Université de Montréal

Enantioselective Synthesis of Piperidinones and Piperidines

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Abbreviation

$[\alpha]_D$	Specific rotation
Ac	Acetyl
Boc	*tert*-Butoxycarbonyl
δ	Chemical shift in ppm
c	Concentration in milligrams per milliliter
calcd.	Calculated
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
Et	Ethyl
EtOAc	Ethyl acetate
equiv.	Equivalents
h	Hours (s)
HRMS	High resolution mass spectrum
Hz	Hertz
IR	Infrared spectroscopy
LiHMDS	Lithium bis(trimethylsilyl)amide
μL	Microliter
Me	Methyl
MeOH	Methanol
mg	Milligram
min	Minute
MHz	Megahertz
mL	Milliliter
mmol	Millimole
MS	Mass spectrum
ppm	Parts per million
SAR	Structure activity relationship

TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TEA	Triethyl amine
TFA	Trifluoroacetic acid
THF	Tetrahydofuran
TLC	Thin layer chromatography

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Abstract

The goal of this study was to synthesize novel piperidine and piperidinones with aminomethyl and hydroxymethyl appendages, to be used as probes, scaffolds or mimics. We have demonstrated the efficiency and practicality of nitroalkane conjugate Michael addition to α,β-unsaturated lactams while studying the effects of different nitroalkane substitutents on the stereoselectivity. The noteworthy features of this approach are its operational simplicity, the efficiency of the nitroalkane conjugate addition, and the facile preparation of 2- and 4-substituted 6-oxo-piperidinones.

Résumé

Nous avons exploré et exploité un nouveau type d'addition de Michael des nitroalcanes pour la synthèse des pipéridines et pipéridinones diversifiés, substitués par des amines et des alcools. Nous avons démontré l'efficacité et la facilité de l'addition conjuguée des nitroalcanes aux amides cycliques α,β-insaturés, et étudié la stéréosélectivité de l'addition. A l'aide de cette réaction, nous avons généré une série de pipéridinones diversifiées, des acides α-aminés, des nitrocyclopropanes et une nouvelle classe de pipéridines substituées par des amines et des alcools. Finalement, nous avons développé une méthode simple et efficace pour l'addition conjuguée des nitroalcanes afin d'obtenir des alkylamines substituées.

Chapter 1

1-Peptidomimetics and Structurally Constrained Analogues

1.1 Naturally occuring piperidine derivatives

Polyhydroxylated piperidines can be considered as naturally occurring sugars with a nitrogen in the ring (Figure 1).[1] Nojirimycin **(1)** was the first naturally occurring *D*-glucopyranose with nitrogen in the ring. This class of compounds are trivially referred to as "azasugars". They are inhibitors of glycohydrolases, which are key enzymes in the synthesis and processing of glycoproteins. The inhibition of glycohydrolases of potential therapeutic value for the treatment of viral infections[2], cancer[3], diabetes[4] and obesity[5]. Thus the synthesis of such "azasugars" have become the object of intense synthetic efforts in the last decade.[6]

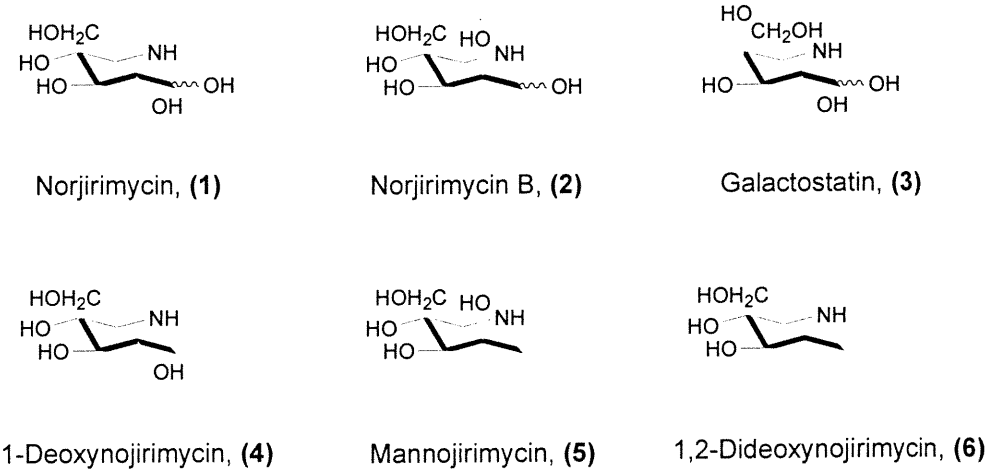
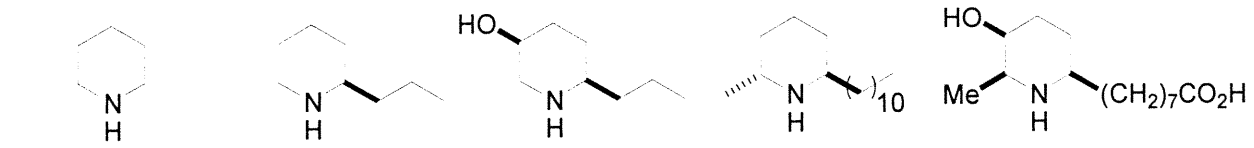


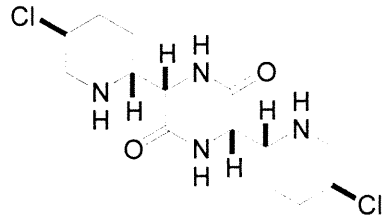
Figure 1. Polyhydroxylated piperidine alkaloids

Piperidine alkaloids exhibit an extensive range of pharmacological properties and biological activities.[7] There is a wide occurrence of optically active 2-substituted piperidines in a large number of natural products of biological importance.[8] For example, the natural products Coniine **(8)**, Pseudoconhydrin **(9)**, Solenospin A **(10)**, Carpamic acid **(11)**, DKP593A **(12)**, Histrionicotoxin **(13)** and Coniceine **(14)** (Figure 2), all contain a

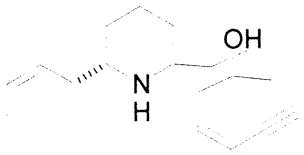
piperidine nucleus. Along with the immunomodulators FK-506, **(15)** and Rapamycin, **(16)** being the focus of many studies, the importance of the piperidine ring system and its valuable pharmacological properties have inspired numerous, versatile and stereocontrolled routes to substituted piperidines.[9]



Piperidine, **(7)** Coniine, **(8)** Pseudoconhydrine, **(9)** Solenopsin A, **(10)** Carpamic Acid, **(11)**

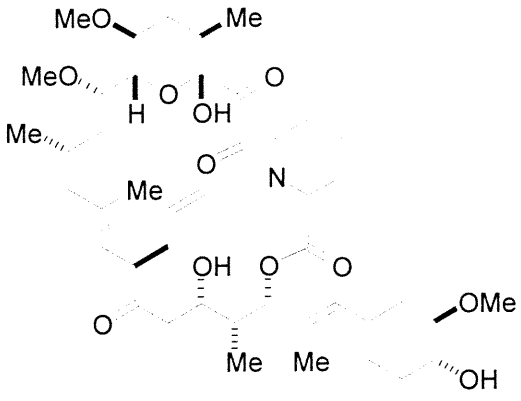


DKP593A, **(12)**

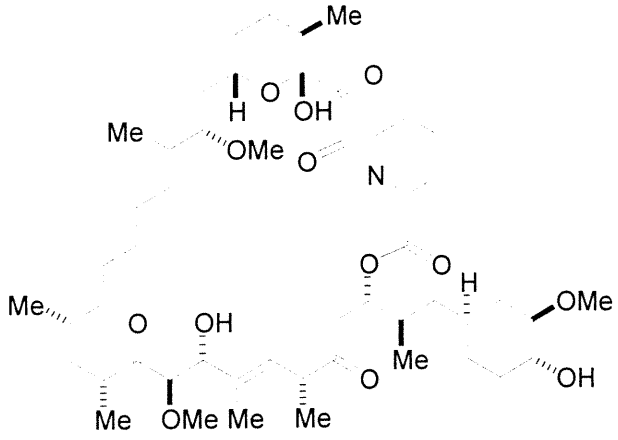


Histrionicotoxin, **(13)**

Coniceine, **(14)**



FK-506, **(15)**

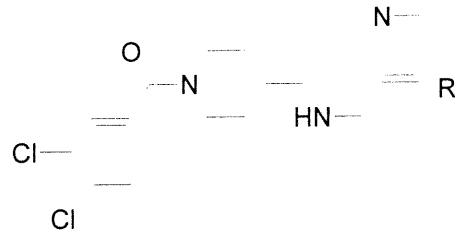


Rapamycin, **(16)**

Figure 2. Piperidine derivatives in natural products

1.2 Piperidine derivatives in medicinal chemistry

It has been known that disubstituted piperidines (Figure 3) are highly potent ligands for various receptors and that they are frequently found as a key structural element in compounds possessing broad therapeutic effects.[10] All current tricyclic antidepressants have a common mechanism of action, which consists of raising synaptic levels of neurotransmitters, norepinephrine (NE) and 5-hydroxytryptamine (5-HT), believed to be involved in depressive pathophysiology.[11] Many studies have focused on the role of central serotoninergic (5-HT) systems, in particular of the 5-HT_{1A} receptors, where they have been implicated in many psychiatric and neurological disorders. However, the antidepressant effects of 5-HT_{1A} partial agonists do not exceed those of currently available treatments, neither in terms of clinical efficacy nor in terms of rapidity of onset. Thus, a novel 5-HT_{1A} pharmacophore along with a series of 1,4-disubstituted piperidine derivatives that bind with high affinity and selectivity to 5-HT_{1A} receptors have been reported. Piperidine compounds of the general formula **17** (Figure 3) have shown nanomolar affinity for 5-HT_{1A} binding sites.[12] With the 5-HT receptor being widely distributed in a variety of animal species, selective antagonism of this receptor could exert beneficial effects in a number of pathophysiological disorders; Thus, a general method for the rapid multiple synthesis of similar 1,4-disubstituted piperidines would be of great value for drug discovery or lead optimization.[13]



1,4-Disubstituted Piperidine, **17**

Figure 3. 1,4-Disubstituted piperidine ligands as 5-HT_{1A} pharmacophores

The excitatory amino acid neurotransmitters glutamate and aspartate are recognized as important mediators of neuronal function in the central nervous system (CNS).[14]

Experiments have distinguished three distinct receptor subtypes, which are classified by the agonists which selectively activate them. They are *N*-methyl-D-aspartic acid (NMDA) **18**, quisqualic acid (QUIS) **19**, and kainic acid (KA) **20**.[15] NMDA receptors have played a significant role in events leading to cell death both in cerebral ischemia and a variety of neuronal disorders, including Alzheimer's disease and Huntington's chorea.[16] A strategic prevention for such biological misfortunes, could be the intervention of excitatory amino acid overstimulation and subsequent prevention of neuronal degeneration by NMDA receptor antagonists.[14] Following the discovery of *D* and *L*-α-aminoadipic acid as a selective antagonist, structurally constrained related derivatives were proposed and subsequently prepared to study their structure activity relationships.[17]

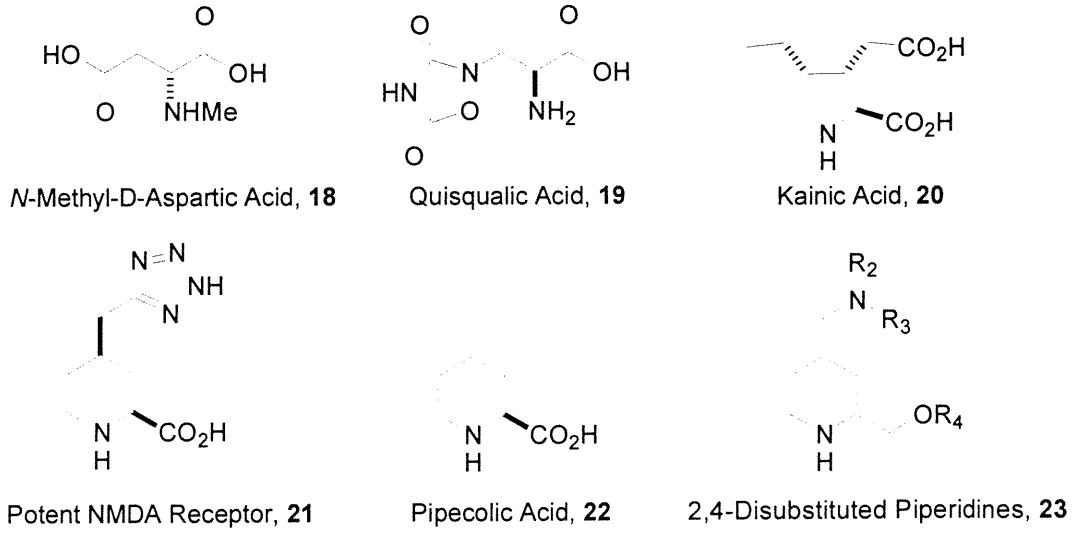


Figure 4. Selective NMDA receptor antagonists with pipecolic acid and 2,4-disubstituted piperidine framework

On that note, preparation of a series of *cis*-4-(tetrazolylalkyl)piperidine-2-carboxylic acids **21** as functional analogs of pipecolic acid **22**, with similarities to 2,4-disubstituted piperidine skeleton **23**, have yielded potent and selective NMDA receptor antagonists[14] (Figure 1). (*S*)-Pipecolic acid **22**, the next higher homolog of proline, is a nonproteinogenic amino acid widely distributed in plants. This amino acid is a precursor to numerous bioactive compounds such as synthetic peptides[18], synthetic drugs[19], potential enzyme inhibitors[20] or the antifungal antibiotics.[21] The chair-like conformation of the six membered

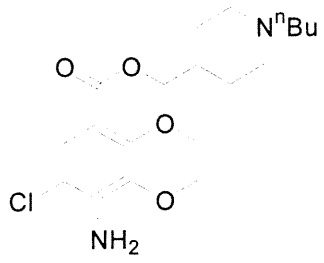
pipecolic acid and piperidine derivatives, have potential utility in the area of constrained amino acids[22] and peptidomimetics. The incorporation of this cyclic amino acid with well-defined stereochemical and structural properties, is a useful tool to study peptide conformation and protein folding.[23] It is known that by holding the side-chain and the backbone of the piperidine ring derivatives in a limited number of conformations, active analogs of biologically active peptides containing this amino acid, or derivatives with a similar skeleton, could provide valuable insight into ligand binding.[24] Pipecolic acid analogs often find a role in β-turn mimics and they can be used to replace certain natural amino acids in the original peptide to direct peptide chains into favourable orientations. For example, replacement of proline for its higher homologue pipecolic acid, has been reported to bring a significant change in bioactivity of proline-containing peptides and leads to interesting model compounds for studies on peptide conformation.[23]

1.3 Design of nonpeptide ligands

Bioactive peptides influence a multitude of physiological processes by signal transduction transported through receptors as neurotransmitters, neuromodulators, and hormones. Because of their ready metabolism and poor bioavailability, peptides are often unsuitable as therapeutic agents and viable drug candidates. Hence, peptide bonds and peptide fragments have been replaced with a wide variety of structural moieties in attempts to convert peptides into chemically stable and orally available molecules. To address this problem, peptidomimetics, compounds that act as substitutes for peptides in their interaction with receptors or enzymes have been routinely explored, because of their higher metabolic stability, better bioavailibility, and longer duration of action.[24] The following requirements have been proposed for increased specificity and improved pharmacokinetics of a peptidomimetic: a) metabolic stability, b) good bioavailability, c) tight binding d) high receptor affinity and e) high receptor selectivity. One major problem in the advent of such valuable biological agents is the discovery of lead structures. One successful approach in the development of peptidomimetics involves formation of conformationally restricted analogues that imitate the receptor-bound conformation of the endogenous ligands as closely as possible.[25] Such analogues may possess increased metabolic stability and

receptor selectivity, along with fewer side effects.[26] Thus, conformationally restricted analogues of peptides that show these required characteristics for recognition by receptors, remain a valuable tool in the hands of medicinal chemists for the design of nonpeptide ligands and possible drugs.

A major objective in the development of low molecular weight, nonpeptidic peptidomimetics is the close reproduction of the bioactive topology. Small polyfunctional, conformationally constrained, mono- or polycyclic molecular scaffolds which can be substituted by the essential pharmacophores are ideal for this transformation.[27] The discovery of such structures in high throughput screening, as in collections of substances (compound libraries) or single compounds have become an important strategy in discovering lead compounds.[24] For example, the design of 1,4-disubstituted piperidine scaffolds could yield a potentially fruitful strategy in obtaining a lead structures of non-peptidic ligand in screening of compound libraries prepared through parallel synthesis or an alternative solid phase approach. One example of such an approach, is the discovery of SB 204070 **24** (Figure 5), a potent and selective 5-HT_4 receptor antagonist.[28] This promising drug candidate was identified from a library of compounds generated through a 4-hydroxymethyl piperidine.



SB 204070 **24**

Figure 5. Discovery of a 5-HT_4 receptor antagonist via high throughput screening

With an appropriate and successful design and subsequent modification of similar lead structures, the likelihood that similar peptide mimetics could become drug candidates is very encouraging.[27]

1.4 2,4-Disubstituted piperidines and 6-oxo-piperidines as potential scaffolds or mimics

Due to their often potent biological activities,[17] we propose a novel class of 2,4-disubstituted piperidines and 6-oxo-piperidines as constrained analogs of naturally occurring (*S*)-pipecolic acid, to be used as potential scaffolds or mimics for various receptors (Figure 6). Structures **25** and **26** could also be valuable building blocks for the preparation of pharmaceuticals. To this end, a general method for the rapid synthesis of compounds **25** and **26** along with the derivatization of the 2,4-disubstituted 6-oxo-piperidine ligands is presented.

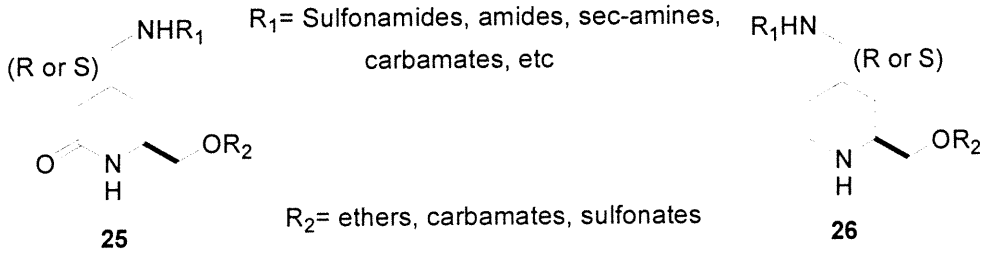


Figure 6. 2-Piperidine and 6-oxo-piperidine scaffolds for possible derivatization through parallel synthesis

In the course of this study, we sought to synthesize 2,4-disubstituted piperidine and 6-oxo-piperidine scaffolds via a nitro Michael addition as outlined in the retrosynthetic analysis shown in Figure 7. The α,β-unsaturated lactam precursor **28** was prepared by two distinct approaches; one involving a key cyclization step from the readily available (*S*)-lysine **29** and the other through a kinetic resolution of compound **30**. The stereochemical outcome of the reactions with various nitroalkanes were studied in detail and a detailed synthetic strategy to the formation of a sulfonamide/carbamate library is presented. Furthermore, the synthesis of novel γ-substituted α-amino acids and formation of 3,4-methano-6-oxo-pipecolic acids will also be presented.

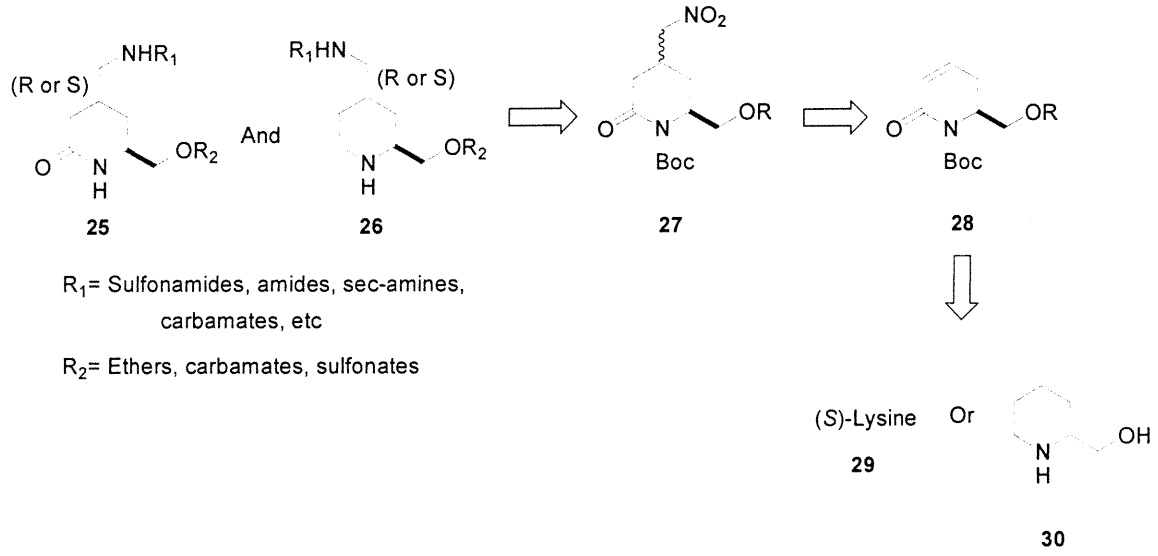


Figure 7. A retrosynthetic analysis for obtaining 2,4-disubstituted piperidines and 6-oxo-piperidines

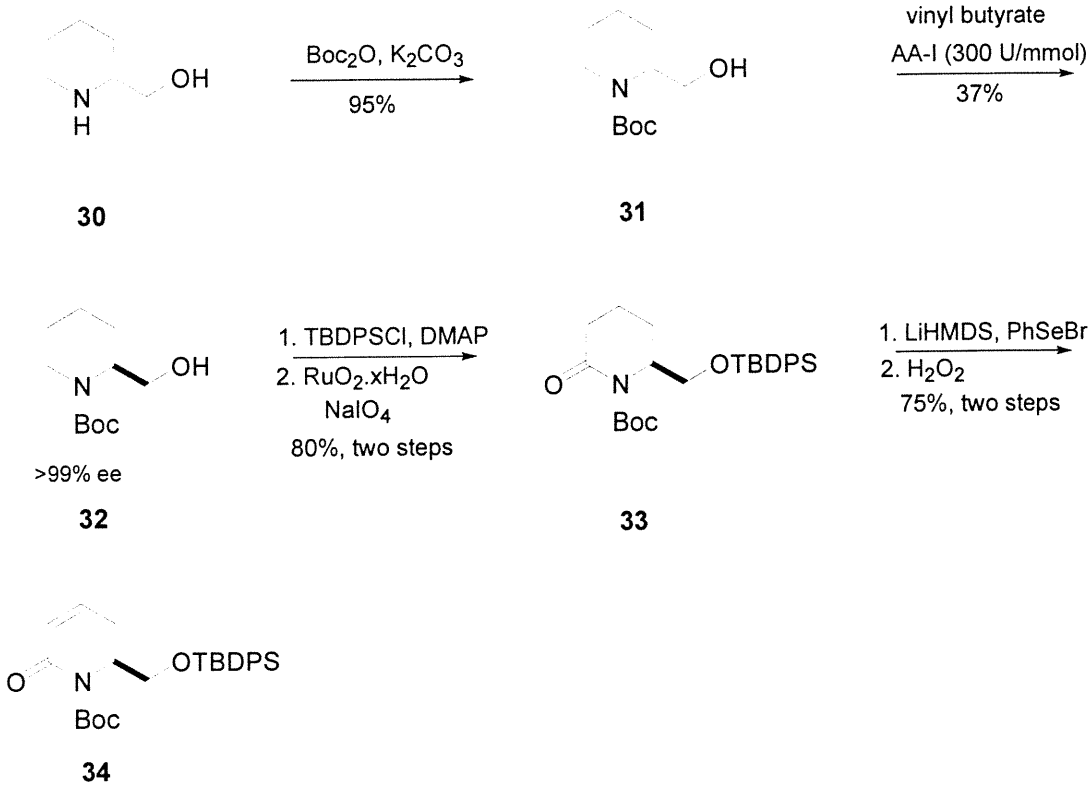
Chapter 2

2-Synthesis of 2,4-Substituted Piperidine and 6-Oxo-piperidine Scaffolds via a Nitro Michael Addition

2.1 Michael addition of nitroalkanes

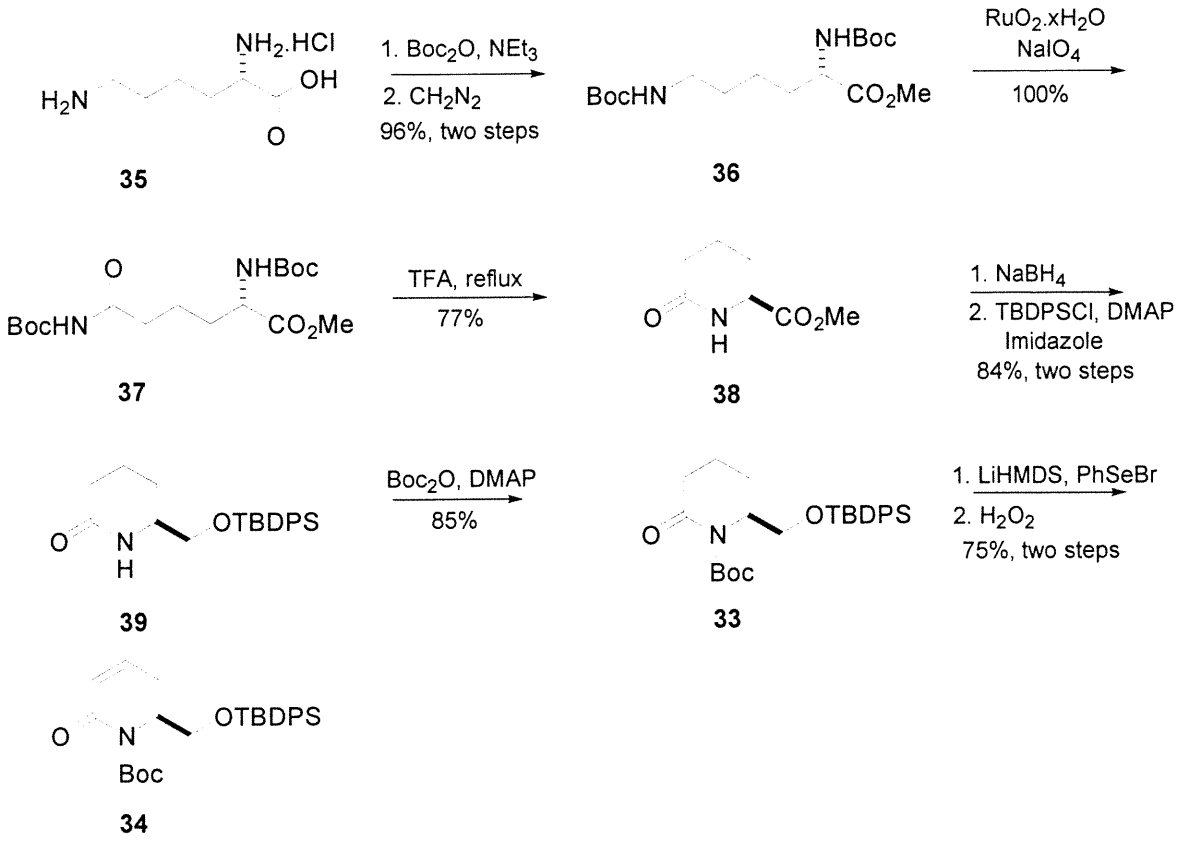
The Michael addition of nitroalkanes provides a powerful synthetic tool in organic synthesis.[29] Conjugate addition of nitroalkyl groups to α,β-unsaturated carbonyl compounds is a highly useful reaction for the introduction of nitroalkyl groups. Furthermore, denitration of the adduct leads to a conjugate addition of secondary alkyl groups.[30] Nef oxidation of the nitro to the corresponding aldehyde[31] or exploiting the newly formed nitro Michael adduct in nitro-aldol reactions[32] is also a useful synthetic tool. The method to obtain the aminoalkyl group consists of the reduction of the nitro group. The precursor required for the Michael addition was the α,β-unsaturated lactam **34** (Scheme 1).

We devised two approaches to the synthesis of precursor **34**. Derivative **31** was obtained from **30** by treatment of **30** with Boc_2O under aqueous basic conditions to give the racemic free alcohol **31** (Scheme 1). It was possible to get the *N*-protected amino alcohol **32** in exceptional enantiomeric purity and in satisfactory overall yield with the AA-I (enzyme acylase I from Aspergillus species)-catalyzed butyrylation of racemic **31** in wet toluene.[9g] The butyrate derivative and the alcohol were readily separated by flash chromatography, and the enantiomerically enriched alcohol was submitted to a second enzymatic resolution to give enantiomerically pure **32** in 37% overall yield for the two steps. With a ready supply of this chiral building block in hand, we turned our attention to the synthesis of the Michael precusor **34**. Protection of the primary alcohol as the TBDPS ether followed by the ruthenium tetroxide oxidation, yielded compound **33** in 80% overall yield. The synthesis of **34** was completed by the formation of the phenylselenyl intermediate of **33** and oxidative elimination in 75% over two steps. This provided a concise 7-step synthesis of **34**, starting from a readily available and inexpensive precursor **30**. Given the importance of piperidine heterocycles,[6-9] this chiron should be useful in a variety of applications.



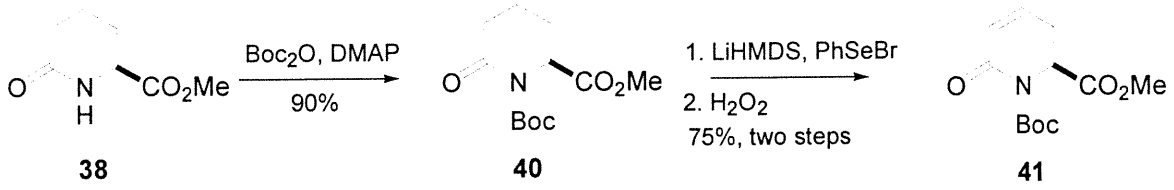
Scheme 1. Preparation of the nitro Michael alcohol precursor through a kinetic resolution

A second method for the preparation of the enantiopure lactam derivative **34** utilizing the readily available (*S*)-lysine is described below. *N*-Boc protection and esterification of the readily available (*S*)-lysine hydrochloride **35** were achieved with Boc_2O under basic conditions, followed by the addition of diazomethane to give **36** in 96% overall yield. Oxidation of the *N*-protected primary amine with ruthenium tetroxide[9h] gave **37** in quantitative yield. Direct cyclization of **37** to methyl 6-oxopipecolate **38,** was readily achieved in refluxing trifluoroacetic acid in 77% yield. Sodium borohydride reduction of **38**, followed by protection of the crude primary alcohol with TBDPSCl gave **39** in 85% overall yield. *N*-Boc protection with Boc_2O, under basic conditions, followed once again by a selenium mediated oxidative elimination yielded compound **34** in 60% overall yield. This 9-step sequence to **34** is somewhat longer compared to the one shown in Scheme 1, but has the advantage of starting from readily available and inexpensive (*S*)-lysine and the overall yield is better.

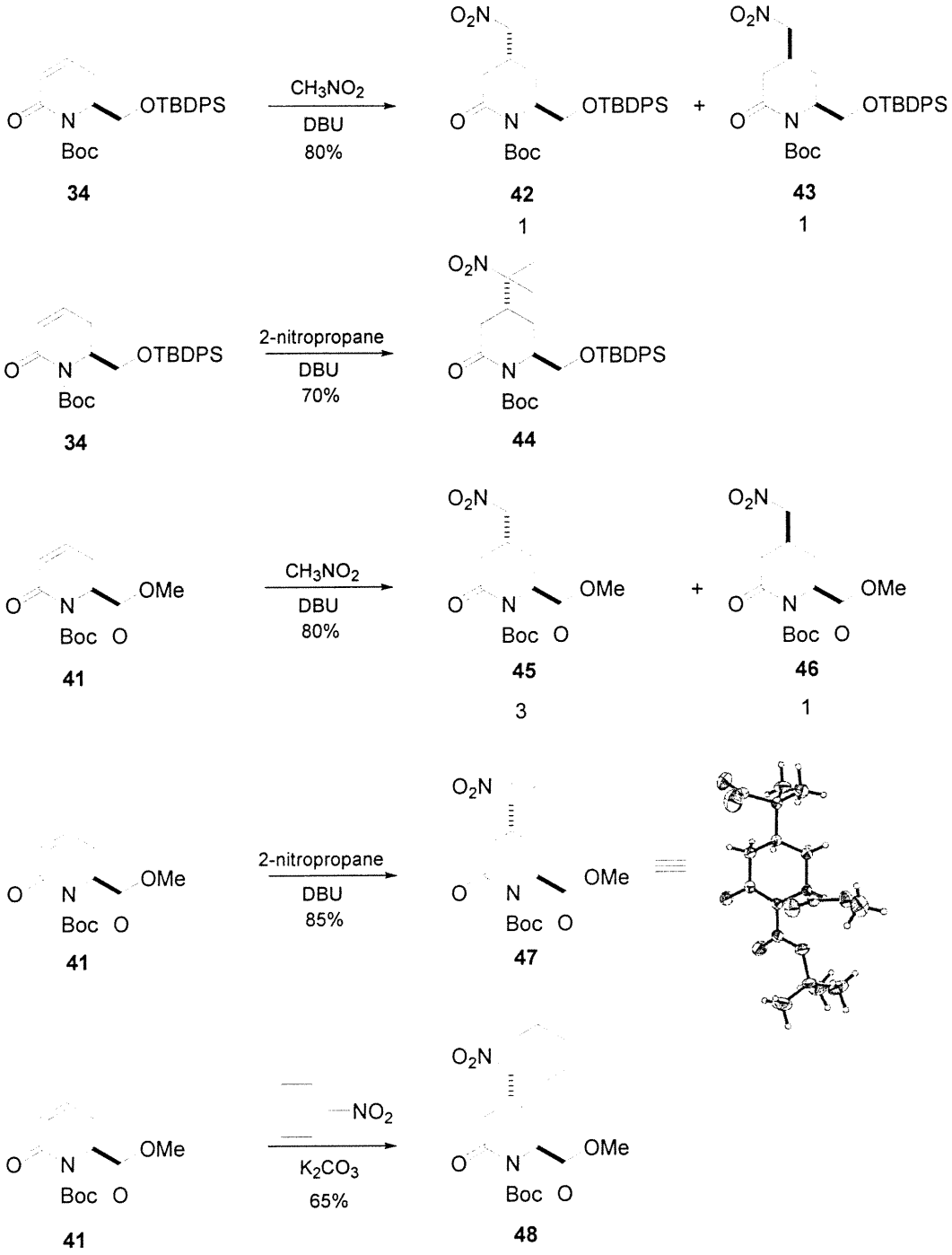


Scheme 2. Preparation of the nitro Michael alcohol precursor starting from (*S*)-lysine

A second Michael precursor was considered in which the hydroxymethyl group was replaced with an ester as in **41**. The common intermediate **38**, was *N*-Boc protected under basic conditions in 85% yield, and the remainder of the sequence followed the same protocol as in Scheme 2 to give **41** in 60% overall yield.



Scheme 3. Preparation of the nitro Michael methyl ester precursor starting from (*S*)-lysine



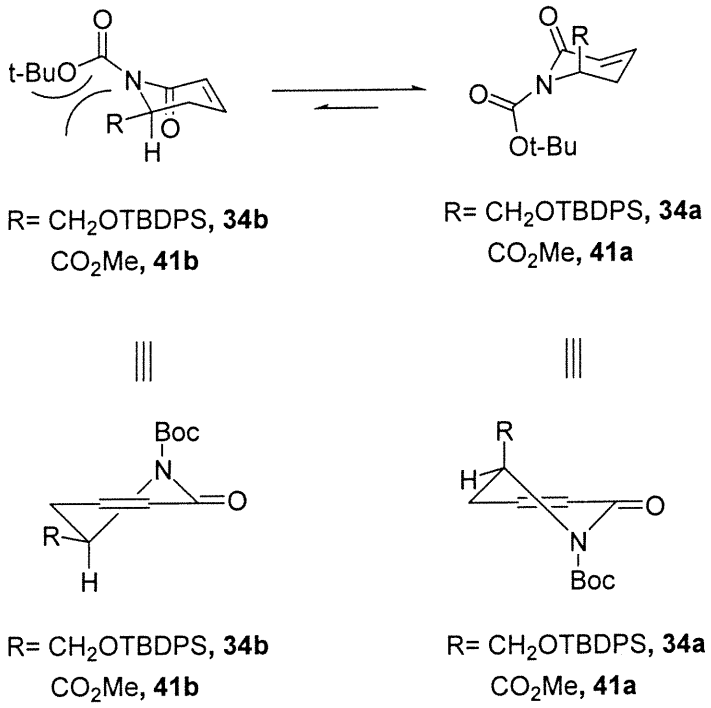
Scheme 4. Nitro Michael addition on α-β-unsaturated 6-oxo-piperidines

Relying on literature precedents in different contexts,[33] we chose DBU as a base to study the Michael addition of nitroalkanes to **34** and **41**. It was also of interest, to study the stereochemical outcome of the reactions with various nitroalkanes, since the steric and

electronic requirements to the approach could be different due to the nature of the substituents. As shown in Scheme 4, compound **34** was reacted in neat nitromethane in the presence of DBU to yield compounds **42** and **43** in a ratio of 1:1 which were readily separable by flash chromatography. Along with further nOe measurements of adduct **42** corroborating the *anti* stereochemistry, it was observed that the anti adduct **42** had a higher polarity than the *syn* adduct **43**. A single adduct **44** was obtained in the case of 2-nitropropane. The stereochemical outcome of the addition of nitromethane to the ester derivative **41** was found to be different when compared with compound **34**. A 3:1 ratio of the *anti/syn*, compounds **45** and **46** respectively, was obtained and the stereochemical assignment was made by analogy to the adduct with 2-nitropropane, compound **47**, which was confirmed by X-ray crystallography (Scheme 4). nOe measurements of appropriate derivatives, **55** and **58** (Schemes 7 and 8), are constant with this conclusion. Since nitrocyclohexane is not as readily available as the other nitroalkanes, we ran the Michael addition in acetonitrile in the presence of potassium carbonate. This yielded the single *trans* adduct **48**, where again the stereochemical assignment was made by analogy to the adduct with 2-nitropropane, **47**.

2.2 Rationalization of the stereochemical outcome

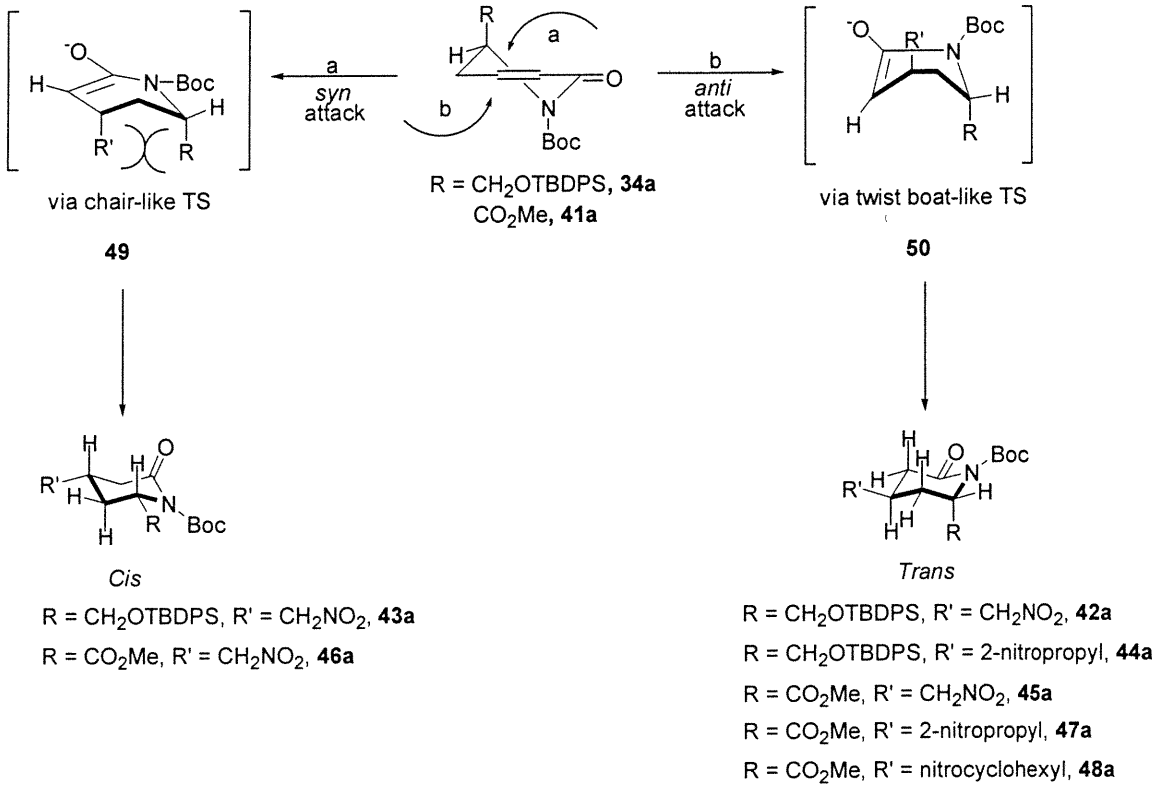
The effect of allylic 1,3-strain ($A^{1,3}$ strain) on imide-like *N*-acyl piperidines have been the object of intense synthetic and computational studies in the past.[34] The reason of this exocyclic double bond giving rise to a special case of $A^{1,3}$ strain, is due to the ground state overlap of the pair of electrons on nitrogen with the acyl carbonyl group.[35] This $A^{1,3}$ strain has been demonstrated to make the C-2 axial-substituted *N*-acylpiperidines more stable than the corresponding 2-equatorial isomers.[36] Calculations on lactam **41** have demonstrated that the conformer having the carboxylate in a pseudo-axial disposition **41a**, is more stable by 5 kcal mol^{-1}, than the corresponding pseudo-equatorial conformer **41b** (Scheme 5).[37] A preference for the pseudo-axial C-2 substituted lactams **34a** and **41a**, could be rationalized with the consequence of a strong $A^{1,3}$ strain between the C-2 substitution of 6-oxo-piperidines **34** and **41**, and the Boc protecting group on the nitrogen atom (See **34b** and **41b**).[36]



Scheme 5. Proposed rationalization of possible conformations for lactams 34 and 41

Based on precedent literature reports,[36b, 38] we expected a stereoelectronically *syn* bias to operate during the addition of nitroalkanes to lactams **34a** and **41a**; hence, the major pathway for the incoming nitroalkanes was supposed to be via a chair-like transition state to give enolate **49** and a majority of the *cis* adducts (Scheme 6). However, we observed no stereoselectivity for the conjugate addition of nitromethane to lactam **34a**. Furthermore, when the steric demand of the nucleophile was increased with the addition of 2-nitropropane, a complete *trans* stereoselectivity was observed to give the single diastereoisomer **44a** (Scheme 6). Similar results were also observed for lactam **41a**; the addition of nitromethane to 6-oxo-piperidine **41a** gave a majority of *trans* adduct **45a**. The addition of the bulkier 2-nitropropane and nitrocyclohexane, resulted once again in a complete *trans* stereoselectivity giving single diastereoisomers **47a** and **48a**. We propose the reaction pathway via an equatorial attack, for compounds **47a** and **48a**, due to a strong 1,3-diaxial interaction between the C-2 carboxylate of lactam **41a** and the bulky incoming 2-nitropropane and nitrocyclohexane (see **49**). This is via a twist boat-like transition state (see **50**), which collapses to the *trans* chair conformer. For the smaller nitromethane, the competing steric interaction with the carboxylate of lactam **40a** is not as pronounced as the

bulky nitroalkanes. Thus, a stereoelectronically *trans* majority is formed with a preference via the lower in energy twist boat-like transition state **50** over the chair-like one **49**.



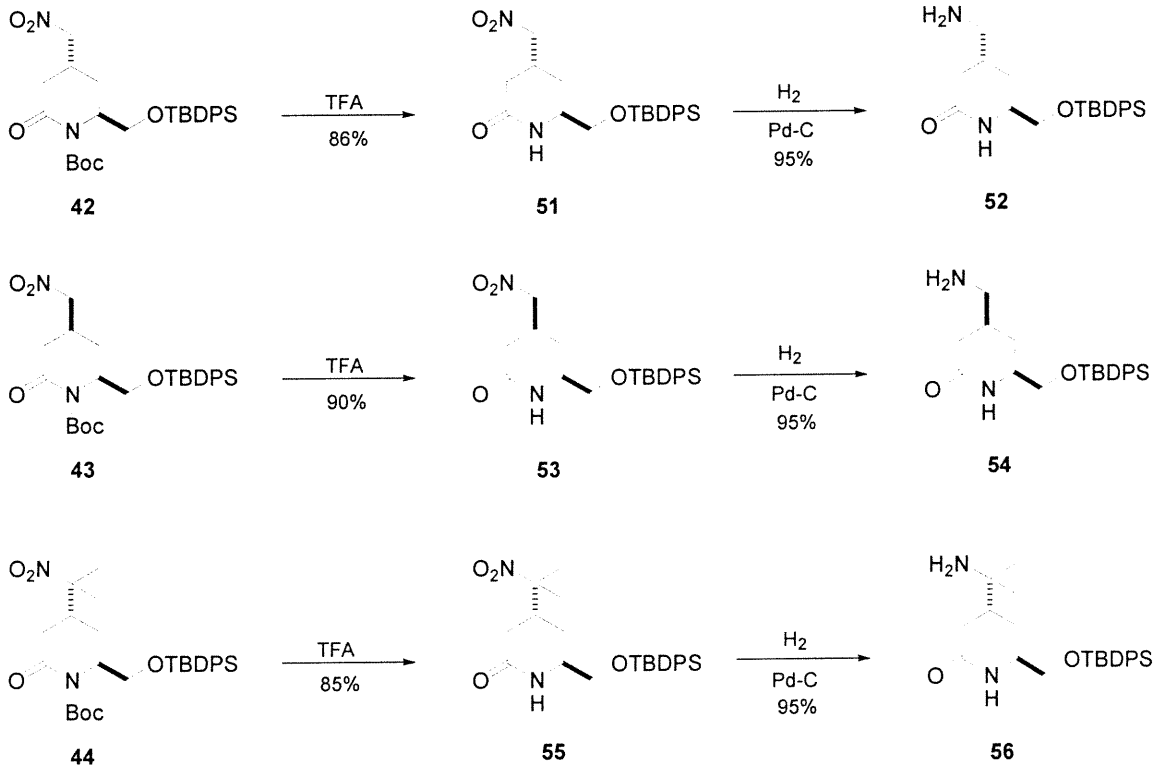
Scheme 6. Proposed rationalization of the stereochemical outcome of nitro Michael addition

The same analogy could be applied to compound **44a**, where once again due to a strong steric interaction, the *trans* chair conformer is formed via the lower in energy twist boat-like transition state producing a favored equatorial attack. However, in the absence of the carboxylate interaction and a lack of bulky nitroalkanes, it appears that both transition states are equally populated during the Michael addition of nitromethane to lactam **34a**, and therefore a 1:1 mixture of diastereoisomers **42a** and **43a** is obtained. In the nitromethane series for lactam **34a**, attempts to equilibrate each diastereoisomer independently, under the reaction conditions, showed no change of stereochemical composition. We therefore conclude, the results observed for the Michael addition of nitroalkanes, are the kinetic outcome and not the result of thermodynamic equilibration. The following proves that the observed diastereoselectivity for the conjugate addition of nitroalkanes to cyclic lactams

34a and **40a**, could be controlled by an appropriate choice of nucleophilic reagents and an even more appropriate choice of C-2 substitution. In our opinion, the significane of the $A^{1,3}$ strain and the size of the nucleophile are the key factors responsible for the observed diastereoselectivity in these conjugate addition reactions.

2.3 Synthesis of 2,4-disubstituted piperidine and 6-oxo-piperidine scaffolds

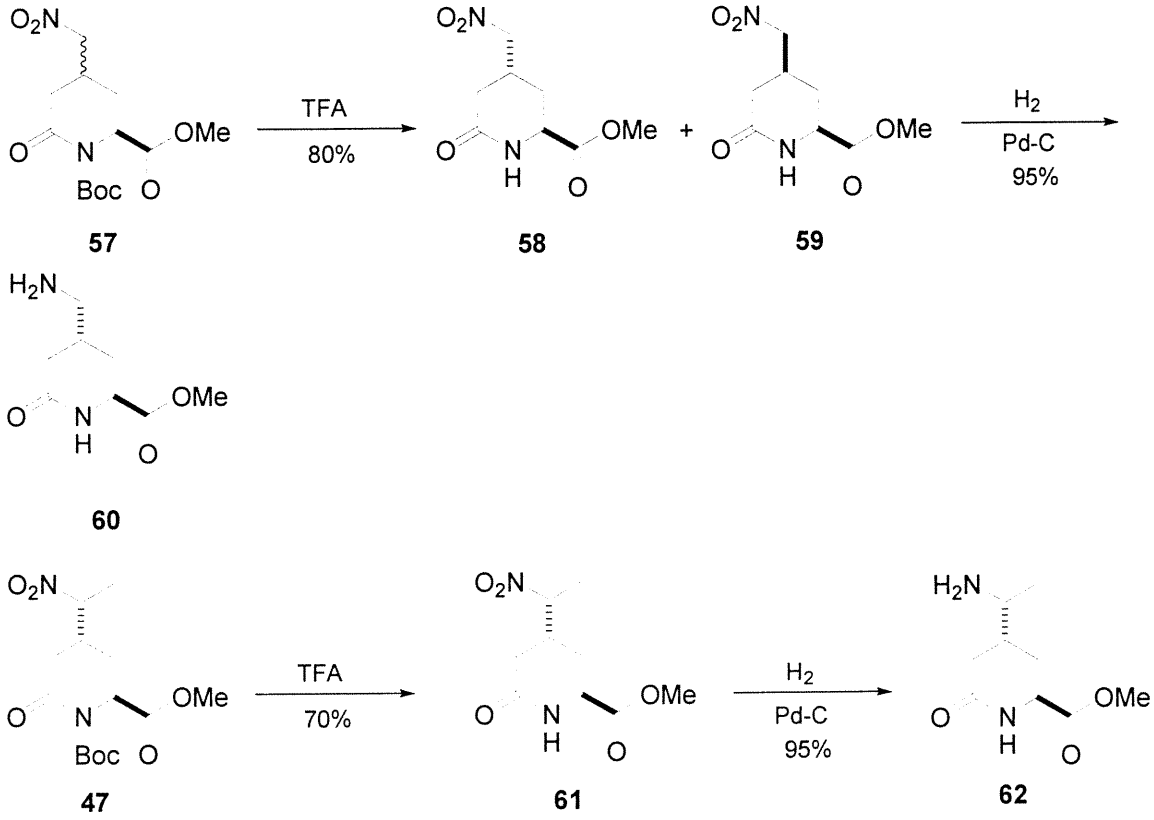
With compounds **42**, **43** and **44** in hand, we were ready for further elaboration towards the synthesis of 4-aminomethyl and 2-hydroxymethyl piperidine and 6-oxo-piperidine scaffolds.



Scheme 7. Synthesis of 4-aminomethyl-6-oxo-piperidine scaffolds

In order to complete the 6-oxo-piperidine aminomethyl synthesis, the *N*-Boc protecting groups of compounds **42**, **43** and **44** were removed under acidic conditions to obtain compounds **51**, **53** and **55** in yields ranging from 85% to 90%. High pressure hydrogenation of the latter was followed to give compounds **52**, **54** and **56** in 95% yields. It should be pointed out that reduction of the *N*-Boc intermediates, **42** and **43**, resulted in an

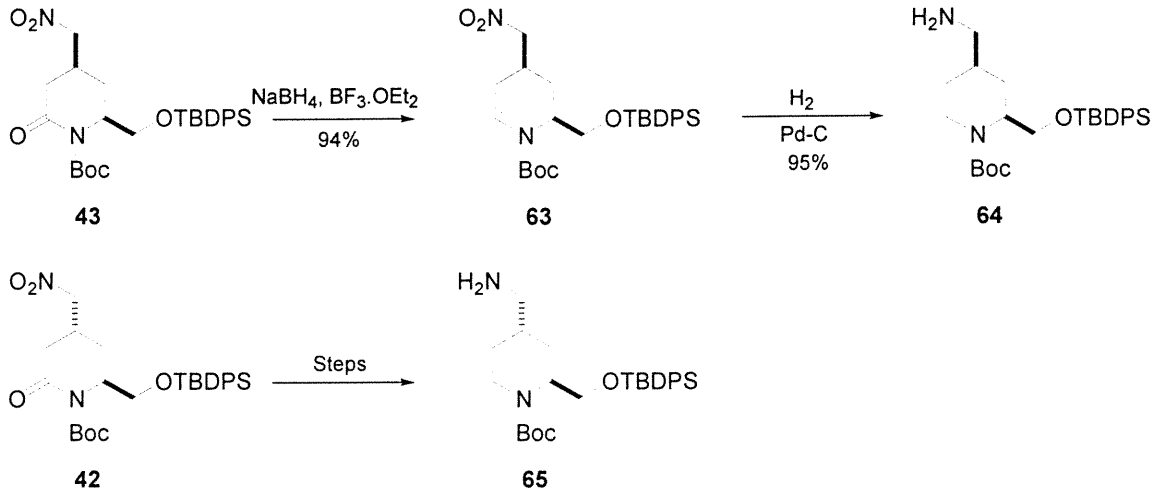
intramolecular attack of the amino group on the lactam carbonyl because of its imide-like character (Scheme 10). These kind of ring-switching reactions have been reported with *N*-Boc pyrrolidinone derivatives,[39] to furnish rearranged lactams. To circumvent this, we first removed the Boc protecting group before the hydrogenation.



Scheme 8. Synthesis of 4-aminomethyl-6-oxo-pipecolic acid scaffolds

The 6-oxopipecolic acid series was manipulated in a similar way. The *N*-Boc protecting groups of compounds **57** and **47** were removed under acidic conditions in 80% yield, to give compounds **58**, **59** and to give **61** in 70% yield (Scheme 8). Once again, it was observed that the *anti* adduct **58** had a higher polarity than the *syn* adduct **59**; further nOe measurements of adduct **58** were in accord with the tentative stereochemical assignments. Adducts **58** and **59** were separated by flash chromatography, and compounds **58** and **61** were reduced under high pressure hydrogenation to the corresponding amino analogs, **60** and **62**, in 95% yield.

In order to complete the piperidine aminomethyl synthesis, we chose a new sequence of reactions to generate 2,4-disubstituted piperidine scaffolds. In an attempt to reduce the lactam carbonyl selectively in the presence of sodium borohydride and $BF_3.Et_2O$, we observed an efficient transformation to the corresponding enecarbamate **63**. Catalytic hydrogenation afforded the piperidine analog **64** in 95% yield. The same sequence was also successfully applied to compound **42** to give **65** in equally good yield.



Scheme 9. Synthesis of 4-aminomethyl piperidine scaffolds

Along with substituted piperidine and piperidinone ring systems being the target of considerable synthetic efforts,[6-10] our 10-step concise synthesis of stereochemically well defined, enantiopure 2,4-disubstituted piperidine and 6-oxo-piperidine scaffolds could be of great value in the quest for peptidomimetics and for a variety of synthetic applications.

2.4 Generation of a library of compounds

Having a wide range of 4-aminomethyl-2-hydroxymethyl 6-oxo-piperidines available, we were now poised to introduce two points of diversity. To this end, we chose to prepare a library of 4-sulfonamides and 2-carbamates as diversity points to take advantage of possible hydrophobic and H-bonding effects. Table 1 lists the derivatization of the aminoalkyl handles and tables 2 and 3 list the structures of 31 compounds prepared in this series. The

protocol features the treatment of the aminomethyl compound with the appropriate sulfonyl halide, removal of the TBDPS group and conversion of the primary alcohol to the carbamate. Each derivative was purified on a small silica gel column affording a clean library of 6-oxo-piperidines with 4-sulfonamide and 2-ureadomethyl groups in enantiopure form. Compounds **77**, **87**, **97**, and **106** were fully characterized for experimental purposes, and the remaining of the sulfonamide/carbamate libraries 1 and 2 were characterized by HRMS. On an ending note, the benzoyl and urea derivatives **74** and **75**, were prepared in the advent of a future benzoyl/carbamate or urea/carbamate library.

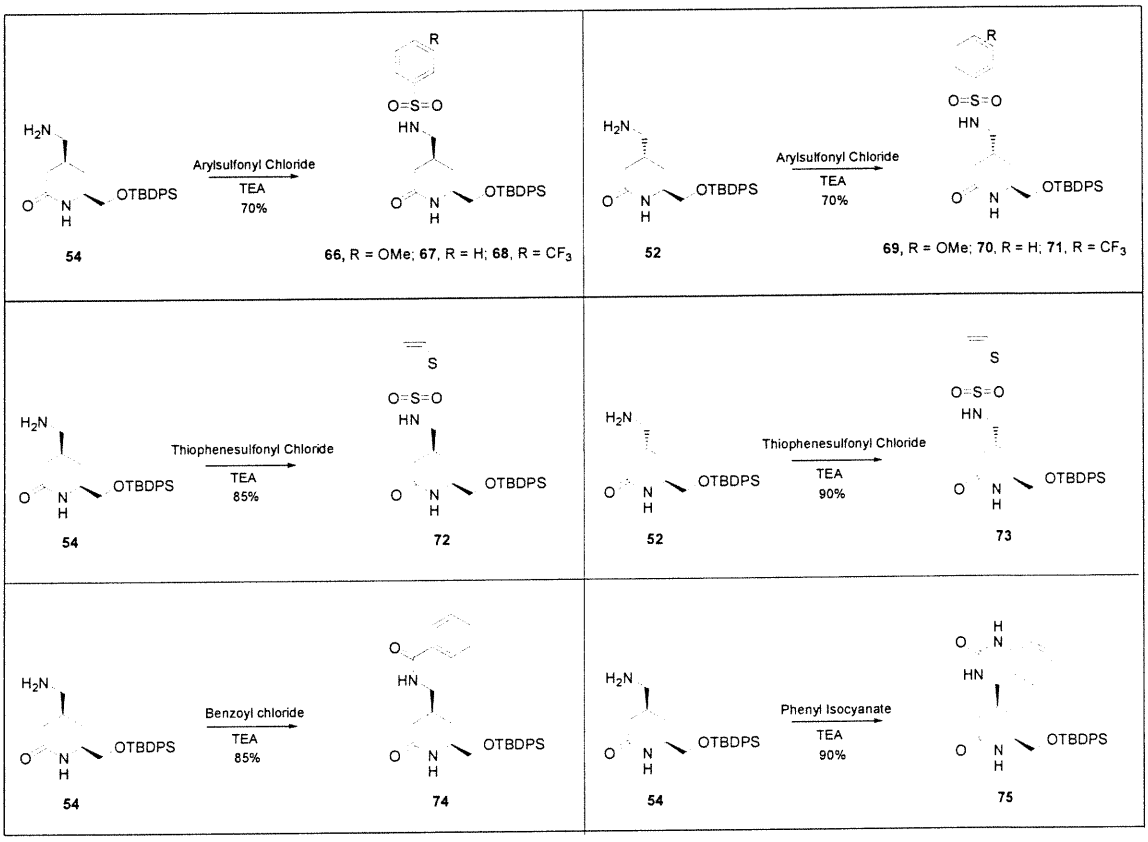


Table 1. Derivatization of the aminoalkyl handle

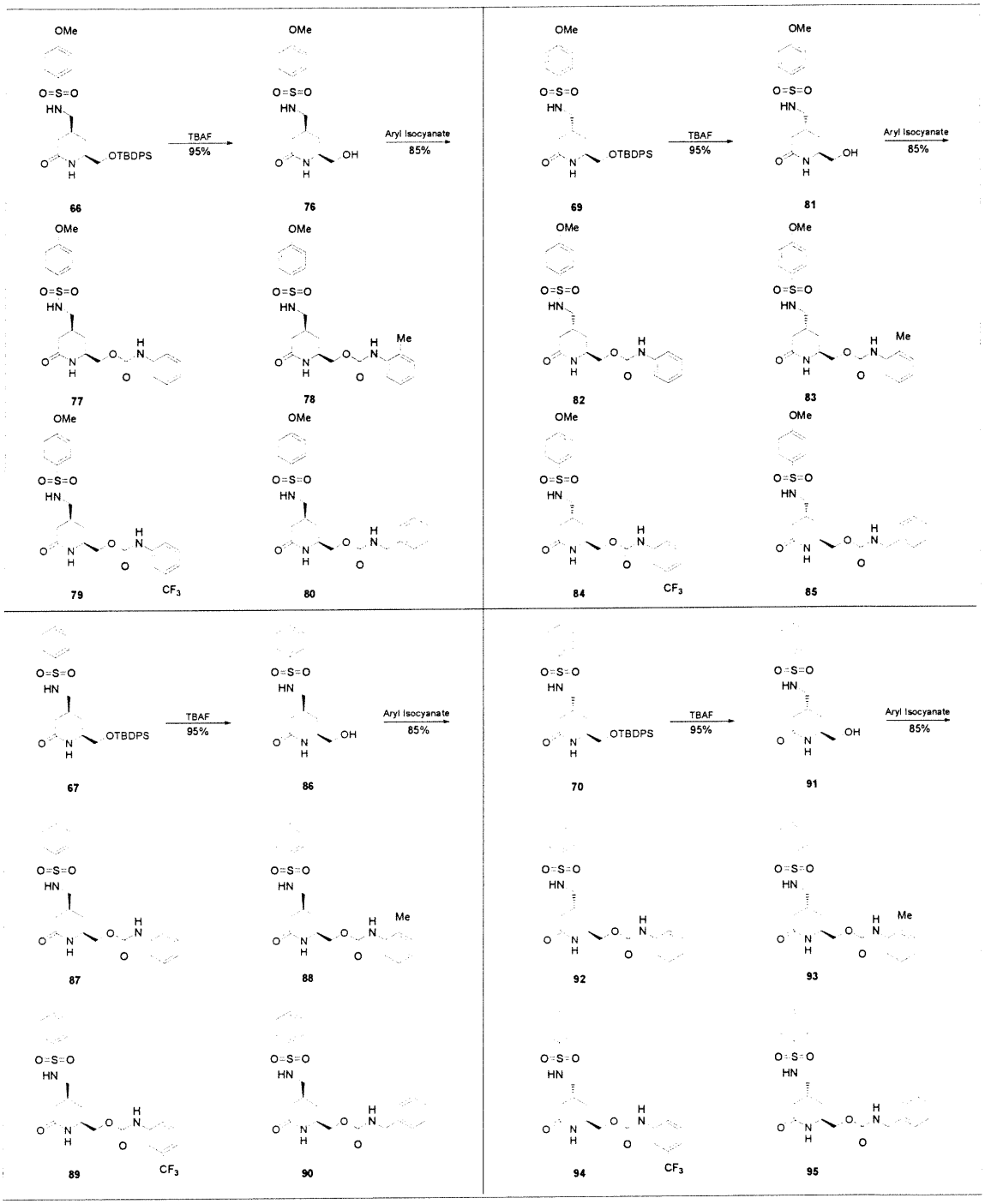


Table 2. Generation of sulfonamide/carbamate library 1 through parallel synthesis

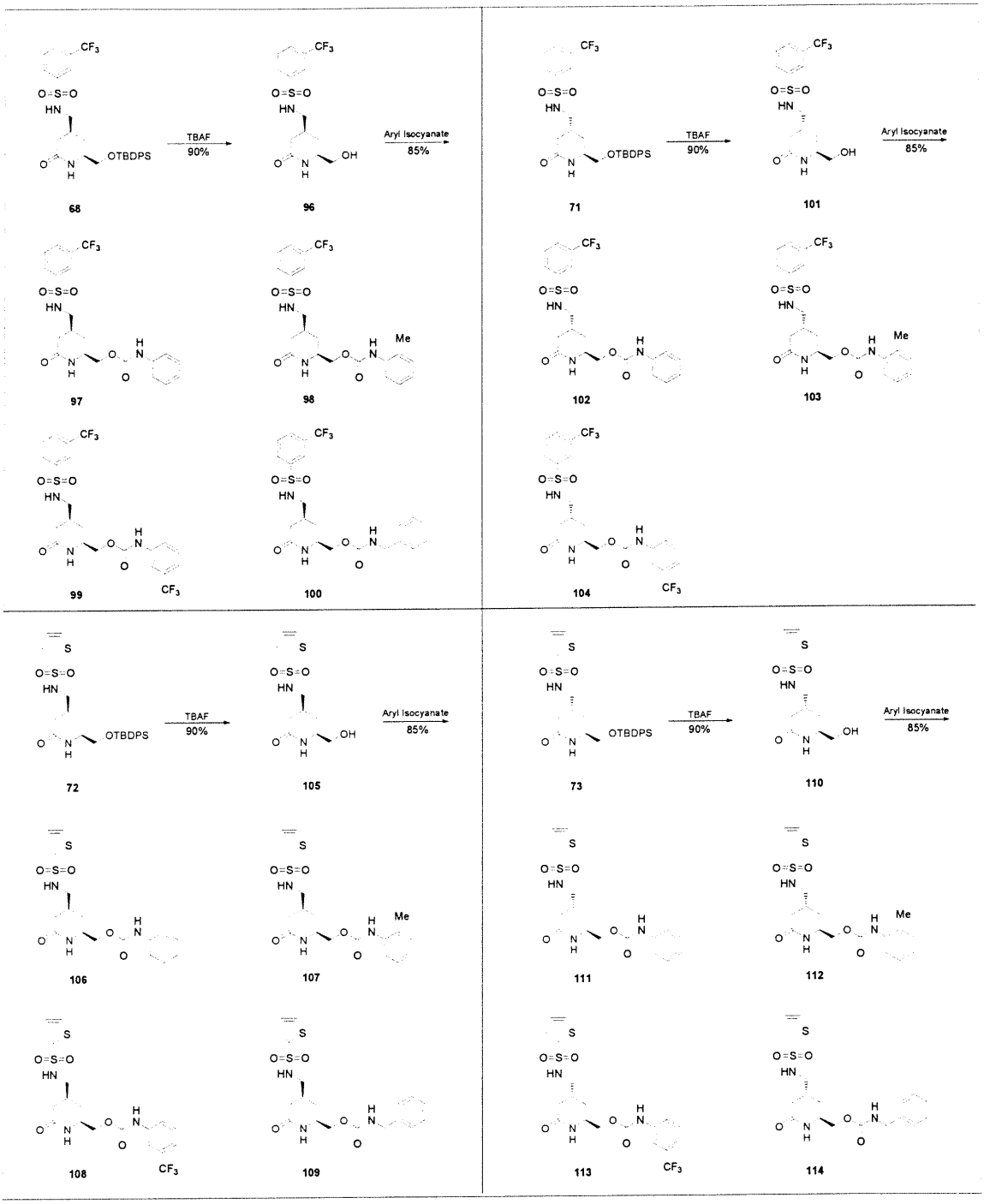
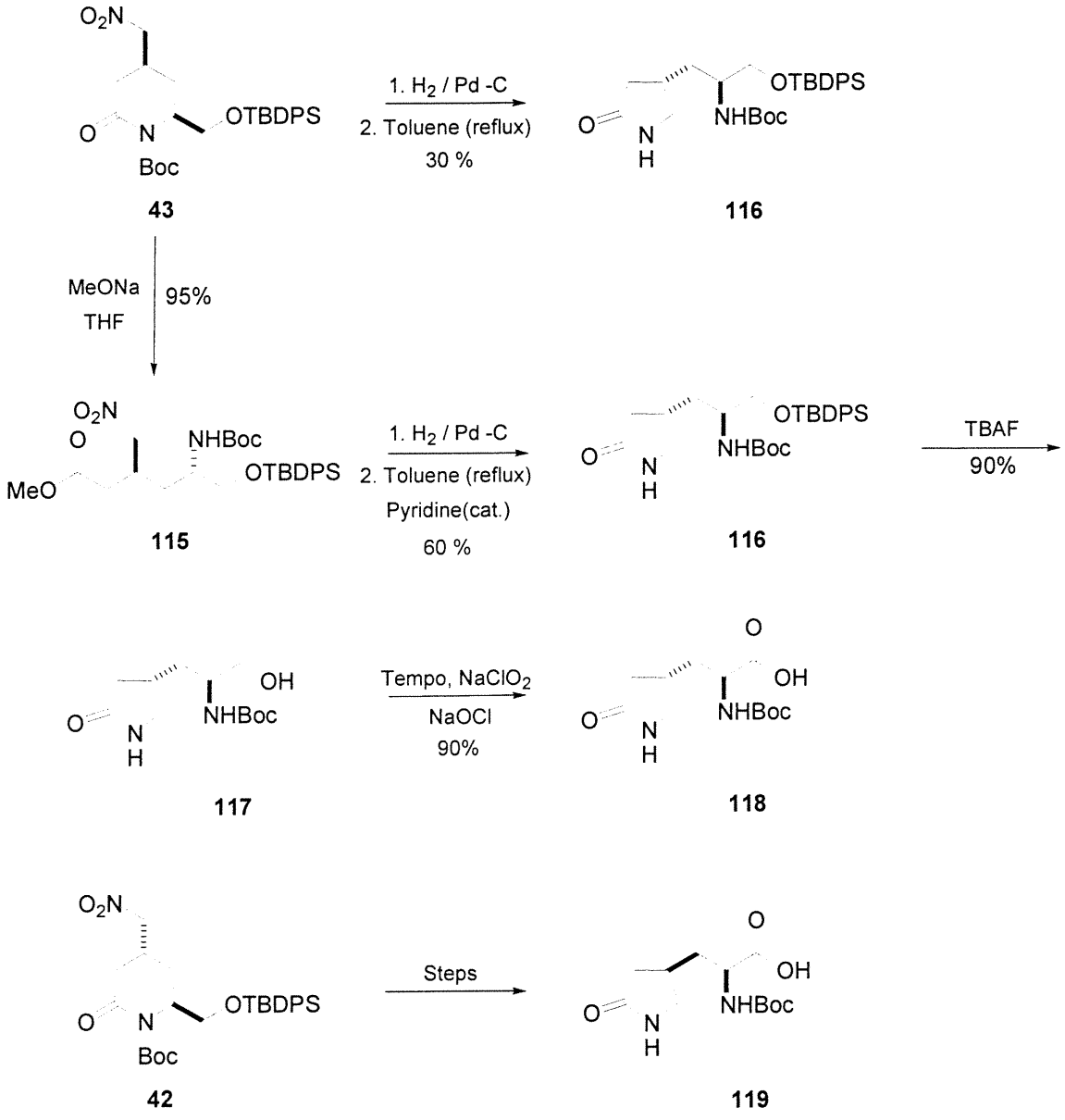


Table 3. Generation of sulfonamide/carbamate library 2 through parallel synthesis

2.5 Synthesis of novel γ-substituted α-amino acids

As previously mentioned, reduction of the aminomethyl 6-oxo-piperidines resulted in the formation of the ring contracted lactam **116**. We exploited this reaction towards the preparation of γ-substituted α-amino acids, which can be considered as analogs of lysine.[39]



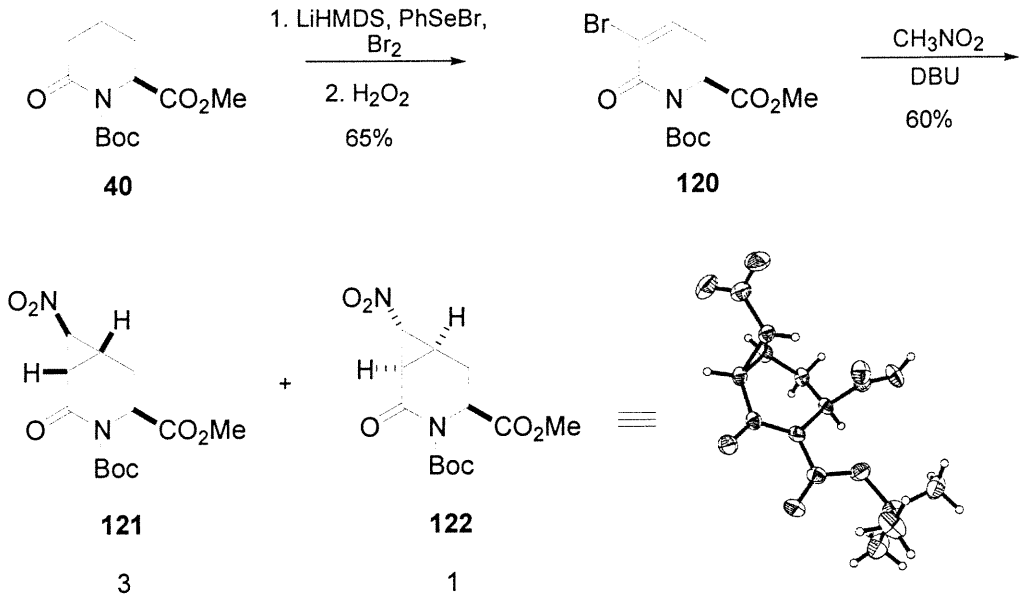
Scheme 10. Synthesis of γ-substituted α-amino acid pyrrolidinones from nitro Michael derivatives

Catalytic hydrogenation of **43**, followed by heating to reflux the resulting aminomethyl product in toluene afforded the 2-pyrrolidinone analog **116** in 30% yield. This yield could be significantly improved by adopting a different protocol. Treatment of **43** with sodium methoxide led to the methyl ester **115**, which on hydrogenation and heating to reflux in toluene in the presence of a catalytic amount of pyridine, gave **116** in 60% overall yield. Deprotection of the silyl group and oxidation of the primary alcohol[40] led to the novel γ–substituted α-amino acid **118** in excellent yield. The diastereoisomeric **119** was prepared in a similar manner from the 4-*R* nitromethyl analog **42**.

This novel class of γ-substituted α-amino acids **118** and **119**, may have potential utility as constrained amino acids[22] and peptidomimetics.[24, 39] These compounds could also be valuable building blocks for the preparation of pharmaceuticals or as potential scaffolds or mimics.[23, 27] To this end, a general method for the rapid synthesis of these derivatives has been demonstrated.

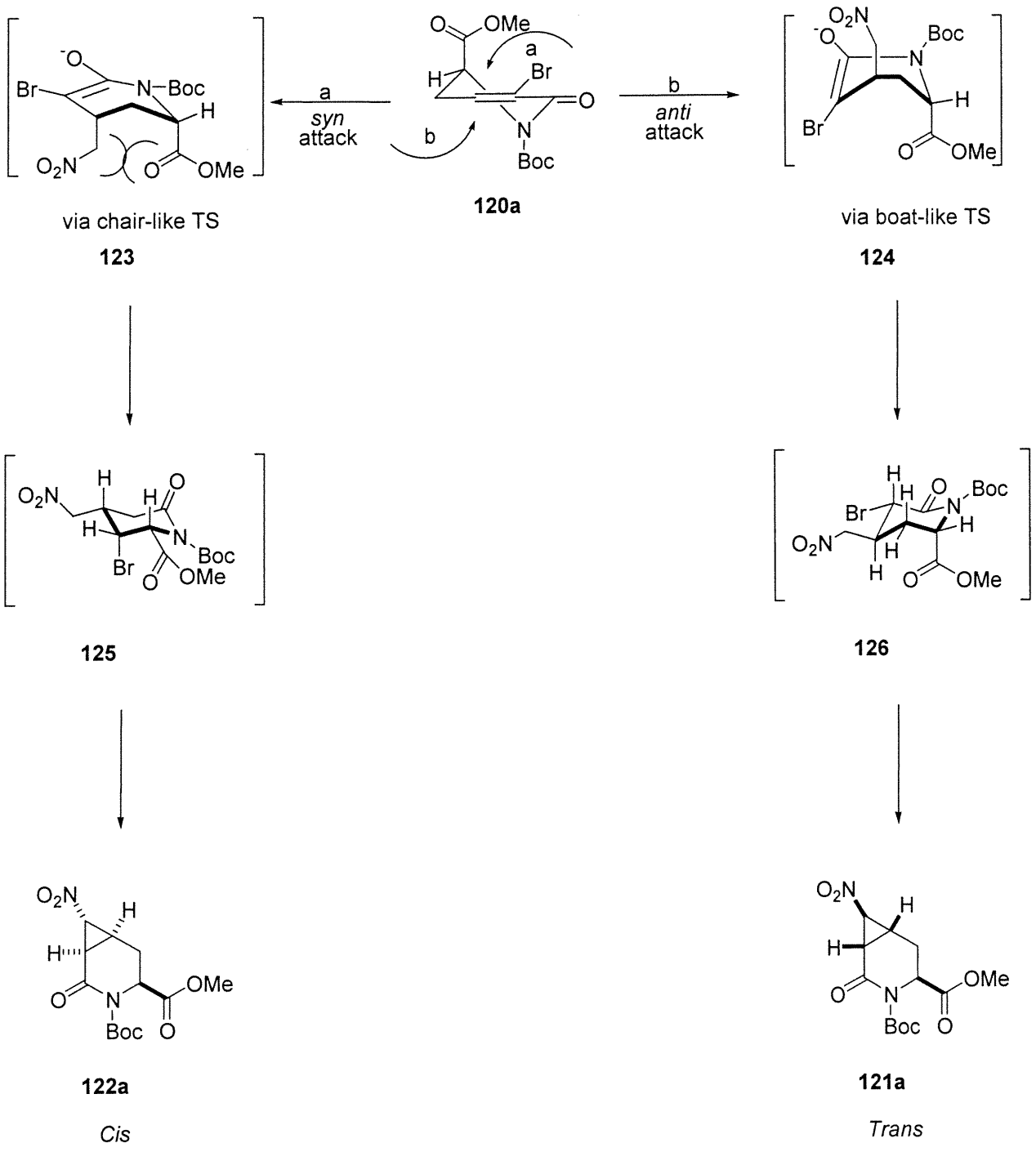
2.6 Synthesis of 3,4-methano-6-oxo-pipecolic acid

Previous work from our laboratory has described the synthesis of 4,5-methano prolines and 5,6-methano pipecolic acids.[41] In the context of the present work we studied the nitro Michael reaction on the α-bromo α,β-unsaturated lactam **120** as a reactive olefin with a leaving group on the α-carbon. We treated the enolate derived from **40** with PhSeBr and Br_2, which led to the α-bromo α,β-unsaturated lactam analog **120** in 65% overall yield (Scheme 11). To our surprise, treatment of **120** with DBU in neat nitromethane resulted in the formation of two isomeric nitrocyclopropanes in a ratio of 3:1. The structure of the minor product **122** was ascertained by single crystal X-ray crystallography as shown in Scheme 11. The structure of the major isomer was assigned to be **121** by analogy.



Scheme 11. Synthesis of constrained nitromethano-6-oxo-piperidines

Since the carboxylate at C-2 was demonstrated to be in a pseudo-axial position for lactam **41** (Scheme 5), we reasoned that the same conformation could be observed for compound **120**. Furthermore, it was of interest to us, that like its non-bromo analog **41**, the major product corresponded to an *anti* attack giving a majority of the *trans* adduct **121**. This is probably due to the steric interaction between the C-2 carboxylate of lactam **120** and the incoming nitromethane (see **123**). The *anti* reaction pathway is via the lower in energy twist boat-like transition state to give enolate **124**, which collapses to the *trans* chair conformer **126**. Hereafter, the nitromethyl adduct **126** undergoes intramolecular attack with ejection of the 2-bromo group enabling the formation of the cyclopropane. Thus, the proposed mechanism of this nitro Michael cyclopropanation is both intermolecular Michael addition and intramolecular cyclization process. Attempts to equilibrate, under the reaction conditions, the exo orientation of the nitro group of each diastereoisomer independently, showed no change of stereochemical composition. We therefore conclude, the results observed are the kinetic outcome and not the result of thermodynamic equilibration. Although, the exo orientation of the nitro group, of the *trans* isomer, was ascertained by nOe studies and X-ray crystallography, we have no explanation for the basis of this stereoselectivity.



Scheme 12. Proposed rationalization of the stereochemical outcome of the nitro Michael addition to lactam 120

The generality of this nitro Michael cyclopropanation reaction, and the preferred diastereoselectivity with bulkier nitroalkanes, still needs to be established. Nonetheless, 4-5-nitromethano-6-oxopipecolic acids **121** and **122** represent interesting bicyclic and

constrained cyclic amino acid derivatives that could be of use as β-turn mimetics on the one hand[23], and as a piperidine scaffold with a potential amino vector as an additional point of diversity on the other.[27]

2.7 Conclusion

We have produced a general method for the rapid synthesis of a novel class of 2,4-disubstituted piperidines and 6-oxo-piperidines as constrained analogs of naturally occuring (*S*)-pipecolic acid. To take advantage of possible hydrophobic and H-bonding effects, we prepared a library of 4-sulfonamides and 2-carbamates to be used as potential scaffolds or mimics for various receptors. Furthermore, a general method for the synthesis of novel γ-substituted α-amino acids and formation of 3,4-methano-6-oxo-pipecolic acids were also presented. With the importance of the piperidine ring system in natural products[9] along with its valuable pharmacological properties[7], our synthesis of the latter chiral ligands could be of great value for a variety of synthetic applications.

Chapter 3

3.1 General experimental notes

All yields reported are isolated products after chromatographic purification except where indicated. The ratio of isomers were determined from ^{1}H-NMR spectra. Melting points (mp) were measured on a Fisher-Johns apparatus, and they are uncorrected. Nuclear magnetic resonance of proton spectra (^{1}H-NMR) and carbon-13 (^{13}C-NMR) were recorded on a Bruker AMX-300 (300 MHz) or a Bruker AMX-400 (400 MHz) spectrometer in a deuterated solvent as indicated with $CHCl_3$ (H, δ = 7.27 ppm; C, δ = 77.23 ppm) as internal reference. Chemical shifts (δ) and coupling constants (J) are expressed in ppm (part per million) and Hz (Hertz), respectively. The abbreviations used for the description of the peaks are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; dd, doublet of doublets; doublet of triplets. DEPT experiments were performed routinely, methyl (CH_3) and methyne (CH) give positive signal (+), methylene (CH_2) gives a negative signal (-), and carbon without hydrogen gives no signal (0). ^{13}C-NMR and DEPT data are listed together. All chemical shifts are measured from the center of the resolved peaks, the unresolved multiplet and broad peaks are normally indicated as a range.

Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were determined on a VG Micro Mass 1212 and a Kratos MS-50 TCTA mass spectrometer, respectively, with desorption chemical ionization (CI), or fast atom bombardment (FAB). Infrared Spectra (IR) were conducted on a Perkin-Elmer 781 or Paragon 1000 infrared spectrophotometer in a chloroform solution with a sodium chloride cell.

Optical rotations ($[\alpha]_D$) were measured at the sodium line with a Perkin-Elmer 241 polarimeter at ambient temperature.

X-ray analysis was performed on the Enraf-Nonius CAD-4 diffractometer using graphite monochromatized Mo K α radiation and the structure solved using direct methods (MULTAN80) and difference Fourier calculations (SHELX76).

All original data and spectra are available from Professor Stephen Hanessian, Université de Montréal.

Chromatography

Flash chromatography was carried out according to the procedure of Still[42] using silica gel 60 (0.040-0.063 mm, 230-400 mesh ASTA) (E. Merck).

Thin layer chromatography (TLC) was performed using commercial precoated glass-backed Silica Gel 60 F254 plates with a layer thickness of 250 μm (E. Merck). This technique was used to follow the course of reactions, to determine the suitable solvent system for flash chromatography, and to check fractions of flash chromatography. A mixture of EtOAc-H on v/v basis, as indicated, was used as eluent.

TLC visualization

UV 254 lamp was used to view TLC plates with UV light active compounds. To develop plates, they were dipped into the stain solution and heated to develop the colored spots.

(a) *Molybdate-Ceric solution*

This solution was prepared by dissolving 50 g of ammonium molybdate (VI) tetrahydrate, $(NH_4)_6Mo_7O_{24}.4H_2O$ and 20 g of ammonium cerium (IV) sulfate dihydrate, $(NH_4)_4Ce(SO_4).2H_2O$ in a solution of 1800 mL of distilled water and 200 mL of concentrated sulfuric acid.

(b) *Ninhydrin solution*

This solution was prepared by dissolving 2 g of ninhydrin dihydrate in a solution of 600 mL of butanol and 18 mL of acetic acid. This solution was used with with nitrogen-containing compounds.

(c) *$KMnO_4$ solution*

A 10% aqueous solution of $KMnO_4$ was used with olefinic compounds.

Solvents

Hexanes, EtOAc and DCM were distilled to remove any non-volatile material for chromatography and general use.

Anhydrous solvents were dried and distilled over suitable drying agents as listed below:

Solvent	Drying agent
THF	sodium/benzophenone
DCM	calcium hydride
toluene	calcium hydride
triethylamine	calcium hydride
acetone	calcium hydride

Reagents

All reagents were purchased from Aldrich, Sigma or Lancaster, and were used without further purification, except where indicated. All commercially unavailable reagents were prepared following known procedures.

Anhydrous Reaction Conditions

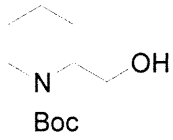
All anhydrous reactions were carried out under an atmosphere of dry nitrogen and argon. The glass vessels, luer lock syringes, needles, and stirring bars were oven-dried at 110-140 ^{0}C or flame-dried with a propane torch, and cooled to room temperature under a current of dry nitrogen. Micro-syringes were dried under vacuum using an oil pump at room temperature for at least 2 h prior to use.

Temperature Control

The temperature expressed in the reaction schemes and in the text of the experimental part are the temperatures of the outside of reaction vessels except where indicated.

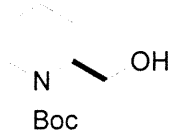
-78 °C	acetone-dry ice bath
-40 °C	acetone bath with liquid cooler
0 °C (internal)	salt-ice-water bath
0 °C	ice-water bath
room temperature	ambient temperature

3.2 Experimental notes



2-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (31)

2-(Hydroxymethyl)piperidine **30** (10 g, 87 mmol) was dissolved in THF (150 mL) and treated with aqueous 1 M K_2CO_3 (250 mL, 250 mmol) and di-*tert*-butyldicarbonate (22 mL, 96 mmol). The solution was stirred at room temperature overnight, and then 5 % aqueous HCl was added until pH = 2. The organic phase was separated and the aqueous phase was saturated with water (100 mL) and extracted twice with AcOEt (100 mL). The combined organic extracts were washed with brine (50 mL) and dried over sodium sulfate. The solvent was removed *under vacuo* and the yellow oil was purified by crystallization from MeOH-Et_2O to give the title compound **31** (17.8 g, 95 %) with identical spectroscopic data to that reported in the literature.[9g]



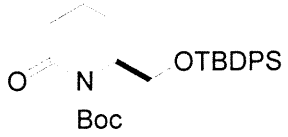
***(S)*-2-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (32)**

AA-I (36 g, 300 U/mmol) was added to a solution of *N*-Boc-2-(hydroxymethyl)piperidine **31** (6.5 g, 30 mmol) in toluene (200 mL). The mixture was stirred at room temperature for 5 minutes, and then was treated with vinyl butyrate (3.9 mL, 30 mmol). The heterogeneous suspension was stirred at room temperature for 9 h, and diluted with DCM (100 mL). The enzyme was removed by filtration and washed with DCM (50 mL). After evaporation of the solvent, the crude product was purified by flash column chromatography, eluting with a 80-20% EtOAc/Hexane solvent gradient to give a enantiomerically enriched compound **31**

(4.1 g, 63%) and a butyrate derivative (2.9 g, 33%). The product was submitted to a second enzymatic resolution using wet toluene (100 mL), AA-I (11.5 g, 300 U/mmol), and vinyl butyrate (5.0 mL, 38.5 mmol). This mixture was stirred at room temperature for 8.5 h. The same work-up and purification procedure as described above gave a butyrate derivative (1.9 g, 35%) and the enantiomeric pure alcohol **32** (4.7 g, 58%) with reported 99.6% ee. The enantiomeric pure alcohol had identical spectroscopic data and specific rotation $[\alpha]_D$ to that reported in the literature.[9g]

Reported $[\alpha]_D$ –40.5° (*c* 1.0, $CHCl_3$)

Calculated $[\alpha]_D$ –39.8° (*c* 1.0, $CHCl_3$)



(*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (33)

To a solution of compound **32** (1.9 g, 8.8 mmol) in DCM (80 mL) was added TBDPSCl (4.85 mL, 2 equiv.), imidazole (2.1 g, 3.5 equiv.) and DMAP (0.11 g, 0.1 equiv.). The mixture was vigorously stirred until the starting material was no longer detectable by TLC. The reaction mixture was poured into DCM (150 mL) after adding an aqueous solution of ammonium chloride (100 ml). The organic layer was separated and immediately washed with water (50 mL), brine (50 mL) and dried over sodium sulfate. The solvent was removed *under vacuo* and the crude oil was dissolved in EtOAc (120 mL). RuO_2 hydrate (350 mg) and 10% aqueous $NaIO_4$ (350 mL) were added to the solution and the mixture was vigorously stirred until the starting material was no longer detectable by TLC. The aqueous layer was extracted with EtOAc (75 mL). The combined organic solutions was treated with isopropyl alcohol (6 mL) for 2-3 h to decompose the RuO_4 oxidant and filtered. The filtrate was washed with water (50 mL) and dried over sodium sulfate. The solution was then filtered and evaporated *in vacuo*. The crude product was purified by flash column

chromatography, eluting with a 25-75% EtOAc/Hexane solvent gradient to give the title compound **33** (3.29 g, 80%).

$[\alpha]_D$ –32.6° (*c* 8.2 , $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.70-7.64(m, 4H), 7.45-7.35(m, 6H), 4.34-4.28(m, 1H), 3.74-3.70(d, J = 4.7 Hz, 2H), 2.48-2.45(t, 2H), 2.16-2.13(m, 1H), 1.95-1.85(m, 2H), 1.70-1.60(m, 1H), 1.45(s, 9H), 1.06(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.74(0), 152.52(0), 135.44(+), 132.93(0), 129.70(+), 127.65(+), 82.52(0), 64.08(-), 55.94(+), 34.64(-), 27.80(+), 26.68(+), 24.28(-), 19.03(0), 17.42(+)

IR: (NaCl): 3071, 3050, 2958, 2932, 2858, 1770, 1716, 1473, 1428, 1392, 1368, 1293, 1253, 1147, 1113, 1027, 926, 870, 824, 792, 772, 742, 703, 614 cm^{-1}

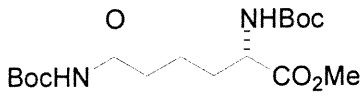
MS: 468.2 (m+1), 410.1, 368.1, 310.0, 290.1, 274.1, 232.0, 212.1, 197.0, 170.0, 135.0, 90.9

HRMS: $C_{27}H_{37}NO_4Si$, calcd.: 467.24923; found: 490.23906 (m+Na)

***(S)*-2,6-Bis-*tert*-butoxycarbonylamino-hexanoic acid methyl ester (36)**

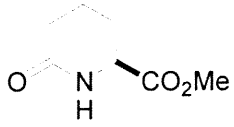
To a suspension of *(S)*-lysine monohydrochloride **35** (3.0 g, 16.4 mol) in a 0.1 molar 10% solution of triethylamine (1.5 mL) in MeOH was added di-*tert*-butyl dicarbonate (15 mL, 4 equiv.). The mixture was heated at reflux for 10 min and then left stirring for 18 h. After the solution was removed *in vacuo*, the residue was worked up in hexanes (100 mL) and water (100 mL). The hexane layer was separated and discarded. The aqueous layer was extracted with DCM (150 mL), and the extracts were combined and dried over sodium sulfate. The solvent was filtered and removed *in vacuo*. Freshly prepared diazomethane in Et_2O was distilled directly into the crude product, redissolved in DCM (50 mL) until a yellow coloration of the solution was observed. The excess diazomethane was neutralized with acetic acid **36** (added until the disappearance of the yellow coloration). The resulting

white crystalline solid (5.6 g, 95%) had identical spectroscopic data to that reported in the literature.[9h]



(*S*)-2,6-Bis-*tert*-butoxycarbonylamino-6-oxo-hexanoic acid methyl ester (37)

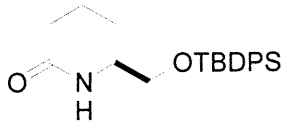
A solution of **36** (4.65 g, 12.9 mmol) in EtOAc (170 mL) was added to a mixture of RuO_2 hydrate (500 mg) and 10% aqueous $NaIO_4$ (520 mL). The mixture was vigorously stirred until the starting material was no longer detectable by TLC and the layers were separated. The aqueous layer was extracted with EtOAc (75 mL), and the combined organic layers were treated with isopropyl alcohol (6 mL) for 2-3 h to decompose the RuO_4 oxidant and the precipitate was filtered. The filtrate was washed with water (50 mL), dried over sodium sulfate, followed by the solid being filtered and evaporated *in vacuo*. The crude product was purified by flash column chromatography, eluting with a 50-50% EtOAc/ Hexanes to give the title compound **37** (4.83 g, 100%) with identical spectroscopic data to that reported in the literature.[9h]



(*S*)-6-Oxo-piperidine-2-carboxylic acid methyl ester (38)

Compound **37** (1.95 g, 5.42 mmol) was dissolved in trifluoroacetic acid (50 mL) and the solution was heated at reflux for 14 h. The solvent was removed *in vacuo*, the crude oil dissolved in DCM (90 mL), washed with 10% sodium bisulfate, brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the yellow oil was purified by flash column chromatography, eluting with EtOAc which afforded the title compound **38** as a

colorless oil (0.629 g, 77%) with identical spectroscopic data to that reported in the literature.[9h]



(*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-piperidin-6-one (39)

To a solution of ester **38** (0.81 g, 5.17 mmol) in ethanol (50 mL) was added sodium borohydride (0.25 g, 1.2 equiv.). The solution was stirred for 3.5 h at room temperature. The reaction mixture was cooled down to 0 °C and concentrated HCl was added (2 mL) until the pH was less than 3. The white precipitate was then removed by filteration through a sintered glass funnel containing silica (~ 1 inch thick), and the solid washed with EtOH (3 x 50 mL). The filtrate was concentrated under reduced pressure and the resulting oil was dissolved in toluene (50 mL). After removing the solvent under reduced pressure, the crude product was dissolved in DCM (50 mL), dried over sodium sulfate, and the solvent was removed *in vacuo* to yield the crude product as a yellow oil with identical spectroscopic data to that reported in the literature.[9h] The crude oil was used without further purification, dissolved in DCM (25 mL) and DMF (25 mL). To the solution was added TBDPSCl (2.7 mL, 2 equiv.), imidazole (1.23 g, 3.5 equiv.) and DMAP (63 mg, 0.1 equiv.). The mixture was vigorously stirred until the starting material was no longer detectable by TLC. The reaction mixture was poured into Et_2O (150 mL) after adding an aqueous solution of ammonium chloride (100 ml). The organic layer was separated, successively washed with water, brine and dried over sodium sulfate. The solvent was removed *under vacuo* and the yellow oil was purified by flash column chromatography, eluting with EtOAc to give the title compound **39** (1.59 g, 84%).

$[\alpha]_D$ –7.5° (*c* 6.0, $CHCl_3$)

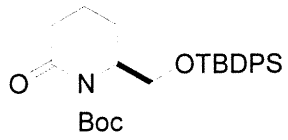
^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.70-7.64(m, 4H), 7.45-7.35(m, 6H), 6.44(b, 1H), 3.6-3.57(m, 1H), 3.52-3.46(m,2H), 2.36-2.32(m, 1H), 2.25-2.21(m, 1H), 1.78-1.59(m, 3H), 1.27-1.20(m, 1H), 1.04(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) =171.75(0), 135.35(+), 132.74(0), 129.80(+), 127.72(+), 67.34(-), 54.20(+), 31.44(-), 26.71(+), 24.24(-), 19.34(-), 19.03(0)

IR: (NaCl): 2954, 2860, 2245, 1656, 1471, 1392, 1111, 926, 823, 689, 614, 517 cm^{-1}.

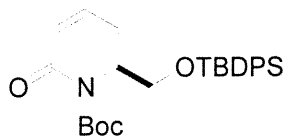
MS: 368.1 (m+1), 310.1, 290.1, 232.2, 197.1, 170.0, 132.9

HRMS: $C_{22}H_{29}NO_2Si$, calcd.: 367.19683; found: 368.20465 (m+1)



***(S)*-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (33)**

To a solution of compound **39** (2.0 g, 5.4 mmol) in acetonitrile (54 mL) was added triethylamine (1.5 mL, 2 equiv.), Boc_2O (2.5 mL, 2 equiv.) and DMAP (0.66 g, 1 equiv.). The mixture was vigorously stirred until the starting material was no longer detectable by TLC. The solvent was removed *under vacuo* and EtOAc (100 mL) was poured into the reaction mixture followed by adding an aqueous solution of ammonium chloride (100 mL). The organic layer was separated and successively washed with an aqueous solution of sodium bicarbonate (50 mL), water (50 mL), brine (50 mL) and dried over sodium sulfate. The solvent was removed *under vacuo* and the yellow oil was purified by flash column chromatography, eluting with a 25-75% EtOAc/Hexane solvent gradient to give the title compound **33** (2.15 g, 85%) with identical spectroscopic data to that reported of the above.



(*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-oxo-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (34)

To a solution of the *N*-Boc amide **33** (1.0 g, 2.15 mmol) dissolved in anhydrous THF (22 mL) at –78 °C, under an atmosphere of N_2, was added LiHMDS (2.58 mL, 1.2 equiv.) 1 M solution in THF. After 45 min, PhSeBr (0.61 g, 1.2 equiv.) dissolved in THF (5 mL) was added and the reaction mixture was left stirring at –78 °C for 1 h and warmed up to room temperature over a further period of 60 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were washed with brine and dried over sodium sulfate. After filtration and evaporation the yellow oil was dissolved in DCM (15mL) and treated with H_2O_2 (30%, 2 mL) at 0 °C. After adding drops of pyridine to pH ~ 7 the mixture was stirred at room temperature for 90 min, then quenched with saturated aqueous Na_2CO_3 (5 mL) and the aqueous layer was extracted with DCM (25 mL). The combined organic layers were washed with brine (10 mL) and dried over sodium sulfate. Filteration and removal of solvent *under vacuo,* gave a yellow oil that was purified by flash column chromatography, eluting with a 25-75% EtOAc/Hexane solvent gradient to give the title compound **34** (0.75 g, 75%).

$[\alpha]_D$ + 4.4° (*c* 2.3, $CHCl_3$)

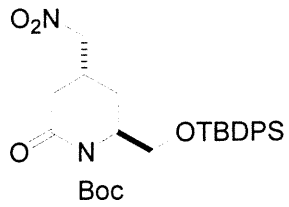
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.70-7.64(m, 4H), 7.45-7.35(m, 6H), 6.44-6.41(m, 1H), 5.84-5.82(dd, J = 2.4 Hz, 9.9 Hz, 1H), 4.61-4.57(m, 1H), 3.77-3.71(m, 2H), 2.68-2.60(m, 2H), 1.49(s, 9H), 1.04(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 162.74(0), 152.11(0), 140.39(+), 135.39(+), 132.90(0), 129.73(+), 127.68(+), 125.62(+), 82.65(0), 62.53(-), 54.15(+), 27.90(+), 26.71(+), 24.99(-), 19.06(0)

IR: (NaCl): 3073, 2961, 2860, 2250, 1760, 1711, 1634, 1472, 1393, 1296, 1244, 1155, 1113, 812, 702, 613, 505 cm^{-1}

MS: 466.3 (m+1), 388.2, 366.2, 352.2, 230.6, 135.1

HRMS: $C_{27}H_{35}NO_4Si$, calcd.: 465.23358; found: 466.24142 (m+1)



(2*S*, 4*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-nitromethyl-6-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (42)

To a solution of the *N*-Boc unsaturated amide **34** (2.0 g, 4.20 mmol) dissolved in nitromethane (40 mL, 64 equiv.) at room temperature, under an atmosphere of N_2, was added DBU (1 mL, 1.5 equiv.). The reaction was left stirring at room temperature for 2.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (25 mL) and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (25 mL) and dried over sodium sulfate, filtered and removed *under vacuo* to give a 1:1, *syn* to *anti*, diastereoisomers. The diastereoisomers were separated by flash column chromatography, eluting with a 10-90% EtOAc/Hexane solvent gradient to give the title compound **42** (0.903 g, 40%) and its diastereoisomer title compound **43** (0.903 g, 40%).

For **42**:

$[\alpha]_D$ –33.5° (*c* 2.0, $CHCl_3$)

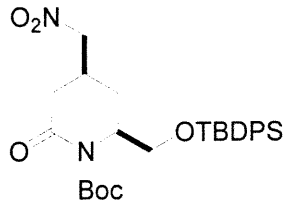
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.70-7.64(m, 4H), 7.45-7.35(m, 6H), 4.57-4.21(m, 3H), 3.79-3.71(m, 2H), 3.23-3.14(m, 1H), 2.73-2.63(m, 1H), 2.28-2.21(m, 2H), 1.75-1.67(dt, J = 5.4 Hz, 13.0Hz, 1H), 1.46(s, 9H), 1.05(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 168.67(0), 151.92(0), 135.47(+), 132.49(0), 129.89(+), 127.79(+), 83.24(0), 79.61(-), 64.36(-), 54.89(+), 37.72(-), 29.0(-), 28.81(+), 27.78(+), 26.62(+), 18.93(0)

IR: (NaCl): 3072, 1770, 1718, 1472, 1428, 1391, 1369, 1294, 1250, 1150, 1113, 1055, 938, 850, 741, 703, 614, 505 cm^{-1}

MS: 549.3 (m+Na), 522.2, 445.2, 427.3, 413.2, 291.1, 199.1, 154.1

HRMS: $C_{28}H_{38}O_6N_2SiNa$, calcd.: 549.23968; found: 549.23969 (m+Na)



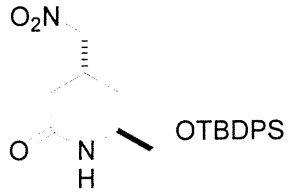
(2*S*, 4*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-nitromethyl-6-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (43)

For **43**:

$[\alpha]_D$ –32.7° (*c* 5.9, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.63-7.59(m, 4H), 7.45-7.36(m, 6H), 4.35-4.28(m, 3H), 3.87-3.84(dd, J = 4.10Hz, 10.4Hz, 1H), 3.56-3.53(dd, J = 2.15 Hz, 10.40 Hz, 1H), 2.68-2.63(m, 2H), 2.31-2.18(m, 2H), 1.78-1.69(m, 1H), 1.47(s, 9H), 1.04(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 170.07(0), 152.20(0), 135.43(+), 132.61(0), 129.80(+), 127.72(+), 83.22(-), 78.85(0), 65.42(-), 54.49(+), 38.04(-), 29.89(+), 27.77(+), 26.72(-), 26.65(+), 19.00(0)



(2*S*, 4*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-nitromethyl-piperidin-6-one (51)

To a solution of compound **42** (0.96 g, 1.80 mmol) dissolved in DCM (20 mL) at 0 °C was added TFA (1.8 mL, 13 equiv.). The mixture was left stirring at 0 °C for 30 min, quenched with saturated aqueous Na_2CO_3 (5 mL) and the aqueous layer was extracted with DCM (25 mL). The combined organic layers were washed with brine (10 mL) and dried over sodium sulfate, filtered and evaporated *under vacuo*. The crude yellow oil was purified by flash

column chromatography, eluting with 100% EtOAc to give the title compound **51** (0.66 g, 86%).

$[\alpha]_D$ +20.6° (*c* 1.6, $CHCl_3$)

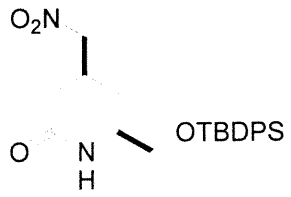
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.70-7.64(m, 4H), 7.45-7.35(m, 6H), 6.54(b, 1H), 4.35-4.26(m, 1H), 3.66-3.59(m, 1H), 3.58-3.55(s, 2H), 2.79-2.75(m, 1H), 2.54-2.48(dd, J = 5.5 Hz, 17.5 Hz, 1H), 2.18-2.12(dd, J = 7.9 Hz, 17.5 Hz, 1H), 1.81-1.75(m, 1H), 1.69-1.62(m, 1H), 1.06(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 169.23(0), 135.41(+), 132.46(0), 129.97(+), 127.82(+), 78.45(-), 66.59(-), 50.88(+), 34.40(-), 28.82(+), 26.69(+), 26.13(-), 19.02(0).

IR: (NaCl): 3072, 2931, 2858, 1670, 1553, 1472, 1428, 1382, 1341, 1113, 999, 824, 800, 742, 703 cm^{-1}

MS: 427.3 (m+1), 369.2, 349.02, 291.1, 271.2, 229.1, 199.1, 135.1

HRMS: $C_{23}H_{30}N_2O_4Si$, Calcd.: 426.19749; found : 427.20618 (m+1)



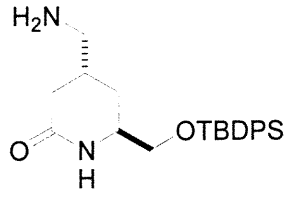
(2*S*, 4*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-nitromethyl-piperidin-6-one (53)

Using the same procedure, we obtained compound **53** (0.384 g, 90%) from **43** (0.530 g, 1.0 mmol).

$[\alpha]_D$ –20.0° (*c* 2.0, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.70-7.64(m, 4H), 7.45-7.35(m, 6H), 6.38(b, 1H), 4.33-4.26(m, 2H), 3.65-3.63(m, 2H), 3.47(t, J = 9.30 Hz, 1H), 2.78-2.62(m, 1H), 2.12-2.04(m, 1H), 1.89-1.80(m, 1H), 1.25-1.30(t, J = 4.2 Hz, 1H), 1.05(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 168.70(0), 136.13(+), 133.14(0), 130.75(+), 128.52(+), 79.99(-), 67.85(-), 54.25(+), 35.31(-), 32.09(+), 29.00(-), 27.44(+), 19.80(+)



(*2S*, 4*R*)-4-Aminomethyl-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-piperidin-6-one (52)

A solution of **51** (0.24 g, 0.56 mmol) in MeOH (6 mL) was hydrogenated over 10% Pd/C (20 mg) at 60 psi H_2. The mixture was stirred until the starting material was no longer detectable by TLC. The reaction mixture was filtered through celite®, the pad was washed with DCM (20 mL) and the solvent was removed *under vacuo* to give the desired product **52** (0.222 g, 95%).

$[\alpha]_D$ +11.8° (*c* 6.3, $CHCl_3$)

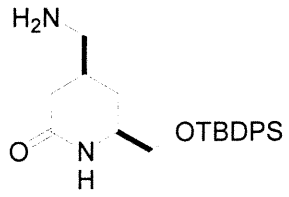
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.70-7.64(m, 4H), 7.45-7.35(m, 6H), 6.36(b, 1H), 3.63-3.44(m, 3H), 2.67-2.57(m, 2H), 2.44-2.38(dd, J = 5.4 Hz, 17.4 Hz, 1H), 2.11-1.82(m + b, 4H), 1.64-1.54(m, 2H), 1.05(s, 9H).

^{13}C-NMR (400MHz, $CDCl_3$): δ(ppm) = 171.45(0), 135.49(+), 132.86(0), 129.91(+), 127.84(+), 67.31(-), 51.42(+), 45.75(-), 35.23(-), 32.54(+), 26.82(+), 26.46(-), 19.14(0).

IR: (NaCl): 3205, 3050, 2931, 2858, 1662, 1472, 1428, 1391, 1340, 1308, 1265, 1113, 1007, 938, 824, 740, 703, 614 cm^{-1}.

MS: 397.2 (m+1), 361.2, 241.1, 197.1, 181.0, 154.1, 135.1, 121.0.

HRMS: $C_{23}H_{32}N_2O_2Si$, Calcd.: 396.59796; found : 397.23114 (m+1)



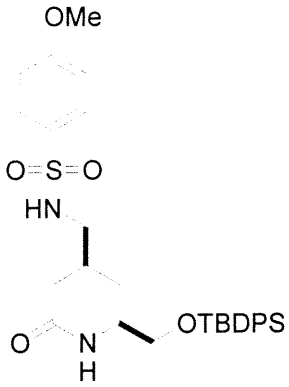
(2*S*, 4*S*)-4-Aminomethyl-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-piperidin-6-one (54)

Using the same procedure, we obtained compound **54** (0.28 g, 95 %) from **53** (0.3 g, 0.7 mmol).

$[\alpha]_D$ -3.2° (*c* 4.7, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.70-7.64(m, 4H), 7.45-7.35(m, 6H), 6.33(b, 1H), 3.65-3.55(m, 2H), 3.46-3.42(m, 1H), 3.08-2.72(b, 2H), 2.71-2.50(m, 3H), 2.03-1.93(d, J = 10.0 Hz, 1H), 1.81-1.79(d, J = 10.9 Hz, 1H), 1.04-0.85(s+m, 10H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.28(0), 135.36(+), 132.58(0), 129.85(+), 127.77(+), 67.45(-), 54.06(+), 46.42(-), 35.59(-), 34.55(-), 29.45(+), 28.51(-), 26.68(+), 19.04(0)



(2*S*, 4*S*)-*N*-[2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-oxo-piperidin-4-ylmethyl]-4-methoxy-benzenesulfonamide (66)

To a solution of **54** (50 mg, 0.13 mmol) dissolved in DCM (1 mL) was added 4-methoxy benzene sulfonyl chloride (54 mg, 2 equiv.) and triethylamine (40 µL, 2 equiv.). The mixture was left stirring at room temperature for 24 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **66** (52 mg, 70%).

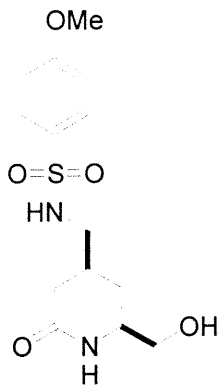
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.77-7.60(d, J = 8.9 Hz, 2H), 7.62-7.60(m, 4H), 7.42-7.37(m, 6H), 6.93-6.91(d, J = 8.9 Hz, 2H), 6.44(B, 1H), 6.22-6.19(t, J = 6.09 Hz, 1H), 3.81(s, 3H), 3.60-3.47(m, 3H), 2.81-2.76(2H, m), 2.08-1.97(m, 2H), 1.62-1.59(m, 2H), 1.03(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.13(0), 162.74(0), 135.51(+), 132.79(0), 131.50(0), 129.93(+), 129.04(+), 127.87(+), 114.26(+), 67.11(-), 60.40(-), 55.57(+), 51.11(+), 46.32(-), 34.77(-), 29.97(+), 26.80(+),19.14(0)

IR: (NaCl): 3395, 3073, 2933, 2860, 1663, 1598, 1498, 1467, 1428, 1337, 1307, 1159, 1113, 1028, 824 cm^{-1}

MS: 567.3 (m+1), 551.3, 509.3, 431.2, 411.2, 289.1, 171.0

HRMS: $C_{30}H_{38}N_2O_5SSi$, Calcd.: 566.22712; found: 567.23498 (m+1)



(2*S*, 4*S*)-*N*-(2-Hydroxymethyl-6-oxo-piperidin-4-ylmethyl)-4-methoxy-benzene sulfonamide (76)

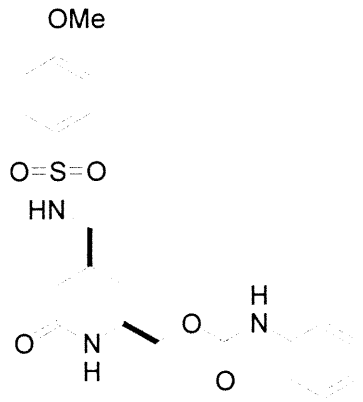
To a solution of **66** (137 mg, 0.24 mmol) dissolved in THF (3 mL) was added a 1 M solution of TBAF (0.5 mL, 2 equiv.) in THF. The mixture was left stirring at room

temperature for 2 h. The reaction mixture was purified directly by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **76** (71 mg, 90%).

^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 7.80-7.78(d, J = 8.9 Hz, 2H), 7.09-7.07(d, J = 8.90 Hz, 2H), 3.87(s, 3H), 3.52-3.47(m, 3H), 2.81-2.78(m, 2H), 2.40-2.34(dd, J = 4.80 Hz, 17.06 Hz, 1H), 2.16-2.09(m, 1H), 2.06-1.99(dd, J = 9.43 Hz, 16.24 Hz, 1H), 1.84-1.81(d, J = 14.04 Hz, 1H), 1.61-1.57(m, 1H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 176.77(0), 166.90(0), 135.77(0), 132.65(+), 117.93(+), 68.22(-), 58.77(+), 55.25(+), 50.32(-), 38.09(-), 33.22(+), 29.73(-)

IR: (NaCl): 3274, 2928, 2397, 1627, 1597, 1498, 1460, 1413, 1328, 1260, 1154, 1094, 1024, 835, 735, 668, 562 cm^{-1}



(2*S*, 4*S*)-Phenyl-carbamic acid 4-[(4-methoxy-benzenesulfonylamino)-methyl]-6-oxo-piperidin-2-ylmethyl ester (77)

To a solution of **76** (19 mg, 0.05 mmol) dissolved in pyridine (0.5 mL) under an atmosphere of N_2 was added phenyl isocyanate (14 μL, 2.5 equiv.). The reaction mixture was heated to 80 °C and left stirring for 16 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **77** (19 mg, 85%).

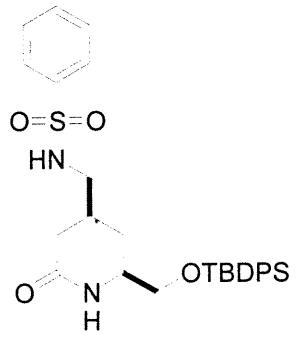
^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 7.80-7.78(d, J = 8.9 Hz, 2H), 7.44-7.42(d, J = 8.14 Hz, 2H), 7.30-7.26(m, 2H), 7.13-7.01(m, 2H), 4.23-4.19(dd, J = 4.2 Hz, 11.12Hz, 1H), 4.06-4.02(dd, J = 5.5 Hz, 11.14 Hz, 1H), 3.87(s, 3H), 3.62-3.70(m, 1H), 3.33-3.14(s, 2H), 2.82-2.81(d, J = 5.44 Hz, 1H), 2.03-1.96(m, 2H), 1.30-1.22(m, 2H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 174.01, 164.20, 155.67, 139.7, 133.4, 130.50, 129.60, 123.93, 119.61, 115.21, 67.61, 55.93, 52.84, 35.66, 33.65, 30.54, 28.60

IR: (NaCl): 2358, 1724, 1634, 1598, 1503, 1463, 1418, 1325, 1258, 1152, 1091, 1023, 835, 755, 691, 668 cm^{-1}

MS: 448.1 (m+1), 307.1, 289.0, 154.0

HRMS: $C_{21}H_{25}N_3O_6S$, Calcd.: 447.14643; found : 448.15421 (m+1)



(2*S*, 4*S*)-*N*-[2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-oxo-piperidin-4-ylmethyl]-benzenesulfonamide (67)

To a solution of **54** (100 mg, 0.25 mmol) dissolved in acetonitrile (2.5 mL) was added sulfonyl benzene chloride (80 μL, 2.5 equiv.) and triethylamine (87 μL, 2.5 equiv.). The reaction was left stirring at room temperature for 48 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with a 100% EtOAc solvent gradient to give the title compound **67** (93 mg, 70%).

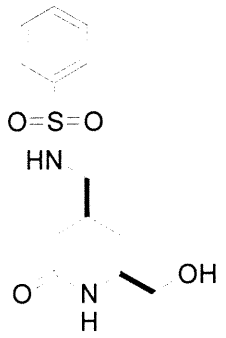
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.84-7.82(d, J =7.13 Hz, 2H), 7.63-7.52(m, 4H), 7.48-7.36(m, 9H), 6.42(b, 1H), 6.22-6.19(b, 1H), 3.59-3.42(m, 3H), 2.84-2.80(m, 2H), 2.38-2.33(dd, J = 4.1 Hz, 16.23 Hz, 1H), 2.08-2.00(m, 2H), 1.61-1.58(m, 2H), 1.04(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.07(0), 140.00(0), 135.52(+), 132.77(0), 132.60(+), 129.95(+), 129.14(+), 127.88(+), 126.86(+), 67.10(-), 51.13(+), 46.38(-), 34.71(-), 30.02(+), 26.80(+), 26.07(-), 19.14(0)

IR: (NaCl): 3314, 3072, 2999, 2931, 2859, 2248, 1963, 1897, 1824, 1650, 1472, 1328, 1247, 1161, 1113, 1008, 910, 824, 734, 704, 614, 584, 505 cm^{-1}

MS: 537.3 (m+1), 479.2, 401.2, 381.2, 307.1, 267.1, 224.1, 191.1, 154.1, 137,1

HRMS: $C_{29}H_{36}N_2O_4SSi$, Calcd.: 536.21653; found : 537.22438 (m+1)



(2*S*, 4*S*)-*N*-(2-Hydroxymethyl-6-oxo-piperidin-4-ylmethyl)-benzenesulfonamide (86)

To a solution of **67** (93 mg, 0.17 mmol) dissolved in THF (2 mL) was added a 1 M solution of TBAF (0.35 mL, 2 equiv.) in THF. The mixture was left stirring at room temperature for 2 h. The reaction mixture was directly purified by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **86** (46 mg, 90%).

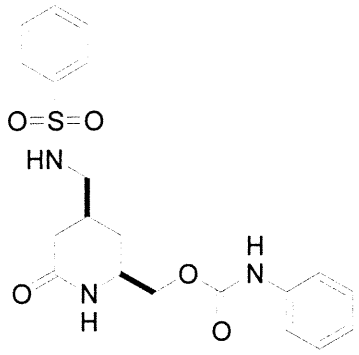
^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 7.87-7.85(d, J = 6.11 Hz, 2H), 7.63-7.56(m, 3H), 3.50-3.41(m, 3H), 2.77-2.84(m, 2H), 2.39-2.35(dd, J = 3.94 Hz, 15.8Hz, 1H), 2.13-2.00(m, 2H), 1.85-1.81(m, 1H), 1.65-1.58(m, 1H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 176.75(0), 144.39(0), 136.22(+), 132.84(+), 130.44(+), 68.21(-), 55.24(+), 50.33(-), 38.04(-), 33.29(+), 29.71(-)

IR: (NaCl): 3273, 2927, 2366, 1629, 1447, 1413, 1324, 1157, 1092, 1053, 756, 720, 690, 584 cm^{-1}

MS: 299.2 (m+1), 289.2, 267.2, 167.2, 154.2, 136.1, 123.1, 109.1, 95.0

HRMS: $C_{13}H_{18}N_2O_4S$, Calcd.: 298.09872; found : 299.10727 (m+1)



(2*S*, 4*S*)-Phenyl-carbamic acid 4-(benzenesulfonylamino-methyl)-6-oxo-piperidin-2-yl methyl ester (87)

To a solution of **86** (10 mg, 0.03 mmol) dissolved in pyridine (0.3 mL) under an atmosphere of N_2 was added phenyl isocyanate (9 µL, 2.5 equiv.). The reaction mixture was heated to 80 °C and left stirring for 16 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **87** (12 mg, 92%).

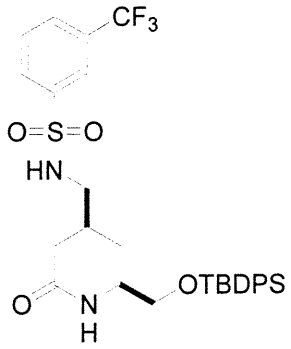
^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 7.88-7.85(m, 2H), 7.65-7.55(m, 3H), 7.45-7.43(d, J = 7.89 Hz, 2H), 7.31-7.26(m, 2H), 7.05-7.01(m, 1H), 4.12-4.04(m, 2H), 3.75-3.72(m, 1H), 2.84-2.82(d, J = 6.79 Hz, 2H), 2.43-2.37(dd, J = 4.48 Hz, 17.15 Hz, 2H), 2.28-2.17(m, 1H), 2.07-2.02(dd, J = 9.08 Hz, 14.19 Hz, 1H), 2.00-1.88(m, 1H), 1.72-1.64(m, 1H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 176.72(0), 157.02(0), 144.56(0), 142.25(0), 136.21(+), 132.82(+), 132.37(+), 130.44(+), 126.72(+), 122.41(+), 70.07(-), 52.82(+), 50.30(-), 37.99(-), 33.23(+), 30.04(-)

IR: (NaCl): 3274, 3066, 2926, 2856, 2364, 1729, 1648, 1601, 1540, 1504, 1446, 1418, 1326, 1230, 1159, 1091, 1030, 755, 690 cm^{-1}

MS: 418.3 (m+1), 397.5, 307.3, 176.1, 154.1, 136.1

HRMS: $C_{20}H_{23}N_3O_5S$, Calcd.: 417.13589; found : 418.14374 (m+1)



(2*S*, 4*S*)-*N*-[2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-oxo-piperidin-4-ylmethyl]-3-trifluoromethyl-benzenesulfonamide (68)

To a solution of **54** (100 mg, 0.25 mmol) dissolved in acetonitrile (2.5 mL) was added 3-(trifluoromethyl) sulfonyl benzene chloride (0.1 mL, 2.5 equiv.) and triethylamine (87 µL, 2.5 equiv.). The reaction was left stirring at room temperature for 48 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with 100% EtOAc to give the title compound **68** (87 mg, 72%).

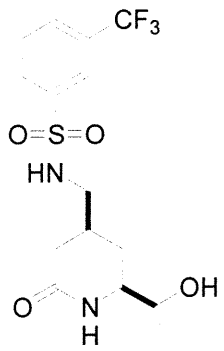
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 8.13(s,1H), 8.05-8.03(d, J = 7.9 Hz), 7.81-7.79(d, J = 7.77 Hz, 1H), 7.64-7.61(m, 5H), 7.45-7.36(m, 6H), 6.51-6.48(t, J = 6.13 Hz, 1H), 6.42(b, 1H), 3.61-3.47(m, 3H), 2.90-2.82(m, 2H), 2.42-2.37(dd, J = 4.18 Hz, 16.44 Hz, 1H), 2.16-2.08(m, 2H), 1.65-1.61(m, 2H), 1.04(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.16(0), 141.44(0), 135.51(+), 135.48(+), 132.71(0), 131.88(0), 131.55(0), 130.13(+), 129.95(+), 129.16(+), 127.88(+), 123.97(+), 67.10(-), 51.20(+), 46.35(-), 34.51(-), 30.17(+), 26.77(+), 26.18(-), 19.12(0)

IR: (NaCl): 3321, 3073, 2931, 2860, 2249, 1964, 1896, 1825, 1651, 1472, 1428, 1327, 1163, 1107, 1072, 999, 910, 824, 739, 702, 652, 614, 587, 504 cm^{-1}

MS: 605.4 (m+1), 577.7, 549.6, 176.1, 155.1, 137.1

HRMS: $C_{30}H_{35}F_3N_2O_4SSi$, Calcd.: 604.20398; found: 605.21175 (m+1)



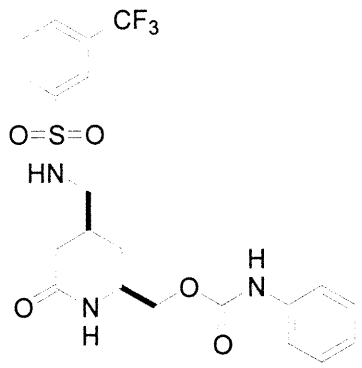
(2*S*, 4*S*)-*N*-(2-Hydroxymethyl-6-oxo-piperidin-4-ylmethyl)-3-trifluoromethylbenzene sulfonamide (96)

To a solution of **68** (50 mg, 0.08 mmol) dissolved in THF (1 mL) was added a 1 M solution of TBAF (0.16 mL, 2 equiv.) in THF. The mixture was left stirring at room temperature for 2 h. The reaction mixture was directly purified by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **96** (26 mg, 90%).

^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 8.20-8.12(m, 2H), 7.96-7.94(dd, J = 0.58 Hz, 0.62 Hz, 1H), 7.83-7.79(m, 1H), 3.50-3.45(m, 3H), 2.91-2.83(m, 2H), 2.41-2.36(dd, J = 3.94 Hz, 15.8 Hz, 1H), 2.18-2.02(m, 2H), 1.87-1.82(m, 1H), 1.66-1.59(m, 1H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 174.11(0), 143.45(+), 132.05(0), 131.88(0), 131.57(+), 130.21(+), 123.22(0), 124.66(+), 65.68(-), 52.70(+), 47.77(-), 35.44(-), 30.86(+), 27.18(-)

IR: (NaCl): 3288, 2930, 2454, 2071, 1642, 1453, 1434, 1328, 1163, 1132, 1107, 1071, 806, 696, 653, 589 cm^{-1}



(2*S*, 4*S*)-Phenyl-carbamic acid 6-oxo-4-[(3-trifluoromethyl-benzenesufonylamino)-methyl]-piperidin-2-ylmethyl ester (97)

To a solution of **96** (8 mg, 0.02 mmol) dissolved in pyridine (0.2 mL) under an atmosphere of N_2 was added phenyl isocyanate (6 μL, 2.5 equiv.). The reaction mixture was heated to 80 °C and left stirring for 16 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **97** (9 mg, 92%).

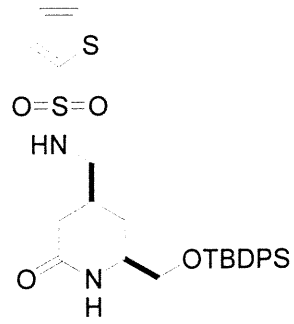
^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 8.14-8.11(m, 2H), 7.95-7.93(d, J = 7.48 Hz, 1H), 7.81-7.77(t, J = 7.82 Hz, 1H), 7.44-7.42(d, J = 7.87 Hz, 2H), 7.29-7.25(t, J = 7.56 Hz, 2H), 7.04-7.01(t, J = 7.41 Hz, 1H), 4.23-4.19(dd, J = 4.1 Hz, J = 11.15 Hz, 1H), 4.05-4.02(dd, J = 5.59 Hz, J = 11.07 Hz, 1H), 3.70-3.64(m, 1H), 2.88-2.86(d, J = 5.67 Hz, 2H), 2.40-2.37(d, J = 14.23 Hz, 1H), 2.07-1.95(m, 3H), 1.29-1.21(m, 1H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 176.95, 157.22, 145.99, 142.49, 135.95, 135.65, 134.11, 132.75, 132.37, 127.22, 126.71, 125.91, 122.34, 70.37, 55.56, 50.88, 38.32, 36.51, 32.22

IR: (NaCl): 3245, 3072, 2929, 2858, 2361, 1734, 1652, 1601, 1547, 1503, 1464, 1447, 1428, 1327, 1222, 1163, 1133, 1112, 1072, 1030, 999, 939, 904, 824 cm^{-1}

MS: 486.2 (m+1), 458.3, 391.3, 335.1, 307.1, 154.1

HRMS: $C_{21}H_{22}F_3N_3O_5S$, Calcd.: 485.12326; found: 486.12762 (m+1)



(2*S*, 4*S*)-Thiophene-2-sulfonic acid [2-(*tert*-butyl-diphenyl-silanyloxymethyl)-6-oxo-piperidin-4-ymethyl]-amide (72)

To a solution of **54** (135 mg, 0.34 mmol) dissolved in acetonitrile (1 mL) was added sulfonyl thiophene chloride (0.25 g, 4 equiv.) and triethylamine (0.1 mL, 2 equiv.). The mixture was left stirring at room temperature for 48 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with 100% EtOAc to give the title compound **72** (140 mg, 76%).

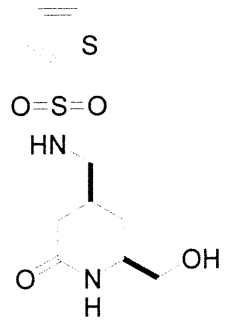
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.63-7.62(m, 4H), 7.56-7.55(dd, J = 1.28 Hz, 1H), 7.50-7.48(dd, J = 1.28 Hz, 5.00 Hz, 1H), 7.45-7.37(m, 6H), 7.03-7.01(dd, J = 3.77 Hz, 4.98Hz), 6.58(b, 1H), 6.52(s, 1H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.42(0), 141.05(0), 135.55(+), 132.65(+), 131.88(+), 131.71(+), 129.98(+), 127.91(+), 127.85(+), 67.42(-), 54.05(+), 47.74(-), 35.37(-), 32.63(+), 28.39(-), 26.80(+), 19.16(0)

IR: (NaCl): 3400, 3072, 2931, 2858, 1964, 1895, 1826, 1651, 1472, 1428, 1338, 1266, 1227, 1156, 1113, 1015, 938, 856, 824, 796, 739, 614, 505 cm^{-1}

MS: 543.2 (m+1), 485.1, 407.1, 369.4, 307.1

HRMS: $C_{27}H_{34}N_2O_4S_2Si$, Calcd.: 542.17298; found : 543.18074 (m+1)



(2*S*, 4*S*)-Thiophene-2-sulfonic acid (2-hydroxymethyl-6-oxo-piperidin-4-ylmethyl)-amide (105)

To a solution of **72** (140 mg, 0.26 mmol) dissolved in THF (3 mL) was added a 1 M solution of TBAF (0.5 mL, 2 equiv.) in THF. The mixture was left stirring at room temperature for 2 h. The reaction mixture was directly purified by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **105** (71 mg, 90%).

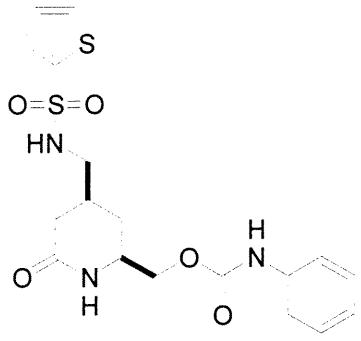
^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 7.79-7.78(dd, J = 1.32 Hz, J = 5.02 Hz, 1H), 7.62-7.61(dd, J = 1.32 Hz, J = 3.73 Hz, 1H), 7.17-7.15(dd, J = 3.74 Hz, J = 5.01 Hz), 3.51-3.43(m, 3H), 2.93-2.87(m, 2H), 2.43-2.37(m, 1H), 2.17-2.12(m, 1H), 2.08-2.02(dd, J = 8.62 Hz, J =17.21 Hz, 1H), 1.88-1.83(m, 1H), 1.67-1.60(m, 1H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 176.57(0), 145.20(0), 135.42(+), 135.23(+), 130.92(+), 68.06(-), 55.11(+), 48.50(-), 37.92(-), 33.07(+), 29.61(-)

IR: (NaCl): 3098, 2924, 2363, 1636, 1457, 1405, 1336, 1226, 1156, 1065, 1016, 724, 668 cm^{-1}

MS: 305.1(m+1); 289.1, 241.1, 221.1, 197.1, 154.1

HRMS: $C_{11}H_{16}N_2O_4S_2$, Calcd.: 304.05528; found : 305.06304 (m+1)



(2*S*, 4*S*)-Phenyl-carbamic acid 4-(benzenesulfonylamino-methyl)-6-oxo-piperidin-2-ylm ethyl ester (106)

To a solution of **105** (18 mg, 0.06 mmol) dissolved in pyridine (0.6 mL) under an atmosphere of N_2 was added phenyl isocyanate (16 μL, 2.5 equiv.). The reaction mixture was heated to 80 °C and left stirring for 16 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **106** (21 mg, 82%).

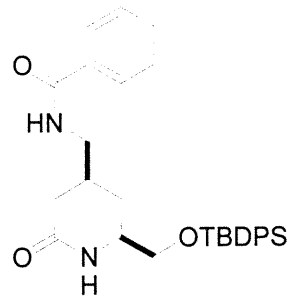
^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 7.78-7.76(dd, J = 1.32 Hz, J = 4.96 Hz, 1H), 7.62-7.61(dd, J = 1.35 Hz, J = 3.73 Hz, 1H), 7.44-7.42(d, J = 7.65 Hz, 2H), 7.30-7.26(m, 2H), 7.16-7.14(dd, J = 3.73 Hz, J = 5.02 Hz, 1H), 7.05-7.03(m, 1H), 4.23-4.20(m, 1H), 4.13-4.06(m, 2H), 3.70-3.66(dd, J = 5.14 Hz, 11.16 Hz, 1H), 2.92-2.91(d, J = 5.93 Hz, 2H), 2.41-2.38(dd, J = 2.16 Hz, 12.59 Hz, 1H), 2.07-1.95(m, 1H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 177.00(0), 157.93(0), 145.70(0), 142.50(0), 135.55(+), 135.39(+), 132.38(+), 131.06(+), 126.72(+), 122.36(+), 70.39(-), 55.59(+), 52.16(-), 38.41(-), 36.36(+), 32.29(-)

IR: (NaCl): 3268, 2923, 2360, 1732, 1652, 1600, 1545, 1502, 1446, 1406, 1316, 1225, 1156, 1087, 1017, 854, 735, 694, 519 cm^{-1}

MS: 424.1 (m+1), 391.3, 307.1, 289.1, 154.1, 136.0

HRMS: $C_{18}H_{21}N_3O_5S_2$, Calcd.: 423.09239; found : 424.10016 (m+1)



(2*S*, 4*S*)-1-[2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-oxo-piperidine-4-ylmethyl]-benzamide (74)

To a solution of **54** (30 mg, 0.075 mmol) dissolved in DCM (0.75 mL) was added benzoyl chloride (11 µL, 1.2 equiv.) and the reaction was left stirring at room temperature for 18 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with 100% EtOAc to give the title compound **74** (32 mg, 86%).

$[\alpha]_D$ –5.8° (*c* 15.1, $CHCl_3$)

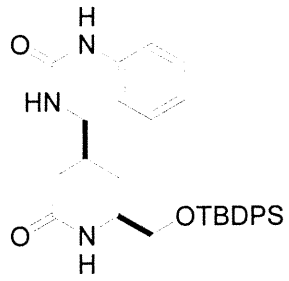
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.76-7.74(d, J = 8.6 Hz, 2H), 7.64-7.60(m, 4H), 7.45-7.37(m, 9H), 6.95(b, 1H), 6.27(b, 1H), 3.62-3.51(m, 2H), 3.43-3.62(m, 3H), 2.52-2.47(dd, J = 2.8 Hz, 17.1 Hz, 1H), 2.18-2.16(m, 1H), 2.02-1.96(dd, J = 11.0 Hz, 16.3 Hz, 2H), 1.79-1.76(m, 1H), 1.04(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 168, 45(0), 165.35(0), 132.91(+), 131.67(0), 130.12(0), 129.01(+), 127.44(+), 125.95(+), 125.34(+), 124.45(+), 65.07(-), 51.54(+), 41.95(-), 33.28(-), 30.35(+), 26.24(-), 24.25(+), 16.60(0)

IR: (NaCl): 3458, 3396, 3073, 2932, 2860, 2360, 2247, 1656, 1519, 1428, 1280, 1280, 1113, 896, 823, 796 cm^{-1}

MS: 501.2 (m+1), 443.1, 423.1, 307.0, 289.0, 231.1, 197.1

HRMS: $C_{30}H_{36}N_2O_3Si$, Calcd.: 500.24096; found : 501.25748 (m+1)



(2*S*, 4*S*)-1-[2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-oxo-piperidine-4-ylmethyl]-3-phenyl-urea (75)

To a solution of **54** (30 mg, 0.075 mmol) dissolved in DCM (0.75 mL) was added phenyl isocyanate (20 μL, 2.5 equiv.) and the reaction was left stirring at room temperature for 18 h. The solvent was removed *under vacuo* and the resulting product was purified by flash column chromatography, eluting with 100% EtOAc to give the title compound **75** (35 mg, 90%).

$[\alpha]_D$ –5.4° (*c* 10.4, $CHCl_3$)

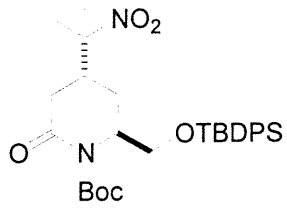
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.89(b, 1H), 7.64-7.62(m, 4H), 7.46-7.34(m, 8H), 7.21-7.17(t, J = 7.5 Hz, 2H), 6.94-6.90(t, J =7.0 Hz, 1H), 6.43(b, 1H), 6.12(b, 1H), 3.65-3.62(dd, J = 3.1 Hz, 10.0 Hz, 1H), 3.55-3.50(m, 1H), 3.46-3.35(m, 1H), 2.95-2.92(m, 1H), 2.58-2.54(d, J = 15.3 Hz, 1H), 1.07-0.89(m + s, 10H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.83, 156.10, 139.42, 135.34, 132.44, 130.00, 128.82, 127.84, 122.24, 118.84, 67.27, 54.08, 44.26, 35.93, 32.82, 28.28, 26.72, 19.07

IR: (NaCl): 3395, 3073, 2932, 2860, 2247, 1646, 1553, 1500, 1312, 1232, 1114, 823, 704, 652 cm^{-1}

MS: 516.2 (m+1), 458.1, 307.0, 154.0

HRMS: $C_{30}H_{37}N_3O_3Si$, Calcd.: 515.26048; found : 516.26835 (m+1)



(2*S*, 4*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-(1-methyl-1-nitro-ethyl)-6-oxo-piperidine-1-carboxylic acid *tert*-bytl ester (44)

To a solution of compound **34** (0.1 g, 0.21 mmol) dissolved in 2-nitropropane (2 mL, 111 equiv.) at room temperature, under an atmosphere of N_2, was added DBU (49 µL, 1.5 equiv.). The mixture was left stirring at room temperature for 6 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and the aqueous layer was extracted with EtOAc (10 mL) . The combined organic layers were washed with brine (5 mL) and dried over sodium sulfate, filtered and removed *under vacuo* to give a yellow crude oil which was purified by flash column chromatography, eluting with a 25-75% EtOAc/Hexane solvent gradient to give the title compound **44** (84 mg, 70%).

$[\alpha]_D$ –7.5° (*c* 4.0, $CHCl_3$)

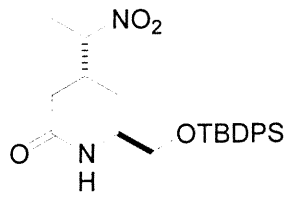
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.68-7.63(m, 4H), 7.44-7.26(m, 6H), 4.35-4.32(m, 1H), 3.78-3.66(m, 2H), 3.13-3.08(m, 1H), 2.60-2.54(m, 1H), 2.33-2.26(dd, J = 11.78 Hz, J = 16.94 Hz, 1H), 2.13-2.09(dd, J = 2.70 Hz, J = 13.39 Hz, 1H), 1.56(s, 6H), 1.43(S, 9H), 1.05(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 169.35(0), 151.78(0), 135.46(+), 132.50(0), 129.83(+), 127.74(+), 89.98(0), 83.16(0), 64.11(-), 54.72(+), 37.41(+), 35.88(-), 27.74(+), 26.34(-), 26.34(-), 26.59(+), 23.21(+), 21.94(+), 18.91(0)

IR: (NaCl): 3426, 3073, 3059, 2932, 2859, 1770, 1717, 1590, 1539, 1472, 1428, 1393, 1369, 1346, 1291, 1250, 1151, 1112, 1087, 1053, 1027, 998, 890, 882, 852, 823, 778, 743, 704, 614 cm^{-1}

MS: 555.3 (m+1), 517.2, 477.3, 455.3, 441.2, 408.3, 366.2, 319.1, 307.1, 272.1, 230.1

HRMS: $C_{30}H_{42}N_2O_6Si$, Calcd.: 554.28122; found: 555.28906 (m+1)



(2*S*, 4*R*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-(1-methyl-1-nitro-ethyl)-piperidin-6-one (55)

To a solution of the compound **44** (80 mg, 0.14 mmol) dissolved in DCM (1.5 mL) at 0 °C was added TFA (0.15 mL, 13 equiv.). The mixture was left stirring at 0 °C for 30 min. The reaction mixture was quenched with saturated aqueous Na_2CO_3 (1 mL) and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were washed with brine (5 mL) and dried over sodium sulfate, filtered and removed *under vacuo*. The crude yellow oil was purified by flash column chromatography, eluting with EtOAc to give the title compound **55** (54 mg, 85%).

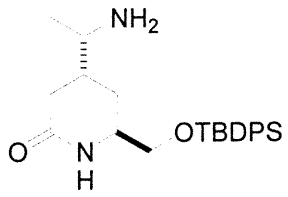
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.65-7.62(m, 4H), 7.47-7.39(m, 6H), 6.37(b, 1H), 3.61-3.51(m, 3H), 2.62-2.58(m, 1H), 2.40-2.34(m, 1H), 2.13-2.06(dd, J = 12.42 Hz; 16.9 Hz; 1H), 1.78-1.75(m, 1H), 1.63-1.54(m+s, 4H), 1.53(s, 3H), 1.06(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 170.40(0), 135.38(+), 132.51(0), 129.89(+), 127.77(+), 89.92(0), 66.08(-), 51.28(+), 37.20(+), 32.94(+), 26.63(+), 24.49(-), 23.66(-), 21.74(+), 18.97(+)

IR: (NaCl): 3213, 3072, 2931, 2858, 1669, 1590, 1539, 1472, 1428, 1400, 1375, 1346, 1320, 1265, 1187, 1113, 1047, 998, 926, 853, 824, 800, 705, 703, 614 cm^{-1}

MS: 455 (m+1), 291, 221, 199, 154, 136

HRMS: $C_{25}H_{34}N_2O_4Si$, Calcd.: 454.22879; found: 455.23660 (m+1)



(2*S*, 4*R*)-4-(1-Amino-1-methyl-ethyl)-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-piperidin-6-one (56)

A solution of **55** (18 mg, 0.04 mmol) in MeOH (1 mL) was hydrogenated over 10% Pd/C (5 mg) at 60 psi H_2. The mixture was stirred until the starting material was no longer detectable on a TLC plate. The reaction mixture was filtered through celite® and the pad was washed with DCM (5 mL). The solvent was removed *under vacuo* and the resulting product **56** (16 mg, 95%) was used without further purification.

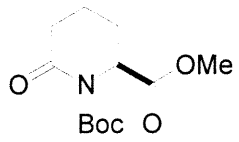
$[\alpha]_D$ +36.5° (*c* 1.7, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.65-7.62(m, 4H), 7.44-7.26(m, 6H), 6.23(B, 1H), 3.57-3.54(m, 3H), 2.45-2.40(dd, J = 4.65, 16.96 Hz, 1H), 1.88-1.81(dd, J = 12.00 Hz, 16.96 Hz, 1H), 1.89-1.86(d, J = 13.52, 1H), 0.99(s, 3H), 0.97(s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 172.43(0), 135.36(+), 132.69(0), 129.78(+), 127.71(+), 66.65(-), 51.88(+), 50.54(0), 39.32(+), 33.29(-), 28.27(+), 27.31(+), 26.66(+), 24.01(-), 18.99(0)

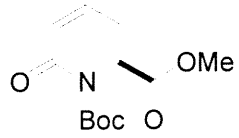
IR: (NaCl): 3206, 3072, 3050, 2961, 2931, 2858, 2360, 2240, 1666, 1538, 1472, 1428, 1390, 1365, 1189, 1113, 910, 824, 737, 703, 614

HRMS: $C_{25}H_{36}N_2O_2Si$, Calcd.: 424.25460; found: 425.26242 (m+1)



***(S)*-6-Oxo-piperidine-1-carboxylic acid *tert*-butyl ester 2-carboxylic acid methyl ester (40).**

To a solution of **38** (2.5 g, 15.92 mmol) in DCM (16 mL) was added triethylamine (4.3 mL, 2 equiv.), Boc_2O (7.31 mL, 2 equiv.) and DMAP (1.94 g, 1 equiv.). The mixture was vigorously stirred until the starting material was no longer detectable on a TLC plate. The solvent was removed *under vacuo* and the residue was dissolved in EtOAc (50 mL) and extracted with an aqueous solution of ammonium chloride (50 mL). The organic layer was separated and washed with an aqueous solution of sodium bicarbonate (25 mL), water (25 mL), brine (25 mL) and dried over sodium sulfate. The solvent was removed *under vacuo* and the yellow oil was purified by flash column chromatography, eluting with a 50-50% EtOAc/Hexane solvent gradient to give the title compound **40** (3.68 g, 90%) with identical spectroscopic data to that reported in the literature.[9h]



(*S*)-6-Oxo-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 2-carboxylic acid methyl ester (41)

To a solution of compond **40** (1.0 g, 3.92 mmol) dissolved in anhydrous THF (35 mL) at –78 °C, under an atmosphere of N_2, was added LiHMDS (4.70 mL, 1.2 equiv.) 1 M solution in THF. After 45 min, PhSeBr(1.11 g, 1.2 equiv.) dissolved in THF (10 mL) was added to the reaction mixture. The reaction was left stirring at –78 °C for 1 h and warmed up to room temperature over a further period of 60 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Once filtered and removed *under vacuo,* the yellow oil was used without further purification. This material was dissolved in DCM (15 mL) and treated with H_2O_2 (30%, 2 mL) at 0 °C. After adding drops of pyridine to pH ~ 7 and the mixture was stirred at room temperature for 90 min, then treated with saturated aqueous Na_2CO_3 (5 mL), and the aqueous layer was extracted with DCM (35 mL). The combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. Filteration and removal of solvent gave a yellow oil

which was purified by flash column chromatography, eluting with a 50-50% EtOAc/Hexane solvent gradient to give the title compound **41** (0.75 g, 75%).

$[\alpha]_D$ +31.0° (*c* 2.0, $CHCl_3$)

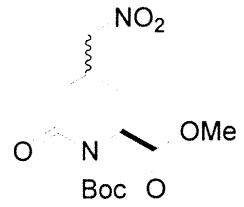
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 6.57-6.52(m, 1H), 5.89-5.85(m, 1H), 4.99-4.97(dd, J = 1.16 Hz, 6.49 Hz, 1H), 3.66(s, 3H), 1.46(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 170.92(0), 162.12(0), 152.09(0), 139.68(+), 126.30(+), 83.39(0), 55.40(+), 52.67(+), 27.76(+), 26.99(-)

IR: (NaCl): 3627, 3539, 3408, 2981, 2600, 2386, 2253, 1714, 1632, 1476, 1458, 1438, 1399, 1369, 1292, 1154, 1088, 1048, 1007, 983, 961, 924, 895, 854, 815, 778, 756, 648, 593 cm^{-1}

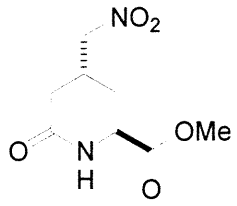
MS: 255.1 (m), 200.6, 191.1, 172.0, 156.6, 96.0

HRMS: $C_{12}H_{17}NO_5$, Calcd.: 255.11067; found: 255.11187 (m)



(2*S*, 4*RS*)-4-Nitromethyl-6-oxo-piperidine-1-carboxylic acid tert-butyl ester 2-carboxylic acid methyl ester (57)

To a solution of **41** (0.85 g, 3.32 mmol) dissolved in nitromethane (35 mL, 195 equiv.) at room temperature, under an atmosphere of N_2, was added DBU (0.65 mL, 1.3 equiv.). The reaction was left stirring at room temperature for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (25 mL) and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (25 mL) and dried over sodium sulfate, filtered and removed *under vacuo* to give a 3:1, *anti* to *syn*, non-separable diastereoisomers. The diastereoisomers were purified by flash column chromatography, eluting with a 50-50% EtOAc/Hexane solvent gradient to give the non-separable title compound **57** (0.84 g, 80%).



(2*S*, 4*R*)-4-Nitromethyl-6-oxo-piperidine-2-carboxylic acid methyl ester (58)

To a solution of compound **57** (70 mg, 0.22 mmol) dissolved in DCM (4 mL) at 0 ^{0}C was added TFA (0.22 mL, 13 equiv.). The mixture was left stirring at 0 ^{o}C for 25 min, then quenched with saturated aqueous Na_2CO_3 (1 mL) and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were washed with brine (5 mL) and dried over sodium sulfate. Once filtered, the solvent was removed *under vacuo* to give the 3:1, *anti* to *syn*, mixture of diastereoisomers which were now separable by flash column chromatography. Eluting with a 85-15% EtOAc/Hexane solvent gradient we obtained the *anti* **58** (25 mg, 60%) and syn **59** (8 mg, 20%).

Note: Compound **59** was never characterized.

For **58**:

$[\alpha]_D$ +20.0^o (*c* 1.3, $CHCl_3$)

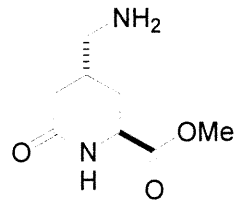
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 6.50(b, 1H), 4.38-4.37(d, J = 7.01Hz, 2H), 4.24-4.22(m, 1H), 3.80(s, 3H), 2.80-2.75(m, 1H), 2.64-2.57(m, 1H), 2.33-2.29(d, J = 13.58 Hz,1H), 2.22-2.15(dd, J = 10.30 Hz, 17.51 Hz, 1H), 1.96-1.88(m, 1H)

^{13}C-NMR (400MHz, $CDCl_3$): δ(ppm) = 171.07(0), 168.95(0), 78.43(-), 52.92(+), 52.54(+), 34.18(-), 29.08(+), 27.53(-)

IR: (NaCl): 3362, 2958, 2360, 1741, 1667, 1551, 1436, 1378, 1335, 1217, 1151, 1121, 1062, 1012, 971, 911

MS: 217.0 (m+1), 186.0, 157.0

HRMS: $C_8H_{12}N_2O_5$, Calcd.: 216.07462; found: 217.08201 (m+1)



(2*S*, 4*R*)-4-Aminomethyl-6-oxo-piperidine-2-carboxylic acid methyl ester (60)

A solution of **58** (50 mg, 0.23 mmol) in MeOH (2 mL) was hydrogenated over 10% Pd/C (5 mg) at 60 psi H_2. The mixture was stirred until the starting material was no longer detectable on a TLC plate. The reaction mixture was filtered through celite® and the pad was washed with DCM (5 mL). The solvent was removed *under vacuo* and the resulting product **60** (41 mg, 95%) was used without further purification.

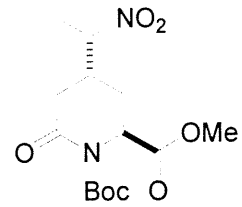
$[\alpha]_D$ +6.6° (*c* 5.0, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 6.56(b, 1H), 4.19-4.16(m, 1H), 3.76(s, 3H), 2.68-2.63(m, 2H), 2.53-2.47(dd, J = 4.72 Hz, 17.42 Hz, 1H), 2.23-2.20(d, J = 12.82 Hz, 1H), 2.08-2.02(dd, J = 9.62 Hz, 17.34 Hz, 1H), 1.89-1.78(m, 2H), 1.42-1.37(b, 2H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.99(0), 171.38(0), 53.13(-), 52.57(-), 46.16(+), 35.04(+), 33.01(-), 28.09(-)

IR: (NaCl): 3369, 2955, 2360, 1737, 1657, 1480, 1441, 1408, 1327, 1219, 1005, 962

HRMS: $C_8H_{14}N_2O_3$, Calcd.: 186.10044; found: 187.10325 (m+1)



(2*S*, 4*R*)-4-(1-Methyl-1-nitro-ethyl-)-6-oxo-piperidine-1-carboxylic acid *tert*-butyl-ester 2-carboxylic acid methyl ester (47)

To a solution of compound **41** (0.352 g, 1.37 mmol) dissolved in 2-nitropropane (25 mL, 200 equiv.) at room temperature, under an atmosphere of N_2, was added DBU (0.27 mL, 1.5 equiv.). The mixture was left stirring at room temperature for 6 h, then treated with saturated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted with EtOAc (15 ml). The combined organic layers were washed with brine (5 mL) and dried over sodium sulfate, filtered and removed *under vacuo* to give a yellow crude oil which was purified by flash column chromatography, eluting with a 50-50% EtOAc/Hexane solvent gradient to give the title compound **47** (0.4 g, 85%).

$[\alpha]_D$ +26.9° (*c* 1.8, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 4.82-4.79(dd, J = 2.49 Hz, 5.72Hz, 1H), 3.80(s, 3H), 2.71-2.68(dd, J = 2.60 Hz, 5.47 Hz, 1H), 2.65-2.49(m, 1H), 2.33-2.24(dd, J = 11.64 Hz, 16.57 Hz, 1H), 2.18-2.04(m, 1H), 1.84-1.73(m, 2H), 1.54(s, 6H), 1.50(s, 9H)

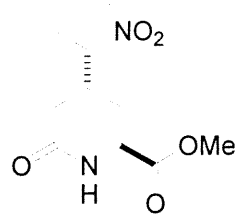
^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.12(0), 167.87(0), 151.51(0), 89.46(0), 84.08(0), 56.92(+), 52.77(+), 37.83(+), 35.82(-), 27.72(+), 27.00(-), 23.85(+), 21.35(+).

IR: (NaCl): 3064, 2984, 2932, 1779, 1750, 1725, 1543, 1458, 1371, 1290, 1249, 1212, 1150, 852, 748, 708 cm^{-1}

MS: 345.2 (m+1), 307.2, 289.2, 245.2, 198.2, 154.1, 137.1

HRMS: $C_{15}H_{24}N_2O_7$, Calcd.: 344.15835; found: 345.16710 (m+1)

X-Ray Diffraction Analysis Data (see annex)



(2*S*, 4*R*)-4-(1-Methyl-1-nitro-ethyl-)-6-oxo-piperidine-2-carboxylic acid methyl ester (61)

To a solution of **47** (0.1 g, 0.29 mmol) dissolved in DCM (3 mL) at 0 °C was added TFA (0.29 mL, 13 equiv.). The mixture was left stirring at 0 °C for 25 min. The reaction mixture

was quenched with saturated aqueous Na_2CO_3 (1 mL) and the aqueous layer was extracted with DCM (10 mL). The combined organic layers were washed with brine (5 mL) and dried over sodium sulfate, filtered and removed *under vacuo*. The crude yellow oil was purified by flash column chromatography, eluting with a 100% EtOAc solvent gradient to give the title compound **61** (49 mg, 70%).

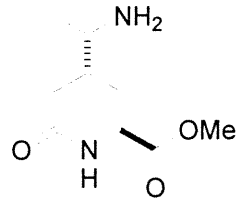
$[\alpha]_D$ +52.5° (*c* 0.8, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.14(b, 1H), 4.20-4.17(m, 1H), 3.76 (s, 3H), 2.48-2.40(m, 2H), 2.17-2.08(m, 2H), 1.76-1.68(dt, J = 6.04 Hz, 12.84 Hz, 1H), 1.54(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 171.43(0), 170.41(0), 89.67(0), 52.91(+), 37.94(+), 32.75(-), 26.01(-), 23.59(+), 21.69(+)

IR: (NaCl): 3240, 2994, 2955, 1744, 1618, 1538, 1470, 1402, 1377, 1348, 1326, 1215, 1148, 1104, 1058, 1004, 964, 854 cm^{-1}

HRMS: $C_{10}H_{16}N_2O_5$, Calcd.: 244.10592; found: 245.11375 (m+1)



(2*S*, 4*R*)-4-(1-amino-1-methyl-ethyl)-6-oxo-piperidine-2-carboxylic acid methyl ester (62)

A solution of **61** (49 mg, 0.2 mmol) in MeOH (2 mL) was hydrogenated over 10% Pd/C (10 mg) at 60 psi H_2. The mixture was stirred until the starting material was no longer detectable by TLC. The reaction mixture was filtered through celite® and the pad was washed with DCM (5 mL). The solvent was removed *under vacuo* and the resulting product **62** (41 mg, 95%).

$[\alpha]_D$ +31.0° (*c* 2.6, $CHCl_3$)

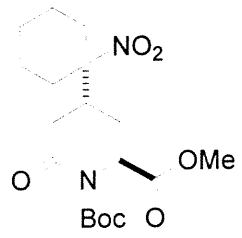
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.27(b, 1H), 4.18-4.16(m 1H), 3.70(s, 3H), 2.48-2.42(m, 1H), 2.33-2.30(d, J = 11.20 Hz, 1H), 2.15-2.08(dd, J = 11.71 Hz, 17.33 Hz, 1H), 1.88(b, 2H), 1.72-1.58(m, 2H), 1.06(s, 3H), 1.03(s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 172.53(0), 172.20(0), 53.52(+), 52.51(+), 50.46(0), 40.22(+), 32.98(-), 28.11(+), 27.03(+), 25.78(-)

IR: (NaCl): 3352, 2966, 2363, 1737, 1657, 1478, 1440, 1407, 1370, 1333, 1217, 1114, 1055, 1003, 963, 918 cm^{-1}

MS: 214.13(m), 200.1, 182.1, 170.1, 156.1, 155.1, 139.1, 126.9, 113.8, 86.6, 72.0

HRMS: $C_{10}H_{18}N_2O_3$, Calcd.: 214.13174; found: 214.13174 (m)



(2*S*, 4*R*)-4-(1-Nitro-cyclohexyl)-6-oxo-piperidine-1-caboxylic acid *tert*-butyl ester 2-carboxylic acid methyl ester (48)

To a solution of **41** (25 mg, 0.1 mmol) dissolved in acetonitrile (1 mL) at room temperature, under an atmosphere of N_2, was added potassium carbonate (69 mg, 5 equiv.), tertra-*n*-butyl ammonium bromide (16 mg, 0.5 equiv.), and nitrocyclohexane (25 μL, 6 equiv.). The reaction was left stirring at room temperature for 7 days. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with brine (5 mL) and dried over sodium sulfate, filtered and removed *under vacuo* to give a yellow crude oil which was purified by flash column chromatography, eluting with a 25-75% EtOAc/Hexane solvent gradient to give the title compound **48** (25mg, 65%).

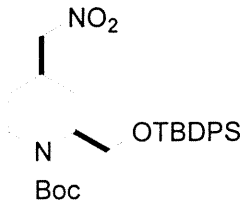
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 4.79-4.77(dd, J = 2.47 Hz, 5.78, 1H), 3.78(s, 3H), 2.72-2.66(m,1H), 2.50-2.57(m, 4H), 2.20-2.11(m, 1H), 1.74-1.53(m, 5H), 1.51-1.49(s+m, 10H), 1.47-1.23(m, 4H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) =171.36(0), 168.04(0), 151.60(0), 92.44(0), 84.02(0), 56.93(-), 52.73(+), 38.25(-), 35.38(+), 31.91(-), 30.56(-), 27.73(+), 26.54(-), 24.37(-), 21.93(-), 21.87(-)

IR: (NaCl): 3064, 2945, 2870, 1779, 1749, 1725, 1538, 1453, 1371, 1290, 1260, 1210, 1151, 847 cm^{-1}

MS: 385.0 (m+1), 329.0, 307.0, 285.0, 260.0, 238.0, 178.0, 154.0, 137.0

HRMS: $C_{18}H_{28}N_2O_7$, Calcd.: 384.18978; found: 385.19755 (m+1)



(2*S*, 4*S*)-2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-nitromethyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (63)

To a solution of **43** (50 mg, 0.09 mmol) dissolved in THF (1 mL) under an atmosphere of N_2, was added $NaBH_4$ (15 mg, 4 equiv.). The reaction mixture was left stirring at room temperature for 4 h and then cooled to –78 °C and $BF_3.OEt_2$(25 ul, 2 equiv.) was added. The reaction mixture was left stirring at –78 °C for 3.5 h. The reaction was quenched by adding saturated aqueous NH_4Cl (1 mL) and the aqueous layer was extracted with EtOAc (5 mL). The combined organic layers were washed with brine (1 mL) and dried over sodium sulfate, filtered and removed *under vacuo*. The crude yellow oil was purified by flash column chromatography, eluting with a 20-80% EtOAc/Hexane solvent gradient to give the title compound **63** (45mg, 94%).

$[\alpha]_D$ –60.0° (*c* 2.0, $CHCl_3$)

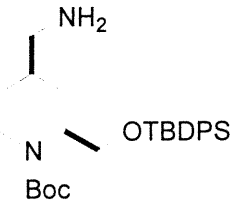
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.67-7.63(m, 4H), 7.41-7.38(m, 6H), 6.85(b, 1H), 4.76(b, 1H), 4.45-4.27(m, 3H), 3.79-3.75(dd, J = 6.07 Hz, 10.34 Hz, 1H), 3.40-3.35(t, J = 10.30 Hz, 1H), 3.05-3.04(b, 1H), 2.36(b, 1H), 2.07-2.00(m, 1H), 1.51-1.23(m, 9H), 1.07(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 149.22, 132.97, 130.30, 127.44, 125.28, 123.91, 100.34, 78.81, 77.45, 58.46, 47.39, 26.11, 25.55, 24.32, 21.27, 16.59

IR: (NaCl): 2930, 2858, 2283, 1693, 1473, 1413, 1391, 1365, 1248, 1157, 1112, 823, 471, 702

MS: 511.3 (m+1), 455.2, 437.2, 397.1, 377.1, 353.1, 333.2, 292.1, 246.1, 199.1, 154.1

HRMS: $C_{28}H_{38}N_2O_5Si$, Calcd.: 510.25506; found: 511.26283 (m+1)



(2*S*, 4*R*)-4-Aminomethyl-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (64)

A solution of **63** (50 mg, 0.1 mmol) in MeOH (2 mL) was hydrogenated over 10% Pd/C (5 mg) at 60 psi H_2. The mixture was stirred until the starting material was no longer detectable by TLC. The reaction mixture was filtered through celite® and the pad was washed with DCM (10 mL). The solvent was removed *under vacuo* and the resulting product **64** (47 mg, 95%).

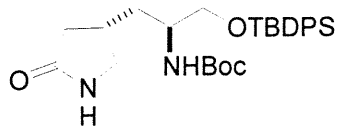
$[\alpha]_D$ -66.5° (*c* 4.2, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.68-7.64(m, 4H), 7.46-7.38(m, 6H), 3.99-3.96(m, 1H), 3.85-3.81(dd, J = 4.08 Hz, 10.22 Hz, 1H), 3.32-3.31(dd, J = 1.65 Hz, 3.29 Hz, 1H), 3.27-3.25(m, 1H), 2.91-2.89(d, J = 6.86 Hz, 1H), 1.94-1.87 (m, 4H), 1.42-1.32(m + s, 11H), 1.06(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 159.37(0), 139.07(+), 136.80(0), 133.40(+), 131.28(+), 83.59(0), 68.72(-), 58.25(+), 48.00(-), 41.50(-), 34.10(+), 31.12(+), 30.69(-), 29.88(-), 29.75(+), 22.42(0)

MS: 483.3 (m+1), 409.2, 383.2, 306.1, 286.2, 197.1, 154.1, 135.1, 96.1

HRMS: $C_{28}H_{42}N_2O_3Si$, Calcd.: 482.29647; found: 483.30429 (m+1)



(1*S*, 3*S*)-[1-(tert-Butyl-diphenyl-silanyloxymethyl)-2-(5-oxo-pyrrolidin-3-yl)-ethyl]carbamic acid *tert*-butyl ester (116)

To a solution of **43** (50 mg, 0.1 mmol) dissolved in anhydrous THF (1 mL) at 0 °C under an atmosphere of N_2 was added NaOMe (0.39 mL, 2.0 equiv.) 0.5 M solution in MeOH. The reaction mixture was left stirring at 0 °C for 45 min, then quenched by adding saturated aqueous NH_4Cl (1 mL) and the aqueous layer was extracted with EtOAc (5 mL). The combined organic layers were washed with brine (5 mL) and dried over sodium sulfate, filtered and removed *under vacuo*. The crude oil was used without further purification, dissolved in MeOH (3 mL) and hydrogenated over 10% Pd/C (5 mg) at 60 psi of H_2. The mixture was stirred until the starting material was no longer detectable on a TLC plate. The reaction mixture was filtered through celite® and the pad was washed with DCM (10 mL). The solvent was removed *under vacuo*, the residue dissolved in toluene (6 mL) and the mixture was heated at reflux for 24 h. The toluene was removed in vacuo and the resulting product was purified by flash column chromatography, eluting with 100% EtOAc to give the title compound **116** (25mg, 60%).

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.69-7.66(dd, J = 1.48 Hz, 7.80 Hz, 4H), 7.46-7.39(m, 6H), 6.51-6.49(d, J = 9.1 Hz, 1H), 3.67-3.51(m+s, 3H), 3.51-3.47(t, J = 8.71 Hz, 1H), 3.03-2.99(dd, J = 7.11 Hz, 9.64 Hz, 1H), 2.53-2.49(m, 1H), 2.42-2.36(dd, J = 8.59 Hz,

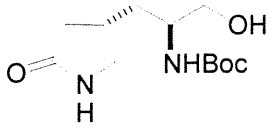
16.73 Hz, 1H), 2.06-2.00(dd, J = 8.06 Hz, 16.93 Hz, 1H), 1.68-1.65(m, 1H), 1.54-1.45(m+s, 10H), 1.06(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) =180.61(0), 158.18(0), 136.70(+), 134.57(0), 130.92(+), 128.83(+), 80.02(0), 67.51(-), 52.24(+), 49.61(-), 38.21(-), 37.04(-), 33.36(+), 28.81(+), 27.35(+), 20.05(0)

IR: (NaCl): 3274, 3072, 2932, 2859, 2382, 1693, 1590, 1490, 1428, 1392, 1366, 1256, 1171, 1113, 998, 824, 798, 741, 703, 614, 505 cm^{-1}

MS: 497.3 (m+1), 441.2, 397.2, 362.2, 319.2, 289.1, 241.1, 199.1, 154.1, 137.0

HRMS: $C_{28}H_{40}N_2O_4Si$, Calcd.: 496.27577; found: 497.28364 (m+1)



(1*S*, 3*S*)-[1-Hydroxymethyl-2-(5-oxo-pyrrolidin-3-yl)-ethyl]-carbamic acid *tert*-butyl ester (117)

To a solution of **116** (35 mg, 0.07 mmol) dissolved in THF (1 mL) was added a 1 M solution of TBAF (0.14 mL, 2 equiv.) in THF. The reaction was left stirring at room temperature overnight. The reaction mixture was directly purified by flash column chromatography, eluting with a 90-10% EtOAc/MeOH solvent gradient to give the title compound **117** (16 mg, 90%).

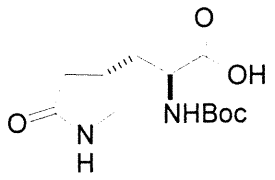
$[\alpha]_D$ –20.9° (*c* 1.2, $CHCl_3$)

^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 3.55-3.41(m, 4H), 3.08-3.02(dd, J = 6.97 Hz, 9.90 Hz, 1H), 2.57-2.49(m, 1H), 2.47-2.38(dd, J = 8.82 Hz, 16.37 Hz, 1H), 2.10-2.02(dd, J = 8.25 Hz, 16.49 Hz, 1H), 1.75-1.67(m, 1H), 1.56-1.43(m+s, 10H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 181.07(0), 158.25(0), 80.60(0), 65.57(-), 52.3(+), 49.51(-), 38.26(-), 37.09(-), 33.42(+), 28.73(+)

IR: (NaCl): 3345, 2930, 1683, 1418, 1366, 1255, 1166, 1062

HRMS: $C_{12}H_{22}N_2O_4$, Calcd.: 258.15796; found: 259.16577 (m+1)



(1*S*, 3*S*)-2-*tert*-Butoxycarbonylamino-3-(5-oxo-pyrrolidin-3-yl)-propionic acid (118)

A mixture of alcohol **117** (100 mg, 0.4 mmol), TEMPO (4.4 mg, 0.07 equiv.), MeCN (2 mL), and sodium phosphate buffer (1.5 mL, 0.67 M, pH = 6.7) is heated to 35 °C. Sodium chlorite (90 mg, 2 equiv.) dissolved in 0.4 mL of water and dilute bleach (0.05 mL, 2.0 mol %) were added simultaneously and the mixture was stirred at 35 °C overnight. After cooling to room temperature, water (5 mL) was added, and the pH was adjusted to 8.0 with 2.0 N NaOH. The reaction was quenched by pouring into cold Na_2SO_3 solution (5 mL). After stirring for 30 min. at room temperature, DCM (10 mL) was added, the organic layer was separated and discarded. More DCM (10 mL) was added, and the aqueous layer was acidified with 2.0 N HCl to pH = 3-4. The organic layer was separated, washed with water (10 mL) and brine (5 mL). Once dried over sodium sulfate, filtered and the solvent removed *under vacuo*, we obtained the title compound **118** (98 mg, 90%) without further purification.

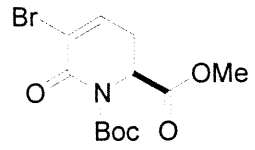
$[\alpha]_D$ –27.6° (*c* 1.2, $CHCl_3$)

^{1}H-NMR (400MHz, CD_3OD): δ(ppm) = 4.23-4.26(dd, J = 15.0 Hz, 7.2 Hz, 1H), 3.52-3.46(m, 1H), 3.12-3.08(dd, J = 6.17 Hz, 8.90 Hz, 1H), 2.57-2.49(m, 1H), 2.45-2.38(dd, J = 8.01 Hz, 15.37 Hz, 1H), 2.25-2.29(m, 1H), 1.75-1.78(m, 1H), 1.45(m+s, 10H)

^{13}C-NMR (100MHz, CD_3OD): δ(ppm) = 177.06(0), 174.72(0), 157.57(0), 70.62(0), 55.86(+), 43.17(-), 40.05(-), 37.04(-), 28.75(+), 23.14(+)

MS: 273.1 (m+1), 256.6, 215.2, 154.1, 137.3, 96.1

HRMS: $C_{12}H_{20}N_2O_5$, Calcd.:272.13722; found: 273.13952 (m+1)



(*S*)-5-Bromo-6-oxo-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 2-carboxylic acid methyl ester (120)

To a solution of **40** (1.07 g, 4.2 mmol) dissolved in anhydrous THF (42 mL) at –78 °C, under an atmosphere of N_2, was added LiHMDS (5.0 mL, 1.2 equiv.) 1 M solution in THF. After 45 min, PhSeBr (1.29 g, 1.3 equiv.) dissolved in THF (5 mL) was added to the reaction mixture. Upon leaving the mixture stirring at –78 °C for 1 h, LiHMDS (2.1 mL, 0.5 equiv.) was added to the reaction mixture once more and left stirring at –78 °C for 30 min. This was followed by the addition of Br_2 (0.43 mL, 2.0 equiv.) and the mixture was left stirring at –78 °C for 1 h and warmed up to room temperature over a further period of 60 min. The mixture was quenched with saturated aqueous NH_4Cl (10 mL), the aqueous layer was extracted with EtOAc (40 mL) and the combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. The filtration and evaporation gave a yellow crude oil which was used without further purification. This material was dissolved in DCM (45 mL) and treated with H_2O_2 (30%, 12 mL) at 0 °C. After adding drops of pyridine to pH ~ 7, the mixture was stirred at room temperature for 90 min and then treated with saturated aqueous Na_2CO_3 (5 mL). The aqueous layer was extracted with DCM (35 mL) and the combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. Filtration and removal of the solvent gave a yellow oil which was purified by flash column chromatography, eluting with a 15-85% EtOAc/Hexane solvent gradient to give the crude product which was purified by flash column chromatography, eluting with a 15-85% EtOAc/Hexane solvent gradient to give the title compound **120** (0.858 g, 65%).

$[\alpha]_D$ +78.3° (*c* 0.6, $CHCl_3$)

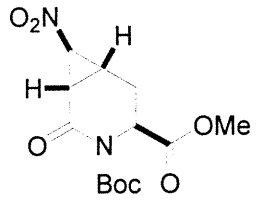
^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 7.02-6.98(m, 1H), 5.06-5.03(m, 1H), 3.73(s, 3H), 2.86-2.82(m, 2H), 1.52(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 170.45(0), 157.50(0), 152.19(0), 140.21(+), 119.67(0), 84.33(0), 55.64(+), 53.00(+), 28.86(-), 27.86(+)

IR: (NaCl): 2982, 2957, 1750, 1727, 1626, 1476, 1457, 1438, 1385, 1370, 1296, 1255, 1217, 1149, 1090, 1061, 1008, 972, 951, 900, 846, 826, 723, 648, 608 cm^{-1}

MS: 335.2 (m+1), 333.2(m+1), 305.8, 277.9, 279.9, 274.1, 235.9, 233.9, 175.9, 173.9

HRMS: $C_{12}H_{16}BrNO_5$, Calcd.: 332.02124; found: 333.02218 (m+1)



(2*S*, 4*R*, 5*S*, 7*S*)-7-Nitro-6-oxo-1-aza-bicyclo[4.1.0]heptane-1-carboxylic acid *tert*-butyl ester 2-carboxylic acid methyl ester (121)

To a solution of compound **120** (100 mg, 0.3 mmol) dissolved in nitromethane (4 mL, 245 equiv.) at room temperature, under an atmosphere of N_2, was added DBU (54 µL, 1.2 equiv.) and left stirring at room temperature for 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with brine (5 mL) and dried over sodium sulfate, filtered and removed *under vacuo* to give 3:1, *anti* to *syn*, mixture of diastereoisomers which were separated by flash column chromatography, eluting with a 15-85% EtOAc/Hexane solvent gradient to give the *anti* diastereoisomer **121** (30 mg, 45%) and its *syn* diastereoisomer **122** (12 mg, 15%).

For **121**:

$[\alpha]_D$ -22.3° (*c* 15, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 4.76-4.74(dd, J = 3.03Hz, 5.80 Hz, 1H), 4.44-4.43(t, J = 2.89 Hz, 1H), 3.82(s, 3H), 2.87-2.84(dd, J = 2.84 Hz, 9.98 Hz, 1H), 2.76-2.69(m, 1H), 2.60-2.56(m, 1H), 1.49(s, 9H)

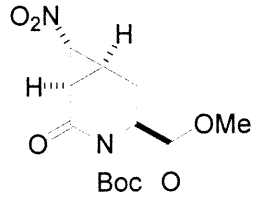
^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 168.20(0), 161.57(0), 149.32(0), 82.29(0), 62.49(+), 54.62(+), 50.71(+), 26.27(+), 25.29(+), 22.86(-), 20.24(+)

IR: (NaCl): 3080, 2983, 1780, 1731, 1551, 1439, 1369, 1294, 1256, 1212, 1153, 1099, 999, 920, 842, 785, 734, 678 cm^{-1}

MS: 315.2 (m+1), 289.2, 259.1, 237.1, 215.1, 154.1, 137.1

HRMS: $C_{13}H_{18}N_2O_7$, Calcd.: 314.11143; found: 315.11858 (m+1)

For **122**:



(2*S*, 4*S*, 5*R*, 7*R*)-7-Nitro-6-oxo-1-aza-bicyclo[4.1.0]heptane-1-carboxylic acid *tert*-butyl ester 2-carboxylic acid methyl ester (122)

^{1}H-NMR (400MHz, $CDCl_3$): δ(ppm) = 4.91-4.86(m, 1H), 3.84(s, 3H), 2.99-2.96(dd, J = 2.30 Hz, 10.00 Hz, 1H), 2.72-2.63(m, 2H), 2.46-2.43(m, 1H), 1.49(s, 9H)

^{13}C-NMR (100MHz, $CDCl_3$): δ(ppm) = 169.44(0), 161.41(0), 148.86(0), 82.31(0), 56.96(+), 52.44(+), 50.83(+), 27.28(+), 25.23(+), 22.82(-), 18.07(+)

X-Ray Diffraction Analysis Data (see Annex)

Chapter 4

4.1 References and notes

[1] Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. "Sugar-mimic Glycosidase Inhibitors: Natural Occurrence, Biological Activity and Prospects for Therapeutic Application" *Tetrahedron: Asymmetry* **2000**, 11, 1645-1680.

[2] Tyms, A. S.; Berrie, E. M.; Ryder, T. A.; Nash, R. J.; Hegarty, M. P.; Taylor, D. L.; Mobberley, M. A.; Davis, J. M.; Bell, E. A.; Jeffries, D. J. "Castanospermine and other Plant Alkaloid Inhibitors of Glucosidase Activity" *Lancet* **1987**, 1025-1026.

[3] (a) Tsumoto, K.; Uno, A.; Kubota, Y.; Shimada, S.; Hori, Y.; Imokawa, G. "Role of Aspargine-linked Carbohydrates in Pulmonary Metastasis of B16-F10 Murine Melanoma Cells: Implication Through Glycosylation Inhibition by Nojirimycin" *Melanoma Res.* **1992**, 2, 33-39. (b) Spearman, M. A.; Jamieson, J. C.; Wright, J. A. "Studies on the Effect of Glycoprotein Processing Inhibitiors of Fusion of L6 Myoblast Cell Lines" *Exp. Cell Res.* **1987**, 168, 116-126.

[4] (a) Reuser, A. J. J.; Wisselaar, H. A. "An Evaluation of the Potential Side-effects of Alpha-glucosidase Inhibitors Used for the Management of Diabetes Mellius" *Eur. J. Clin. Invest.* **1994**, 24, Suppl. 3, 19-24. (b) Leonhardt, W.; Hanefield, M.; Fischer, S.; Schulze, J. "Efficacy of Alpha-glucosidase Inhibitors on Lipids in NIDDM Subjects with Moderate Hyperlipidaemia" *Eur. J. Clin. Invest.* **1994**, Suppl. 3, 45-49. (c) Bischoff, H. "Pharmacology of Alpha-glucosidase Inhibition" *Eur. J. Clin. Invest.* **1994**, Suppl. 3, 3-10. (d) Holt, P.; Thea, D.; Yang, M.; Kotler, D. "Intestinal and Metabolic Responses to an Alpha-glucosidase Inhibitor in Normal Volunteers" *Metab. Clin. Exp.* **1988**, 37, 1163-1170. (e) Rhinehart, B. L.; Robinson, K. M.; Payne, J. J.; Wheatley, M. E.; Fisher, J. L.;

Liu, P. S.; Cheng, W. "Castanospermine Blocks the Hyperglycemic Response to Carbohydrates in Vivo: A Result of Intestinal Disaccharidase Inhibition" *Life Sci.* **1987**, 41, 2325-2331.

[5] (a) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. "Synthesis and α-$_D$-Glucosidase Inhibitory Activity of *N*-Substituded Valiolamine Derivatives as Potential Oral Antidiabetic Agents" *J. Med. Chem.* **1986**, 29, 1038-1046. (b) Azeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C. H.; Liu, P. S. "A Facile, Practical Synthesis of 2,6-Dideoxy-2,6-imino-7-*O*-β-$_D$-glucopyranosyl-$_D$-glycero-*L*-gulo-heptitol" *J. Org. Chem.* **1989**, 54, 2539-2542.

[6] For example: (a) Masson, G.; Compain, P.; Martin, O. R. "A New, Stereocontrolled Approach to Iminosugar *C*-glycosides from L-sorbose" *Org. Lett.* **2000**, 2, 2971-2974. (b) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieraugel, H. "Synthesis Mediated by Ring-closing Metathesis - Applications in the Synthesis of Azasugars and Alkaloids" *Eur. J. Org. Chem.* **1999**, 5, 959-968. (c) Grandel, R.; Kazmaier, U. "A Short Synthesis of Azasugars via Aldol Reaction of Chelated Amino Acid Ester Enolates" *Tetrahedron lett.* **1997**, 38, 8009-8012. (d) Lemerrer, Y.; Poitout, L.; Depezay, J. C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M. J. "Synthesis of Azasugars as Potent Inhibitors of Glycosidases" *Bioorg. Med. Chem.* **1997**, 3, 519-533. (e) Yu, L. B.; Li, J.; Ramirez, J.; Chen, D.; Wang, P. G. " Synthesis of Azasugars via Lanthanide-promoted Aza Diels-Alder Reactions in Aqueous Solution" *J. Org. Chem.* **1997**, 4, 903-907. (f) Huwe, C. M.; Blechert, S. "A Flexible Synthesis of Azasugars via Olefin Metathesis" *Synthesis* **1997**, 61-68.

[7] For example: (a) Tamiz, A. P.; Zhang, J. R.; Flippen-Anderson, J. L.; Zhang, M.; Johnson, K. M.; Deschaux, O.; Tella, S.; Kozikowski, A. P. "Further SAR Studies of

Piperidine-based Analogues of Cocaine. Potent Dopamine and Serotonin Reuptake Inhibitors" *J. Med. Chem.* **2000**, 43, 1215-1222. (b) Chen, M. H.; Chung, F. Z.; Roth, B. D.; Kuo, B. S.; Atherton, J.; Lee, H. T. "Syntheses and Biological Activities of Chiral Piperidines Tachykinin NK3 Antagonists" *Acta Pharm. Sin.* **1999**, 20, 283-288. (c) Swain, C.; Rupniak, N. M. J. "Progress in the Development of Neurokinin Antagonists" *Annu. Rep. Med. Chem.* **1999**, 34, 51-60. (d) Brundish, D.; Bull, A.; Donovan V.; Fullerton, J. D.; German, S. M.; Hayler, J. F.; Janus, D.; Kane, P. D.; McDonnel, M.; Smith, G. P.; Wakeford, R.; Walker, C. V.; Howarth, G.; Hoyle, W.; Allen, M. C.; Ambler, J.; Butler, K.; Talbot, M. D. "Design and Synthesis of Thrombin Inhibitors: Analogues of MD-805 with Reduced Stereogenicity and Improved Potency" *J. Med. Chem.* **1999**, 42, 4584-4603. (e) Daly, J. W. "Alkaloids from Frog Skins – Selective Probes for Ion Channels and Nicotinic Receptors" *Braz. Pharm. Med. Bio. Res.* **1995**, 28, 1033-1042.

[8] For example: (a) Takahata, H.; Kubota, M.; Ikota, N. "A New Synthesis of all Four Stereoisomers of 2-(2,3-Dihydroxypropyl)piperidine via Iterative Asymmetric Dihydroxylation to Cause Enantiomeric Enhancement. Application to Asymmetric Synthesis of Naturally Occuring Piperidine-related Alkaloids" *J. Org. Chem.* **1999**, 64, 8594-8601. (b) Sibi, M. P.; Christensen, J. W. " Enantiospecific Synthesis of (-)-Slaframine and Related Hydroxylated Indolizidines. Utilization of a Nucleophilic Alaninol Synthon Derived from Serine" *J. Org. Chem.* **1999**, 64, 6434-6442. (c) Pili, R. A.; Alves, C. D.; Bockelmann, M. A.; Mascarenhas, Y. P.; Nery, J. G.; Vencato, I. "The Stereochemistry of the Addition of Titanium Enolates of *N*-Propionyl-oxazolidin-2-ones to 5- and 6-Membered *N*-Acyliminium Ions" *Tetrahedron lett.* **1999**, 40, 2891-2894. (d) Reding, M. T.; Buchwald, S. L. "Short Enantioselective Total Syntheses of the Piperidine Alkaloids (*S*)-Coniine and (2*R*,6*R*)-*trans*-Solenopsin A via Catalytic Asymmetric Imine Hydrosilylation" *J. Org. Chem.* **1998**, 63, 6344-6347. (e) Balasubramanian, T.; Hassner, A. "Asymmetric Synthesis of Functionalized Piperidine Derivatives - Synthesis of (*S*)-Anatabine" *Tetrahedron: Asymmetry* **1998**, 9, 2201-2205. (f) Nazabadioko, S.; Perez, R. J.; Brieva, R.; Gotor, V. "Chemoenzymatic Synthesis of (*S*)-2-Cyanopiperidine,

a Key Intermediate in the Route to (*S*)-Pipecolic Acid and 2-Substituted Piperidine Alkaloids" *Tetrahedron: Asymmetry* **1998**, 9, 1597-1604.

[9] For example: (a) Wilkinson, T. J.; Stehle, N. W.; Beak, P. "Enantioselective Syntheses of 2-Alkyl and 2,6-Dialkylpiperidine Alkaloids: Preparation of the Hydrochlorides of (-)-Coniine, (-)-Solenopsin A, and (-)-Dihydropinidine" *Org. Lett.* **2000**, 2, 155-158. (b) Yu, M. S.; Lantos, I.; Peng, Z. Q.; Yu, J.; Cacchio, T. "Asymmetric Synthesis of (-)-Paroxetine using PLE Hydrolysis" *Tetrahedron Lett.* **2000**, 41, 5647-5651. (c) Couty, F. "Asymmetric Synthesis of Pipecolic Acid and Derivatives" *Amino Acids*, **1999**, 297-320. (d) Bailey, P. D.; Millwod, P. A.; Smith, P. D. "Asymmetric Routes to Subtituted Piperidines" *J. Chem. Soc., Chem. Commun.* **1998**, 6, 633-640. (e) Hodgkinson, T. J.; Shipman, M. "Practical Asymmetric Synthesis of both Enantiomers of 6-(Hydroxymethyl)piperidine-2-one" *Synthesis* **1998**, 8, 1141-1144. (f) Nazih, A.; Schneider, M. R.; Mann, A. "Synthesis of Substituted Pipecolinic acids from 4-Alkylpyridines" *Synlett* **1998**,12 1337-1338. (g) Sanchez-Sancho, F.; Herradon, B. " Short Syntheses of (*S*)-Pipecolic Acid, (*R*)-Coniine, and (*S*)-d-Coniceine using Biocatalytically-generated Chiral Building Blocks" *Tetrahedron: Asymmetry* **1998**, 9, 1951-1965. (h) Davies, C. E.; Heightman, T. D.; Hermitage, S. A.; Moloney, M. G. "Convenient Preparation of Racemic and Enantiopure Methyl 6-Oxopipecolate" *Synth. Commun.* **1996**, 26, 687-696.

[10] For example: (a) Oefner, C.; Binggeli, A.; Breu, V.; Bur, D.; Clozel, J. P.; D'Arcy, A.; Fischli, W.; Gruninger, F.; Guller, R.; Hirth, G.; Marki, H. P.; Mathews, S.; Muller, M.; Ridley, R. G.; Stadler, H.; Vieira, E.; Wilhelm, M.; Winkler, F. K.; Wostl, W. "Renin Inhibition by Substituted Piperidines: a Novel Paradigm for the Inhibition of Monomeric Aspartic Proteinases?" *Chem. Biol.* **1999**, 6, 127-131. (b) Vieira, E.; Binggeli, A.; Breu, V.; Bur, D.; Fischli, W.; Guller, R.; Hirth, G.; Marki, H. P.; Muller, M.; Oefner, C.; Scalone, M.; Stadler, H.; Wilhelm, M.; Wostl, W. "Substituted Piperidines – Highly

Potent Renin Inhibitors due to Induced Fit Adaptation of the Active Site" *Bioorg. Med. Chem. Lett.* **1999**, 9, 1397-1402. (c) Kubota, H.; Kakefuda, A.; Okamoto, Y.; Fujii, M.; Yamamoto, O.; Yamagiwa, Y.; Orita, M.; Ikeda, K.; Takeuchi, M.; Shibanuma, T.; Isomura, Y. "Spiro-substituted Piperidines as Neurokinin Receptor Antagonists – III – Synthesis of *N*-[2-(3-4-Dichlorophenyl)-4-(spiro-substituted piperidin-1'-YL)butyl]-*N*-methylbenzamides and Evaluation of NK1-NK2 dual Antagonistic Activities" *Chem. Pharm. Bull.* **1998**, 46, 1538-1544. (d) Whittemore, E, R.; Ilyin, V. I.; Konkoy, C. S.; Woodward, R. M. "Subtype-selective Antagonism of NMDA Receptors by Nylidrin" *Eur. J. Pharmacol.* **1997**, 337, 197-208. (e) Desjardin, M.; Desgagnes, J.; Lacoste, L.; Yang, F.; Morin, M. P.; Lapointe, J.; Chenevert, R. "Synthesis of Inhibitors of Glutamyl-trna Synthetase" *Bioorg. Med. Chem. Lett.* **1997**, 7, 2363-2366.

[11] Broekkamp, C. L. E.; Leysen, D.; Peeters, B. W. M. M.; Pinder, R. M. "Prospects for Improved Antidepressants" *J. Med. Chem.* **1995**, 38, 4615-4633.

[12] (a) Vacher, B.; Bonnaud, B.; Funes, P.; Jubault, N.; Koek, W.; Assie, M. B.; Cosi, C.; Kleven, M. "Novel Derivatives of 2-Pyridinemethylamine as Selective, Potent, and Orally Active Agonists at 5-HT_{1A} Receptors" *J. Med. Chem.* **1999**, 42, 1648-1660. (b)Vacher, B.; Bonnaud, B.; Funes, P.; Jubault, N.; Koek, W.; Assie, M. B.; Cosi, C. "Design and Synthesis of a Series of 6-Substituted-2-pyridinylmethylamine Derivatives as Novel, High-affinity, Selective Agonists at 5-HT_{1A} Receptors" *J. Med. Chem.* **1998**, 41, 5070-5083.

[13] Shey, J. Y.; Sun, C. M. "Liquid Phase Combinatorial Synthesis of Benylpiperazines" *Bioorg. Med. Chem. Lett.* **1999**, 9, 519-522.

[14] Ornstein, P. L.; Schoepp, D. D.; Arnold, M. B.; Leander, J. D.; Lodge, D.; Paschal, J. W.; Elzey, T. "4-(Tetrazoylalkyl)-piperidine-2-carboxylic Acids. Potent and Selective *N*-Methyl-D-aspartic Acid Receptor Antagonists with a Short Duration of Action" *J. Med. Chem.* **1991**, 34, 90-97.

[15] (a) Monaghan, D. T.; Yao, D.; Cotman, C. W. "L-[^{3}H]Glutamate Binds to Kainite-, NMDA- and AMPA-Sensitive Binding Sites: an Autoradiographic Analysis" *Brain Res.* **1985**, 340, 378-383. (b) Foster A. C.; Fagg, G. E. "Comparison of L-[^{3}H]Aspartate, DL-[^{3}H]AP5 and [^{3}H]NMDA as Ligands for NMDA Receptors in Crude Postsynaptic Densities from Rat Brain" *Eur. J. Pharmacol.* **1987**, 133, 291-300.

[16] (a) Choi, D. W. "Glutamate Neurotoxicity and Diseases of the Nervous System" *Neuron* **1988**, 1, 623-634. (b) Greenamyre, J. T. "The Role of Glutamate in Neurotransmission and in Neurologic Disease" *Arch. Neurol.* **1986**, 43, 1058-1072.

[17] (a) Ornstein, P. L.; Schaus, J. M.; Chambers, J. W.; Huser, D. L.; Leander, J. D.; Wong, D. T.; Paschal, J. W.; Jones, N. D.; Deeter, J. B. " Synthesis and Pharmacology of a Series of 3- and 4-(Phosphonoalkyl)pyridine- and -Piperidine-2-carboxylic Acids. Potent *N*-Methyl-$_D$-aspartate Receptor Antagonists" *J. Med. Chem.* **1989**, 32, 827-833. (b) Hutchison, A. J.; Williams, M.; Angst, C.; Reynalda, D. J.; Blanchard, L.; Jackson, R. H.; Wilusz, E. J.; Murphy, D. E.; Bernard, P. S.; Scheinder, J.; Campbell, T.; Guida, W.; Sills, M. A. "4-(Phosphonoalkyl)- and 4-(Phosphonoalkenyl)-2-piperidinecarboxylic Acids: Synthesis, Activity at *N*-Methyl-D-aspartic Acid Receptors, and Anticonvulsant Activity" *J. Med. Chem.* **1989**, 32, 2171-2178.

[18] Copeland, T. D.; Wondrak, E. M.; Tozser, J.; Roberts, M. M.; Oroszlan, S.

"Substitution of Proline with Pipecolic Acid at the Scissile Bond Converts a Peptide Substrate of HIV Proteinase into a Selective Inhibitor" *Biochem. Biophys. Res. Commun.* **1990**, 169, 310-314.

[19] Sahlberg, C. "Synthesis of Carbon-14 Labelled Ropivacaine, a Local Anaesthetic Agent" *J. Labelled Compd. Radiopharm.* **1987**, 24, 529-534.

[20] (a) Flynn, G. A.; Giroux, E. L.; Dage, R. C. "An Acyl-iminium Ion Cyclization Route to a Novel Conformationally Restricted Dipeptide Mimic: Applications to Angiotensin-Converting Enzyme Inhibition" *J. Am. Chem. Soc.* **1987**, 109, 7914-7915. (b) Kikumoto, R.; Tamao, Y.; Tezuka, T.; Tonomura, S.; Hara, H.; Ninomiya, K.; Hijikata, A.; Okamoto, S. "Selective Inhibition of Thombin by (2R, 4R)-4-Methyl-1-[N2-[(3-methyl-1,2,3,4-tetrahydro-8-quinolinyl sulfonyl]-1-arginyl)]-2-piperidinecarboxylic Acid" *Biochemistry* **1984**, 23, 85-90.

[21] Sehgal, S. N.; Baker, H.; Eng, C. P.; Singh, K.; Vezina, C. "Demethoxyrapamycin (AY-24, 668), a New Antifungal Antibiotic" *J. Antibiot.* **1983**, 36, 351-354.

[22] (a) Gibson S. E.; Guillo, N.; Tozer, M. J. "Towards Control of χ-Space: Conformationally Constrained Analogues of Phe, Tyr, Trp and His" *Tetrahedron* **1999**, 55, 585-615. (b) Ezquerra, J.; Pedregal, C.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. "Stereoselective Functionalisation of *N*-Boc Pyroaminoadipic Acid: Synthesis of 5-Substituted Aminoadipic and Pipecolic Acids" *Tetrahedron Lett.* **1995**, 36, 3247-3250.

[23] Maison, W.; Luzen, A.; Kosten, M.; Schlemminger, I.; Westerhoff, O.; Saak, W.;

Martens, J. "Multicomponent Synthesis of Tripeptides Containing Pipecolic Acid Derivatives: Selective Induction of *cis*- and *trans*-Imide Bonds Into Peptide Backbones" *J. Chem. Soc., Perkin Trans. 1* **2000**, 1867-1871.

[24] (a) Gante, J. "Peptidomimetics – Tailored Enzyme Inhibitors" *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1699-1720. (b) Giannis, A.; Kolter, T. "Peptidomimetics for Receptor Ligands-Discovery, Development, and Medical Perspectives" *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1244-1267.

[25] Burt, S. K.; Greer, J. "Search Strategies for Determining Bioactive Conformers of Peptides and Small Molecules" *Annu. Rep. Med. Chem.* **1988**, 23, 285-306.

[26] Rizo, J.; Gierasch, L. M. "Constrained Peptides: Models of Bioactive Peptides and Protein Substructures" *Annu. Rev. Biochem.* **1992**, 61, 387-306.

[27] Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bos, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. "Concepts and Progress in the Development of Peptide Mimetics" *J. Med. Chem.* **1993**, 36, 3041-3049.

[28] Laramie, M. G.; Joiner, G. F.; King, F. D.; Wyman, P. A.; Sutton, J. M.; Bingham, S.; Ellis, E. S.; Sanger, G. J.; Wardle, K. A. "*N*-[1-Butyl-4-piperidinyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide Hydrochloride: The First Potent and Selective 5-HT_4 Receptor Antagonist Amide with Oral Activity" *J. Med. Chem.* **1995**, 38, 4760-4763.

[29] For example: (a) Hanessian, S.; Pham, V. "Catalytic Asymmetric Conjugate Addition of Nitroalkanes to Cycloalkenones" *Org. Lett.* **2000**, 2, 2975-2978. (b) Baldoli, C.; Maiorana, S.; Licandro, E.; Perdicchia, D.; Vandoni, B. "Michael Addition of Nitromethane to Non-racemic Chiral $Cr(CO)_3$ Complexes of Ethyl Cinnamate Derivatives: Stereoselective Synthesis of (-)Baclofen" *Tetrahedron: Asymmetry* **2000**, 11, 2007-2014. (c) Ballini, R.; Bosica, G.; Damiani, M.; Righi, P. "Nitroalkanes as a New Source of 2-Alkylidene-1,4-diols in Two Steps" *Tetrahedron*, **1999**, 55, 13451-13456. (d) Chung, J. Y. L.; Grabowski, E. J. J.; Reider, P. J. "Sequential Nitromethane Conjugate Addition/Elimination-Pd-catalyzed Allylation of Beta-trifloxy Acrylates. Application to Carbapenem Synthesis" *Org. Lett.* **1999**, 1, 1783-1785. (e) Crossley M. J.; Fung, Y. M.; Potter, J. J.; Stamford, A. W. "Convenient Route to Gamma-nitro-alpha-amino Acids – Conjugate Addition of Nitroalkanes to Dehydroalanine Derivatives" *J. Chem. Soc., Perkin Trans. 1* **1998**, 1113-1121. (f) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. "Asymmetric Michael Addition of Nitroalkanes to Prochiral Acceptors Catalyzed by Proline Rubidium Salts" *Tetrahedron*, **1997**, 53, 11223-11236.

[30] For example: (a) Tormo, J. T.; Hays, D. S.; Fu, G. C. "Bu_3SnH-Catalyzed Reduction of Nitroalkanes to Alkanes" *J. Org. Chem.* **1998**, 63, 5296-5297. (b) Crossley, M. J.; Fung, Y. M.; Kyriakopoulos, E.; Potter, J. J. "New Synthetic Routes to Alpha-amino Acids – Reductive Denitration and Oxidative Transformations of Gamma-nitro-alpha-amino Acids" *J. Chem. Soc., Perkin Trans. 1* **1998**, 1123-1130. (c) Miklo, K.; Jasberenyi, J. C.; Kadas, I.; Arvai, G.; Toke, L. "Direct and Indirect Radical Denitrations of Intermediates in the Synthesis of Sorgolactone and its Nuclear Analogs" *Tetrahedron Lett.* **1996**, 37, 3491-3494. (d) Ballini, R.; Marcantoni, E.; Petrini, M. "A new Synthesis of Phoracantholide, Dihydrorecifeiolide, and Muscone via Alpha-nitro Ketones" *Liebigs Ann.* **1995**, 1381-1383. (e) Ballini, R.; Giantomassi, G. "A Novel Reactivity of Alpha-nitro Ketone Tosylhydrazones with DBU – Synthesis of Alpha, Beta-unsaturated Enone Tosylhydrazones" *Tetrahedron*, **1995**, 51, 4173-4182.

[31] For example: (a) Shahi, S. P; Vankar, Y. D. "Nef Reaction of Benzylic and Secondary

Nitro Compounds Using Bis(trimethylsilyl)peroxide" *Synth. Commun.* **1999**, 29, 4321-4325. (b) Kawakami, T.; Suzuki, H. "Masked Acylation of *m*-Dinitrobenzene and Derivatives with Nitroalkanes under Basic Conditions: Nitromethyl and α-(Hydroxyimino)alkylation" *Tetrahedron lett.* **1999**, 40, 1157-1160. (c) Waldermar, A.; Mieczyslaw, M.; Chantu, R.; Saha-Moller, C. R.; Cong-Gui, Z. "A Mild and Efficient Nef Reaction for the Conversion of Nitro to Carbonyl Group by Dimethyldioxirane (DMD) Oxidation of Nitronate Anions" *Synlett* **1998**, 1335-1336. (d) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F.; Rosati, O. "Oxone® Promoted Nef Reaction – Simple Conversion of Nitro Group into Carbonyl" *Synth. Commun.* **1998**, 28, 3057-3064.

[32] For example: (a) Ghosh, A. K.; Fidanze, S. "Asymmetric Synthesis of (-)-Tetrahydrolipstatin: An Anti-aldol-based Strategy" *Org. Lett.* **2000**, 2, 2405-2407. (b) Menzel, A.; Ohrlein, R.; Griesser, H.; Wehner, V.; Jager, V., "A Short Synthesis of L-Acosamine Based on Nitroaldol Addition. Analysis of the Key Step Concerning Solvent and Temperature Effects" *Synthesis* **1999**, 1691-1702. (c) Corey, E. J.; Zhang, F. Y. "Re- and Si-face-selective Nitroaldol Reactions Catalyzed by a Rigid Chiral Quaternary Ammonium Salt: A Highly Stereoselective Synthesis of the HIV Protease Inhibitor Amprenavir (Vertex 478)" *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 1931-1934. (d) Kisanga, P. B.; Verkade, J. G. "$P(RNCH_2CH_2)_3N$: An Efficient Promoter for the Nitroaldol (Henry) Reaction" *J. Org. Chem.* **1999**, 64, 4298-4303. (e) Shibasaki, M.; Sasai, H.; Arai, T. "Asymmetric Catalysis with Heterobimetallic Compounds" *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1237-1256.

[33] (a) Ono, N.; Kamimura, A.; Miyake, H.; Hamamoto, I.; Kaji, A. "New Synthetic Methods. Conjugate Addition of Alkyl Groups to Electron Deficient Olefins with Nitroalkanes as Alkyl Anion Equivalents" *J. Org. Chem.* **1985**, 50, 3692-3698. (b) Ono, N.; Kamimura, A.; Kaji, A. "Michael Addition of Secondary Nitroalkanes to β-

Substituted α,β-Unsaturated Compounds" *Synthesis* **1984**, 226-227.

[34] For example: (a) Beak, P.; Zajdel, W. J. "Dipole-Stabilized Carbanions: The α' Lithiation of Piperidides" *J. Am. Chem. Soc.* **1984**, 106, 1010-1018. (b) Quick, J.; Mondello, C.; Humora, M.; Brennen, T. "Synthesis of 2,6-Diacetonylpiperidine. X-ray Diffraction Analysis of its *N*-Benzoyl Derivatives" *J. Org. Chem.* **1978**, 43, 2705-2708. (c) Fraser, R. R.; Grindley T. B. "The "A" Value for the Methyl Group in 2-Methylpiperidines" *Tetrahedron Lett.* **1974**, 47, 4169-4172. (d) Chow, Y. L.; Colon, C. J.; Tam, J. N. S. "$A^{(1,\ 3)}$ Interaction and Conformational Energy of Axial-axial 1,3-Dimethyl Interaction" *Can. J. Chem.* **1968**, 46, 2821-2825. (e) Scott, J. W.; Durham, L. J.; deJongh, H. A. P.; Burckhardt, U.; Johnson, W. S. "Revision of the Configuration of Vertramine and Jervine" *Tetrahedron Lett.* **1967**, 25, 2381-2386.

[35] Johnson, F. "Allylic Strain in Six-membered Rings" *Chem. Rev.* **1968**, 68, 375-415.

[36] (a) Hoffmann, R. W. "Allylic 1,3-Strain as a Controlling Factor in Stereoselective Transformations" *Chem. Rev.* **1989**, 89, 1841-1860. (b) Brown, J. D.; Foley, M. A.; Comins, D. L. "A Highly Stereocontrolled, Four-Step Synthesis of Lasubine II" *J. Am. Chem. Soc.* **1988**, 110, 7445-7447.

[37] Muller, M.; Schoenfelder, A.; Didier, B.; Mann, A.; Wermuth, C. G. "The Synthesis of α-Amino-γ-substituted Adipic Acids: Stereoelectronic Effects during the 1,4-Addition of Organocuprates to Methyl *N-tert*-Butoxy-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate" *J. Chem. Soc., Chem. Commun.* **1999**, 683-684.

[38] Deslongchamps, P., in *Stereoelectronic Effects in Organic Chemistry,* Pergamon, Oxford, **1983**, p.209.

[39] Murray, P. J.; Starkey, I. D.; Davies, J. E. "The Enantiospecific Synthesis of Novel Lysine Analogues Incorporating a Pyrrolidine Containing Side Chain" *Tetrahedron Lett.* **1998**, 39, 6721-6724.

[40] Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. "Oxidation of Primary Alcohols to Carboxylic Acids with Sodium Chlorite Catalyzed by TEMPO and Bleach" *J. Org. Chem.* **1999**, 64, 2564-2566.

[41] (a) Hanessian, S.; Reinhold, U.; Saulnier, M.; Claridge, S. "Probing the Importance of Spacial and Conformational Domains in Captopril Analogs for Angiotensin Converting Enzyme Activity" *Bioorg. Med. Chem. Lett.* **1998**, 8, 2123-2128. (b) Hanessian, S.; Reinhold, U.; Gentile, G. "The Synthesis of Enantiopure ω-Methanoprolines and ω-Methanopipecolic Acids by a Novel Cyclopropanation Reaction: The Flattening of Proline" *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1881-1884.

[42] Still, W. C.; Kahn, M.; Mitra, A. "Rapid Chromatographic Techniques for Preparative Separations with Moderate Resolution" *J. Org. Chem.* **1978**, 43, 2923-2925.

Annex

CRYSTAL AND MOLECULAR STRUCTURE OF

C15 H24 N2 O7 COMPOUND (HAN286)

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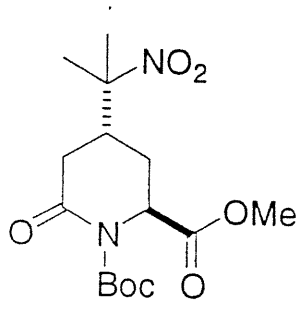


Structure résolue au laboratoire de diffraction des rayons X de l'Université de Montréal par Dr. Michel Simard.

Table 1. Crystal data and structure refinement for C15 H24 N2 O7.

Identification code	HAN286
Empirical formula	C15 H24 N2 O7
Formula weight	344.362
Temperature	293(2)K
Wavelength	1.54178Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.3560(2)Å α = 90° b = 16.3419(4)Å β = 90° c = 17.1211(5)Å γ = 90°
Volume	1778.35(9)$Å^3$
Z	4
Density (calculated)	1.2862 Mg/m^3
Absorption coefficient	0.863 mm^{-1}
F(000)	736.0
Crystal size	0.68 x 0.06 x 0.06 mm
Theta range for data collection	3.74 to 72.95°
Index ranges	-6<=h<=7, -20<=k<=20, -21<=l<=21
Reflections collected	21550
Independent reflections	3529 [R(int) = 0.0507]
Absorption correction	Multi-scan
Max. and min. transmission	0.9640 and 0.8340
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3529 / 0 / 223
Goodness-of-fit on F^2	0.987
Final R indices [I>2sigma(I)]	R1 = 0.0576, wR2 = 0.1455
R indices (all data)	R1 = 0.0806, wR2 = 0.1564
Absolute structure parameter	0.2(4)
Largest diff. peak and hole	0.176 and -0.160 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C15 H24 N2 O7.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(6)	2658(4)	6073(2)	64(1)	80(1)
O(7)	5463(4)	5029(2)	-491(2)	92(1)
O(8)	8124(4)	4886(1)	329(1)	60(1)
O(12)	6705(4)	5276(2)	1996(2)	73(1)
O(13)	10009(3)	5742(1)	1947(1)	63(1)
O(141)	2025(6)	7416(3)	2858(2)	120(1)
O(142)	1245(5)	8373(2)	2071(3)	135(2)
N(1)	6041(4)	5961(1)	494(1)	44(1)
N(14)	2491(5)	7929(2)	2383(2)	72(1)
C(2)	7747(4)	6245(2)	1006(1)	37(1)
C(3)	7362(4)	7110(2)	1315(2)	44(1)
C(4)	5190(4)	7178(2)	1660(2)	39(1)
C(5)	3673(5)	7050(2)	982(2)	60(1)
C(6)	4061(5)	6318(2)	474(2)	49(1)
C(7)	6445(5)	5246(2)	50(2)	52(1)
C(8)	8997(6)	4104(2)	22(2)	59(1)
C(9)	10708(8)	3915(2)	596(3)	98(2)
C(10)	9859(7)	4259(3)	-775(2)	84(1)
C(11)	7344(8)	3448(2)	35(3)	109(2)
C(12)	8050(5)	5681(2)	1696(2)	45(1)
C(13)	10598(8)	5311(3)	2647(3)	94(1)
C(14)	4806(4)	7982(2)	2113(2)	49(1)
C(15)	5103(7)	8742(2)	1638(2)	76(1)
C(16)	6100(6)	8009(3)	2856(2)	77(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C15 H24 N2 O7.

	x	y	z	U(eq)
H(2)	9054	6250	703	45
H(3A)	8402	7240	1711	53
H(3B)	7513	7501	893	53
H(4)	5003	6723	2026	47
H(5A)	2260	7008	1193	71
H(5B)	3714	7534	654	71
H(9A)	11701	4358	606	146
H(9B)	11411	3420	444	146
H(9C)	10108	3847	1107	146
H(10A)	10664	4756	-772	126
H(10B)	8721	4310	-1141	126
H(10C)	10748	3811	-927	126
H(11A)	7968	2933	-104	163
H(11B)	6255	3580	-332	163
H(11C)	6753	3410	550	163
H(13A)	10107	5608	3095	141
H(13B)	12101	5262	2670	141
H(13C)	9977	4775	2643	141
H(15A)	4735	9211	1946	113
H(15B)	4217	8719	1184	113
H(15C)	6547	8783	1478	113
H(16A)	7561	8072	2726	115
H(16B)	5907	7509	3142	115
H(16C)	5652	8463	3171	115

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C15 H24 N2 O7.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$$

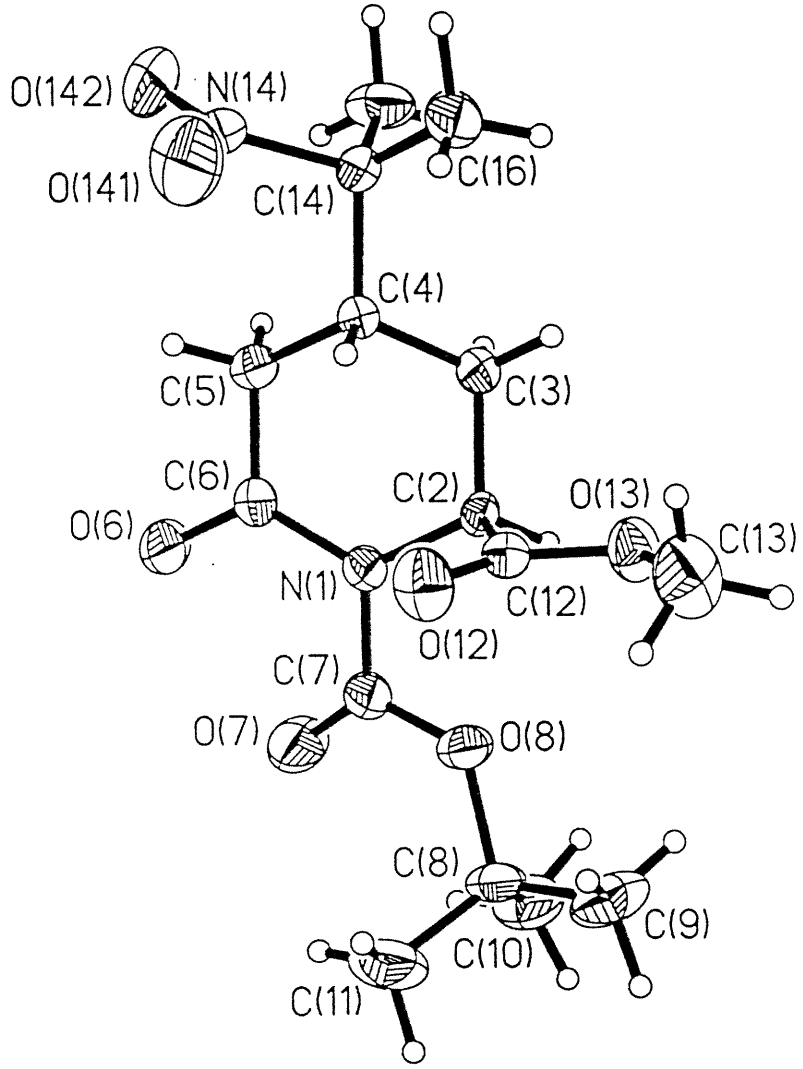
	U11	U22	U33	U23	U13	U12
O(6)	55(2)	92(2)	93(2)	-38(2)	-28(1)	14(1)
O(7)	79(2)	107(2)	89(2)	-53(2)	-24(2)	25(2)
O(8)	65(2)	49(1)	65(1)	-15(1)	-5(1)	12(1)
O(12)	68(2)	78(2)	73(2)	23(1)	0(1)	-12(1)
O(13)	55(1)	66(1)	67(1)	14(1)	-18(1)	-2(1)
O(141)	93(2)	143(3)	125(3)	0(3)	54(2)	-32(2)
O(142)	56(2)	104(3)	244(5)	-46(3)	-11(2)	23(2)
N(1)	41(1)	47(1)	43(1)	-6(1)	-3(1)	-1(1)
N(14)	49(2)	68(2)	97(2)	-41(2)	11(2)	0(2)
C(2)	29(1)	43(2)	40(1)	-2(1)	2(1)	3(1)
C(3)	40(2)	41(2)	52(2)	-1(1)	-1(1)	-3(1)
C(4)	33(1)	38(1)	46(1)	-4(1)	0(1)	-2(1)
C(5)	48(2)	59(2)	72(2)	-24(2)	-9(2)	10(2)
C(6)	40(2)	52(2)	55(2)	-4(2)	-8(1)	0(1)
C(7)	48(2)	56(2)	54(2)	-13(2)	-2(1)	-1(1)
C(8)	71(2)	33(2)	72(2)	-8(2)	13(2)	6(1)
C(9)	117(4)	69(3)	106(3)	-3(2)	-11(3)	45(3)
C(10)	99(3)	72(2)	81(2)	-9(2)	28(2)	9(2)
C(11)	120(4)	45(2)	162(4)	-9(3)	31(4)	-12(2)
C(12)	44(2)	39(2)	51(2)	-1(1)	-1(1)	1(1)
C(13)	100(3)	93(3)	89(3)	34(3)	-41(2)	-3(3)
C(14)	36(2)	48(2)	62(2)	-12(2)	7(1)	-1(1)
C(15)	98(3)	43(2)	86(2)	-11(2)	14(2)	1(2)
C(16)	62(2)	95(3)	74(2)	-38(2)	-4(2)	-2(2)

Table 5. Bond lengths [Å] and angles [°] for C15 H24 N2 O7

O(6)-C(6)	1.204(3)	O(7)-C(7)	1.171(4)
O(8)-C(7)	1.309(4)	O(8)-C(8)	1.489(3)
O(12)-C(12)	1.196(4)	O(13)-C(12)	1.321(3)
O(13)-C(13)	1.439(4)	O(141)-N(14)	1.205(4)
O(142)-N(14)	1.200(5)	N(1)-C(6)	1.387(4)
N(1)-C(7)	1.418(4)	N(1)-C(2)	1.470(3)
N(14)-C(14)	1.545(4)	C(2)-C(12)	1.511(4)
C(2)-C(3)	1.529(4)	C(3)-C(4)	1.505(4)
C(4)-C(5)	1.525(4)	C(4)-C(14)	1.544(4)
C(5)-C(6)	1.499(4)	C(8)-C(10)	1.492(5)
C(8)-C(9)	1.498(5)	C(8)-C(11)	1.502(5)
C(14)-C(15)	1.496(4)	C(14)-C(16)	1.516(5)
C(7)-O(8)-C(8)	124.1(3)	C(12)-O(13)-C(13)	118.6(3)
C(6)-N(1)-C(7)	119.9(2)	C(6)-N(1)-C(2)	123.4(2)
C(7)-N(1)-C(2)	116.5(2)	O(142)-N(14)-O(141)	124.0(4)
O(142)-N(14)-C(14)	117.5(4)	O(141)-N(14)-C(14)	118.4(3)
N(1)-C(2)-C(12)	111.6(2)	N(1)-C(2)-C(3)	112.4(2)
C(12)-C(2)-C(3)	108.3(2)	C(4)-C(3)-C(2)	110.5(2)
C(3)-C(4)-C(5)	105.7(2)	C(3)-C(4)-C(14)	113.8(2)
C(5)-C(4)-C(14)	113.5(2)	C(6)-C(5)-C(4)	116.5(3)
O(6)-C(6)-N(1)	123.1(3)	O(6)-C(6)-C(5)	118.8(3)
N(1)-C(6)-C(5)	118.1(3)	O(7)-C(7)-O(8)	126.0(3)
O(7)-C(7)-N(1)	125.2(3)	O(8)-C(7)-N(1)	108.8(2)
O(8)-C(8)-C(10)	108.3(3)	O(8)-C(8)-C(9)	102.4(3)
C(10)-C(8)-C(9)	111.6(3)	O(8)-C(8)-C(11)	110.3(3)
C(10)-C(8)-C(11)	113.1(4)	C(9)-C(8)-C(11)	110.5(3)
O(12)-C(12)-O(13)	125.1(3)	O(12)-C(12)-C(2)	125.5(3)
O(13)-C(12)-C(2)	109.2(2)	C(15)-C(14)-C(16)	111.3(3)
C(15)-C(14)-C(4)	114.4(2)	C(16)-C(14)-C(4)	111.1(3)
C(15)-C(14)-N(14)	109.2(3)	C(16)-C(14)-N(14)	105.5(3)
C(4)-C(14)-N(14)	104.6(2)		

Table 6. Torsion angles [°] for C15 H24 N2 O7.

C(6)-N(1)-C(2)-C(12)	104.0(3)
C(7)-N(1)-C(2)-C(12)	-71.0(3)
C(6)-N(1)-C(2)-C(3)	-17.8(4)
C(7)-N(1)-C(2)-C(3)	167.1(2)
N(1)-C(2)-C(3)-C(4)	50.4(3)
C(12)-C(2)-C(3)-C(4)	-73.4(3)
C(2)-C(3)-C(4)-C(5)	-64.7(3)
C(2)-C(3)-C(4)-C(14)	170.0(2)
C(3)-C(4)-C(5)-C(6)	49.6(4)
C(14)-C(4)-C(5)-C(6)	175.1(3)
C(7)-N(1)-C(6)-O(6)	-3.7(4)
C(2)-N(1)-C(6)-O(6)	-178.6(3)
C(7)-N(1)-C(6)-C(5)	177.2(3)
C(2)-N(1)-C(6)-C(5)	2.3(4)
C(4)-C(5)-C(6)-O(6)	161.6(3)
C(4)-C(5)-C(6)-N(1)	-19.2(4)
C(8)-O(8)-C(7)-O(7)	-3.5(5)
C(8)-O(8)-C(7)-N(1)	178.4(2)
C(6)-N(1)-C(7)-O(7)	20.7(5)
C(2)-N(1)-C(7)-O(7)	-164.0(3)
C(6)-N(1)-C(7)-O(8)	-161.1(3)
C(2)-N(1)-C(7)-O(8)	14.1(3)
C(7)-O(8)-C(8)-C(10)	68.6(4)
C(7)-O(8)-C(8)-C(9)	-173.3(3)
C(7)-O(8)-C(8)-C(11)	-55.6(4)
C(13)-O(13)-C(12)-O(12)	-1.9(5)
C(13)-O(13)-C(12)-C(2)	174.5(3)
N(1)-C(2)-C(12)-O(12)	-29.2(4)
C(3)-C(2)-C(12)-O(12)	95.0(4)
N(1)-C(2)-C(12)-O(13)	154.4(2)
C(3)-C(2)-C(12)-O(13)	-81.4(3)
C(3)-C(4)-C(14)-C(15)	58.5(3)
C(5)-C(4)-C(14)-C(15)	-62.5(4)
C(3)-C(4)-C(14)-C(16)	-68.6(3)
C(5)-C(4)-C(14)-C(16)	170.4(3)
C(3)-C(4)-C(14)-N(14)	178.0(3)
C(5)-C(4)-C(14)-N(14)	57.0(3)
O(142)-N(14)-C(14)-C(15)	13.9(4)
O(141)-N(14)-C(14)-C(15)	-170.2(3)
O(142)-N(14)-C(14)-C(16)	133.7(4)
O(141)-N(14)-C(14)-C(16)	-50.4(4)
O(142)-N(14)-C(14)-C(4)	-109.0(3)
O(141)-N(14)-C(14)-C(4)	66.9(4)



ORTEP view of the C15 H24 N2 O7

compound with the numbering scheme adopted. Ellipsoids drawn at

30% probality level. Hydrogens represented by sphere of arbitrary size.

REFERENCES

Flack, H.D. (1983). Acta Cryst. A39, 876-881.

International Tables for Crystallography (1992). Vol. C. Tables 4.2.6.8 and 6.1.1.4, Dordrecht: Kluwer Academic Publishers.

SAINT (1999) Release 6.06; Integration Software for Single Crystal Data. Bruker AXS Inc., Madison, WI 53719-1173.

Sheldrick, G.M. (1996). SADABS, Bruker Area Detector Absorption Corrections. Bruker AXS Inc., Madison, WI 53719-1173.

Sheldrick, G.M. (1997). SHELXS97, Program for the Solution of Crystal Structures. Univ. of Gottingen, Germany.

Sheldrick, G.M. (1996). SHELXL96, Program for the Refinement of Crystal Structures. Univ. of Gottingen, Germany.

SHELXTL (1997) Release 5.10; The Complete Software Package for Single Crystal Structure Determination. Bruker AXS Inc., Madison, WI 53719-1173.

SMART (1999) Release 5.059; Bruker Molecular Analysis Research Tool. Bruker AXS Inc., Madison, WI 53719-1173.

Spek, A.L. (1995. PLATON, Molecular Geometry Program, July 1995 version. University of Utrecht, Utrecht, Holland.

XPREP (1997) Release 5.10; X-ray data Preparation and Reciprocal space Exploration Program. Bruker AXS Inc., Madison, WI 53719-1173.

CRYSTAL AND MOLECULAR STRUCTURE OF

C13 H18 N2 O7 COMPOUND (HAN282)

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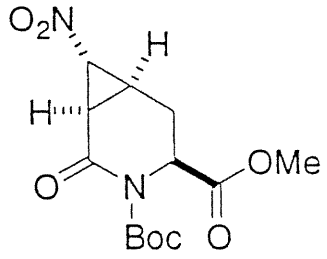


Structure résolue au laboratoire de diffraction des rayons X de l'Université de Montréal par Dr. Michel Simard.

Table 1. Crystal data and structure refinement for C13 H18 N2 O7.

Identification code	HAN282
Empirical formula	C13 H18 N2 O7
Formula weight	314.294
Temperature	293(2)K
Wavelength	1.54178Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 10.4922(2)Å α = 90° b = 6.3802(2)Å β = 114.5290(10)° c = 12.3684(3)Å γ = 90°
Volume	753.25(3)$Å^3$
Z	2
Density (calculated)	1.3857 Mg/m^3
Absorption coefficient	0.970 mm^{-1}
F(000)	332.0
Crystal size	0.80 x 0.24 x 0.05 mm
Theta range for data collection	3.93 to 72.64°
Index ranges	-12<=h<=10, -6<=k<=7, -13<=l<=15
Reflections collected	5693
Independent reflections	2343 [R(int) = 0.0300]
Absorption correction	Multi-scan
Max. and min. transmission	0.9720 and 0.6600
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2343 / 1 / 198
Goodness-of-fit on F^2	1.094
Final R indices [I>2sigma(I)]	R1 = 0.0615, wR2 = 0.1717
R indices (all data)	R1 = 0.0671, wR2 = 0.1770
Absolute structure parameter	0.0(3)
Largest diff. peak and hole	0.328 and -0.308 $e.Å^{-3}$

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for C13 H18 N2 O7.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(2)	4901(3)	6599(4)	5940(3)	68(1)
O(8)	2849(3)	3789(5)	5511(3)	73(1)
O(9)	3630(2)	1183(4)	6850(3)	68(1)
O(13)	6090(3)	2638(5)	9082(2)	63(1)
O(14)	6585(3)	-688(5)	8854(2)	68(1)
O(71)	9573(4)	6990(6)	9931(4)	100(1)
O(72)	9903(3)	7310(6)	8327(4)	93(1)
N(3)	5214(3)	3233(4)	6620(2)	43(1)
N(7)	9285(3)	6603(6)	8888(4)	66(1)
C(1)	7217(3)	5554(5)	6976(3)	45(1)
C(2)	5685(3)	5220(5)	6468(3)	45(1)
C(4)	6162(3)	1488(5)	7241(3)	41(1)
C(5)	7586(3)	1614(5)	7182(3)	45(1)
C(6)	8214(3)	3757(5)	7382(3)	46(1)
C(7)	8114(3)	5169(5)	8301(3)	48(1)
C(8)	3758(4)	2830(6)	6243(3)	50(1)
C(9)	2275(4)	223(7)	6649(4)	59(1)
C(10)	2740(5)	-1595(9)	7539(5)	84(1)
C(11)	1571(6)	-511(10)	5394(4)	89(2)
C(12)	1400(6)	1735(11)	6959(4)	93(2)
C(13)	6266(3)	1277(5)	8497(3)	46(1)
C(14)	6694(5)	-1175(11)	10027(5)	90(2)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C13 H18 N2 O7.

	x	y	z	U(eq)
H(1)	7525	6726	6630	54
H(4)	5713	203	6821	49
H(5A)	8230	674	7773	54
H(5B)	7483	1123	6407	54
H(6)	9066	3904	7247	55
H(7)	7637	4623	8775	57
H(10A)	3290	-2565	7319	125
H(10B)	1929	-2297	7536	125
H(10C)	3292	-1059	8321	125
H(11A)	1244	676	4875	134
H(11B)	791	-1390	5305	134
H(11C)	2225	-1294	5194	134
H(12A)	1903	2196	7764	140
H(12B)	546	1064	6877	140
H(12C)	1185	2920	6434	140
H(14A)	7494	-474	10609	134
H(14B)	6797	-2661	10154	134
H(14C)	5862	-714	10100	134

Table 4. Anisotropic parameters ($Å^2 \times 10^3$) for C13 H18 N2 O7.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$$

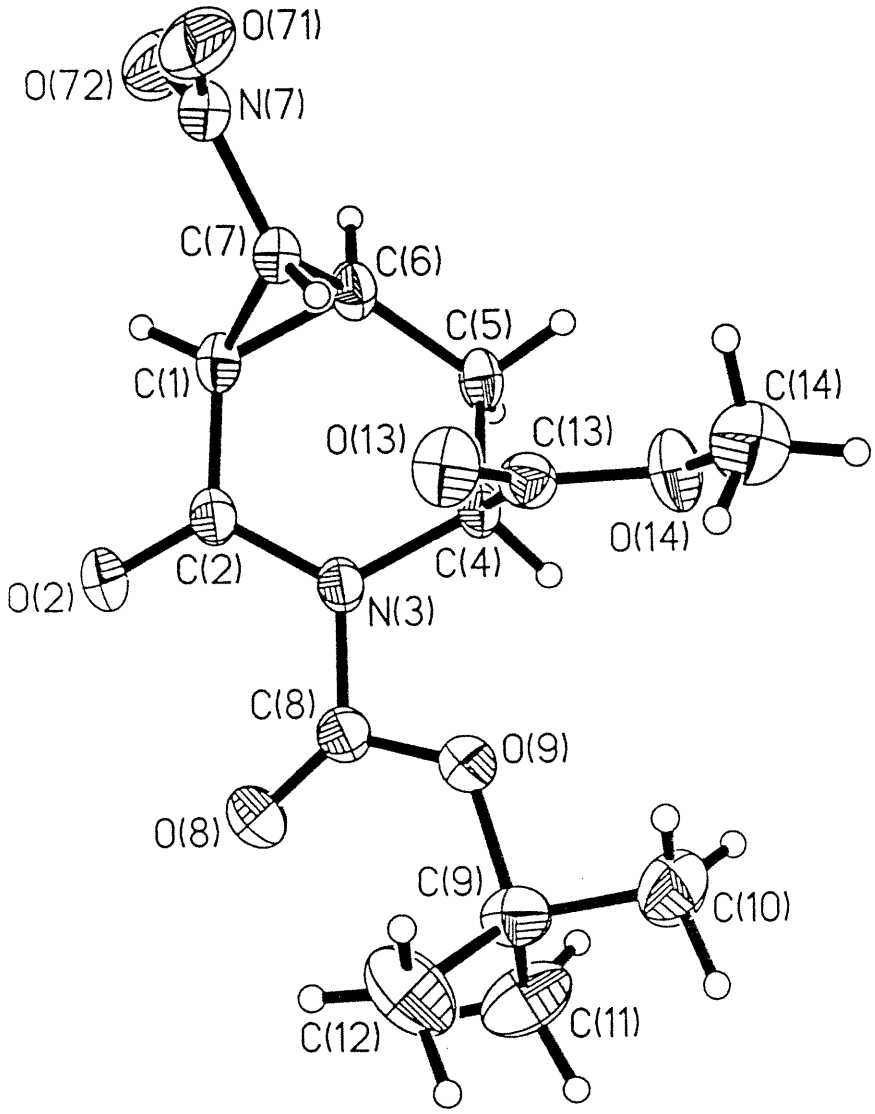
	U11	U22	U33	U23	U13	U12
O(2)	63(1)	41(1)	83(2)	16(1)	14(1)	11(1)
O(8)	56(2)	64(2)	75(2)	20(2)	3(1)	9(1)
O(9)	46(1)	55(2)	88(2)	19(1)	13(1)	0(1)
O(13)	85(2)	59(2)	57(2)	-4(1)	39(1)	2(1)
O(14)	92(2)	54(2)	59(2)	23(1)	34(1)	18(1)
O(71)	104(2)	70(2)	83(2)	-20(2)	-5(2)	-21(2)
O(72)	70(2)	73(2)	140(3)	0(2)	47(2)	-17(2)
N(3)	47(1)	34(2)	43(1)	1(1)	14(1)	5(1)
N(7)	55(2)	39(2)	88(3)	0(2)	13(2)	2(1)
C(1)	58(2)	33(2)	47(2)	7(1)	23(1)	3(1)
C(2)	52(2)	35(2)	44(2)	2(1)	17(1)	6(1)
C(4)	49(2)	28(1)	43(2)	1(1)	15(1)	5(1)
C(5)	61(2)	30(2)	47(2)	-1(1)	27(1)	11(1)
C(6)	50(2)	37(2)	59(2)	7(2)	31(2)	8(1)
C(7)	46(2)	35(2)	57(2)	2(1)	17(2)	2(1)
C(8)	48(2)	43(2)	49(2)	-4(2)	9(1)	1(1)
C(9)	52(2)	63(2)	61(2)	-13(2)	25(2)	-4(2)
C(10)	82(3)	73(3)	109(4)	18(3)	52(3)	-8(2)
C(11)	100(4)	102(4)	70(3)	-36(3)	41(3)	-42(3)
C(12)	93(3)	121(5)	72(3)	3(3)	39(3)	40(4)
C(13)	43(2)	48(2)	47(2)	2(2)	19(1)	1(1)

Table 5. Bond lengths [Å] and angles [°] for C13 H18 N2 O7

O(2)-C(2)	1.197(4)	O(8)-C(8)	1.177(4)
O(9)-C(8)	1.331(4)	O(9)-C(9)	1.471(5)
O(13)-C(13)	1.193(4)	O(14)-C(13)	1.325(4)
O(14)-C(14)	1.442(6)	O(71)-N(7)	1.222(5)
O(72)-N(7)	1.217(5)	N(3)-C(2)	1.401(4)
N(3)-C(8)	1.423(4)	N(3)-C(4)	1.478(4)
N(7)-C(7)	1.461(5)	C(1)-C(2)	1.479(5)
C(1)-C(6)	1.491(4)	C(1)-C(7)	1.533(5)
C(4)-C(13)	1.518(5)	C(4)-C(5)	1.528(5)
C(5)-C(6)	1.493(5)	C(6)-C(7)	1.488(5)
C(9)-C(12)	1.488(6)	C(9)-C(11)	1.491(6)
C(9)-C(10)	1.533(7)		
C(8)-O(9)-C(9)	123.4(3)	C(13)-O(14)-C(14)	116.3(4)
C(2)-N(3)-C(8)	120.6(3)	C(2)-N(3)-C(4)	123.6(3)
C(8)-N(3)-C(4)	115.7(2)	O(72)-N(7)-O(71)	124.8(4)
O(72)-N(7)-C(7)	119.1(4)	O(71)-N(7)-C(7)	116.1(4)
C(2)-C(1)-C(6)	121.2(3)	C(2)-C(1)-C(7)	120.5(3)
C(6)-C(1)-C(7)	58.9(2)	O(2)-C(2)-N(3)	122.5(3)
O(2)-C(2)-C(1)	120.4(3)	N(3)-C(2)-C(1)	117.1(3)
N(3)-C(4)-C(13)	110.2(3)	N(3)-C(4)-C(5)	113.3(3)
C(13)-C(4)-C(5)	113.4(3)	C(6)-C(5)-C(4)	114.4(2)
C(7)-C(6)-C(1)	62.0(2)	C(7)-C(6)-C(5)	121.0(3)
C(1)-C(6)-C(5)	116.7(3)	N(7)-C(7)-C(6)	116.6(3)
N(7)-C(7)-C(1)	116.6(3)	C(6)-C(7)-C(1)	59.1(2)
O(8)-C(8)-O(9)	127.2(4)	O(8)-C(8)-N(3)	125.1(4)
O(9)-C(8)-N(3)	107.7(3)	O(9)-C(9)-C(12)	110.1(4)
O(9)-C(9)-C(11)	109.5(3)	C(12)-C(9)-C(11)	112.3(4)
O(9)-C(9)-C(10)	101.3(3)	C(12)-C(9)-C(10)	110.6(4)
C(11)-C(9)-C(10)	112.5(4)	O(13)-C(13)-O(14)	124.6(3)
O(13)-C(13)-C(4)	126.4(3)	O(14)-C(13)-C(4)	109.0(3)

Table 6. Torsion angles [°] for C13 H18 N2 O7.

C(8)-N(3)-C(2)-O(2)	-6.0(5)
C(4)-N(3)-C(2)-O(2)	178.3(3)
C(8)-N(3)-C(2)-C(1)	175.0(3)
C(4)-N(3)-C(2)-C(1)	-0.7(5)
C(6)-C(1)-C(2)-O(2)	-165.5(3)
C(7)-C(1)-C(2)-O(2)	124.7(4)
C(6)-C(1)-C(2)-N(3)	13.5(5)
C(7)-C(1)-C(2)-N(3)	-56.3(4)
C(2)-N(3)-C(4)-C(13)	100.9(3)
C(8)-N(3)-C(4)-C(13)	-75.0(3)
C(2)-N(3)-C(4)-C(5)	-27.5(4)
C(8)-N(3)-C(4)-C(5)	156.7(3)
N(3)-C(4)-C(5)-C(6)	43.0(4)
C(13)-C(4)-C(5)-C(6)	-83.7(3)
C(2)-C(1)-C(6)-C(7)	-109.1(3)
C(2)-C(1)-C(6)-C(5)	3.6(5)
C(7)-C(1)-C(6)-C(5)	112.7(3)
C(4)-C(5)-C(6)-C(7)	40.0(4)
C(4)-C(5)-C(6)-C(1)	-31.8(4)
O(72)-N(7)-C(7)-C(6)	33.4(5)
O(71)-N(7)-C(7)-C(6)	-146.2(4)
O(72)-N(7)-C(7)-C(1)	-33.6(5)
O(71)-N(7)-C(7)-C(1)	146.8(3)
C(1)-C(6)-C(7)-N(7)	-106.5(3)
C(5)-C(6)-C(7)-N(7)	147.7(3)
C(5)-C(6)-C(7)-C(1)	-105.9(3)
C(2)-C(1)-C(7)-N(7)	-143.1(3)
C(6)-C(1)-C(7)-N(7)	106.5(3)
C(2)-C(1)-C(7)-C(6)	110.4(3)
C(9)-O(9)-C(8)-O(8)	2.9(6)
C(9)-O(9)-C(8)-N(3)	-176.2(3)
C(2)-N(3)-C(8)-O(8)	23.0(5)
C(4)-N(3)-C(8)-O(8)	-161.0(4)
C(2)-N(3)-C(8)-O(9)	-157.9(3)
C(4)-N(3)-C(8)-O(9)	18.1(4)
C(8)-O(9)-C(9)-C(12)	-64.5(5)
C(8)-O(9)-C(9)-C(11)	59.4(5)
C(8)-O(9)-C(9)-C(10)	178.4(4)
C(14)-O(14)-C(13)-O(13)	1.2(6)
C(14)-O(14)-C(13)-C(4)	-178.7(3)
N(3)-C(4)-C(13)-O(13)	-26.1(5)
C(5)-C(4)-C(13)-O(13)	102.2(4)
N(3)-C(4)-C(13)-O(14)	153.7(3)
C(5)-C(4)-C(13)-O(14)	-78.0(3)



ORTEP view of the C13 H18 N2 O7

compound with the numbering scheme adopted. Ellipsoids drawn at

30% probality level. Hydrogens represented by sphere of arbitrary size.

REFERENCES

Flack, H.D. (1983). Acta Cryst. A39, 876-881.

Flack, H.D. and Schwarzenbach, D. (1988). Acta Cryst. A44, 499-506.

International Tables for Crystallography (1992). Vol. C. Tables 4.2.6.8 and 6.1.1.4, Dordrecht: Kluwer Academic Publishers.

SAINT (1999) Release 6.06; Integration Software for Single Crystal Data. Bruker AXS Inc., Madison, WI 53719-1173.

Sheldrick, G.M. (1996). SADABS, Bruker Area Detector Absorption Corrections. Bruker AXS Inc., Madison, WI 53719-1173.

Sheldrick, G.M. (1997). SHELXS97, Program for the Solution of Crystal Structures. Univ. of Gottingen, Germany.

Sheldrick, G.M. (1996). SHELXL96, Program for the Refinement of Crystal Structures. Univ. of Gottingen, Germany.

SHELXTL (1997) Release 5.10; The Complete Software Package for Single Crystal Structure Determination. Bruker AXS Inc., Madison, WI 53719-1173.

SMART (1999) Release 5.059; Bruker Molecular Analysis Research Tool. Bruker AXS Inc., Madison, WI 53719-1173.

Spek, A.L. (1995. PLATON, Molecular Geometry Program, July 1995 version. University of Utrecht, Utrecht, Holland.

XPREP (1997) Release 5.10; X-ray data Preparation and Reciprocal space Exploration Program. Bruker AXS Inc., Madison, WI 53719-1173.