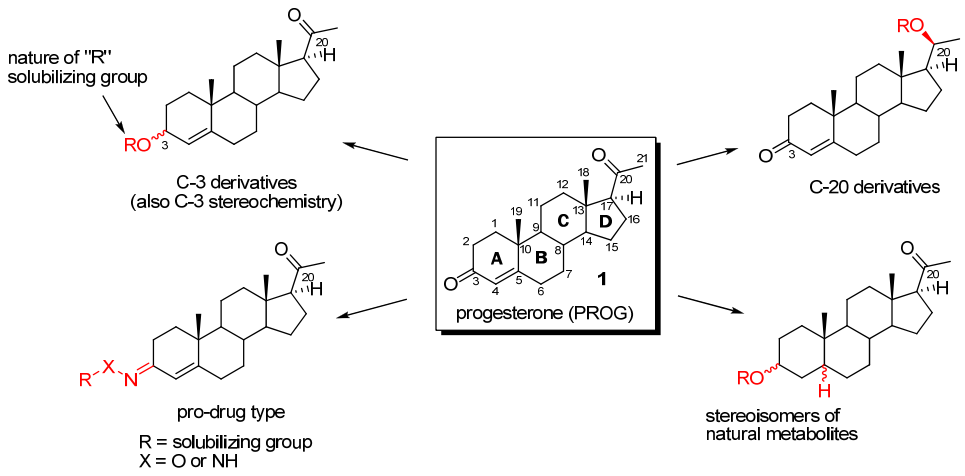


Figure 3. Overview of approach to the development of progesterone analogues.

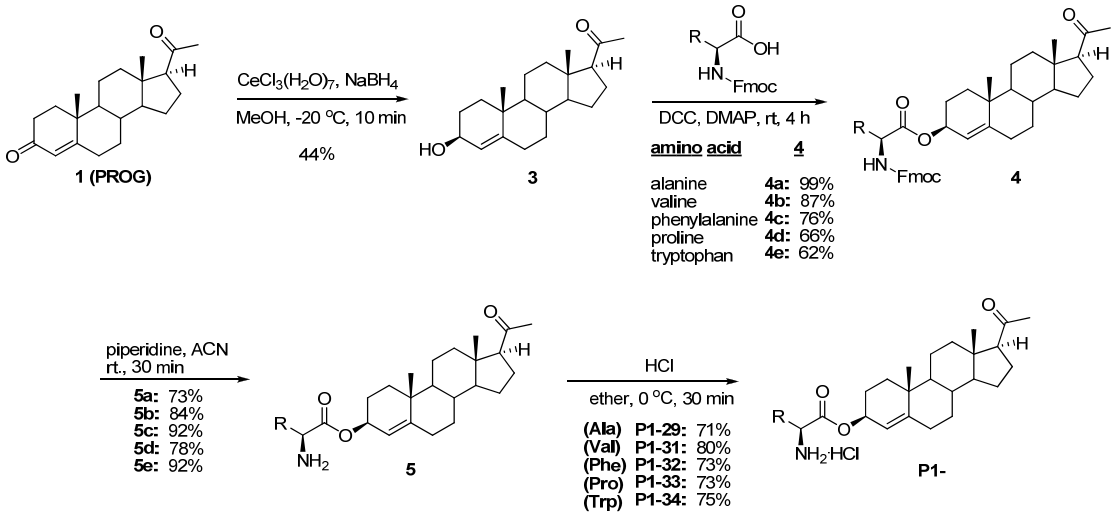
The fundamental strategy chosen to enhance progesterone's water solubility was through the tethering of an amino acid to the compound. Amino acids are non-toxic and provide a good degree of solubilizing capacity via the polarity of their amino group. In addition, if the amino acid - progesterone conjugate were to remain intact in vivo, it might be possible for the compound to take advantage of amino acid active transport proteins that are known to be present within the BBB.[114] Derivatization of progesterone at either the carbon-3 (C-3) or C-20 carbonyl was planned in order to examine the relative effect of such selective modification. The degree of saturation and orientation of substituents on either the alpha (α, below plane of the page) or beta (β, above plane of the page) face was also believed to be of potential importance to the SAR. One final aim of particular priority was to develop a water soluble progesterone prodrug. A prodrug would by definition regenerate progesterone in vivo and would therefore maintain its clinical efficacy.

2. Results and Discussion

2.1 Synthesis of Progesterone Analogue Compounds

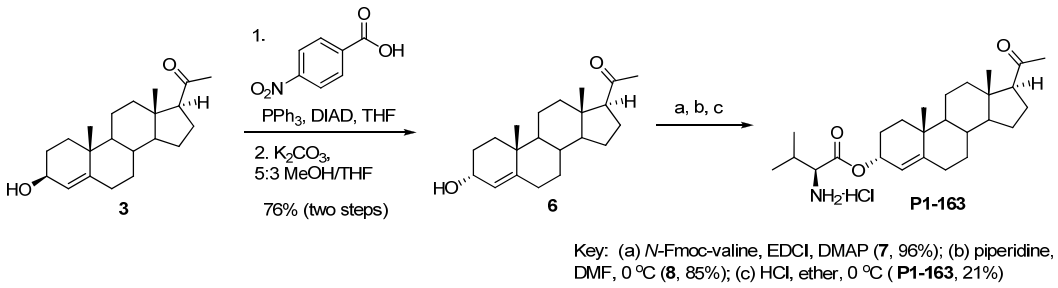
2.1.1 C-3 and C-20 Progesterone Derivatives

Selective reduction of the allylic C-3 carbonyl of progesterone (PROG) was achieved via the method of Luche using cerium trichloride heptahydrate in methanol (Scheme 2).[115] The reaction was run at low temperature and was terminated after only 10 min in order to avoid additional over-reduction of the more sterically hindered C-20 carbonyl. The C-3 reduction product **3** was then coupled with a series of different *N*-Fmoc protected amino acids under standard acid-alcohol coupling conditions using *N,N′*-dicyclohexylcarbodiimide (DCC) in dichloromethane (DCM) with a catalytic amount of 4-di(methylamino)pyridine (DMAP) to give the ester substrates **4a – 4e**. Following ester formation, the Fmoc protecting group was easily removed by treatment with an excess of piperidine in acetonitrile (ACN) to give the free amines **5a – 5e**, which were then prepared as their respective hydrochloride (HCl) salts.



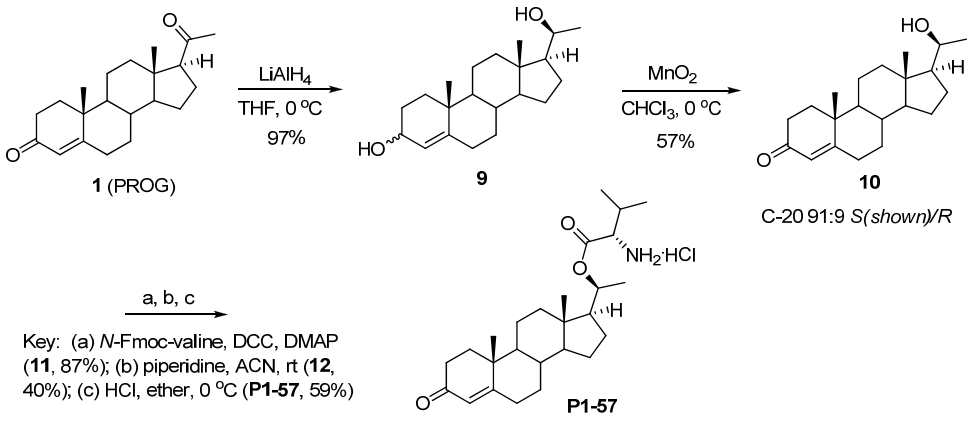
Scheme 2. Preparation of C-3 amino acid tethered PROG analogues.

The 3α-hydroxy Luche reduction product **3** was converted to the 3β-hydroxy isomer (**6**, Scheme 3) through inversion of the stereocenter under Mitsunobu conditions. The PROG-valine derivative of **6** was subsequently prepared through the same coupling, deprotection, and salt formation series of steps as previously employed.



Scheme 3. Synthesis of analogue **P1-163** by Mitsunobu inversion.

Preparation of the C-20 amino acid tethered amino acid analogue **P1-57** began with a total reduction of PROG using lithium aluminum hydride (LAH) to give the di-hydroxyl compound **9**. Allylic oxidation of **9** with MnO_2 gave the C-20 mono-hydroxy derivative **10**, which was then coupled with valine through the same series of steps as had proven successful for the C-3 tethered series of analogues.



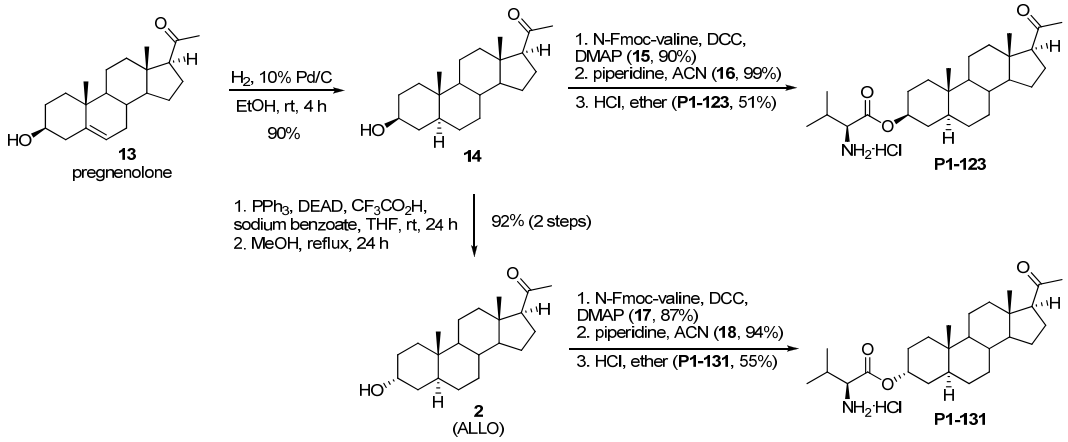
Scheme 4. Preparation of C-20 valine tethered PROG analogue **P1-57**.

2.1.2 Allopregnanolone Series Derivatives

The progesterone metabolite allopregnanolone (ALLO) has shown many of the same neuroprotective benefits afforded by PROG.[116] ALLO achieved the same reduction in levels of the pro-inflammatory cytokines IL-1β and TNF-α among brain-injured rats as that achieved with PROG, but at half the dose (4 mg/kg ALLO versus 8 mg/kg PROG).[97] In light of this finding, and with the knowledge that PROG rapidly metabolizes to ALLO in the brain, it has been hypothesized that the neuroprotective benefits associated with PROG may in fact arise from the actions of ALLO.[117] ALLO is known to have a greater affinity for the $GABA_A$ receptor than PROG.[118] One study has reported that the suppression of neurogenic edema in rat meninges resulting from the administration of ALLO was reversed through subsequent treatment with the $GABA_A$ receptor antagonist bicuculline.[119]

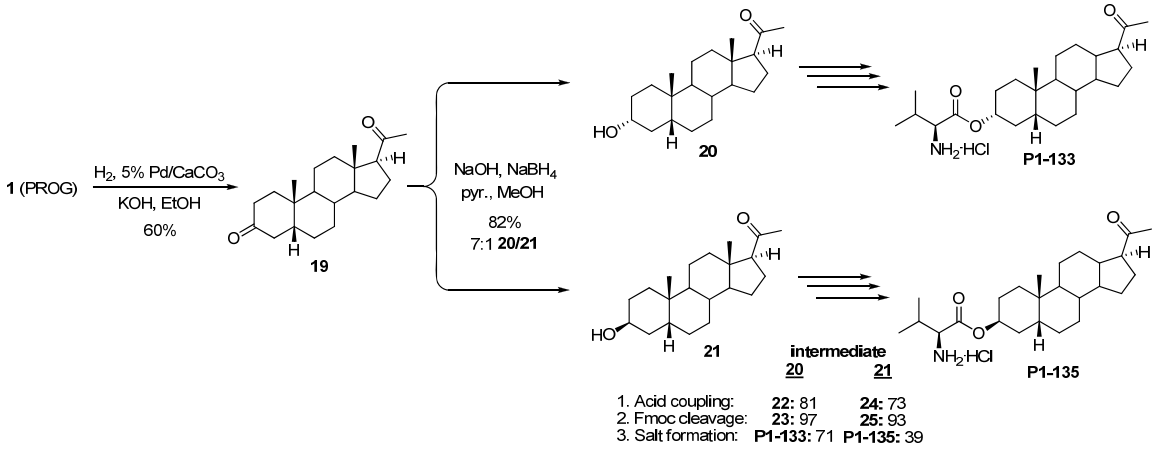
The development of water soluble ALLO derivatives was therefore an additional goal of interest. It was desired to access all four diastereomers resulting from reduction of the PROG A-ring C-4 to C-5 double bond and C-3 carbonyl in order to assess their relative solubilities and potential bioactivity.

Synthesis of epiallopregnanolone (**14**, Scheme 5) was achieved by catalytic reduction of the commercially available steroid pregnenolone (**13**).[120] Amino acid coupling, deprotection, and salt formation proceeded as with previous analogues to give the 3β-5α ALLO isomer derivative **P1-123**. Mitsunobu inversion of the 3β-hydroxy center of **14** gave ALLO (**2**) in good yield.[121] ALLO was then prepared as its valine coupled HCl salt to give the 3α-5α compound **P1-131**.



Scheme 5. Preparation of 5α ALLO isomer derivatives **P1-123** and **P1-131**.

The two 5β ALLO isomers were prepared from PROG (**1**, Scheme 6). Hydrogenation of PROG in the presence of hydroxides is known to provide the 5β reduction product (**19**).[122] Treatment of **19** with $NaBH_4$ in methanol led to selective reduction of the C-3 carbonyl in the presence of the C-20 ketone.[123] The reduction was selective for C-3 but did give a 7:1 mixture of 3α-hydroxy (**20**) to 3β-hydroxy (**21**) products. These compounds were separated by conventional column chromatography and carried forward as in previous series to give the 3α-5β derivative **P1-133** and 3β-5β derivative **P1-135**.

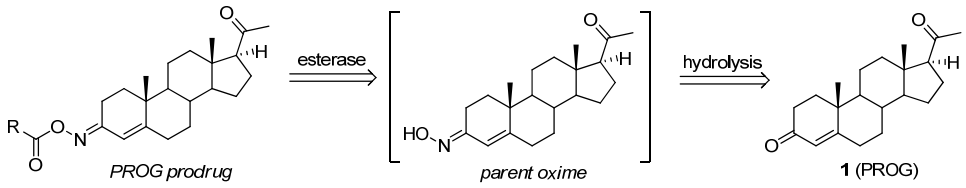


Scheme 6. Preparation of 5β ALLO isomer derivatives **P1-133** and **P1-135**.

2.1.3 Progesterone Prodrug Compounds

Oximes

One strategy taken towards the development of a progesterone prodrug was to utilize an oxime linker between the PROG scaffold and the solubilizing amino acid (Scheme 7). The oxime ester was believed to be readily susceptible to cleavage by endogenous esterases. The oxime moiety itself was also thought to be potentially labile to hydrolysis in vivo, which would subsequently regenerate the known active PROG compound.

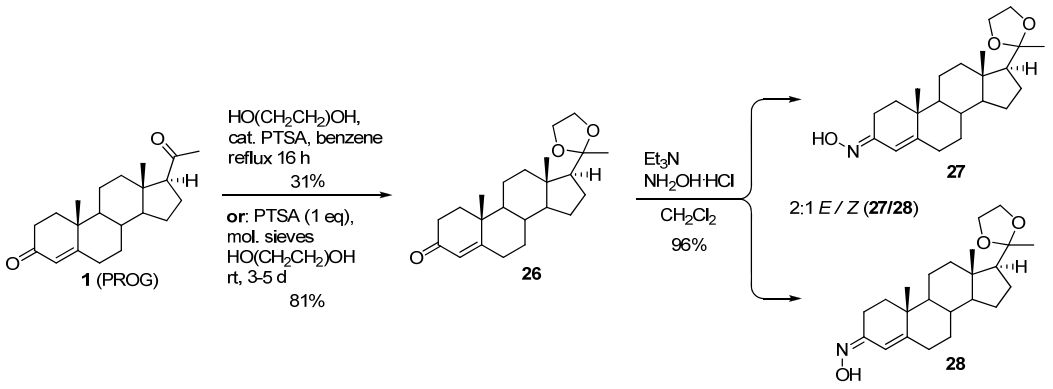


Scheme 7. Hypothetical pathway leading from PROG prodrug to PROG in vivo.

Regioselective oximation of progesterone was desired in order to both minimize alteration to the molecule and to keep the final molecular weight of the compound within the limit of 500, as specified by Lipinski to be associated with the majority of drug-like molecules.[124] As will be presented in a later section, initial biological data implied that alterations to the A-ring of PROG were better tolerated than similar alterations at the D-ring, so a method for selective protection of the C-20 ketone was developed.

Formation of a ketal at C-20 was originally carried out with approximately 15 eq ethylene glycol under catalytic oxalic acid conditions in refluxing benzene.[125] The reaction gives a mixture of C-3 and C-20 mono-ketal products, along with the C-3/C-20 diketal and starting PROG, all in roughly equal quantities. The desired C-20 ketal can be selectively crystallized from this mixture of components and was isolated by this method

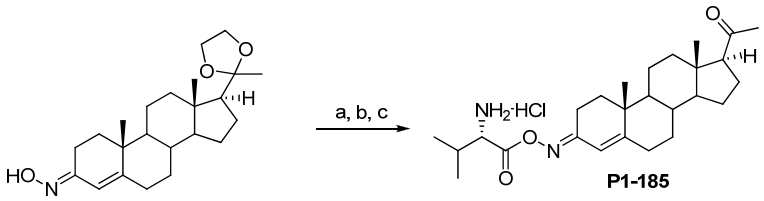
at a maximum of 31% yield (**26**, Scheme 8). An improvement to this strategy was found through application of a procedure developed for selective C-9 ketalization of the Wieland-Miescher ketone[126] which utilizes ethylene glycol as solvent and a stoichiometric amount of *p*-toluenesulfonic acid (PTSA). The reaction with PROG required more time (3-5 d) than for the Wieland-Miescher ketone but nevertheless gave excellent selectivity for ketalization at the C-20 position with much improved yield (81%). The protected steroid **26** was then added to hydroxylamine to afford a 2:1 *E/Z* mixture of oximes **27** and **28** that were separable by conventional chromatography and isolated in excellent yield.



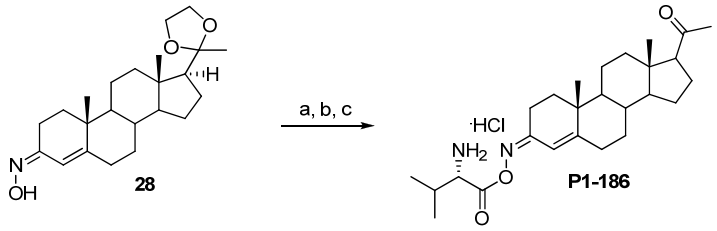
Scheme 8. Selective PROG ketalization and oxime formation.

The oxime products **27** and **28** were each then coupled to *N*-Fmoc protected valine (**29** and **31**, Scheme 9). The ketal was found to be easily removed at this point through treatment with PTSA in acetone. The free amine products resulting from subsequent Fmoc cleavage were however found to be unstable when concentrated at room temperature for any length of time. NMR analysis indicated that the amino acid side chain was being lost to give the C-20 deprotected oxime as the main isolated product. The reaction procedure was therefore modified to incorporate a low temperature workup

and rapid conversion of the free amine products into their HCl salt. This served to eliminate the unintended cleavage of the amino acid side chain. Both the *E* oxime prodrug compound **P1-185** and the *Z* oxime derivative **P1-186** were isolated as white solids in good yield.



Key: (a) *N*-Fmoc-valine, DCC, DMAP (**29**, 99%); (b) PTSA, acetone (**30**, 99%); (c) (**i**) piperidine, ACN, 0 °C; (**ii**) HCl, ether, 0 °C (**P1-185**, 67% from **30**)



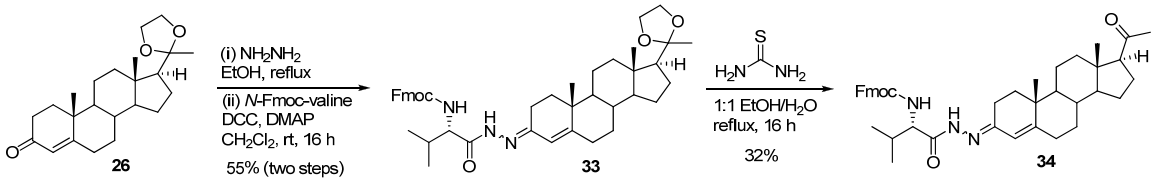
Key: (a) *N*-Fmoc-valine, DCC, DMAP (**31**, 99%); (b) PTSA, acetone (**32**, 89%); (c) (i) piperidine, ACN, 0 °C; (ii) HCl, ether, 0 °C (**P1-186**, 61% from **32**)

Scheme 9. Preparation of oxime based PROG prodrug compounds **P1-185** and **P1-186**.

Hydrazides

A second approach to the generation of PROG in vivo was thought to be through a prodrug incorporating a hydrazine, as opposed to oxime, linker between the steroid and amino acid solubilizing group. The PROG C-20 ketal **26** was first condensed with hydrazine to give the intermediate hydrazone as an inseparable mixture of *E* and *Z* isomers (Scheme 10). As this compound mixture was found to be unstable, in later runs the crude was submitted directly to amino acid coupling following workup, without intermediate purification. The C-20 ketal of compound **33** was found to be resistant to removal under typical PTSA/acetone conditions. After screening several methods,

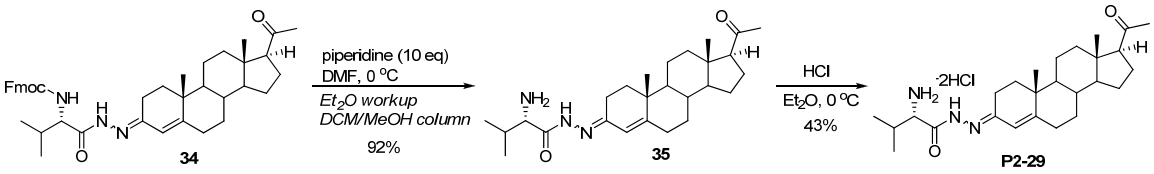
treatment of ketal **33** with thiourea in a 1:1 EtOH/H_2O[127] was found to give the best results for cleavage of the ketal while also maintaining the integrity of the hydrazide system.



Scheme 10. Hydrazide formation and C-20 ketal removal with thiourea.

The next step towards the preparation of a hydrazine based PROG prodrug required cleavage of the Fmoc protecting group from compound **34**. This was initially run using a 5:2 mixture of acetonitrile/DMF with 10 equiv piperidine at room temperature for 30 minutes. The reaction appeared to proceed well, showing a characteristic baseline spot for the free amine by TLC. However, following workup and column chromatography using silica gel, the main products isolated did not correspond with the R_f of the main product seen by TLC within the crude reaction mixture. NMR analysis indicated that the product had incorporated two additional carbons, one being a methyl group appearing as a doublet. The initial hypothesis was that acetonitrile may have become incorporated into the molecule following cleavage of the Fmoc group. The reaction was run again under temperature controlled conditions using only DMF as solvent. However, the same main products were isolated following chromatography. A significant remaining variable not previously considered was the potential role of acetaldehyde, which could be present as an impurity in the ethyl acetate that had been used during both workup and chromatography conditions. The reaction was run again using diethyl ether as the solvent

for workup and a mixture of DCM/MeOH for chromatography (Scheme 11). This time, the desired free amine was recovered in good yield, still as a mixture of *E/Z* isomers, but without the additional carbons. The substrate **35** was then subjected to salt forming conditions which led to the di-HCl salt **P2-29**.



Scheme 11. Fmoc deprotection and completion of hydrazide prodrug **P2-29** synthesis.

An x-ray crystallographic structure later confirmed that the amino acid side chain of **35** had indeed incorporated a two carbon segment following Fmoc deprotection to form an imidazolidin-4-one heterocycle (compound **36**, Figure 4). An imine tethered imidazolidin-4-one such as **36** is not a commonly reported chemical moiety in the literature and therefore further investigation into the extent to which the reaction may be useful could be of interest.

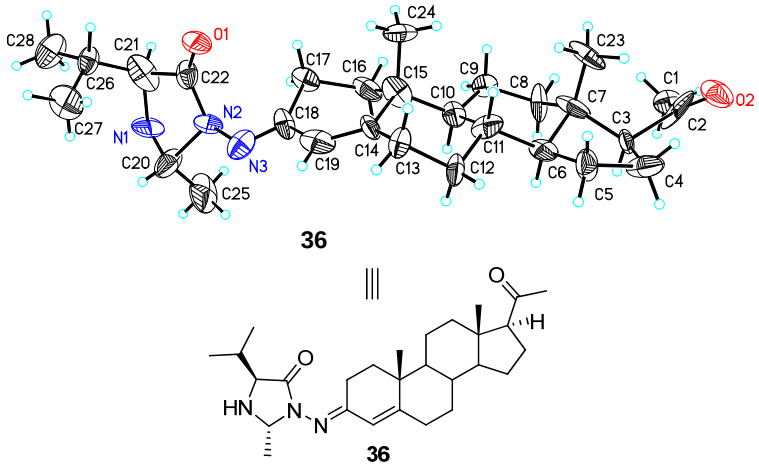


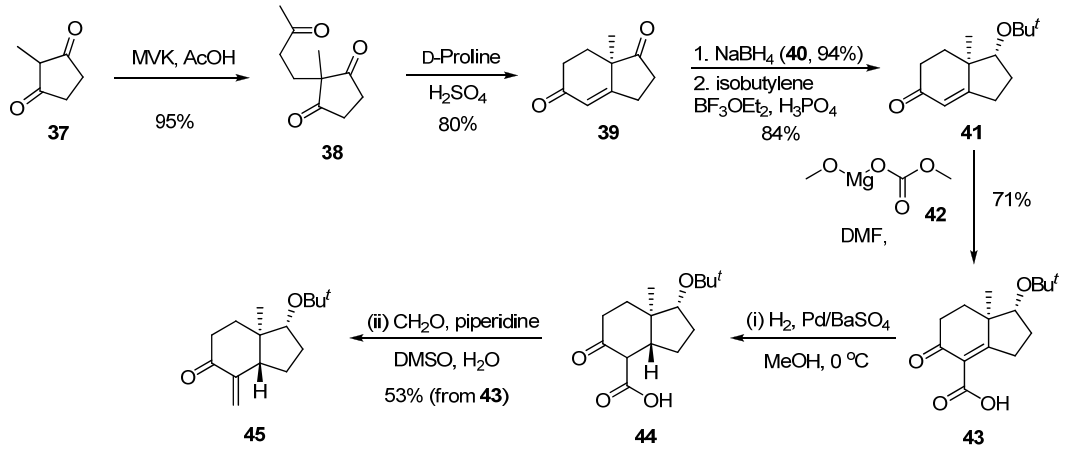
Figure 4. Imidazolidin-4-one tethered PROG derivative **36**.

2.1.4 Enantiomeric Progesterone Compounds

The enantiomer of progesterone (*ent*-PROG) has shown similar efficacy to PROG and ALLO across several measures relevant to neuroprotection, including the reduction of cerebral edema, reduction of pro-inflammatory cytokine expression, and reduction in pro-apoptotic p53 protein expression.[115] *Ent*-PROG treatment was also shown to result in significantly increased glutathione reductase activity, a measure of its potential to minimize oxidative stress following TBI, relative to both PROG and ALLO. Although it binds with moderate affinity to the classical progesterone receptor (PR), *ent*-PROG does not activate PR-mediated gene transcription. Thus it is thought that *ent*-PROG is able to achieve its neuroprotective effects either through transcription-independent PR-mediated signaling or via PR-independent pathways. In light of these findings, and with the goal of providing a compound of improved efficacy relative to PROG or ALLO, the development of a complementary set of *ent*-PROG based analogue compounds was pursued.

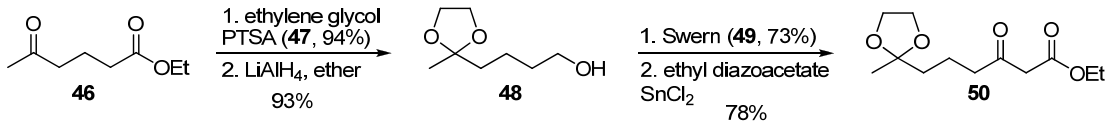
The synthesis of *ent*-PROG closely followed the methods previously described for the preparation of 19-norsteroids[128] as well as the later extensions to this work by Rychnovsky and co-workers in their application to the total synthesis of *ent*-cholesterol.[129] Addition of methyl vinyl ketone (MVK) to 2-methyl-1,3-cyclopentadione (**37**, Scheme 12) gave the triketone **38**.[130] The organocatalyst D-proline was then used in order to achieve asymmetric cyclization of **38** to give the Hajos-Parrish ketone (**39**).[131] Sodium borohydride reduction of **39** was followed by protection of the newly formed secondary alcohol **40** as its *tert*-butyl ether (**41**). Introduction of an α-methylene group was achieved through initial carbonation of **41** with Stiles' reagent, methyl magnesium

carbonate (MMC), in DMF.[132] Selective reduction of the C-4 – C-5 double bond of compound **43** was immediately followed by decarboxylation of the unstable saturated intermediate **44** to give the enone **45** with trans ring junction.



Scheme 12. Synthesis of enone **45**, CD ring fragment of *ent*-PROG.

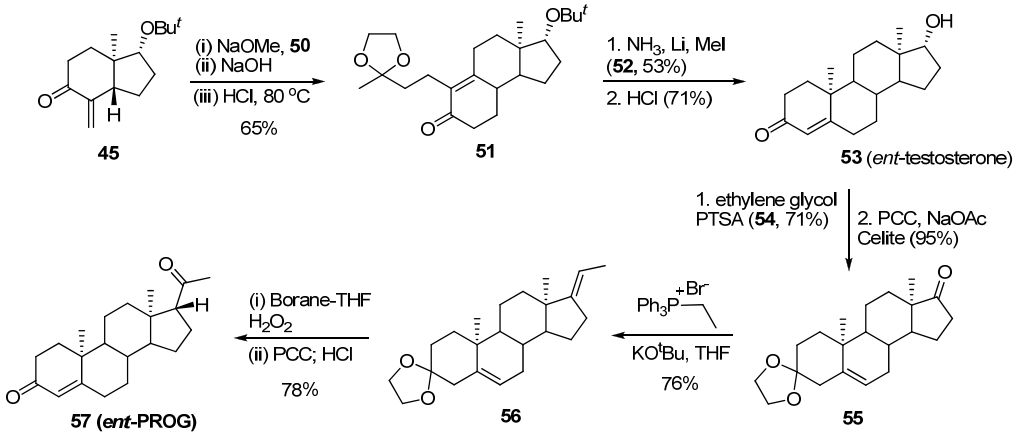
Synthesis of the β-keto ester annulating agent **50** began with ketalization of ethyl-5-oxohexanoate and subsequent reduction of the ester **47** with $LiAlH_4$ to give alcohol **48** (Scheme 13). Swern oxidation of **48** was followed by tin(II) chloride catalyzed coupling with ethyl diazoacetate to give the β-keto ester **50**.[133]



Scheme 13. Preparation of β-keto ester annulating agent **50**.

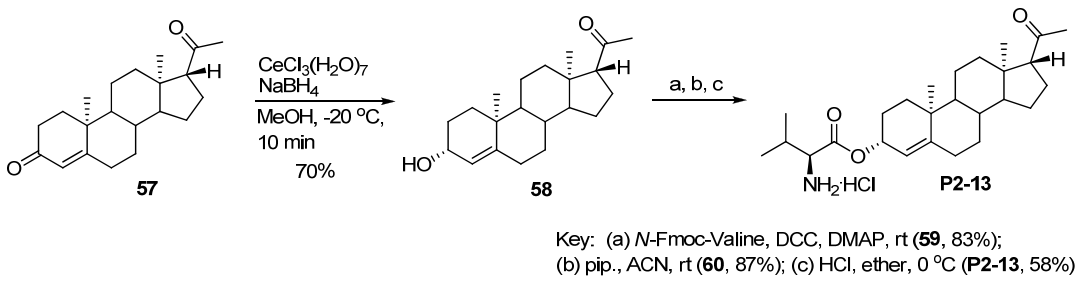
Michael addition of β-keto ester **50** to enone **45**, along with *in situ* Robinson annulation, saponification, and finally decarboxylation, gave the BCD ring system **51**.

Reductive alkylation served to introduce what would become the C-19 methyl group of *ent*-PROG.[134] Reflux of **52** overnight in methanolic HCl gave *ent*-testosterone (**53**). *Ent*-testosterone was then prepared as the C-3 ketal **54** and the C-17 secondary alcohol was oxidized using pyridinium chlorochromate (PCC) to give ketone **55**. Treatment of **55** with ethyltriphenylphosphonium bromide under Wittig conditions gave the alkene **56**. A final three step sequence involving hydroboration, oxidation, and acid catalyzed removal of the ketal was carried out without intermediate purification steps to give *ent*-PROG (**57**) in good yield.[135]



Scheme 14. Completion of *ent*-PROG (**57**) synthesis.

Luche reduction of *ent*-PROG gave the C-3 α-hydroxy compound **58** (Scheme 15). The same series of reactions involving amino acid coupling, Fmoc cleavage, and HCl salt formation that had been developed for the C-3 *nat*-PROG series of compounds was applied here to give the *ent*-PROG derivative **P2-13**. Additional analogues derived from *ent*-PROG will be pursued pending the accumulation of more data regarding possible structure-activity relationships as discovered through the screening of *nat*-PROG derivatives.



Scheme 15. Synthesis of *ent*-PROG derivative **P2-13**.

2.2 Solubility and Biological Testing Data

2.2.1 Solubility Data

Several compounds have thus far been screened for solubility (Figure 5). Solubility testing was done in phosphate buffered saline, which is considered to be a good model system for physiological conditions. Compounds were added in small portions at room temperature with stirring until a visible endpoint of saturation was reached. Neither PROG nor ALLO showed any degree of solubility by this method (designated at < 0.05 mg/mL solubility). The valine coupled C-3-β-hydroxy PROG derivative **P1-31** showed the best solubility (3.85 mg/mL) of the different amino acid substituted analogues within that series. Compound **P1-133**, the 3α-5β ALLO isomer, showed the highest solubility within that group, though this was still fairly low (0.33 mg/mL). Both the *E* and *Z* oxime derivatives **P1-185** and **P1-186** however showed excellent solubility, with values of 13.0 and 15.2 mg/mL respectively. These values far surpass the desired target of at least 1.0 mg/mL which would allow for facile compound formulation in an aqueous based solution.

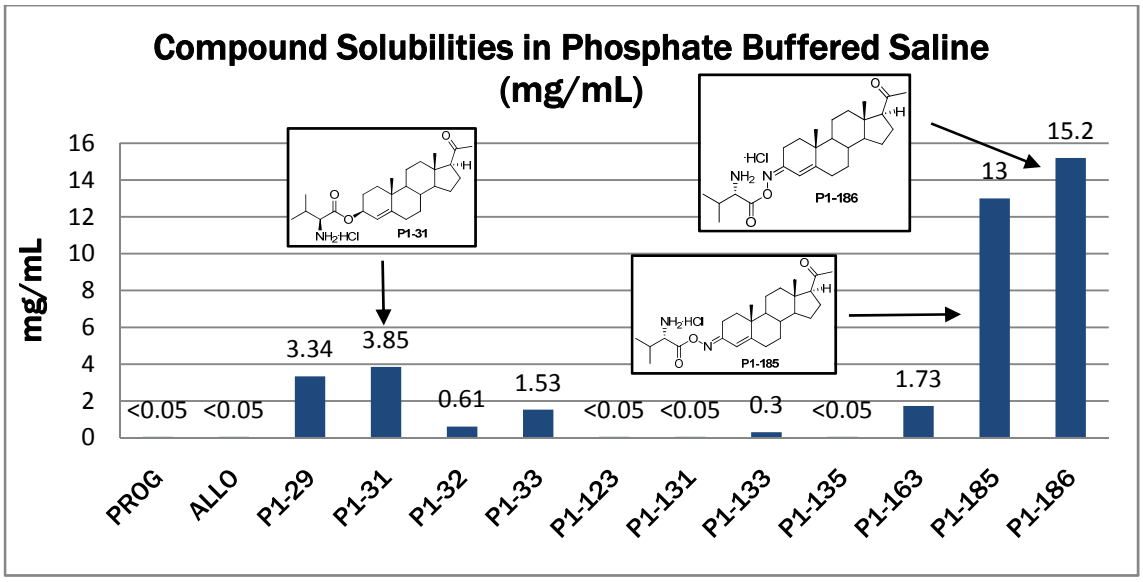


Figure 5. PROG analogue solubilities in phosphate buffered saline.

2.2.2 In Vitro Assay Screening Data

Primary cortical cells were seeded in multi-well plates and cultured for 8 days. Cells were then pre-treated with various concentrations of a different PROG analogue (0.1, 1, 5, 10, 20, 40, and 80 μM) for 24 h. Cells were next exposed to glutamate (0.5μM) for the following 24 h. Cytotoxicity was assessed by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay, which is based on the ability of a mitochondrial dehydrogenase enzyme from viable cells to cleave the tetrazolium rings of the pale yellow MTT. This reaction forms dark blue formazan crystals which are largely impermeable to cell membranes, thus resulting in their accumulation within healthy cells. Solubilization of the cells results in the liberation of the crystals, which are then also solubilized. The number of surviving cells is directly proportional to the level of the formazan product created.

When the concentration of a given test compound is not considered, both PROG and ALLO showed greater protection against cell death than any of the analogues (Table 2). However, several of the derivatives proved to be significantly more potent than PROG or ALLO when all compounds are compared at the 5 μM concentration. The P1-185 and P1-186 oxime prodrug compounds achieved the highest levels of cell survival among the new compounds screened thus far. The C-20 reduced PROG derivative **P1-57** and the *ent*-PROG derivative **P2-13** also showed significant reductions in cell death.

compound	**reduction in cell death** ***best concentration*** (%)	**reduction in cell death** ***at 5 μM*** (%)
PROG	42 (20 μM)	4
ALLO	40 (80 μM)	-3
P1-57	30 (10 μM)	23
P1-185	27 (5 μM)	27
P1-186	34 (5 μM)	34
P2-13	26 (5 μM)	26

Table 2. Reduction in cortical neuron cell death caused by glutamate toxicity.

2.2.3 In Vivo Cerebral Edema Assay Data

A well established whole animal model of TBI was employed in order to investigate the potential efficacy of the PROG analogue compounds relative to PROG in reducing cerebral edema following injury. Anesthetized male rats were first subjected to cortical contusion and were then given two 8 mg/kg doses of the test compound, the first at 1 h post-surgery and the second at 6 h. The animals were then sacrificed and tissue samples were taken from both injured and non-injured sections of the brain. Wet and dry weights were collected for each sample and cerebral edema (% water content) was determined as

the difference in wet and dry weights divided by the wet weight. A "% mean difference" value could then be calculated based on the relative edema difference between injured and non-injured tissue samples for a given animal. The "sham" animals did not receive an injury but served as a control group for possible anesthesia and stress factors. The "vehicle" group were subjected to cortical injury but received only the drug carrier (22.5% 2-hydroxypropyl-β-cyclodextrine in water).

Several of the analogues showed equivalent efficacy to progesterone in the cerebral edema assay, including the valine tethered C-3-β-hydroxy PROG derivative **P1-31** and the oxime based prodrug compound **P1-185**. Compound **P1-131**, the valine coupled derivative of ALLO itself, showed the greatest edema reduction among the ALLO isomer group. Perhaps most notably though was the activity of oxime prodrug **P1-186**, which showed an average reduction in edema levels almost twice that of PROG.

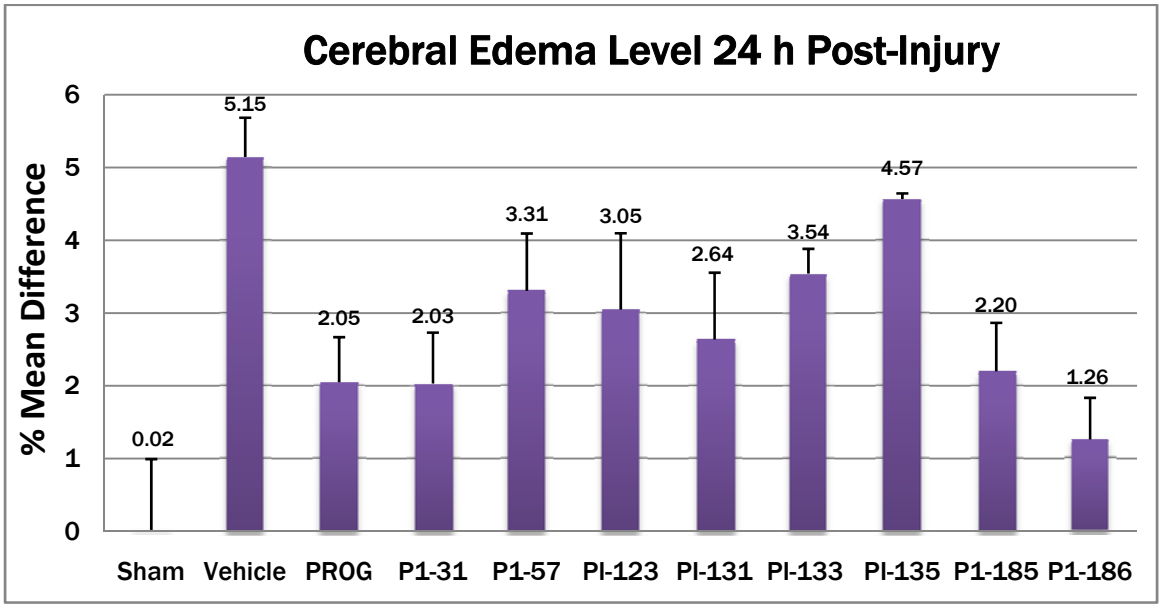


Figure 6. Cerebral edema level assay data for PROG and test compounds.

2.2.4 Pharmacokinetic Screening Data

Select compounds were submitted for pharmacokinetic analysis in a non-injury whole animal rat study. The C-3-β-hydroxy PROG derivatives **P1-31** (valine tether) and **P1-33** (proline tether) were chosen in order to observe any potential differences in the stability of the compounds that may be attributable to the amino acid component. The natural ALLO derivative **P1-131** was selected based on its activity in the cerebral edema assay and as an example of a compound containing a saturated A ring. Finally, the oxime derived compound **P1-186** was also submitted in order to evaluate its potential to act as a prodrug in vivo as envisioned.

The compounds were intravenously (IV) dosed at 10 mg/kg and serum samples were taken at several time points over the course of 12 h. Serum concentration levels were determined for the analogues, as well as for their respective parent compound. The derivatives **P1-31** and **P1-33** behaved very similarly in vivo (Figure 7). The amino acid side chain in both compounds was cleaved almost immediately to give rapid conversion to their mutual parent, the C-3-β-hydroxy compound **3**. However, in the case of the ALLO derivative **P1-131**, the valine tethered compound was stable for a prolonged period of time and only gradually converted to its parent, ALLO (**2**, Figure 8). The data indicates a distinct difference in the susceptibility of the amino acid side chain to hydrolysis resulting from relatively small differences in saturation and conformation. The more sterically congested A-ring of **P1-131** could be thought to provide some protection to active esterases relative to the unsaturated A-ring of **P1-31** type compounds, or perhaps also important is the relative α- (**P1-131**) or β- (**P1-31)** face orientation of the side chain.

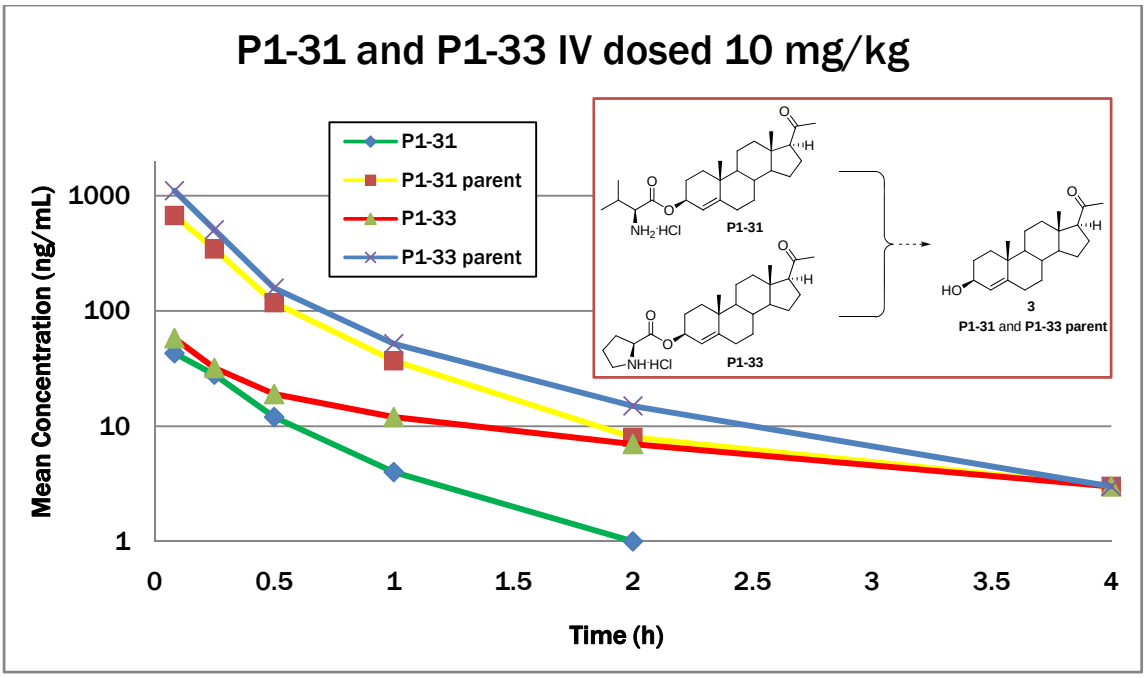


Figure 7. Pharmacokinetic data for **P1-31** and **P1-33** IV dosed at 10 mg/kg.

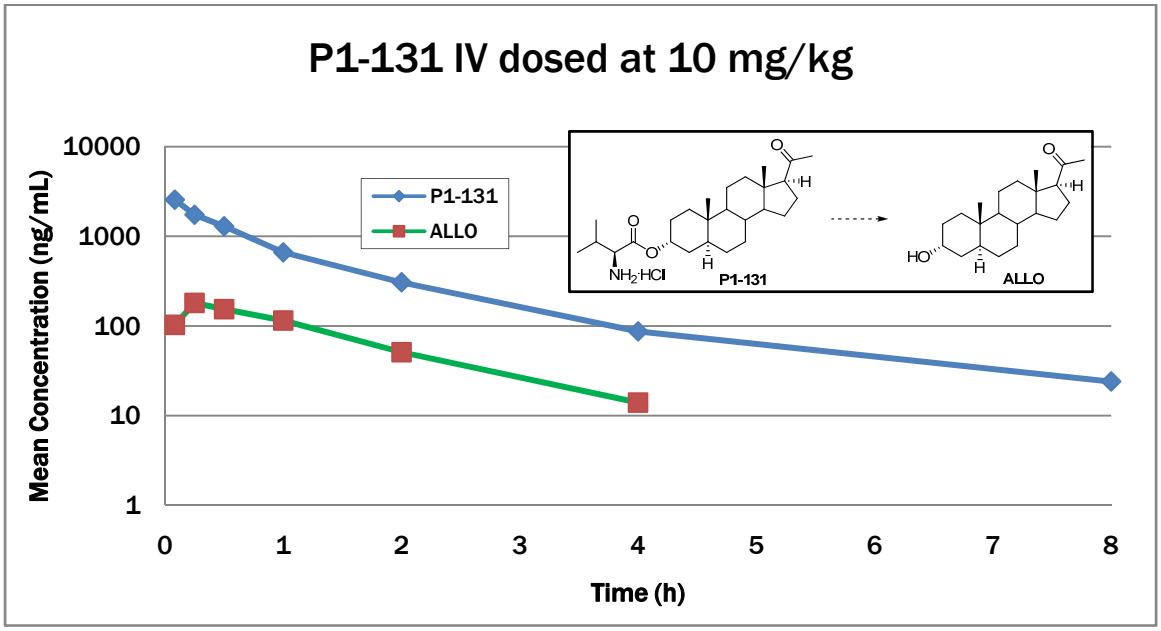


Figure 8. Pharmacokinetic data for **P1-131** IV dosed at 10 mg/kg.

The oxime based compound **P1-186** did indeed generate PROG in vivo when dosed either IV or intraperitoneally (IP) at 10 mg/kg (Figure 9). The PROG levels observed via both modes of administration reached a maximum of approximately 100 ng/mL, which compares favorably to a previously reported maximum serum concentration of 28 ng/mL when PROG was administered IP at 4 mg/kg to male rats.[136] Despite the observance of PROG however, the amino acid tether of compound **P1-186** is readily cleaved to give primarily the parent oxime **P2-02** (Figure 8), which is stable in vivo for several hours. The potential implication of this data is that it is the intermediate oxime compound (**P2-02**) that may be responsible for achieving the neuroprotective effects observed in both the in vitro and cerebral edema assays, not progesterone, as might have been suspected.

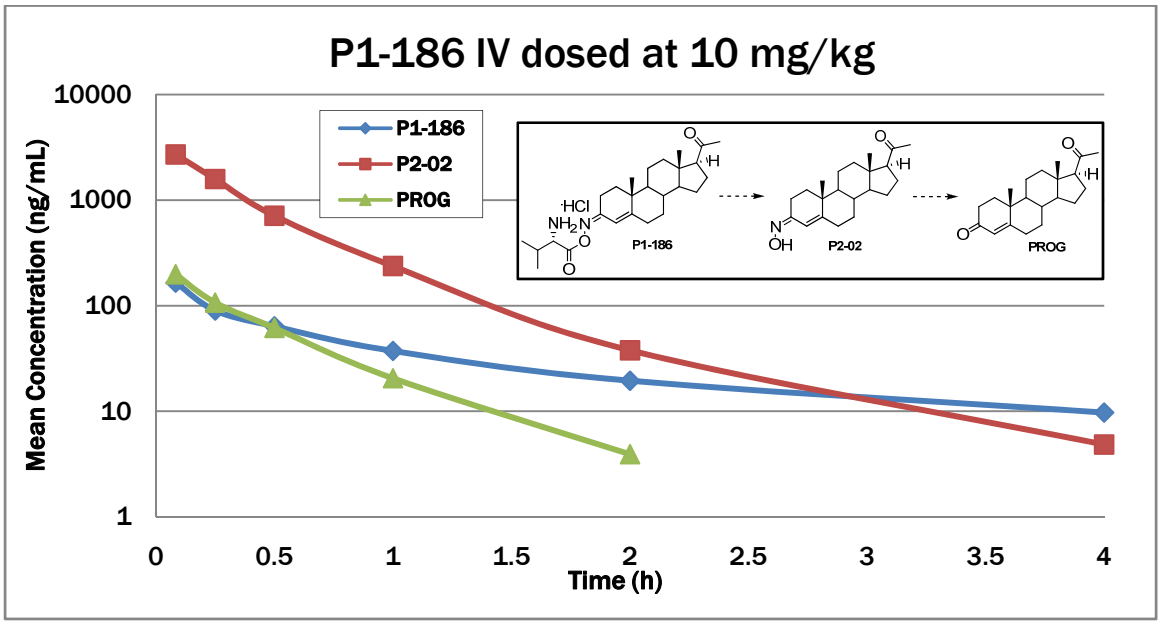


Figure 9. Pharmacokinetic data for **P1-186** IV dosed at 10 mg/kg.

4. Conclusion

Several novel analogues of progesterone, its natural metabolite allopregnanolone, and the enantiomer of progesterone were synthesized and screened for solubility as well as for their potential as neuroprotective agents (Figure 10). The use of an amino acid tether was shown to be an effective method for greatly enhancing the solubility of progesterone and other related steroidal compounds. Several compounds have shown nearly equivalent activity to PROG and ALLO in an in vitro assay designed to assess their ability to enhance neuronal cell survival. The C-3-β-hydroxy derivative **P1-31** and the oxime derived compound **P1-186** both showed equivalent or enhanced capacity relative to PROG for reducing cerebral edema following cranial injury in a whole animal model of traumatic brain injury. In addition, initial pharmacokinetic studies have shown that the use of a more highly water soluble prodrug of PROG is a viable strategy for delivering PROG in vivo, as well as for achieving neuroprotective effects.

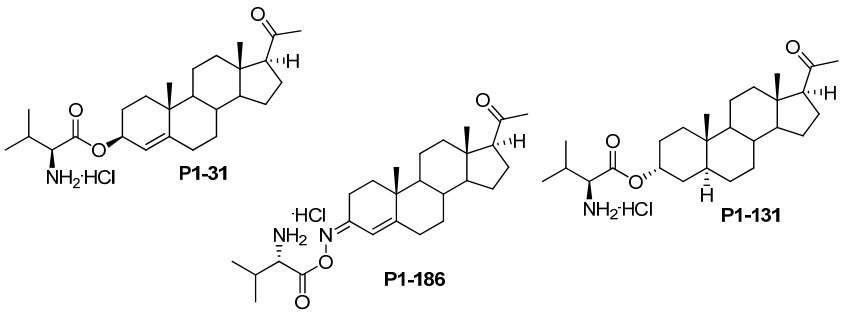


Figure 10. Water soluble lead compounds for the treatment of TBI.

S1. Experimental Procedures and Characterization Data

S1.1 Part 1: Azetine Chemistry

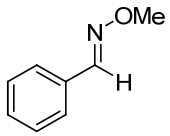
General

All reagents were obtained from Aldrich, except L-valinol, which was obtained from both Aldrich and Lancaster. Reactions requiring anhydrous conditions were performed in oven-dried glassware under dry argon or nitrogen. All solvents used were anhydrous or kept dry over activated 4 Å molecular sieves. The following abbreviations may be used: dichloromethane (DCM), diethyl ether (ether), deionized water (DI), hexane (hex), ethyl acetate (EA), tetrahydrofuran (THF), dimethylaminoformamide (DMF), acetonitrile (ACN), phosphomolybdic acid (PMA) round bottomed flask (RBF), hours (h), minutes (min), millimole (mmol), equivalents (eq). Reaction progress was monitored via thin-layer chromatography (TLC) on pre-coated glass-backed plates (silica gel 60 Å F_{254}, 0.25 mm thickness) purchased from EM Science. Flash chromatography was carried out with silica gel 60 Å (230 - 400 mesh) from Sorbent Technologies. Automated chromatography was performed on an Isco Combiflash Companion. Unless otherwise stated, organic extracts were dried over commercially available magnesium sulfate and the solvents were removed by rotary evaporation. Brine refers to a saturated sodium chloride solution. ^{1}H and ^{13}C NMR spectra were recorded on either a 400 MHz Inova spectrometer or 600 MHz Inova spectrometer in deuterated chloroform ($CDCl_3$) and referenced to the residual solvent peak (^{1}H δ 7.27 ppm, ^{13}C δ 77.23 ppm) unless otherwise noted. Chemical shifts are reported in parts per million (δ), and coupling constants are reported in hertz (Hz). The following abbreviations will be used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Mass spectra were obtained on

either a VG 70-S Nier Johnson or JEOL Mass Spectrometer. Elemental analyses were performed by Atlantic Microlab (Norcross, Georgia). Experimental design and data analysis for factorial experiments were facilitated by Design Expert 7 software from StatEase.

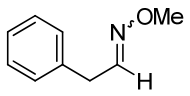
Oximes:

General Procedure for the Preparation of Oximes. Representative example for **77a**. To a 100 mL RBF, 98 % methoxylamine hydrochloride (4.09 g, 48.0 mmol, 1.20 eq) was added with 30 mL absolute ethanol. Anhydrous pyridine (12.9 mL, 160 mmol, 4.00 eq) was added over the course of one min. Benzaldehyde (4.06 mL, 40.0 mmol) was then added quickly and the reaction was left to stir at room temperature for 4 h. The ethanol was then removed to reveal a white solid and clear liquid. DCM (50 mL) was added and the solution was extracted with 5% citric acid (3 X 50 mL). The citric acid washes were combined and extracted with 50 mL DCM. The organic layers were combined, washed with brine, dried, filtered, and concentrated to give a clear oil. The oil was distilled under vacuum (0.18 mbar, 30-32 °C) to give 4.52 g (84%) clear liquid.

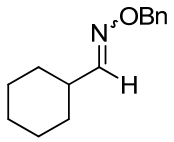


Benzaldehyde *O*-methyl-oxime (77a). (84%) clear oil; R_f = 0.60 (4:1 hex/EA); 25:1 mixture of isomers; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 8.04 (s, 1H), 7.55 (d, 2H, *J* = 3.6 Hz), 7.37-7.34 (m, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 148.72, 132.38, 130.00, 128.85, 127.18, 62.17; IR (neat): 2937, 2898, 2817,

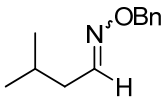
1462, 1447, 1211, 1049, 946, 916, 844, 753, 690 cm^{-1}; HRMS-ESI *m/z* 136.0756 ($[M+H]^+$, $C_8H_{10}NO$ requires 136.0757).



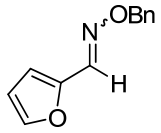
Phenyl-acetaldehyde *O*-methyl-oxime (77b). (62%) clear oil; R_f = 0.63 (2:1 hex/EA); 1.2:1 mixture of isomers ^1H NMR (400 MHz, $CDCl_3$) major isomer: δ 7.48 (t, 1H, *J* = 6.4 Hz), 7.36-7.22 (m, 5H), 3.89 (s, 3H), 3.54 (d, 2H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) both isomers: δ 149.9, 149.3, 137.1, 136.5, 129.0, 128.9, 127.0, 126.8, 62.0, 61.9, 36.1, 32.4; IR (neat): 2938, 2899, 1495, 1454, 1069, 1028, 845, 743, 697 cm^{-1}; HRMS-ESI *m/z* 150.0909 ($[M+H]^+$, $C_9H_{12}NO$ requires 150.0913).



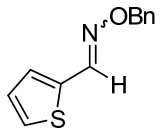
Cyclohexanecarbaldehyde *O*-benzyl-oxime (77c). (82%) colorless oil; R_f = 0.71 (2:1 hex/EA); 3:1 mixture of isomers; ^1H NMR (400 MHz, $CDCl_3$) major isomer: δ 7.40-7.30 (m, 6H), 5.07 (s, 2H), 2.29-2.20 (m, 1H), 1.81-1.66 (m, 5H), 1.39-1.13 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) both isomers: δ 156.7, 155.7, 138.5, 137.8, 128.6, 128.5, 128.0, 128.0, 127.8, 75.7 (2C), 38.7, 34.7, 30.6, 29.8, 26.1, 26.0, 25.6, 25.4; IR (neat): 2924, 2852, 1449, 1364, 1017, 908, 731, 696 cm^{-1}; HRMS-ESI *m/z* 218.1538 ($[M+H]^+$, $C_{14}H_{20}NO$ requires 218.1539).



3-Methyl-butyraldehyde *O*-benzyl-oxime (77d). (86%) clear oil; R_f = 0.73 (2:1 hex/EA); 1.4:1 mixture of isomers; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 7.47 (t, 1H, *J* = 6.8 Hz), 7.39-7.29 (m, 5H), 5.08 (s, 2H), 2.28 (dd, 1H, *J* = 7.2, 6.0 Hz), 2.09 (t, 1H, *J* = 6.8 Hz), 1.89-1.77 (m, 1H), 0.95 (t, 6H, *J* = 6.0); ^{13}C NMR (100 MHz, $CDCl_3$) both isomers: δ 151.9, 151.2, 138.3, 137.9, 128.6, 128.6, 128.4, 128.1, 128.0, 127.9, 75.8, 75.7, 38.4, 34.8, 30.0, 26.5, 22.7, 22.5; IR (neat): 3032, 2956, 1467, 1368, 1058, 1011, 732, 696 cm^{-1}; HRMS-ESI *m/z* 192.1380 ($[M+H]^+$, $C_{12}H_{18}NO$ requires 192.1383).

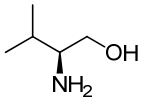


Furan-2-carbaldehyde *O*-benzyl-oxime (77e). (86%) clear oil; R_f = 0.62 (2:1 hex/EA); 1.6:1 mixture of isomers; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 7.51 (s, 1H), 7.48-7.32 (m, 6H), 7.26 (d, 1H, *J* = 3.6 Hz), 6.53-6.52 (m, 1H), 5.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) both isomers: δ 147.3, 145.5, 144.4, 143.4, 139.5, 137.7, 137.3, 136.7, 118.1, 113.1, 112.4, 111.8, 77.2; IR (neat): 3032, 2926, 1479, 1454, 1366, 1036, 950, 738, 695, 594 cm^{-1}; HRMS-ESI *m/z* 202.0861 ($[M+H]^+$, $C_{12}H_{12}NO_2$ requires 202.0863).



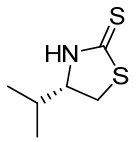
Thiophene-2-carbaldehyde *O*-benzyl-oxime (77f). (86%) clear oil; R_f = 0.63, 0.66 (2:1 hexane/ethyl actate); ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 7.72 (s, 1H), 7.54 (d, 1H, *J* = 4.8 Hz), 7.49-7.33 (m, 6H), 7.10 (t, 1H, *J* = 4.8 Hz), 5.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) both isomers: δ 144.0, 140.9, 137.7, 137.4, 135.8, 132.0, 131.6 (2C), 129.7, 128.7, 128.6, 128.2, 128.1 (2C), 127.7, 127.4, 126.4, 76.9, 76.7; IR (neat): 3030, 2924, 1604, 1209, 1013, 909, 694, 595 cm^{-1}; HRMS-ESI *m/z* 218.0632 ($[M+H]^+$, $C_{12}H_{12}NOS$ requires 218.0634).

Traditional Auxiliaries, Azetines, and Alkylation Products:



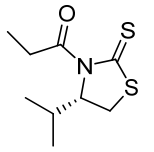
L-Valinol (84). To an oven dried, inert gas flushed 3-neck 500 mL RBF fitted with a condenser was added 150 mL molecular sieve dried THF. The solvent was chilled in an ice bath and lithium aluminum hydride (4.89 g, 128 mmol, 1.50 eq) was added. In a separate 100 mL RBF, L-valine (10.0 g, 85.4 mmol) was added and the flask was fitted with an airtight rubber sleeve. The sleeve was connected to the reaction flask and the L-valine was added in small portions over the course of 20 min. The sleeve was then removed and replaced with a stopper. The flask was allowed to warm gradually to room temperature and then was set for reflux overnight. Heating was removed after 18 h reflux and the mixture was cooled to room temperature and then chilled in an ice bath. The condenser was removed and replaced with an addition funnel and an additional 125 mL diethyl ether was added. A 5 mL volume of DI was then added dropwise over the course of 5 minutes. This caused vigorous bubbling. After the bubbling had subsided, a 5 mL volume of 10% NaOH was added, followed by an additional 10 mL DI. The mixture was

then allowed to stir for 30 min while equilibrating back to room temperature. The mixture of white solid and clear solvent was warmed slightly in a water bath and filtered. The solid was washed three times with ether (3 X 100 mL). The organic layers were combined, dried, filtered, and concentrated to give a cloudy colorless oil of initial crude mass 10.3 g that partly solidified at room temperature. The crude mixture was transferred to a 100 mL RBF and set for distillation. The desired product was recovered at 40-42 °C (2.0 mbar) as a clear colorless oil of mass 6.16 g (70%) that solidified on cooling. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (dd, 1H, *J* = 10.4, 3.6 Hz), 3.21 (dd, 1H, *J* = 10.4, 8.0 Hz), 2.50-2.45 (m, 3H), 1.53-1.48 (m, 1H), 0.83 (d, 3H, *J* = 4.0 Hz), 0.81 (d, 3H, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.5, 58.4, 31.1, 19.4, 18.4.



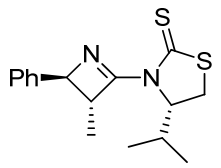
4 (*S*)-Isopropyl-thiazolidine-2-thione (85). A 500 mL RBF was fitted with a large magnetic stirring bar and 16.5 g KOH dissolved completely at room temperature in 200 mL DI. The L-valinol was then transferred with rinsing to give overall 4.97 g (48.1 mmol) valinol in 250 mL of a 1 N KOH solution. After the valinol had completely dissolved, carbon disulfide (16.0 mL, 241 mmol, 5.00 eq) was added in bulk. The flask was fitted with a water cooled condenser and set in an oil bath at 100 ^{o}C to reflux overnight for 24 h. The flask was then cooled to room temperature and extracted with DCM (3 X 100 mL). Combined extractions were washed with brine, dried, filtered, and concentrated. The sample was recovered as a cloudy beige oil that solidified on cooling. The resulting off-white solid was recrystallized from ether to give 5.56 g (71.6%) white

crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (bs, 1H), 4.05 (m, 1H), 3.52 (dd, 1H, *J* = 12.0, 8.1 Hz), 3.34 (dd, 1H, *J* = 12.6, 8.4 Hz), 1.97 (m, 1H), 1.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.06, 70.22, 35.91, 32.10, 18.89, 18.30.



1-((*S*)-4-Isopropyl-2-thioxo-thiazolidin-3-yl)-propan-1-one (72). A 100 mL RBF with magnetic stirring bar was charged with 1.02 g thiazolidinethione **85**. The flask was evacuated and flushed with inert gas and 25 mL dry DCM was added. The flask was chilled to -78 ^{o}C and allowed to equilibrate. After 15 minutes, pyridine (0.767 mL, 9.49 mmol, 1.50 eq) was added. Ten minutes following pyridine addition, the propionyl chloride (0.714 mL, 8.22 mmol, 1.30 eq) was added dropwise over the course of 10 minutes. The solution was left at -78 ^{o}C for 3 h and the flask was then removed from the ice bath to warm to room temperature overnight. The solution was transferred to a separatory funnel with DCM rinse, washed once each with 50 mL portions of DI, 5% oxalic acid, and DI, dried with magnesium sulfate, filtered, and concentrated to give a bright yellow oil of crude yield 1.69 g. The sample was eluted on a 40 g column with a 5-10% EA in hex gradient over 10 column volumes (CV) followed by an additional 10 CV elution. Fractions were combined and concentrated to give 1.30 g (95%) yellow oil. R_f = 0.65 (2:1 hex/EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (dt, 1H, *J* = 6.6, 1.2 Hz), 3.49 (dd, 1H, *J* = 11.6, 8.0 Hz), 3.32 (m, 1H), 3.14 (m, 1H), 3.00 (d, 1H, *J* = 11.6 Hz), 2.34 (m, 1H), 1.14 (t, 3H, *J* = 7.2 Hz), 1.04 (d, 3H, *J* = 7.2 Hz), 0.95 (d, 3H, *J* = 7.2 Hz);

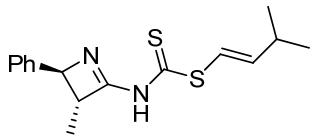
^{13}C NMR (100 MHz, $CDCl_3$) δ 202.83, 175.02, 71.78, 32.19, 30.94, 30.56, 19.18, 17.85, 9.11.



4(*S*)-Isopropyl-3-(3(*R*)-methyl-4(*S*)-phenyl-3,4-dihydro-azet-2-yl)-thiazolidine-2-thione (79). Oxime ether route: To a 25 mL RBF was added a small stir bar and compound **7** (0.250 g, 1.15 mmol). The flask was evacuated and gas flushed two times. A 7.5 mL portion of anhydrous DCM was added and the mixture was brought to 0 °C. The titanium tetrachloride (0.504 mL, 4.60 mmol, 4.00 eq) was then added dropwise, which caused the formation of a thick yellow precipitate. The (-)-sparteine (0.661 mL, 2.88 mmol, 2.50 eq) was then added dropwise. The mixture gradually became a thick brown liquid over the course of about 45 minutes. This was chilled to -78 °C and the oxime ether (0.466 g, 3.45 mmol, 3.00 eq) was added via syringe. The reaction was left for 15 minutes at -78 °C and was then transferred back to a 0 °C bath. The reaction was left to stir for a total of 22 h. A 20 mL volume of saturated ammonium chloride was added to the flask with stirring and the solution was transferred to a separatory funnel with 30 mL DI, followed by extraction with DCM (3 X 30 mL). The DCM extractions were washed with saturated sodium bicarbonate, then brine, dried, filtered, and concentrated. Combiflash column chromatography run on a 40 g column with a 10:1 to 2:1 hex/EA gradient over the course of 35 CV provided the azetine/pyrimidinone mixture as a pale yellow solid of mass 0.110 g (31.4%) in a 3:1 ratio.

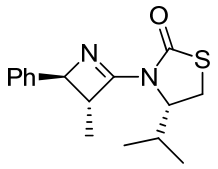
Transmetallation route: An oven dried 250 mL flask with stir bar was charged with Schwartz' reagent Cp_2ZrHCl (4.75 g, 17.5 mmol, 1.75 eq). The flask was evacuated and inert gas flushed and the reagent was then dissolved in 25 mL dry DCM. This was cooled in a cold water bath and benzonitrile (1.53 mL, 15.0 mmol, 1.50 eq) was then added. This was allowed to stir for 2 h. This was then chilled to 0 ^{o}C in an ice bath and the $TiCl_4$ (3.29 mL, 30.0 mmol, 3.00 eq) was added dropwise. The ice bath was removed and the flask was then left to stir for one hour. A second oven dried 250 mL RBF was cooled under vacuum and then the auxiliary **72** (2.17 g, 10.0 mmol) was added. Compound **72** was dissolved in 75 mL dry DCM and then chilled in the ice bath. After 10 minutes, the $TiCl_4$ (1.15 mL, 10.5 mmol, 1.05 eq) was added dropwise. The sparteine (5.74 mL, 25.0 mmol, 2.50 eq) was then added and this was left to stir in the ice bath for 45 minutes. The ice bath was moved from enolate to hydrozirconation flask and the enolate solution was added by cannula with steady rapid drop rate over 5 min. After complete addition, the flask was left to equilibrate to room temperature and stir overnight. The reaction was cooled in an ice bath and quenched with 50 mL saturated ammonium chloride after total 19 hours. Three 100 mL DCM extractions were combined, washed with DI and brine, dried, filtered, and concentrated to give a yellow/brown solid of crude mass 3.98 g. A 175 mL column was loaded and run in 12:1 hex/EA, ramped to 9:1, 4:1, and 3:1 in 500 mL portions. The combined azetine/pyrimidinone fractions were concentrated to give a pale brown solid that was re-dissolved in a minimal amount of warm EA and recrystallized with hexane to give an off-white powder of mass 0.911 g (30%). R_f = 0.30 (2:1 hex/EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.97 (ddd, 1H, *J* = 5.2, 1.2, 0.8 Hz), 4.11 (d, 1H, *J* = 1.6 Hz),

3.95 (dq, 1H, *J* = 7.2, 1.6 Hz), 3.67 (dd, 1H, *J* = 12.0, 8.8), 3.18 (dd, 1H, *J* = 11.6, 1.2 Hz), 2.80 (m, 1H), 1.56 (d, 3H, *J* = 7.3 Hz), 1.11 (d, 3H, *J* = 6.9 Hz), 1.06 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.48, 173.52, 140.55, 128.65, 127.67, 126.39, 71.04, 69.88, 52.09, 30.93, 30.70, 19.37, 16.91, 16.32; IR (neat): 2968, 1575, 1494, 1455, 1374, 1274, 1173, 856.9, 737.3 cm^{-1}.



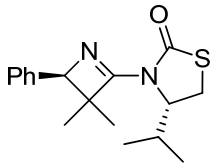
((3*R*,4*S*)-3-Methyl-4-phenyl-3,4-dihydro-azet-2-yl)-dithiocarbamic acid (*E*)-3-methyl-but-1-enyl ester (88). 2,2,6,6-tetramethylpiperidine (TMP) (0.061 mL, 0.36 mmol, 1.2 eq) was added to a 10 mL oven dried flask fitted with a stir bar and diluted in 0.72 mL dry THF. This was chilled to 0 ^{o}C and a 0.21 mL volume (0.33 mmol, 1.1 eq) of 1.6 M butyl lithium was added dropwise over 15 minutes. The solution color became clear pale brown. The solution was allowed to stir for 20 minutes and was then cooled to -78 ^{o}C. The azetine **3** (0.091 g, 0.30 mmol) was dissolved in 0.60 mL THF and transferred to the base solution dropwise. The solution color yellowed slightly. An additional 0.40 mL THF was used to rinse the azetine flask and this was also transferred dropwise. The solution was left to stir at -78 ^{o}C for one hour and was then quenched with approximately 2 mL saturated ammonium chloride. The solution was extracted with 10-15 mL EA, washed with DI and brine, dried, and concentrated to give a yellow oil. Purification by column chromatography with a 10-20% EA in hexane gradient provided the sample for analysis. R_f = 0.64 (1:1 hex/EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (bs, 1H), 7.39 (m, 5H), 6.73 (dd, 1H, *J* = 15.6, 1.6 Hz), 5.95 (q, 1H, *J* = 6.6 Hz), 4.79 (d, 1H,

J = 2.0 Hz), 3.31 (dq, 1H, *J* = 6.4, 1.6 Hz), 2.51 (m, 1H), 1.52 (d, 3H, *J* = 7.2 Hz), 1.09 (d, 6H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.99, 170.29, 142.33, 137.79, 129.23, 129.01, 128.96, 120.79, 67.69, 53.12, 32.34, 22.19, 13.76; IR (neat): 3266, 3030, 2961, 2926, 2057, 1710, 1606, 1382, 976.6, 853.1 cm^{-1}; HRMS-ESI *m/z* 305.1157 ($[M+H]^+$, $C_{16}H_{21}N_2S_2$ requires 305.1146); Anal. Calcd for $C_{16}H_{20}N_2S_2$: C, 63.12; H, 6.62; N, 9.20; S, 21.06. Found C, 63.28; H, 6.59; N, 8.86; S, 20.25.



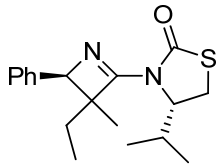
(S)-4-Isopropyl-3-((3R,4S)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-thiazolidin-2-one (92). To a 100 mL RBF, 0.304 g azetine (1.00 mmol) was added with a stir bar and the flask was evacuated and inert gas flushed. Anhydrous DCM was added (50 mL) and the flask was chilled to -78 ^{o}C. Oxygen was bubbled through the solution and after 45 minutes, ozone gas was then bubbled through the solution at 1.5 psi and 3.4 V. A light blue color was seen in solution after 1 hour. The ozone was discontinued and oxygen was bubbled through the reaction mixture for 45 minutes. A 3.0 eq portion (0.22 mL) of methyl sulfide was added dropwise at -78 ^{o}C. The reaction was then left to slowly equilibrate to room temperature and stir overnight. The solvent was then evaporated to yield an off white solid. This was re-dissolved in 25 mL DCM and washed with DI (3 X 30 mL). The DI washes were combined and extracted with DCM. The organic layers were combined, washed with brine, dried, filtered, and concentrated. The sample was recovered as a clear light brown oil of that was loaded neat onto a 40 g silica column and run on a 5-20% EA in hex gradient over 20 CV followed by an additional 15

CV at 20% EA to give 0.170 g (59%) pale yellow oil. R_f = 0.23 (1:1 hex/EA); $[\alpha]^{23}_D$ +126.3 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.52, (dq, 1H, *J* = 4.8, 1.6 Hz), 4.41 (d, 1H, *J* = 1.2 Hz), 3.56 (m, 2H), 3.16 (dd, 1H, *J* = 11.6, 0.8 Hz), 2.74 (m, 1H), 1.48 (d, 3H, *J* = 7.2 Hz), 1.08 (d, 3H, *J* = 7.2 Hz), 1.05 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.07, 171.77, 140.86, 128.62, 127.59, 126.24, 70.41, 61.07, 50.65, 29.80, 27.44, 19.17, 16.49, 15.52; IR (neat): 3030, 2964, 2930, 2876, 1687, 1594, 1463, 1401, 1293, 1177, 965.0, 764.3 cm^{-1}; HRMS-ESI *m/z* 289.1361 ($[M+H]^+$, $C_{16}H_{21}N_2OS$ requires 289.1375); Anal. Calcd for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.71; O, 5.55; S, 11.12. Found C, 66.14; H, 7.04; N, 9.22; O, 7.24; S, 10.94.



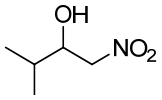
(S)-3-((R)-3,3-Dimethyl-4-phenyl-3,4-dihydro-azet-2-yl)-4-isopropyl-thiazolidin-2-one (93a). To an oven dried 5 mL RBF with stir bar was added 0.066 mL TMP (0.39 mmol, 1.2 eq) and 0.60 mL dry THF and the solution was cooled to 0 °C. After 10 minutes, a 0.22 mL volume of 1.6 M butyl lithium (0.36 mmol, 1.1 eq) was added and the solution was left to stir at 0 °C for 15 minutes. The base flask was then chilled to -78 °C and let equilibrate for 10 minutes. The thiazolidinone azetine **92** (0.093 g, 0.32 mmol) was dried under vacuum, dissolved in 0.40 mL THF, and transferred dropwise to the base flask. This was left to stir at -78 °C for 1 h. The methyliodide (0.10 mL, 1.6 mmol, 5.0 eq) was next added dropwise and the flask was moved to a 0 °C ice bath. The reaction was quenched after 2 hours at 0 °C with 1 mL saturated ammonium chloride. The solution was extracted with 25 mL EA, washed with brine, dried, filtered, and

concentrated to give a pale brown oil of mass 0.096 g. Column chromatography in 5-25% EA in hex gave the product as a pale brown oil of yield 0.020 g (22%). R_f = 0.21 (2:1 hex/EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, 2H, *J* = 7.2 Hz), 7.28 (t, 1H, *J* = 7.2 Hz), 7.17 (d, 2H, *J* = 7.2 Hz), 4.72 (t, 1H, *J* = 6.6 Hz), 4.61 (s, 1H), 3.64 (dd, 1H, *J* = 12.6, 8.4 Hz), 3.21 (d, 1H, *J* = 11.4 Hz), 2.70 (m, 1H), 1.57 (s, 3H), 1.12 (d, 3H, *J* = 4.8 Hz), 1.11(d, 3H, *J* = 4.8 Hz), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.29, 171.51, 139.64, 128.40, 127.34, 126.97, 72.40, 60.71, 53.25, 29.79, 27.96, 23.75, 19.98, 19.20, 16.76; IR (neat): 3065, 2968, 2930, 2872, 1718, 1671, 1471, 1386, 1266, 1181, 953.4, 764.3 cm^{-1}; HRMS-ESI *m/z* 303.1520 ($[M+H]^+$, $C_{17}H_{23}N_2OS$ requires 303.1531).

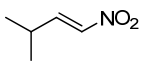


(S)-3-((R)-3-Ethyl-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-4-isopropyl-thiazolidin-2-one (93b). Prepared according to the method described for compound **93a**: (29%) clear oil; R_f = 0.47 (1:1 hex/EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, 2H, *J* = 7.2 Hz), 7.28 (dd, 1H, *J* = 9.0, 4.8 Hz), 7.19 (d, 2H, *J* = 7.2 Hz), 4.72 (dd, 1H, *J* = 8.1, 5.4 Hz), 4.67 (s, 1H), 3.63 (dd, 1H, *J* = 15.0, 8.4 Hz), 3.22 (d, 1H, *J* = 10.2 Hz), 2.74 (m, 1H), 1.88 (m, 2H), 1.13 (d, 3H, *J* = 4.2 Hz), 1.12 (d, 3H, *J* = 4.2), 1.06 (t, 3H, *J* = 7.2 Hz), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.90, 171.43, 140.02, 128.32, 127.16, 127.11, 68.65, 60.63, 57.20, 29.72, 28.73, 27.88, 19.20, 17.89, 16.70, 9.77; IR (neat): 3061, 2964, 2926, 2876, 1702, 1594, 1459, 1393, 1266, 1158, 980.4, 737 cm^{-1}.

Free N-H Auxiliary Compounds:

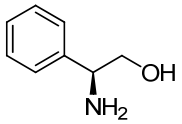


3-Methyl-1-nitro-butan-2-ol. To a 500 mL RBF with stir bar was added 46.1 mL isobutyraldehyde (500 mmol) with 190 mL (3.50 mol, 7.00 eq) freshly distilled nitromethane. A 2.00 mL portion of 3 N KOH in methanol was added slowly dropwise. Solution pH was monitored with pH paper until, at an apparent pH of 8.0, a color change to clear pale orange and a warming of the solution was observed. This was left to stir at ambient temperature for 1 h. Concentrated H_2SO_4 was then added dropwise. After a total of 20 drops, the solution became cloudy and colorless with the formation of a white precipitate. The solution was left to stir for 1 h after complete addition. The mixture was concentrated to remove excess nitromethane and then filtered through a 1 cm pad of Celite in a medium frit glass ground filter. The clear light amber filtrate was then set for distillation (0.40 mbar). The major product was recovered at 68 °C as 63.2 g (94.9%) clear oil. R_f = 0.56 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48-4.36 (m, 2H), 4.11-4.06 (m, 1H), 2.75 (bs, 1H), 1.82-1.72 (m, 1H), 0.97 (t, 6H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.5, 73.6, 31.9, 18.5, 17.6; IR (neat): 3440, 2966, 1548, 1381, 1066, 714 cm^{-1}; HRMS-ESI *m/z* 134.0809 ($[M+H]^+$, $C_5H_{12}NO_3$ requires 134.0812).



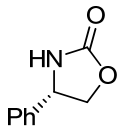
3-Methyl-1-nitro-but-1-ene (107). To a 500 mL RBF with magnetic stirring bar was added 3-methyl-1-nitro-butan-2-ol (25.0 g, 188 mmol). The flask was evacuated and inert gas flushed twice in succession. This was diluted in 150 mL anhydrous diethyl

ether and dicyclohexylcarbodiimide (46.5 g, 225 mmol, 1.20 eq) was added in portions. Copper (I) chloride (0.465 g, 4.69 mmol, 0.025 eq) was then added and the brownish green solution was left to stir at room temperature overnight. A white precipitate was observed in solution after approximately 30 minutes. The reaction was left to stir for a total of 36 h at which point the mixture was diluted with 100 mL pentane and filtered through a medium frit glass ground filter to give a clear dark brown filtrate. The concentrate was distilled and the nitroalcohol was recovered at 30 °C (0.40 mbar) as a clear oil of mass 18.6 g (86%). 85:15 mix of cis/trans isomers. Major (*trans*) isomer: pale amber oil; R_f = 0.69 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, 1H, *J* = 6.8, 7.2), 6.91 (dd, 1H, *J* = 13.2, 1.6), 2.62-2.50 (m, 1H), 1.10 (d, 6H, *J* = 7.2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.6, 138.3, 28.5, 21.12 (2C); IR (neat): 2968, 2874, 1645, 1522, 1467, 1347, 969, 842, 728, 563 cm^{-1}.



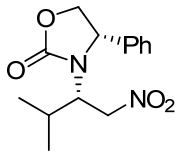
L-Phenylglycinol. An oven dried 500 mL three neck RBF with stir bar was fitted with a glass stopper, rubber septum, and condenser. The flask was evacuated and inert gas flushed 95% lithium aluminum hydride (4.96 g, 124 mmol, 1.50 eq) was added. The flask was set in an ice bath and 200 mL anhydrous THF was added. The phenylglycine (12.5 g, 82.7 mmol) was added to a separate 100 mL RBF connected to a hose and 24/40 adapter for gradual solid addition to the reaction mixture. The phenylglycine was added in portions over the course of 30 minutes. Bubbling was observed only after complete addition. The solution color darkened to a light orange. After 30 minutes at 0 °C the

flask was allowed to equilibrate to room temperature and was then set for reflux and left to stir overnight. After 12 h the darker orange solution was cooled to room temperature and then to 0 °C and a 100 mL volume of ether was added. The condenser was replaced by an addition funnel and the reaction was quenched with 5 mL DI, 5 mL 10% NaOH, and an additional 10 mL DI. The suspension was allowed to stir for one half hour and was then filtered. The precipitate was rinsed several times with ether. The organic extracts were combined, dried, filtered, and concentrated to give a dark orange oil that solidified on cooling. The solid was re-dissolved with heating in a minimum amount of ethyl acetate and was then prompted to recrystallize with gradual addition of hexane and cooling in an ice bath. The recovered yellow crystals were washed with cold pentane and dried under high vacuum to give 7.62 g (67%) white crystalline solid. R_f = 0.02 (95:5 DCM/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 4.05 (dd, 1H, *J* = 8.4, 4.4 Hz), 3.74 (dd, 1H, *J* = 11.2, 4.0 Hz), 3.56 (dd, 1H, *J* = 10.8, 8.4 Hz), 2.27 (bs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 128.8, 127.7, 126.7, 68.2, 57.5.



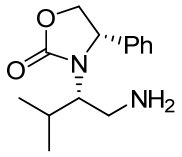
4-Phenyl-oxazolidin-2-one (106). An oven dried 250 mL three-necked RBF was fitted with a thermometer adapter, a 12 inch insulated Vigreux column connected to a distillation condenser, and a glass stopper. An argon inlet line was connected at the vacuum outlet of the condenser apparatus. After the system had been evacuated and inert gas flushed, (*S*)-phenylglycinol (17.1 g, 124 mmol) and anhydrous potassium carbonate (1.72 g, 12.4 mmol, 0.100 eq) were added and dissolved in diethyl carbonate (30.2 mL,

249 mmol, 2.00 eq). The mixture was lowered into a preheated 125 °C oil bath. The distillation receiver flask was cooled in an ice bath. Ethanol distillation was complete after 3 h. The flask was allowed to cool to room temperature and the solution was diluted in dichloromethane. The organic phase was washed with water and brine, dried, filtered, and concentrated to give a yellow solid. This was redissolved in a minimum amount of hot ethyl acetate and allowed to cool. Crystals formed which were filtered off and washed with cold ether. The filtrate was collected and concentrated in a 250 mL RBF, which resulted in the formation of a second crop of crystals. Both crops were combined to give 17.0 g (84%) white crystalline solid. R_f = 0.42 (95:5 DCM/MeOH); mp 124-126 °C; $[\alpha]^{23}_D$ +48.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.33 (m, 5H), 6.27 (bs, 1H), 4.96 (t, 1H, *J* = 8.0 Hz), 4.73 (t, 1H, *J* = 8.8 Hz), 4.18 (dd, 1H, *J* = 8.8, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 139.7, 129.3, 128.9, 126.2, 72.7, 56.5; IR (film): 3246, 1736, 1704, 1399, 1234, 1097, 923, 695 cm^{-1}; HRMS-ESI *m/z* 164.0703 ($[M+H]^+$, $C_9H_{10}NO_2$ requires 164.0706).



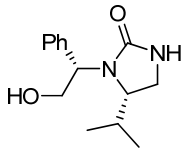
(*S*)-3-((*S*)-2-Methyl-1-nitromethyl-propyl)-4-phenyl-oxazolidin-2-one (108). To an oven dried 200 mL RBF with stir bar was added oxazolidinone **106** (1.25 g, 7.66 mmol) and 18-Crown-6 (2.02 g, 8.04 mmol, 1.05 eq). This was dissolved in 50 mL dry THF and chilled to 0 °C. After equilibration, the potassium *t*-butoxide was added (8.04 mL, 8.04 mmol, 1.05 eq) and the solution was left to stir for one hour. The solution was then further chilled to -78 °C and a solution of the nitroalkene **107** (0.970 g, 8.43 mmol,

1.10 eq) in 10 mL THF was then added dropwise over the course of 10 minutes. After 30 minutes, a 20 mL volume of saturated ammonium chloride was added and the solution was allowed to warm to room temperature. The solution was extracted with ether (2 X 100 mL) and the combined organic phases were washed with water and brine, dried, filtered, and concentrated. The resulting clear colorless oil was stored overnight in the refrigerator. Although intended to be purified by column chromatography (3:7 EA/pentane), white crystals had formed in solution. These were filtered and washed in cold pentane to provide 1.85 g (87%) white crystalline solid. R_f = 0.46 (1:1 EA/hex); mp 87-90 ^oC; $[\alpha]^{23}_D$ +63.7 (*c* 1.00, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.41 (m, 3 H), 7.32-7.30 (m, 2H), 5.10 (dd, 1H, *J* = 12.8, 9.6 Hz), 4.82 (dd, 1H, *J* = 8.8, 7.2 Hz), 4.64 (t, 1H, *J* = 8.8 Hz), 4.48 (dd, 1H, *J* = 8.8, 4.4 Hz), 4.26 (dd, 1H, *J* = 8.8, 8.0 Hz), 3.50 (dt, 1H, *J* = 9.2, 3.6 Hz), 2.19-2.07 (m, 1H), 1.03 (d, 3H, *J* = 6.8 Hz), 0.93 (d, 3H, *J* = 6.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 136.9, 129.9, 129.6, 127.9, 74.9, 70.3, 62.3, 59.3, 29.8, 20.3, 19.9; IR (film): 2967, 1739, 1550, 1413, 1225, 1034, 764, 701 cm^{-1}; HRMS-ESI *m/z* 279.1337 ($[M+H]^+$, $C_{14}H_{19}N_2O_4$ requires 279.1339).



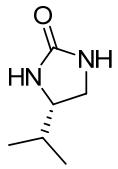
(*S*)-3-((*S*)-1-Aminomethyl-2-methyl-propyl)-4-phenyl-oxazolidin-2-one (109). To a 100 mL RBF with stir bar was added compound **108** (1.48 g,3.00 mmol), a 250 mg portion of 10% palladium on carbon, and vacuum dried ammonium formate (1.73 g, 26.6 mmol, 5.00 eq). These were dried together under vacuum for 30 minutes. The flask was then flushed with inert gas and a 30 mL volume of anhydrous methanol was added. This

was allowed to stir at room temperature for 5 hours with periodic venting. The reaction mixture was then filtered through a fine frit glass ground filter to give a clear colorless filtrate that was concentrated to reveal a clear crystalline residue. The filtrate was concentrated to near dryness by rotary evaporation to give a clear thick oil. A stir bar was added. Crystals formed upon cooling to room temperature. The mixture was diluted further with ether, filtered, and rinsed with chilled ether. A second recrystallization from the filtrate afforded additional product for a total of 1.20 g (91%) white crystalline solid. R_f = 0.02 (90:9:1 DCM/MeOH/NEt_3); mp 131-133 ^oC; $[\alpha]^{23}_D$ +16.1 (*c* 1.00, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 5H), 4.75 (dd, 1H, *J* = 8.8, 7.2 Hz), 4.58 (t, 1H, *J* = 9.2 Hz), 4.16 (dd, 1H, *J* = 8.8, 7.2 Hz), 3.23-3.17 (m, 1H), 2.90 (dt, 1H, *J* = 9.2, 2.8 Hz), 2.82 (dd, 1H, *J* = 13.6, 3.2 Hz), 1.71-1.63 (m, 1H), 0.76 (d, 3H, *J* = 6.4 Hz), 0.70 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 137.3, 129.7, 129.5, 127.9, 70.6, 61.3, 59.8, 38.6, 28.3, 20.0, 19.2; IR (film): 3350, 2966, 1728, 1578, 1475, 1251, 1069, 908, 761, 727 cm^{-1}; HRMS-ESI *m/z* 249.1596 ($[M+H]^+$, $C_{14}H_{21}N_2O_2$ requires 249.1598).



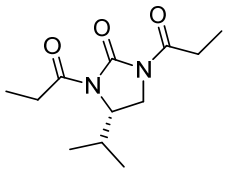
(*S*)-1-((*S*)-2-Hydroxy-1-phenyl-ethyl)-5-isopropyl-imidazolidin-2-one (110). A 500 mL RBF with magnetic stirring bar was charged with compound **109** (8.20 g, 33.0 mmol) and the flask was evacuated and flushed with inert gas. An approximate 200 mL volume of anhydrous methanol was then added. A 21.8 g (330 mmol, 10.0 eq) portion of powdered 85% potassium hydroxide was dried under vacuum then added and the clear

colorless solution was refluxed for 2 h. The flask was cooled to 0 °C and 3 N HCl (110 mL) was added, followed by aqueous saturated ammonium chloride (50 mL). A white precipitate was observed. The solution was then concentrated by rotary evaporation to remove the methanol. The remaining aqueous phase was diluted with DI and extracted with ether (3 X 100 mL). The recovered organic layers were washed with brine, dried, filtered, and concentrated to give a white crystalline solid of mass 6.79 g (83%) that required no further purification. R_f = 0.56 (9:1 DCM/MeOH); mp 98-100 °C; $[\alpha]^{23}_D$ +36.5 (*c* 1.00, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.28 (s, 1H), 5.12 (1H, *J* = 7.8 Hz), 4.29-4.23 (m, 2H), 4.00-3.97 (m, 1H), 3.48-3.45 (m, 1H), 3.31 (t, 1H, *J* = 9.6 Hz), 3.24-3.21 (m, 1H) 2.08-2.03 (m, 1H), 0.92 (d, 3H, *J* = 6.6 Hz), 0.78 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 138.1, 128.9, 127.9, 127.5, 65.1, 61.3, 60.4, 38.8, 27.0, 17.9, 14.3; IR (film): 3281, 2959, 1678, 1495, 1447, 1263, 1063, 763, 701 cm^{-1}; HRMS-ESI *m/z* 249.1596 ($[M+H]^+$, $C_{14}H_{21}N_2O_2$ requires 249.1596).



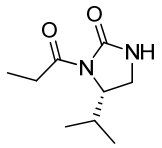
(*S*)-4-Isopropyl-imidazolidin-2-one (111). A 100 mL RBF with stirring bar and 0.497 g (2.00 mmol) compound **110** was evacuated and inert gas flushed. The starting material was diluted in 40 mL anhydrous methanol and a 0.497 g portion of 20% $Pd(OH)_2$ on carbon was added. The flask was sequentially filled with hydrogen from a balloon and evacuated by house vacuum. The balloon was eventually left on the flask at ambient pressure and stirred for 6 hours. The mixture was then filtered through an approximate 1 cm layer of Celite in a fine frit glass ground filter and rinsed with

methanol. The combined filtrates were brought down to dryness to give a white solid that was set to dry under vacuum overnight. The solid was redissolved in a minimum amount of warmed methanol and allowed to cool to room temperature with solvent evaporation as induced by argon flow into the flask. The resulting precipitate was filtered with cold ether washes to give 0.234 g (91%) white crystalline solid. R_f = 0.21 (95:5 DCM/MeOH); mp 210-212 °C; $[\alpha]^{23}_{D}$ -28.9 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53-3.47 (m, 2H), 3.21-3.14 (m, 1H), 2.41 (bs, 2H), 1.73-1.61 (m, 1H), 0.92 (d, 3H, *J* = 6.8 Hz), 0.86 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 58.9, 44.6, 33.0, 18.3, 17.8; IR (solid): 3224, 2956, 2854, 1683, 1445, 1387, 1367, 1254, 1104, 701, 560 cm^{-1}; HRMS-ESI *m/z* 129.1020 ($[M+H]^+$, $C_6H_{13}N_2O$ requires 129.1022).



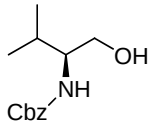
(*S*)-4-Isopropyl-1,3-dipropionyl-imidazolidin-2-one (112). A 250 mL RBF with magnetic stirring bar was charged with 4-isopropyl-imidazolidinone **111** (1.28 g, 10.0 mmol) and the flask was evacuated and inert gas flushed. A 25.0 mL volume of anhydrous THF was then added and the mixture was chilled in an ice bath. A 25.0 mL (25.0 mmol, 2.50 eq) volume of 1.0 M LiHMDS in THF was then added quickly dropwise, which caused the solution to clear. Propionyl chloride (2.17 mL, 25.0 mmol, 2.50 eq) was then added and the reaction was left to stir overnight gradually equilibrate to room temperature. The solution was quenched with saturated ammonium chloride and transferred to a separatory flask with DI and ether rinse. The aqueous phase was washed

with additional ether (2 X 50 mL). The organic layers were then washed with DI and brine, dried, filtered, and concentrated to give a pale amber oil. The oil was loaded onto a 250 mL silica column in 98:2 DCM/MeOH (1500 mL). The main product was collected as a white waxy solid of mass 2.21 g (92%). R_f = 0.79 (95:5 DCM/MeOH); $[\alpha]^{23}_{D}$ +59.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31-4.27 (m, 1H), 3.74 (dd, 1H, *J* = 12.0, 2.8 Hz), 3.60 (dd, 1H, *J* = 12.0, 9.2 Hz), 3.02-2.83 (m, 4H), 2.38-2.30 (m, 1H), 1.16 (t, 6H, *J* = 7.2 Hz), 0.92 (d, 3H, *J* = 6.8 Hz), 0.76 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 174.7, 152.5, 54.7, 40.2, 30.2, 29.9, 29.0, 18.2, 14.4, 8.7, 8.6; IR (film): 2964, 1750, 1693, 1362, 1251, 1199, 864, 806 cm^{-1}; HRMS-ESI *m/z* 241.1543 ($[M+H]^+$, $C_{12}H_{21}N_2O_3$ requires 241.1547).



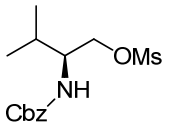
(*S*)-5-Isopropyl-1-propionyl-imidazolidin-2-one (113). A 100 mL RBF was charged with compound **112** (2.90 g, 12.1 mmol) and 30.0 mL THF (0.40 M). The solution was chilled to -78 °C and 12.1 mL (12.1 mmol, 1.00 eq) of 1.00 M potassium *tert*-butoxide in THF was added dropwise over the course of 10 minutes. The reaction was left to stir at -78 °C for a total of 4 h. The solution was then transferred dropwise by cannula to a second flask containing 50 mL stirring DI at room temperature. The resulting solution was then transferred to a separatory funnel and the aqueous phase was extracted with a mixture of EA and ether (2 X 50 mL). The organic layers were combined, washed with brine, dried, filtered, and concentrated to give a crude oil of 2.6

g. The oil was prepared as a silica cake and loaded onto a 260 mL silica column in 99:1 DCM/MeOH. Main product containing fractions were combined and submitted to preparative HPLC in 3-10% IPA in hexane over 90 minutes at a 25 mL/min flow rate. Main peak fractions were combined to give a clear oil of mass 0.873 of 90-95% purity as determined by ^{1}H NMR (37% yield). R_f = 0.30 (95:5 DCM/MeOH); $[\alpha]^{23}_{D}$ +80.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (s, 1H), 4.39 (dt, 1H, *J* = 9.2, 3.6 Hz), 3.42 (t, 1H, *J* = 9.2 Hz), 3.24-3.21 (m, 1H), 3.00-2.83 (m, 2H), 2.43-2.35 (m, 1H), 1.13 (t, 3H, *J* = 7.2 Hz), 0.88 (d, 3H, *J* = 6.8 Hz), 0.83 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 157.7, 58.4, 37.7, 29.4, 28.9, 18.2, 14.7, 8.99; IR (film): 3309, 2962, 1729, 1683, 1375, 1295, 1247, 807 cm^{-1}; HRMS-ESI *m/z* 185.1285 ($[M+H]^+$, $C_9H_{17}N_2O_2$ requires 185.1285).

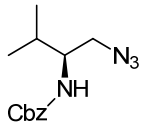


(*S*)-benzyl 1-hydroxy-3-methylbutan-2-ylcarbamate (114). A 1 L RBF was charged with L-valinol (15.5 g, 150 mmol) and 200 mL DCM. A 5% aqueous solution of $NaHCO_3$ (13.9 g in 250 mL DI, 165 mmol, 1.10 eq) was added to the reaction flask. The solution was found to be at pH 10. Benzyl chloroformate (23.6 mL, 165 mmol, 1.10 eq) was added in bulk, which caused the solution to become cloudy. The mixture was left to stir at room temperature for 20 h. The aqueous and organic layers were separated and the aqueous layer was extracted with an additional 150 mL DCM. The organic layers were combined, washed with brine, dried, filtered, and concentrated to give a cloudy colorless oil that solidified under vacuum. The solid was recrystallized from 3:1 hex/EA and the

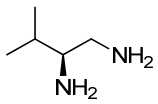
precipitate was washed with chilled ether to give 31.8 g (89%) recovered product. R_f = 0.33 (1:1 EA/hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5H), 5.18-5.08 (m, 2H), 4.99 (d, 1H, *J* = 7.2 Hz), 3.71 (dd, 1H, *J* = 10.8, 3.6 Hz), 3.64 (dd, 1H, *J* = 11.4, 6.0 Hz), 3.55-3.45 (m, 1H), 2.30 (s, 1H), 1.91-1.80 (m, 1H), 0.96 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 136.6, 128.7, 128.4, 128.3, 67.1, 64.0, 58.8, 29.4, 19.7, 18.7.



(*S*)-2-(benzyloxycarbonylamino)-3-methylbutyl methanesulfonate (115). A 250 mL RBF was charged with *N*-(benzyloxycarbonyl)-L-valinol **114** (15.74 g, 66.3 mmol) and 75 mL DCM. Triethylamine (10.3 mL, 73.6 mmol, 1.11 eq) was added and the solution was cooled to 0 °C. Mesyl chloride (5.67 mL, 73.0 mmol, 1.10 eq) was added in bulk and the solution was allowed to equilibrate to room temperature. The solution was washed with 1 M HCl (20 mL), saturated sodium bicarbonate, and brine, and was dried, filtered, concentrated, and dried under vacuum. The resulting off-white solid was redissolved in approximately 50 mL 1:5 EA/hexane mixture with heating to 60 °C. The solution was cooled in an ice-bath and the resulting precipitate was filtered and washed with cold ether to give a white crystalline solid of mass 18.74 g (90%) after drying. R_f = 0.44 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.16-5.06 (m, 2H), 4.90 (d, 1H, *J* = 9.2 Hz), 4.29 (d, 2H, *J* = 4.4 Hz), 3.76-3.67 (m, 1H), 2.97 (s, 2H), 1.94-1.84 (m, 1H), 1.00 (d, 3H, *J* = 6.8 Hz), 0.97 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 136.5, 128.8, 128.5, 128.3, 69.6, 67.2, 55.8, 37.5, 29.2, 19.5, 18.7.

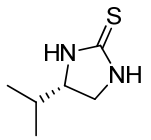


(*S*)-benzyl 1-azido-3-methylbutan-2-ylcarbamate (116). A 1 L RBF was charged with compound **115** (20.2 g, 64.0 mmol), toluene (150 mL) and DI (150 mL). After complete dissolution, sodium azide (33.3 g, 512 mmol, 8.00 eq) and tetrabutylammonium bromide (2.06 g, 6.40 mmol, 0.100 eq) were added. The reaction mixture was then heated to 85-90 °C for 20 hours. The reaction was allowed to cool to room temperature and the organic layer was separated, washed with phosphate buffer solution (pH 5, 0.5 M) and brine, dried, filtered, and concentrated to give a pale amber oil. The oil was purified by column chromatography silica with initial loading in 1:9 ether/hex (2 L) then 2 L 1:3, and 1 L 1:2. Product containing fractions were combined, concentrated, and dried to give 14.9 g (89%) clear colorless oil. R_f = 0.21 (1:3 EA/hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.20-5.09 (m, 2H), 4.81 (d, 1H, *J* = 8.4 Hz), 3.64-3.56 (m, 1H), 3.46 (d, 2H, *J* = 4.8 Hz), 1.88-1.79 (m, 1H), 0.97 (d, 3H, *J* = 6.6 Hz), 0.94 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3, 136.6, 128.8, 128.4, 128.3, 67.1, 56.3, 53.2, 29.9, 19.6, 18.6.



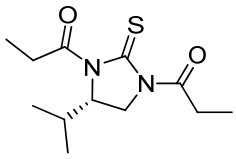
(*S*)-3-methylbutane-1,2-diamine (117). Dried compound **116** (14.8 g, 56.4 mmol) was dissolved in 75 mL 3 M MeOH-HCl solution and put under argon. A 2.96 g (20% by weight) portion of 10% palladium on carbon was added to a 500 mL hydrogenation

vessel and the vessel was evacuated and inert gas flushed. The starting material solution was then transferred under argon to the hydrogenation vessel by cannula. The vessel was set for hydrogenation at 90 psi for 24 h using a Parr hydrogenator. The solution was filtered through a short pad of Celite to give a clear yellow oil that was dried under vacuum. Powdered sodium hydroxide was added to the oil with stirring and some additional methanol to reach a pH of 10. The solution was concentrated by and set for distillation (voltameter 45, under pump vacuum at 5 mbar). The main product was collected between 40-45 °C as a clear oil of mass 3.35 g (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75-2.67 (m, 1H), 2.60 (bs, 4H), 2.44-2.35 (m, 2H), 1.60-1.48 (m, 1H), 0.84 (t, 6H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.0, 45.5, 31.8, 19.3, 17.8.



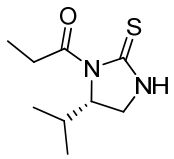
(*S*)-4-isopropylimidazolidine-2-thione (118). Compound **117** (2.77 g, 27.1 mmol) was added to a 25 mL RBF and dissolved in DI (5.0 mL) and ethanol (5.0 mL). The flask was fitted with a condenser and placed in a room temperature oil bath. Carbon disulfide (0.35 mL) was then added slowly dropwise. The oil bath was heated to 80 °C and the remaining carbon disulfide was added (1.79 mL total, 29.8 mmol, 1.10 eq) slowly so as not to precipitate any solid out of solution. (Note: after about 1.5 mL carbonyl disulfide had been added, a solid did precipitate. This went back into solution eventually with the addition of 1 mL each of ethanol and DI and heating to 100 °C). The reaction mixture was then heated further to reflux for one hour and concentrated HCl (0.100 mL, 1.21 mmol, 0.050 eq) was added. The solution became dark green. It was then allowed to

reflux for 8 h. The solution was cooled, which caused the product to precipitate out of solution. The resulting precipitate was then filtered and washed with a small amount of cold ether to give 2.45 g (63%) grey-white crystalline solid after drying. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (bs, 1H), 6.98 (bs, 1H), 3.79-3.66 (m, 2H), 3.37 (t, 1H, *J* = 7.4 Hz), 1.79-1.66 (m, 1H), 0.91 (d, 3H, *J* = 6.4 Hz), 0.85 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 63.5, 48.4, 32.8, 18.3, 18.1.



(*S*)-1,1'-(4-isopropyl-2-thioxoimidazolidine-1,3-diyl)dipropan-1-one (119). A 100 mL RBF was charged with 4-isopropyl-imidazolidine-2-thione **118** (1.44 g, 10.0 mmol) and the flask was evacuated and inert gas flushed. Anhydrous DCM (35.0 mL) was then added, followed by 4-(dimethylamino)-pyridine (12 mg) and pyridine (2.02 mL, 25.0 mmol, 2.50 eq), and the solution was chilled in an ice bath. Propionyl chloride (2.39 mL, 27.5 mmol, 2.75 eq) was added slowly dropwise and the solution was allowed to equilibrate to room temperature and stir for 12 h. The solution was quenched with 25 mL water. The organic layer was separated, washed with brine, dried, filtered, and concentrated to give a yellow oil of crude mass 2.80 g. The oil was loaded neat onto a 150 mL silica column and run with 250 mL 5:1 hex/EA, then 250 mL 4:1 hex/EA. The main product containing fractions were combined and dried under vacuum to give 2.44 g (95%) of the diacylated imidazolidinethione. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52-4.45 (m, 1H), 3.96 (dd, 1H, *J* = 12.0, 2.4 Hz), 3.74 (dd, 1H, *J* = 12.4, 9.2 Hz), 3.38-3.10 (m, 4H), 2.32-2.20 (m, 1H), 1.16 (dt, 6H, *J* = 6.8, 1.2 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 0.75 (d,

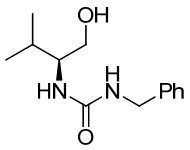
3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 176.5, 176.2, 59.5, 45.2, 33.0 (2C), 29.9, 18.4, 15.0, 9.1, 9.0.



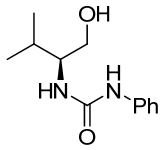
(*S*)-1-(5-isopropyl-2-thioxoimidazolidin-1-yl)propan-1-one (120). Compound **119** (0.256 g, 1.00 mmol) was added to an oven dried 25 mL RBF and the flask was evacuated and flushed with inert gas. Anhydrous THF (7.5 mL) was added and the solution was chilled to -78 °C. Potassium t-butoxide (1.00 mL 1.0 M soln. in THF, 1.00 mmol, 1.00 eq) was then added slowly dropwise and the reaction was stirred for 8 h. The solution was transferred dropwise while still cold to a stirring solution of 10 mL 1 M HCl. The aqueous layer was extracted with ethyl acetate (2 X 20 mL). The organic layers were combined, washed with brine, dried, filtered, and concentrated. The resulting pale brown oil was loaded onto a 12 g silica column and run in a 9:1 hex/EA solvent system. Product containing fractions were combined, concentrated, and dried under vacuum to give 0.053 g (23%) of the desired product as a cloudy colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (bs, 1H), 4.73-4.71 (m, 1H), 3.54 (t, 1H, *J* = 10.8 Hz), 3.44-3.24 (m, 2H), 2.40-2.30 (m, 1H), 1.15 (dt, 3H, *J* = 7.2, 1.8 Hz), 0.88 (d, 3H, *J* = 7.2 Hz), 0.83 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 175.6, 63.8, 41.6, 31.5, 29.4, 18.2, 14.8, 9.1.

Isocyanate Derived Auxiliaries and Azetines:

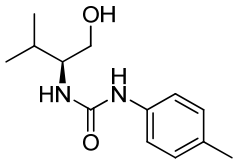
General Procedure for Formation of Ureas from L-Valinol and Isocyanates. Representative example for **124b**. A 5.16 g (50.0 mmol) portion of L-valinol was added to a 250 mL RBF with magnetic stirring bar and the flask was evacuated and flushed with argon. The valinol was completely dissolved in 100 mL of molecular sieve dried THF and the solution was chilled in an ice bath. After equilibration, a 5.98 mL (55 mmol, 1.10 eq) volume of phenyl isocyanate was added quickly dropwise. The solution was allowed to stir and gradually equilibrate to room temperature over the course of 18 h. The solvent was completely removed under vacuum and the resulting off-white solid was recrystallized in ethyl acetate/hexanes.



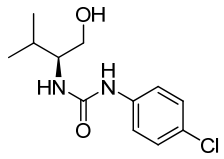
1-Benzyl-3-((*S*)-1-hydroxymethyl-2-methyl-propyl)-urea (124a). (75%) white solid; R_f = 0.14 (95:5 DCM/MeOH); mp 132-134 °C; $[\alpha]^{23}_D$ -29.5 (*c* 1.00, MeOH); ^{1}H NMR (600 MHz, DMSO) δ 7.33-7.20 (m, 5H), 6.32 (t, 1H, *J* = 5.6 Hz), 5.73 (d, 1H, *J* = 8.4 Hz), 4.60 (t, 1H, *J* = 4.8 Hz), 4.20 (d, 2H, *J* = 6.4 Hz), 3.42-3.37 (m, 2H), 3.30-3.25 (m, 1H), 1.86-1.78 (m, 1H), 0.85 (d, 3H, *J* = 7.2 Hz), 0.81 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO) δ 158.4, 141.1, 128.3, 127.0, 126.6, 62.0, 55.8, 42.9, 28.3, 19.9, 17.8; IR (solid): 3511, 3304, 2958, 2871, 1573, 1514, 1385, 1365, 1233, 1061, 694 cm^{-1}; HRMS-ESI *m/z* 237.1595 ($[M+H]^+$, $C_{13}H_{21}N_2O_2$ requires 237.1598).



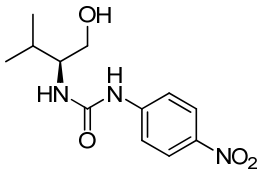
1-((*S*)-1-Hydroxymethyl-2-methyl-propyl)-3-phenyl-urea (124b). (79%) white solid; R_f = 0.17 (95:5 DCM/MeOH); mp 121-124 °C; $[\alpha]^{23}_D$ -45.1 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 8.45 (s, 1H), 7.36 (dd, 2H, *J* = 8.8, 1.2 Hz), 7.22-7.18 (m, 2H), 6.88-6.84 (m, 1H), 5.97 (d, 1H, *J* = 8.8 Hz), 4.68 (t, 1H, *J* = 5.2 Hz), 4.11 (q, 1H, *J* = 5.6 Hz), 3.17 (d, 2H, *J* = 5.2 Hz), 1.90-1.81 (m, 1H), 0.88 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO) δ 155.3, 140.7, 128.8, 120.9, 117.4, 61.6, 55.6, 28.4, 19.8, 18.0; IR (solid): 3304, 2959, 2873, 1634, 1551, 1442, 1387, 1368, 1229, 1073, 726 cm^{-1}; HRMS-ESI *m/z* 223.1438 ($[M+H]^+$, $C_{12}H_{19}N_2O_2$ requires 223.1441).



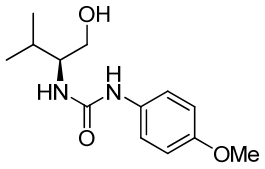
1-((*S*)-1-Hydroxymethyl-2-methyl-propyl)-3-*p*-tolyl-urea (124c). (99%) white solid; R_f = 0.19 (95:5 DCM/MeOH); mp 146-150 °C; $[\alpha]^{23}_D$ -34.3 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 8.35 (bs, 1H), 7.27-7.24 (m, 2H), 7.01 (d, 2H, *J* = 8.0 Hz), 5.92 (d, 1H, *J* = 8.4 Hz), 4.68 (t, 1H, *J* = 5.2 Hz), 3.48-3.42 (m, 2H), 3.37-3.31 (m, 1H), 2.20 (s, 3H), 1.88-1.83 (m, 1H), 0.88 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO) δ 155.3, 138.2, 129.5, 129.1, 117.4, 61.6, 55.5, 28.3, 20.3, 19.8, 17.9; IR (solid): 3315, 2963, 2874, 1592, 1559, 1405, 1389, 1227, 1060, 814 cm^{-1}; HRMS-ESI *m/z* 237.1594 ($[M+H]^+$, $C_{13}H_{21}N_2O_2$ requires 237.1598).



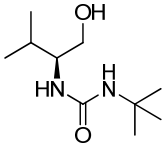
1-(4-Chloro-phenyl)-3-((*S*)-1-hydroxymethyl-2-methyl-propyl)-urea (124d). (91%) white solid; R_f = 0.21 (95:5 DCM/MeOH); mp 143-145 °C; $[\alpha]^{23}_D$ -42.3 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 8.61 (s, 1H), 7.39 (d, 2H, *J* = 8.4 Hz), 7.24 (d, 2H, *J* = 8.4 Hz), 6.01 (d, 1H, *J* = 8.0 Hz), 4.72 (s, 1H), 3.43-3.35 (m, 3H), 1.90-1.78 (m, 1H), 0.87 (d, 3H, *J* = 6.4 Hz), 0.84 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO) δ 155.1, 139.7, 128.6, 124.3, 118.9, 61.5, 55.6, 28.4, 19.8, 18.0; IR (solid): 3445, 3348, 2931, 2871, 1617, 1557, 1387, 1369, 1235, 1079, 819, 755 cm^{-1}; HRMS-ESI *m/z* 257.1047 ([M+H]$^+$, $C_{12}H_{18}ClN_2O_2$ requires 257.1051).



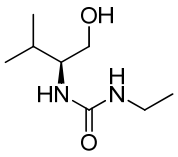
(*S*)-1-(1-hydroxy-3-methylbutan-2-yl)-3-(4-nitrophenyl)urea (124e). (67%) off-white solid; Rf = 0.10 (95:5 DCM/MeOH); mp 149-150 °C; $[\alpha]^{23}_D$ -51.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 9.25 (s, 1H), 8.13 (d, 2H, *J* = 9.2 Hz), 7.59 (d, 2H, *J* = 9.6 Hz), 6.28 (d, 1H, *J* = 8.4 Hz), 4.75 (s, 1H), 3-49-3.37 (m, 3H), 1.90-1.82 (m, 1H), 0.89 (d, 3H, *J* = 6.8 Hz), 0.86 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO) δ 154.4, 147.3, 140.3, 125.3, 116.6, 61.3, 55.8, 28.4, 19.7, 18.0; IR (solid): 3339, 2963, 1679, 1497, 1370, 1407, 1326, 1220, 1112, 844, 747 cm^{-1}; HRMS-ESI *m/z* 268.1289 ([M+H]$^+$, $C_{12}H_{18}N_3O_4$ requires 268.1292).



1-((*S*)-1-Hydroxymethyl-2-methyl-propyl)-3-(4-methoxy-phenyl)-urea (124f). (90%) white solid; R_f = 0.16 (95:5 DCM/MeOH); mp 150-153 °C; $[\alpha]^{23}_D$ -37.5 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 8.26 (s, 1H), 7.24 (d, 2H, *J* = 9.2 Hz), 6.76 (d, 2H, *J* = 8.8 Hz), 5.84 (d, 1H, *J* = 8.4 Hz), 4.62 (t, 1H, *J* = 4.8 Hz), 3.64 (s, 3H), 3.42-3.38 (m, 2H), 3.34-3.29 (m, 1H), 1.86-1.77 (m, 1H), 0.85 (d, 3H, *J* = 6.4 Hz), 0.81 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO) δ 155.5, 153.7, 133.9, 118.9, 113.9, 61.6, 55.5, 55.1, 28.3, 19.8, 17.9; IR (solid): 3390, 3289, 2957, 2873, 1633, 1556, 1505, 1388, 1367, 1243, 1178, 823 cm^{-1}; HRMS-ESI *m/z* 253.1543 ($[M+H]^+$, $C_{13}H_{21}N_2O_3$ requires 253.1547).

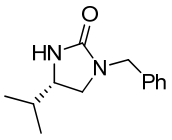


1-*tert*-Butyl-3-((*S*)-1-hydroxymethyl-2-methyl-propyl)-urea (124g). (99%) white solid; mp 138-141 °C; $[\alpha]^{23}_D$ -36.7 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 5.71 (s, 1H), 5.47 (d, 1H, *J* = 8.8 Hz), 4.58 (t, 1H, *J* = 5.2 Hz), 3.37-3.30 (m, 2H), 3.26-3.12 (m, 1H), 1.83-1.75 (m, 1H), 1.20 (s, 9H), 0.83 (d, 3H, *J* = 6.4 Hz), 0.78 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, DMSO) δ 157.7, 62.0, 55.1, 48.9, 29.4 (3C), 28.3, 19.8, 17.6; IR (solid): 3379, 3217, 2962, 2871, 1652, 1558, 1388, 1361, 1215, 1078, 976, 662 cm^{-1}; HRMS-ESI *m/z* 203.1751 ($[M+H]^+$, $C_{10}H_{23}N_2O_2$ requires 203.1754).

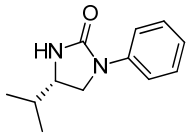


1-Ethyl-3-((*S*)-1-hydroxymethyl-2-methyl-propyl)-urea (124h). (72%) white solid; mp 99-101 °C; $[\alpha]^{23}_{D}$ -36.9 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (bs, 1H), 5.35 (d, 1H, *J* = 8.0 Hz), 4.27 (bs, 1H), 3.65 (dd, 1H, *J* = 10.8, 2.8 Hz), 3.56-3.46 (m, 2H), 3.20-3.13 (m, 2H), 1.85-1.77 (m, 1H), 1.10 (t, 3H, *J* = 7.2 Hz), 0.92 (t, 6H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 64.8, 58.1, 35.3, 29.7, 19.7, 18.9, 15.6; IR (solid): 3427, 3344, 2972, 2871, 1617, 1573, 1377, 1240, 1059, 971 cm^{-1}; HRMS-ESI *m/z* 175.1438 ($[M+H]^+$, $C_8H_{19}N_2O_2$ requires 175.1441).

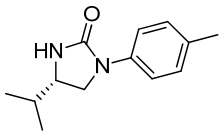
General Procedure for the Cyclization of Ureas to Imidazolidinones. Representative example for **125b**: Urea (8.76 g, 39.4 mmol) was dissolved in 100 mL THF and the flask was sealed, flushed with inert gas, and chilled in an ice bath. Postassium *t*-butoxide (11.2 g, 94.6 mmol, 2.40 eq) was added to the solution in portions. A 50 mL solution of tosyl chloride (9.02 g, 47.3 mmol, 1.20 eq) was then added to the solution dropwise over the course of 10 minutes. The reaction was quenched with DI (100 mL). The aqueous layer was extracted with ether (2 X 200 mL), the organic layers combined, washed with brine, dried, filtered, and concentrated. The recovered dark amber oil was loaded neat onto a 400 mL silica column in 99:1 DCM/MeOH (1 L, then 2 L 98:2).



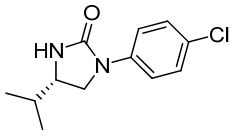
(*S*)-1-Benzyl-4-isopropyl-imidazolidin-2-one (125a). (90%) white solid; R_f = 0.25 (2:1 hex/EA); mp 38-40 °C; $[\alpha]^{23}_D$ +42.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 5.58 (s, 1H), 4.43-4.33 (m, 2H), 3.35 (d, 1H, *J* = 6.4 Hz), 2.18-2.13 (m, 1H), 1.86 (d, 1H, *J* = 4.4 Hz), 1.45-1.36 (m, 1H), 1.02 (d, 3H, *J* = 6.8 Hz), 0.95 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 138.6, 128.9, 127.7 (2C), 45.5, 45.0, 31.1 (2C), 20.2, 19.3; IR (solid): 3286, 3065, 2960, 2869, 1654, 1525, 1380, 1364, 1265, 1026, 734, 694 cm^{-1}; HRMS-ESI *m/z* 219.1491 ($[M+H]^+$, $C_{13}H_{19}N_2O$ requires 219.1492).



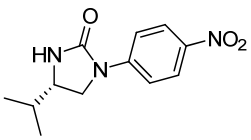
(*S*)-4-Isopropyl-1-phenyl-imidazolidin-2-one (125b). (19%) white solid; R_f = 0.25 (1:1 EA/hex); mp 111-113 °C; $[\alpha]^{23}_D$ -15.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, 2H, *J* = 7.2 Hz), 7.34 (t, 2H, *J* = 7.8 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 5.51 (s, 1H), 3.95 (t, 1H, *J* = 9.0 Hz), 3.58 (dd, 1H, *J* = 9.0, 7.2 Hz), 3.55 (dq, 1H, *J* = 6.6, 1.8 Hz), 1.80-1.74 (m, 1H), 1.00 (d, 3H, *J* = 6.6 Hz), 0.97 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 140.3, 129.0, 122.6, 117.8, 55.0, 49.2, 33.4, 18.3, 18.0; IR (solid): 3236, 3099, 2964, 2868, 1693, 1500, 1409, 1390, 1367, 1258, 747 cm^{-1}; HRMS-ESI *m/z* 205.1334 ($[M+H]^+$, $C_{12}H_{17}N_2O$ requires 205.1335).



(*S*)-4-Isopropyl-1-*p*-tolyl-imidazolidin-2-one (125c). (23%) white waxy solid; R_f = 0.22 (95:5 DCM/MeOH); mp 141-145 °C; $[\alpha]^{23}_D$ -21.2 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.42 (m, 2H), 7.14 (d, 2H, *J* = 8.4 Hz), 5.60 (s, 1H), 3.96-3.89 (m, 1H), 3.58-3.49 (m, 2H), 2.31 (s, 3H), 1.80-1.71 (m, 1H), 0.99 (d, 3H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 137.8, 132.2, 124.5, 117.9, 55.1, 49.4, 33.4, 20.9, 18.3, 18.0; IR (solid): 3224, 2961, 2871, 1697, 1514, 1406, 1368, 1313, 1222, 806, 754 cm^{-1}; HRMS-ESI *m/z* 219.1495 ($[M+H]^+$, $C_{13}H_{19}N_2O$ requires 219.1492).

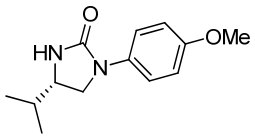


(*S*)-1-(4-Chloro-phenyl)-4-isopropyl-imidazolidin-2-one (125d). (39%) white solid; R_f = 0.15 (2:1 hex/EA); mp 138-141 °C; $[\alpha]^{23}_D$ -34.6 (*c* 1.00, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.46 (m, 2H), 7.28-7.24 (m, 2H), 6.00 (bs, 1H), 3.91-3.85 (m, 1H), 3.55-3.49 (m, 2H), 1.78 (m, 1H), 0.97 (d, 3H, *J* = 6.4 Hz), 0.94 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 138.9, 128.9, 127.5, 118.8, 54.9, 49.1, 33.3, 18.2, 17.9; IR (solid): 3238, 3098, 2961, 2872, 1694, 1494, 1402, 1370, 1262, 1089, 817, 754 cm^{-1}; HRMS-ESI *m/z* 239.0953 ($[M+H]^+$, $C_{12}H_{16}ClN_2O$ requires 239.0946).

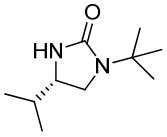


(*S*)-4-isopropyl-1-(4-nitrophenyl)imidazolidin-2-one (125e). (56%); R_f = 0.26 (1:1 ea/hex); mp 207-209 °C; $[\alpha]^{23}_D$ -40.6 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20-8.15 (m, 2H), 7.85-7.78 (m, 3H), 3.98 (t, 1H, *J* = 9.6 Hz), 3.59 (dd, 1H, *J* = 10.0, 6.4

Hz), 3.50 (dd, 1H, *J* = 15.6, 6.8 Hz), 1.72-1.59 (m, 1H), 0.88 (t, 6H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 146.6, 140.4, 124.7, 116.1, 53.6, 47.9, 32.7, 17.7, 17.5; IR (solid): 3213, 3101, 2960, 1716, 1594, 1500, 1389, 1368, 1260, 1111, 845, 750 cm^{-1}; HRMS-ESI *m/z* 250.1184 ($[M+H]^+$, $C_{12}H_{16}N_3O_3$ requires 250.1186).

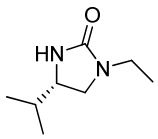


(*S*)-4-Isopropyl-1-(4-methoxy-phenyl)-imidazolidin-2-one (125f). (60%) off-white waxy solid; R_f = 0.50 (1:1 hex/EA); mp 49-52 °C; $[\alpha]^{23}_D$ +81.3 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, 2H, *J* = 8.8 Hz), 7.10 (s, 1H), 6.83-6.79 (m, 2H), 3.74 (s, 3H), 2.40 (d, 1H, *J* = 5.6 Hz), 2.27-2.22 (m, 1H), 1.92 (d, 1H, *J* = 4.0 Hz), 1.48-1.39 (m, 1H), 1.05 (d, 3H, *J* = 6.8 Hz), 0.95 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 156.1, 131.5, 121.0, 114.3, 55.7, 45.7, 31.5, 31.1, 20.2, 19.3; IR (solid): 3320, 3068, 2962, 2839, 1666, 1513, 1410, 1370, 1237, 1021, 823, 680 cm^{-1}; HRMS-ESI *m/z* 235.1446 ($[M+H]^+$, $C_{13}H_{19}N_2O_2$ requires 235.1441).



(*S*)-1-*tert*-Butyl-4-isopropyl-imidazolidin-2-one (125g). (38%) white solid; R_f = 0.60 (95:5 DCM/MeOH)); mp 68-70 °C; $[\alpha]^{23}_D$ +214.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.20 (s, 1H), 2.26 (d, 1H, *J* = 6.6 Hz), 2.08-2.05 (m, 1H), 1.79 (t, 1H, *J* = 3.6 Hz), 1.42-1.35 (m, 1H), 1.31 (s, 9H), 1.03 (d, 3H, *J* = 6.6 Hz), 0.95 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 50.9, 45.2, 31.2, 30.9, 29.0, 20.2, 19.4; IR

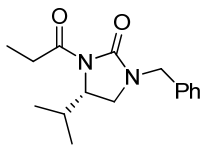
(solid): 3280, 3061, 2959, 1651, 1542, 1389, 1360, 1300, 1219, 1031, 662 cm^{-1}; HRMS-ESI *m/z* 185.1647 ($[M+H]^+$, $C_{10}H_{21}N_2O$ requires 185.1648).



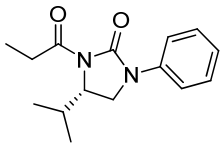
(*S*)-1-Ethyl-4-isopropyl-imidazolidin-2-one (125h). (88%) pale amber oil; R_f = 0.37 (95:5 DCM/MeOH); $[\alpha]^{23}_D$ +72.7 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (bs, 1H), 3.22-3.15 (m, 2H), 2.26 (d, 1H, *J* = 6.4 Hz), 2.09-2.05 (m, 1H), 1.79 (d, 1H, *J* = 4.4 Hz), 1.41-1.32 (m, 1H), 1.08 (t, 3H, *J* = 7.2 Hz), 1.00 (d, 3H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 45.1, 35.6, 31.0, 30.9, 20.1, 19.2, 15.1; IR (neat): 3306, 2961, 2874, 1656, 1519, 1377, 1363, 1291, 971, 852 cm^{-1}; HRMS-ESI *m/z* 157.1339 ($[M+H]^+$, $C_8H_{17}N_2O$ requires 157.1335).

General Procedure for Acylation of *N*-alkyl Imidazolidinones. Representative example for **126b:** A 100 mL RBF with magnetic stir bar was charged with compound **125b** (1.00 g, 4.90 mmol) and the flask was evacuated and inert gas flushed. The compound was then dissolved in 40 mL anhydrous THF and cooled to 0 °C. A 3.37 mL volume of 1.6 M butyl lithium in hexane (5.39 mmol, 1.10 eq) was then added dropwise and the solution was left to stir for 5-10 minutes. The propionyl chloride (0.510 mL, 5.87 mmol, 1.20 eq) was then added over 5 minutes and the reaction was stirred for one hour. The reaction was quenched half saturated aqueous ammonium chloride. The aqueous layer was extracted with ether (2 X 50 mL). The organic layers were combined, washed

with brine, dried, filtered, and concentrated. The crude oil was loaded neat onto a silica column and eluted with a 5-10% ethyl acetate in hexanes gradient.

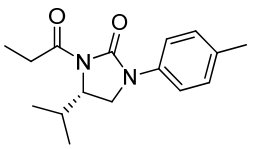


(*S*)-1-Benzyl-4-isopropyl-3-propionyl-imidazolidin-2-one (126a). (51%) colorless oil; R_f = 0.61 (2:1 hex/EA); $[\alpha]^{23}_D$ +47.6 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.21 (m, 5H), 5.16-5.06 (m, 2H), 3.02-2.86 (m, 2H), 2.44-2.40 (m, 1H), 2.13 (d, 1H, *J* = 6.4 Hz), 1.96 (d, 1H, *J* = 4.0 Hz), 1.57-1.47 (m, 1H), 1.15 (t, 3H, *J* = 8.0 Hz), 0.94 (d, 3H, *J* = 6.4 Hz), 0.87 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 165.2, 138.1, 128.6, 127.2, 127.1, 47.9, 45.5, 32.5, 32.1, 29.7, 19.8, 18.5, 9.7; IR (neat): 2962, 2876, 1694, 1403, 1352, 1175, 1022, 970, 696 cm^{-1}; HRMS-ESI *m/z* 275.1753 ($[M+H]^+$, $C_{16}H_{23}N_2O_2$ requires 275.1754).

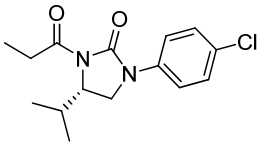


(*S*)-4-Isopropyl-1-phenyl-3-propionyl-imidazolidin-2-one (126b). (87%) white solid; R_f = 0.50 (2:1 hex/EA); mp 40-43 °C; $[\alpha]^{23}_D$ +73.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.54 (m, 2H), 7.42-7.37 (m, 2H), 7.18-7.15 (m, 1H), 4.46-4.42 (m, 1H), 3.91 (t, 1H, *J* = 9.6 Hz), 3.55 (dd, 1H, *J* = 9.6, 2.4 Hz), 3.12-2.89 (m, 2H), 2.48-2.38 (m, 1H), 1.20 (t, 3H, *J* = 7.6 Hz), 0.97 (d, 3H, *J* = 7.2 Hz), 0.85 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 153.3, 138.9, 129.2, 124.6, 119.3, 54.9, 43.4, 29.8,

29.1, 18.3, 14.8, 9.1; IR (film): 2961, 2875, 1725, 1682, 1371, 1240, 852, 757, 690 cm^{-1}; HRMS-ESI *m/z* 261.1595($[M+H]^+$, $C_{15}H_{21}N_2O_2$ requires 261.1598).

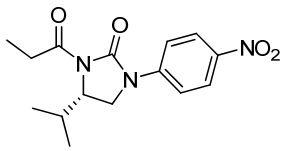


(*S*)-4-Isopropyl-3-propionyl-1-*p*-tolyl-imidazolidin-2-one (126c). (84%) white waxy solid; R_f = 0.49 (2:1 hex/EA); mp 44-48 °C; $[\alpha]^{23}_D$ +39.1 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (dt, 2H, *J* = 8.8, 2.4 Hz), 7.18 (d, 2H, *J* = 8.8 Hz), 4.42 (ddd, 1H, *J* = 9.6, 3.6, 2.4 Hz), 3.87 (t, 1H, *J* = 9.6 Hz), 3.52 (dd, 1H, *J* = 9.6, 2.8 Hz), 3.11-2.91 (m, 2H), 2.47-2.38 (m, 1H), 2.34 (s, 3H), 1.19, (t, 3H, *J* = 7.6 Hz), 0.95 (d, 3H, *J* = 6.8 Hz), 0.84 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 153.3, 136.3, 134.3, 129.7, 119.4, 54.9, 43.4, 29.7, 29.1, 21.0, 18.3, 14.7, 9.1; IR (solid): 2964, 1718, 1679, 1516, 1403, 1370, 1241, 819, 757, 740, 514 cm^{-1}; HRMS-ESI *m/z* 275.1753 ($[M+H]^+$, $C_{16}H_{23}N_2O_2$ requires 275.1754).

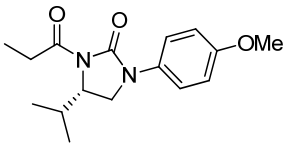


(*S*)-1-(4-Chloro-phenyl)-4-isopropyl-3-propionyl-imidazolidin-2-one (126d). (98%) white solid; R_f = 0.50 (2:1 hex/EA); mp 105-106 °C; $[\alpha]^{23}_D$ -34.6 (*c* 1.00, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.49 (m, 2H), 7.36-7.32 (m, 2H), 4.45-4.41 (m, 1H), 3.86 (t, 1H, *J* = 9.6 Hz), 3.52 (dd, 1H, *J* = 9.6, 2.8 Hz), 3.10-2.90 (m, 2H), 2.47-2.39 (m, 1H), 1.19 (t, 3H, *J* = 7.2 Hz), 0.96 (d, 3H, *J* = 6.8 Hz), 0.82 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 153.2, 137.5, 129.6, 129.2, 120.3; IR (solid): 2970, 2876,

1720, 1669, 1495, 1376, 1365, 1092, 823, 610 cm^{-1}; HRMS-ESI *m/z* 295.1215 ($[M+H]^+$, $C_{15}H_{20}ClN_2O_2$ requires 295.1208).

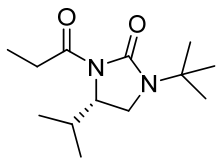


(*S*)-4-isopropyl-1-(4-nitrophenyl)-3-propionylimidazolidin-2-one (126e). (60%) pale tan solid; R_f = 0.53 (1:1 EA/hex); mp 88-90 ^oC; $[\alpha]^{23}_D$ +71.7 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.28-8.24 (m, 2H), 7.79-7.75 (m, 2H), 4.50-4.46 (m, 1H), 3.93 (t, 1H, *J* = 9.2 Hz), 3.62 (dd, 1H, *J* = 9.2, 2.8 Hz), 3.11-2.91 (m, 2H), 2.49-2.41 (m, 1H), 1.20 (t, 3H, *J* = 7.2 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 0.82 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 153.1, 144.7, 143.4, 125.1, 118.0, 54.8, 43.2, 30.0, 29.1, 18.3, 14.7, 8.9; IR (solid): 3074, 2965, 1731, 1699, 1594, 1513, 1502, 1391, 1373, 1327, 1224, 1113, 842, 748, 693 cm^{-1}; HRMS-ESI *m/z* 306.1447 ($[M+H]^+$, $C_{15}H_{20}N_3O_4$ requires 306.1448).

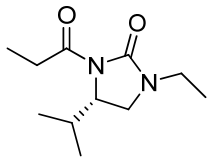


(*S*)-4-Isopropyl-1-(4-methoxy-phenyl)-3-propionyl-imidazolidin-2-one (126f). (40%) white solid; R_f = 0.36 (2:1 hex/EA); mp 85-88 °C; $[\alpha]^{23}_D$ +81.3 (*c* 1.00, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.11-7.07 (m, 2H), 6.97-6.92 (m, 2H), 3.83 (s, 3H), 2.96-2.90 (m, 2H), 2.38-2.34 (m, 1H), 2.17 (d, 1H, *J* = 6.4 Hz), 1.72 (d, 1H, *J* = 4.0 Hz), 1.18-1.12 (m, 1H), 1.16 (t, 3H, *J* = 7.2 Hz), 0.87 (d, 3H, *J* = 6.8 Hz), 0.63 (d, 3H, *J* = 6.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 164.0, 159.2, 131.4, 130.3, 114.5, 55.7, 46.2, 32.3, 31.5, 28.6, 19.8, 17.4, 9.4; IR (solid): 2968, 1703, 1513, 1367, 1345, 1228, 1076, 1021, 800, 592 cm^{-1}; HRMS-ESI *m/z* 291.1711 ([M+H]$^+$, $C_{16}H_{23}N_2O_3$ requires 291.1703).



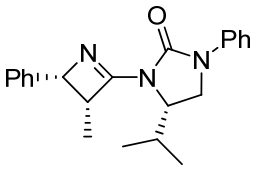
(*S*)-1-*tert*-Butyl-4-isopropyl-3-propionyl-imidazolidin-2-one (126g). (41%) clear oil; R_f = 0.64 (2:1 hex/EA); $[\alpha]^{23}_D$ -26.2 (*c* 1.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26-4.20 (m, 2H), 3.66 (dd, 1H, *J* = 15.6, 10.4 Hz), 2.94-2.84 (m, 1H), 2.57-2.47 (m, 1H), 2.10-2.03 (m, 1H), 1.37 (s, 9H), 1.15 (t, 3H, *J* = 7.2 Hz), 1.07 (d, 3H, *J* = 6.8 Hz), 1.03 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 153.2, 68.8, 51.2, 48.8, 32.8, 30.5, 29.0 (3 C), 20.3, 17.1, 9.1; IR (film): 2972, 1702, 1536, 1390, 1366, 1266, 1170, 907, 760, 703 cm^{-1}; HRMS-ESI *m/z* 241.1908 ([M+H]$^+$, $C_{13}H_{25}N_2O_2$ requires 241.1911).



(*S*)-1-Ethyl-4-isopropyl-3-propionyl-imidazolidin-2-one (126h). (46%) colorless oil; R_f = 0.65 (2:1 hex/EA); $[\alpha]^{23}_D$ +45.0 (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98-3.81 (m, 2H), 2.90-2.72 (m, 2H), 2.50-2.46 (m, 1H), 2.29 (d, 1H, *J* = 6.8 Hz), 2.11 (d, 1H, *J* = 3.6 Hz), 1.70-1.62 (m, 1H), 1.18 (t, 3H, *J* = 7.2 Hz), 1.10 (t, 3H, *J* = 7.2 Hz), 1.01 (d, 3H, *J* = 6.4 Hz), 0.92 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3,

165.0, 45.3, 40.0, 32.2, 31.9, 29.8, 19.9, 18.5, 14.2, 9.6; IR (neat): 2964, 2876, 1692, 1360, 1213, 1102, 1044, 795 cm^{-1}; HRMS-ESI *m/z* 213.1604 ($[M+H]^+$, $C_{11}H_{21}N_2O_2$ requires 213.1598).

General Procedure for Preparation of Azetines from *N*-Alkyl Imidazolidinone Auxiliaries. Representative example for **127b/128b:** An oven dried 50 mL RBF with magnetic stirring bar was charged with compound **126b** (0.260 g, 1.00 mmol) and 10 mL anhydrous dichloromethane. The solution was chilled to 0 °C and the flask was evacuated and argon flushed twice in succession. After temperature equilibration, a 0.439 mL (4.00 mmol, 4.00 eq) volume of $TiCl_4$ was added dropwise over the course of 5 minutes, followed immediately by dropwise addition of 0.574 mL (2.50 mmol, 2.50 eq) (-)-sparteine. The reaction mixture was stirred at 0 °C for 45 minutes. The oxime ether (0.405 g, 3.00 mmol, 3.00 eq) was added dropwise over the course of 5 minutes. The flask was allowed to equilibrate to room temperature after 30 minutes and stirred overnight. The solution was quenched after 24 h with half saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane (3 X 25 mL). The organic layers were combined and washed with saturated sodium bicarbonate and brine. The recovered organic layer was then dried, filtered and concentrated to give a pale amber, cloudy that was loaded neat onto a 50 mL silica and eluted with 99:1 dichloromethane/methanol. The two azetine diastereomers co-eluted. The azetine product fractions were combined, concentrated, and dried to give 0.232 g off-white solid. A second column was run with 70 mL silica in 500 mL 9:1 hex/EA, followed by 1 L 4:1 hex/EA.



(*S*)-4-Isopropyl-3-((3*R*,4*R*)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-1-phenyl-imidazolidin-2-one (127a). (22%) white solid; R_f = 0.34 (1:1 EA/hex); mp 138-141 °C; $[\alpha]^{23}_{D}$ +70.8 (*c* 1.00, $CHCl_3$);^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, 2H, *J* = 7.8 Hz), 7.40-7.33 (m, 4H), 7.25 (m, 3H), 7.13 (t, 1H, *J* = 7.2 Hz), 5.06 (d, 1H, *J* = 4.2 Hz), 4.46 (dt, 1H, *J* = 9.6, 3.0 Hz), 4.17 (dq, 1H, *J* = 4.8, 4.2 Hz), 4.05 (t, 1H, *J* = 9.6 Hz), 3.66 (dd, 1H, *J* = 9.6, 2.4 Hz), 2.93-2.86 (m, 1H), 1.02 (d, 3H, *J* = 7.2 Hz), 0.92 (dd, 6H, *J* = 7.2, 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 152.9, 139.8, 138.9, 129.2, 128.1, 127.3, 127.1, 124.1, 118.7, 65.9, 54.8, 45.6, 43.8, 27.7, 18.2, 14.1, 12.7; IR (solid): 3033, 2967, 2933, 1711, 1595, 1405, 1405, 1366, 1272, 1174, 971, 755, 735, 690 cm^{-1}; HRMS-ESI *m/z*: 348.2068 ($[M + H]^+$, $C_{22}H_{26}N_3O$ requires 348.2070); Anal. Calcd for $C_{22}H_{25}N_3O$: C, 76.05; H, 7.25; N, 12.09; O, 4.60. Found C, 75.78; H, 7.26; N, 11.87; O, 4.59.

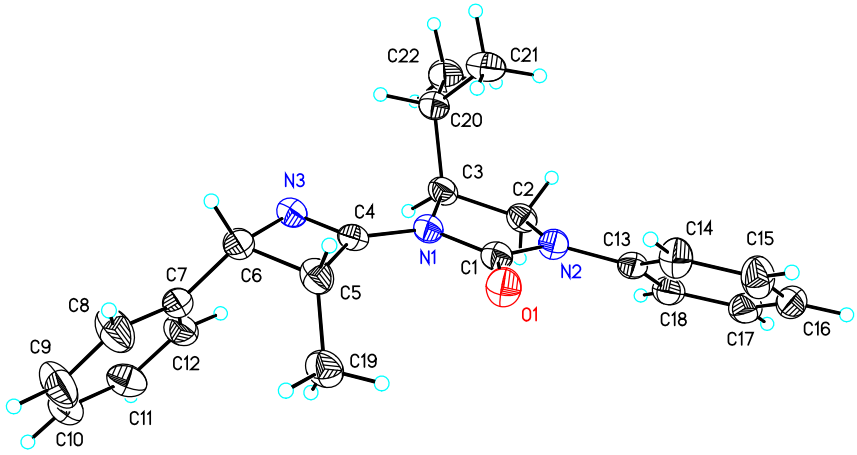


Table 7. Crystal data and structure refinement for compound **127a**.

Identification code	CMN196_0m	
Empirical formula	C22 H25 N3 O	
Formula weight	347.45	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.7914(2) Å	α = 90°.
	b = 15.6058(5) Å	β = 90°.
	c = 18.4686(6) Å	γ = 90°.
Volume	1957.40(11) $Å^3$	
Z	4	
Density (calculated)	1.179 Mg/m^3	
Absorption coefficient	0.576 mm^{-1}	
F(000)	744	
Crystal size	0.48 x 0.37 x 0.32 mm^3	
Theta range for data collection	8.59 to 66.13°.	
Index ranges	-7<=h<=7, -15<=k<=16, -18<=l<=21	
Reflections collected	8241	
Independent reflections	2998 [R(int) = 0.0204]	
Completeness to theta = 66.13°	92.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8372 and 0.7696	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2998 / 0 / 243	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0273, wR2 = 0.0744	
R indices (all data)	R1 = 0.0279, wR2 = 0.0749	
Absolute structure parameter	0.0(2)	
Extinction coefficient	0.0064(5)	
Largest diff. peak and hole	0.118 and -0.114 $e.Å^{-3}$	

Table 8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **127a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	221(2)	4265(1)	493(1)	36(1)
C(2)	3067(2)	3603(1)	939(1)	36(1)
C(3)	3451(2)	4570(1)	913(1)	37(1)
C(4)	1642(2)	5669(1)	196(1)	37(1)
C(5)	98(2)	6131(1)	-233(1)	42(1)
C(6)	1756(3)	6837(1)	-216(1)	45(1)
C(7)	2624(2)	7136(1)	-922(1)	42(1)
C(8)	1702(3)	7778(1)	-1306(1)	67(1)
C(9)	2456(4)	8058(1)	-1958(1)	76(1)
C(10)	4176(3)	7724(1)	-2226(1)	59(1)
C(11)	5097(3)	7084(1)	-1848(1)	55(1)
C(12)	4322(2)	6790(1)	-1201(1)	46(1)
C(13)	-60(2)	2746(1)	858(1)	35(1)
C(14)	-2034(2)	2731(1)	1038(1)	46(1)
C(15)	-2977(2)	1954(1)	1129(1)	54(1)
C(16)	-1985(3)	1192(1)	1046(1)	50(1)
C(17)	-26(3)	1207(1)	865(1)	49(1)
C(18)	944(2)	1979(1)	767(1)	41(1)
C(19)	-482(2)	5780(1)	-972(1)	50(1)
C(20)	3639(2)	5008(1)	1657(1)	45(1)
C(21)	1837(3)	4880(1)	2128(1)	59(1)
C(22)	5511(3)	4704(1)	2032(1)	59(1)
N(1)	1716(2)	4870(1)	515(1)	36(1)
N(2)	965(2)	3532(1)	790(1)	36(1)
N(3)	3021(2)	6233(1)	213(1)	47(1)
O(1)	-1426(1)	4377(1)	251(1)	47(1)

Table 9. Bond lengths [Å] and angles [°] for **127a**.

C(1)-O(1)	1.2168(16)
C(1)-N(2)	1.3653(17)
C(1)-N(1)	1.3867(18)
C(2)-N(2)	1.4581(17)
C(2)-C(3)	1.5326(19)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-N(1)	1.4658(17)
C(3)-C(20)	1.5382(19)
C(3)-H(3)	1.0000
C(4)-N(3)	1.2858(18)
C(4)-N(1)	1.3798(17)
C(4)-C(5)	1.4984(19)
C(5)-C(19)	1.523(2)
C(5)-C(6)	1.575(2)
C(5)-H(5)	1.0000
C(6)-N(3)	1.501(2)
C(6)-C(7)	1.506(2)
C(6)-H(6)	0.967(16)
C(7)-C(12)	1.373(2)
C(7)-C(8)	1.378(2)
C(8)-C(9)	1.379(3)
C(8)-H(8)	0.9500
C(9)-C(10)	1.371(3)
C(9)-H(9)	0.9500
C(10)-C(11)	1.369(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.384(2)
C(11)-H(11)	0.9500
C(12)-H(12)	0.9500
C(13)-C(14)	1.381(2)
C(13)-C(18)	1.388(2)
C(13)-N(2)	1.4166(17)
C(14)-C(15)	1.383(2)

C(14)-H(14)	0.9500
C(15)-C(16)	1.375(2)
C(15)-H(15)	0.9500
C(16)-C(17)	1.372(2)
C(16)-H(16)	0.9500
C(17)-C(18)	1.385(2)
C(17)-H(17)	0.9500
C(18)-H(18)	0.9500
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-C(21)	1.515(2)
C(20)-C(22)	1.524(2)
C(20)-H(20)	1.0000
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800

O(1)-C(1)-N(2)	127.40(12)
O(1)-C(1)-N(1)	125.86(12)
N(2)-C(1)-N(1)	106.74(11)
N(2)-C(2)-C(3)	103.62(11)
N(2)-C(2)-H(2A)	111.0
C(3)-C(2)-H(2A)	111.0
N(2)-C(2)-H(2B)	111.0
C(3)-C(2)-H(2B)	111.0
H(2A)-C(2)-H(2B)	109.0
N(1)-C(3)-C(2)	101.16(10)
N(1)-C(3)-C(20)	111.89(11)
C(2)-C(3)-C(20)	115.03(10)
N(1)-C(3)-H(3)	109.5
C(2)-C(3)-H(3)	109.5
C(20)-C(3)-H(3)	109.5

N(3)-C(4)-N(1)	125.58(13)
N(3)-C(4)-C(5)	101.15(11)
N(1)-C(4)-C(5)	133.27(13)
C(4)-C(5)-C(19)	118.79(12)
C(4)-C(5)-C(6)	79.96(11)
C(19)-C(5)-C(6)	116.98(12)
C(4)-C(5)-H(5)	112.5
C(19)-C(5)-H(5)	112.5
C(6)-C(5)-H(5)	112.5
N(3)-C(6)-C(7)	115.29(13)
N(3)-C(6)-C(5)	88.90(10)
C(7)-C(6)-C(5)	118.68(12)
N(3)-C(6)-H(6)	111.9(9)
C(7)-C(6)-H(6)	109.0(9)
C(5)-C(6)-H(6)	111.9(9)
C(12)-C(7)-C(8)	118.32(15)
C(12)-C(7)-C(6)	122.13(14)
C(8)-C(7)-C(6)	119.55(14)
C(7)-C(8)-C(9)	120.70(17)
C(7)-C(8)-H(8)	119.6
C(9)-C(8)-H(8)	119.6
C(10)-C(9)-C(8)	120.70(17)
C(10)-C(9)-H(9)	119.6
C(8)-C(9)-H(9)	119.6
C(11)-C(10)-C(9)	118.87(16)
C(11)-C(10)-H(10)	120.6
C(9)-C(10)-H(10)	120.6
C(10)-C(11)-C(12)	120.49(16)
C(10)-C(11)-H(11)	119.8
C(12)-C(11)-H(11)	119.8
C(7)-C(12)-C(11)	120.87(15)
C(7)-C(12)-H(12)	119.6
C(11)-C(12)-H(12)	119.6
C(14)-C(13)-C(18)	119.47(13)
C(14)-C(13)-N(2)	120.83(13)
C(18)-C(13)-N(2)	119.66(12)

C(13)-C(14)-C(15)	119.56(15)
C(13)-C(14)-H(14)	120.2
C(15)-C(14)-H(14)	120.2
C(16)-C(15)-C(14)	121.19(15)
C(16)-C(15)-H(15)	119.4
C(14)-C(15)-H(15)	119.4
C(17)-C(16)-C(15)	119.22(14)
C(17)-C(16)-H(16)	120.4
C(15)-C(16)-H(16)	120.4
C(16)-C(17)-C(18)	120.52(15)
C(16)-C(17)-H(17)	119.7
C(18)-C(17)-H(17)	119.7
C(17)-C(18)-C(13)	120.03(14)
C(17)-C(18)-H(18)	120.0
C(13)-C(18)-H(18)	120.0
C(5)-C(19)-H(19A)	109.5
C(5)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(5)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(21)-C(20)-C(22)	111.79(13)
C(21)-C(20)-C(3)	112.82(12)
C(22)-C(20)-C(3)	109.70(13)
C(21)-C(20)-H(20)	107.4
C(22)-C(20)-H(20)	107.4
C(3)-C(20)-H(20)	107.4
C(20)-C(21)-H(21A)	109.5
C(20)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(20)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(20)-C(22)-H(22A)	109.5
C(20)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5

C(20)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(4)-N(1)-C(1)	125.17(12)
C(4)-N(1)-C(3)	122.15(11)
C(1)-N(1)-C(3)	112.68(10)
C(1)-N(2)-C(13)	125.46(11)
C(1)-N(2)-C(2)	112.00(11)
C(13)-N(2)-C(2)	121.99(11)
C(4)-N(3)-C(6)	89.99(11)

Symmetry transformations used to generate equivalent atoms:

Table 10. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **127a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	38(1)	39(1)	31(1)	1(1)	-3(1)	1(1)
C(2)	33(1)	43(1)	33(1)	3(1)	-2(1)	2(1)
C(3)	36(1)	45(1)	30(1)	5(1)	-3(1)	-5(1)
C(4)	50(1)	37(1)	25(1)	-1(1)	0(1)	0(1)
C(5)	48(1)	39(1)	41(1)	5(1)	7(1)	10(1)
C(6)	68(1)	33(1)	35(1)	-2(1)	7(1)	3(1)
C(7)	61(1)	33(1)	34(1)	-2(1)	2(1)	0(1)
C(8)	96(1)	53(1)	53(1)	13(1)	23(1)	33(1)
C(9)	118(2)	59(1)	52(1)	22(1)	21(1)	35(1)
C(10)	88(1)	55(1)	35(1)	5(1)	9(1)	-3(1)
C(11)	54(1)	70(1)	40(1)	0(1)	4(1)	2(1)
C(12)	52(1)	50(1)	37(1)	4(1)	-5(1)	4(1)
C(13)	40(1)	37(1)	28(1)	2(1)	-8(1)	-3(1)
C(14)	38(1)	43(1)	58(1)	9(1)	-6(1)	2(1)
C(15)	42(1)	59(1)	62(1)	17(1)	-10(1)	-11(1)
C(16)	66(1)	43(1)	41(1)	9(1)	-15(1)	-14(1)
C(17)	70(1)	38(1)	39(1)	-1(1)	-4(1)	0(1)
C(18)	50(1)	41(1)	33(1)	-2(1)	0(1)	3(1)

C(19)	47(1)	55(1)	46(1)	11(1)	-12(1)	3(1)
C(20)	57(1)	45(1)	32(1)	3(1)	-7(1)	-10(1)
C(21)	75(1)	66(1)	36(1)	-9(1)	4(1)	-8(1)
C(22)	67(1)	66(1)	44(1)	8(1)	-22(1)	-17(1)
N(1)	40(1)	37(1)	31(1)	3(1)	-5(1)	-3(1)
N(2)	34(1)	36(1)	37(1)	2(1)	-4(1)	0(1)
N(3)	64(1)	44(1)	32(1)	5(1)	-6(1)	-13(1)
O(1)	40(1)	45(1)	55(1)	9(1)	-12(1)	0(1)

Table 11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **127a**.

	x	y	z	U(eq)
H(2A)	3851	3299	568	44
H(2B)	3389	3366	1422	44
H(3)	4662	4685	621	44
H(5)	-1071	6290	68	51
H(6)	1370(20)	7331(10)	65(8)	41(4)
H(8)	534	8030	-1120	81
H(9)	1778	8487	-2224	91
H(10)	4719	7933	-2666	71
H(11)	6277	6839	-2032	65
H(12)	4973	6343	-946	56
H(14)	-2738	3252	1099	55
H(15)	-4336	1945	1252	65
H(16)	-2648	662	1113	60
H(17)	670	683	806	59
H(18)	2298	1983	637	50
H(19A)	708	5644	-1249	74
H(19B)	-1256	6210	-1233	74
H(19C)	-1270	5259	-909	74
H(20)	3780	5637	1569	53
H(21A)	1680	4269	2237	88

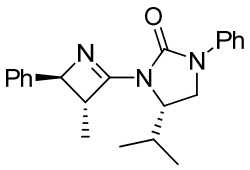
H(21B)	667	5088	1872	88
H(21C)	1998	5200	2581	88
H(22A)	5719	5038	2474	88
H(22B)	6637	4781	1706	88
H(22C)	5382	4096	2157	88

Table 12. Torsion angles [°] for **127a**.

N(2)-C(2)-C(3)-N(1)	-18.66(12)
N(2)-C(2)-C(3)-C(20)	102.11(13)
N(3)-C(4)-C(5)-C(19)	114.96(14)
N(1)-C(4)-C(5)-C(19)	-65.7(2)
N(3)-C(4)-C(5)-C(6)	-0.41(11)
N(1)-C(4)-C(5)-C(6)	178.98(15)
C(4)-C(5)-C(6)-N(3)	0.34(10)
C(19)-C(5)-C(6)-N(3)	-116.96(13)
C(4)-C(5)-C(6)-C(7)	118.80(14)
C(19)-C(5)-C(6)-C(7)	1.50(19)
N(3)-C(6)-C(7)-C(12)	8.7(2)
C(5)-C(6)-C(7)-C(12)	-94.86(18)
N(3)-C(6)-C(7)-C(8)	-171.21(15)
C(5)-C(6)-C(7)-C(8)	85.25(19)
C(12)-C(7)-C(8)-C(9)	0.7(3)
C(6)-C(7)-C(8)-C(9)	-179.39(18)
C(7)-C(8)-C(9)-C(10)	-2.2(3)
C(8)-C(9)-C(10)-C(11)	2.4(3)
C(9)-C(10)-C(11)-C(12)	-1.1(3)
C(8)-C(7)-C(12)-C(11)	0.5(2)
C(6)-C(7)-C(12)-C(11)	-179.35(15)
C(10)-C(11)-C(12)-C(7)	-0.3(2)
C(18)-C(13)-C(14)-C(15)	0.4(2)
N(2)-C(13)-C(14)-C(15)	-177.46(13)
C(13)-C(14)-C(15)-C(16)	0.2(2)
C(14)-C(15)-C(16)-C(17)	-0.4(2)
C(15)-C(16)-C(17)-C(18)	0.0(2)

C(16)-C(17)-C(18)-C(13)	0.5(2)
C(14)-C(13)-C(18)-C(17)	-0.7(2)
N(2)-C(13)-C(18)-C(17)	177.12(12)
N(1)-C(3)-C(20)-C(21)	57.22(15)
C(2)-C(3)-C(20)-C(21)	-57.48(17)
N(1)-C(3)-C(20)-C(22)	-177.45(11)
C(2)-C(3)-C(20)-C(22)	67.85(16)
N(3)-C(4)-N(1)-C(1)	-179.92(13)
C(5)-C(4)-N(1)-C(1)	0.8(2)
N(3)-C(4)-N(1)-C(3)	-0.7(2)
C(5)-C(4)-N(1)-C(3)	-179.94(13)
O(1)-C(1)-N(1)-C(4)	-7.2(2)
N(2)-C(1)-N(1)-C(4)	172.42(12)
O(1)-C(1)-N(1)-C(3)	173.46(13)
N(2)-C(1)-N(1)-C(3)	-6.88(15)
C(2)-C(3)-N(1)-C(4)	-162.96(11)
C(20)-C(3)-N(1)-C(4)	74.08(15)
C(2)-C(3)-N(1)-C(1)	16.36(14)
C(20)-C(3)-N(1)-C(1)	-106.60(13)
O(1)-C(1)-N(2)-C(13)	1.3(2)
N(1)-C(1)-N(2)-C(13)	-178.39(11)
O(1)-C(1)-N(2)-C(2)	172.89(14)
N(1)-C(1)-N(2)-C(2)	-6.76(15)
C(14)-C(13)-N(2)-C(1)	-38.65(19)
C(18)-C(13)-N(2)-C(1)	143.52(13)
C(14)-C(13)-N(2)-C(2)	150.51(13)
C(18)-C(13)-N(2)-C(2)	-27.32(18)
C(3)-C(2)-N(2)-C(1)	16.64(14)
C(3)-C(2)-N(2)-C(13)	-171.40(11)
N(1)-C(4)-N(3)-C(6)	-179.03(13)
C(5)-C(4)-N(3)-C(6)	0.42(12)
C(7)-C(6)-N(3)-C(4)	-121.85(13)
C(5)-C(6)-N(3)-C(4)	-0.39(11)

Symmetry transformations used to generate equivalent atoms:



(*S*)-4-Isopropyl-3-((3*R*,4*S*)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-1-phenyl-imidazolidin-2-one (128a). (39%) white solid; R_f = 0.23 (1:1 EA/hex); mp 145-148 °C; $[\alpha]^{23}_{D}$ +133.1 (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dt, 2H, *J* = 7.6, 1.2 Hz), 7.42-7.29 (m, 7H), 7.15 (t, 1H, *J* = 7.6 Hz), 4.44 (d, 1H, *J* = 1.6 Hz), 4.40 (dt, 1H, *J* = 9.6, 3.2 Hz), 4.04 (t, 1H, *J* = 9.6 Hz), 3.66 (dd, 1H, *J* = 9.6, 2.4 Hz), 3.60 (dq, 1H, *J* = 6.8, 1.6 Hz), 3.02-2.94 (m, 1H), 1.58 (d, 3H, *J* = 6.9 Hz), 1.01 (d, 3H, *J* = 6.8 Hz), 0.94 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 153.0, 141.6, 139.0, 129.3, 128.6, 127.5, 126.3, 124.2, 118.7, 70.5, 55.1, 50.7, 43.9, 27.8, 18.2, 16.0, 14.2; IR (solid): 3030, 2968, 2925, 1724, 1595, 1406, 1365, 1292, 1188, 758, 699 cm^{-1}; HRMS-ESI *m/z*: 348.2068 ($[M + H]^+$, $C_{22}H_{26}N_3O$ requires 348.2070); Anal. Calcd for $C_{22}H_{25}N_3O$: C, 76.05; H, 7.25; N, 12.09; O, 4.60. Found C, 75.80; H, 7.22; N, 11.94; O, 4.52.

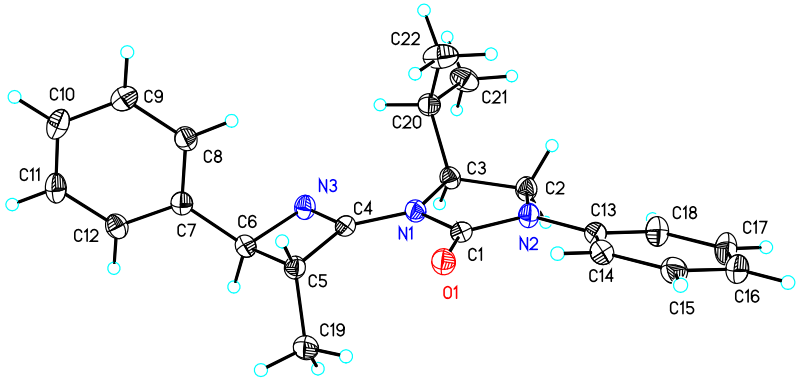


Table 13. Crystal data and structure refinement for **128a**.

Identification code	cmn196b_0m	
Empirical formula	C22 H25 N3 O	
Formula weight	347.45	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.41700(10) Å	α = 90°.
	b = 18.3781(5) Å	β = 90°.
	c = 19.1656(5) Å	γ = 90°.
Volume	1908.02(8) $Å^3$	
Z	4	
Density (calculated)	1.210 Mg/m^3	
Absorption coefficient	0.591 mm^{-1}	
F(000)	744	
Crystal size	0.52 x 0.23 x 0.16 mm^3	
Theta range for data collection	8.45 to 66.16°.	
Index ranges	-5<=h<=6, -21<=k<=20, -21<=l<=21	
Reflections collected	8089	
Independent reflections	2879 [R(int) = 0.0189]	
Completeness to theta = 66.16°	92.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9114 and 0.7488	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2879 / 0 / 238	
Goodness-of-fit on F^2	1.089	
Final R indices [I>2sigma(I)]	R1 = 0.0288, wR2 = 0.0700	
R indices (all data)	R1 = 0.0296, wR2 = 0.0706	
Absolute structure parameter	0.0(2)	
Largest diff. peak and hole	0.117 and -0.175 $e.Å^{-3}$	

Table 14. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **128a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1646(2)	10021(1)	9334(1)	25(1)
C(2)	666(3)	9988(1)	10528(1)	31(1)
C(3)	-947(3)	9416(1)	10158(1)	27(1)
C(4)	-1639(3)	9251(1)	8880(1)	25(1)
C(5)	-1556(3)	9349(1)	8099(1)	27(1)
C(6)	-3812(2)	8818(1)	8158(1)	27(1)
C(7)	-3631(2)	8098(1)	7795(1)	26(1)
C(8)	-1646(3)	7634(1)	7920(1)	30(1)
C(9)	-1425(3)	6983(1)	7562(1)	34(1)
C(10)	-3185(3)	6783(1)	7074(1)	36(1)
C(11)	-5185(3)	7233(1)	6957(1)	36(1)
C(12)	-5393(3)	7886(1)	7313(1)	30(1)
C(13)	4119(3)	10804(1)	10124(1)	28(1)
C(14)	5899(3)	10998(1)	9636(1)	31(1)
C(15)	7638(3)	11528(1)	9797(1)	36(1)
C(16)	7631(3)	11871(1)	10440(1)	39(1)
C(17)	5886(3)	11673(1)	10926(1)	41(1)
C(18)	4135(3)	11142(1)	10776(1)	37(1)
C(19)	-2027(3)	10088(1)	7769(1)	38(1)
C(20)	-554(3)	8628(1)	10394(1)	31(1)
C(21)	-1343(3)	8547(1)	11155(1)	42(1)
C(22)	2081(3)	8363(1)	10286(1)	48(1)
N(1)	-295(2)	9539(1)	9423(1)	27(1)
N(2)	2316(2)	10262(1)	9984(1)	28(1)
N(3)	-3435(2)	8796(1)	8940(1)	29(1)
O(1)	2541(2)	10189(1)	8775(1)	32(1)

Table 15. Bond lengths [Å] and angles [°] for **128a**.

C(1)-O(1)	1.2169(16)
C(1)-N(2)	1.3713(17)
C(1)-N(1)	1.3851(17)
C(2)-N(2)	1.4624(18)
C(2)-C(3)	1.5399(19)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-N(1)	1.4690(17)
C(3)-C(20)	1.531(2)
C(3)-H(3)	1.0000
C(4)-N(3)	1.2877(18)
C(4)-N(1)	1.3763(18)
C(4)-C(5)	1.5087(19)
C(5)-C(19)	1.5202(19)
C(5)-C(6)	1.568(2)
C(5)-H(5)	1.0000
C(6)-C(7)	1.498(2)
C(6)-N(3)	1.5131(17)
C(6)-H(6)	1.0000
C(7)-C(12)	1.385(2)
C(7)-C(8)	1.393(2)
C(8)-C(9)	1.383(2)
C(8)-H(8)	0.9500
C(9)-C(10)	1.386(2)
C(9)-H(9)	0.9500
C(10)-C(11)	1.381(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.385(2)
C(11)-H(11)	0.9500
C(12)-H(12)	0.9500
C(13)-C(14)	1.390(2)
C(13)-C(18)	1.395(2)
C(13)-N(2)	1.4206(18)
C(14)-C(15)	1.390(2)

C(14)-H(14)	0.9500
C(15)-C(16)	1.384(2)
C(15)-H(15)	0.9500
C(16)-C(17)	1.377(2)
C(16)-H(16)	0.9500
C(17)-C(18)	1.390(2)
C(17)-H(17)	0.9500
C(18)-H(18)	0.9500
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-C(22)	1.522(2)
C(20)-C(21)	1.527(2)
C(20)-H(20)	1.0000
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800

O(1)-C(1)-N(2)	127.86(12)
O(1)-C(1)-N(1)	124.94(12)
N(2)-C(1)-N(1)	107.20(11)
N(2)-C(2)-C(3)	104.71(10)
N(2)-C(2)-H(2A)	110.8
C(3)-C(2)-H(2A)	110.8
N(2)-C(2)-H(2B)	110.8
C(3)-C(2)-H(2B)	110.8
H(2A)-C(2)-H(2B)	108.9
N(1)-C(3)-C(20)	113.37(12)
N(1)-C(3)-C(2)	101.53(11)
C(20)-C(3)-C(2)	115.45(11)
N(1)-C(3)-H(3)	108.7
C(20)-C(3)-H(3)	108.7
C(2)-C(3)-H(3)	108.7

N(3)-C(4)-N(1)	125.64(12)
N(3)-C(4)-C(5)	100.85(11)
N(1)-C(4)-C(5)	133.51(12)
C(4)-C(5)-C(19)	121.01(12)
C(4)-C(5)-C(6)	80.27(10)
C(19)-C(5)-C(6)	117.09(12)
C(4)-C(5)-H(5)	111.7
C(19)-C(5)-H(5)	111.7
C(6)-C(5)-H(5)	111.7
C(7)-C(6)-N(3)	115.25(11)
C(7)-C(6)-C(5)	117.76(11)
N(3)-C(6)-C(5)	89.02(10)
C(7)-C(6)-H(6)	111.0
N(3)-C(6)-H(6)	111.0
C(5)-C(6)-H(6)	111.0
C(12)-C(7)-C(8)	118.31(13)
C(12)-C(7)-C(6)	120.85(13)
C(8)-C(7)-C(6)	120.81(12)
C(9)-C(8)-C(7)	120.75(14)
C(9)-C(8)-H(8)	119.6
C(7)-C(8)-H(8)	119.6
C(8)-C(9)-C(10)	120.26(15)
C(8)-C(9)-H(9)	119.9
C(10)-C(9)-H(9)	119.9
C(11)-C(10)-C(9)	119.44(14)
C(11)-C(10)-H(10)	120.3
C(9)-C(10)-H(10)	120.3
C(10)-C(11)-C(12)	120.12(14)
C(10)-C(11)-H(11)	119.9
C(12)-C(11)-H(11)	119.9
C(11)-C(12)-C(7)	121.09(14)
C(11)-C(12)-H(12)	119.5
C(7)-C(12)-H(12)	119.5
C(14)-C(13)-C(18)	118.94(14)
C(14)-C(13)-N(2)	122.00(12)
C(18)-C(13)-N(2)	119.05(13)

C(15)-C(14)-C(13)	120.05(13)
C(15)-C(14)-H(14)	120.0
C(13)-C(14)-H(14)	120.0
C(16)-C(15)-C(14)	121.01(15)
C(16)-C(15)-H(15)	119.5
C(14)-C(15)-H(15)	119.5
C(17)-C(16)-C(15)	118.92(15)
C(17)-C(16)-H(16)	120.5
C(15)-C(16)-H(16)	120.5
C(16)-C(17)-C(18)	120.94(14)
C(16)-C(17)-H(17)	119.5
C(18)-C(17)-H(17)	119.5
C(17)-C(18)-C(13)	120.14(15)
C(17)-C(18)-H(18)	119.9
C(13)-C(18)-H(18)	119.9
C(5)-C(19)-H(19A)	109.5
C(5)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(5)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(22)-C(20)-C(21)	111.13(13)
C(22)-C(20)-C(3)	113.15(13)
C(21)-C(20)-C(3)	109.67(13)
C(22)-C(20)-H(20)	107.5
C(21)-C(20)-H(20)	107.5
C(3)-C(20)-H(20)	107.5
C(20)-C(21)-H(21A)	109.5
C(20)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(20)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(20)-C(22)-H(22A)	109.5
C(20)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5

C(20)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(4)-N(1)-C(1)	123.70(11)
C(4)-N(1)-C(3)	122.54(11)
C(1)-N(1)-C(3)	113.52(11)
C(1)-N(2)-C(13)	125.43(12)
C(1)-N(2)-C(2)	111.96(11)
C(13)-N(2)-C(2)	121.86(11)
C(4)-N(3)-C(6)	89.80(10

Symmetry transformations used to generate equivalent atoms:

Table 16. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **128a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	28(1)	21(1)	27(1)	0(1)	-3(1)	1(1)
C(2)	36(1)	32(1)	25(1)	-1(1)	0(1)	-4(1)
C(3)	28(1)	30(1)	22(1)	0(1)	-1(1)	-1(1)
C(4)	28(1)	22(1)	25(1)	-2(1)	-2(1)	1(1)
C(5)	30(1)	26(1)	24(1)	-1(1)	0(1)	-2(1)
C(6)	25(1)	30(1)	24(1)	-1(1)	-2(1)	0(1)
C(7)	27(1)	28(1)	22(1)	2(1)	4(1)	-5(1)
C(8)	31(1)	32(1)	28(1)	0(1)	-3(1)	-2(1)
C(9)	37(1)	28(1)	38(1)	1(1)	4(1)	0(1)
C(10)	44(1)	30(1)	34(1)	-8(1)	9(1)	-8(1)
C(11)	37(1)	40(1)	30(1)	-7(1)	0(1)	-12(1)
C(12)	28(1)	36(1)	27(1)	0(1)	0(1)	-3(1)
C(13)	29(1)	25(1)	32(1)	-1(1)	-6(1)	1(1)
C(14)	32(1)	30(1)	29(1)	0(1)	-5(1)	0(1)
C(15)	34(1)	36(1)	38(1)	6(1)	-6(1)	-5(1)
C(16)	37(1)	34(1)	47(1)	-3(1)	-10(1)	-7(1)
C(17)	40(1)	40(1)	42(1)	-15(1)	-5(1)	-5(1)
C(18)	34(1)	41(1)	34(1)	-8(1)	1(1)	-4(1)

C(19)	50(1)	32(1)	33(1)	6(1)	-8(1)	-5(1)
C(20)	36(1)	29(1)	28(1)	3(1)	-2(1)	-3(1)
C(21)	40(1)	49(1)	36(1)	14(1)	1(1)	-1(1)
C(22)	53(1)	42(1)	50(1)	10(1)	11(1)	15(1)
N(1)	33(1)	26(1)	23(1)	2(1)	-2(1)	-4(1)
N(2)	31(1)	28(1)	24(1)	-3(1)	0(1)	-5(1)
N(3)	31(1)	30(1)	26(1)	-3(1)	2(1)	-4(1)
O(1)	37(1)	32(1)	26(1)	2(1)	0(1)	-7(1)

Table 17. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **128a**.

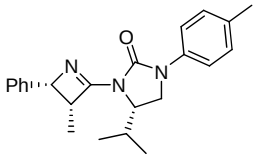
	x	y	z	U(eq)
H(2A)	-364	10385	10720	37
H(2B)	1619	9763	10913	37
H(3)	-2722	9546	10227	32
H(5)	-86	9104	7889	32
H(6)	-5388	9071	8036	32
H(8)	-431	7766	8254	36
H(9)	-60	6672	7652	41
H(10)	-3018	6341	6822	43
H(11)	-6420	7094	6631	43
H(12)	-6768	8194	7224	36
H(14)	5925	10769	9192	37
H(15)	8850	11657	9460	43
H(16)	8812	12238	10543	47
H(17)	5878	11901	11370	49
H(18)	2947	11010	11117	44
H(19A)	-3469	10314	7989	57
H(19B)	-2337	10027	7268	57
H(19C)	-579	10400	7836	57
H(20)	-1661	8313	10106	37
H(21A)	-1287	8032	11287	62

H(21B)	-3029	8731	11212	62
H(21C)	-220	8825	11454	62
H(22A)	3209	8655	10572	72
H(22B)	2528	8411	9793	72
H(22C)	2201	7851	10425	72

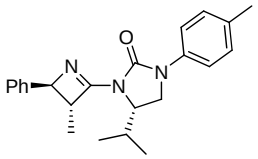
Table 18. Torsion angles [°] for **128a**.

N(2)-C(2)-C(3)-N(1)	-9.94(14)
N(2)-C(2)-C(3)-C(20)	113.11(13)
N(3)-C(4)-C(5)-C(19)	117.83(15)
N(1)-C(4)-C(5)-C(19)	-61.6(2)
N(3)-C(4)-C(5)-C(6)	1.98(11)
N(1)-C(4)-C(5)-C(6)	-177.47(16)
C(4)-C(5)-C(6)-C(7)	-119.89(13)
C(19)-C(5)-C(6)-C(7)	120.15(14)
C(4)-C(5)-C(6)-N(3)	-1.66(9)
C(19)-C(5)-C(6)-N(3)	-121.62(12)
N(3)-C(6)-C(7)-C(12)	132.83(13)
C(5)-C(6)-C(7)-C(12)	-124.06(14)
N(3)-C(6)-C(7)-C(8)	-49.11(17)
C(5)-C(6)-C(7)-C(8)	54.00(17)
C(12)-C(7)-C(8)-C(9)	1.0(2)
C(6)-C(7)-C(8)-C(9)	-177.14(13)
C(7)-C(8)-C(9)-C(10)	-0.1(2)
C(8)-C(9)-C(10)-C(11)	-1.1(2)
C(9)-C(10)-C(11)-C(12)	1.5(2)
C(10)-C(11)-C(12)-C(7)	-0.6(2)
C(8)-C(7)-C(12)-C(11)	-0.6(2)
C(6)-C(7)-C(12)-C(11)	177.51(13)
C(18)-C(13)-C(14)-C(15)	-0.8(2)
N(2)-C(13)-C(14)-C(15)	-179.57(13)
C(13)-C(14)-C(15)-C(16)	-0.2(2)
C(14)-C(15)-C(16)-C(17)	0.9(2)
C(15)-C(16)-C(17)-C(18)	-0.7(2)

C(16)-C(17)-C(18)-C(13)	-0.3(2)
C(14)-C(13)-C(18)-C(17)	1.0(2)
N(2)-C(13)-C(18)-C(17)	179.80(14)
N(1)-C(3)-C(20)-C(22)	56.86(17)
C(2)-C(3)-C(20)-C(22)	-59.67(17)
N(1)-C(3)-C(20)-C(21)	-178.44(12)
C(2)-C(3)-C(20)-C(21)	65.03(16)
N(3)-C(4)-N(1)-C(1)	179.20(13)
C(5)-C(4)-N(1)-C(1)	-1.5(2)
N(3)-C(4)-N(1)-C(3)	-6.7(2)
C(5)-C(4)-N(1)-C(3)	172.60(14)
O(1)-C(1)-N(1)-C(4)	-7.6(2)
N(2)-C(1)-N(1)-C(4)	172.24(13)
O(1)-C(1)-N(1)-C(3)	177.87(13)
N(2)-C(1)-N(1)-C(3)	-2.30(15)
C(20)-C(3)-N(1)-C(4)	68.79(17)
C(2)-C(3)-N(1)-C(4)	-166.74(12)
C(20)-C(3)-N(1)-C(1)	-116.60(13)
C(2)-C(3)-N(1)-C(1)	7.87(15)
O(1)-C(1)-N(2)-C(13)	4.6(2)
N(1)-C(1)-N(2)-C(13)	-175.18(12)
O(1)-C(1)-N(2)-C(2)	174.87(14)
N(1)-C(1)-N(2)-C(2)	-4.95(15)
C(14)-C(13)-N(2)-C(1)	-19.2(2)
C(18)-C(13)-N(2)-C(1)	161.98(14)
C(14)-C(13)-N(2)-C(2)	171.46(13)
C(18)-C(13)-N(2)-C(2)	-7.3(2)
C(3)-C(2)-N(2)-C(1)	9.69(15)
C(3)-C(2)-N(2)-C(13)	-179.68(12)
N(1)-C(4)-N(3)-C(6)	177.49(14)
C(5)-C(4)-N(3)-C(6)	-2.03(11)
C(7)-C(6)-N(3)-C(4)	122.38(12)
C(5)-C(6)-N(3)-C(4)	1.92(11)

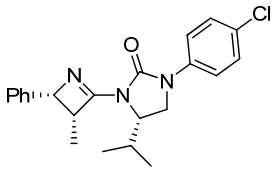


(*S*)-4-Isopropyl-3-((3*R*,4*R*)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-1-*p*-tolyl-imidazolidin-2-one (127b). Prepared according to the method described for compound **127a**: (22%) white solid; R_f = 0.17 (2:1 hex/EA); mp 158-161 °C; $[\alpha]^{23}_D$ +61.5 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.42 (m, 2H), 7.37-7.33 (m, 2H), 7.28-7.25 (m, 3H), 7.19 (d, 2H, *J* = 8.4 Hz), 5.06 (d, 1H, *J* = 4.4 Hz), 4.45 (dt, 1H, *J* = 9.6, 2.8 Hz), 4.20-4.14 (m, 1H), 4.04 (t, 1H, *J* = 9.6 Hz), 3.64 (dd, 1H, *J* = 9.6, 2.8 Hz), 2.94-2.86 (m, 1H), 2.34 (s, 3H), 1.01 (d, 3H, *J* = 6.8 Hz), 0.93 (d, 3H, *J* = 3.2 Hz), 0.91 (d, 3H, *J* = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 153.0, 139.9, 136.4, 133.8, 129.8, 128.1, 127.4, 127.1, 118.8, 65.9, 54.8, 45.5, 43.9, 27.7, 21.0, 18.2, 14.1, 12.7; IR (solid): 2962, 2928, 1706, 1594, 1517, 1402, 1271, 1199, 975, 804, 735, 698, 509 cm^{-1}; HRMS-ESI *m/z* 362.2220 ($[M+H]^+$, $C_{23}H_{28}N_3O$ requires 362.2227).

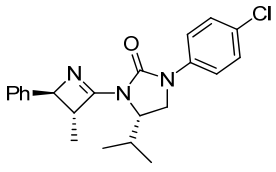


(*S*)-4-Isopropyl-3-((3*R*,4*S*)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-1-*p*-tolyl-imidazolidin-2-one (128b). (44%) waxy off-white solid; R_f = 0.45 (95:5 DCM/MeOH); $[\alpha]^{23}_D$ +83.8 (*c* 0.70, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, 2H, *J* = 8.4 Hz), 7.39-7.27 (m, 5H), 7.19 (d, 2H, *J* = 8.0 Hz), 4.43 (d, 1H, *J* = 1.6 Hz), 4.38 (dt, 1H, *J* = 9.6, 3.2 Hz), 4.02 (t, 1H, *J* = 9.2 Hz), 3.63 (dd, 1H, *J* = 10, 2.8 Hz), 3.59 (dq, 1H, *J* = 7.2,

1.6 Hz), 3.01-2.93 (m, 1H), 2.34 (s, 3H), 1.58 (d, 3H, *J* = 7.6 Hz), 1.00 (d, 3H, *J* = 7.6 Hz), 0.94 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 153.0, 141.6, 136.4, 133.9, 129.8, 128.6, 127.5, 126.3, 118.9, 70.5, 55.1, 50.7, 44.0, 27.8, 21.0, 18.2, 16.0, 14.2; IR (film): 3030, 2961, 1725, 1598, 1517, 1405, 1370, 1293, 1181, 1104, 969, 815, 699 cm^{-1}; HRMS-ESI *m/z* 362.2219 ([M+H]$^+$, $C_{23}H_{28}N_3O$ requires 362.2227).

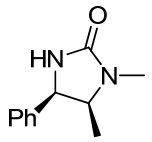


(*S*)-1-(4-Chloro-phenyl)-4-isopropyl-3-((3*R*,4*R*)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-imidazolidin-2-one (127c). (21%) white solid; R_f = 0.20 (1:1 hex/EA); mp 143-146 °C; $[\alpha]^{23}_D$ +42.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 2H), 7.37-7.25 (m, 7H), 5.06 (d, 1H, *J* = 4.4 Hz), 4.47 (dt, 1H, *J* = 9.6, 3.2 Hz), 4.20-4.13 (m, 1H), 4.01 (t, 1H, *J* = 9.6 Hz), 3.64 (dd, 1H, *J* = 9.6, 2.8 Hz), 2.96-2.88 (m, 1H), 1.02 (d, 3H, *J* = 6.8 Hz), 0.91 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 152.8, 139.8, 137.6, 129.2, 129.2, 128.1, 127.3, 127.2, 119.7, 65.9, 54.8, 45.6, 43.7, 27.7, 18.2, 14.1, 12.7; IR (solid): 2968, 2932, 1709, 1592, 1579, 1489, 1397, 1370, 1270, 1168, 1120, 977, 737, 701, 508 cm^{-1}; HRMS-ESI *m/z* 382.1679 ([M+H]$^+$, $C_{22}H_{25}ClN_3O$ requires 382.1681).



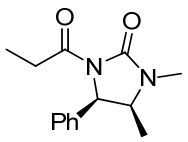
(*S*)-1-(4-Chloro-phenyl)-4-isopropyl-3-((3*R*,4*S*)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-imidazolidin-2-one (128c). (24%) white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56-7.24 (m, 9H), 4.44 (s, 1H), 4.39 (dt, 1H, *J* = 9.0, 3.0 Hz), 4.00 (t, 1H, *J* = 9.6 Hz), 3.63 (dd, 1H, *J* = 9.6, 2.4 Hz), 3.58 (dq, 1H, *J* = 7.2, 1.8 Hz), 3.01-2.95 (m, 1H), 1.57 (d, 3H, *J* = 7.2 Hz), 1.01 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 6.6 Hz).

Ephedrine Derived Auxiliaries and Azetines:



(4*R*,5*S*)-1,5-Dimethyl-4-phenyl-imidazolidin-2-one (131). A 250 mL RBF was charged with (1*R*,2*S*)-(-)-ephedrine hydrochloride (25.0 g, 124.0 mmol), and urea (22.3 g, 372 mmol, 3.00 eq). The flask was fitted with a condenser and heated at 170-175 °C in a pre-heated oil bath for 30 minutes. The resulting clear colorless melt was then heated at 200-210 °C for 1 hour. The flask was then cooled to 95 °C and 20 mL DI was added, which caused a white precipitate to form. The precipitate was filtered and washed with 20-40 mL portions of 5% aqueous HCl and DI. The resulting solid was redissolved in a minimum amount of ethanol at 60 °C and recrystallized on cooling to give 11.52 g (49%) white crystalline solid. R_f = 0.26 (95:5 DCM/MeOH); mp = 158-161 °C; $[\alpha]^{23}_D$ -41.7 (*c* 0.90, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.00 (s, 1H), 4.74 (d, 1H, *J* = 8.4 Hz), 3.86 (dq, 1H, *J* = 8.4, 6.4 Hz), 2.72 (s, 3H), 0.72 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 138.0, 128.3, 127.9, 127.0, 57.9, 57.5, 27.9, 14.1; IR (film): 3258 (br), 2972, 2856, 1652, 1436, 1262, 1089, 1069, 703 cm^{-1}; HRMS-ESI *m/z*

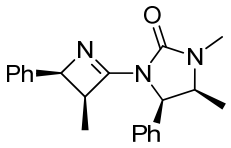
191.1180 ([M+H]$^+$, $C_{11}H_{15}N_2O$ requires 191.1179); Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73; O, 8.41. Found C, 68.28; H, 7.42; N, 14.89; O, 8.90.



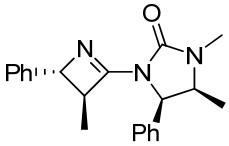
(4*R*,5*S*)-1,5-Dimethyl-4-phenyl-3-propionyl-imidazolidin-2-one (132). A 500 mL RBF was charged with compound **131** (9.51 g, 50.0 mmol). A 150 mL volume of anhydrous THF was added. The mixture was chilled in an ice bath and 24.0 mL 2.5 M butyl lithium (60.0 mmol, 1.20 eq) was added quickly dropwise. After 30 minutes, propionyl chloride (6.52 mL, 75.0 mmol, 1.50 eq) was added. The reaction was quenched after 1 h with 50 mL saturated aqueous bicarbonate solution and the THF was removed by rotary evaporation. The residue was partitioned between DCM and DI. The aqueous layer was extracted with DCM (3 X 75 mL). The organic layers were combined, washed with brine, dried, filtered, and concentrated to give a pale amber solid. The solid was recrystallized from hex/EA and washed with cold hexane to give 10.7 g (87%) white crystalline solid. R_f = 0.33 (1:1 EA/hex); mp = 106-107 °C; $[\alpha]^{23}_D$ -51.1 (*c* 1.00, CH_2Cl_2) {lit.[48] $[\alpha]^{23}_D$ -54.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.18 (m, 3H), 7.08-7.06 (m, 2H), 5.21 (d, 1H, *J* = 8.8 Hz), 3.82 (dq, 1H, *J* = 8.8, 6.8 Hz), 2.92 (q, 2H, *J* = 7.6 Hz), 2.75 (s, 3H), 1.03 (t, 3H, *J* = 7.6 Hz), 0.73 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 156.2, 137.0, 128.7, 128.2, 127.1, 59.5, 54.2, 29.5, 28.3, 15.1, 8.7; IR (film): 3034, 2980, 2941, 2880, 1729, 1687, 1455, 1374, 1258, 1058, 946, 703 cm^{-1}; HRMS-ESI *m/z* 247.1441 ([M+H]$^+$, $C_{14}H_{19}N_2O_2$ requires 247.1441);

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37; O, 12.99. Found C, 68.21; H, 7.46; N, 11.37; O, 13.01.

General procedure for azetine synthesis via oxime addition to ephedrine derived auxiliary. Representative example for **133a/134a**: An oven dried 500 mL RBF was charged with auxiliary **132** (1.00 g, 4.06 mmol) was added with 150 mL anhydrous DCM (0.02 M). The solution was chilled to 0 °C, evacuated and inert gas flushed twice, and the titanium tetrachloride (1.78 mL, 16.2 mmol, 4.00 eq) was added, followed after 5 minutes by dropwise addition of (-)-sparteine (2.33 mL, 10.2 mmol, 2.50 eq). The solution gradually thickened and darkened to a dark purple. This was left to stir for 30 minutes. The oxime (2.33 g, 12.2 mmol, 3.00 eq) was then added. The solution was left to warm gradually to room temperature and stir for 48 h. The mixture had lightened to a medium brown color. The solution was cooled in an ice bath and a 50 mL volume of half saturated ammonium chloride was added. The organic phase was removed and the aqueous phase was extracted with dichloromethane (2 X 50 mL). The organic layers were combined, washed with aqueous sodium bicarbonate and brine, dried, filtered, and concentrated to give a dark amber oil. The oil was loaded neat onto a 120 g silica column and run on a 1-10% IPA in hex gradient over 20 CV. The initially eluting main peak fractions were separately isolated and concentrated to reveal to give 0.602 g white solid. This product is known to be the *cis* isomer. The second main product was isolated as 0.334 g white solid (*trans* isomer). Total yield was 69% with a ratio of 1.8:1 *cis* to *trans*.

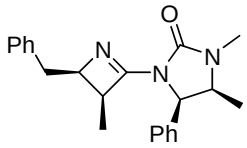


(4*R*,5*S*)-1,5-Dimethyl-3-((3*S*,4*S*)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-4-phenyl-imidazolidin-2-one (133a). (0.602 g, 45%) white solid; R_f = 0.25 (95:5 DCM/MeOH); mp 162-165 ^oC; $[\alpha]^{23}_D$ +214.2 (*c* 1.00, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.18 (m, 10H), 5.31 (d, 1H, *J* = 8.0 Hz), 4.80 (d, 1H, *J* = 4.4 Hz), 4.08-4.01 (m, 2H), 2.82 (s, 3H), 0.95 (d, 3H, *J* = 7.6 Hz), 0.83 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.4, 140.1, 136.0, 128.8, 128.4, 127.9, 127.5, 127.3, 127.0, 65.5, 58.6, 55.9, 45.0, 28.2, 15.0, 12.8; IR (film): 3030, 2976, 2934, 1718, 1602, 1459, 1397, 1285, 969, 907, 703 cm^{-1}; HRMS-ESI *m/z* 334.1914 ($[M+H]^+$, $C_{21}H_{24}N_3O$ requires 334.1914); Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60; O, 4.80. Found C, 75.36; H, 7.12; N, 12.55; O, 4.86.

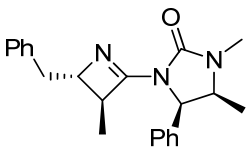


(4*R*,5*S*)-1,5-Dimethyl-3-((3*S*,4*R*)-3-methyl-4-phenyl-3,4-dihydro-azet-2-yl)-4-phenyl-imidazolidin-2-one (134a). (0.334 g, 25%) white solid; R_f = 033 (95:5 DCM/MeOH); mp 144-146 ^oC; $[\alpha]^{23}_D$ +32.7 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (m, 3H), 7.27-7.24 (m, 2H), 7.15-7.13 (m, 3H), 6.88-6.84 (m, 2H), 5.26 (d, 1H, *J* = 8.4 Hz), 4.31 (d, 1H, *J* = 1.6 Hz), 4.09-4.02 (m, 1H), 3.30 (dq, 1H, *J* = 7.2, 1.6 Hz), 2.84 (s, 3H), 1.61 (d, 3H, *J* = 8.4 Hz), 0.89 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 156.3, 141.7, 136.0, 128.7, 128.3, 128.2, 127.5, 127.0, 125.9,

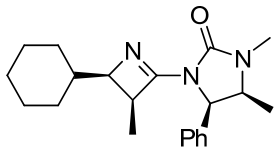
69.9, 59.0, 55.6, 50.8, 28.2, 16.1, 15.1; IR (film): 2960, 2933, 1721, 1598, 1426, 1397, 1293, 1181, 957, 783, 747, 706 cm^{-1}; HRMS-ESI *m/z* 334.1913 ($[M+H]^+$, $C_{21}H_{24}N_3O$ requires 334.1914); Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60; O, 4.80. Found C, 75.53; H, 6.92; N, 12.58; O, 4.81.



(4*S*,5*R*)-1-((3*S*,4*R*)-4-Benzyl-3-methyl-3,4-dihydro-azet-2-yl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (133b). (0.307 g, 22%) white solid; R_f = 0.33 (95:5 DCM/MeOH); mp = 180-183; $[\alpha]^{23}_D$ +10.2 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.11 (m, 10H), 5.15 (d, 1H, *J* = 8.4 Hz), 4.02-3.93 (m, 2H), 3.81-3.75 (m, 1H), 3.14 (dd, 1H, *J* = 14.8, 4.8 Hz), 2.75 (dd, 1H, *J* = 14.8, 10.0 Hz), 2.77 (s, 3H), 1.35 (d, 3H, *J* = 7.6 Hz), 0.76 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 156.4, 139.3, 135.9, 129.0, 128.8, 128.5, 128.4, 127.2, 126.1, 63.7, 58.4, 55.8, 43.2, 37.2, 28.1, 14.9, 11.8; IR (solid): 2932, 1713, 1569, 1426, 1399, 1262, 738, 699 cm^{-1}; HRMS-ESI *m/z* 348.2060 ($[M+H]^+$, $C_{22}H_{26}N_3O$ requires 348.2070); Anal. Calcd for $C_{21}H_{25}N_3O$: C, 76.05; H, 7.25; N, 12.09; O, 4.60. Found C, 76.06; H, 7.29; N, 12.09; O, 4.60.

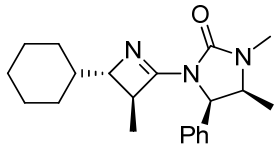


(4*S*,5*R*)-1-((3*S*,4*S*)-4-Benzyl-3-methyl-3,4-dihydro-azet-2-yl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (134b). (0.773 g, 55%) off white solid; R_f = 0.33 (95:5 DCM/MeOH); mp = 84-87; $[\alpha]^{23}_D$ -15.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.33 (m, 3H), 7.19-7.15 (m, 5H), 6.97-6.96 (m, 2H), 5.14 (d, 1H, *J* = 8.4 Hz), 3.98 (m, 1H), 3.44 (dt, 1H, *J* = 5.2, 1.2 Hz), 3.24 (dq, 1H, *J* = 7.2, 1.2 Hz), 2.83 (dd, 1H, *J* = 13.6, 5.6 Hz), 2.79 (s, 3H), 2.54 (dd, 1H, *J* = 13.6, 8.0 Hz), 1.33 (d, 3H, *J* = 7.2 Hz), 0.81 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 156.4, 138.7, 135.9, 129.1, 128.6, 128.3, 128.1, 127.4, 126.1, 68.7, 58.8, 55.7, 45.7, 41.0, 28.2, 15.6, 15.0; IR (film): 3028, 2930, 1720, 1597, 1422, 1393, 1260, 973, 751, 699 cm^{-1}; HRMS-ESI *m/z* 348.2067 ($[M+H]^+$, $C_{22}H_{26}N_3O$ requires 348.2070); Anal. Calcd for $C_{21}H_{25}N_3O$: C, 76.05; H, 7.25; N, 12.09; O, 4.60. Found C, 75.93; H, 7.28; N, 12.07; O, 4.78.

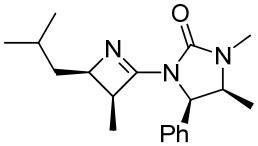


(4*S*,5*R*)-1-((3*S*,4*R*)-4-Cyclohexyl-3-methyl-3,4-dihydro-azet-2-yl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (133c). (0.354 g, 26%) white solid; R_f = 0.27 (95:5 DCM/MeOH); mp = 150-153; $[\alpha]^{23}_D$ -2.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.23 (m, 3H), 7.13-7.11 (m, 2H), 5.12 (d, 1H, *J* = 8.4 Hz), 3.90 (m, 1H), 3.70 (m, 1H), 3.15 (dd, 1H, *J* = 10.8, 3.6 Hz), 2.74 (s, 3H), 1.99 (d, 1H, *J* = 13.2 Hz), 1.69-1.61 (m, 4H), 1.38 (d, 3H, *J* = 7.2 Hz), 1.37-1.33 (m, 1H), 1.21-1.11 (m, 3H), 0.92 (dq, 1H, *J* = 12.6, 2.4 Hz), 0.79 (dq, 1H, *J* = 12.6, 2.4 Hz), 0.73 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 156.6, 136.0, 128.6, 128.2, 127.2, 67.9, 58.3, 56.0, 42.6, 39.3,

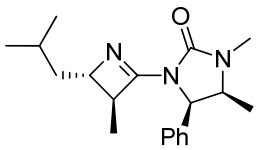
30.4, 30.3, 28.1, 26.8, 26.2, 26.0, 14.9, 11.9; IR (film): 2919, 2848, 1710, 1596, 1426, 1397, 1260, 751, 700 cm^{-1}; HRMS-ESI *m/z* 340.2379 ($[M+H]^+$, $C_{21}H_{30}N_3O$ requires 340.2383); Anal. Calcd for $C_{21}H_{29}N_3O$: C, 74.30; H, 8.61; N, 12.38; O, 4.71. Found C, 69.94; H, 8.26; N, 11.25; O, 4.70.



(4*S*,5*R*)-1-((3*S*,4*S*)-4-Cyclohexyl-3-methyl-3,4-dihydro-azet-2-yl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (134c). (0.637 g, 46%) white solid; R_f = 0.29 (95:5 DCM/MeOH); mp = 118-120; $[\alpha]^{23}_D$ -47.3 (*c* 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.29-7.23 (m, 3H), 7.12 (d, 2H, *J* = 7.2 Hz), 5.11 (d, 1H, *J* = 8.4 Hz), 3.97-3.93 (m, 1H), 3.25 (q, 1H, *J* = 7.2 Hz), 2.98 (d, 1H, *J* = 7.2 Hz), 2.77 (s, 3H), 1.58-1.56 (m, 4H), 1.40 (d, 3H, *J* = 7.2 Hz), 1.34 (d, 1H, *J* = 12.0 Hz), 1.23-1.18 (m, 1H), 1.07-1.00 (m, 3H), 0.85-0.73 (m, 2H), 0.79 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 156.6, 135.9, 128.4, 128.0, 127.4, 72.9, 58.7, 55.6, 43.4, 41.9, 29.1, 28.2, 28.1, 26.6, 26.0 (2 C), 16.3, 15.1; IR (film): 2920, 2851, 1723, 1599, 1422, 1394, 1369, 1349, 1286, 1260, 753, 700 cm^{-1}; HRMS-ESI *m/z* 340.2380 ($[M+H]^+$, $C_{21}H_{30}N_3O$ requires 340.2383); Anal. Calcd for $C_{21}H_{29}N_3O$: C, 74.30; H, 8.61; N, 12.38; O, 4.71. Found C, 74.15; H, 8.58; N, 12.34; O, 4.73.

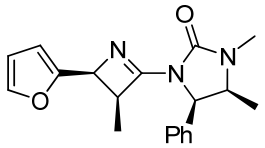


(4*S*,5*R*)-1-((3*S*,4*R*)-4-Isobutyl-3-methyl-3,4-dihydro-azet-2-yl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (133d). (0.334 g, 26%) waxy solid; R_f = 0.33 (95:5 DCM/MeOH); $[\alpha]^{23}_D$ +30.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.23 (m, 3H), 7.12 (d, 2H, *J* = 7.2 Hz), 5.10 (d, 1H, *J* = 7.8 Hz), 3.94-3.89 (m, 1H), 3.72-3.68 (m, 1H), 3.65-3.62 (m, 1H), 2.74 (s, 3H), 1.67-1.60 (m, 1H), 1.47-1.42 (m, 1H), 1.37-1.33 (m, 1H), 1.31 (d, 3H, *J* = 7.2 Hz), 0.84 (d, 6H, *J* = 6.0 Hz), 0.73 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 156.5, 136.0, 128.7, 128.3, 127.2, 61.6, 58.3, 55.8, 42.7, 40.2, 28.1, 25.4, 23.3, 23.0, 14.9, 11.6; IR (film): 2957, 2914, 1711, 1597, 1463, 1428, 1398, 1365, 1263, 743, 701 cm^{-1}; HRMS-ESI *m/z* 314.2223 ($[M+H]^+$, $C_{19}H_{28}N_3O$ requires 314.2227); Anal. Calcd for $C_{19}H_{27}N_3O$: C, 72.81; H, 8.68; N, 13.41; O, 5.10. Found C, 71.66; H, 8.68; N, 12.80; O, 6.77.

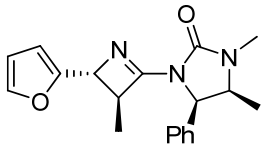


(4*S*,5*R*)-1-((3*S*,4*S*)-4-Isobutyl-3-methyl-3,4-dihydro-azet-2-yl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (134d). (0.441 g, 35%) waxy solid; R_f = 0.27 (95:5 DCM/MeOH); $[\alpha]^{23}_D$ -51.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.22 (m, 3H), 7.10 (d, 2H, *J* = 7.8 Hz), 5.08 (d, 1H, *J* = 7.8 Hz), 3.96-3.90 (m, 1H), 3.21 (dd, 1H, *J* = 9.0, 5.4 Hz), 3.10 (q, 1H, *J* = 7.2 Hz), 2.75 (s, 3H), 1.52-1.47 (m, 1H), 1.41 (d, 3H, *J* = 7.2 Hz), 1.39-1.35 (m, 1H), 1.07-1.02 (m, 1H), 0.76 (t, 9H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 156.5, 135.8, 128.5, 128.1, 127.3, 67.1, 58.7, 55.7, 46.8, 44.1, 28.2, 26.0, 23.2, 23.0, 15.9, 15.0; IR (film): 2954, 2928, 2868, 1723, 1601, 1424, 1394,

1261, 753, 700 cm^{-1}; HRMS-ESI *m/z* 314.2224 ($[M+H]^+$, $C_{19}H_{28}N_3O$ requires 348.2227); Anal. Calcd for $C_{19}H_{27}N_3O$: C, 72.81; H, 8.68; N, 13.41; O, 5.10. Found C, 71.15; H, 8.79; N, 12.82; O, 7.36.

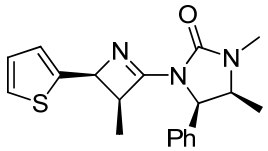


(4*S*,5*R*)-1-((3*S*,4*S*)-4-Furan-2-yl-3-methyl-3,4-dihydro-azet-2-yl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (133e). (0.448 g, 34%) off white solid; R_f = 0.35 (95:5 DCM/MeOH); mp = 135-138; $[\alpha]^{23}_D$ -86.6 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 4H), 7.18-7.16 (m, 2H), 6.27 (dd, 1H, *J* = 3.2, 1.6 Hz), 6.17 (d, 1H, *J* = 3.2 Hz), 5.23 (d, 1H, *J* = 8.4 Hz), 4.72 (d, 1H, *J* = 4.4 Hz), 4.04-3.94 (m, 2H), 2.78 (s, 3H), 1.17 (d, 3H, *J* = 7.2 Hz), 0.78 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 156.2, 153.8, 142.2, 135.8, 128.8, 128.4, 127.3, 110.2, 108.3, 60.2, 58.5, 55.8, 45.7, 28.2, 15.0, 12.8; IR (film): 2973, 2934, 1722, 1597, 1459, 1423, 1394, 1286, 1261, 974, 733, 701 cm^{-1}; HRMS-ESI *m/z* 324.21706 ($[M+H]^+$, $C_{19}H_{22}N_3O$ requires 324.1707); Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57.; H, 6.55; N, 12.99; O, 9.89. Found C, 68.80; H, 6.64; N, 12.43; O, 10.20.



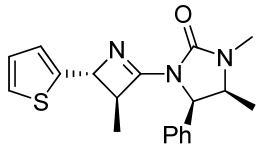
(4*S*,5*R*)-1-((3*S*,4*R*)-4-Furan-2-yl-3-methyl-3,4-dihydro-azet-2-yl)-3,4-dimethyl-5-phenyl-imidazolidin-2-one (134e). (0.387 g, 30%) off white solid; R_f = 0.33 (95:5

DCM/MeOH); mp = 154-157; $[\alpha]^{23}_{D}$ -71.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.15 (m, 6H), 6.13 (q, 1H, *J* = 3.0, 1.8 Hz), 5.68 (d, 1H, *J* = 3.0 Hz), 5.15 (d, 1H, *J* = 8.4 Hz), 4.27 (s, 1H), 4.00-3.96 (m, 1H), 3.59 (q, 1H, *J* = 15.0, 7.2 Hz), 2.78 (s, 3H), 1.53 (d, 3H, *J* = 7.2 Hz), 0.80 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 156.2, 154.8, 141.7, 135.5, 128.6, 128.2, 127.3, 110.3, 106.0, 63.4, 58.9, 55.7, 48.2, 28.2, 15.9, 15.1; IR (film): 2970, 2931, 1716, 1597, 1456, 1426, 1398, 1291, 1169, 965, 751, 742, 702 cm^{-1}; HRMS-ESI *m/z* 324.1706 ($[M+H]^+$, $C_{19}H_{22}N_3O$ requires 324.1707); Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57.; H, 6.55; N, 12.99; O, 9.89. Found C, 70.56; H, 6.52; N, 12.92; O, 9.89.

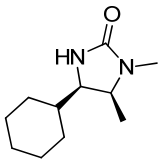


(4*R*,5*S*)-1,5-Dimethyl-3-((3*S*,4*S*)-3-methyl-4-thiophen-2-yl-3,4-dihydro-azet-2-yl)-4-phenyl-imidazolidin-2-one (133f). (0.320 g, 23%) off white solid; R_f = 0.26 (95:5 DCM/MeOH); mp = 171-174; $[\alpha]^{23}_{D}$ -174.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 3H), 7.22-7.19 (m, 3H), 6.97 (dt, 1H, *J* = 3.6, 3.2 Hz), 6.88 (d, 1H, *J* = 3.6 Hz), 5.28 (d, 1H, *J* = 8.0 Hz), 4.99 (d, 1H, *J* = 4.4 Hz), 4.09-3.99 (m, 2H), 2.82 (s, 3H), 1.13 (d, 3H, *J* = 7.6 Hz), 0.82 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 156.2, 143.8, 135.8, 128.8, 128.4, 127.3, 126.8, 124.9, 124.2, 62.1, 58.5, 55.8, 45.7, 28.2, 15.0, 12.9; IR (film): 2971, 2931, 1721, 1593, 1458, 1423, 1394, 1366, 1284, 1260, 752, 730, 700 cm^{-1}; HRMS-ESI *m/z* 340.1477 ($[M+H]^+$, $C_{19}H_{22}N_3OS$

requires 340.1478); Anal. Calcd for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.24; N, 12.38; O, 4.71. Found C, 67.17; H, 6.37; N, 12.32; O, 4.70.

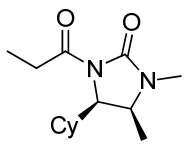


(4*R*,5*S*)-1,5-Dimethyl-3-((3*S*,4*R*)-3-methyl-4-thiophen-2-yl-3,4-dihydro-azet-2-yl)-4-phenyl-imidazolidin-2-one (134f). (0.527 g, 38%) off white solid; R_f = 0.29 (95:5 DCM/MeOH); mp = 166-169; $[\alpha]^{23}_D$ -10.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 3H), 7.24-7.22 (m, 2H), 7.07 (dd, 1H, *J* = 5.2, 1.2 Hz), 6.82 (dd, 1H, *J* = 5.2, 3.6 Hz), 6.61 (d, 1H, *J* = 3.6 Hz), 5.22 (d, 1H, *J* = 8.0 Hz), 4.53 (d, 1H, *J* = 1.2 Hz), 4.07-4.00 (m, 1H), 3.48 (dq, 1H, *J* = 7.6, 1.2 Hz), 2.83 (s, 3H), 1.59 (d, 3H, *J* = 7.2 Hz), 0.86 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 156.2, 145.8, 135.6, 128.7, 128.3, 127.4, 126.6, 124.1, 123.7, 65.9, 58.9, 55.6, 51.6, 28.2, 15.9, 15.1; IR (film): 2965, 2929, 1717, 1593, 1425, 1397, 1367, 1290, 752, 729, 700 cm^{-1}; HRMS-ESI *m/z* 340.1477 ($[M+H]^+$, $C_{19}H_{22}N_3OS$ requires 340.1478); Anal. Calcd for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.24; N, 12.38; O, 4.71. Found C, 67.14; H, 6.24; N, 12.27; O, 4.70.



(4*R*,5*S*)-4-cyclohexyl-1,5-dimethylimidazolidin-2-one (135). A Parr hydrogenating vessel was charged with 30 mL DI, rhodium trichloride hydrate (0.189 g, 0.902 mmol, 0.0478 eq), Aliquat 336 (0.472 mL), 30 mL dichloroethane, and ephedrine auxiliary **131**

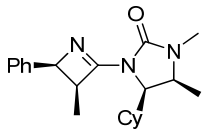
(3.59 g, 18.9 mmol). The vessel was sealed, evacuated, flushed with hydrogen and agitated at 70-75 psi. The mixture was left to stir a total of 36 h. The solution was filtered through acidic alumina in a fine frit glass filter funnel. The solution was then treated with activated charcoal and re-filtered through Celite in a medium frit glass filter funnel to give a clear, mostly colorless filtrate. The solution was somewhat grey on concentration. This was filtered once more through Celite to give a pale amber solution that was concentrated to reveal an off-white solid. The solid was recrystallized from a minimum amount of ethyl acetate to give 1.91 g (53%) white crystalline product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (bs, 1H), 3.62-3.55 (m, 1H), 3.27 (dt, 1H, J = 9.2, 1.6 Hz), 2.73 (s, 3H), 1.78-1.42 (m, 6H), 1.31-0.85 (m, 5H), 1.08 (d, 3H, J = 6.4 Hz).



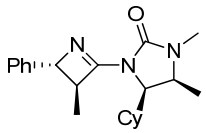
(4*R*,5*S*)-4-cyclohexyl-1,5-dimethyl-3-propionylimidazolidin-2-one (136). A 100 mL RBF was charged with compound **135** (1.13 g, 5.76 mmol) and the flask was evacuated and flushed with inert gas. Anhydrous THF was added to prepare a 0.30 M solution. The solution was chilled to 0 °C. A 3.96 mL volume of 1.6 M butyllithium was then added quickly dropwise and the solution was stirred for 30 minutes. Propionyl chloride (0.750 mL, 8.64 mmol, 1.50 eq) was then added and the solution was left to equilibrate to room temperature and stir overnight. The reaction was quenched with sodium bicarbonate solution (25 mL). The THF was removed by evaporation and the remaining aqueous phase was extracted with DCM (3 X 25 mL). The organic layers were combined, washed with brine, dried, filtered, and concentrated to give a pale amber

oil. The oil was loaded neat onto a 40 g silica column and eluted with 0-100% EA in hex over 20 minutes. The main product was isolated as 1.10 g (76%) white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (dd, 1H, *J* = 6.8, 2.8 Hz), 3.66-3.59 (m, 1H), 3.02-2.86 (m, 1H), 2.85-2.76 (m, 1H), 2.71 (s, 3H), 1.70-1.53 (m, 6H), 1.27 (d, 3H, *J* = 7.2 Hz), 1.18-1.01 (m, 5H), 1.11 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 156.7, 59.0, 54.8, 39.2, 32.6, 29.3, 27.8 (2C), 27.0, 26.3 (2C), 13.2, 9.2.

The following compounds were prepared according to the procedures described for the synthesis of azetine compounds of type **133/134**:

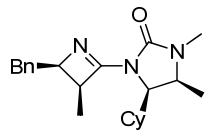


(4*R*,5*S*)-4-cyclohexyl-1,5-dimethyl-3-((3*S*,4*S*)-3-methyl-4-phenyl-3,4-dihydroazet-2-yl)imidazolidin-2-one (137a). *cis* azetine: (22%) clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H), 4.92-4.85 (m, 1H), 4.76 (d, 1H, *J* = 6.0 Hz), 4.32 (dd, 1H, *J* = 7.6, 2.4 Hz), 3.84-3.73 (m, 1H), 2.79 (s, 3H), 1.82-1.55 (m, 6H), 1.39 (d, 3H, *J* = 6.0 Hz), 1.34 (d, 3H, *J* = 7.2 Hz), 1.28-1.08 (m, 5H).

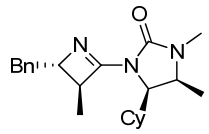


(4*R*,5*S*)-4-cyclohexyl-1,5-dimethyl-3-((3*S*,4*R*)-3-methyl-4-phenyl-3,4-dihydroazet-2-yl)imidazolidin-2-one (138a). *trans* azetine: (18%) clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H), 4.35 (d, 1H, *J* = 1.6 Hz), 4.12 (dd, 1H, *J* = 7.6, 3.2 Hz),

3.84-3.77 (m, 1H), 3.48 (dq, 1H, *J* = 7.2, 1.6 Hz), 2.76 (s, 3H), 1.83-1.58 (m, 6H), 1.51 (d, 3H, *J* = 7.2 Hz), 1.38 (d, 3H, *J* = 6.8 Hz), 1.40-1.10 (m, 5H).



(4*S*,5*R*)-1-((3*S*,4*R*)-4-benzyl-3-methyl-3,4-dihydroazet-2-yl)-5-cyclohexyl-3,4-dimethylimidazolidin-2-one (137b). *cis* azetine: (13%) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H), 4.21-4.16 (m, 1H), 4.08 (dd, 1H, *J* = 7.2 Hz, 3.6 Hz), 3.88-3.75 (m, 2H), 3.18 (dd, 1H, *J* = 14.8, 4.8 Hz), 2.81 (dd, 1H, *J* = 14.8, 10.0 Hz), 2.74 (s, 3H), 1.85-1.63 (m, 6H), 1.45-1.14 (m, 5H), 1.36 (d, 3H, *J* = 7.2 Hz), 1.29 (d, 3H, *J* = 7.2 Hz).

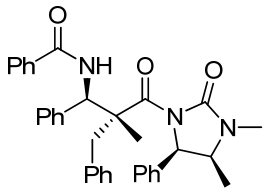


(4*S*,5*R*)-1-((3*S*,4*S*)-4-benzyl-3-methyl-3,4-dihydroazet-2-yl)-5-cyclohexyl-3,4-dimethylimidazolidin-2-one (138b). *trans* azetine: (45%) white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 5H), 4.03 (dd, 1H, *J* = 7.2, 3.2 Hz), 3.80-3.73 (m, 1H), 3.50 (dq, 1H, *J* = 5.2, 1.6 Hz), 3.36 (dq, 1H, *J* = 7.2, 1.6 Hz), 3.14 (dd, 1H, *J* = 14.0, 5.2 Hz), 2.84-2.78 (m, 1H), 2.74 (s, 3H), 1.88-1.60 (m, 6H), 1.49-1.10 (m, 5H), 1.36 (d, 3H, *J* = 7.2 Hz), 1.29 (d, 3H, *J* = 7.2 Hz).

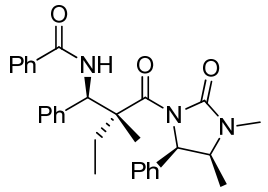
Azetine Addition Products:

General Procedure for the Alkylation of Azetines. Representative example for substrate **146a**: A solution of 0.133 g (0.400 mmol) *cis* azetine **133a** in anhydrous THF (4 mL) was chilled to 0 °C under argon. Lithium hexamethyldisilazide (1.60 mL 1.0 M solution in THF, 1.60 mmol) was added dropwise. After 45 minutes, benzyl bromide (0.0714 mL, 0.600 mmol) was added and the solution was stirred 30 min. The reaction was quenched with 1 N HCl and ethyl acetate was added. The organic layer was washed with 1 N HCl. The aqueous layers were combined and extracted with ethyl acetate. The aqueous layer was basified to pH > 9 with 4 N NaOH and extracted with dichloromethane. The organic layers were combined and dried with anhydrous potassium carbonate. The solution was filtered and concentrated to give a brown oil that was carried on to the next step without further purification.

General Procedure for Hydrolytic Ring Opening of Azetines to $\beta^{2,2,3}$-amino Carbonyl Derivatives. Representative example for **146a**: To a solution of azetine alkylation crude sample in DCM (5 mL) was added 0.0837 mL (0.600 mmol) triethylamine and 0.232 mL (2.00 mmol) volume of benzoyl chloride at room temperature. The solution was stirred for 1 h and quenched with half saturated ammonium chloride. The aqueous layer was extracted with dichloromethane. The organic layers were washed with aqueous saturated sodium bicarbonate and brine, dried with anhydrous potassium carbonate, filtered, and concentrated. Column chromatography on silica with 10-20% ethyl acetate in hexanes provided the desired product **146a** as an oil of mass 0.150 g (69%).

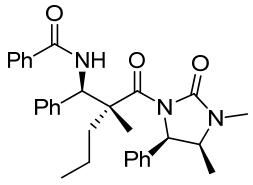


***N*-[(1*R*,2*R*)-2-Benzyl-3-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenyl-imidazolidin-1-yl)-2-methyl-3-oxo-1-phenyl-propyl]-benzamide (146a)**. (69%) colorless oil; R_f = 0.60 (95:5 DCM/MeOH); $[\alpha]^{23}_D$ +30.2 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-6.88 (m, 20H), 6.44 (bs, 1H), 5.07 (d, 1H, *J* = 8.4 Hz), 4.18 (d, 1H, *J* = 13.8 Hz), 3.75-3.70 (m, 1H), 2.82 (s, 3H), 2.36 (d, 1H, *J* = 13.2 Hz), 1.18 (s, 3H), 0.67 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.4, 166.2, 155.5, 139.6, 137.9, 136.9, 135.0, 131.2, 130.6, 129.3, 128.5, 128.4, 128.3, 128.1, 127.8, 127.5, 127.3, 127.1, 126.7, 62.5, 57.1, 54.3, 54.1, 39.9, 28.6, 19.9, 15.1; IR (neat): 3439, 3316, 3034, 2984, 1725, 1664, 1513, 1424, 1247, 1073, 911, 703 cm^{-1}; HRMS-ESI *m/z* 546.2748 ($[M+H]^+$, $C_{35}H_{36}N_3O_3$ requires 546.2751).

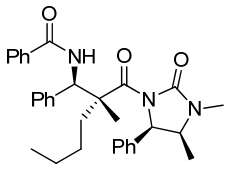


***N*-[(1*R*,2*R*)-2-((4*S*,5*R*)-3,4-Dimethyl-2-oxo-5-phenyl-imidazolidine-1-carbonyl)-2-methyl-1-phenyl-butyl]-benzamide (146b).** (63%) colorless oil; R_f = 0.49 (95:5 DCM/MeOH); $[\alpha]^{23}_D$ +12.3 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47-6.91 (m, 16H), 6.33 (bs, 1H), 5.30 (d, 1H, *J* = 8.4 Hz), 3.89-3.84 (m, 1H), 2.87-2.81 (m, 1H), 2.83 (s, 3H), 1.25 (s, 3H), 1.12-1.06 (m, 1H), 0.75-0.72 (m, 6H); ^{13}C NMR (150 MHz,

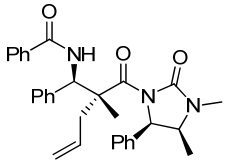
$CDCl_3$) δ 176.3, 166.2, 155.4, 139.8, 137.0, 135.0, 131.2, 129.1, 128.5, 128.4, 128.0, 127.9, 127.4, 127.2, 62.4, 57.2, 54.3, 53.9, 28.6, 28.0, 18.5, 15.1, 9.0; IR (neat): 3447, 3312, 3065, 3034, 2968, 2880, 1729, 1660, 1513, 1386, 1258, 911, 703 cm^{-1}; HRMS-ESI *m/z* 484.2591 ($[M+H]^+$, $C_{30}H_{34}N_3O_3$ requires 484.2595).



***N*-[(1*R*,2*R*)-2-((4*S*,5*R*)-3,4-Dimethyl-2-oxo-5-phenyl-imidazolidine-1-carbonyl)-2-methyl-1-phenyl-pentyl]-benzamide (146c).** (71%) white solid; R_f = 0.63 (95:5 DCM/MeOH); mp 174-176 °C; $[\alpha]^{23}_D$ +9.7 (*c* 1.00, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.50-6.94 (m, 16H), 6.36 (bs, 1H), 5.32 (d, 1H, *J* = 8.4 Hz), 3.92-3.87 (m, 1H), 2.86 (s, 3H), 2.80 (bt, 1H, *J* = 10.2 Hz), 1.30 (s, 3H), 1.30-1.26 (m, 1H), 1.06-1.05 (m, 1H), 0.83 (t, 3H, *J* = 7.2 Hz), 0.78 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.4, 166.2, 155.4, 139.8, 137.0, 135.1, 131.4, 129.1, 128.5, 128.4, 128.0, 127.9, 127.3, 127.2, 62.4, 57.4, 54.3, 53.5, 37.4, 28.6, 19.2, 18.1, 15.1, 14.8; IR (neat): 3451, 3300, 3034, 2961, 2876, 1729, 1664, 1513, 1386, 1227, 911 cm^{-1}; HRMS-ESI *m/z* 498.2739 ($[M+H]^+$, $C_{31}H_{36}N_3O_3$ requires 498.2751); Anal. Calcd for $C_{31}H_{35}N_3O_3$: C, 74.82; H, 7.09; N, 8.44; O, 9.65. Found C, 73.64; H, 7.04; N, 8.18; O, 9.52.

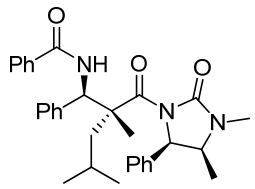


***N*-[(1*R*,2*R*)-2-((4*S*,5*R*)-3,4-Dimethyl-2-oxo-5-phenyl-imidazolidine-1-carbonyl)-2-methyl-1-phenyl-hexyl]-benzamide (146d).** (61%) colorless oil; R_f = 0.64 (95:5 DCM/MeOH); $[\alpha]^{23}_D$ +11.6 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-6.95 (m, 16H), 6.37 (bs, 1H), 5.33 (d, 1H, *J* = 7.8 Hz), 3.91-3.87 (m, 1H), 2.86 (s, 3H), 2.85-2.79 (m, 1H), 1.30 (s, 3H), 1.27-1.19 (m, 3H), 1.07 (t, 1H, *J* = 12.0 Hz), 0.96 (m, 1H), 0.81 (t, 3H, *J* = 7.2 Hz), 0.78 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.5, 166.2, 155.4, 139.8, 137.0, 135.1, 131.1, 129.0, 128.5, 128.4, 127.9, 127.9, 127.4, 127.3, 62.4, 57.4, 54.4, 53.5, 34.9, 28.6, 27.1, 23.3, 19.2, 15.1, 14.1; IR (neat): 3451, 3304, 3034, 2961, 2872, 1729, 1664, 1513, 1424, 1355, 1216, 911 cm^{-1}; HRMS-ESI *m/z* 512.2901 ($[M+H]^+$, $C_{32}H_{38}N_3O_3$ requires 512.2908); Anal. Calcd for $C_{32}H_{37}N_3O_3$: C, 75.12; H, 7.29; N, 8.21; O, 9.38. Found C, 74.62; H, 7.38; N, 7.98; O, 9.50.



***N*-[(1*R*,2*R*)-2-((4*S*,5*R*)-3,4-Dimethyl-2-oxo-5-phenyl-imidazolidine-1-carbonyl)-2-methyl-1-phenyl-pent-4-enyl]-benzamide (146e).** (71%) colorless oil; R_f = 0.52 (95:5 DCM/MeOH); $[\alpha]^{23}_D$ +7.5 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$, 55 ^{o}C) δ 7.45-6.90 (m, 16H), 6.43 (bs, 1H), 5.62-5.55 (m, 1H), 5.26 (d, 1H, *J* = 7.8 Hz), 4.99-4.95 (m, 2H), 3.87-3.82 (m, 1H), 3.64 (dd, 1H, *J* = 13.8, 7.8 Hz), 2.84 (s, 3H), 1.79 (dd, 1H, *J* = 13.8, 6.6 Hz), 1.27 (s, 3H), 0.74 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.4, 166.2, 155.4, 139.4, 136.9, 135.0, 134.2, 131.2, 129.0, 128.5, 128.4, 128.1, 127.8, 127.5, 127.3, 127.2, 118.3, 62.4, 56.8, 54.3, 53.2, 39.5, 28.5, 19.3, 15.1; IR (neat): 3451, 3316, 3065, 3034, 2980, 2937, 1729, 1664, 1513, 1386, 1224, 915, 703 cm^{-1}; HRMS-ESI

m/z 496.2595 ([M+H]$^+$, $C_{31}H_{34}N_3O_3$ requires 496.2595); Anal. Calcd for $C_{31}H_{33}N_3O_3$: C, 75.13; H, 6.71; N, 8.48; O, 9.68. Found C, 75.36; H, 7.12; N, 12.55; O, 4.86.



***N*-[(1*R*,2*R*)-2-((4*S*,5*R*)-3,4-Dimethyl-2-oxo-5-phenyl-imidazolidine-1-carbonyl)-2,4-dimethyl-1-phenyl-pentyl]-benzamide (146f).** (66%) colorless oil; R_f = 0.59 (95:5 DCM/MeOH); $[\alpha]^{23}_D$ +4.1 (*c* 0.50, CH_2Cl_2);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-6.88 (m, 16 H), 6.656 (bs, 1H), 5.29 (d, 1H, *J* = 7.8 Hz), 3.90 (m, 1H), 2.88 (s, 3H), 2.88-2.85 (m, 1H), 1.61-1.55 (m, 1H), 1.29 (s, 3H), 1.03 (dd, 1H, *J* = 14.4, 4.2 Hz), 0.84 (dd, 6H, *J* = 6.6, 2.4 Hz), 0.77 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 166.1, 155.4, 139.7, 136.9, 135.1, 131.1, 129.2, 128.5, 128.4, 128.0, 127.8, 127.3, 127.2, 127.0, 62.7, 56.9, 54.3, 53.2, 42.7, 28.6, 25.6, 25.2, 23.4, 19.7, 15.1; IR (neat): 3451, 3320, 3034, 2957, 1729, 1664, 1513, 1390, 1312, 1231, 911, 703 cm^{-1}; HRMS-ESI *m/z* 534.2727 ([M+Na]$^+$, $C_{32}H_{37}N_3O_3Na$ requires 534.2729); Anal. Calcd for $C_{32}H_{37}N_3O_3$: C, 75.12; H, 7.29; N, 8.21; O, 9.38. Found C, 71.38; H, 7.15; N, 5.26; O, 8.87.

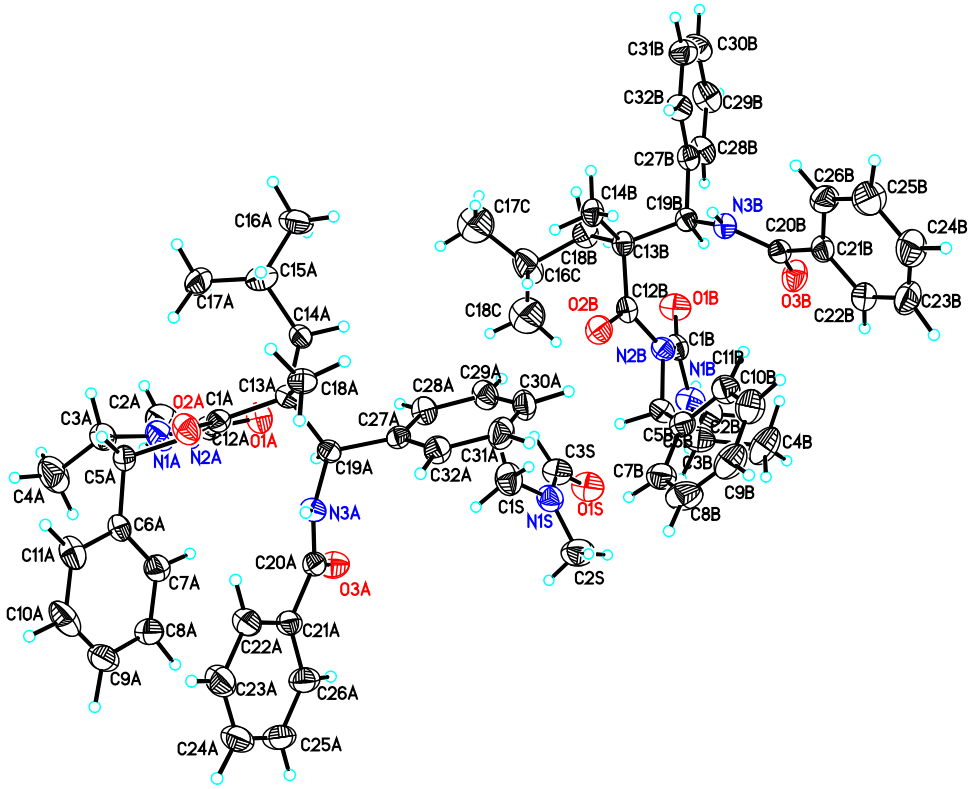


Table 19. Crystal data and structure refinement for **146f**.

Identification code	A2304s	
Empirical formula	C33.50 H40.50 N3.50 O3.50	
Formula weight	548.19	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.5010(4) Å	α = 90°.
	b = 21.4606(9) Å	β = 102.648(2)°.
	c = 12.8318(5) Å	γ = 90°.
Volume	3090.3(2) $Å^3$	
Z	4	
Density (calculated)	1.178 Mg/m^3	
Absorption coefficient	0.609 mm^{-1}	
F(000)	1176	
Crystal size	0.34 x 0.32 x 0.25 mm^3	

Theta range for data collection	3.53 to 66.14°.
Index ranges	-13<=h<=10, -25<=k<=24, -13<=l<=14
Reflections collected	15046
Independent reflections	7842 [R(int) = 0.0225]
Completeness to theta = 66.14°	88.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8626 and 0.8196
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7842 / 1 / 1024
Goodness-of-fit on F^2	1.024
Final R indices [I>2sigma(I)]	R1 = 0.0303, wR2 = 0.0808
R indices (all data)	R1 = 0.0309, wR2 = 0.0815
Absolute structure parameter	0.08(13)
Extinction coefficient	0.00220(13)
Largest diff. peak and hole	0.466 and -0.264 e.$Å^{-3}$

Table 20. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **146f**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1A)	191(2)	10504(1)	8315(2)	43(1)
N(2A)	1239(1)	9905(1)	9595(1)	28(1)
N(3A)	1940(1)	8369(1)	9638(1)	26(1)
N(1B)	6051(2)	7348(1)	2958(1)	40(1)
N(2B)	6942(1)	7687(1)	4577(1)	29(1)
N(3B)	9863(1)	7870(1)	5693(1)	28(1)
O(1A)	1637(1)	9895(1)	7869(1)	37(1)
O(2A)	2076(1)	9555(1)	11225(1)	38(1)
O(3A)	726(1)	8160(1)	8051(1)	38(1)
O(1B)	7290(1)	8184(1)	3030(1)	42(1)
O(2B)	6861(1)	8057(1)	6188(1)	40(1)
O(3B)	9705(1)	7174(1)	4337(1)	44(1)
C(1A)	1091(2)	10087(1)	8515(2)	32(1)
C(2A)	-68(3)	10848(2)	7312(3)	63(1)
C(3A)	-141(2)	10723(1)	9291(2)	47(1)
C(4A)	-1441(3)	10911(2)	9149(3)	64(1)
C(5A)	268(2)	10175(1)	10051(2)	35(1)
C(6A)	-693(2)	9698(1)	10110(2)	31(1)
C(7A)	-1165(2)	9313(1)	9256(2)	36(1)
C(8A)	-2098(2)	8913(1)	9296(2)	44(1)
C(9A)	-2562(2)	8885(1)	10203(2)	48(1)
C(10A)	-2085(2)	9258(1)	11064(2)	51(1)
C(11A)	-1162(2)	9668(1)	11017(2)	41(1)
C(12A)	2165(2)	9597(1)	10296(2)	28(1)
C(13A)	3238(2)	9297(1)	9939(1)	26(1)
C(14A)	3996(2)	9750(1)	9410(2)	28(1)
C(15A)	4532(2)	10323(1)	10048(2)	39(1)
C(16A)	5576(2)	10562(1)	9608(3)	59(1)
C(17A)	3622(3)	10846(1)	9991(3)	57(1)
C(18A)	4071(2)	9034(1)	10950(2)	31(1)
C(19A)	2712(2)	8762(1)	9149(1)	25(1)

C(20A)	955(2)	8112(1)	9034(2)	28(1)
C(21A)	122(2)	7783(1)	9602(2)	31(1)
C(22A)	123(2)	7892(1)	10670(2)	39(1)
C(23A)	-710(2)	7599(1)	11139(2)	49(1)
C(24A)	-1551(2)	7207(1)	10534(2)	53(1)
C(25A)	-1564(2)	7103(1)	9470(2)	51(1)
C(26A)	-729(2)	7390(1)	9002(2)	42(1)
C(27A)	3651(2)	8391(1)	8750(1)	26(1)
C(28A)	3977(2)	8573(1)	7813(2)	34(1)
C(29A)	4867(2)	8265(1)	7452(2)	38(1)
C(30A)	5446(2)	7765(1)	8010(2)	40(1)
C(31A)	5106(2)	7570(1)	8925(2)	41(1)
C(32A)	4214(2)	7878(1)	9295(2)	34(1)
C(1B)	6822(2)	7783(1)	3461(2)	33(1)
C(2B)	5737(2)	7293(2)	1808(2)	48(1)
C(3B)	5813(2)	6860(1)	3669(2)	41(1)
C(4B)	6584(3)	6287(1)	3615(2)	61(1)
C(5B)	6069(2)	7209(1)	4742(2)	34(1)
C(6B)	6451(2)	6785(1)	5697(2)	33(1)
C(7B)	5584(2)	6511(1)	6138(2)	42(1)
C(8B)	5885(3)	6071(1)	6939(2)	51(1)
C(9B)	7064(2)	5898(1)	7313(2)	50(1)
C(10B)	7938(2)	6185(1)	6900(2)	47(1)
C(11B)	7634(2)	6621(1)	6097(2)	40(1)
C(12B)	7290(2)	8123(1)	5412(2)	29(1)
C(13B)	8204(2)	8652(1)	5392(1)	29(1)
C(14B)	7633(2)	9199(1)	4668(2)	37(1)
C(18B)	8572(2)	8896(1)	6542(2)	33(1)
C(19B)	9285(2)	8376(1)	4990(2)	27(1)
C(20B)	10090(2)	7315(1)	5276(2)	31(1)
C(21B)	10836(2)	6857(1)	6035(2)	33(1)
C(22B)	10619(2)	6227(1)	5842(2)	41(1)
C(23B)	11278(2)	5784(1)	6515(2)	52(1)
C(24B)	12180(2)	5969(1)	7354(2)	57(1)
C(25B)	12411(2)	6596(1)	7529(2)	57(1)
C(26B)	11740(2)	7045(1)	6879(2)	41(1)

C(27B)	10203(2)	8857(1)	4819(2)	30(1)
C(28B)	10267(2)	9008(1)	3773(2)	37(1)
C(29B)	11113(2)	9425(1)	3577(2)	45(1)
C(30B)	11907(2)	9705(1)	4424(2)	45(1)
C(31B)	11851(2)	9558(1)	5462(2)	40(1)
C(32B)	11013(2)	9133(1)	5660(2)	34(1)
C(16C)	6416(2)	9424(1)	4829(2)	60(1)
C(17C)	6493(7)	10083(4)	5374(6)	76(1)
C(18C)	5414(6)	9212(4)	4088(6)	76(1)
C(16D)	6416(2)	9424(1)	4829(2)	60(1)
C(17D)	6443(7)	10173(4)	4941(6)	76(1)
C(18D)	5548(6)	9479(4)	3705(5)	76(1)
C(1S)	2927(2)	7997(1)	4683(2)	52(1)
C(2S)	2398(3)	7045(1)	3593(3)	57(1)
C(3S)	3011(2)	7980(1)	2803(2)	46(1)
N(1S)	2835(2)	7683(1)	3670(1)	41(1)
O(1S)	2893(2)	7751(1)	1906(1)	52(1)

Table 21. Bond lengths [Å] and angles [°] for **146f**.

N(1A)-C(1A)	1.351(3)
N(1A)-C(2A)	1.456(3)
N(1A)-C(3A)	1.464(3)
N(2A)-C(12A)	1.401(2)
N(2A)-C(1A)	1.414(3)
N(2A)-C(5A)	1.488(2)
N(3A)-C(20A)	1.342(2)
N(3A)-C(19A)	1.461(2)
N(1B)-C(1B)	1.350(3)
N(1B)-C(2B)	1.446(3)
N(1B)-C(3B)	1.454(3)
N(2B)-C(12B)	1.413(3)
N(2B)-C(1B)	1.423(3)
N(2B)-C(5B)	1.484(2)
N(3B)-C(20B)	1.356(3)

N(3B)-C(19B)	1.473(2)
O(1A)-C(1A)	1.217(2)
O(2A)-C(12A)	1.222(2)
O(3A)-C(20A)	1.236(2)
O(1B)-C(1B)	1.211(3)
O(2B)-C(12B)	1.213(2)
O(3B)-C(20B)	1.227(2)
C(3A)-C(4A)	1.520(3)
C(3A)-C(5A)	1.536(3)
C(5A)-C(6A)	1.520(3)
C(6A)-C(7A)	1.385(3)
C(6A)-C(11A)	1.388(3)
C(7A)-C(8A)	1.385(3)
C(8A)-C(9A)	1.384(3)
C(9A)-C(10A)	1.377(4)
C(10A)-C(11A)	1.390(4)
C(12A)-C(13A)	1.547(2)
C(13A)-C(18A)	1.541(3)
C(13A)-C(14A)	1.557(2)
C(13A)-C(19A)	1.564(3)
C(14A)-C(15A)	1.531(3)
C(15A)-C(16A)	1.524(3)
C(15A)-C(17A)	1.525(3)
C(19A)-C(27A)	1.518(2)
C(20A)-C(21A)	1.502(3)
C(21A)-C(26A)	1.389(3)
C(21A)-C(22A)	1.390(3)
C(22A)-C(23A)	1.388(3)
C(23A)-C(24A)	1.384(4)
C(24A)-C(25A)	1.380(4)
C(25A)-C(26A)	1.385(3)
C(27A)-C(32A)	1.386(3)
C(27A)-C(28A)	1.392(3)
C(28A)-C(29A)	1.382(3)
C(29A)-C(30A)	1.378(3)
C(30A)-C(31A)	1.380(3)

C(31A)-C(32A)	1.389(3)
C(3B)-C(4B)	1.527(4)
C(3B)-C(5B)	1.538(3)
C(5B)-C(6B)	1.513(3)
C(6B)-C(7B)	1.381(3)
C(6B)-C(11B)	1.390(3)
C(7B)-C(8B)	1.382(4)
C(8B)-C(9B)	1.387(4)
C(9B)-C(10B)	1.381(4)
C(10B)-C(11B)	1.379(3)
C(12B)-C(13B)	1.550(3)
C(13B)-C(18B)	1.536(3)
C(13B)-C(14B)	1.551(3)
C(13B)-C(19B)	1.563(2)
C(14B)-C(16C)	1.537(3)
C(19B)-C(27B)	1.527(3)
C(20B)-C(21B)	1.510(3)
C(21B)-C(26B)	1.387(3)
C(21B)-C(22B)	1.389(3)
C(22B)-C(23B)	1.391(3)
C(23B)-C(24B)	1.380(4)
C(24B)-C(25B)	1.381(4)
C(25B)-C(26B)	1.391(3)
C(27B)-C(32B)	1.394(3)
C(27B)-C(28B)	1.398(3)
C(28B)-C(29B)	1.386(3)
C(29B)-C(30B)	1.392(3)
C(30B)-C(31B)	1.383(3)
C(31B)-C(32B)	1.390(3)
C(16C)-C(18C)	1.400(8)
C(16C)-C(17C)	1.571(8)
C(1S)-N(1S)	1.448(3)
C(2S)-N(1S)	1.455(3)
C(3S)-O(1S)	1.231(3)
C(3S)-N(1S)	1.335(3)

C(1A)-N(1A)-C(2A)	120.2(2)
C(1A)-N(1A)-C(3A)	112.51(18)
C(2A)-N(1A)-C(3A)	123.5(2)
C(12A)-N(2A)-C(1A)	132.23(15)
C(12A)-N(2A)-C(5A)	117.48(16)
C(1A)-N(2A)-C(5A)	109.80(15)
C(20A)-N(3A)-C(19A)	120.29(16)
C(1B)-N(1B)-C(2B)	122.4(2)
C(1B)-N(1B)-C(3B)	113.10(16)
C(2B)-N(1B)-C(3B)	122.9(2)
C(12B)-N(2B)-C(1B)	128.12(17)
C(12B)-N(2B)-C(5B)	115.96(15)
C(1B)-N(2B)-C(5B)	108.87(15)
C(20B)-N(3B)-C(19B)	120.40(16)
O(1A)-C(1A)-N(1A)	125.74(19)
O(1A)-C(1A)-N(2A)	127.23(17)
N(1A)-C(1A)-N(2A)	107.00(17)
N(1A)-C(3A)-C(4A)	114.6(2)
N(1A)-C(3A)-C(5A)	101.35(17)
C(4A)-C(3A)-C(5A)	115.9(2)
N(2A)-C(5A)-C(6A)	112.01(17)
N(2A)-C(5A)-C(3A)	101.54(16)
C(6A)-C(5A)-C(3A)	114.99(16)
C(7A)-C(6A)-C(11A)	118.64(19)
C(7A)-C(6A)-C(5A)	121.66(17)
C(11A)-C(6A)-C(5A)	119.60(19)
C(6A)-C(7A)-C(8A)	120.86(19)
C(9A)-C(8A)-C(7A)	120.2(2)
C(10A)-C(9A)-C(8A)	119.3(2)
C(9A)-C(10A)-C(11A)	120.5(2)
C(6A)-C(11A)-C(10A)	120.4(2)
O(2A)-C(12A)-N(2A)	116.55(17)
O(2A)-C(12A)-C(13A)	120.10(17)
N(2A)-C(12A)-C(13A)	123.32(16)
C(18A)-C(13A)-C(12A)	107.01(15)
C(18A)-C(13A)-C(14A)	106.98(15)

C(12A)-C(13A)-C(14A)	115.39(15)
C(18A)-C(13A)-C(19A)	110.91(15)
C(12A)-C(13A)-C(19A)	106.05(13)
C(14A)-C(13A)-C(19A)	110.48(14)
C(15A)-C(14A)-C(13A)	117.83(17)
C(16A)-C(15A)-C(17A)	108.8(2)
C(16A)-C(15A)-C(14A)	109.3(2)
C(17A)-C(15A)-C(14A)	111.97(19)
N(3A)-C(19A)-C(27A)	112.74(15)
N(3A)-C(19A)-C(13A)	109.29(14)
C(27A)-C(19A)-C(13A)	113.64(14)
O(3A)-C(20A)-N(3A)	121.27(17)
O(3A)-C(20A)-C(21A)	121.25(16)
N(3A)-C(20A)-C(21A)	117.45(16)
C(26A)-C(21A)-C(22A)	119.8(2)
C(26A)-C(21A)-C(20A)	117.57(19)
C(22A)-C(21A)-C(20A)	122.44(17)
C(23A)-C(22A)-C(21A)	120.0(2)
C(24A)-C(23A)-C(22A)	119.7(2)
C(25A)-C(24A)-C(23A)	120.6(2)
C(24A)-C(25A)-C(26A)	119.9(2)
C(25A)-C(26A)-C(21A)	120.0(2)
C(32A)-C(27A)-C(28A)	118.32(17)
C(32A)-C(27A)-C(19A)	122.37(16)
C(28A)-C(27A)-C(19A)	119.31(17)
C(29A)-C(28A)-C(27A)	120.97(19)
C(30A)-C(29A)-C(28A)	120.51(19)
C(29A)-C(30A)-C(31A)	118.91(19)
C(30A)-C(31A)-C(32A)	121.0(2)
C(27A)-C(32A)-C(31A)	120.29(19)
O(1B)-C(1B)-N(1B)	125.77(19)
O(1B)-C(1B)-N(2B)	127.33(19)
N(1B)-C(1B)-N(2B)	106.87(17)
N(1B)-C(3B)-C(4B)	111.2(2)
N(1B)-C(3B)-C(5B)	100.67(18)
C(4B)-C(3B)-C(5B)	115.7(2)

N(2B)-C(5B)-C(6B)	116.52(15)
N(2B)-C(5B)-C(3B)	102.25(15)
C(6B)-C(5B)-C(3B)	113.33(18)
C(7B)-C(6B)-C(11B)	118.5(2)
C(7B)-C(6B)-C(5B)	118.72(19)
C(11B)-C(6B)-C(5B)	122.59(17)
C(6B)-C(7B)-C(8B)	120.6(2)
C(7B)-C(8B)-C(9B)	120.5(2)
C(10B)-C(9B)-C(8B)	119.1(2)
C(11B)-C(10B)-C(9B)	120.2(2)
C(10B)-C(11B)-C(6B)	121.0(2)
O(2B)-C(12B)-N(2B)	116.53(17)
O(2B)-C(12B)-C(13B)	119.97(17)
N(2B)-C(12B)-C(13B)	123.47(15)
C(18B)-C(13B)-C(12B)	106.13(15)
C(18B)-C(13B)-C(14B)	107.96(17)
C(12B)-C(13B)-C(14B)	111.36(15)
C(18B)-C(13B)-C(19B)	112.00(15)
C(12B)-C(13B)-C(19B)	108.64(15)
C(14B)-C(13B)-C(19B)	110.68(15)
C(16C)-C(14B)-C(13B)	115.87(17)
N(3B)-C(19B)-C(27B)	110.67(14)
N(3B)-C(19B)-C(13B)	111.26(14)
C(27B)-C(19B)-C(13B)	114.53(16)
O(3B)-C(20B)-N(3B)	123.00(19)
O(3B)-C(20B)-C(21B)	120.34(18)
N(3B)-C(20B)-C(21B)	116.64(17)
C(26B)-C(21B)-C(22B)	119.7(2)
C(26B)-C(21B)-C(20B)	122.51(19)
C(22B)-C(21B)-C(20B)	117.70(19)
C(21B)-C(22B)-C(23B)	120.2(2)
C(24B)-C(23B)-C(22B)	120.1(2)
C(23B)-C(24B)-C(25B)	119.5(2)
C(24B)-C(25B)-C(26B)	121.0(2)
C(21B)-C(26B)-C(25B)	119.3(2)
C(32B)-C(27B)-C(28B)	118.60(19)

C(32B)-C(27B)-C(19B)	122.80(17)
C(28B)-C(27B)-C(19B)	118.54(18)
C(29B)-C(28B)-C(27B)	120.7(2)
C(28B)-C(29B)-C(30B)	120.2(2)
C(31B)-C(30B)-C(29B)	119.5(2)
C(30B)-C(31B)-C(32B)	120.4(2)
C(31B)-C(32B)-C(27B)	120.61(19)
C(18C)-C(16C)-C(14B)	116.4(4)
C(18C)-C(16C)-C(17C)	123.6(5)
C(14B)-C(16C)-C(17C)	112.2(3)
O(1S)-C(3S)-N(1S)	125.6(2)
C(3S)-N(1S)-C(1S)	122.1(2)
C(3S)-N(1S)-C(2S)	120.4(2)
C(1S)-N(1S)-C(2S)	117.1(2)

Table 22. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **146f**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1A)	37(1)	42(1)	52(1)	16(1)	14(1)	9(1)
N(2A)	24(1)	33(1)	29(1)	-5(1)	8(1)	2(1)
N(3A)	26(1)	33(1)	19(1)	1(1)	4(1)	-3(1)
N(1B)	39(1)	49(1)	28(1)	1(1)	1(1)	-4(1)
N(2B)	29(1)	33(1)	27(1)	1(1)	9(1)	0(1)
N(3B)	31(1)	30(1)	23(1)	0(1)	6(1)	2(1)
O(1A)	41(1)	44(1)	27(1)	4(1)	8(1)	8(1)
O(2A)	37(1)	54(1)	27(1)	-4(1)	12(1)	0(1)
O(3A)	38(1)	44(1)	28(1)	0(1)	-1(1)	-7(1)
O(1B)	47(1)	52(1)	28(1)	4(1)	9(1)	-8(1)
O(2B)	50(1)	42(1)	36(1)	-4(1)	25(1)	-4(1)
O(3B)	50(1)	44(1)	34(1)	-10(1)	5(1)	8(1)
C(1A)	26(1)	32(1)	38(1)	2(1)	5(1)	1(1)
C(2A)	53(2)	60(2)	74(2)	31(2)	11(1)	18(1)
C(3A)	39(1)	32(1)	74(2)	1(1)	23(1)	2(1)

C(4A)	52(2)	52(2)	96(2)	20(2)	33(2)	20(1)
C(5A)	28(1)	36(1)	41(1)	-12(1)	10(1)	0(1)
C(6A)	24(1)	34(1)	34(1)	0(1)	8(1)	5(1)
C(7A)	35(1)	39(1)	36(1)	-3(1)	11(1)	-2(1)
C(8A)	36(1)	37(1)	60(2)	-4(1)	12(1)	-4(1)
C(9A)	34(1)	39(1)	73(2)	9(1)	20(1)	0(1)
C(10A)	44(1)	63(2)	55(2)	19(1)	29(1)	9(1)
C(11A)	34(1)	57(1)	33(1)	-2(1)	9(1)	8(1)
C(12A)	27(1)	29(1)	28(1)	-6(1)	7(1)	-5(1)
C(13A)	24(1)	28(1)	26(1)	1(1)	6(1)	-1(1)
C(14A)	25(1)	29(1)	34(1)	0(1)	11(1)	0(1)
C(15A)	42(1)	33(1)	40(1)	1(1)	5(1)	-9(1)
C(16A)	33(1)	40(1)	106(3)	-1(2)	16(1)	-9(1)
C(17A)	63(2)	31(1)	88(2)	-17(1)	42(2)	-14(1)
C(18A)	28(1)	34(1)	28(1)	2(1)	0(1)	-3(1)
C(19A)	23(1)	27(1)	25(1)	2(1)	5(1)	0(1)
C(20A)	26(1)	27(1)	30(1)	-1(1)	5(1)	1(1)
C(21A)	25(1)	27(1)	41(1)	2(1)	6(1)	1(1)
C(22A)	32(1)	40(1)	48(1)	1(1)	13(1)	-1(1)
C(23A)	46(1)	46(1)	62(2)	6(1)	27(1)	2(1)
C(24A)	37(1)	38(1)	91(2)	11(1)	29(1)	-1(1)
C(25A)	37(1)	33(1)	82(2)	-1(1)	12(1)	-8(1)
C(26A)	32(1)	33(1)	59(2)	1(1)	4(1)	-4(1)
C(27A)	27(1)	26(1)	24(1)	-3(1)	4(1)	-2(1)
C(28A)	36(1)	38(1)	28(1)	2(1)	8(1)	3(1)
C(29A)	39(1)	50(1)	30(1)	-6(1)	14(1)	1(1)
C(30A)	34(1)	45(1)	43(1)	-12(1)	12(1)	6(1)
C(31A)	42(1)	32(1)	48(1)	1(1)	6(1)	11(1)
C(32A)	36(1)	32(1)	35(1)	4(1)	9(1)	2(1)
C(1B)	30(1)	41(1)	28(1)	0(1)	6(1)	5(1)
C(2B)	49(1)	63(2)	31(1)	-5(1)	6(1)	-4(1)
C(3B)	39(1)	47(1)	35(1)	1(1)	4(1)	-9(1)
C(4B)	95(2)	45(2)	43(2)	-11(1)	13(1)	4(1)
C(5B)	27(1)	38(1)	36(1)	1(1)	9(1)	-1(1)
C(6B)	37(1)	32(1)	30(1)	-3(1)	11(1)	-4(1)
C(7B)	41(1)	43(1)	44(1)	-3(1)	14(1)	-8(1)

C(8B)	66(2)	47(1)	47(2)	5(1)	23(1)	-17(1)
C(9B)	73(2)	35(1)	41(2)	5(1)	13(1)	2(1)
C(10B)	52(1)	42(1)	44(1)	6(1)	8(1)	9(1)
C(11B)	40(1)	40(1)	42(1)	6(1)	12(1)	2(1)
C(12B)	30(1)	31(1)	28(1)	2(1)	10(1)	6(1)
C(13B)	31(1)	30(1)	25(1)	-1(1)	7(1)	3(1)
C(14B)	39(1)	36(1)	37(1)	8(1)	11(1)	3(1)
C(18B)	36(1)	36(1)	29(1)	-5(1)	10(1)	5(1)
C(19B)	27(1)	32(1)	23(1)	-3(1)	5(1)	1(1)
C(20B)	28(1)	32(1)	34(1)	-5(1)	11(1)	-1(1)
C(21B)	31(1)	33(1)	37(1)	-1(1)	14(1)	3(1)
C(22B)	37(1)	36(1)	52(1)	-6(1)	12(1)	2(1)
C(23B)	59(2)	29(1)	71(2)	1(1)	23(1)	6(1)
C(24B)	56(2)	43(2)	71(2)	15(1)	10(1)	14(1)
C(25B)	48(1)	49(2)	64(2)	7(1)	-7(1)	7(1)
C(26B)	39(1)	33(1)	48(1)	2(1)	3(1)	0(1)
C(27B)	31(1)	32(1)	28(1)	4(1)	10(1)	4(1)
C(28B)	35(1)	47(1)	29(1)	6(1)	9(1)	6(1)
C(29B)	45(1)	55(2)	38(1)	17(1)	18(1)	6(1)
C(30B)	39(1)	47(1)	52(1)	13(1)	16(1)	-2(1)
C(31B)	40(1)	37(1)	43(1)	2(1)	8(1)	-4(1)
C(32B)	36(1)	38(1)	28(1)	2(1)	8(1)	0(1)
C(16C)	45(1)	58(2)	79(2)	33(1)	22(1)	19(1)
C(16D)	45(1)	58(2)	79(2)	33(1)	22(1)	19(1)
C(1S)	53(2)	59(2)	46(2)	-6(1)	15(1)	6(1)
C(2S)	63(2)	55(2)	59(2)	-4(1)	24(1)	-17(1)
C(3S)	43(1)	50(2)	44(2)	1(1)	7(1)	-6(1)
N(1S)	39(1)	47(1)	39(1)	-4(1)	12(1)	-2(1)
O(1S)	56(1)	63(1)	38(1)	2(1)	9(1)	-7(1)

Table 23. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **146f**.

	x	y	z	U(eq)
H(16C)	6347	9159	5454	72
H(17A)	6839	10381	4949	115
H(17B)	6996	10059	6096	115
H(17C)	5692	10220	5414	115
H(18A)	5441	9377	3381	113
H(18B)	4689	9359	4293	113
H(18C)	5413	8756	4065	113
H(16D)	6096	9194	5386	72
H(17D)	7097	10294	5533	115
H(17E)	5685	10319	5083	115
H(17F)	6564	10361	4277	115
H(18D)	5828	9805	3286	113
H(18E)	4746	9582	3794	113
H(18F)	5527	9079	3332	113
H(1)	-850(30)	10892(17)	7040(30)	81(10)
H(2)	340(30)	10634(17)	6780(30)	80(10)
H(3)	240(30)	11269(19)	7430(30)	90(11)
H(4)	420(30)	11075(14)	9550(20)	55(7)
H(5)	-1940(20)	10563(13)	8729(19)	48(7)
H(6)	-1600(30)	11330(20)	8640(30)	102(12)
H(7)	-1600(30)	10995(15)	9950(30)	74(9)
H(8)	600(20)	10321(14)	10750(20)	52(7)
H(9)	-842(19)	9297(10)	8624(17)	32(5)
H(10)	-2520(30)	8607(15)	8670(20)	64(8)
H(11)	-3250(30)	8586(14)	10310(20)	59(8)
H(12)	-2420(20)	9261(13)	11680(20)	56(7)
H(13)	-830(20)	9919(12)	11620(20)	40(6)
H(14)	3550(20)	9877(11)	8705(19)	34(6)
H(15)	4630(19)	9508(10)	9244(15)	28(5)
H(16)	4880(30)	10181(18)	10730(30)	88(11)

H(17)	2970(30)	10687(14)	10370(20)	61(8)
H(18)	3990(30)	11199(19)	10330(30)	86(11)
H(19)	3280(30)	10987(19)	9130(30)	97(12)
H(20)	5970(30)	10937(17)	10000(30)	75(10)
H(21)	5260(30)	10627(19)	8770(30)	98(12)
H(22)	6160(30)	10266(14)	9680(20)	58(8)
H(23)	3660(20)	8716(12)	11253(18)	42(6)
H(24)	4320(20)	9366(13)	11488(19)	44(6)
H(25)	4770(20)	8895(11)	10713(17)	32(5)
H(26)	2183(19)	8951(10)	8563(17)	29(5)
H(27)	2128(18)	8259(11)	10314(19)	30(6)
H(28)	730(20)	8171(11)	11088(17)	34(6)
H(29)	-680(20)	7657(13)	11880(20)	51(7)
H(30)	-2070(30)	7017(16)	10950(20)	73(9)
H(31)	-2140(30)	6844(14)	9050(20)	55(7)
H(32)	-740(20)	7362(12)	8190(20)	46(7)
H(33)	3590(20)	8913(12)	7417(18)	37(6)
H(34)	5070(20)	8390(11)	6770(19)	40(6)
H(35)	6130(20)	7552(11)	7797(17)	36(6)
H(36)	5480(20)	7213(13)	9321(19)	45(6)
H(37)	3950(20)	7713(12)	9939(19)	41(6)
H(38)	6220(30)	6926(15)	1580(20)	65(8)
H(39)	5920(30)	7652(16)	1540(20)	64(9)
H(40)	4840(30)	7221(14)	1540(20)	62(8)
H(41)	4920(20)	6751(12)	3490(19)	46(7)
H(42)	6430(30)	6105(15)	2830(30)	70(9)
H(43)	6320(30)	5967(17)	4180(30)	83(10)
H(44)	7500(40)	6470(20)	3780(30)	107(13)
H(45)	5340(20)	7450(13)	4813(19)	48(7)
H(46)	4780(30)	6658(14)	5910(20)	55(7)
H(47)	5310(20)	5902(13)	7240(20)	48(7)
H(48)	7290(30)	5585(15)	7900(20)	62(8)
H(49)	8750(30)	6098(13)	7180(20)	56(8)
H(50)	8320(30)	6791(14)	5830(20)	59(8)
H(51)	7610(20)	9099(12)	3910(20)	44(6)
H(52)	8200(20)	9568(12)	4843(17)	42(6)

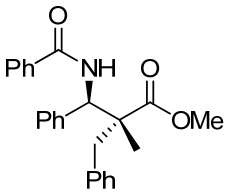
H(53)	7900(20)	9040(12)	6750(18)	40(6)
H(54)	9150(20)	9224(12)	6519(18)	41(6)
H(55)	8930(20)	8586(12)	7085(18)	38(6)
H(56)	8983(17)	8189(10)	4284(16)	23(5)
H(57)	10060(20)	7938(11)	6370(20)	34(6)
H(58)	10040(20)	6093(11)	5236(19)	36(6)
H(59)	11040(30)	5360(16)	6350(20)	69(9)
H(60)	12660(30)	5654(16)	7770(20)	70(9)
H(61)	13100(30)	6711(16)	8110(30)	78(10)
H(62)	11900(20)	7481(15)	7020(20)	57(7)
H(63)	9660(20)	8855(11)	3213(19)	39(6)
H(64)	11190(20)	9512(13)	2840(20)	48(7)
H(65)	12500(20)	10021(13)	4260(20)	52(7)
H(66)	12380(20)	9763(12)	6010(20)	43(6)
H(67)	11010(19)	9034(11)	6408(18)	34(6)
H(1S)	2100(30)	8045(15)	4800(20)	71(9)
H(2S)	3320(30)	8402(19)	4580(30)	93(11)
H(3S)	3640(30)	7798(17)	5340(30)	91(11)
H(4S)	2790(40)	6840(20)	4250(30)	104(14)
H(5S)	1570(40)	7084(19)	3590(30)	107(13)
H(6S)	2500(30)	6897(15)	2850(30)	73(9)
H(7S)	3290(30)	8428(16)	2990(20)	68(9)

Table 24. Hydrogen bonds for **146f** [Å and °].

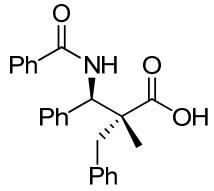
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3A)-H(27)...O(1S)#1	0.88(2)	2.31(2)	3.168(2)	164(2)
N(3B)-H(57)...O(3A)#2	0.86(2)	2.18(3)	3.035(2)	174(2)

Symmetry transformations used to generate equivalent atoms:

#1 x,y,z+1 #2 x+1,y,z



(2*R*,3*R*)-3-Benzoylamino-2-benzyl-2-methyl-3-phenyl-propionic acid methyl ester (147). Compound **146a** (0.050 g, 0.092 mmol) was dissolved in 1.5 mL anhydrous MeOH, chilled to 0 °C, and sodium methoxide (0.200 mL 0.5 M in MeOH, 0.10 mmol, 1.10 eq) was added. The solution was allowed to warm to room temperature and refluxed for 16 h. Water was added and the methanol was removed by evaporation. The aqueous layer was extracted with DCM, acidified with saturated ammonium chloride and further extracted with DCM. The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated. Column chromatography on silica and elution with a 0-50% ethyl acetate in hexanes gradient gave compound **147** as 0.029 g (82%) clear oil. Rf = 0.53 (1:1 hexanes/EtOAc); $[\alpha]^{23}_{D}$ +72.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, 1H, *J* = 9.2 Hz), 7.95-7.92 (m, 2H), 7.54-7.47 (m, 3H), 7.33-7.21 (m, 8H), 7.13-7.10 (m, 2H), 5.17 (d, 1H, *J* = 9.2 Hz), 3.62 (s, 3H), 3.49 (d, 1H, *J* = 13.2 Hz), 2.84 (d, 1H, *J* = 13.2 Hz), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 166.4, 139.5, 136.6, 134.5, 131.8, 130.3, 128.8, 128.6, 128.5, 128.0, 127.9, 127.2, 127.1, 60.6, 52.3, 51.4, 44.5, 19.6; IR (solid): 1728, 1645, 1514, 1485, 1201, 1104, 701 cm^{-1}; HRMS-ESI *m/z* 388.1905 ($[M+H]^+$, $C_{25}H_{26}NO_3$ requires 388.1907).



(2*R*,3*R*)-3-Benzoylamino-2-benzyl-2-methyl-3-phenyl-propionic acid (148). Compound **146a** (0.100 g, 0.183 mmol) was dissolved in 1.5 mL 4:1 THF/H_2O and chilled to 0 °C. A 0.075 mL volume of 30% aqueous hydrogen peroxide (0.73 mmol, 4.0 eq) was added dropwise, followed by lithium hydroxide (0.0070 g in 0.5 mL DI, 0.29 mmol, 1.6 eq). The reaction was allowed to equilibrate to room temperature and stir for 16 h. Sodium sulfite (0.7 mmol in 1 mL DI) was added and the THF was removed by evaporation. The aqueous phase was extracted with dichloromethane. The aqueous phase was then cooled in an ice bath, acidified to pH 1 with 10% HCl, and extracted with ethyl acetate. The ethyl acetate layers were combined, dried with $MgSO_4$, filtered, and concentrated to give 0.055 g (80%) compound **148** as a clear oil. Rf = 0.20 (1:1 hexanes/EtOAc); $[\alpha]^{23}_{D}$ +73.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (bs, 1H), 8.47 (d, 1H, *J* = 9.2 Hz), 7.88-7.84 (m, 2H), 7.55-7.16 (m, 13H), 5.26 (d, 1H, *J* = 9.2 Hz), 3.46 (d, 1H, *J* = 13.2 Hz), 2.93 (d, 1H, *J* = 13.2 Hz), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 166.9, 139.1, 136.2, 134.3, 132.0, 130.4, 128.9, 128.7, 128.6, 128.1(2C), 127.3, 127.2, 60.2, 51.2, 44.2, 19.8; IR (solid): 3030, 1626, 1519, 1485, 1203, 908, 698, 585 cm^{-1}; HRMS-ESI *m/z* 374.1745 ($[M+H]^+$, $C_{24}H_{24}NO_3$ requires 374.1751).

Optimization Study Raw Data and Analysis

Main effects on *yield*:

Total azetine yield:
ANOVA for selected factorial model
Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	1533.00	3	511.00	11.71	0.0189
A-Concentration	*480.50*	*1*	*480.50*	*11.01*	*0.0294*
B-Temperature	*128.00*	*1*	*128.00*	*2.93*	*0.1619*
C-Time	*924.50*	*1*	*924.50*	*21.19*	*0.0100*
Residual	174.50	4	43.62		
Cor Total	1707.50	7			

The Model F-value of 11.71 implies the model is significant. There is only a 1.89% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, C are significant model terms.

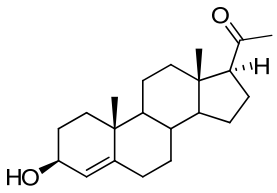
Main effects on *diastereoselectivity*:

Model not significant:

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	3.98	3	1.33	1.81	0.2845
A-Concentration	*2.21*	*1*	*2.21*	*3.01*	*0.1578*
B-Temperature	*0.50*	*1*	*0.50*	*0.68*	*0.4551*
C-Time	*1.28*	*1*	*1.28*	*1.75*	*0.2567*
Residual	2.93	4	0.73		
Cor Total	6.91	7			

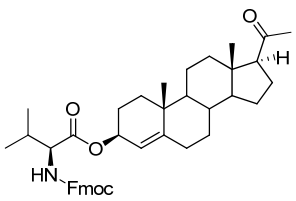
S1.2 Part 2: Progesterone Chemistry

C-3 Progesterone Derivatives



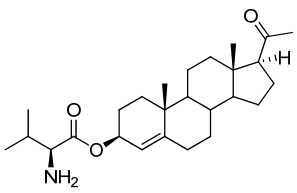
3β-Hydroxy-progesterone (3). Progesterone (3.14 g, 10.0 mmol) was added with cerium chloride heptahydrate (3.73 g, 10.0 mmol, 1.00 eq) to an oven dried three necked 250 mL RBF with thermometer. Methanol (100 mL) was added under argon and the solution was chilled to -20 °C. Sodium borohydride (0.189 g, 5.00 mmol, 0.500 eq) was then added in bulk. After 10 minutes, 37 mL acetone was added and the solution was warmed to ambient temperature. Water (25 mL) was added and the solvent volume was reduced by approximately 100 mL. Ether was added, along with more water, which caused the solution to become clear and colorless. The aqueous layer was extracted with ether. The organic layers were combined, washed with brine, dried, filtered, and concentrated to give 3.14 g white solid. The solid was prepared as a silica cake, loaded onto a 500 mL silica column, and eluted with 3 L 20% ethyl acetate in hexanes, followed by 2 L 25% ethyl acetate in hexanes. Initially eluting pure fractions were combined and concentrated to give 1.56 g white solid that was 90% pure as determined by proton NMR (other 10% was progesterone). (44%) white solid; R_f = 0.38 (1:1 EA/hex, PMA stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (d, 1 H, *J* = 1.6 Hz), 4.18-4.12 (m, 1 H), 2.51 (t, 1 H, *J* = 8.8 Hz), 2.25-0.77 (m, 20 H), 2.11 (s, 3 H), 1.04 (s, 3 H), 0.62 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 147.4, 123.8, 68.1, 63.9, 56.5, 54.5, 44.3, 39.1, 37.5, 36.1, 35.6, 33.1, 32.3, 31.7, 29.6, 24.6, 22.9, 21.2, 19.1, 13.6; IR (solid): 3495, 2927, 2847,

1691, 1362, 1038 cm^{-1}; HRMS-ESI *m/z* 299.2379 ($[M+H-H_2O]^+$, $C_{21}H_{31}O$ requires 299.2369).

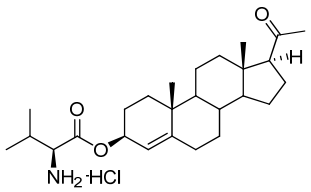


***N*-Fmoc-L-valine-3β-progesterone (4b).** An oven dried 50 mL RBF was charged with 90% 3-β-hydroxy-progesterone (0.352 g, 1.00 mmol), *N*-Fmoc-L-valine (0.373 g, 1.10 mmol, 1.10 eq), and dimethylaminopyridine (DMAP) (0.0122 g, 0.100 mmol, 0.100 eq). The flask was sealed, evacuated, and inert gas flushed and 15 mL anhydrous dichloromethane was added, followed by addition of 1.10 mL (1.10 mmol, 1.10 eq) 1 M dicyclohexylcarbodiimide (DCC) in dichloromethane. The solution was stirred overnight then filtered through Celite. The filtrate was concentrated, prepared as a silica cake and eluted on a 40 g silica column with a 0-25% ethyl acetate in hexanes gradient. The main product was isolated as 0.554 g (87%) clear oil that foamed on drying. R_f = 0.40 (1:1 EA/hex, PMA stain); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 7.2 Hz), 7.63-7.61 (m, 2H), 7.41 (t, 2H, *J* = 7.2 Hz), 7.33 (t, 2H, *J* = 7.2 Hz), 5.35 (d, 1H, *J* = 9.0 Hz), 5.31 (t, 1H, *J* = 7.8 Hz), 5.21 (s, 1H), 4.40 (d, 2H, *J* = 7.2 Hz), 4.31 (dd, 1H, *J* = 9.0, 4.2 Hz), 4.25 (t, 1H, *J* = 7.2 Hz), 2.52 (t, 1H, *J* = 9.0 Hz), 2.23-2.16 (m, 3H), 2.12 (s, 3H), 2.05-1.96 (m, 3H), 1.78-1.55 (m, 6H), 1.50-1.33 (m, 4H), 1.25-1.10 (m, 2H), 1.06 (s, 3H), 1.00 (d, 3H, *J* = 7.2 Hz), 0.93 (d, 3H, *J* = 7.2 Hz), 0.90-0.79 (m, 2H), 0.64 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 172.1, 156.5, 149.8, 144.2, 144.0, 141.5, 127.9, 127.2, 125.3, 120.2, 118.9, 118.8, 72.2, 72.1, 67.2, 63.8, 59.3, 59.2, 56.5, 54.2, 47.5, 47.4, 44.3, 39.0,

37.5, 36.0, 35.0, 33.0, 32.3, 31.6, 25.2, 24.6, 23.0, 19.2, 19.1, 19.0, 17.7, 13.6; IR (solid): 3360, 2936, 1701, 1390, 1352, 1198, 740 cm^{-1}.

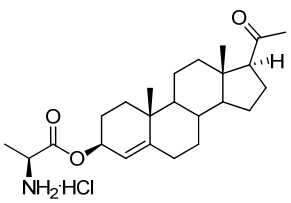


3β-L-Valine-progesterone (5b). A 25 mL RBF was charged with *N*-Fmoc-L-valine-3-β-progesterone **4b** (0.340 g, 0.533 mmol). The flask was evacuated and inert gas flushed and 5 mL of acetonitrile was added. Piperidine (0.527 mL, 5.33 mmol, 10.0 eq) was added and the clear colorless solution was stirred at room temperature for 30 min. The solvent was removed with addition of toluene for complete removal of piperidine. A white solid formed that was re-dissolved in a minimum amount of toluene, loaded onto a 12 g silica column, and eluted with 0-75% ea in hexanes over 35 min. Main product containing fractions were combined and dried to give 0.196 g (89%) white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29-5.23 (m, 1H), 5.20 (d, 1H, *J* = 1.6 Hz), 3.27 (d, 1H, *J* = 4.8 Hz), 2.52 (t, 1H, *J* = 9.2 Hz), 2.36-1.93 (m, 6H), 2.11 (s, 3H), 1.79-1.08 (m, 14H), 1.06 (s, 3H), 0.98 (d, 3H, *J* = 6.8 Hz), 0.95-0.77 (m, 3H), 0.90 (d, 3H, *J* = 6.8 Hz), 0.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 175.6, 149.3, 119.3, 71.3, 63.8, 60.2, 56.4, 54.2, 44.3, 39.0, 37.5, 36.0, 35.2, 33.0, 32.3 (2 C), 31.7, 25.3, 24.6, 22.9, 21.1, 19.6, 19.0, 17.3, 13.6; IR (solid): 2934, 2843, 1724, 1705, 1384, 1354, 1166, 1146, 978, 873, 852 cm^{-1}; HRMS-ESI *m/z* 416.3156 ($[M+H]^+$, $C_{26}H_{42}NO_3$ requires 416.3159).

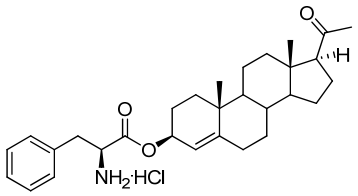


3β-L-Valine-progesterone-HCl (P1-31). A 10 mL RBF was charged with compound **5b** (0.083 g, 0.20 mmol) and the flask was evacuated and flushed with argon. Anhydrous ether (2 mL) was added and the solution was chilled in an ice bath. Hydrogen chloride solution (0.10 mL 2.0 M in ether, 0.20 mmol, 1.0 eq) was added dropwise. A white precipitate formed in solution. The solution was stirred for 30 min. The precipitate was filtered and washed with chilled ether. The product was isolated as 68 mg (75%) white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (bs, 2H), 5.35 (t, 1H, *J* = 7.8 Hz), 5.27 (s, 1H), 3.89 (d, 1H, *J* = 4.8 Hz), 2.53-2.46 (m, 2H), 2.23-0.78 (m, 21H), 2.12 (s, 3H), 1.17 (d, 3H, *J* = 7.2 Hz), 1.14 (d, 3H, *J* = 7.2 Hz), 1.06 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (150 MHz, 60 °C, $CDCl_3$) δ 209.1, 168.5, 150.3, 118.6, 73.6, 64.0, 58.9, 56.7, 54.3, 44.3, 39.3, 37.7, 36.3, 35.0, 33.3, 32.5, 31.5, 30.3, 25.3, 24.7, 23.3, 21.4, 19.3, 18.7, 18.6, 13.6; IR (film): 2932, 2848, 2600, 1737, 1702, 1380, 1355, 1219, 1109 cm^{-1}; HRMS-ESI *m/z* 416.3160 ($[M-Cl]^+$, $C_{26}H_{42}NO_3$ requires 416.3159); Anal. Calcd for $C_{26}H_{42}ClNO_3$+½H_2O: C, 67.73; H, 9.40; N, 3.04. Found C, 67.95; H, 9.06; N, 3.07.

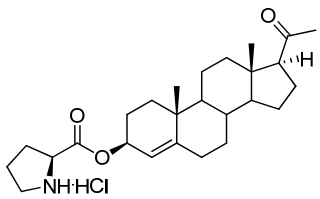
The following compounds were prepared by the methods as described above:



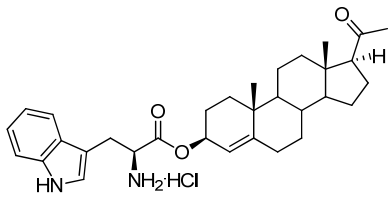
3β-L-Alanine-progesterone-HCl (P1-29). (52% from P1-30) white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (bs, 2H), 5.25 (t, 1H, *J* = 7.6 Hz), 5.14 (s, 1H), 4.12 (d, 1H, *J* = 7.6 Hz), 2.64 (bs, 1H), 2.43 (t, 1H, *J* = 8.8 Hz), 2.20-0.68 (m, 21H), 2.04 (s, 3H), 1.65 (d, 3H, *J* = 7.2 Hz), 0.99 (s, 3H), 0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 170.1, 150.1, 118.4, 73.4, 63.8, 56.4, 54.1, 49.5, 44.2, 39.0, 37.5, 36.0, 35.0, 33.0, 32.3, 31.7, 25.0, 24.6, 23.0, 21.2, 19.0, 16.4, 13.5; IR (film): 2934, 2849, 1741, 1703, 1237, 1207, 1113, 916, 731 cm^{-1}; HRMS-ESI *m/z* 388.2847 ([M-Cl]$^{+}$, $C_{24}H_{38}NO_3$ requires 388.2846); Anal. Calcd for $C_{24}H_{38}ClNO_3$+½H_2O: C, 66.57; H, 9.08; N, 3.23. Found C, 66.42; H, 9.01; N, 3.19.



3β-L-Phenylalanine-progesterone-HCl (P1-32). (51% from P1-30) white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (bs, 2H), 7.30-7.21 (m, 5H), 5.17 (bs, 1H), 4.97 (s, 1H), 4.32 (bs, 1H), 3.47-3.29 (m, 2H), 2.48 (t, 1H, *J* = 8.6 Hz), 2.20-0.68 (m, 20H), 2.10 (s, 3H), 0.97 (s, 3H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 168.8, 149.9, 134.2, 130.1, 129.0, 127.8, 118.2, 73.6, 63.8, 56.4, 54.5, 54.1, 44.2, 39.0, 37.4, 36.6, 36.0, 34.8, 33.0, 32.2, 31.7, 24.9, 24.6, 23.0, 21.2, 18.9, 13.6; IR (film): 2929, 2848, 1732, 1701, 1233, 1202, 1109, 912, 729, 700 cm^{-1}; HRMS-ESI *m/z* 464.3160 ([M-Cl]$^{+}$, $C_{30}H_{42}NO_3$ requires 464.3159); Anal. Calcd for $C_{30}H_{42}ClNO_3$+½H_2O: C, 70.77; H, 8.51; N, 2.75. Found C, 70.74; H, 8.31; N, 2.78.

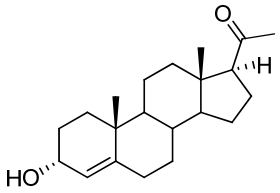


3β-L-Proline-progesterone-HCl (P1-33). (38% from P1-30) white solid. ^{1}H NMR (400 MHz, DMSO) δ 10.32 (bs, 1H), 9.02 (bs, 1H), 5.26 (s, 1H), 5.22 (s, 1H), 4.33 (s, 1H), 3.40 (s, 1H), 3.20 (d, 2H, *J* = 7.2 Hz), 2.56 (t, 1H, *J* = 8.6 Hz), 2.30-0.73 (m, 23H), 2.05 (s, 3H), 1.02 (s, 3H), 0.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 168.9, 150.6, 118.0, 74.1, 63.8, 59.5, 56.4, 54.0, 46.6, 44.2, 38.9, 37.5, 35.9, 34.8, 33.0, 32.6, 31.7, 29.4, 25.1, 24.5, 24.0, 22.9, 21.1, 19.0, 13.5; IR (film): cm^{-1}; HRMS-ESI *m/z* 414.3005 ($[M-Cl]^+$, $C_{26}H_{40}NO_3$ requires 414.3003); Anal. Calcd for $C_{26}H_{40}ClNO_3$+½H_2O: C, 68.03; H, 9.00; N, 3.05. Found C, 68.21; H, 8.89; N, 3.02.



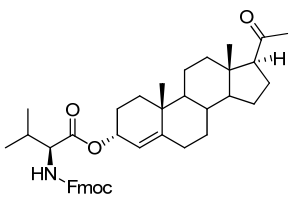
3β-L-Tryptophan-progesterone-HCl (P1-34). (43% from P1-30) white solid. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (bs, 1H), 8.62 (bs, 2H), 7.53 (d, 1H, *J* = 7.6 Hz), 7.36 (d, 1H, *J* = 7.6 Hz), 7.24 (s, 1H), 7.08 (t, 1H, *J* = 7.4 Hz), 6.99 (t, 1H, *J* = 7.4 Hz), 5.07 (bs, 1H), 4.73 (s, 1H), 4.14 (bs, 1H), 3.46-3.20 (m, 2H), 2.54 (t, 1H, *J* = 8.8 Hz), 2.20-0.67 (m, 20H), 2.05 (s, 3H), 0.95 (s, 3H), 0.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 169.3, 150.3, 136.4, 126.9, 126.6, 122.0, 119.3, 118.5, 118.1, 112.1, 105.9, 74.1, 63.8, 56.4, 54.0, 53.6, 44.2, 39.0, 37.5, 35.9, 34.7, 33.0, 32.3, 31.7, 26.1, 25.0, 24.6, 23.0, 21.1, 19.0, 13.6; IR (film): 2929, 2849, 1732, 1701, 1456, 1435, 1354, 1218, 1108, 730

cm^{-1}; HRMS-ESI *m/z* 503.3271 ($[M-Cl]^+$, $C_{32}H_{43}N_2O_3$ requires 503.3268); Anal. Calcd for $C_{32}H_{43}ClN_2O_3$+¾H_2O: C, 69.54; H, 8.12; N, 5.07. Found C, 69.57; H, 8.06; N, 5.04.



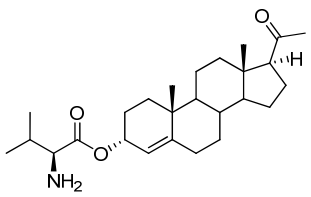
3α-Hydroxy-progesterone (6). Ester formation: Compound **3** (0.560 g, 1.59 mmol), triphenylphosphine (0.877 g, 3.34 mmol, 2.10 eq), and *p*-nitrophenylbenzoic acid (0.559 g, 3.34 mmol, 2.10 eq) were added to a 100 mL oven dried flask that was evacuated and inert gas flushed. A 20 mL volume of anhydrous THF was added. The solution was cooled to 0 °C and diisopropylazodicarbonate (0.693 mL in 10 mL THF solution, 3.34 mmol, 2.10 eq) was added dropwise over 1 h. The solution was stirred at 0 °C for an additional 1 h. The reaction was diluted with 50 mL ether and washed with saturated sodium bicarbonate solution (3 X 25 mL). The aqueous layers were combined and extracted with ether. The organic layers were combined, dried, filtered, and concentrated to give a pale orange oil. The oil was loaded onto a 40 g silica column in a minimum amount of DCM and eluted with 0-25% ea in hex over 35 min. Main peak fractions were combined and concentrated to give a clear oil that crystallized on standing. Crude wet mass was 0.820 g. Saponification: The esterification product (0.613 g, 1.32 mmol) was dissolved in 12 mL 5:3 MeOH/THF in a 25 mL RBF and potassium carbonate (0.364 g, 2.63 mmol, 2.00 eq), dissolved in 2 mL DI, was added. A white precipitate formed in solution that gradually dissolved over the course of 1 h. The solvents were removed and

the aqueous layer was extracted with ether. The organic layers were combined, washed with brine, dried, filtered, and concentrated. The resulting white solid was re-dissolved in a minimum amount of DCM and eluted on a 40 g silica column with 0-35% ea in hexanes gradient over 40 min. The desired major product was isolated as 0.380 g (91%) white solid. R_f = 0.31 (1:1 EA/hex, PMA stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (dd, 1H, *J* = 4.8, 1.6 Hz), 4.10-4.06 (m, 1H), 2.53 (t, 1H, *J* = 9.2 Hz), 2.27-0.82 (m, 20H), 2.12 (s, 3H), 0.99 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 150.1, 121.1, 64.4, 63.9, 56.5, 54.1, 44.4, 39.2, 37.7, 36.0, 32.9, 32.5, 31.9, 31.7, 28.0, 24.6, 23.0, 21.7, 18.3, 13.6; IR (solid): 3485, 3414, 2929, 2842, 1694, 1356, 1015 cm^{-1}; HRMS-ESI *m/z* 299.2366 ($[M+H-H_2O]^+$, $C_{21}H_{31}O$ requires 299.2369).

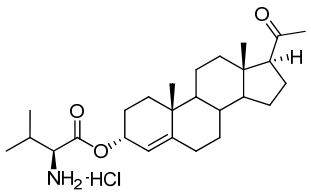


***N*-Fmoc-L-valine-3α-progesterone (7).** Compound **6** (0.100 g, 0.314 mmol), *N*-Fmoc-valine (0.213 g, 0.628 mmol, 2.00 eq), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) (0.120 g, 0.628 mmol, 2.00 eq), and DMAP (4 mg, 0.10 eq) were added to an oven dried 25 mL RBF. The flask was evacuated and inert gas flushed and 6 mL anhydrous DCM was added. The reaction was stirred at room temperature for 36 h. The solution was quenched and washed with saturated ammonium chloride solution (2 X 20 mL). The aqueous layers were combined and extracted with DCM. The organic layers were combined, washed with brine, dried, filtered, and concentrated. The clear oil was loaded in a minimum amount of DCM onto a 12 g silica

column and eluted with a 0-15% ea in hex gradient over 45 minutes. The desired product was obtained as 0.193 g (96%) white foam. R_f = 0.63 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 7.6 Hz), 7.63 (d, 2H, *J* = 7.2 Hz), 7.41 (t, 2H, *J* = 7.2 Hz), 7.33 (dt, 2H, *J* = 7.2, 0.8 Hz), 5.44 (d, 1H, *J* = 4.4 Hz), 5.36 (d, 1H, *J* = 8.8 Hz), 5.19 (d, 1H, *J* = 2.4 Hz), 4.48-4.44 (m, 1H), 4.35-4.23 (m, 3H), 2.43 (t, 1H, *J* = 8.8 Hz), 2.28-0.79 (m, 20H), 2.09 (s, 3H), 1.00 (d, 3H, *J* = 6.8 Hz), 0.99 (s, 3H), 0.94 (d, 3H, *J* = 7.2 Hz), 0.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 172.0, 156.5, 152.9, 144.2, 143.9, 141.5, 127.9, 127.3, 125.5, 125.4, 120.2, 116.5, 69.0, 67.2, 63.8, 59.2, 56.2, 53.9, 47.5, 44.2, 38.9, 37.6, 35.8, 32.5, 31.7, 31.6, 25.1, 24.5, 22.9, 21.6, 19.3, 18.1, 17.6, 13.5; IR (solid): 3335, 2935, 1700, 1449, 1237, 1195, 759, 740 cm^{-1}.

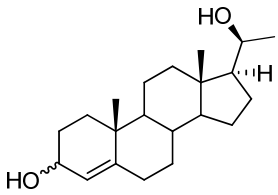


3*α*-L-Valine-progesterone (8). Prepared according to the method described for compound **5b**. (85%) clear oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.44 (d, 1H, *J* = 4.8 Hz), 5.17 (s, 1H), 3.28 (d, 1H, *J* = 4.8 Hz), 2.53 (t, 1H, *J* = 9.0 Hz), 2.27-0.86 (m, 22H), 2.12 (s, 3H), 1.01 (s, 3H), 1.00 (d, 3H, *J* = 6.6 Hz), 0.91 (d, 3H, *J* = 7.2 Hz), 0.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 175.5, 152.5, 117.1, 68.1, 63.9, 60.1, 56.4, 54.0, 44.3, 39.1, 37.6, 35.9, 32.6, 32.5 (2C), 32.4, 31.7, 25.2, 24.6, 23.0, 21.6, 19.6, 18.2, 17.3, 13.6; IR (solid): 2933, 2872, 1722, 1704, 1383, 1358, 1237, 1178, 976 cm^{-1}; HRMS-ESI *m/z* 416.3155 ($[M+H]^+$, $C_{26}H_{42}NO_3$ requires 416.3159).



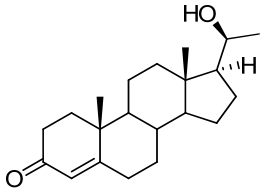
3α-L-Valine-progesterone-HCl (P1-163). Prepared according to the method described for compound **P1-31**. (21%) white powdery solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (d, 1H, *J* = 4.4 Hz), 5.25 (s, 1H), 3.82 (d, 1H, *J* = 3.2 Hz), 2.53 (t, 1H, *J* = 9.2 Hz), 2.48-2.37 (m, 1H), 2.29-0.79 (m, 22H), 2.12 (s, 3H), 1.15 (d, 3H, *J* = 6.8 Hz), 1.11 (d, 3H, *J* = 6.8 Hz), 1.00 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 169.7, 153.3, 116.3, 70.0, 63.9, 59.0, 56.3, 53.9, 44.3, 39.0, 37.6, 35.9, 32.5, 32.4 (2C), 31.7, 30.6, 25.0, 24.6, 23.0, 21.6, 18.7, 18.2 (2C), 13.6; IR (film): 2935, 2876, 2620, 1734, 1703, 1383, 1357, 1228, 731 cm^{-1}; Anal. Calcd for $C_{26}H_{42}ClNO_3$+½H_2O: C, 67.73; H, 9.40; N, 3.04. Found C, 67.00; H, 9.53; N, 3.04.

C-20 Progesterone Derivatives



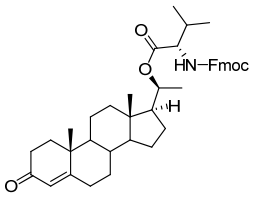
3,20-Hydroxy-progesterone (9). An oven dried RBF was charged with 25 mL anhydrous THF and chilled in an ice bath. A 4.50 mL volume (9.00 mmol, 2.25 eq) of 2.0 M lithium aluminum hydride in THF was added. A separate ~10 mL solution of progesterone (1.26 g, 4.00 mmol) in anhydrous THF was prepared in a dry flask. The solution was transferred to the reaction flask dropwise over 30 minutes. The mixture was

heated under reflux for 1 h, cooled to room temperature, and quenched by the addition of ethyl acetate, followed by aqueous sodium sulfate. Solid sodium sulfate was added to remove excess water. The remaining salts were filtered and washed with THF. The organic filtrates were combined and concentrated to give 1.24 g (90%) white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (d, 1H, J = 0.8 Hz), 4.19-4.10 (m, 1H), 3.76-3.68 (m, 1H), 2.24-0.71 (m, 22H), 1.13 (d, 3H, J = 6.0 Hz), 1.05 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 123.6, 70.7, 68.1, 58.6, 55.8, 54.6, 42.6, 40.1, 37.5, 35.9, 35.6, 33.3, 32.4, 29.7, 25.8, 24.6, 23.8, 21.1, 19.1, 12.7; IR (solid): 3300, 2920, 2865, 1435, 1375, 1021, 853 cm^{-1}; HRMS-ESI *m/z* 301.2524 ($[M+H-H_2O]^+$, $C_{21}H_{33}O$ requires 301.2526).

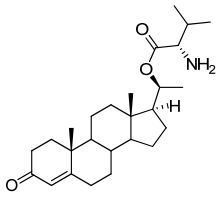


20-*S*-Hydroxy-progesterone (10). A 100 mL RBF was charged with 1.00 g crude compound **9** and 5.00 g manganese dioxide (activated by heating in oven for 2 days then cooled in a dessicator) and the reactants were suspended in 30 mL chloroform. The mixture was stirred at room temperature overnight. The mixture was then filtered through a pad of Celite and rinsed with chloroform. The clear, colorless filtrate was evaporated to dryness to give an off-white solid. The solid was recrystallized from ethyl acetate/hexane to give 0.565 g (57%) white solid. R_f = 0.26 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 3.77-3.70 (m, 1H), 2-47-0.91 (m, 21H), 1.19 (s, 3H), 1.15 (d, 3H, J = 6.0 Hz), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 171.8, 124.0,

70.7, 58.5, 55.5, 54.0, 42.5, 39.8, 38.8, 35.9, 35.6, 34.2, 33.1, 32.2, 25.8, 24.6, 24.0, 21.1, 17.6, 12.6; IR (solid): 3525, 2939, 2864, 1670, 1609, 1117, 857 cm^{-1}; HRMS-ESI *m/z* 317.2473 ($[M+H]^+$, $C_{21}H_{32}O_2$ requires 317.2475).

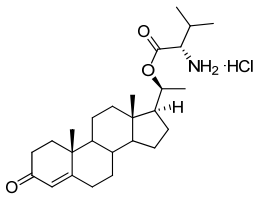


20-*S*-*N*-Fmoc-L-valine-progesterone (11). Prepared according to the method described for compound **4b**. (87%) white foam; R_f = 0.65 (1:1 EA/hex); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 8.0 Hz), 7.62 (d, 2H, *J* = 7.6 Hz), 7.42-7.37 (m, 2H), 7.33 (t, 2H, *J* = 7.2 Hz), 5.71 (s, 1H), 5.41 (d, 1H, *J* = 8.8 Hz), 4.97-4.90 (m, 1H), 4.48-4.16 (m, 4H), 2.43-0.80 (m, 21H), 1.20 (d, 3H, *J* = 6.0 Hz), 1.08 (s, 3H), 0.99 (d, 3H, *J* = 6.8 Hz), 0.94 (d, 3H, *J* = 7.2 Hz), 0.67 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.0, 171.8, 171.7, 156.4, 144.2, 143.9, 141.5, 127.9, 127.3, 125.3, 124.0, 120.2, 74.4, 67.3, 59.2, 55.4, 55.0, 53.9, 47.4, 42.4, 39.1, 38.7, 35.7, 35.6, 34.1, 33.0, 32.1, 31.5, 25.6, 24.4, 21.1, 20.0, 19.1, 17.8, 17.4, 12.7; IR (solid): 3307, 2935, 1716, 1668, 1229, 1029, 739 cm^{-1}; HRMS-ESI *m/z* 638.3847 ($[M+H]^+$, $C_{41}H_{52}NO_5$ requires 638.3840).



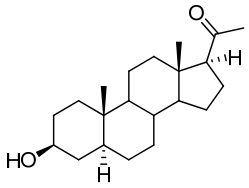
20-*S*-L-Valine-progesterone (12). Prepared according to the method described for compound **5b**. (40%) white powdery solid; R_f = 0.06 (1:1 EA/hex); ^1H NMR (400 MHz,

$CDCl_3$) δ 5.72 (s, 1H), 4.93-4.86 (m, 1H), 3.23 (d, 1H, *J* = 4.4 Hz), 2.46-2.23 (m, 5H), 2.10-0.80 (m, 18H), 1.17 (s, 3H), 1.16 (d, 3H, *J* = 6.4 Hz), 0.98 (d, 3H, *J* = 7.2 Hz), 0.88 (d, 3H, *J* = 6.8 Hz), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 175.1, 171.5, 124.0, 73.4, 59.9, 55.4, 55.1, 54.0, 42.5, 39.2, 38.8, 35.9, 35.6, 34.2, 33.0, 32.2 (2 C), 25.6, 24.4, 21.1, 20.0, 19.5, 17.6, 17.1, 12.7; IR (film): 2933, 1721, 1672, 1381, 1187, 1071, 864 cm^{-1}; HRMS-ESI *m/z* 416.3156 ($[M+H]^+$, $C_{26}H_{42}NO_3$ requires 416.3159).

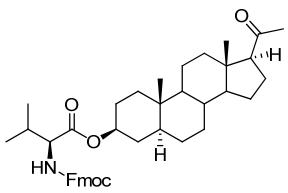


20-*S*-L-Valine-progesterone HCl salt (P1-57). Prepared according to the method described for compound **P1-31**. (59%) off-white solid; ^{1}H NMR (400 MHz, DMSO) δ 8.51 (bs 2H), 5.63 (s, 1H), 4.86 (q, 1H, *J* = 10.0, 5.6 Hz), 3.79 (bs 1H), 2.46-0.82 (m, 23H), 1.15 (d, 3H, *J* = 6.0 Hz), 1.14 (s, 3H), 0.99 (d, 3H, *J* = 6.4 Hz), 0.95 (d, 3H, *J* = 6.4 Hz), 0.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 171.5, 168.2, 124.0, 76.0, 58.6, 55.5, 54.8, 54.0, 42.5, 39.2, 38.8, 35.9, 35.6, 34.2, 33.0, 32.2, 30.1, 25.5, 24.3, 21.1, 19.9, 18.6, 18.5, 17.6, 12.7; IR (solid): 2935, 2870, 1733, 1667, 1378, 1331, 1228, 1071, 863 cm^{-1}; HRMS-ESI *m/z* 416.3152 ($[M-Cl]^+$, $C_{26}H_{42}NO_3$ requires 416.3159); Anal. Calcd for $C_{26}H_{42}ClNO_3+H_2O$: C, 66.43; H, 9.43; N, 2.98. Found C, 66.35; H, 9.24; N, 3.00.

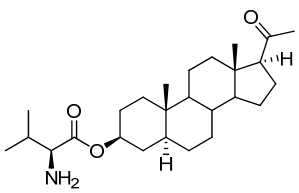
Allopregnanolone Derivatives



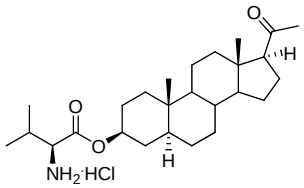
3β-hydroxy-5α-pregnan-20-one (14). An oven dried 500 mL RBF was charged with 10% palladium on carbon (0.400 g) and 5-pregnen-3-beta-ol-20-one (4.00 g, 12.6 mmol) and the flask was evacuated and flushed with argon. A 200 mL volume of absolute ethanol was added and the flask was flushed with hydrogen. The reaction was stirred at room temperature for 4 h. The mixture was filtered through Celite and the recovered clear, colorless filtrate was concentrated to reveal a white solid of mass 4.08 g. The solid was recrystallized from hex/EA (~3:1 total 175 mL) to give 3.19 g white solid. A second recrystallization provided an additional 0.43 g for a total of 3.62 g (90%) white crystalline solid. R_f = 0.38 (1:1 EA/hex, PMA); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.62-3.57 (m, 1H), 2.52 (t, 1H, *J* = 9.0 Hz), 2.18-1.97 (m, 2H), 2.11 (s, 3H), 1.83-0.86 (m, 20H), 0.81 (s, 3H), 0.71-0.65 (m, 1H), 0.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.0, 71.5, 64.0, 56.9, 54.4, 45.0, 44.5, 39.3, 38.3, 37.2, 35.7 (2C), 32.2, 31.7 (2C), 28.8, 24.6, 23.0, 21.5, 13.7, 12.5; IR (solid): 3426, 3375, 2930, 2845, 1697, 1682, 1385, 1036 cm^{-1}; HRMS-ESI *m/z* 319.2629 ($[M+H]^+$, $C_{21}H_{35}O_2$ requires 319.2632).



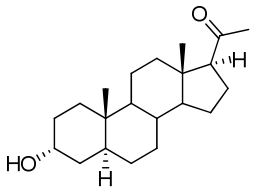
3β-*N*-Fmoc-L-valine-5α-pregnan-20-one (15). Prepared according to the method described for compound **4b**. (90%) white foam; R_f = 0.69 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 7.6 Hz), 7.61 (d, 2H, *J* = 6.8 Hz), 7.41 (t, 2H, *J* = 7.6 Hz), 7.33 (t, 2H, *J* = 7.2 Hz), 5.34 (d, 1H, *J* = 9.2 Hz), 4.83-4.73 (m, 1H), 4.49-4.20 (m, 4H), 2.52 (m, 1H), 2.23-0.66 (m, 23H), 2.12 (s, 3H), 0.98 (d, 3H, *J* = 6.8 Hz), 0.92 (d, 3H, *J* = 6.8 Hz), 0.83 (s, 3H), 0.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 171.8, 156.4, 144.1/144.0, 141.5, 127.9, 127.3, 125.3, 120.2, 75.0, 67.2, 64.0, 59.2, 56.7, 54.1, 47.4, 44.8, 44.4, 39.2, 36.9, 35.7, 35.6, 34.1, 32.1, 31.8, 31.6, 28.6, 27.6, 24.6, 23.0, 21.4, 19.1, 17.7, 13.7, 12.4; IR (solid): 3344, 2931, 1701, 1449, 1200, 739 cm^{-1}; HRMS-ESI *m/z* 640.3979 ($[M+H]^+$, $C_{41}H_{54}NO_5$ requires 640.3983).



3β-L-valine-5α-pregnan-20-one (16). Prepared according to the method described for compound **5b**. (99%) clear/white semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77-4.65 (m, 1H), 3.26 (d, 1H, *J* = 4.4 Hz), 2.87 (bs, 2H), 2.51 (t, 1H, *J* = 9.2 Hz), 2.36-0.62 (m, 23H), 2.09 (s, 3H), 0.96 (d, 3H, *J* = 7.2 Hz), 0.88 (d, 3H, *J* = 6.4 Hz), 0.81 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.0, 174.7, 74.4, 64.0, 59.7, 56.8, 54.2, 44.8, 44.4, 39.2, 36.9, 35.7, 35.6, 34.2, 32.2, 32.1, 31.8, 28.6, 27.6, 24.6, 23.0, 21.4, 19.3, 17.4, 13.7, 12.4; IR (solid): 2927, 2849, 1729, 1703, 1385, 1358, 1224, 1006 cm^{-1}; HRMS-ESI *m/z* 418.3310 ($[M+H]^+$, $C_{26}H_{44}NO_3$ requires 418.3316).

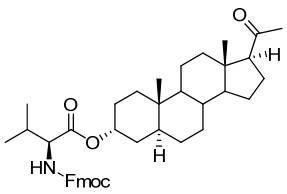


3β-L-valine-5α-pregnan-20-one HCl salt (P1-123). Compound **16** (0.317 g, 0.759 mmol) was dissolved in ~2:1 anhydrous ether/DCM (6 mL total) under argon. The clear, slightly amber solution was chilled in an ice bath and 0.759 mL (0.759 mmol, 1.0 eq) 1 M HCl in ether solution was added slowly dropwise. A white precipitate was observed in solution. The solution was stirred at 0 °C for 30 min and then filtered. The precipitate was washed with ice chilled ether. The product was recovered as a slightly off-white solid of mass 0.175 g (51%). ^{1}H NMR (400 MHz, DMSO) δ 8.55 (bs, 1H), 4.80-4.69 (m, 1H), 3.80 (s, 1H), 3.37 (s, 1H), 2.56 (t, 1H, *J* = 8.8 Hz), 2.22-2.12 (m, 1H), 2.08-0.65 (m, 23H), 2.05 (s, 3H), 0.98 (d, 3H, *J* = 7.2 Hz), 0.93 (d, 3H, *J* = 6.8 Hz), 0.79 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 167.9, 76.3, 63.9, 58.6, 56.7, 54.2, 44.8, 44.4, 39.1, 36.9, 35.6, 35.5, 33.9, 32.1, 31.8, 30.1, 28.6, 27.4, 24.6, 22.9, 21.4, 18.5, 18.4, 13.6, 12.4; IR (solid): 3369, 2927, 2850, 2620, 1732, 1703, 1382, 1359, 1222, 1002 cm^{-1}; HRMS-ESI *m/z* 418.3316 ([M-Cl]$^{+}$, $C_{26}H_{44}NO_3$ requires 418.3316); Anal. Calcd for $C_{26}H_{44}ClNO_3$: C, 68.77; H, 9.77; O, 10.57. Found C, 68.76; H, 9.89; O, 10.84.

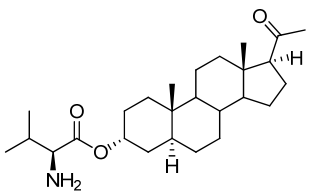


Allopregnanolone (2). An oven dried 100 mL RBF with magnetic stir bar was charged with 1.59 g (5.00 mmol) compound **14** and 15 mL anhydrous THF.

Diethylazodicarboxylate (2.85 mL 40% soln. in toluene, 6.25 mmol, 1.25 eq) was added, followed by trifluoroacetic acid (0.482 mL, 6.25 mmol, 1.25 eq) and the flask was set in a room temperature water bath. To this pale amber suspension was added triphenylphosphine (1.64 g, 6.25 mmol, 1.25 eq). Sodium benzoate (0.901 g, 6.25 mmol, 1.25 eq) was then added and the suspension was stirred under argon for 24 h at room temperature. The THF was completely removed with methanol addition/evaporation. Methanol (20 mL) was then added. The flask was fitted with a drying tube topped condenser and set for reflux. After 24 h, the methanol was removed and the remaining solid was redissolved in DCM. The organic layer was washed with DI (3 X 20 mL). The aqueous layers were combined and extracted with DCM. The organic layers were combined, dried, filtered, and concentrated to give a white solid. The solid was prepared as a silica cake and eluted with 0-35% EA in hex on a 120 g silica column over 40 min. Main product containing fractions were combined and concentrated to give 1.46 g (92%) white solid. R_f = 0.38 (1:1 ea/hex, PMA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06-4.04 (m, 1H), 2.53 (t, 1H, *J* = 9.2 Hz), 2.19-1.96 (m, 2H), 2.11 (s, 3H), 1.73-0.74 (m, 21H), 0.78 (s, 3H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 66.7, 64.0, 56.9, 54.4, 44.5, 39.3 (2C), 36.3, 36.0, 35.7, 32.4, 32.1, 31.8, 29.2, 28.6, 24.6, 22.9, 21.0, 13.7, 11.4; IR (solid): 3252, 2913, 2850, 1706, 1446, 1351, 1004 cm^{-1}; HRMS-ESI *m/z* 319.2633 ($[M+H]^+$, $C_{21}H_{35}O_2$ requires 319.2632).

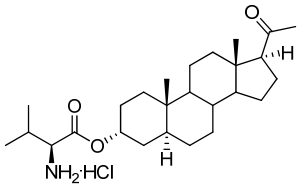


3α-*N*-Fmoc-L-valine-5α-pregnan-20-one (17). Prepared according to the method described for compound **4b**. (87%) white foam; R_f = 0.65 (1:1 EA/hex, PMA stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 7.6 Hz), 7.64 (d, 2H, *J* = 7.6 Hz), 7.42 (t, 2H, *J* = 7.2 Hz), 7.33 (t, 2H, *J* = 7.2 Hz), 5.37 (d, 1H, *J* = 8.4 Hz), 5.13 (s, 1H), 4.46-4.33 (m, 3H), 4.27 (t, 1H, *J* = 7.2 Hz), 2.49-0.68 (m, 24H), 2.09 (s, 3H), 1.02 (d, 3H, *J* = 7.2 Hz), 0.95 (d, 3H, *J* = 7.2 Hz), 0.79 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 171.7, 156.5, 144.2/143.9, 141.5, 127.9, 127.3, 125.4, 120.2, 71.7, 67.3, 63.9, 59.3, 56.7, 54.3, 47.5, 44.4, 40.2, 39.1, 35.9, 35.5, 33.2, 33.0, 31.8 (2C), 31.7, 28.3, 26.3, 24.5, 22.9, 21.0, 19.3, 17.7, 13.6, 11.5; IR (film): 3364, 2931, 1698, 1387, 1353, 1232, 1036, 739 cm^{-1}; HRMS-ESI *m/z* 640.3989 ($[M+H]^+$, $C_{41}H_{54}NO_5$ requires 640.3988).

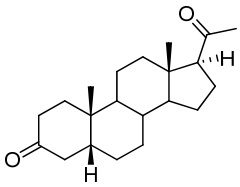


3α-L-Valine-5α-pregnan-20-one (18). A 25 mL RBF was charged with compound **17 (**0.320 g, 0.500 mmol), 5 mL ACN, and 3 mL DMF. Piperidine (0.494 mL, 5.00 mmol, 10.0 eq) was added. The solution was stirred at room temperature for 30 min. Toluene was added and the solution was concentrated 3 times with addition of toluene. The pale amber oil was loaded in a minimum amount of toluene onto a 12 g silica column. The column was eluted with 0-100% EA in hex over 40 minutes. Main product fractions were combined to give 0.196 g (94%) sticky white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.09 (t, 1H, *J* = 2.4 Hz), 3.89 (bs, 2H), 3.37 (d, 1H, *J* = 4.8 Hz), 2.52 (t, 1H, *J* = 9.0 Hz), 2.19-0.76 (m, 23H), 2.11 (s, 3H), 1.01 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 6.6

Hz), 0.80 (s, 3H), 0.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.0, 174.6, 70.9, 64.0, 59.7, 56.9, 54.3, 44.4, 40.3, 39.2, 36.0, 35.6, 33.2, 33.0, 32.2, 32.0, 31.7, 28.4, 26.4, 24.5, 23.0, 21.0, 19.4, 17.3, 13.7, 11.5; IR (solid): 2931, 2856, 1724, 1701, 1388, 1356, 1227, 1153, 975 cm^{-1}; HRMS-ESI *m/z* 418.3306 ([M+H]$^+$, $C_{26}H_{44}NO_3$ requires 418.3302).

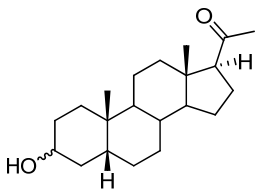


3α-L-Valine-5α-pregnan-20-one HCl salt (P1-131). Prepared according to the method described for compound **P1-31**. (55%) slightly off-white solid; ^{1}H NMR (600 MHz, DMSO) δ 8.56 (bs, 1H), 5.06 (s, 1H), 3.84 (s, 1H), 2.59-0.66 (m, 26H), 2.05 (s, 3H), 1.02 (d, 3H, *J* = 7.2 Hz), 0.96 (d, 3H, *J* = 6.6 Hz), 0.77 (s, 3H), 0.51 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.9, 168.3, 73.2, 64.0, 58.7, 56.8, 54.2, 44.4, 40.2, 39.1, 35.9, 35.6, 33.2, 32.8, 31.9, 31.7, 30.2, 28.3, 26.2, 24.5, 23.0, 21.0, 18.6, 18.4, 13.6, 11.6; IR (film): 2927, 2852, 2620, 1733, 1702, 1382, 1353, 1226, 1155, 974 cm^{-1}; HRMS-ESI *m/z* 418.3314 ([M-Cl]$^+$, $C_{26}H_{44}NO_3$ requires 418.3316); Anal. Calcd for $C_{26}H_{44}ClNO_3$: C, 68.77; H, 9.77; O, 10.57. Found C, 67.78; H, 9.89; O, 11.54.



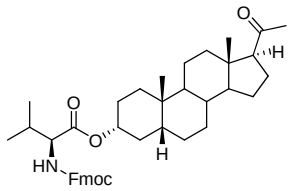
5β-Pregnane-3,20-dione (19). A three necked 500 mL RBF was charged with progesterone (2.00 g, 6.36 mmol), 5% Pd/$CaCO_3$ (0.180 g, 9% w/w), 200 mL absolute

ethanol, and KOH (0.360 g in 1 mL DI). The flask was evacuated and flushed with hydrogen and the reaction stirred for 1 h. The ethanol was removed and the residue was redissolved in ether and washed with water. The water layer was extracted with ether (2 X 50 mL). The aqueous layer was then acidified to pH <3 with 1 M HCl and extracted with ether. The organic layers were combined, dried, filtered, and concentrated to give an off-white solid of mass 2.08 g. The sample was loaded in a minimum amount of toluene onto a 120 g silica column and eluted with 0-35 % ea in hex gradient. The main product was recovered as 1.20 g (60%) white solid. R_f = 0.51 (1:1 EA/hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.69 (t, 1H, *J* = 15 Hz), 2.55 (t, 1H, *J* = 9.0 Hz), 2.34 (dt, 1H, *J* = 14.4, 5.4 Hz), 2.21-1.09 (m, 20H), 2.12 (s, 3H), 1.02 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 213.3, 209.7, 64.0, 56.8, 44.5, 44.4, 42.5, 40.9, 39.3, 37.4, 37.1, 35.7, 35.1, 31.8, 26.7, 25.9, 24.6, 23.1, 22.8, 21.4, 13.6; IR (film): 2931, 2852, 1716, 1698, 1439, 1352 cm^{-1}; HRMS-ESI *m/z* 317.2473 ($[M+H]^+$, $C_{21}H_{33}O_2$ requires 317.2475).



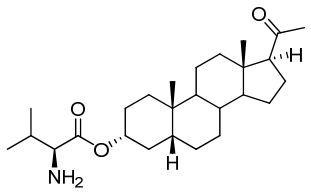
3-Hydroxy-5β-pregnane-20-one (20/21). A 250 mL RBF was charged with compound **19** (1.00 g, 3.16 mmol) and 40 mL absolute ethanol. The solution was warmed in an oil bath to 50 °C and sodium borohydride (0.179 g, 4.74 mmol, 1.50 eq) was added. The reaction was stirred for 10 min and 75-100 mL hot water was added until a slight cloudiness remained in solution. The solution was then allowed to cool gradually to room temperature and chilled in a 4 °C freezer for 3 h. The mixture was filtered and

the white solid was washed with 30% ethanol in DI. After drying, the recovered solids were loaded in a minimum amount of DCM onto a 120 g silica column and eluted with 0-25% EA/hex over 60 min. Main product containing fractions were combined and concentrated to give 0.710 g (71%) 3α-hydroxy-5β-pregnane-20-one and 0.110 g (11%) 3β-hydroxy-5β-pregnane-20-one isomer. Major product (3-alpha-hydroxy-5-beta): (71%) white solid; R_f = 0.30 (1:1 EA/hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.67-3.62 (m, 1H), 2.53 (t, 1H, *J* = 9.6 Hz), 2.18-0.96 (m, 23H), 2.11 (s, 3H), 0.92 (s, 3H), 0.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.0, 71.9, 64.1, 56.9, 44.5, 42.2, 40.6, 39.4, 36.6, 36.0, 35.5, 34.8, 31.8, 30.7, 27.3, 26.6, 24.6, 23.5, 23.1, 21.0, 13.6; IR (film): 3391, 2927, 2847, 1702, 1352, 1040 cm^{-1}; HRMS-ESI *m/z* 319.2638 ([M+H]$^+$, $C_{21}H_{35}O_2$ requires 319.2632). Minor product (3-beta-hydroxy-5-beta): (11%) white solid; R_f = 0.41 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (t, 1H, *J* = 2.8 Hz), 2.53 (t, 1H, *J* = 9.2 Hz), 2.20-1.00 (m, 23H), 2.11 (s, 3H), 0.96 (s, 3H), 0.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.0, 67.2, 64.1, 57.0, 44.6, 39.9, 39.5, 36.7, 35.8, 35.4, 33.7, 31.8, 30.1, 28.0, 26.7, 26.4, 24.6, 24.1, 23.0, 21.3, 13.7; IR (film): 3330, 2924, 2871, 1701, 1352, 1032 cm^{-1}; HRMS-ESI *m/z* 319.2636 ([M+H]$^+$, $C_{21}H_{35}O_2$ requires 319.2632).

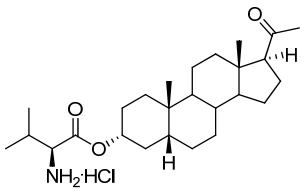


3α-*N*-Fmoc-L-valine-5β-pregnane-20-one (22). Prepared according to the method described for compound **4b**. (81%) white foam; R_f = 0.66 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 7.2 Hz), 7.63 (t, 2H, *J* = 6.4 Hz), 7.41 (dt, 2H, *J* = 7.6,

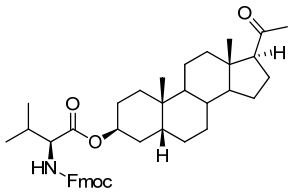
1.6 Hz), 7.33 (t, 2H, 7.6 Hz), 5.32 (d, 1H, *J* = 9.2 Hz), 4.87-4.78 (m, 1H), 4.48 (dd, 1H, *J* = 10.4, 6.4 Hz), 4.38-4.20 (m, 3H), 2.49-0.86 (m, 24H), 2.09 (s, 3H), 1.00 (d, 3H, *J* = 6.8 Hz), 0.94 (d, 2H, *J* = 8.0 Hz), 0.93 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.9, 171.7, 156.5, 144.2/143.8, 141.5, 127.9, 127.3, 125.4, 125.3, 120.2, 75.6, 67.2, 64.0, 59.3, 56.7, 47.4, 44.4, 42.0, 40.5, 39.3, 35.9, 35.1, 34.8, 32.3, 31.8, 31.5, 27.0, 26.9, 26.4, 24.6, 23.4, 23.0, 21.0, 19.2, 17.8, 13.6; IR (film): 3335, 2931, 2868, 1700, 1448, 1194, 1022, 740 cm^{-1}; HRMS-ESI *m/z* 640.3993 ($[M+H]^+$, $C_{41}H_{54}NO_5$ requires 640.3997).



3α-L-valine-5β-pregnane-20-one (23). Prepared according to the method described for compound **5b**. (97%) white foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84-4.72 (m, 1H), 3.26 (d, 1H, *J* = 4.8 Hz), 2.54 (t, 1H, *J* = 8.8 Hz), 2.18-0.85 (m, 25H), 2.11 (s, 3H), 0.99 (d, 3H, *J* = 7.2 Hz), 0.94 (s, 3H), 0.91 (d, 3H, *J* = 7.2 Hz), 0.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.9, 174.9, 74.9, 64.1, 60.0, 56.9, 44.5, 42.0, 40.6, 39.4, 36.0, 35.1, 34.8, 32.4, 32.2, 31.8, 27.1, 26.9, 26.5, 24.6, 23.5, 23.0, 21.0, 19.5, 17.3, 13.6; IR (film): 2929, 2867, 1726, 1703, 1384, 1357, 1174, 988 cm^{-1}; HRMS-ESI *m/z* 418.3310 ($[M+H]^+$, $C_{26}H_{44}NO_3$ requires 418.3316).

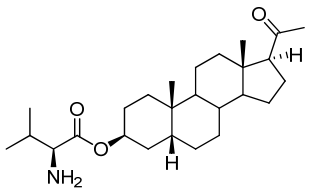


3α-L-Valine-5β-pregnane-20-one HCl salt (P1-133). Prepared according to the method described for compound **P1-31**. (71%) white solid; ^{1}H NMR (600 MHz, DMSO) δ 8.58 (bs, 1H), 4.79 (s, 1H), 3.79 (s, 1H), 2.58 (t, 1H, *J* = 9.0 Hz), 2.42-0.82 (m, 25H), 2.05 (s, 3H), 1.00 (d, 3H, *J* = 7.2 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 0.91 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 168.0, 64.0, 58.7, 56.7, 44.5, 42.1, 40.6, 39.3, 36.0, 35.1, 34.8, 32.2, 31.7, 30.1, 27.0, 26.8, 26.4, 24.6, 23.4 (2C), 23.0, 21.0, 18.6, 18.5, 13.6; IR (solid): 2929, 2866, 2600, 1737, 1702, 1379, 1356, 1194, 979 cm^{-1}; HRMS-ESI *m/z* 418.3311 ([M-Cl]$^{+}$, $C_{26}H_{44}NO_3$ requires 418.3316); Anal. Calcd for $C_{26}H_{44}ClNO_3$: C, 68.77; H, 9.77; N, 3.08. Found C, 68.21; H, 9.91; N, 3.07.

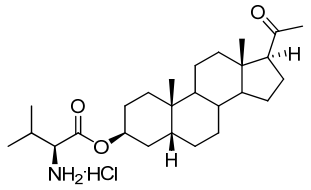


3β-*N*-Fmoc-L-valine-5β-pregnane-20-one (24). Prepared according to the method described for compound **4b**. (73%) white foam; R_f = 0.66 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 7.6 Hz), 7.62 (d, 2H, *J* = 7.2 Hz), 7.41 (t, 2H, *J* = 7.6 Hz), 7.32 (dt, 2H, *J* = 7.6, 1.2 Hz), 5.36 (d, 1H, *J* = 9.2 Hz), 5.19 (s, 1H), 4.50-4.28 (m, 3H), 4.24 (t, 1H, *J* = 7.2 Hz), 2.57-0.84 (m, 24H), 2.12 (s, 3H), 1.00 (d, 3H, *J* = 7.2 Hz), 0.98 (s, 3H), 0.93 (d, 3H, *J* = 6.4 Hz), 0.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 171.7, 156.5, 144.1/144.0, 141.5, 127.9, 127.3, 125.3, 120.2, 72.3, 67.2, 64.0, 59.2, 56.9,

47.4, 44.5, 40.1, 39.4, 37.7, 35.8, 35.1, 31.8, 31.7, 31.0, 30.8, 26.6, 26.3, 25.2, 24.6, 24.1, 23.0, 21.3, 19.2, 17.7, 13.6; IR (solid): 3335, 2930, 2870, 1700, 1448, 1202, 1020, 739 cm^{-1}; HRMS-ESI *m/z* 640.3997 ($[M+H]^+$, $C_{41}H_{54}NO_5$ requires 640.3997).



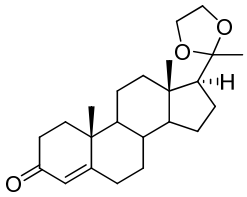
3β-L-Valine-5β-pregnane-20-one (25). Prepared according to the method described for compound **5b**. (93%) white foam; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 3.34 (d, 1H, *J* = 4.8 Hz), 2.54 (t, 1H, *J* = 9.2 Hz), 2.20-0.86 (m, 25H), 2.11 (s, 3H), 1.00 (d, 3H, *J* = 7.2 Hz), 0.97 (s, 3H), 0.91 (d, 3H, *J* = 6.8 Hz), 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 174.8, 71.4, 64.1, 60.1, 56.9, 44.6, 40.1, 39.4, 37.7, 35.8, 35.1, 32.3, 31.8, 31.0, 30.8, 26.6, 26.3, 25.3, 24.6, 24.1, 23.0, 21.3, 19.5, 17.3, 13.6; IR (film): 2929, 2868, 1723, 1703, 1447, 1385, 1357, 1152, 1019 cm^{-1}; HRMS-ESI *m/z* 418.3312 ($[M+H]^+$, $C_{26}H_{44}NO_3$ requires 418.3316).



3β-L-Valine-5β-pregnane-20-one HCl salt (P1-135). Prepared according to the method described for compound **P1-31**. (39%) slightly off-white solid; ^1H NMR (600 MHz, DMSO) δ 8.47 (bs, 1H), 5.13 (s, 1H), 3.86 (s, 1H), 2.56 (t, 1H, *J* = 9.0 Hz), 2.22-2.14 (m, 1H), 2.08-0.84 (m, 23H), 2.05 (s, 3H), 1.01 (d, 3H, *J* = 6.6 Hz), 0.95 (d, 3H, *J* =

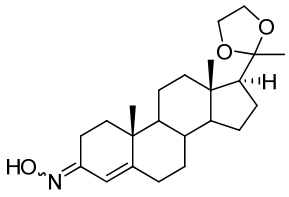
6.4 Hz), 0.94 (s, 3H), 0.51 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.8, 168.1, 74.0, 64.1, 58.8, 57.0, 44.5, 40.1, 39.4, 37.6, 35.8, 35.1, 31.8, 30.9, 30.6, 30.3, 26.5, 26.3, 25.1, 24.6, 24.0, 23.1, 21.3, 18.7, 18.4, 13.7; IR (film): 2928, 2865, 2620, 1734, 1703, 1378, 1354, 1224, 1154, 1019 cm^{-1}; HRMS-ESI *m/z* 418.3312 ($[M-Cl]^+$, $C_{26}H_{44}NO_3$ requires 418.3316); Anal. Calcd for $C_{26}H_{44}ClNO_3$: C, 68.77; H, 9.77; N, 3.08. Found C, 68.08; H, 9.74; N, 3.05.

Progesterone Pro-Drug Series Compounds



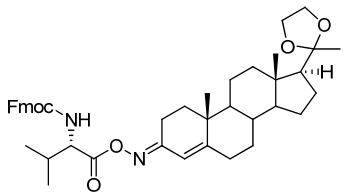
20-Ketal-progesterone (26). Progesterone (3.46 g, 11.0 mmol) and ethylene glycol (110 mL, 1.98 mol, 180 eq) were added to a 250 mL RBF. Activated powdered 4 Å molecular sieves (1.98 g, 10 X theoretical yield H_2O) were added, followed by PTSA (2.09 g, 11.0 mmol, 1.00 eq) and the reaction was stirred at room temperature for 5 d. Ether and saturated sodium bicarbonate were added. The aqueous phase was extracted with ether. The organic layers were combined and washed again with saturated sodium bicarbonate. The organic phase was separated, magnesium sulfate was added to the point of free flowing, and the solution was stirred at room temperature overnight. The solution was filtered and concentrated and the resulting white solid was loaded in a minimum amount of DCM onto a 120 g silica column and eluted with 0-30% EA in hex over 45 min. The desired C-20 ketal was recovered as 3.20 g (81%) white solid. R_f = 0.38 (1:1

EA/hex, PMA stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1 H), 4.03-3.84 (m, 4 H), 2.48-2.22 (m, 4 H), 2.15-1.98 (m, 2 H), 1.88-1.37 (m, 9 H), 1.29 (s, 3 H), 1.24-1.12 (m, 2 H), 1.18 (s, 3 H), 1.09-0.88 (m, 3 H), 0.81 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 171.8, 124.0, 112.0, 65.4, 63.4, 58.3, 55.9, 53.9, 42.0, 39.4, 38.8, 35.9, 35.3, 34.2, 33.1, 32.1, 24.8, 23.9, 23.1, 21.0, 17.6, 13.1; IR (solid): 2937, 2882, 1668, 1621, 1437, 1372, 1228, 1051, 1040, 862, cm^{-1}; HRMS-ESI *m/z* 359.2577 ($[M+H]^+$, $C_{23}H_{35}O_3$ requires 359.2581).



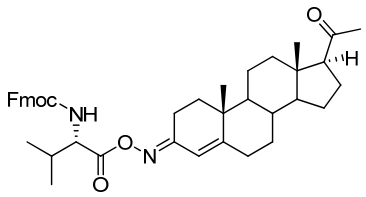
3-Hydroxy-oxime-20-ketal-progesterone (27/28). Hydroxylamine HCl (2.78 g, 40.0 mmol, 4.00 eq) was added to a 100 mL oven dried RBF with 15 mL anhydrous dichloromethane. Triethylamine (6.97 mL, 50.0 mmol, 5.00 eq) was added and the mixture was stirred for 45 minutes. Compound **26** (3.58 g, 10.0 mmol) was dissolved in 20 mL anhydrous DCM and added quickly dropwise to the reaction mixture. The reaction was stirred for 24 h at room temp. The solution was quenched with the addition of DI. The organic layer was washed with water. The aqueous washes were combined and extracted with dichloromethane. The organic layers were combined, dried, filtered, and concentrated with 10 g silica. The silica cake was eluted with a 0-25% EA in hex gradient over 60 minutes on a 120 g silica column. The main products were recovered as 2.23 g (60%) *E* oxime and 1.33 g (36%) *Z* oxime, both as white solids. *E* isomer: R_f = 0.48 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (bs, 1H), 5.77 (s, 1H), 4.03-3.84

(m, 4H), 3.08-3.02 (m, 1H), 2.35-0.77 (m, 19H), 1.30 (s, 3H), 1.06 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 156.0, 117.3, 112.1, 65.4, 63.4, 58.4, 56.1, 53.9, 42.0, 39.6, 38.1, 35.5, 34.8, 32.7, 32.3, 24.8, 24.0, 23.1, 21.3, 18.9, 18.0, 13.1; IR (solid): 3434, 2934, 2885, 1626, 1435, 1219, 1163, 1053 cm^{-1}; HRMS-ESI *m/z* 374.2677 ($[M+H]^+$, $C_{23}H_{36}NO_3$ requires 374.2690). *Z* isomer: R_f = 0.38 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (bs, 1H), 6.47 (d, 1H, *J* = 1.2 Hz), 4.03-3.84 (m, 4H), 2.40-0.78 (m, 20H), 1.30 (s, 3H), 1.10 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 154.2, 112.1, 110.3, 65.4, 63.4, 58.3, 56.0, 54.1, 42.1, 39.5, 39.1, 36.4, 35.4, 33.2, 32.6, 24.9, 24.8, 23.9, 23.1, 21.2, 18.3, 13.2; IR (solid): 3403, 2936, 2870, 1626, 1434, 1218, 1150, 1052 cm^{-1}; HRMS-ESI *m/z* 374.2677 ($[M+H]^+$, $C_{23}H_{36}NO_3$ requires 374.2690).



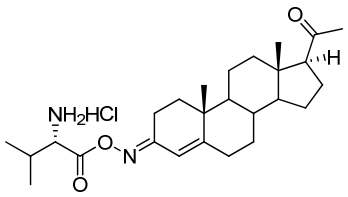
***N*-Fmoc-valine-3-*E*-oxime-20-ketal-progesterone (29).** Prepared according to the method described for compound **4b**. (99%) clear oil that foamed on drying; R_f = 0.54 (1:1 EA/hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 7.8 Hz), 7.61 (dd, 2H, *J* = 7.2, 3.0 Hz), 7.42-7.39 (m, 2H), 7.32 (t, 2H, *J* = 7.6 Hz), 5.98 (s, 1H), 5.46 (d, 1H, *J* = 9.6 Hz), 4.44-4.40 (m, 3H), 4.24 (t, 1H, *J* = 7.2 Hz), 4.02-3.86 (m, 4H), 3.01 (d, 1H, *J* = 16.8), 2.37-0.81 (m, 20H), 1.30 (s, 3H), 1.08 (s, 3H), 1.02 (d, 3H, *J* = 7.2 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 0.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 164.2, 162.4, 156.4, 144.1, 143.9, 127.9, 127.3, 125.3, 120.2, 115.9, 112.0, 67.3, 65.4, 63.4, 58.4, 58.3, 56.0, 53.7, 47.3, 42.0, 39.5, 38.3, 35.3, 34.4, 33.1, 32.1, 31.9, 24.7, 23.9, 23.1, 21.2, 21.0, 19.1,

18.0, 17.8, 13.1; IR (film): 3347, 2937, 2880, 1756, 1718, 1513, 1374, 1339, 1239, 911, 710 cm^{-1}; HRMS-ESI *m/z* 695.4059 ($[M+H]^+$, $C_{43}H_{55}N_2O_6$ requires 695.4055).



***N*-Fmoc-valine-3-*E*-oxime-progesterone (30).** Compound **29** (0.265 g, 0.381 mmol) was dissolved in 15 mL acetone and 0.0164 g (0.0953 mmol, 0.250 eq) PTSA was added. The reaction was stirred at room temperature for 2 h then heated to 40 °C for 1 h. Ethyl acetate was added and the reaction was concentrated to remove acetone. Ethyl acetate was added and washed with water (2 X 10 mL). The aqueous layers were combined and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried, and concentrated. The recovered oil was re-dissolved in DCM and prepared as a silica cake with 0.750 g silica. The cake was eluted on a 12 g silica column with a 0-35% EA in hex gradient over 45 minutes. The main product was recovered as 0.245 g (99%) waxy off-white solid. R_f = 0.52 (1:1 EA/hex, PMA stain); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 7.8 Hz), 7.61 (dd, 2H, *J* = 7.2, 2.4 Hz), 7.42-7.39 (m, 2H), 7.32 (t, 2H, *J* = 7.2 Hz), 6.00 (s, 1H), 5.46 (d, 2H, *J* = 9.6 Hz), 4.40-4.40 (m, 3H), 4.24 (t, 1H, *J* = 7.2 Hz), 3.03 (d, 1H, *J* = 17.4 Hz), 2.53 (t, 1H, *J* = 9.6 Hz), 2.37-0.85 (m, 19H), 2.12 (s, 3H), 1.08 (s, 3H), 1.02 (d, 3H, *J* = 7.2 Hz), 0.99 (d, 3H, *J* = 6.6 Hz), 0.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.6, 170.1, 164.1, 161.8, 156.4, 144.1, 143.9, 141.5, 127.9, 127.3, 125.3, 120.2, 116.2, 67.4, 63.7, 58.4, 56.3, 53.6, 47.4, 44.1, 38.9, 38.3, 35.8, 34.4, 32.9,

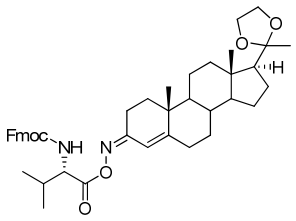
32.1, 31.9, 31.7, 24.6, 23.0, 21.4, 21.0, 19.1, 18.1, 17.8, 13.5; HRMS-ESI *m/z* 651.3799 ($[M+H]^+$, $C_{41}H_{51}N_2O_5$ requires 651.3793).



3-Valine-*E*-oxime-progesterone HCl (P1-185). Oxime compound **30** (0.260 g, 0.400 mmol) was added to an oven dried 50 mL RBF and the flask was evacuated and inert gas flushed. Anhydrous ACN (20 mL) was added and the clear colorless solution was chilled to 0 °C. Freshly distilled piperidine (0.395 mL, 4.00 mmol, 10.0 eq) was added and the solution was stirred and allowed to gradually equilibrate to room temperature over 30 min. The reaction was concentrated with added toluene to give a clear oil. The oil was loaded neat with minimum DCM rinse onto a 12 g silica column and eluted with 0-80% ea in hexane over 40 min. Main product containing fractions were combined and concentrated by rotary evaporation at 10 °C. After being brought to complete dryness and re-dissolved in 10 mL ethyl acetate, the sample was concentrated and dried under high vacuum while being chilled in an ice bath. Anhydrous ether (7-8 mL) was added and the clear colorless solution was allowed to cool to 0 °C. HCl ether solution (0.195 mL, 2.0 M. 1.0 eq) was added dropwise to the rapidly stirring solution. A white precipitate was observed. The mixture was stirred for 15 minutes at 0 °C, then filtered through a 15 mL fine frit glass ground filter and washed with ice chilled anhydrous ether. (67%, two steps) white solid; R_f = 0.25 (1:1 EA/hex, PMA stain); ^{1}H NMR (400 MHz, DMSO) δ 8.71 (bs, 2H), 5.90 (s, 1H), 4.00 (bs, 1H), 3.53 (bs, 1H), 3.03

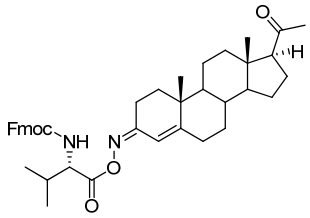
(d, 1H, *J* = 16.8 Hz), 2.56 (t, 1H, *J* = 9.0 Hz), 2.40-0.79 (m, 20H), 2.06 (s, 3H), 1.05 (s, 3H), 1.02 (d, 3H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.8 Hz), 0.56 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.6, 166.5, 164.8, 162.5, 115.9, 63.7, 58.4, 56.3, 53.6, 44.1, 38.9, 38.3, 35.8, 34.5, 33.0, 32.2, 31.8, 30.3, 24.6, 23.0, 21.5, 19.2, 18.4, 17.9, 15.3, 13.5; IR (solid): 2933, 2874, 2648, 1760, 1699, 1627, 1377, 1358, 1185, 847 cm^{-1}; HRMS-ESI *m/z* 429.3109 ([M-Cl]$^+$, $C_{26}H_{41}N_2O_3$ requires 429.3112); Anal. Calcd for $C_{26}H_{41}ClN_2O_3$+½H_2O: C, 65.87; H, 8.93; N, 5.91. Found C, 66.03; H, 8.90; N, 5.83.

The following compounds were prepared according to the methods developed for the *E*-oxime pro-drug series:

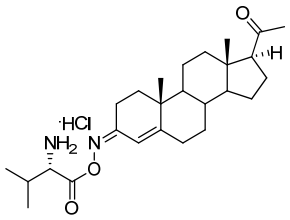


***N*-Fmoc-valine-3-*Z*-oxime-20-ketal-progesterone (31).** (99%) white foam; R_f = 0.50 (1:1 EA/hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 7.8 Hz), 7.62-7.60 (m, 2H), 7.43-7.36 (m, 2H), 7.32 (t, 2H, *J* = 7.2 Hz), 6.33 (s, 1H), 5.45 (d, 1H, *J* = 9.6 Hz), 4.44 (dd, 1H, *J* = 9.0, 4.8 Hz), 4.40 (d, 2H, *J* = 7.2 Hz), 4.24 (t, 1H, *J* = 7.2 Hz), 4.03-3.84 (m, 4H), 2.60-0.74 (m, 21H), 1.30 (s, 3H), 1.12 (s, 3H), 1.04 (d, 3H, *J* = 6.6 Hz), 1.00 (d, 3H, *J* = 7.2 Hz), 0.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 165.7, 161.4, 156.4, 144.1, 144.0, 141.5, 127.9, 127.3, 125.3, 120.2, 112.0, 110.8, 67.3, 65.4, 63.4, 58.4, 58.3, 56.0, 54.0, 47.4, 42.1, 39.5, 39.4, 35.7, 35.3, 34.2, 33.5, 32.6, 31.9, 25.8, 23.9, 23.1, 21.1, 19.3, 18.0, 17.9, 13.1; IR (solid): 3318, 2935, 2876, 1716, 1468, 1371,

1309, 1236, 1042, 862, 739 cm^{-1}; HRMS-ESI *m/z* 695.4054 ($[M+H]^+$, $C_{43}H_{55}N_2O_6$ requires 695.4066).

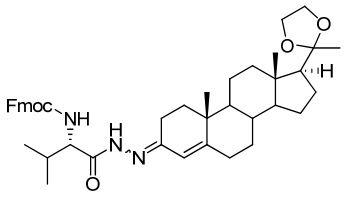


***N*-Fmoc-valine-3-*Z*-oxime-progesterone (32).** (89%) white foam; R_f = 0.40 (1:1 EA/hex); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 7.6 Hz), 7.61 (dd, 2H, *J* = 7.2, 2.4 Hz), 7.40 (t, 2H, *J* = 7.6 Hz), 7.32 (t, 2H, *J* = 7.6 Hz), 6.35 (s, 1H), 5.47 (d, 1H, *J* = 8.8 Hz), 4.44 (dd, 1H, *J* = 9.2, 4.8 Hz), 4.40 (d, 2H, *J* = 6.8 Hz), 4.24 (t, 1H, *J* = 7.2 Hz), 2.62-0.86 (m, 21H), 2.12 (s, 3H), 1.11 (s, 3H), 1.04 (d, 3H, *J* = 6.8 Hz), 1.00 (d, 3H, *J* = 7.2 Hz), 0.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.6, 170.2, 165.1, 161.3, 156.4, 144.1, 143.9, 141.5, 127.9, 127.3, 125.3, 120.2, 110.9, 67.3, 63.7, 58.4, 56.2, 53.8, 47.3, 44.1, 39.3, 38.8, 35.7 (2C), 33.3, 32.5, 31.9, 31.7, 24.7, 24.5, 23.0, 21.2, 19.3, 18.0, 17.9, 13.5; IR (solid): 3327, 2935, 1699, 1449, 1371, 1355, 1235, 1032, 859, 760, 740 cm^{-1}; HRMS-ESI *m/z* 651.3793 ($[M+H]^+$, $C_{41}H_{51}N_2O_5$ requires 651.3793).



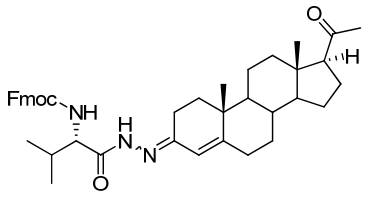
3-Valine-*Z*-oxime-progesterone HCl (P1-186). (61%, two steps) white solid; ^1H NMR (400 MHz, DMSO) δ 8.74 (bs, 3H), 6.50 (s, 1H), 3.98 (s, 1H), 3.37 (s, 1H), 2.56 (t, 1H, *J* = 8.8 Hz), 2.48-0.82 (m, 20H), 2.06 (s, 3H), 1.09 (s, 3H), 1.01 (d, 3H, *J* = 7.2 Hz), 0.98 (d, 3H, *J* = 6.4 Hz), 0.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 167.0,

166.0, 162.0, 111.3, 63.7, 58.2, 56.2, 53.8, 44.1, 39.3, 38.9, 35.7 (2C), 33.3, 32.5, 31.7, 30.3, 24.7, 24.6, 23.0, 21.3, 19.1, 18.5, 18.1, 13.6; IR (solid): 2935, 1756, 1698, 1620, 1379, 1356, 1185, 852 cm^{-1}; HRMS-ESI *m/z* 429.3108 ($[M\text{-}Cl]^+$, $C_{26}H_{41}N_2O_3$ requires 429.3112); Anal. Calcd for $C_{26}H_{41}ClN_2O_3+½H_2O$: C, 65.87; H, 8.93; N, 5.91. Found C, 65.44; H, 8.94; N, 5.82.

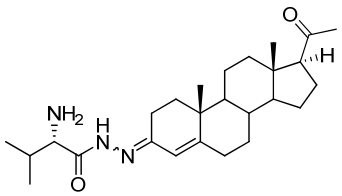


***N*-Fmoc-valine-3-hydrazide-20-ketal-progesterone (33).** Compound **26** (1.79 g, 5.00 mmol) was added to an oven dried 250 mL RBF with 50 mL absolute ethanol. Hydrazine (1.28 mL, 25.0 mmol, 5.00 eq) was added and the reaction was set to reflux overnight. DMF was added and the solution was concentrated (40 °C water bath to 25 mbar). Brine was added and the solution was extracted with EA. The organic layers were combined, washed with brine, dried, filtered, and concentrated. The crude mixture (assumed to be 5.00 mmol), was dissolved in anhydrous DCM and added with *N*-Fmoc-L-valine (1.87 g, 5.50 mmol, 1.10 eq) and DMAP (0.0611 g, 0.500 mmol, 0.100 eq) to a 250 mL RBF under argon. After complete dissolution of the reaction components, DCC (5.50 mL 1 M soln. in DCM, 5.50 mmol, 1.10 eq) was added. After stirring overnight, the mixture was filtered through Celite. The filtrate was concentrated and prepared as a silica cake that was eluted on a 120 g silica column with 0-45% EA in hex over 45 min. Main peak containing fractions were combined and concentrated to give 1.91 g (55%) off-white solid that was a ~2:1 mixture of the two main products. R_f = 0.37/0.32 (1:1

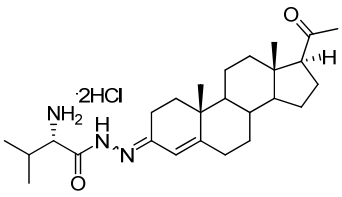
EA/hex); major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (bs, 1H), 7.72-7.16 (m, 8H), 5.80 (s, 1H), 5.65 (d, 1H, *J* = 9.2 Hz), 5.16 (dd, 1H, 9.6,4.4 Hz), 4.35-3.74 (m, 7H), 2.50-0.64 (m, 21H), 1.30 (s, 3H), 1.06-1.00 (m, 6H), 0.92 (d, 3H, *J* = 6.4 Hz), 0.80 (s, 3H); IR (solid): 3273, 2931, 2874, 1662, 1505, 1240, 1050, 739 cm^{-1}; HRMS-ESI *m/z* 716.4032 ([M+Na]$^+$, $C_{43}H_{55}N_3O_5Na$ requires 716.4045).



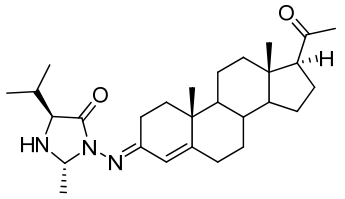
***N*-Fmoc-valine-3-hydrazide-progesterone (34).** Compound **33** (0.732 g, 1.05 mmol) was added to a 15 mL 0.85 M thiourea 1:1 ethanol/water solution. The mixture was heated to reflux overnight. An orange-amber mass of insoluble oily semi-solid had formed. The ethanol was removed and DCM and DI were added. The aqueous layer was extracted with DCM (3 X 50 mL). The organic layers were combined, washed with brine, dried, filtered, and concentrated with silica. The silica cake was eluted through a 40 g silica column with 0-35% ea in hex over 45 minutes. The desired product(s) were isolated as 0.216 g (32%) off-white solid in a 3:2 mixture of *E/Z* hydrazides. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (bs, 1H), 7.80-7.25 (m, 8H), 5.87 (s, 1H), 5.67 (d, 1H, *J* = 10.0 Hz), 5.16 (dd, 1H, *J* = 9.6, 4.4 Hz), 4.41-4.16 (m, 3H), 2.60-0.78 (m, 21H), 2.13 (s, 3H), 1.04 (s, 3H), 1.01 (d, 3H, *J* = 6.8 Hz), 0.92 (d, 3H, *J* = 6.8 Hz), 0.65 (s, 3H); IR (solid): 3270, 2931, 1698, 1666, 1505, 1234, 1030, 739 cm^{-1}; HRMS-ESI *m/z* 650.3944 ([M+H]$^+$, $C_{41}H_{52}N_3O_4$ requires 650.3952).



3-Valine-hydrazide-progesterone (35). Compound mixture **34** (0.130 g, 0.200 mmol) was dried in a 25 mL RBF and placed under argon. DMF (5 mL) was added which completely dissolved the substrate. The solution was chilled in an ice bath and piperidine (0.206 mL, 2.00 mmol, 10.0 eq) was added. The ice bath was removed after 15 minutes and the reaction stirred an additional 15 minutes. Ether was added along with brine. The aqueous layer was extracted with ether (4 X 20 mL). The organic layers were combined, washed with brine, dried, filtered, and concentrated. The sample was loaded in a minimum amount of DCM onto a 12 g silica column and eluted with 0-5 % MeOH in DCM over 35 min (initial 5 min 100% DCM). Main peak containing fractions were combined and concentrated to give 0.079 g (92%) clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (bs, 1H), 6.06 (s, 1H), 5.30 (s, 1H), 3.42 (d, 1H, J = 3.6 Hz), 2.60-0.78 (m, 22H), 2.11 (s, 3H), 1.06 (s, 3H), 1.01 (d, 3H, J = 6.8 Hz), 0.86 (d, 3H, J = 6.8 Hz), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 170.0, 156.9, 154.5, 121.5, 63.8, 60.1, 56.3, 53.6, 44.1, 38.9, 37.9, 35.9, 34.9, 32.5, 32.2, 31.7, 30.8, 24.6, 23.0, 21.6, 20.8, 19.8, 17.9, 16.1, 13.5; IR (solid): 3236, 2933, 2874, 1666, 1385, 1358, 1206, 910, 728 cm^{-1}; HRMS-ESI *m/z* 428.3268 ($[M+H]^+$, $C_{26}H_{42}N_3O_2$ requires 428.3272).



3-Valine-hydrazide-progesterone (P2-29). Prepared according to the method described for compound **P1-31**. (43%) off-white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 6.59 (s, 1H), 6.16 (s, 1H), 4.62-4.59 (m, 1H), 3.96 (bs, 2H), 3.02-0.86 (m, 23H), 2.12 (s, 3H) 1.24 (d, 3H, *J* = 7.2 Hz), 1.18 (d, 3H, *J* = 6.8 Hz), 1.11 (s, 3H), 0.67 (s, 3H); HRMS-ESI *m/z* 428.3268 ($[M+H-2HCl]^+$, $C_{26}H_{42}N_3O_2$ requires 428.3272); Anal. Calcd for $C_{26}H_{43}Cl_2N_3O_2$+½H_2O: C, 61.29; H, 8.70; N, 8.25. Found C, 61.57; H, 8.85; N, 8.14.



(2R,5S)-3-((E)-((10R,13S,17S)-17-acetyl-10,13-dimethyl-7,8,9,11-tetrahydro-1H-cyclopenta[a]phenanthren-3(2H,6H,10H,12H,13H,14H,15H,16H,17H)-ylidene)amino)-5-isopropyl-2-methylimidazolidin-4-one (36). Compound mixture **35** (0.140 g, 0.215 mmol) was dried in a 25 mL RBF and placed under argon. Acetonitrile was added (5 mL) along with DMF (2 mL) to completely dissolve the substrate. The solution was chilled in an ice bath and piperidine (0.213 mL, 2.15 mmol, 10.0 eq) was added. The ice bath was removed after 15 minutes and the reaction stirred an additional 15 minutes. Ethyl acetate was added along with half saturated ammonium chloride solution. The aqueous layer was extracted with EA and the organic layers were combined, washed with brine, dried, filtered, and concentrated. Dichloromethane was added and twice concentrated with the sample. The resulting pale amber oil was loaded in a minimum amount of DCM onto a 12 g silica column run in 0-100% ea in hex over 40 minutes. The two main products were isolated separately as white crystalline solids (87%

combined yield). First eluting product: R_f = 0.32 (95:5 DCM/MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.99 (s, 1H), 4.81 (q, 1H, *J* =5.4 Hz), 3.48 (d, 1H, *J* = 3.6 Hz), 2.54-2.48 (m, 1H), 2.40-0.80 (m, 21H), 2.11 (s, 3H), 1.32 (d, 3H, *J* =5.4 Hz), 1.12 (s, 3H), 1.03 (d, 3H, *J* = 6.6 Hz), 0.94 (d, 3H, *J* = 7.2 Hz), 0.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.6, 170.5, 170.2, 160.8, 120.7. 73.3, 63.8, 63.7, 56.4, 53.8, 44.1, 39.0, 38.5, 35.8 (2C), 32.7, 32.2, 31.8, 31.7, 25.0, 24.6, 23.0, 21.7, 21.3, 19.7, 17.7, 17.4, 13.5; HRMS-ESI *m/z* 454.3430 ($[M+H]^+$, $C_{28}H_{44}N_3O_2$ requires 454.3428).

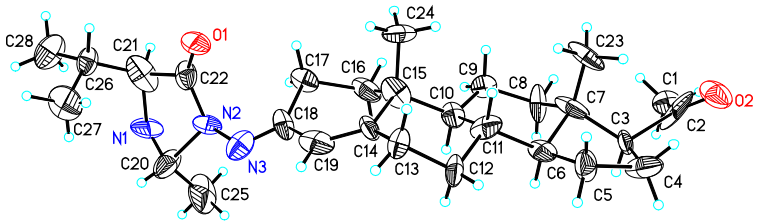


Table 3. Crystal data and structure refinement for compound **36**.

Identification code	p2264s	
Empirical formula	C28 H42 N3 O2	
Formula weight	452.65	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 65.281(5) Å	α= 90°.
	b = 5.9668(6) Å	β= 96.847(6)°.
	c = 10.6916(8) Å	γ = 90°.
Volume	4134.8(6) Å^3	
Z	4	
Density (calculated)	0.727 Mg/m^3	
Absorption coefficient	0.355 mm^{-1}	
F(000)	988	
Crystal size	0.42 x 0.07 x 0.03 mm^3	
Theta range for data collection	2.73 to 66.48°.	

Index ranges	-76<=h<=73, -6<=k<=6, -12<=l<=12
Reflections collected	12330
Independent reflections	5937 [R(int) = 0.0866]
Completeness to theta = 66.48°	96.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9894 and 0.8651
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5937 / 1 / 306
Goodness-of-fit on F^2	1.061
Final R indices [I>2sigma(I)]	R1 = 0.1571, wR2 = 0.3866
R indices (all data)	R1 = 0.2305, wR2 = 0.4236
Absolute structure parameter	0.6(14)
Extinction coefficient	0.0037(6)
Largest diff. peak and hole	0.470 and -0.465 e.$Å^{-3}$

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **36**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7848(2)	9880(16)	229(10)	77(3)
C(2)	7735(2)	7790(50)	566(12)	172(10)
C(3)	7708(2)	7628(19)	2101(7)	74(3)
C(4)	7531(2)	5830(30)	2338(10)	110(5)
C(5)	7615(1)	4960(20)	3706(8)	86(4)
C(6)	7793(2)	6514(17)	4199(8)	70(3)
C(7)	7914(2)	7010(20)	2988(9)	102(5)
C(8)	8056(2)	8767(15)	3384(8)	75(3)
C(9)	8202(1)	8149(17)	4510(8)	59(2)
C(10)	8120(2)	7366(16)	5624(8)	68(3)
C(11)	7947(1)	5526(18)	5307(9)	74(3)
C(12)	7834(1)	5150(20)	6470(7)	78(3)
C(13)	7987(1)	3970(20)	7503(9)	89(4)

C(14)	8161(1)	5750(20)	7770(8)	72(3)
C(15)	8274(2)	6423(19)	6765(9)	79(3)
C(16)	8411(2)	8180(20)	7177(8)	88(4)
C(17)	8554(1)	7870(18)	8496(7)	65(3)
C(18)	8398(2)	7393(15)	9437(8)	66(3)
C(19)	8219(2)	6168(19)	8992(11)	91(4)
C(20)	8602(2)	10730(20)	12206(13)	114(5)
C(21)	8947(2)	9100(20)	12024(11)	116(6)
C(22)	8806(2)	8060(20)	11094(9)	74(3)
C(23)	8004(2)	4861(16)	2499(9)	90(4)
C(24)	8415(2)	4540(30)	6332(12)	116(5)
C(25)	8496(3)	12760(30)	11592(12)	154(7)
C(26)	9042(1)	7889(18)	13190(8)	68(3)
C(27)	8878(2)	7200(50)	14037(12)	225(13)
C(28)	9221(2)	9170(20)	13950(12)	115(5)
N(1)	8823(2)	11492(19)	12320(9)	116(4)
N(2)	8616(1)	9159(14)	11010(7)	72(2)
N(3)	8416(1)	7846(18)	10547(9)	90(3)
O(1)	8830(1)	6236(15)	10687(7)	95(3)
O(2)	7666(2)	6024(15)	-98(7)	111(4)

Table 5. Bond lengths [Å] and angles [°] for compound **36**.

C(1)-C(2)	1.51(2)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-O(2)	1.32(3)
C(2)-C(3)	1.674(15)
C(3)-C(7)	1.592(14)
C(3)-C(4)	1.619(16)
C(3)-H(3)	1.0000
C(4)-C(5)	1.585(13)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900

C(5)-C(6)	1.533(13)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(11)	1.573(11)
C(6)-C(7)	1.622(13)
C(6)-H(6)	1.0000
C(7)-C(8)	1.429(16)
C(7)-C(23)	1.531(13)
C(8)-C(9)	1.491(11)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.441(11)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.583(13)
C(10)-C(15)	1.588(14)
C(10)-H(10)	1.0000
C(11)-C(12)	1.535(12)
C(11)-H(11)	1.0000
C(12)-C(13)	1.563(12)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.560(14)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-C(19)	1.340(13)
C(14)-C(15)	1.430(12)
C(15)-C(16)	1.416(14)
C(15)-C(24)	1.557(15)
C(16)-C(17)	1.607(13)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-C(18)	1.543(12)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-N(3)	1.209(11)

C(18)-C(19)	1.411(14)
C(19)-H(19)	0.9500
C(20)-N(1)	1.502(16)
C(20)-C(25)	1.509(18)
C(20)-N(2)	1.597(14)
C(20)-H(20)	1.0000
C(21)-C(22)	1.416(14)
C(21)-C(26)	1.509(15)
C(21)-N(1)	1.690(17)
C(21)-H(21)	1.0000
C(22)-O(1)	1.189(13)
C(22)-N(2)	1.396(13)
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-C(27)	1.539(14)
C(26)-C(28)	1.545(12)
C(26)-H(26)	1.0000
C(27)-H(27A)	0.9800
C(27)-H(27B)	0.9800
C(27)-H(27C)	0.9800
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
N(2)-N(3)	1.552(11)

C(2)-C(1)-H(1A)	109.5
C(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(2)-C(1)-H(1C)	109.5

H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(2)-C(2)-C(1)	132.4(12)
O(2)-C(2)-C(3)	114.3(14)
C(1)-C(2)-C(3)	113.2(17)
C(7)-C(3)-C(4)	108.6(9)
C(7)-C(3)-C(2)	114.7(7)
C(4)-C(3)-C(2)	110.6(10)
C(7)-C(3)-H(3)	107.5
C(4)-C(3)-H(3)	107.5
C(2)-C(3)-H(3)	107.5
C(5)-C(4)-C(3)	100.9(9)
C(5)-C(4)-H(4A)	111.6
C(3)-C(4)-H(4A)	111.6
C(5)-C(4)-H(4B)	111.6
C(3)-C(4)-H(4B)	111.6
H(4A)-C(4)-H(4B)	109.4
C(6)-C(5)-C(4)	106.4(9)
C(6)-C(5)-H(5A)	110.4
C(4)-C(5)-H(5A)	110.4
C(6)-C(5)-H(5B)	110.4
C(4)-C(5)-H(5B)	110.4
H(5A)-C(5)-H(5B)	108.6
C(5)-C(6)-C(11)	115.0(8)
C(5)-C(6)-C(7)	104.9(9)
C(11)-C(6)-C(7)	110.0(7)
C(5)-C(6)-H(6)	108.9
C(11)-C(6)-H(6)	108.9
C(7)-C(6)-H(6)	108.9
C(8)-C(7)-C(23)	116.9(11)
C(8)-C(7)-C(3)	118.6(9)
C(23)-C(7)-C(3)	108.9(10)
C(8)-C(7)-C(6)	104.9(9)
C(23)-C(7)-C(6)	111.3(8)
C(3)-C(7)-C(6)	93.5(8)
C(7)-C(8)-C(9)	112.8(8)

C(7)-C(8)-H(8A)	109.0
C(9)-C(8)-H(8A)	109.0
C(7)-C(8)-H(8B)	109.0
C(9)-C(8)-H(8B)	109.0
H(8A)-C(8)-H(8B)	107.8
C(10)-C(9)-C(8)	118.8(8)
C(10)-C(9)-H(9A)	107.6
C(8)-C(9)-H(9A)	107.6
C(10)-C(9)-H(9B)	107.6
C(8)-C(9)-H(9B)	107.6
H(9A)-C(9)-H(9B)	107.0
C(9)-C(10)-C(11)	112.0(8)
C(9)-C(10)-C(15)	119.0(8)
C(11)-C(10)-C(15)	106.8(7)
C(9)-C(10)-H(10)	106.1
C(11)-C(10)-H(10)	106.1
C(15)-C(10)-H(10)	106.1
C(12)-C(11)-C(6)	109.9(7)
C(12)-C(11)-C(10)	109.1(9)
C(6)-C(11)-C(10)	106.1(7)
C(12)-C(11)-H(11)	110.6
C(6)-C(11)-H(11)	110.6
C(10)-C(11)-H(11)	110.6
C(11)-C(12)-C(13)	108.2(8)
C(11)-C(12)-H(12A)	110.1
C(13)-C(12)-H(12A)	110.1
C(11)-C(12)-H(12B)	110.1
C(13)-C(12)-H(12B)	110.1
H(12A)-C(12)-H(12B)	108.4
C(14)-C(13)-C(12)	102.3(9)
C(14)-C(13)-H(13A)	111.3
C(12)-C(13)-H(13A)	111.3
C(14)-C(13)-H(13B)	111.3
C(12)-C(13)-H(13B)	111.3
H(13A)-C(13)-H(13B)	109.2
C(19)-C(14)-C(15)	124.8(10)

C(19)-C(14)-C(13)	114.8(9)
C(15)-C(14)-C(13)	119.0(8)
C(16)-C(15)-C(14)	109.7(9)
C(16)-C(15)-C(24)	104.5(9)
C(14)-C(15)-C(24)	113.4(10)
C(16)-C(15)-C(10)	107.2(9)
C(14)-C(15)-C(10)	110.0(8)
C(24)-C(15)-C(10)	111.8(8)
C(15)-C(16)-C(17)	117.9(9)
C(15)-C(16)-H(16A)	107.8
C(17)-C(16)-H(16A)	107.8
C(15)-C(16)-H(16B)	107.8
C(17)-C(16)-H(16B)	107.8
H(16A)-C(16)-H(16B)	107.2
C(18)-C(17)-C(16)	103.5(8)
C(18)-C(17)-H(17A)	111.1
C(16)-C(17)-H(17A)	111.1
C(18)-C(17)-H(17B)	111.1
C(16)-C(17)-H(17B)	111.1
H(17A)-C(17)-H(17B)	109.0
N(3)-C(18)-C(19)	115.3(11)
N(3)-C(18)-C(17)	127.1(11)
C(19)-C(18)-C(17)	117.4(8)
C(14)-C(19)-C(18)	123.4(10)
C(14)-C(19)-H(19)	118.3
C(18)-C(19)-H(19)	118.3
N(1)-C(20)-C(25)	100.3(13)
N(1)-C(20)-N(2)	95.5(9)
C(25)-C(20)-N(2)	101.1(9)
N(1)-C(20)-H(20)	118.6
C(25)-C(20)-H(20)	118.6
N(2)-C(20)-H(20)	118.6
C(22)-C(21)-C(26)	122.5(11)
C(22)-C(21)-N(1)	102.4(11)
C(26)-C(21)-N(1)	114.2(8)
C(22)-C(21)-H(21)	105.4

C(26)-C(21)-H(21)	105.4
N(1)-C(21)-H(21)	105.4
O(1)-C(22)-N(2)	123.8(11)
O(1)-C(22)-C(21)	124.0(12)
N(2)-C(22)-C(21)	109.7(11)
C(7)-C(23)-H(23A)	109.5
C(7)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(7)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(15)-C(24)-H(24A)	109.5
C(15)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(15)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(20)-C(25)-H(25A)	109.5
C(20)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(20)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(21)-C(26)-C(27)	111.7(9)
C(21)-C(26)-C(28)	114.1(9)
C(27)-C(26)-C(28)	111.1(11)
C(21)-C(26)-H(26)	106.5
C(27)-C(26)-H(26)	106.5
C(28)-C(26)-H(26)	106.5
C(26)-C(27)-H(27A)	109.5
C(26)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
C(26)-C(27)-H(27C)	109.5
H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(26)-C(28)-H(28A)	109.5

C(26)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
C(26)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
C(20)-N(1)-C(21)	102.0(9)
C(22)-N(2)-N(3)	119.4(8)
C(22)-N(2)-C(20)	111.2(8)
N(3)-N(2)-C(20)	115.1(8)
C(18)-N(3)-N(2)	114.0(10)

Symmetry transformations used to generate equivalent atoms:

Table 6. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **36**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	89(7)	41(6)	102(8)	3(6)	15(6)	8(6)
C(2)	41(6)	390(30)	85(9)	154(15)	-7(6)	27(12)
C(3)	95(7)	82(8)	37(4)	-31(5)	-25(5)	40(7)
C(4)	89(7)	146(13)	103(9)	54(9)	46(7)	63(9)
C(5)	72(6)	125(11)	59(6)	-15(7)	-3(5)	-35(7)
C(6)	101(7)	44(6)	68(6)	9(5)	23(5)	39(6)
C(7)	172(12)	90(10)	57(6)	21(6)	66(7)	68(10)
C(8)	129(9)	33(5)	51(5)	12(4)	-38(6)	-49(6)
C(9)	55(5)	48(6)	74(6)	5(5)	14(4)	-9(5)
C(10)	101(7)	39(6)	60(5)	-4(5)	-3(5)	21(6)
C(11)	70(6)	60(7)	94(7)	46(6)	21(5)	25(6)
C(12)	89(7)	92(8)	46(5)	5(6)	-27(5)	5(7)
C(13)	69(6)	121(10)	69(6)	-10(7)	-22(5)	3(7)
C(14)	66(5)	112(10)	37(4)	-29(6)	6(4)	-5(7)
C(15)	87(7)	76(8)	80(7)	-10(6)	36(6)	-61(7)
C(16)	134(9)	78(8)	61(6)	8(6)	45(6)	27(8)
C(17)	83(6)	54(6)	65(5)	15(5)	40(5)	-13(6)
C(18)	126(9)	26(5)	43(5)	-8(4)	-4(6)	-5(6)

C(19)	137(10)	49(7)	99(8)	40(7)	58(8)	49(8)
C(20)	105(9)	95(10)	126(10)	-50(9)	-52(8)	49(9)
C(21)	116(9)	146(14)	90(8)	-35(9)	34(7)	-97(10)
C(22)	110(8)	53(7)	55(6)	12(5)	-4(6)	6(7)
C(23)	174(11)	35(6)	76(6)	-17(5)	74(7)	-9(7)
C(24)	83(7)	158(13)	115(9)	-7(9)	37(7)	63(9)
C(25)	239(17)	108(12)	101(9)	-63(9)	-40(11)	28(14)
C(26)	78(6)	53(6)	65(6)	-4(5)	-21(5)	-9(6)
C(27)	122(10)	460(40)	112(9)	109(17)	90(9)	54(17)
C(28)	84(7)	106(11)	146(11)	7(9)	-28(7)	-25(8)
N(1)	136(9)	100(8)	116(7)	-29(7)	37(7)	66(8)
N(2)	80(5)	57(6)	85(5)	-18(5)	29(5)	14(5)
N(3)	69(5)	87(7)	107(7)	3(6)	-15(5)	-2(5)
O(1)	103(5)	91(6)	91(5)	-40(5)	12(4)	28(5)
O(2)	165(9)	95(7)	74(5)	0(5)	19(6)	66(7)

Table 7. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **36**.

	x	y	z	U(eq)
H(1A)	7994	9757	555	115
H(1B)	7788	11192	601	115
H(1C)	7834	10045	-690	115
H(3)	7661	9130	2370	89
H(4A)	7394	6545	2320	132
H(4B)	7523	4598	1711	132
H(5A)	7504	5022	4263	103
H(5B)	7663	3394	3671	103
H(6)	7735	7953	4484	84
H(8A)	7977	10116	3582	90
H(8B)	8135	9151	2682	90
H(9A)	8295	6969	4249	70
H(9B)	8289	9478	4750	70

H(10)	8050	8685	5963	81
H(11)	8009	4094	5044	89
H(12A)	7711	4197	6247	94
H(12B)	7788	6601	6789	94
H(13A)	7920	3656	8269	106
H(13B)	8040	2553	7187	106
H(16A)	8329	9562	7233	106
H(16B)	8503	8436	6516	106
H(17A)	8651	6599	8458	78
H(17B)	8634	9247	8729	78
H(19)	8135	5610	9591	110
H(20)	8548	10074	12963	137
H(21)	9066	9583	11578	139
H(23A)	8126	5231	2081	136
H(23B)	7901	4127	1897	136
H(23C)	8045	3848	3207	136
H(24A)	8544	5209	6116	174
H(24B)	8344	3783	5592	174
H(24C)	8447	3460	7016	174
H(25A)	8566	13232	10877	231
H(25B)	8500	13988	12207	231
H(25C)	8352	12396	11295	231
H(26)	9102	6468	12894	81
H(27A)	8786	6074	13601	338
H(27B)	8797	8515	14225	338
H(27C)	8946	6561	14824	338
H(28A)	9353	8579	13737	173
H(28B)	9214	8965	14853	173
H(28C)	9211	10765	13741	173

Table 8. Torsion angles [°] for compound **36**.

O(2)-C(2)-C(3)-C(7)	102.1(12)
C(1)-C(2)-C(3)-C(7)	-74.0(16)
O(2)-C(2)-C(3)-C(4)	-21.2(15)

C(1)-C(2)-C(3)-C(4)	162.7(9)
C(7)-C(3)-C(4)-C(5)	22.9(10)
C(2)-C(3)-C(4)-C(5)	149.6(11)
C(3)-C(4)-C(5)-C(6)	9.8(10)
C(4)-C(5)-C(6)-C(11)	-159.7(8)
C(4)-C(5)-C(6)-C(7)	-38.6(10)
C(4)-C(3)-C(7)-C(8)	-152.3(9)
C(2)-C(3)-C(7)-C(8)	83.4(15)
C(4)-C(3)-C(7)-C(23)	70.8(9)
C(2)-C(3)-C(7)-C(23)	-53.5(16)
C(4)-C(3)-C(7)-C(6)	-43.2(10)
C(2)-C(3)-C(7)-C(6)	-167.5(13)
C(5)-C(6)-C(7)-C(8)	169.7(9)
C(11)-C(6)-C(7)-C(8)	-66.0(10)
C(5)-C(6)-C(7)-C(23)	-62.9(12)
C(11)-C(6)-C(7)-C(23)	61.3(13)
C(5)-C(6)-C(7)-C(3)	48.9(10)
C(11)-C(6)-C(7)-C(3)	173.2(9)
C(23)-C(7)-C(8)-C(9)	-65.3(12)
C(3)-C(7)-C(8)-C(9)	161.2(8)
C(6)-C(7)-C(8)-C(9)	58.6(11)
C(7)-C(8)-C(9)-C(10)	-54.2(13)
C(8)-C(9)-C(10)-C(11)	47.0(11)
C(8)-C(9)-C(10)-C(15)	172.5(9)
C(5)-C(6)-C(11)-C(12)	-64.1(11)
C(7)-C(6)-C(11)-C(12)	177.7(9)
C(5)-C(6)-C(11)-C(10)	178.1(8)
C(7)-C(6)-C(11)-C(10)	59.9(11)
C(9)-C(10)-C(11)-C(12)	-167.7(8)
C(15)-C(10)-C(11)-C(12)	60.3(9)
C(9)-C(10)-C(11)-C(6)	-49.4(10)
C(15)-C(10)-C(11)-C(6)	178.6(7)
C(6)-C(11)-C(12)-C(13)	175.0(9)
C(10)-C(11)-C(12)-C(13)	-69.1(10)
C(11)-C(12)-C(13)-C(14)	62.4(10)
C(12)-C(13)-C(14)-C(19)	132.4(10)

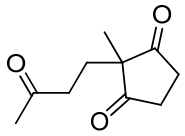
C(12)-C(13)-C(14)-C(15)	-60.5(12)
C(19)-C(14)-C(15)-C(16)	-19.6(17)
C(13)-C(14)-C(15)-C(16)	174.8(9)
C(19)-C(14)-C(15)-C(24)	96.8(13)
C(13)-C(14)-C(15)-C(24)	-68.9(12)
C(19)-C(14)-C(15)-C(10)	-137.3(11)
C(13)-C(14)-C(15)-C(10)	57.1(13)
C(9)-C(10)-C(15)-C(16)	60.5(12)
C(11)-C(10)-C(15)-C(16)	-171.6(8)
C(9)-C(10)-C(15)-C(14)	179.8(9)
C(11)-C(10)-C(15)-C(14)	-52.3(11)
C(9)-C(10)-C(15)-C(24)	-53.4(12)
C(11)-C(10)-C(15)-C(24)	74.5(10)
C(14)-C(15)-C(16)-C(17)	48.3(13)
C(24)-C(15)-C(16)-C(17)	-73.5(11)
C(10)-C(15)-C(16)-C(17)	167.7(8)
C(15)-C(16)-C(17)-C(18)	-55.5(11)
C(16)-C(17)-C(18)-N(3)	-150.3(11)
C(16)-C(17)-C(18)-C(19)	34.1(11)
C(15)-C(14)-C(19)-C(18)	1.8(18)
C(13)-C(14)-C(19)-C(18)	168.0(9)
N(3)-C(18)-C(19)-C(14)	171.8(11)
C(17)-C(18)-C(19)-C(14)	-12.1(15)
C(26)-C(21)-C(22)-O(1)	-44.8(18)
N(1)-C(21)-C(22)-O(1)	-174.5(11)
C(26)-C(21)-C(22)-N(2)	117.8(12)
N(1)-C(21)-C(22)-N(2)	-11.8(11)
C(22)-C(21)-C(26)-C(27)	-64.1(18)
N(1)-C(21)-C(26)-C(27)	60.3(15)
C(22)-C(21)-C(26)-C(28)	168.8(11)
N(1)-C(21)-C(26)-C(28)	-66.7(12)
C(25)-C(20)-N(1)-C(21)	-142.8(9)
N(2)-C(20)-N(1)-C(21)	-40.5(10)
C(22)-C(21)-N(1)-C(20)	36.1(11)
C(26)-C(21)-N(1)-C(20)	-98.5(11)
O(1)-C(22)-N(2)-N(3)	9.5(14)

C(21)-C(22)-N(2)-N(3)	-153.1(9)
O(1)-C(22)-N(2)-C(20)	147.3(11)
C(21)-C(22)-N(2)-C(20)	-15.4(12)
N(1)-C(20)-N(2)-C(22)	37.8(12)
C(25)-C(20)-N(2)-C(22)	139.3(11)
N(1)-C(20)-N(2)-N(3)	177.4(9)
C(25)-C(20)-N(2)-N(3)	-81.0(13)
C(19)-C(18)-N(3)-N(2)	179.0(8)
C(17)-C(18)-N(3)-N(2)	3.4(15)
C(22)-N(2)-N(3)-C(18)	-71.0(12)
C(20)-N(2)-N(3)-C(18)	152.8(10)

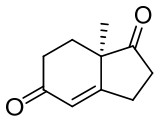
Symmetry transformations used to generate equivalent atoms:

Enantiomeric Progesterone Synthesis

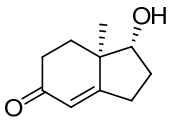
The following compounds were prepared according to previously published methods.[128,129]



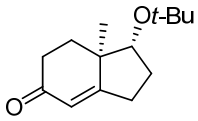
2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (38). (95%) amber oil; R_f = 0.62 (95:5 DCM/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87-2.69 (m, 4 H), 2.43 (t, 2 H, *J* = 7.2), 2.08 (s, 3 H), 1.86 (t, 2 H, *J* = 7.2), 1.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0 (2 C), 208.1, 55.3, 37.6, 34.9 (2 C), 30.2, 27.9, 19.2; IR (film): 2930, 1712, 1366, 1169; HRMS-ESI *m/z* 183.1014 ($[M+H]^+$, $C_{10}H_{15}O_3$ requires 183.1016).



(*R*)-7a-Methyl-2,3,7,7a-tetrahydro-6*H*-indene-1,5-dione (39). (80%) pale tan solid; R_f = 0.47 (95:5 DCM/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (d, 1H, *J* = 2.4), 3.00-2.90 (m, 1H), 2.82-2.70 (m, 2H), 2.56-2.37 (m, 3H), 2.09 (ddd, 1H, *J* = 13.6, 2.4, 2.0), 1.83 (dt, 1H, *J* = 13.6, 5.2), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 198.4, 170.0, 124.0, 48.9, 36.0, 33.0, 29.3, 27.0, 20.7; IR (solid): 2970, 2876, 1742, 1699, 1660, 1447, 1146 cm^{-1}; HRMS-ESI *m/z* 165.0911 ([M+H]$^+$, $C_{10}H_{13}O_2$ requires 165.0910).

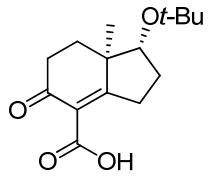


(1*R*,7a*R*)-1-Hydroxy-7a-methyl-1,2,3,6,7,7a-hexahydro-inden-5-one (40). (94%) amber semisolid; R_f = 0.17 (95:5 DCM/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (s, 1H), 3.84 (t, 1H, *J* = 8.8 Hz), 2.75-2.64 (m, 1H), 2.57-2.33 (m, 4H), 2.17-2.07 (m, 2H), 1.88-1.72 (m, 2H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 175.6, 123.5, 80.7, 45.4, 34.2, 33.5, 29.2, 26.6, 15.3; IR (film): 3335 (br), 2935, 1632, 1326, 1221, 1075 cm $^{-1}$; HRMS-ESI *m/z* 167.1068 ([M+H]$^+$, $C_{10}H_{15}O_2$ requires 167.1067).

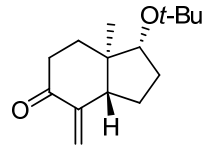


(1*R*,7a*R*)-1-*tert*-Butoxy-7a-methyl-1,2,3,6,7,7a-hexahydro-inden-5-one (41). (84%) pale yellow solid; R_f = 0.48 (95:5 DCM/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (s, 1 H), 3.56 (dd, 1 H, *J* = 9.6, 7.6 Hz), 2.72-2.63 (m, 1 H), 2.55-2.47 (m, 1 H),

2.46-2.31 (m, 2 H), 2.05-1.93 (m, 2 H), 1.84-1.67 (m, 2 H), 1.17 (s, 9 H), 1.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 175.8, 123.1, 79.8, 73.2, 45.0, 34.5, 33.6, 29.7, 28.8 (3C), 27.0, 15.9; IR (solid): 2972, 1669, 1361, 1198, 1089 cm^{-1}; HRMS-ESI *m/z* 223.1691 ($[M+H]^+$, $C_{14}H_{23}O_2$ requires 223.1693).

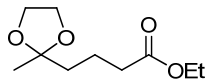


(-)-(1*R*,7a*R*)-5,6,7,7a-Tetrahydro-1-*tert*-butoxy-7a-methyl-5-oxo-4-indancarboxylic acid (43). (71%) brown-yellow solid; R_f = 0.21 (DCM/EA); $[\alpha]^{23}_D$ -31.1 (*c* = 1.00, $CHCl_3$) [lit. -37 (*c* = 1.02 $CHCl_3$)][129]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (dd, 1H, *J* = 10.2, 7.2 Hz), 3.33-3.15 (m, 2H), 2.84-2.61 (m, 2H), 2.12-2.03 (m, 2H), 1.93-1.77 (m, 2H), 1.19 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 196.5, 164.5, 120.5, 78.9, 73.7, 48.5, 33.7, 32.1, 31.6, 30.1, 28.8 (3C), 16.5; IR (solid): 2967, 2750, 1732, 1625, 1599, 1437, 1190, 1099 cm^{-1}; HRMS-ESI *m/z* 267.1588 ($[M+H]^+$, $C_{15}H_{23}O_4$ requires 267.1591).

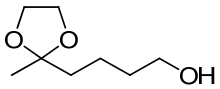


(-)-(1*R*,3a*S*,7a*R*)-1-*tert*-Butoxy-7a-methyl-3a,6,7,7a,-tetrahydro-4-methyleneindan-5(4*H*)-one (45). (79%) brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (q, 1H, *J* = 2.8, 1.6 Hz), 5.01 (q, 1H, *J* = 2.4, 1.6 Hz), 3.64-3.57 (m, 1H), 2.59-1.48 (m, 9H), 1.16 (s, 9H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 147.5, 118.3, 80.2,

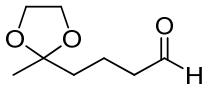
72.8, 49.1, 43.3, 36.2, 34.1, 31.9, 28.9 (3C), 22.9, 11.4; IR (film): 2970, 2874, 1694, 1361, 1191, 1090 cm^{-1}; HRMS-ESI *m/z* 237.1847 ($[M+H]^+$, $C_{15}H_{25}O_2$ requires 237.1849).



5-[(1,3-Dioxolan-2-yl)ethyl]hexanoate (47). (93%) pale amber oil; R_f = 0.40 (2:1 hex/EA, PMA stain); ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, 2H, *J* = 7.2 Hz), 3.96-3.91 (m, 4H), 2.32 (t, 2H, *J* = 7.2 Hz), 1.78-1.64 (m, 4H), 1.32 (s, 3H), 1.25 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 109.9, 64.8 (2C), 60.4, 38.5, 34.5, 24.0, 19.8, 14.4; IR (neat): 2981, 2880, 1731, 1375, 1176, 1050, 855 cm^{-1}; HRMS-ESI *m/z* 203.11277 ($[M+H]^+$, $C_{10}H_{19}O_4$ requires 203.1278).

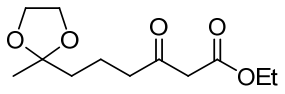


5-(1,3-Dioxolan-2-yl)hexanol (48). (99%) clear oil**;** R_f = 0.14 (1:1 hex/EA, PMA stain); ^1H NMR (600 MHz, $CDCl_3$) δ 3.97-3.91 (m, 4H), 3.65 (t, 2H, *J* = 6.6 Hz), 1.69-1.66 (m, 2H), 1.61-1.56 (m, 3H), 1.50-1.45 (m, 2H), 1.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 110.2, 64.8 (2C), 63.0, 39.0, 33.0, 24.0, 20.4; IR (neat): 3417 (br), 2942, 2873, 1376, 1220, 1139, 1037 cm^{-1} ; HRMS-ESI *m/z* 160.13330 ($[M-OH+NH_3]^+$, $C_8H_{18}NO_2$ requires 160.1332).

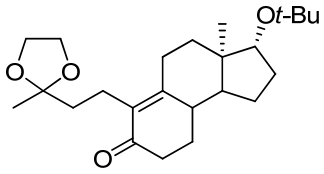


5-(1,3-Dioxolan-2-yl)hexanal (49). (81%) amber oil**;** R_f = 0.37 (1:1 hex/EA, PMA stain); ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, 1H, *J* = 1.6 Hz), 3.97-3.88 (m, 4H), 2.46

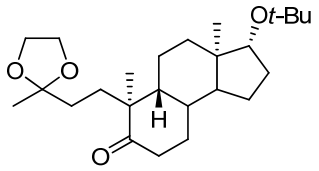
(dt, 2H, J = 7.2, 1.6 Hz), 1.79-1.64 (m, 4H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 109.8, 64.8 (2C), 44.0, 38.4, 24.0, 16.8; IR (film): 2982, 2881, 1721, 1376, 1211, 1068, 852 cm^{-1} ; HRMS-ESI *m/z* 159.1014 ([M+H]$^+$, $C_8H_{15}O_3$ requires 159.1016).



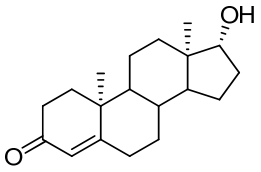
Ethyl 7-(1,3-Dioxolan-2-yl)-3-oxooctanoate (50). (78%) pale green-amber oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.19 (q, 2H, J = 7.2 Hz), 3.95-3.91 (m, 4H), 3.43 (s, 2H), 2.58 (t, 2H, J = 7.2 Hz), 1.74-1.63 (m, 4H), 1.31 (s, 3H), 1.28 (t, 3H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.8, 167.5, 110.0, 64.8 (2C), 61.5, 49.5, 43.0, 38.2, 23.9, 18.2, 14.3 cm^{-1}.



(-)-3*β*-*tert*-Butoxy-3a*β*-methyl-1,2,3,3a,4,5,8,9,9a*β*,9b*α*-dodecahydro-6-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]-7*H*-benz[*e*]inden-7-one (51). (72%) brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98-3.91 (m, 4H), 3.40 (t, 1H, J = 8.4 Hz), 2.84-2.75 (m, 1H), 2.50-1.04 (m, 17H), 1.14 (s, 9H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 160.2, 134.1, 110.0, 80.4, 72.7, 64.8 (2C), 51.0, 42.2, 39.1, 38.2, 37.2, 36.8, 31.3, 28.9 (3C), 26.9, 26.8, 24.1, 23.7, 20.3, 11.1; IR (film): 2970, 2872, 1663, 1361, 1194, 1095, 1058 cm^{-1}; HRMS-ESI *m/z* 391.2837 ([M+H]$^+$, $C_{24}H_{39}O_4$ requires 391.2843).

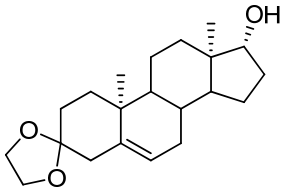


(-)-3*β*-*tert*-Butoxy-3a*β*,5a*β*-dimethyl-1,2,3,3a,4,5,5a,6,8,9,9a*β*,9b*α*-dodecahydro-6-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]-7*H*-benz[*e*]inden-7-one (52). (53%) brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98-3.91 (m, 4H), 3.37 (t, 1H, *J* = 8.4 Hz), 2.61-2.40 (m, 1H), 2.28-2.19 (m, 1H), 1.96-0.90 (m, 17H), 1.36 (s, 3H), 1.13 (s, 9H), 1.10 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1, 110.5, 80.8, 72.5, 64.7, 64.7, 50.8, 50.6, 47.8, 42.7, 38.3, 36.9, 35.0, 33.2, 31.2, 31.0, 29.2, 28.9 (3C), 24.0, 23.6, 21.4, 21.1, 11.8; IR (film): 2967, 2937, 1703, 1360, 1195, 1067, 1040, 948 cm^{-1}; HRMS-ESI *m/z* 407.3154 ($[M+H]^+$, $C_{25}H_{43}O_4$ requires 407.3156).

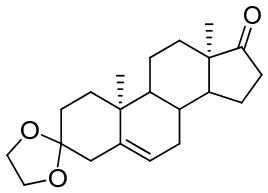


***ent*-Testosterone (53).** (71%) white solid; R_f = 0.22 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 3.68-3.62 (m, 1H), 2.48-2.23 (m, 4H), 2.13-1.98 (m, 2H), 1.89-1.23 (m, 10H), 1.19 (s, 3H), 1.13-0.88 (m, 4H), 0.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.8, 171.5, 124.1, 81.8, 54.1, 50.7, 43.0, 38.9, 36.6, 35.9, 35.8, 34.1, 33.0, 31.7, 30.6, 23.5, 20.8, 17.6, 11.2; IR (solid): 3391, 2930, 2880, 1645, 1612, 1229, 1056 cm^{-1}; HRMS-ESI *m/z* 289.2158 ($[M+H]^+$, $C_{19}H_{29}O_2$ requires 289.2162).

The following compounds were prepared based on previously published methods.[135]

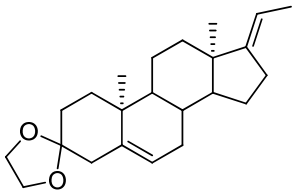


***ent*-(17β)-17-Hydroxyandrost-5-en-3-one cyclic 3-(1,2-ethanediyl acetal) (54).** (71%) white solid; R_f = 0.42 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34-5.30 (m, 1H), 3.96-3.89 (m, 4H), 3.62 (t, 1H, *J* = 8.4 Hz), 2.55 (dq, 1H, *J* = 14.2, 3.0 Hz), 2.12-1.90 (m, 3H), 1.83-0.88 (m, 16H), 1.01 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 122.1, 109.6, 82.0, 64.6, 64.4, 51.5, 50.0, 42.9, 42.0, 36.9, 36.8, 36.5, 32.1, 31.5, 31.2, 30.7, 23.7, 20.8, 19.1, 11.2; IR (solid): 3213, 2933, 2886, 1093, 1058 cm^{-1}; HRMS-ESI *m/z* 333.2426 ($[M+H]^+$, $C_{21}H_{33}O_3$ requires 333.2424).

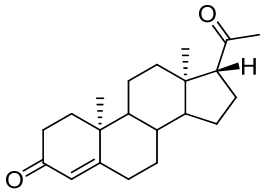


***ent*-Androst-5-ene-3,17-dione cyclic 3-(1,2-ethanediyl acetal) (55).** (95%) white solid; R_f = 0.52 (1:1 EA/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41-5.36 (m, 1H), 3.99-3.92 (m, 4H), 2.59 (dq, 1H, *J* = 14.0, 2.8 Hz), 2.46 (dd, 1H, *J* = 19.2, 8.0 Hz), 2.17-2.03 (m, 3H), 1.99-1.90 (m, 1H), 1.88-1.08 (m, 13H), 1.06 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.4, 140.6, 121.6, 109.5, 64.7, 64.5, 51.9, 50.0, 47.8, 42.0, 36.9, 36.4, 36.0, 31.7, 31.6, 31.2, 30.8, 22.1, 20.5, 19.1, 13.8; IR (solid): 2946, 2933, 2883,

1735, 1373, 1092, 992 cm^{-1}; HRMS-ESI *m/z* 331.2283 ($[M+H]^+$, $C_{21}H_{31}O_3$ requires 331.2268).



***ent*-[(17*Z*)-Pregna-5,17(20)-dien-3-one cyclic (1,2-ethanediyl acetal)] (56).** (76%) white solid; R_f = 0.73 (1:1 EA/hex, KMnO4 stain); ^1H NMR (400 MHz, $CDCl_3$) δ 5.38-5.36 (m, 1H), 5.17-5.10 (m, 1H), 4.00-3.92 (m, 4H), 2.61-2.54 (m, 1H), 2.42-1.07 (m, 21H), 1.05 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 140.4, 122.3, 113.7, 109.7, 64.7, 64.4, 56.6, 49.9, 44.3, 42.0, 37.2, 36.9, 36.5, 31.8 31.6 (2C), 31.3, 24.7, 21.4, 19.1, 16.8, 13.4; IR (solid): 2930, 2881, 1421, 1370, 1255, 1089, 955 cm^{-1}; HRMS-ESI *m/z* 343.2625 ($[M+H]^+$, $C_{23}H_{35}O_2$ requires 343.2632).

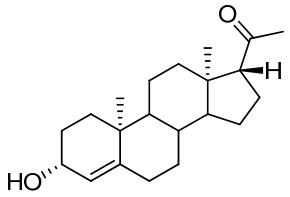


***ent*-Progesterone (57).** (78%) white solid; R_f = 0.41 (1:1 EA/hex); $[\alpha]^{23}_D$ -200.2 (*c* = 1.00, $CHCl_3$) [lit. -200 (*c* = 0.25, $CHCl_3$)][135]; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 1H), 2.51 (t, 1H, *J* = 9.0 Hz), 2.46-0.91 (m, 19H), 2.10 (s, 3H), 1.16 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 199.7, 171.2, 124.1, 63.7, 56.2, 53.8, 44.1, 38.8 (2C), 35.9, 35.7, 34.1, 33.0, 32.1, 31.7, 24.6, 23.0, 21.2, 17.6, 13.5; IR (solid): 2943, 2925,

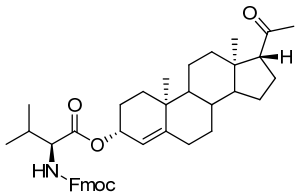
2850, 1697, 1660, 1615, 1437, 1356, 1194, 1162, 948, 871 cm^{-1}; HRMS-ESI *m/z* 315.2319 ($[M+H]^+$, $C_{21}H_{31}O_2$ requires 315.2319).

Enantiomeric Progesterone Derivatives

The following compounds were prepared according to the procedures described above for the synthesis of **P1-31** and related series analogues.

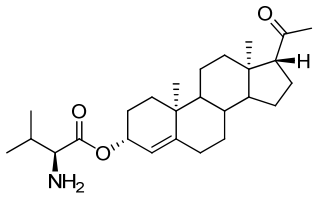


3α-Hydroxy-*ent*-progesterone (58). (47%) white solid; R_f = 0.31 (99:5 DCM/MeOH, PMA stain); ^1H NMR (400 MHz, $CDCl_3$) δ 5.29 (d, 1H, *J* = 1.6 Hz), 4.18-4.13 (m, 1H), 2.45-0.74 (m, 21H), 2.11 (s, 3H), 1.04 (s, 3H), 0.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 147.3, 123.8, 68.1, 63.9, 56.5, 54.5, 44.3, 39.1, 37.5, 36.1, 35.6, 33.1, 32.3, 31.7, 29.6, 24.6, 22.9, 21.2, 19.1, 13.5; IR (solid): 3400, 2932, 2848, 1701, 1662, 1355, 917, 730 cm^{-1}; HRMS-ESI *m/z* 299.2370 ($[M+H-H_2O]^+$, $C_{21}H_{31}O$ requires 299.2369).

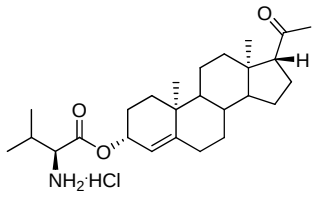


***N*-Fmoc-L-valine-3α-*ent*-progesterone (59).** (83%) white foam; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 7.6 Hz), 7.61 (d, 2H, *J* = 7.6 Hz), 7.41 (t, 2H, *J* = 7.6

Hz), 7.33 (t, 2H, *J* = 7.6 Hz), 5.34 (d, 1H, *J* = 9.2 Hz), 5.31 (s, 1H), 5.24 (s, 1H), 4.40 (d, 2H, *J* = 7.2 Hz), 4.31 (dd, 1H, *J* = 9.2, 4.8 Hz), 4.25 (t, 1H, *J* = 6.8 Hz), 2.53 (t, 1H, *J* = 8.8 Hz), 2.30-0.70 (m, 20H), 2.12 (s, 3H), 1.07 (s, 3H), 0.99 (d, 3H, *J* = 6.8 Hz), 0.93 (d, 3H, *J* = 7.2 Hz), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 172.1, 156.5, 149.8, 144.2, 144.0, 141.5, 127.9, 127.3, 125.3, 120.2, 119.0, 72.1, 67.2, 63.7, 59.2, 56.5, 54.2, 47.4, 44.3, 39.0, 37.5, 36.0, 35.1, 33.0, 32.3, 31.6, 25.3, 24.6, 23.0, 19.2, 19.0, 17.7, 13.6; IR (solid): 3360, 2935, 1702, 1388, 1351, 1205, 734 cm^{-1}.



3*α*-L-Valine-*ent*-progesterone (60). (87%) clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32-5.28 (m, 2H), 5.23 (d, 1H, *J* = 0.8 Hz), 3.28 (d, 1H, *J* = 5.2 Hz), 2.53 (t, 1H, *J* = 9.2 Hz), 2.30-0.75 (m, 21H), 2.12 (s, 3H), 1.07 (s, 3H), 0.98 (d, 3H, *J* = 7.2 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 175.7, 149.5, 119.3, 71.3, 63.9, 60.2, 56.5, 54.2, 44.3, 39.0, 37.5, 36.0, 35.1, 33.0, 32.3 (2C), 31.8, 25.3, 24.6, 23.0, 21.2, 19.6, 19.0, 17.3, 13.6; IR (solid): 2933, 2850, 1724, 1705, 1385, 1357, 1178, 977 cm^{-1}; HRMS-ESI *m/z* 416.3158 ($[M+H]^+$, $C_{26}H_{42}NO_3$ requires 416.3159).



3α-L-Valine-ent-progesterone-HCl (P2-13). (58%) off-white solid; ^{1}H NMR (400 MHz, DMSO) δ 8.53 (bs, 3H), 5.28 (t, 1H, *J* = 8.0 Hz), 5.22 (s, 1H), 3.82 (d, 1H, *J* = 4.8 Hz), 3.34 (s, 1H), 2.56 (t, 1H, *J* = 9.2 Hz), 2.25-0.74 (m, 21H), 2.05 (s, 3H), 1.02 (s, 3H), 0.99 (d, 3H, *J* = 6.8 Hz), 0.94 (d, 3H, *J* = 6.8 Hz), 0.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 168.5, 150.0, 118.7, 73.8, 63.9, 59.2, 56.5, 54.2, 44.2, 39.1, 37.5, 36.0, 35.2, 33.1, 32.3, 31.8, 30.3, 25.4, 24.6, 23.0, 21.2, 19.2, 18.9 (2C), 13.6; IR (solid): 2932, 2849, 2600, 1737, 1702, 1379, 1354, 1219, 1110 cm^{-1}; HRMS-ESI *m/z* 416.3160 ($[M+H]^+$, $C_{26}H_{42}NO_3$ requires 416.3159); Anal. Calcd for $C_{26}H_{41}ClNO_3$+½H_2O: C, 67.73; H, 9.40; N, 3.04. Found C, 67.39; H, 9.24; N, 3.01.

Cerebral Edema Assay Methods

The following procedures were carried out by Iqbal Sayeed and Fahim Atif at the Department of Emergency Medicine Brain Research Laboratory, Emory University School of Medicine:

Surgery

Contusions to the Medio-frontal cortex (MFC) were created with a pneumatic impactor device. Animals were anesthetized using isoflurane (5% induction, 2% maintenance, 700mm N_2O, 300mm O_2), and mounted in a stereotaxic device with the head in a horizontal position and body core temperature was maintained with a homeothermic heating blanket system. Using a SurgiVet™ (model V3304) pulse oximeter, blood SpO_2 was monitored and maintained at levels ≥90%. Under aseptic conditions, a midline incision was made in the scalp and the fascia retracted to expose the cranium. A centered,

bilateral craniotomy was made 3mm anterior to bregma using a 6mm diameter trephan. After the removal of the bone, the tip of the impactor was moved to AP:3.0; ML:0.0, checked for adequate clearance, retracted to its elevated position, and lowered 3.5mm DV. The contusion was then made at a velocity of 2.25m/s with a brain contact time of 0.5 seconds. Following this procedure, the wound cavity was thoroughly cleaned and all bleeding stopped before the fascia and scalp are sutured closed.

Progestin preparation and administration

All experimental treatments by injection (progesterone and analogues) were made in stock solutions using 2-hydroxypropyl-β-cyclodextrin (HBC; 22.5 % w/v solution in H_2O) as the solvent. The HBC vehicle allows progesterone and analogues to be dissolved in a non-toxic, aqueous solution which can be administered safely by a variety of routes. The initial dose of progesterone or analogue given at 1 h post-injury was delivered intraperitoneally (IP) for rapid absorption. All subsequent injections at 6 h post-injury were given subcutaneously.

Edema measure

At 24h post-injury, animals was given an IP overdose of pentobarbital (75mg/kg). The peri-contusional tissue samples from each area were assayed for water content as follows: samples were placed into pre-weighed containers, capped, and then immediately weighed to the nearest 0.0001g. The containers were then uncapped and placed in a vacuum oven and dried at 60 ºC, 0.3atm for 24 h. The containers were then recapped and reweighed to obtain the dry and wet-weight percentages.

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