Bicyclic γ-Lactam Lactone as Chiral non-Racemic Intermediates: Synthesis of (+)-(1*S*, 8a*S*)-1-Hydroxyindolizidine and an Approach to (–)-Slaframine

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in Chemistry

University of Regina

By

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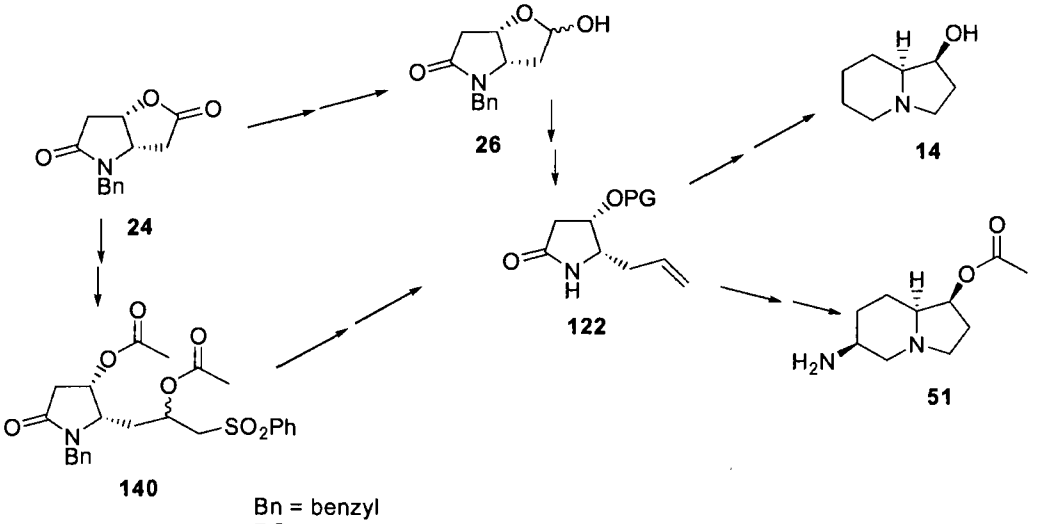
SUPERVISORY AND EXAMINING COMMITTEE

Hypolite Mwinasung Bayirinoba, candidate for the degree of Master of Science in Chemistry, has presented a thesis titled, **Bicyclic γ-Lactam Lactone as Chiral non-Racemic Intermediates: Synthesis of (+)-(1*S*, 8a*S*)-1-Hydroxyindolizidine and an Approach to (—)-Slaframine**, in an oral examination held on October 15, 2008. The following committee members have found the thesis acceptable in form and content, and that the candidate demonstrated satisfactory knowledge of the subject material.

External Examiner:	Dr. Hairuo Qing, Department of Geology
Supervisor:	Dr. Andrew Wee, Department of Chemistry and Biochemistry
Committee Member:	Dr. Dae-Yeon Suh, Department of Chemistry and Biochemistry
Committee Member:	Dr. Ronald Treble, Adjunct Professor, Department of Chemistry and Biochemistry
Chair of Defense:	Dr. Stephen Kirkland, Department of Mathematics and Statistics

Abstract

The synthesis of (+)-(1*S*, 8a*S*)-1-hydroxyindolizidine was achieved and an approach towards the synthesis of (–)-slaframine was developed starting from the chiral bicycli γ-lactam lactone **24**. The alkene system **122** was prepared from **24** and served as a commom intermediate in both syntheses. A direct route to **122** from the chiral bicyclic γ-lactam lactol **26** by means of the Wittig reaction using methylphosphonium ylide was unsuccessful. An indirect route to **122** that involved the reduction of the lactol and subsequent oxidation of the resulting 1° alcohol to the aldehyde prior to the Wittig olefination was employed to furnish **122**, the overall yield of which was low due to the many synthetic steps involved.



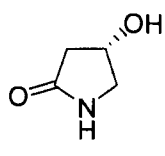
The problem of the low yield was addressed by the use of an alternative route. The Julia-Lythgoe olefination was investigated and this enabled the synthesis of the desired alkene system in good yield.

In the ring closing metathesis (RCM) studies towards the formation of compound **126**, it was found that the Grubbs II catalyst gave the best results in terms of faster conversion rates and yields of the cyclized products. The yields were also found to be a function of the reaction temperature as toluene gave higher yields of **126** compared with CH_2Cl_2.

The ability of the dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate] catalyst to resolve a racemic mixture of diazoacetates was also tested in this study. It was established that while the catalyst may be efficient in effecting C-H insertion reaction of chiral γ-lactam diazoacetates with high regio- and diastereoselectivity, it cannot effect the kinetic resolution of a racemate.

The study also established that the *N*-protecting group on a chiral γ-lactam diazoacetate has an effect on the outcome of the dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate] catalyzed C-H insertion reaction which is evidenced by the varying yields obtained for each of the *N*-protecting groups studied.

Two methods were investigated towards the synthesis of the chiral 4-hydroxy-2-pyrrolidinone (**85**). We found the method that involves the use of the chiral 4-hydroxy-2-butyrolactone (**96**) as starting compound to be the best method as it gave the target compound in high overall yields.



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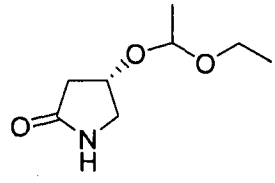

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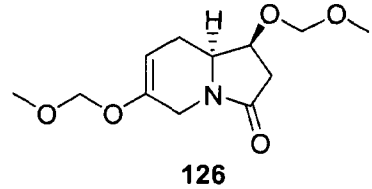

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Scholarships from the Faculty of Graduate Studies and Research (FGSR), teaching assistantships from the Department of Chemistry and Biochemistry and research assistantships from Dr. Wee's NSERC research grant are gratefully acknowledged.

Finally, the author would like to thank the Bayirinoba and Dibaar families in Ghana for their support and constant prayers throughout the author's graduate studies.

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List of Schemes

List of Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
AcCl	acetyl chloride
AIBN	2,2'-azobis(isobutyronitrile)
aq	aqueous
Bn	benzyl
$(BOC)_2O$	di-*tert*-butyl dicarbonate
BOC	*tert*-butoxycarbonyl
br	broad
BzCl	benzoyl chloride
calcd	calculated
CI	chemical ionization
d	doublet
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DMA	*N,N*-dimethylaniline

DMAP	4-(*N,N*-dimethylamino)pyridine
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
EI	electron impact ionization
eq	equivalence
Eq	equation
EtOAc	ethyl acetate
EtOH	ethanol
EVE	ethyl vinyl ether
Fig	figure
h	hour
^{1}H	proton
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectra
IR	infra red
LAH	lithium aluminium hydride

Lit	literature
M	molarity
MeOH	methanol
min	minutes
mmol	millimole
MOM	methoxymethyl
NMR	nuclear magnetic resonance
OAc	acetate
PE	petroleum ether
PhMe	toluene
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
psi	pounds per square inch
Py	pyridine
q	quartet
quant	quantitative
RCM	ring closing metathesis

Red-Al®	sodium bis(2-methoxyethoxy)aluminiumhydride
Rh_2(4*S*-MPPIM)$_4$	dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate]
$Rh_2(OAc)_4$	dirhodium(II) tetraacetate
rt	room temperature
s	singlet
SEM	[β-(trimethylsilyl)ethoxy]methyl
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilylether
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMSOTf	trimethylsilyl triflate
TsOH	*p*-toluenesulfonic acid

CHAPTER 1

1.1 INTRODUCTION

Indolizidine alkaloids, examples of which are as shown in Figure 1 abound in nature appearing in plants as well as in animals. Indolizidine alkaloids have been isolated from orchids (*Dendrobium*), *Tylophora* and *Leguminosae* family of plants. In the animal kingdom, indolizidine alkaloids have been isolated from ants (*Monomorium*) and poison-arrow frogs (*Dendrobates*) species. The 1-azabicycle[4.3.0]-nonane ring system **1** (Fig.1) is derived from the amino acid lysine which is the biological precursor for indolizidine alkaloids.[1,2]

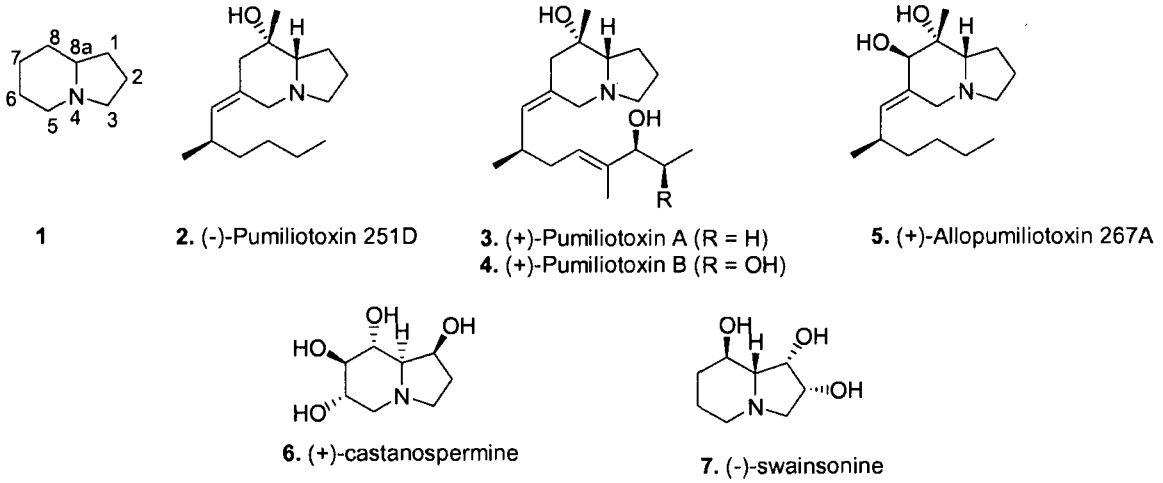


Figure 1: Representative indolizidine alkaloids

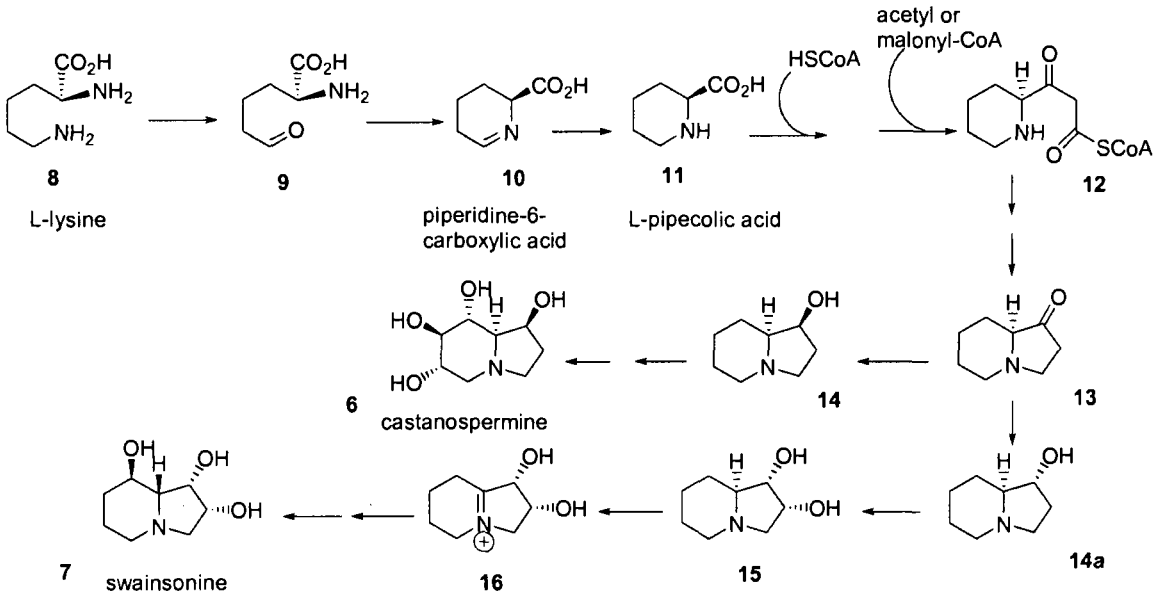
Indolizidine alkaloids are known to elicit desirable and undesirable biological activities.[1,2] The polyhydroxylated alkaloids (+)-**6** and (–)-**7**[3,4m] (Fig.1) possess anti-HIV properties due to its ability to inhibit endoplasmic recticulum α-glucosidase I, which is

responsible for glycoprotein biosynthesis. The HIV requires the glycoprotein in order to multiply. The desirable biological activities coupled with the structural diversity have made indolizidine alkaloids very attractive targets for synthesis over the last thirty years.

Of the many classes of indolizidines, the pumiliotoxins and polyhydroxylated alkaloids constitute the most important classes, with the syntheses and biological activity of these having been widely studied.[4] Pumiliotoxins possess a bicyclic indolizidine core that has a hydroxyl and methyl group at C-8 and an (Z)-configured alkylidene side chain at C-6. Daly and co-workers[5] have shown that the substitution pattern in the alkylidene side chain dictates some of the biological activities of the pumiliotoxins, e.g., (+)-pumiliotoxin 251D (**2**) is a cardiac depressant while both (+)-pumiliotoxin A (**3**) and B (**4**) are cardiac stimulants. Pumiliotoxins are obtained from the skin secretions frogs that belong to the family *Dendrobatidae* found in the rain forests of western Colombia, Panama and Ecuador. The indigenous peoples of Colombia and Panama are known to use these secretions to poison the heads of their blow darts. The alkaloids are not biologically synthesized by the frogs but rather sequestered from the diet. Saporito and co-workers[6] have shown in a recent study that the main diet of the frogs is the orbatid mite and is thus the primary source of the dendrobatid frog alkaloids.

The biosynthesis of indolizidine alkaloids (Scheme 1)[2] starts with L-lysine (**8**) and proceeds through the intermediacy of L-pipecolic acid (**11**). The process of forming pipecolic acid results in loss of the ϵ-amino group in L-lysine. All of the six carbons in pipecolic acid are retained in the indolizidine core with the final two carbons thought to be derived from acetyl or malonyl-SCoA[2] in a Claisen-ester type condensation. Ring

closure then affords the fused bicyclic ring framework **13**. Various indolizidine alkaloids are thus formed from further reactions of **14** or **14a**.



Scheme 1: Biosynthetic pathway of indolizidine alkaloids[2]

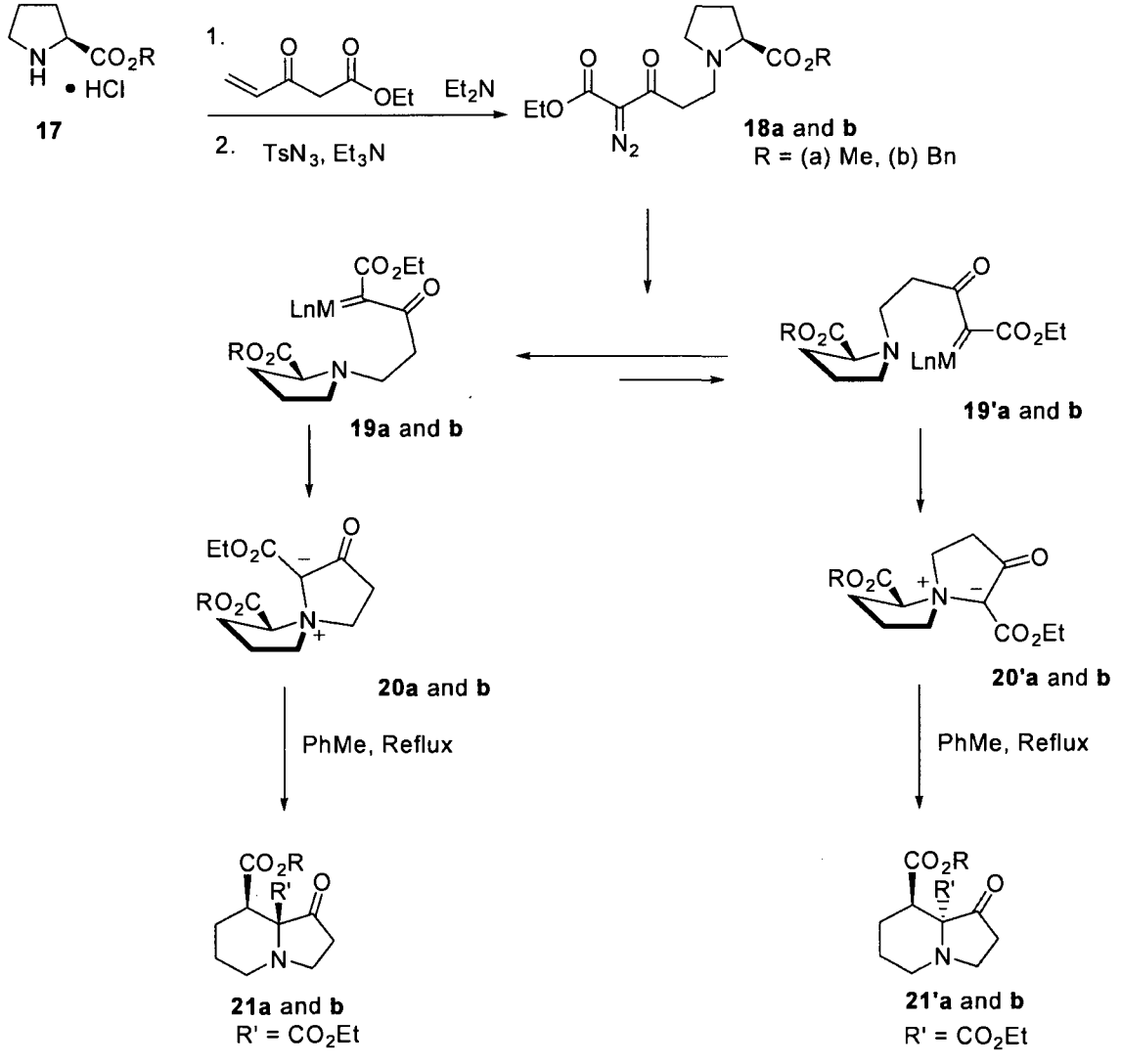
1.2 Common Approaches to the Synthesis of Indolizidine Alkaloids: A Brief Survey

Several chemical syntheses of indolizidine alkaloids have been reported.[6] A survey of the literature on the syntheses of indolizidines to date reveals fourteen general approaches that have been used namely:

The use of (i) chiral pool materials[7] (ii) radical cyclizations[8] (iii) intramolecular Michael-type addition of pyrrole[9] (iv) aza-annulation of *N*-alkylenamines[10] (v) Diels-Alder and dipolar cycloadditions,[11,12] (vi) pyrrolidinylcuprates[13] (vii) reduction of enamines[14] (viii) iminium and acyliminium ion strategies,[15] (ix) pyridinium salts, tetrahydropyridinium and acylpyridinium intermediates[16] (x) enaminones,[17] (xi) the use of chiral auxiliaries

such as α-cyanoamines and oxazolidines,[18] (xii) ammonium ylide rearrangement,[19] (xiii) Rh(II) mediated C-H insertion reactions[20c] and (xiv) titanium mediated cyclizations.[21]

Saba and colleagues[19] applied the Rh(II) catalyzed ammonium ylide strategy to the synthesis of the swainsonine precursors with a quaternary chiral carbon (Scheme 2).



Scheme 2: Synthesis of swainsonine precursors[19]

The chiral proline with the nitrogen atom tethered to an α-diazo keto ester chain were used as the substrates in the synthesis of the alkaloids. The advantages of employing the α-diazoketoester as substrate were twofold:

(i) ylide formation was dominant over the competing C-H insertion process due to the position of the diazo which allowed the easy trapping of the metallocarbene.

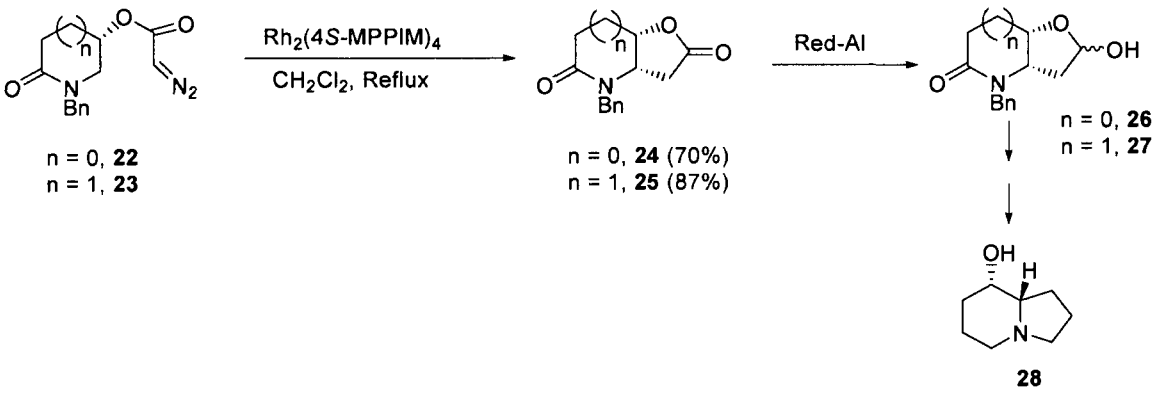
(ii) the substituent on the ylide carbon imposed steric restrictions on the migrating group leading to improved enantioselectivity.

Diazo decomposition was studied using $Rh_2(OAc)_4$ and $Cu(acac)_2$. When toluene was used as reaction solvent, $Cu(acac)_2$ was found to give higher yields of the alkaloids compared to $Rh_2(OAc)_4$. Refluxing of the ylides in toluene triggered the Stevens rearrangement to afford the alkaloids **21** and **21'** in good yields.

The Wee group[20a,b,c,d] has been involved in the synthesis of pyrrolidine, piperidine and indolizidine alkaloids of biological importance. The group has recently developed a novel approach for the syntheses of indolizidine alkaloids.[20c] This approach involves the use of Rh(II) catalyzed C-H insertion to furnish a key intermediate which has one or more of the stereogenic centers in the natural product already set and which can be further elaborated in the target compound.

One of the notable target that has been achieved via this approach is (8*S*, 8a*S*)-8-hydroxyindolizidine (**28**).[20c] The synthesis of this alkaloid provides a good example of Rh(II) catalyzed C-H insertion route to indolizidines. The high regio- and diastereoselectivity provided by $Rh_2(MPPIM)_4$ was utilized in the synthesis of bicyclic

lactones which served as key intermediates in the synthesis of the aforementioned alkaloid.

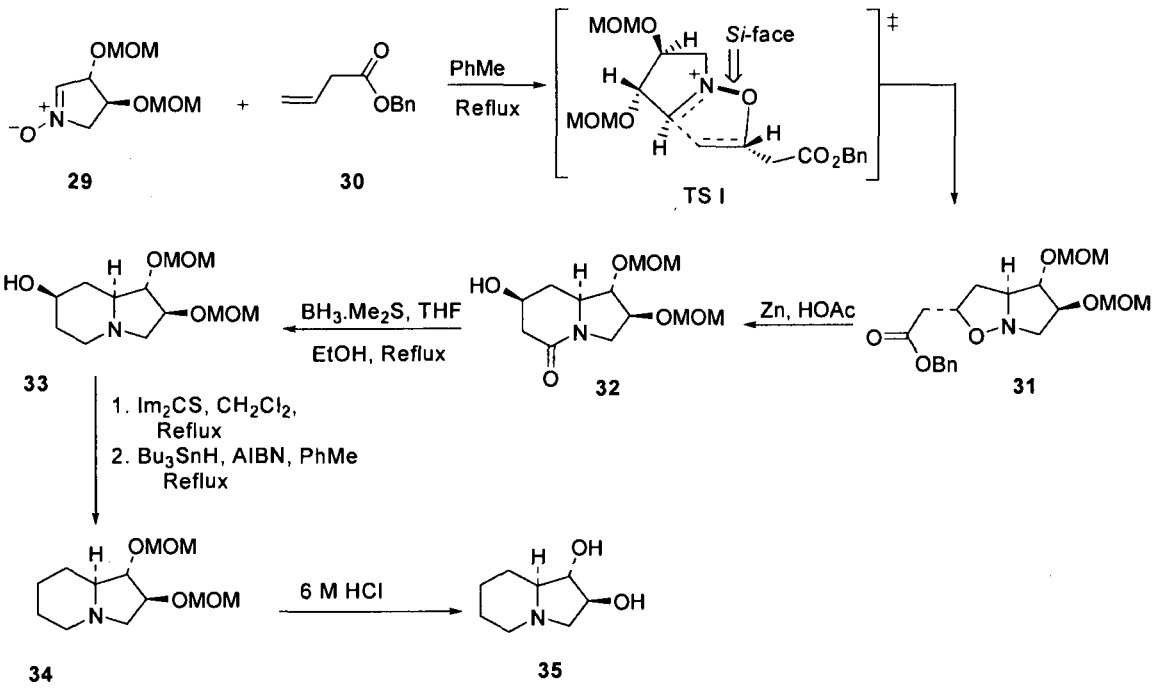


Scheme 3: Synthesis of (8*S*,8a*S*)-8-hydroxyindolizidine[20c] (**28**)

For the synthesis of the indolizidine alkaloid **28** the δ-lactam lactone **25** was required as the key intermediate. The (*S*) configuration at C-8 and C-8a of the target molecule **28** required that both chiral centers of the key intermediate be (*S*)-configured. Rh_2(4*S*-MPPIM)$_4$ effected the C-H insertion of **23** to give **25** in excellent yields. The bicyclic lactam lactone was then transformed into the target molecule **28** in nine steps and 34% overall yield.

Chiral pool strategy accounts for the vast majority of the enantioselective syntheses of indolizidines reported so far. The chiral material either sets or provides a facile entry to one or more of the stereogenic centers of the target molecule.

The synthesis of (+)-lentiginosine (**35**) by Wightman and coworkers[7a] (Scheme 4) typifies the synthesis of indolizidines by the chiral pool approach.



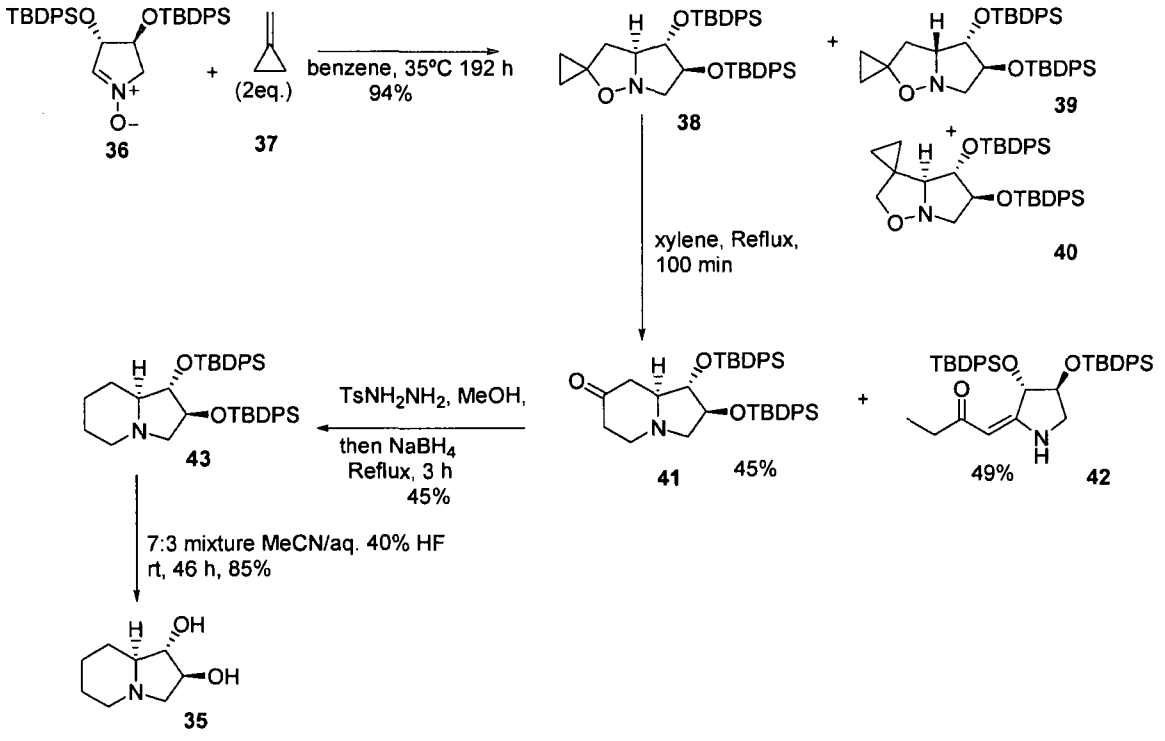
Scheme 4: Synthesis of (+)-lentiginosine (**35**) by Wightman and colleagues[7a]

The dipolar cycloaddition between nitrone **29** derived from L-tartrate and benzyl but-3-enoate provided the cycloadduct **31** containing the isooxazolidine ring.

The cycloadduct **31** arises from the addition of the dipole on the sterically accessible *si*-face of the dipolarophile **30**. The *cis*-diastereoselectivity observed in **31** is in accord with an *exo*-transition state.[22a,b] Hydrogenolysis of the isooxazolidine ring was effected with zinc/acetic acid and then cyclization to furnish the lactam **32**. The lactam carbonyl was subsequently reduced and the resulting intermediate transformed into the target alkaloid **35**.

In contrast to the work of Wightman and coworkers,[7a] the synthesis of **35** reported by Cardano *et al.*[23] (Scheme 5) relied on the methylenecyclopropane 1,3-dipolar cycloaddition strategy to furnish the isooxazolidines **38**, **39**, and **40** in a 12:1:1.5 ratio. The observed diastereoselectivity was ascribed to the bulky TBDPS groups on the nitrone

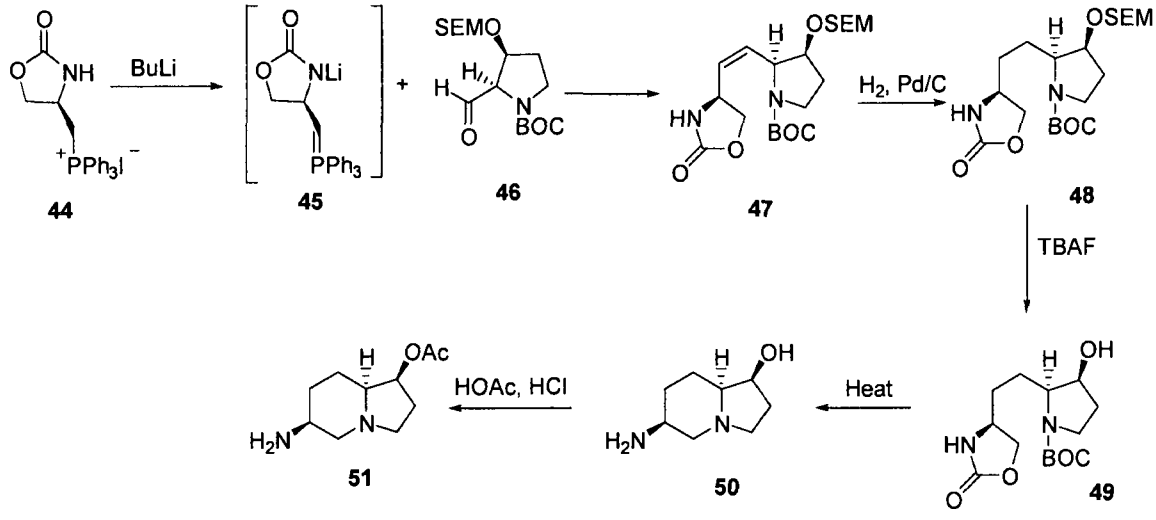
imposing steric constraints thereby resulting in the attack of the dipolarophile *anti* to the vicinal TBDPS groups being favored. Heating the isoxazolidine **38** resulted in the indolizidine **41** and enone **42** in roughly 1:1 ratio. Reduction of the ketone and hydrolysis of the silyl ethers in **41** gave the target compound **35**.



Scheme 5: Synthesis of (+)-lentiginosine (**35**) by Cardano and colleagues[23]

The alkaloid slaframine (**51**), a mycotoxin produced by the fungus *Rhizoctonia leguminicola* causes "slobber syndrome", in animals that ingest mold-infested feeds.[24,25,26] The chemo-ecological importance of this alkaloid stimulated the interest of many researchers and this led to several successful total syntheses of (–) and (±)-**51**[26] mostly by means of chiral pool approach.

The synthesis of (–)-**51** by Sibi and co-workers[26j] illustrates the use of a chiral auxiliary in the synthesis of indolizidines (Scheme 6).



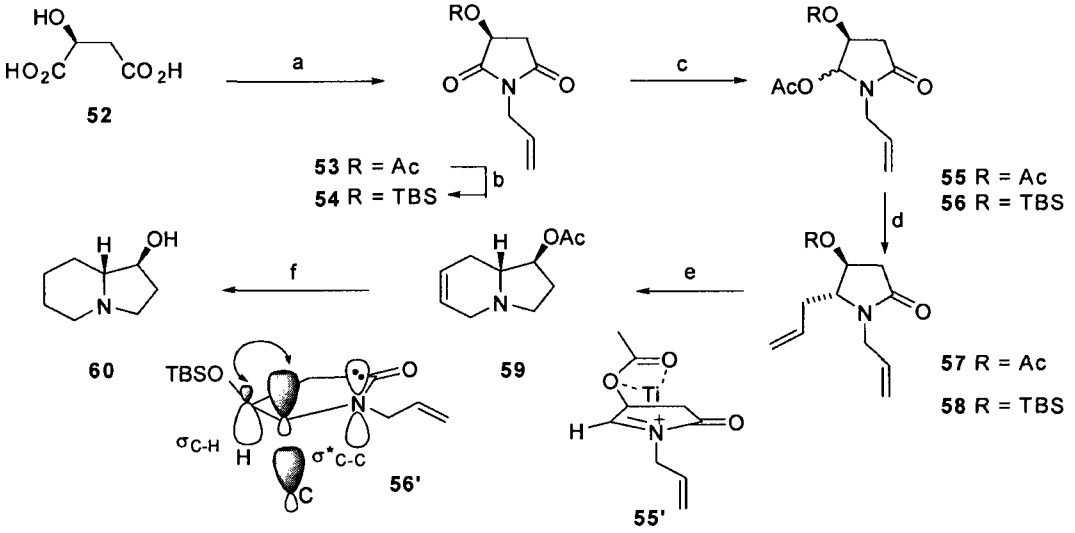
Scheme 6: Synthesis of (–)-slaframine (**51**) by Sibi and co-workers[26j]

Their synthesis is a convergent approach that relies on the chirality inherent in *cis*-3-hydroxyprolinal to provide the requisite stereochemistry in the target molecule. The key step is the annulation of the six-membered piperidine ring onto the hydroxylated proline. The Wittig reaction between **44** and **46** afforded exclusively the *Z*-olefin **47**. This excellent *Z*-selectivity could be attributed firstly, to the stability provided by the coordination of the β-oxygen in **46** to the lithium cation. Secondly, steric interaction between the bulky BOC and phosphine groups favors the formation of the *Z*-isomer over the *E*-isomer. Catalytic hydrogenation followed by TBAF mediated desilylation of the SEM group of **48** gave **49**. On heating **49**, the BOC group was cleaved off to reveal the free amine. Nucleophilic attack of the amine on the oxazolidinone ring occurred at the activated C5 position resulting in the loss of CO_2 and the formation the indolizidine core in the process. This mode of ring opening resulted in the establishment of the correct

stereochemistry at C6 of (–)-slaframine. The resulting product was subsequently *O*-acetylated to furnish the target compound **51**.

Indolizidin-1-ol (**14**) or (**14a**)[27] is a key intermediate in the biosynthetic pathway of indolizidine alkaloids (Scheme 1) and the simplicity of structure has made **14** a popular target for synthetic chemists.

Pilli *et al.*[4f] reported the synthesis of the alkaloid (1*S*, 8a*R*)-1-hydroxyindolizine **60,** the diastereomer of the naturally occurring **14** (Scheme 7) using an *N*-acyliminium ion strategy.



Reagents and conditions: (a) (i) AcCl, reflux; (ii) allylamine, CH_2Cl_2, rt; (iii)AcCl, reflux (**53,** 92%); (b) (i) AcCl, EtOH; (ii) TBSCl, imidazole, DMF (**54**, 80%); (c) (i) $NaBH_4$, EtOH, -23°C; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (**55**, 73%; **56** 65%); (d) allylsilane, TMSOTf ; (e) 4 mol % Grubbs II catalyst, CH_2Cl_2 (**59**, 82%; 95% d.e.); (f) (i) H_2, Pd/C, AcOEt; (ii) $LiAlH_4$, THF, reflux (**60**, 78%).

Scheme 7. Synthesis of (1*S*, 8a*R*)-1-hydroxyindolizine (**60**) by allylation of cyclic chiral *N*-acyliminium ions.[4f]

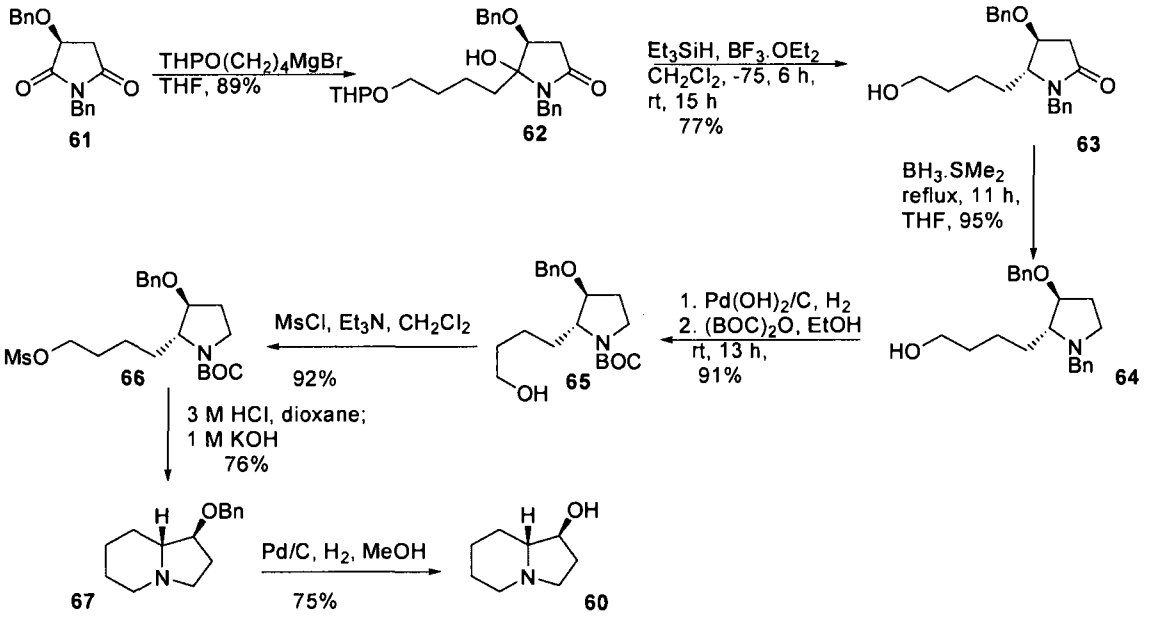
Malic acid **52** was used as the chiral building block; however, since the starting material contains only one of the two stereocenters in the target **60**, the key step in this strategy

involves the installation of the second stereocenter in **60** by allylation of the *N*-acyliminium ions. The *trans* selectivity observed depended on both the strength of the nucleophile and the oxophilicity of the Lewis acid used. A marked improvement in the *trans*:*cis* ratio (7:1) was obtained when allylsilane and 4 eq. of $TiCl_4$ were used. This was ascribed to the strong coordination of the Ti at the neighboring OAc group which sterically shielded nucleophilic attack *cis* to the OAc/Ti complex (**55'** Scheme 7). The use of allylstannanes, which are superior nucleophiles[4l] compared with allysilanes, resulted in low *trans* selectivity for all the Lewis acids investigated except $TiCl_4$. However, when $TiCl_4$ was used together with allylstannanes there was a (*trans* to *cis*) reversal of selectivity to give higher *cis* selectivity. This reversal in selectivity probably resulted from the coordination of an allyltitanium species to the neighboring OAc group and intramolecular delivery of the allyl group. Low *cis* selectivity was also observed for the TBS protected compound **56**; preferential addition of the allyl group to the iminium ion intermediate *trans* to the OTBS group was observed. This was explained on the basis of stabilization of the transition state through hyperconjugation of the developing $\sigma^*_{C\text{-}C}$ orbital with the adjacent σ_{CH} bond (**56'** Scheme 7).[4u]

Huang and coworkers[4p] also reported a concise synthesis of **60** (Scheme 8) making use of the *trans*-selective deoxygenation of the quaternary carbon to install the required chirality at C-8a in the target **60**. This strategy is more advantageous to the *N*-acyliminium ion strategy employed by Pilli and colleagues[4f] as it leads directly to one diastereomer of the target **60**.

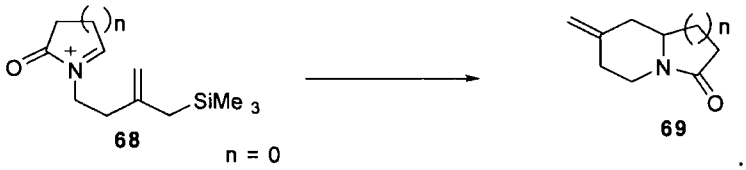
The malimide **61** was treated with the functionalized Grignard reagent to give the *N-O* acetal **62** in 89% yield. Et_3SiH in the presence of $Et_2O\text{-}BF_3$ was used to effect the

reductive dehydroxylation to give the *trans* lactam **63** in 77% yield, which was subsequently reduced to the amine using $BH_3.SMe_2$. Mesylation of the primary alcohol **65** followed by removal of the BOC protecting group resulted in cyclization to give the indolizidine core **67**, which was then easily converted to the target **60**.



Scheme 8: Synthesis of (1*S*, 8a*R*)-1-hydroxyindolizine (**60**) by Huang and colleagues[4p]

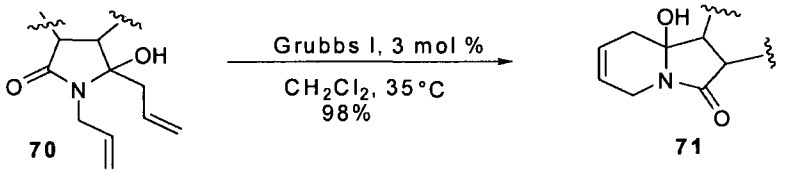
Over the last decade allylsilane/*N*-acyliminium ion[4m,s] cyclization (Eq. 1) and ring closing metathesis (RCM)[28] (Eq. 2) reactions have been popular cyclization strategies for construction of the indolizidine framework. In the case of the *N*-acyliminium ion strategies, the allylsilyl group acts as the nucleophile that traps the acyliminium ion leading to the cyclized structure.



.....[1]

With regard to the RCM strategy, the Ru(II)-mediated cyclization is used to construct either the 5-or 6-membered ring of the indolizidine core. Selectivity is not a problem in this strategy as the configuration at the C-8a junction is dictated by the configuration of the starting diallyl substrate. The alkene moiety resulting from the cyclization lends flexibility to the strategy as it can be transformed into a variety of functional groups.

Kim *et al.*[4q] recently reported the application of the RCM strategy (Eq. 2) to the synthesis of a variety of tetrahydroindolizinones which could be easily transformed into a variety of indolizidine alkaloids .



.....[2]

1.3 The Objectives of This Study

The aims of this study are:

1. To determine the effect that varying the *N*-protecting group of the γ-lactam diazoacetate will have on the Rh_2(4*S*-MPPIM)$_4$ catalyzed C-H insertion reaction, and also the ability of the Rh_2(4*S*-MPPIM)$_4$ catalyst to effect kinetic resolution of a racemic mixture of γ-lactam diazoacetate will be explored.

2. To use the γ-bicyclic lactam lactone derived from $Rh_2(4S\text{-MPPIM})_4$ catalyzed C-H insertion reaction of chiral γ-lactam diazoacetates as a chiral non-racemic intermediate in the synthesis of the alkaloid (+)-(1*S*, 8a*S*)-1-hydroxyindolizidine (**14**) and (–)-slaframine (**51**) (Scheme 15).

CHAPTER 2

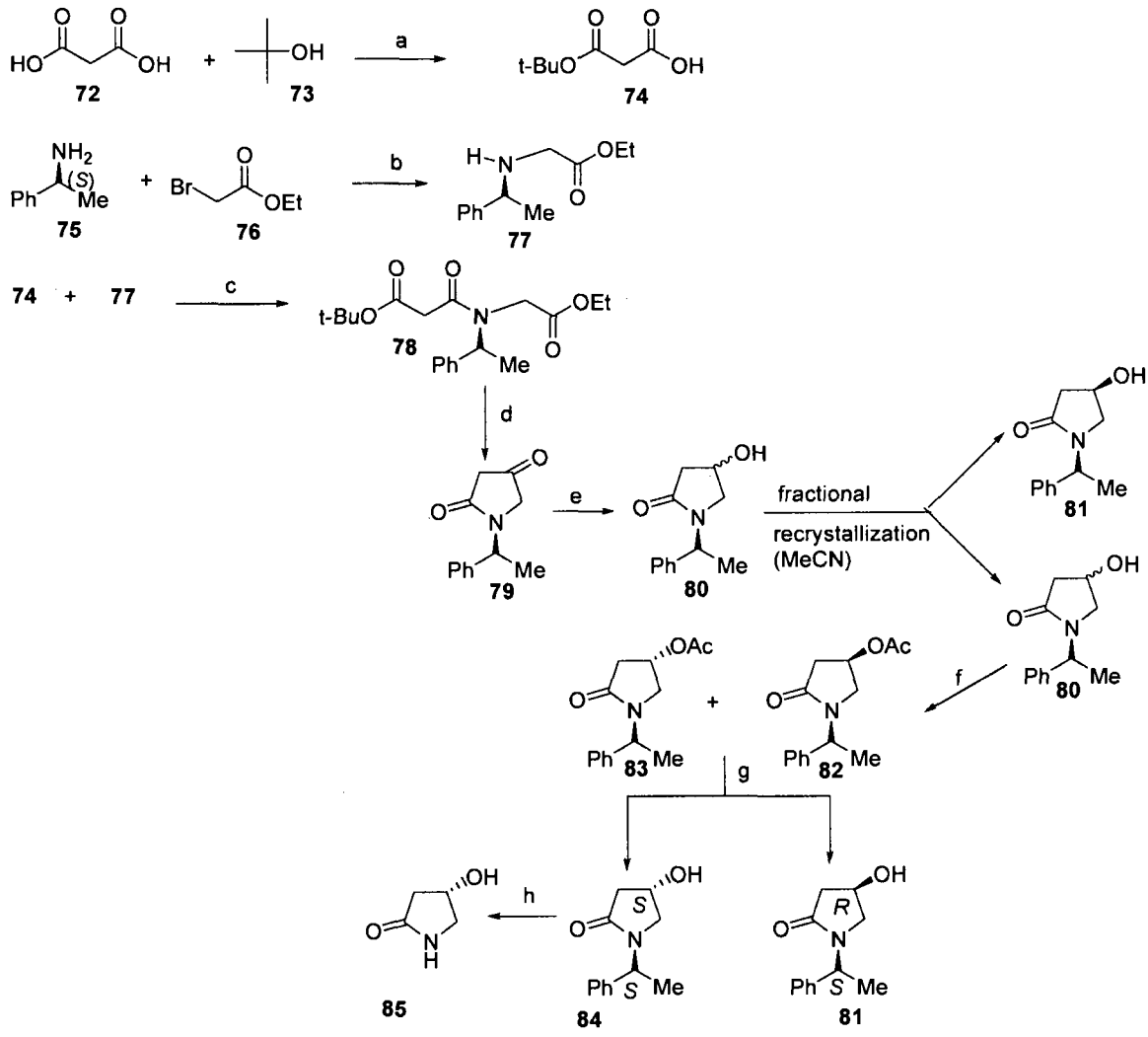
RESULTS AND DISCUSSION

2.1 Synthesis of (–)-(*S*)-4-Hydroxy-2-pyrrolidinone

In order to achieve the objectives of the study, we needed to access the chiral alcohol **85**, the starting material for the entire study, in large amounts to enable the exploration of different reactions.

Using the method reported by Park *et al.*[29] (Scheme 9) **85** was prepared in seven steps starting from malonic acid **72**. The major advantage of the method is that it enables the access of both the *S*- and *R*- enantiomers of **85**. Mono-*t*-butyl malonate **74** was obtained in 48% yield by condensing *t*-butyl alcohol with malonic acid. *N*-alkylation of (*S*)-α-methylbenzylamine with ethyl bromoacetate afforded (*S*)-(α-methylbenzylamino) ethyl acetate **77** in 64% yield. Condensation of **74** and **77** furnished *N*-((*S*)-α-methylbenzyl)-*N*-ethyl acetate malonamide **78**, a key intermediate in the synthesis, in quant yield. The ^{1}H NMR spectrum was complex with the duplication of signals at δ 5.20 and 6.00 (q, 1 H, J = 7.3 Hz, PhC*H*(N)Me), suggesting **78** existed as a mixture of amide rotamers.

An attempted purification of **78** using high vacuum distillation resulted in the decomposition of the compound.



Reagents and conditions: (a) 1 mol eq. DCC, 10 mol % DMAP, MeCN, 0°C → rt. (48%) (b) 1.2 mol eq. Et_3N, CH_2Cl_2, 0°C → rt (64%) (c) 1.1 mol eq. DCC, 10 mol % DMAP, CH_2CH_2, 0°C → rt (d) 1.15 mol eq. KOBu-t, PhMe, (e) 1.2 eq. $NaBH_4$, MeOH, 0°C (f) 1.5 mol eq. AcO_2, 10 mol % DMAP, 4 mol eq. Et_3N, CH_2Cl_2, 0°C → rt (g) 1.5 mol eq. K_2CO_3, MeOH, 0°C → rt (h) $MeSO_3H$, PhMe reflux 120°C

Scheme 9: Synthesis of (–)-(*S*)-4-hydroxy-2-pyrrolidinone (**85**)

KOBu-t mediated Dieckman cyclization (Scheme 9) of **78** gave the γ-lactam **79**. This transformation was found to be base-sensitive as an attempted cyclization using 1.7 mol eq. of base resulted in the decomposition of **78**. The Dieckman cyclization reaction was effected with 1.15 mol eq. of base, to furnish directly the decarboxylated γ-lactam **79**, thereby obviating the need for a decarboxylation step to remove the *t*-butoxycarbonyl group at C-3 as depicted by the mechanism in Figure 2.

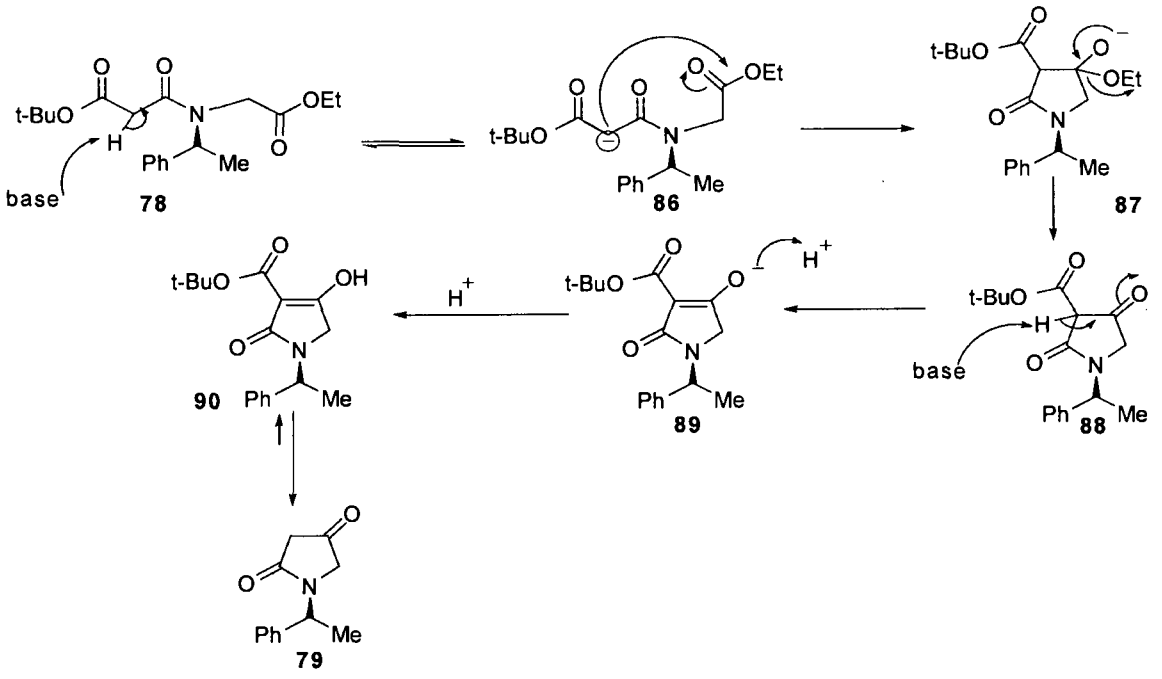


Figure 2: Proposed mechanism for the formation of oxoamide **79**.

Reduction of the ketone function in **79** to furnish the inseparable diastereomeric alcohols **80** was readily effected with $NaBH_4$. At this point, according to the information provided by Park *et. al*,[29] alcohol **84** could be fractionally crystallized out of the diastereomeric mixture **80** using MeCN. However, after crystallization and subsequent *N*-deprotection using $MeSO_3H$, we found that the resulting alcohol gave an optical rotation of $[\alpha]_D^{25}$ =

+46.7° (*c* 1.5, MeOH) which was opposite to an authentic (S)-4-hydroxy-2-pyrrolidinone obtained from Aldrich $[\alpha]_D^{25} = -44°$ (*c* 0.53, MeOH). Since there was no possibility of inversion of stereochemistry at C-4 under the reaction conditions, we concluded that Park and co-workers[29] had misassigned the configuration of the alcohols **81** and **84**. Based on our findings, we report that alcohol **81** rather than **84** is least soluble in MeCN.

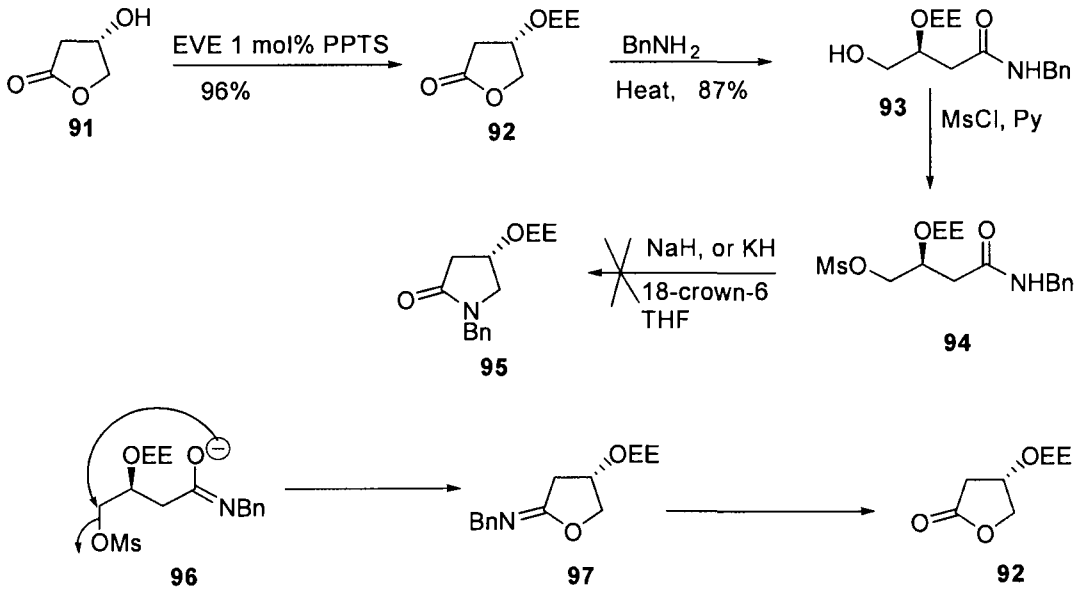
About half of **81** were selectively crystallized out of the diastereomeric mixture **80**. The remaining mixture of alcohols made up of the diastereomer **84** and a small amount of the diastereomer **81** were acylated. The two diastereomers, now well resolved on TLC plate, were readily separated by flash column chromatography. The separated acetates were then hydrolyzed with K_2CO_3 in MeOH to their corresponding alcohols to give a 1:1.4 ratio of **81** to **84**. The total yields of both **81** and **84** were 2.7 g and 2.5 g respectively. The optical rotation of **81** was $[\alpha]_D^{25} = -110°$ (*c* 1, EtOH) which was within range of the literature value of $[\alpha]_D^{18} = -118.8°$ (*c* 1, EtOH) and optical rotation of **84** was $[\alpha]_D^{25} = -155°$ (*c* 1, EtOH) which was also similar to the literature value of $[\alpha]_D^{18} = -177.6°$ (*c* 1, EtOH).

Removal the α-methylbenzyl protecting group on **84** was achieved using $MeSO_3H$ in refluxing PhMe to give the desired **85** with an optical rotation of $[\alpha]_D^{25} = -42.5°$ (*c* 0.53, MeOH) and an 25% overall yield starting from compound **72**. The low overall yield of **85** does not make the method attractive as a means of obtaining starting material for total synthesis from a synthetic point of view.

2.2 Alternate synthesis of (–)-(*S*)-4-Hydroxy-2-pyrrolidinone

It has been demonstrated in our group[20c] that *N*-benzyl-γ-lactam diazoacetate (**22**) give the highest yield of C-H insertion product of bicyclic-γ-lactam lactone (**24**). We therefore investigated an alternative route to prepare (*S*)-4-hydroxy-2-pyrrolidinone with the *N*-benzyl group pre-installed.

Using the method developed by Kawamoto *et al.*[30] (Scheme 10) the hydroxyl group in (*S*)-4-hydroxy-2-butyrolactone was protected as the ethoxyethyl ether using ethyl vinyl ether in the presence of catalytic amounts of pyridinium *para*-toluenesulfonate.

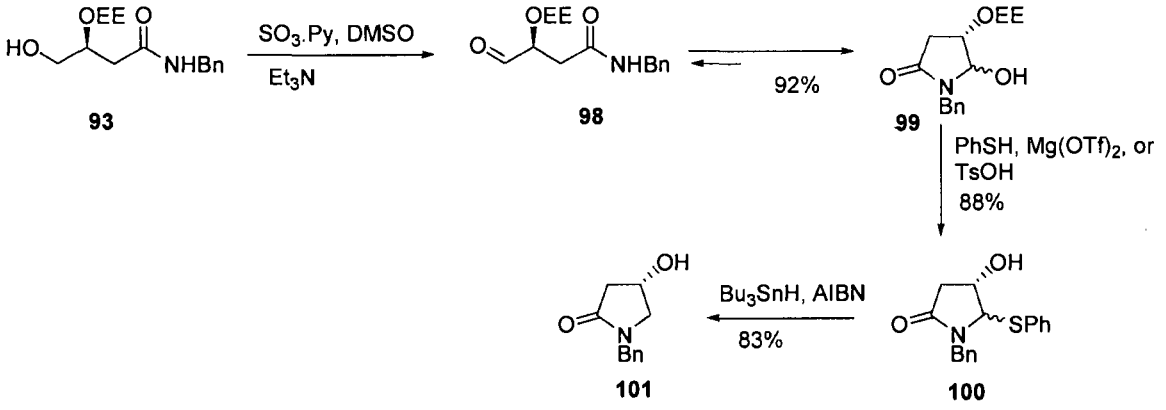


Scheme 10: Attempted synthesis of (*S*)-4-hydroxy-2-pyrrolidinone.

Heating the protected γ-butyrolactone (**91**) in benzylamine resulted in ring opening to furnished the *N*-benzylbutyramide (**93**). According to the reported procedure,[30]

mesylation of the alcohol function of the butyramide **93** followed by treatment with 1.1 mol eq. of NaH or KH would effect ring closure to furnish the γ-lactam. When **93** was subjected to mesylation and base treatment, the IR spectrum of the crude reaction mixture showed a signal 1780 cm^{-1} that suggested the reformation of γ-lactone **92** rather than the desired γ-lactam **95**. The observation can be explained on the basis of a nucleophilic attack by the amide oxygen resulting in the formation of an imine **97**, which subsequently gets hydrolyzed to the lactone **92** when the reaction mixture is processed (Scheme 10).

An alternate route based on the work of Liu[31] (Scheme 11), which starts with the *N*-benzylbutyramide (**93**) was employed to arrive at the target compound.



Scheme 11: Synthesis of (*S*)-4-hydroxy-2-pyrrolidinone (**101**).

Under Parikh-Doering[32] conditions, the alcohol function in **93** was oxidized to the aldehyde **98** which underwent ring closure *in situ* to give 5-hydroxy-γ-lactam (**99**).

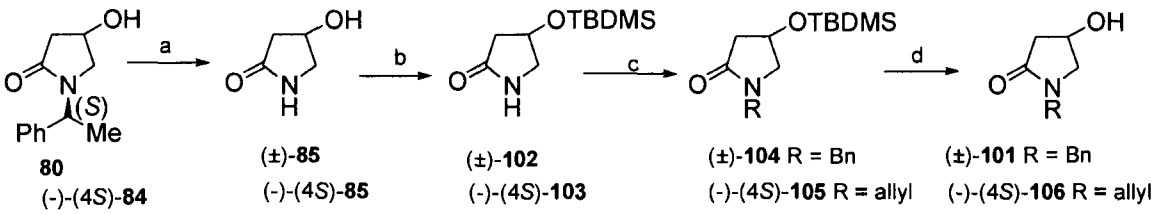
In the presence of thiophenol which was used as both reagent and solvent, and catalytic amounts of $Mg(OTf)_2$ or TsOH, the hydroxyl group at C-5 in **99** was replaced by the phenylthio group. The acid labile ethoxyethyl protecting group was cleaved off in the

process; however, this was of no consequence to the next step as radical reduction of the phenylthio group could be carried out in the presence of unprotected alcohol group.

The phenylthio group was successfully reduced using Bu_3SnH to furnish the target compound **101** in 83% yield and 56% overall yield starting from the (*S*)-4-hydroxy-2-butyrolactone (**91**).

2.3 Preparation of Diazoacetates

In order to prepare the diazoacetates required for the Rh(II) catalyzed reactions, the precursor alcohols **84**, **101**, and **106** had to be prepared. Known reaction protocols were employed in the preparation of the alcohols **84**, **101**, and **116** (Scheme 12). By cleaving off the α-methylbenzyl group from **80** and **84**, we obtained γ-lactams (±)-**85** and (–)-**85** respectively. The alcohol group in each was protected as the silyl ether enroute to the *N*-alkylation reaction with either BnBr or allyl bromide to give (±)-**104** and (–)-**105**, respectively. Hydrolysis of the silyl ether then furnished the respective alcohols (±)-**101** and (–)-**106**.

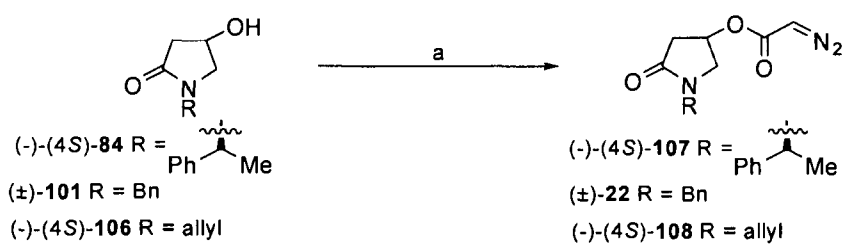


Reagents and conditions: (a) $MeSO_3H$, dry PhMe, reflux 120°C (b) TBDMSCl, imidazole, 10 mol % DMAP, dry DMF, 40°C overnight (c) dry THF, nBuLi, -15°C, BnBr (**104**), allylbromide (**105**), -15°C → rt, 6-7 h (d) 1 M HCl/MeOH, 0°C → rt.

Scheme 12. Synthesis of γ-lactam alcohols.

Having prepared alcohols **84**, (±)-**101** and **106** the next step was the preparation of the diazoacetates that will be used for the $Rh_2(4S\text{-MPPIM})_4$ catalyzed C-H insertion reaction study.

All the diazoacetates were prepared according to the method of House and Blankley[33] (Scheme 13). The alcohol and TsNH=NCHCOCl were dissolved in dry CH_2Cl_2. The bases DMA and *i*-Pr_2NEt were added sequentially over a 1 h period after which the reaction was processed and purified by flash column chromatography.



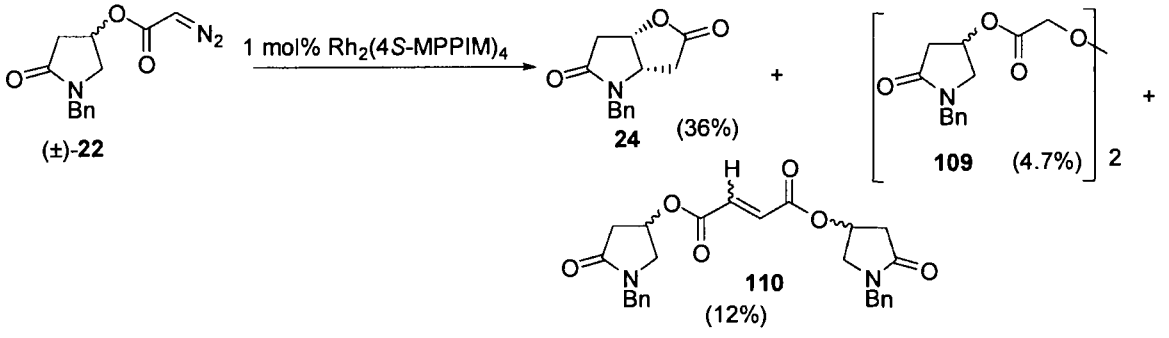
Reagents and conditions: (a) *p*-TsNHN=CHCOCl, CH_2Cl_2, DMA, *i*-Pr_2NEt , 0°C → rt.

Scheme 13. Preparation of diazoacetates

2.4 Rh(II) Catalyzed C-H Insertion Reactions

2.4.1 Attempted Kinetic Resolution Studies:

The $Rh_2(MPPIM)_4$ catalyzed decomposition of the diazoacetate (±)-**22** is shown in Scheme 14. The reaction was carried out at a catalyst loading of 1 mol % and in refluxing DCE.



Scheme 14: Rh(II) catalyzed decomposition of (±)-**22**.

The product distribution was consistent with earlier studies on a similar system[20c] where the products isolated were the bicyclic γ-lactam lactone, ether **109** and alkene **110**.

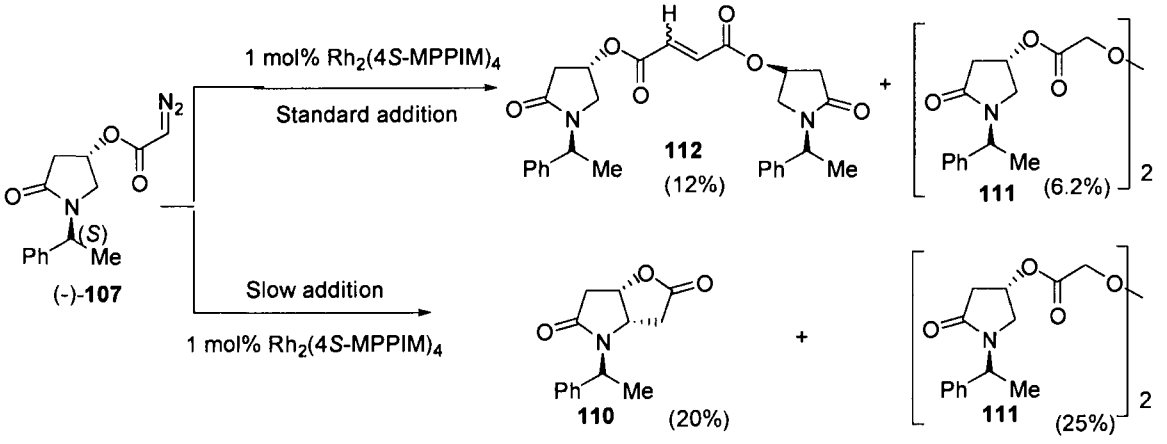
The physical properties, i.e., optical rotation ($[\alpha]_D^{25}$ –34.1° (*c* 0.15, $CHCl_3$)) and melting point (112-114°C) of **24** were within range of the same compound ($[\alpha]_D^{22}$ –38.9° (*c* 0.9, $CHCl_3$))[20c] (114-116°C)[20c] produced from a chiral non-racemic γ-lactam diazoacetate,[20c] and this suggested that **24** was non-racemic. Another interesting result worthy of note was the isolated yield of 36% of **24**. The low yield renders as unattractive the use of $Rh_2(4S\text{-}MPPIM)_4$ in kinetic resolution from a synthetic standpoint. This is because only maximum yield of 50% of the synthetically useful bicyclic γ-lactam lactone (**24**) can be

produced from the (*S*)-γ-lactam diazoacetate. The (*R*)-enantiomer gets converted into dimers.

The inference that can be made based on the foregoing is that Rh_2(4*S*-MPPIM)$_4$ cannot resolve a racemic mixture of γ-lactam diazoacetate systems.

2.4.2 Effect of the Chiral *N*-α-Methylbenzyl Protecting Group on the Rh_2(4*S*-MPPIM)$_4$ Catalyzed C-H Insertion Reaction

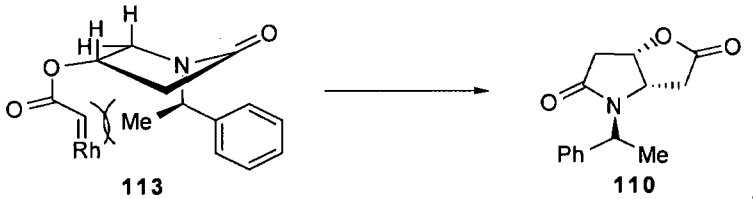
The Rh_2(4*S*-MPPIM)$_4$ catalyzed decomposition of diazoacetate **107** (Scheme 15) was carried out under two conditions; standard addition of diazoacetate to the refluxing catalyst by cannula transfer and also by a controlled addition using a syringe pump. The results obtained in both cases were interesting.



Scheme 15: Rh(II) catalyzed decomposition of (–)-**107**.

In the former case of the standard addition, no C5-H insertion product **110** was formed. Only the ether **111** and the alkene **112** were isolated from the reaction mixture. This

result could be rationalized on the basis of steric effects (Eq. 3) and the competing processes of C-H insertion and dimerization. The C-H insertion reaction of the Rh(II) carbenoid is slow due to the steric hindrance by the α-methylbenzyl group. Since cannula transfer rapidly delivers the substrate into the reaction mixture, and formation of the Rh(II) carbenoid is very fast, the reactive Rh(II) carbenoid underwent preferential dimerization and is also intercepted by trace amounts of water leading to the formation of both alkene and ether dimers, respectively.



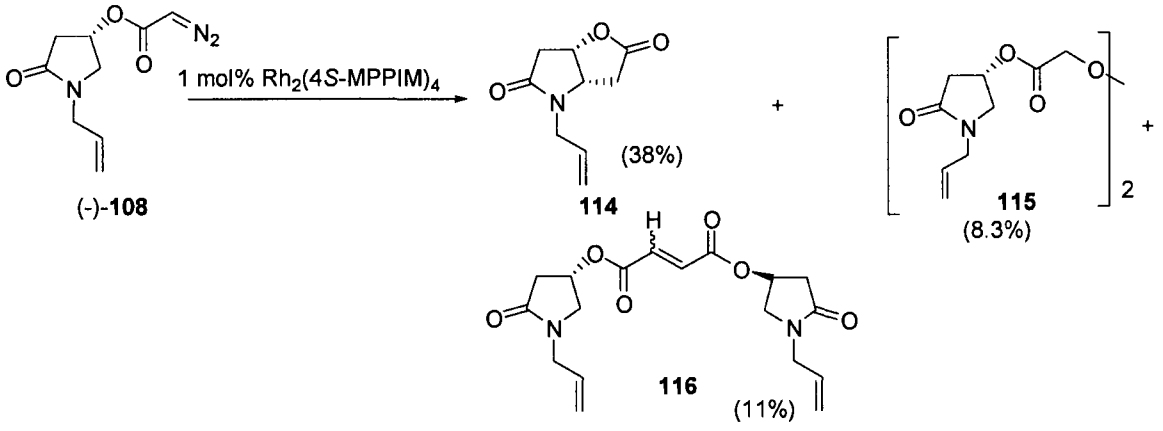
113 **110** .....[3]

Switching to the more controlled mode of addition of substrate to the refluxing solution of the catalyst by the use of a syringe pump afforded the C5-H insertion product **110** together with the ether dimer **111**. This result confirmed the assertion that C-H insertion is a slow process relative to dimerization.

The isolated yield of 20% of **110** brought to the fore the influence of the (*S*)-α-methylbenzyl auxiliary on the Rh_2(4*S*-MPPIM)$_4$ catalyzed C-H insertion reaction. The optimum yield[20c] reported for the Rh_2(4*S*-MPPIM)$_4$ catalyzed C-H insertion reaction of γ-lactam diazoacetate is 70% for the *N*-benzyl protecting group. The observed 20% yield versus the optimum 70% yield suggests that though the C-H insertion reaction is taking place, the methyl moiety on the (*S*)-α-methylbenzyl group impedes the C-H insertion process.

2.4.3 Effect of the *N*-Allyl Protecting Group on the $Rh_2(4S\text{-MPPIM})_4$ Catalyzed C-H Insertion Reaction

The products **114**, **115**, **116** obtained for the $Rh_2(4S\text{-MPPIM})_4$ catalyzed decomposition of diazoacetate (–)-**108** (Scheme 16), under slow addition of substrate to catalyst using a syringe pump were consistent with results obtained in earlier studies on compound **22**.[20c]



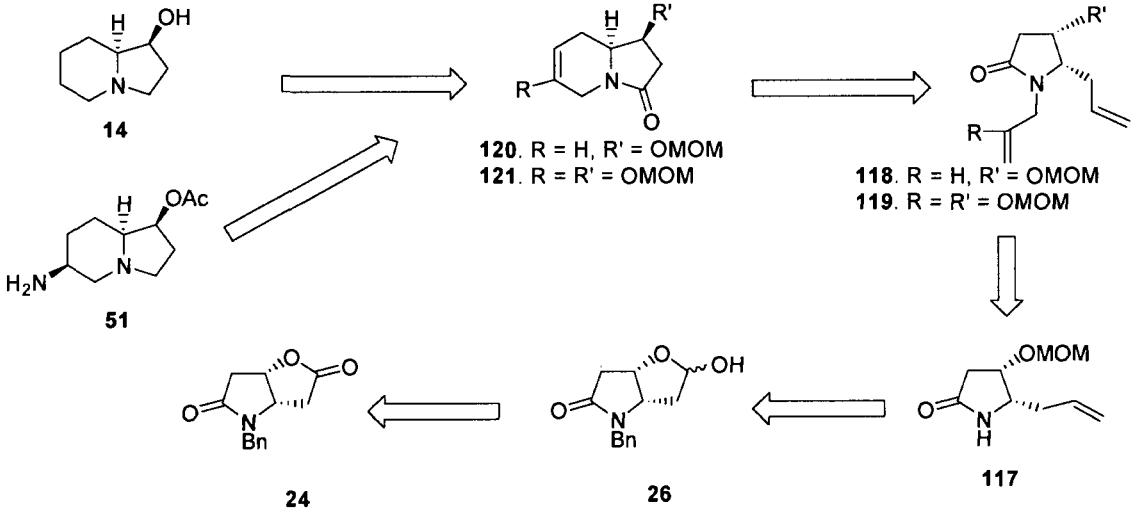
Scheme 16: Rh(II) catalyzed decomposition of (–)-**108**.

The interesting aspect of the reaction was the isolated yield of 38% for the C-H insertion product **114**. On the basis of the relative bulkiness of the *N*-protecting group, i.e., allyl < benzyl < α-methylbenzyl, the hypothesis was that the yield of **114** would be higher than the 70% obtained for the benzyl group. The reaction was repeated three times varying the time of addition of substrate to the catalyst from 2 h, 3 h and 4 h. However, this did not improve the yield. The reason for the observed yield of 38% is yet unknown, thus, further investigations have to be conducted to determine the reason for the low yield.

2.5 Application of Bicyclic γ-Lactam Lactone to the Total Synthesis of Alkaloids

2.5.1 Synthesis of (+)-(1*S*, 8a*S*)-1-Hydroxyindolizidine

The retrosynthetic analysis of (+)-(1*S*, 8a*S*)-1-hydroxyindolizidine is outlined in Scheme 17.

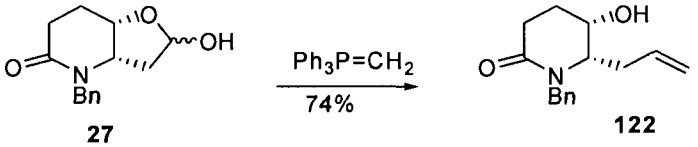


Scheme 17: Retrosynthetic analysis of (+)-(1*S*, 8a*S*)-1-hydroxyindolizidine and (–)-slaframine.

Starting from **24**, chemoselective reduction of the lactone will lead to the lactol **26** and through a series of reactions the lactol will be converted to **117**, which is a key intermediate in the synthesis of indolizidine alkaloids as the fused bicyclic skeletons of different alkaloids could be accessed depending on the 3-carbon fragment that is attached to the amide nitrogen. The fused bicyclic ring framework of the intermediate **120** will then be constructed through ring closing metathesis (RCM)[34] of the diallyl system **118** and then subsequently transformed into the target compound **14**. Using the same RCM

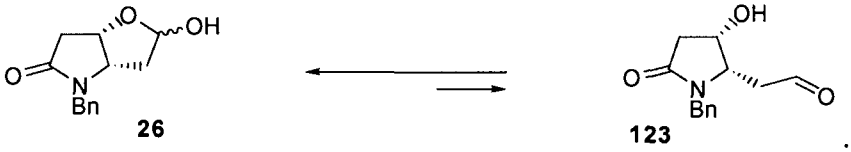
strategy on **119**, the bicyclic system **121** will be constructed and this will serve as an advanced intermediate toward the synthesis of (–)-slaframine **51**.

Lactols, are known to react with phosphonium ylides to give olefins.[35] This reaction has been employed in our group[20c] to make the olefin **122** in good yield (Eq. 4).



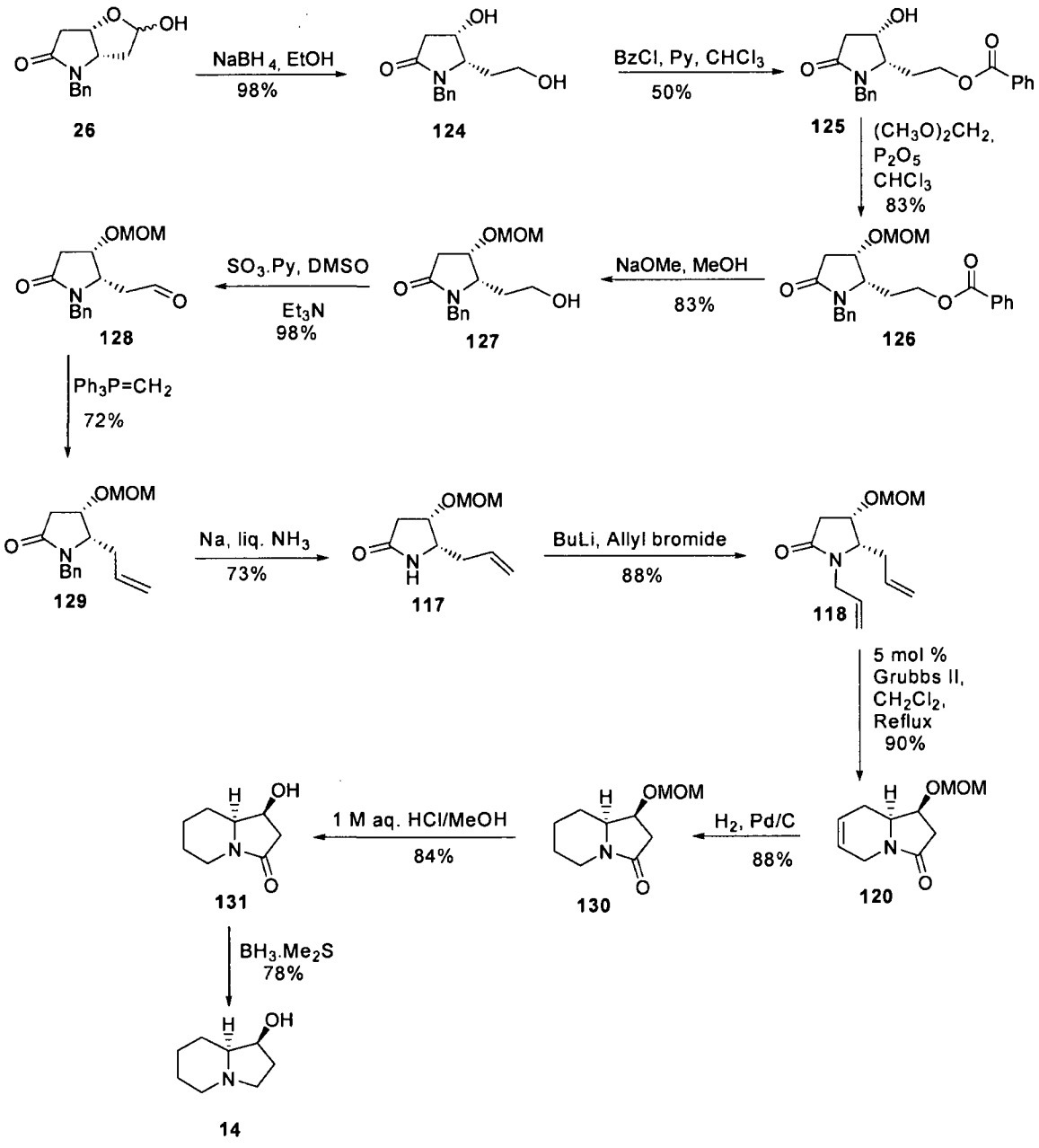
27 **122** .....[4]

The original plan was to employ the Wittig reaction[20c] on the γ-lactam lactol system **26**. Interestingly, no alkene product was formed even after three attempts to fine-tune the reaction temperature parameter. The failure of the reaction can be explained on the basis of ring-chain tautomerism (Eq. 5) in which we postulate the equilibrium lies more to the side of the lactol **26**, hence, there is little or no aldehyde **123** available to react with the ylide.



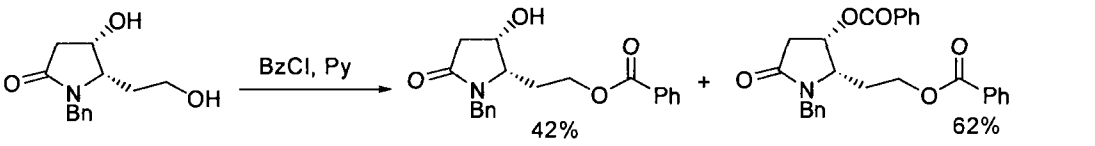
26 **123** .....[5]

The failure of the Wittig reaction described above, necessitated a change in tactic that will require an additional six steps in order to make the desired olefin **129** (Scheme 18).



Scheme 18: Synthesis of (+)-(1*S*, 8a*S*)-1-hydroxyindolizidine.

The lactol **26** was reduced using $NaBH_4$ to furnish the diol **124**. Selective protection of the 1° alcohol of **124** was challenging as the reaction condition of pyridine and BzCl resulted in 42% and 62% of the monobenzoate **125** and dibenzoate **132** respectively (Eq. 6).



124 **125** **132** ...[6]

The best result of 50% conversion to the desired monobenzoate **125** (Scheme 18) was obtained when the reaction was carried out using $CHCl_3$ as co-solvent.[36a,b] The $CHCl_3$ reduces the polarity of the reaction medium which in turn minimizes the nucleophilicity of the 2° alcohol towards the nucleophilic acyl substitution reaction. The unreacted diol was recovered and recycled.

The 2° alcohol in **125** was readily protected as the MOM ether using dimethoxymethane in $CHCl_3$, in the presence of P_2O_5.[37] Filtration of the reaction mixture through a layer of silica gel after the reaction mixture was processed, afforded the MOM ether **126** which was sufficiently pure to be used in the next reaction.

The benzoate in **126** was readily hydrolyzed using sodium methoxide to reveal the 1° alcohol which was oxidized under Parikh-Doering[32] conditions to the aldehyde **128**. The Wittig olefination of **128** was found to be very sensitive to base. The use of large amounts of the phosphonium ylide resulted in decomposition of the aldehyde. The best results were obtained when the ylide was generated at 0°C and then used for the olefination reaction at -40°C.

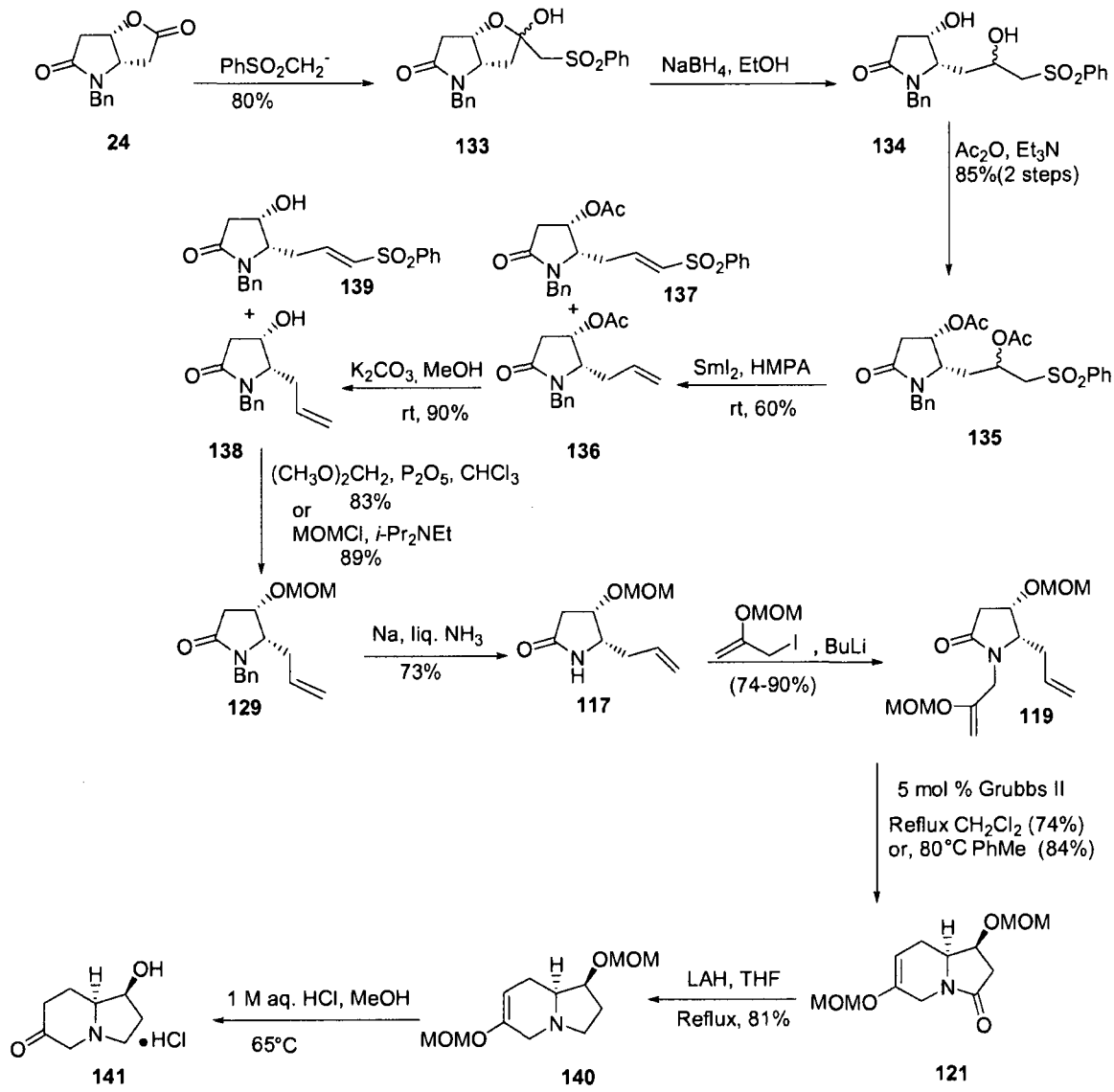
Birch reduction[38] of **129** afforded **117**, the key intermediate in the synthesis. *N*-Allylation of **117** gave the diallyl system **118** in good yield, ready for the RCM reaction. The catalyst of choice for the RCM was the Grubbs II as this gave the shortest reaction time of 1 h and 90% yield of **120** compared to the 6 h reaction time and 95% yield obtained when the Grubbs I catalyst was used.

The double-bond in **120** was hydrogenated over 10% Pd/C at 30 psi using a Parr hydrogenator to afford **130** in 88% yield. The MOM group in **135** was hydrolyzed using methanolic HCl to give **131**, the spectral and physical properties of which were in close agreement with those reported by Greene *et al.*[26t] Finally, the alkaloid **14** was obtained after the reduction of the amide carbonyl in **131** with borane dimethyl sulfide complex. This compound was identical in all respects to the properties reported for **14** in the literature ($[\alpha]_D^{26}$ +19.2° (*c* 0.13, $CHCl_3$), (lit.[26t] $[\alpha]_D^{22}$ +17.4° (*c* 0.4, $CHCl_3$), lit.[27i] $[\alpha]_D^{22}$ +16.4° (*c* 0.28, $CDCl_3$), $[\alpha]_D^{22}$ +18.1° (*c* 0.42, $CDCl_3$)).

2.5.2 An Approach to (–)-Slaframine

To further prove the concept of the applicability of chiral bicyclic γ-lactam lactone **24** in the synthesis of natural products, an approach to the synthesis of (–)-slaframine (**51**) was devised based on the retrosynthetic analysis (Scheme 17).

A different strategy aimed at addressing the low yield of the critical intermediate **117** as a result of the long synthetic route starting from the lactol **26** (Scheme 18) was required. A Julia-Lythgoe olefination[39] on the lactone **24** was investigated as a route for preparing **117** (Scheme 19).



Scheme 19: Preparation of advanced (–)-slaframine intermediate.

Nucleophilic addition of methyl phenyl sulfone anion to the bicyclic γ-lactam lactone (**24**) (Scheme 7) afforded the lactol **133**. By carefully adjusting the reaction parameter, the optimum yield of **133** recorded was 80% for -40→ 0°C reaction temperature. The ^{1}H NMR showed the lactol was composed of two inseparable diastereomers in 1:2 ratio, based on the integration of the benzylic proton signals at δ 4.78 and 5.05.

Addition of $NaBH_4$ to **133** resulted in ring opening to give the diol **134**, which was treated with Ac_2O and catalytic amounts of DMAP to obtain an inseparable diastereomeric mixture of the diacetate **135** in a 1:2 ratio, which was based on the integration of the signal of the methyl protons of the acetate at δ 1.63 and 1.77.

The reductive elimination of the β-acetoxy sulfone **135** using Mg/EtOH and catalytic amounts of $HgCl_2$, developed by Pak *et al.*[40] did not yield the olefin **136**. TLC analysis of the reaction mixture showed the presence of only the starting material, which was readily recovered using flash column chromatography. Switching to 0.1 M SmI_2/HMPA,[41] **136** was obtained in 60% yield together with 10% of **137**. The co-solvent proved to be critical to the success of the reduction as SmI_2/DMPU system did not yield any product, and only the starting material was recovered. Both of the products, **136** and **137** were easily separated using flash column chromatography, however, further purification of **137** using flash column chromatography did not yield a pure compound. The ^1H NMR of the impure **137** showed signals consistent with the alkene moiety at δ 6.25 (d, 1 H, J = 15.1 Hz, C=C*H*SO_2Ph), and δ 6.74-6.85 (m, 1 H, C*H*$_2$CH=C). For large scale reactions the crude reaction mixture was hydrolyzed and then purified to obtain the alcohol **138** which was obtained in an overall yield of 54%; compound **139** was not obtained.

The reductive elimination proceeds via a two-electron mechanism as shown in Figure 3.

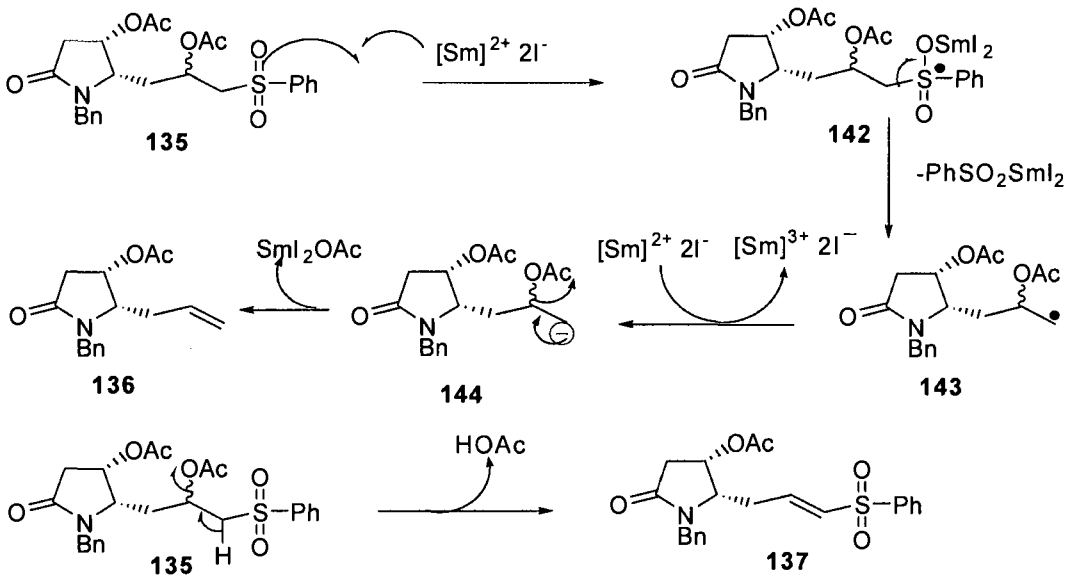


Figure 3: Proposed mechanism of reductive elimination reaction.

The alcohol **138** was protected as the MOM ether before it was debenzylated under Birch's condition[38] to arrive at the critical intermediate **117**. *N*-Allylation to install the 2-methoxymethoxy-1-propene moiety on the lactam nitrogen of **117** gave **119** in yields ranging from 70-90%.

Unlike **118**, the yield of **121** from the RCM reaction on **119** using Grubbs II catalyst was a function of the reaction temperature. Using CH_2Cl_2 as the reaction medium, the yield of the cyclized product was 74% and this contrasted with the 84% recorded when PhMe was the reaction medium. This difference in yield can be explained on the basis of increased temperature, which is required to overcome the steric hindrance imposed by the bulky 2-methoxymethoxy-1-propene moiety.

The plan was to use the vinyl ether moiety in **121** as the template for the eventual installation of the amino function at C-6 of (–)-slaframine (**51**) (Scheme 17). Upon

reduction of the amide carbonyl using LAH the resulting compound **140** was found to be unstable and full characterization of this intermediate was impossible. Heating **140** in methanolic HCl afforded the keto alcohol **141,** which was isolated as the stable hydrochloride salt in quantitative (quant) yield (crude yield). The crude ^{1}H NMR (D_2O) of **141** showed the following signals at δ 1.64-2.49 (m, 8 H, H-2, H-3, H-7, H-8) and 2.91 (d, 1 H, J = 12 Hz, H-5) consistent with its structure.

At this point, owing to the instability of compound **140**, there was not enough material to pursue the synthesis of (–)-slaframine. The synthesis will be pursued after the right conditions for handling **140** have been worked out.

3.0 Summary and Suggestions for Future Work

3.1 Summary

This study has shown that $Rh_2(4S\text{-MPPIM})_4$ catalyst cannot be used to kinetically resolve a racemic mixture of γ-lactam diazoacetates. From the results obtained from the C-H insertion reactions it has been established that the *N*-protecting group on the γ-lactam diazoacetate affects the yield of the bicyclic γ-lactam lactones resulting from the C-H insertion reaction. The yields recorded for all three *N*-protecting groups studied were lower than the 70% reported earlier.[20c]

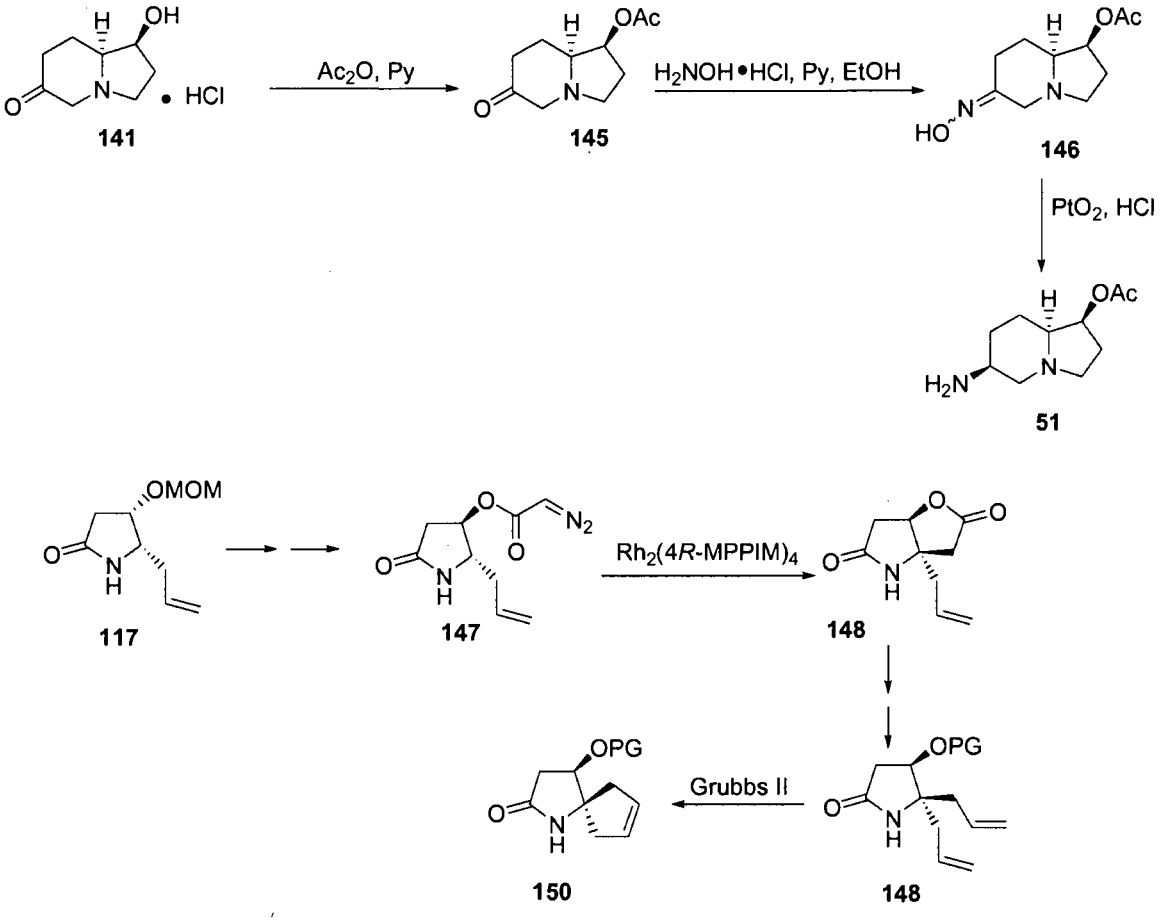
The *cis*-diastereoselectivity obtained for all the bicyclic γ-lactam lactones C-H insertion products make them a very attractive key intermediate in the synthesis of piperidine and pyrrolidine based alkaloids. This has been demonstrated with the total synthesis of the alkaloid (+)-(1*S*, 8a*S*)-1-hydroxyindolizidine (**12**) and also the approach leading to the synthesis of the alkaloid (–)-slaframine (**51**). In both cases, the scope of the applicability of the chiral **24** as a synthetic intermediate was clearly delineated.

Two routes to the key intermediate **117** were investigated. The first route proceeded through the intermediacy of the diol **124**. The drawback of the method was the low yield due to the many synthetic steps involved. Sulfone chemistry was investigated in the second route. This route proved superior to the first route as it enabled the access of the desired alkene system **117** in good yield.

3.2 Future Work

Preparation of the keto acetate **145** using the condition reported by Gensler *et al.*[26b] (Scheme 20) failed and due to paucity of starting material **141**, different methods of preparing **145** could not be investigated. Thus, having devised a route to the advanced intermediate **141**, the plan for the future would be to prepare more of **141** and then investigate the feasibility of the reactions shown in Scheme 20 enroute to the alkaloid (–)-slaframine.

The construction of asymmetric quaternary carbon centers is a daunting task in organic synthesis.[48] However, many natural products possessing beneficial biological activities possess an asymmetric quaternary carbon atom. Having devised a facile entry into the alkene systems such as **117**, we hope to use the existing methodology developed in our group to synthesize spirocyclic systems such as **150** (Scheme 20), which could then be further transformed into other alkaloids.

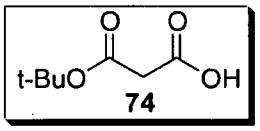


Scheme 20: Proposed future work.

4.0 Experimental

The infrared spectra were recorded on a Perkin-Elmer 1600 FT using either neat product or CH_2Cl_2 as a solvent. Only the diagnostic signals are reported. NMR spectra were recorded using BrukerAC200 QNP and Varian Mercury 300 spectrometers. The chemical shifts were recorded in parts per million (δ) relative to the appropriate reference signal. ^1H NMR (200 MHz or 300 MHz) were recorded in deuteriochloroform ($CDCl_3$) using tetramethylsilane (δ_H0.0) or residual chloroform (δ_H7.24) as reference; multiplicities of signals are given as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad, and coupling constants are given in Hz. ^{13}C were recorded in $CDCl_3$ using the $CDCl_3$ triplet centered at δ 77.0 as reference. Melting points were recorded on the Gallenkamp melting point apparatus. Progress of all reactions was monitored by thin-layer chromatography on Merck® silica gel $60F_{254}$ pre-coated (0.25 mm) on aluminum-backed sheets. Flash chromatography was performed on Merck® silica gel 60 (230-400) mesh. DCE, CH_2Cl_2, MeCN and PhMe were dried by distillation from calcium hydride prior to use. All moisture and air sensitive reactions were conducted under a static pressure of argon. All Rh(II)-catalyzed reactions were conducted in dry DCE at reflux with 1 mol % of the Rh_2(4*S*-MPPIM)$_4$,[42] and references cited therein.

4.1 Preparation of (–)-(*S*)-85: Method A



Mono-*t*-butyl malonate[43]

Malonic acid **72** (25.0 g, 0.240 mol) and DMAP (2.90 g, 0.0200 mol) were dissolved in dry MeCN (130 mL) and dry *t*-butyl alcohol **73** (23 mL, 0.240 mol) was added to the mixture. After stirring for 10 min at rt, the mixture was cooled on an ice bath and by means of cannula transfer, a solution of DCC (49.4 g, 0.240 mol) in dry MeCN (60 mL) was added to the cooled mixture. The cannula was rinsed with MeCN (10 mL) and the reaction was stirred overnight.

The urea was filtered off and the filtrate concentrated under vacuum to afford a thick oil, which was re-dissolved in ether (30 mL) leading to the precipitation of a white solid.

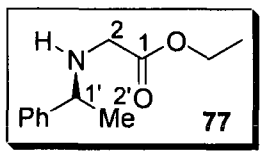
The solid was removed by filtration and aqueous 0.5 M HCl (20 mL) was added to the ether solution and the resulting mixture stirred vigorously for 1 h. The ether was subsequently separated from the acid and then extracted with 1 M NaOH solution (2 x 10 mL). The NaOH extract was cooled to 0°C in an ice bath and then acidified to pH 1 with 10% HCl. The acidified solution was then extracted with CH_2Cl_2 (3 x 15 mL). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give a light yellow oil.

The crude product was purified by means of Kugelrohr distillation (0.15 mmHg, 60°C) to give **74** (19.3 g, 50%), as a colorless viscous oil.

IR (neat) 3300, 1724 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44 (s, 9 H, *t*-Bu) 3.27 (s, 2 H, CH_2) 10.1 (br s, 1 H, CO_2H)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.5, 41.9, 82.3, 165.9, 171.2



Ethyl 2-(*N*-(*S*)-(α-methylbenzylamino)propanoate[44]

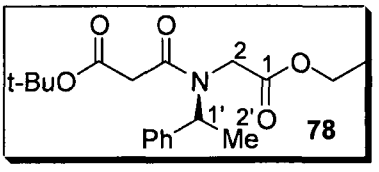
A 250 mL round bottom flask was evacuated and flushed with N_2, after which (*S*)-α-methylbenzylamine **75** (12 mL, 0.0900 mol) and dry CH_2Cl_2 (90 mL) were then added. Freshly re-distilled **76** (11.5 mL, 0.100 mol) was added next and the mixture was cooled to 0°C in an ice bath. By means of cannula transfer, dry Et_3N (15.7 mL, 0.110 mol) was then added to the mixture and after which the cannula was rinsed with dry CH_2Cl_2 (10 mL). Salt formation was visible 30 min into the reaction. The reaction mixture was allowed to stir overnight at rt.

The reaction mixture was washed with water (2 x 50 mL), and then concentrated under vacuum to give an oil, which was subsequently filtered through a pad of silica gel, using 2:1 v/v PE/EtOAc solution. The filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give a light yellow oil. Purification of the liquid was effected by Kugelrohr distillation (0.1 mmHg, 70°C) to afford **77** (16 g, 82%) as a colorless liquid.

$[\alpha]_D^{25}$ –60.3° (*c* 2.28, $CHCl_3$); IR (neat) 3330, 3050, 3025, 1731, 1625 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, 3 H, J = 7.1 Hz, OCH_2CH_3) 1.39 (d, 3 H, J = 6.6 Hz, PhCH(N)*Me*) 2.39 (br s, 1 H, N-H) 3.20 (d, 1 H, J = 17.4 Hz, N-C*H*-C=O) 3.30 (d, 1 H, J = 17.4 Hz, N-C*H'*-C=O) 3.81 (q, 1 H, J = 6.6 Hz, PhC*H*(N)Me) 4.15 (q, 2 H, J = 7.1 Hz, OCH_2CH_3) 7.20-7.36 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 23.6, 48.2, 57.0, 59.9, 125.0, 126.0, 127.8, 144.1, 171.8



78

t-Butyl-*N*-(2-(carboethoxymethyl)-*N*-((*S*)-α-methylbenzyl)malonamide[29]

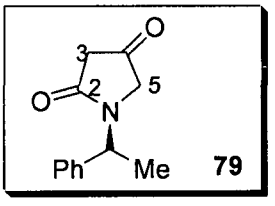
(*S*)-(α-methylbenzylamino)ethyl acetate **77** (14 g, 0.0700 mol), **74** (11.9 g, 0.0700 mol) and DMAP (0.8 g, 6.55 mmol) were mixed together in a 250 mL round bottom flask. Dry CH_2Cl_2 (100 mL) was then added to the mixture which was stirred for 10 min at rt before being cooled to 0°C in an ice bath. By means of cannula transfer, a solution of DCC (16.0 g, 0.0800 mol) in dry CH_2Cl_2 (30 mL) was added to the cooled mixture. Formation of urea was visible with the addition of DCC. The cannula was rinsed with 20 mL dry CH_2Cl_2 and then the reaction mixture was stirred at rt overnight.

The reaction mixture was processed by filtering off the urea followed by the addition of aqueous 0.5 M HCl (50 mL) to the filtrate. The mixture was stirred vigorously for 1 h during which formation of urea was visible. The CH_2Cl_2 layer was separated from the aqueous acid and then washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL) and then brine (2 x 20 mL). The washed organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give a yellow viscous oil. The oil was re-

dissolved in ether, to precipitate urea, which was filtered off. The clear yellow ether filtrate was concentrated under vacuum to afford **78** (24 g, 100%), as a viscous yellow oil which was used in the next reaction without further purification, as an attempted purification by vacuum distillation resulted in decomposition.

$[\alpha]_D^{25}$ –46.7° (*c* 2.14, $CHCl_3$); IR (neat), 1737, 1655 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 1.15 (t, 3 H, J = 7.2 Hz, OCH_2CH_3) 1.36 (d, 3 H, J = 7.0 Hz, PhCH(N)*Me*) 1.94 (s, 9 H, *t*-Bu) 3.24 (d, 1 H, J = 17 Hz, N-C*H*-CO) 3.50 (d, 1 H, J = 17.1 Hz, N-C*H'*-CO) 3.59 (d, 1 H, J = 18.7 Hz, OCC*H*CO) 3.78 (d, 1 H, J = 18.8 Hz, OCC*H'*CO) 3.98 and 4.02 (q, 2 H, J = 7.2 Hz, OCH_2CH_3) 5.20 and 6.00 (q, 1 H, J = 7.3 Hz, PhC*H*(N)Me), 7.12-7.36 (m, 5 H, Ph*H*)



***N*-((*S*)-α-Methylbenzyl)-4-oxo-2-pyrrolidinone**[29]

Dry PhMe (100 mL) was added to **78** (19.2 g, 0.0600 mol) in a 250 mL round bottom flask and then concentrated on a rotary evaporator in order to remove moisture from **78** by azeotropic evaporation. The above process was repeated twice with dry PhMe (100 mL). The concentrated malonamide was flushed with N_2, and then put under static Ar pressure, after which dry PhMe (100 mL) was then added. The mixture stirred to give a homogenous solution before KOBu-t (7.50 g, 0.0600 mol) was then added and the reaction mixture stirred overnight at rt. Addition of the base resulted in cloudy solution, which later became clear with the formation of a brown gummy-like mass at the bottom

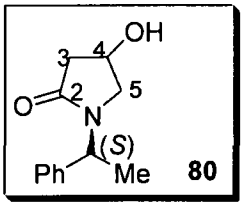
of the flask. TLC analysis of the clear supernatant PhMe layer neither showed formation of **79** nor presence of starting material **78**. Aqueous 1 M HCl (20 mL) was added to the reaction mixture and then stirred for 1 h. The gummy-like mass dissolved in the PhMe layer and subsequent TLC analysis of the PhMe layer showed formation of **79**.

The PhMe layer was separated from the acid and then extracted with aqueous 1 M NaOH (4 x 15 mL).

The combined alkaline extracts were cooled in an ice bath and then acidified to pH 2 with aqueous 1 M HCl. The resulting solution was saturated with solid NaCl. The mixture was then stirred for 1 h, after which it was extracted with CH_2Cl_2 (3 x 40 mL). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford **79** (9.8 g, 84%), as a brown oil.

$[\alpha]_D^{25}$ –117° (*c* 0.15, $CHCl_3$); IR (neat) 1766, 1689 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 1.57 (d, 3 H, J = 7.1 Hz, PhCH(N)*Me*) 3.07 (s, 2 H, H-3) 3.44 (d, 1 H, J = 17.8 Hz, H-5) 3.80 (d, 1 H, J= 17.8 Hz, H-5') 5.80 (q, 1 H, J = 7.1 Hz, PhC*H*(N)Me) 7.25-7.45 (m, 5 H, Ph*H*)

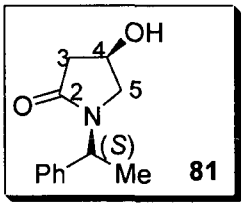


***N*-((*S*)-α-Methylbenzyl)-4-hydroxy-2-pyrrolidinone**[29]

A 500 mL round bottom flask containing a solution of **79** (9.80 g, 0.0500 mol) in MeOH (50 mL) was stirred at 0°C. $NaBH_4$ (11.8 g, 0.310 mol) was added over 15 min. After the

addition of $NaBH_4$ was complete, the reaction mixture was stirred at rt for 30 min by which time the reduction was judged to be complete using TLC analysis.

The reaction mixture was cooled in an ice bath and then quenched by adding five drops of glacial HOAc. The mixture was then concentrated under vacuum to give a grayish solid, and to which was added 1 M NaOH (20 mL) and solid NaCl. The mixture was stirred for 30 min after which the alkaline solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined CH_2Cl_2 extracts were washed with saturated brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give white crystals of **80**, as a mixture of diastereomers.



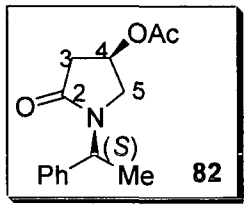
***N*-((*S*)-α-Methylbenzyl)-(*R*)-4-hydroxy-2-pyrrolidinone**[29]

The shinny needles of **81** (1.98 g) were obtained in the pure form from the fractional crystallization of **80** in MeCN.

mp: 138-140°C; $[\alpha]_D^{25}$ –110° (*c* 1, EtOH) (lit[29] $[\alpha]_D^{18}$ –118.8° (*c* 1, EtOH)); IR (KBr) 3325, 1650 cm^{-1}

^1H NMR ($CDCl_3$ 200 MHz): δ 1.42 (d, 3 H, J = 7.1 Hz, PhCH(N)*Me*) 2.31 (dd, 1 H, J = 17.2, 2.0 Hz, H-3) 2.60 (dd, 1 H, J = 17.3, 3.6 Hz, H-3') 2.88 (dd, 1 H, J = 10.8, 3.6 Hz, H-5) 3.29 (br s, 1 H, OH) 3.44 (dd, 1 H, J = 10.8, 5.5 Hz, H-5') 4.26-4.44 (m, 1 H, H-4) 5.38 (q, 1 H, J = 7.1 Hz, PhC*H*(N)Me) 7.08-7.40 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.2, 41.1, 48.4, 51.2, 63.8, 126.5, 127.0, 128.2, 139.5, 172.3



(4*R*)-4-Acetoxy-*N*-((*S*)-α-methylbenzyl)-2-pyrrolidinone

The residual mother liquor from the recrystallization of **80** was concentrated under reduced pressure to give a solid (6.38 g, 30 mmol). To this solid was added dry CH_2Cl_2 (30 mL), DMAP (0.400 g, 3.3 mmol) and Ac_2O (4.4 mL). The mixture was stirred under Ar, in an ice bath for 15 min after which Et_3N (17 mL) was added dropwise to the mixture. The reaction was stirred at rt for 1 h by which time reaction was complete as indicated by TLC analysis.

The reaction was washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL) followed by aqueous 0.5 M HCl solution (1 x 10 mL) and then with water (1 x 10 mL). The washed reaction mixture was dried over anhydrous Na_2SO_4, filtered and concentrated to give a dark brown oil.

The crude diastereomeric mixture was separated into the individual components by flash column chromatography (2:1 v/v of PE/EtOAc) to give **82** (2.6 g, 33%) and **83** (3.8 g, 50%) both as clear oils.

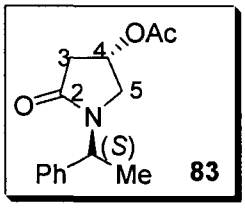
$[\alpha]_D^{21}$ –61° (*c* 2.74, $CHCl_3$); IR(CH_2Cl_2) 3036, 3013, 1736, 1684 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (d, 3 H, J = 7.1 Hz, PhCH(N)*Me*), 1.89 (s, 3 H, O=C-Me), 2.45 (dd, 1 H, J = 17.6, 2.2 Hz, H-3), 2.75 (dd, 1 H, J = 17.6, 6.8 Hz, H-3'), 2.92 (d,

1 H, J = 11.5, 1.6 Hz, H-5), 3.59 (dd, 1 H, J = 11.6, 5.6 Hz, H-5'), 5.14-5.22 (m, 1 H, H-4), 5.46 (q, 1 H, J = 7.0 Hz, PhC*H*(N)Me), 7.16-7.31 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 20.4, 37.7, 40.8, 66.7, 126.5, 127.1, 128.1, 139.2, 169.9, 170.9

(EI)-HRMS calcd for $C_{14}H_{17}NO_3$ for 247.1208, found 247.1213

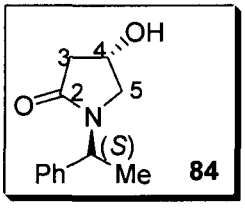


(4*S*)-4-Acetoxy-*N*-((*S*)-α-methylbenzyl)-2-pyrrolidinone

$[\alpha]_D^{21}$ –62.4° (*c* 4.41, $CHCl_3$); IR(CH_2Cl_2) 3036, 3013, 1736, 1684 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.46 (d, 3 H, J = 7.1 Hz, PhCH(N)*Me*), 1.90 (s, 3 H, O=C-Me), 2.45 (dd, 1 H, J = 17.6, 2.3 Hz, H-3), 2.76 (dd, 1 H, J = 17.6, 6.8 Hz, H-3'), 2.93 (d, 1 H, J = 11.5 Hz, H-5), 3.61 (dd, 1 H, J = 11.5, 5.6 Hz, H-5'), 5.14-5.25 (m, 1 H, H-4), 5.47 (q, 1 H, J = 7.1 Hz, PhC*H*(N)Me), 7.21-7.30 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 20.4, 37.7, 40.8, 66.7, 126.5, 127.1, 128.1, 139.2, 169.9, 170.9



(4*S*)-4-Hydroxy-*N*-((*S*)-α-methylbenzyl)-2-pyrrolidinone

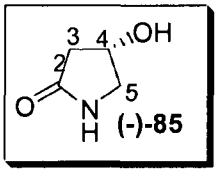
To a solution of **83** (2.10 g, 8.30 mmol) in MeOH (15 mL) was added anhydrous K_2CO_3 (1.73 g, 1.30 mmol). The mixture was stirred at rt for 2 h by which time the reaction was

complete. The MeOH was evaporated under vacuum to give a slurry, to which was added CH_2Cl_2 and anhydrous Na_2SO_4. The mixture was allowed to stand for 1 h and then filtered through a pad of Celite® followed by silica gel using CH_2Cl_2. The CH_2Cl_2 filtrate was concentrated under vacuum to afford **84** (82%), as a yellow oil.

$[\alpha]_D^{25}$ −155° (*c* 1, EtOH) (lit[29] $[\alpha]_D^{18}$ −177.6° (*c* 1, EtOH)); IR (neat) 3350, 1664cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.53 (d, 3 H, J = 7.1 Hz, PhCH(N)*Me*), 2.42 (dd, 1 H, J = 17.3, 2.7 Hz, H-3), 2.67 (dd, 1 H, J = 17.3, 6.5 Hz, H-3'), 3.17 (dd, 1 H, J = 10.8, 5.4 Hz, H-5), 3.26 (dd, 1 H, J = 10.8, 2.5 Hz, H-5'), 3.45 (br s, 1 H, OH), 4.30-4.48 (m, 1 H, H-4), 5.50 (q, 1 H, J = 7.1 Hz, PhC*H*(N)Me), 7.18-7.48 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 40.9, 48.3, 50.9, 63.3, 126.3, 126.9, 127.9, 139.1, 172.1



(-)-85

(–)-(*S*)-4-Hydroxy-2-pyrrolidinone[29]

To 2.50 g (0.0100 mol) of **84** was added dry PhMe (10 mL) and $MeSO_3H$ (1.7 mL) resulting in an immiscible mixture of two layers. The mixture was refluxed at 135°C for 6 h and then allowed to cool down to rt. The two layers were separated and to the acid layer was added MeOH (15 mL) and Amberlite IR 45(OH) resin (preconditioned by washing in 0.5 M NaOH solution, followed by distilled water to remove all the NaOH and finally MeOH). The mixture was stirred at rt until the acidic methanolic solution was neutralized.

The resin was filtered off and washed with MeOH (200 mL). The combined MeOH washings were concentrated down to afford a white solid.

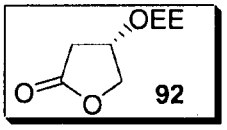
The crude product was purified by flash column chromatography using 2:1 v/v CH_2Cl_2/acetone and acetone to afford (–)-**85** (850 mg, 71%) as colorless crystals.

$[\alpha]_D^{25}$ = –42.5°C (*c* 0.53, MeOH) (purchased from Aldrich: $[\alpha]_D^{23}$ = –43°C (*c* 1, EtOH)); IR (film) 3401-3049, 1666 cm^{-1}.

^1H NMR (CD_3OD, 300 MHz): δ 2.08 (dd, 1 H, J = 17.2, 2.3 Hz, H-3), 2.50 (dd, 1 H, J = 17.3, 6.4 Hz, H-3'), 3.13 (dd, 1 H, J = 10.9, 1.8 Hz, H-5), 3.50 (dd, 1 H, J = 10.9, 5.4 Hz, H-5'), 4.43-4.48 (m, 1 H, H-4), 4.75 (br s, 1 H, OH)

^{13}C NMR (CD_3OD, 75 MHz) δ 40.0, 52.0, 67.1, 178.0

4.1.1 Alternate Synthesis of (*S*)-4-hydroxy-2-pyrrolidinone



(*S*)-4-(1-Ethoxy)ethoxy-γ-butyrolactone[30]

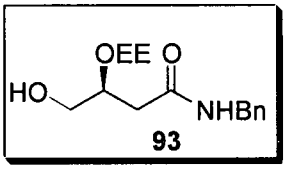
To a solution of **91** (2.00 g, 20 mmol) in dry CH_2Cl_2 (20 mL) was added PPTS (50.2 mg, 0.200 mmol) and EVE (9.4 mL, 90.0 mmol) at rt. The mixture was stirred at rt for 3 h and then concentrated under reduced pressure. The residual oil was purified by flash column chromatography (4:1 v/v PE/EtOAc) to afford an inseparable diastereomeric mixture of **92** (3.3 g, 95%) as a pale yellow oil. The ratio of the diastereomers was 1:1 and is based on the integration of the H-3 proton signals at δ 2.32 and 2.38.

$[\alpha]_D^{26}$ –23° (*c* 1.63, $CHCl_3$); IR (neat) 3000, 1784, 1750 cm^{-1}.

Discernible signals of diastereomer A : ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.01 (t, 3 H, J = 7.1 Hz, OCH_2CH_3), 1.12 (d, 3 H, J = 1.5 Hz, $OCH(CH_3)O$), 2.32 (dd, 1 H, J = 9.5, 2.8 Hz, H-3), 2.38 (dd, 1 H, J = 9.5, 2.9 Hz, H-3'), 3.24-347 (m, 2 H, OCH_2CH_3), 4.10 (dd, 1 H, J = 10.1, 2.2 Hz, H-5), 4.13 (dd, 1 H, J = 10.0, 2.3 Hz, H-5'), 4.37-4.45 (m, 1 H, H-4), 4.59 (ddd, 1 H, J = 10.3, 10.3, 5.3 Hz, $OCH(CH_3)O$)

Discernible signals of diastereomer B : 1.13 (d, 3 H, J = 1.5 Hz, $OCH(CH_3)O$), 2.53 (dd, 1 H, J = 8.4, 6.6 Hz, H-3), 2.59 (dd, 1 H, J = 8.4, 6.6 Hz, H-3'), 4.22 (dd, 1 H, J = 12.5, 4.9 Hz, H-5), 4.13 (dd, 1 H, J = 12.5, 5.1 Hz, H-5')

^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.3, 20.2, 35.3, 36.1, 60.8, 70.0, 73.7, 74.4, 99.3, 175.8



93

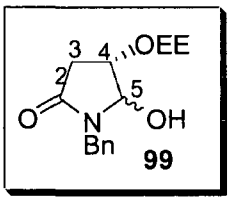
(3*S*)-*N*-Benzyl-3-(1-ethoxy)ethoxy-4-hydroxybutyramide[30]

To **92** (3.30 g, 19.0 mmol) was added $BnNH_2$ (4.1 mL, 40.0 mmol) at rt and then the mixture was stirred for 5 h at 50°C. The excess $BnNH_2$ was removed by Kugelrohr distillation (rt, 0.3 mmHg). The residual oil was purified by flash column chromatography (1:1 v/v PE/EtOAc) to afford **93** (5.1 g, 95%) as a pale yellow viscous oil.

$[\alpha]_D^{26}$ +19° (*c* 0.63, $CHCl_3$); IR (neat) 3500-3100, 3075, 1750, 1648, 1549 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.03-1.26 (m, 6 H, OCH_2CH_3, $OCH(CH_3)O$), 2.30-2.53 (m, 2 H, $CH_2C{=}O$), 3.34-3.64 (m, 4 H, OCH_2CH_3, NCH_2Ph), 3.99-4.09 (m, 1 H, $OCH_2CH(O)CH_2$), 4.29-4.41 (m, 2 H, $HOCH_2CH$), [4.63 (q), 4.74 (q, 1 H, J = 5.2 Hz, $OCH(CH_3)O$], [6.63 (br s), 7.00 (br s, 1 H, N-H] 7.13-7.30 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 19.6, 38.6, 42.7, 60.4, 61.2, 63.5, 64.3, 72.7, 76.3, 99.2, 100.5, 126.6, 126.7, 126.9, 127.0, 127.8, 127.9, 137.7, 169.9, 170.4



99

(4*S*, 5*R*/*S*)-*N*-Benzyl-4-(1-ethoxy)ethoxy-5-hydroxy-2-pyrrolidinone[31]

To a solution of **93** (5.1 g, 18 mmol) in dry DMSO (20 mL) maintained at rt and under argon was added dry Et_3N (15 mL, 108 mmol). The resulting mixture was cooled to 0°C and a solution of SO_3.Py complex (8.7 g, 50 mmol) in dry DMSO (20 mL) was added dropwise via cannula. The mixture was stirred at rt for 16 h, then the excess DMSO was removed by Kugelrohr distillation (rt, 0.25 mmHg). The residual oil was cooled to 0°C and aqueous NaOH (15 mL), brine (50 mL) and NaCl were added. The mixture was stirred for 30 min and then extracted with EtOAc (5 x 100 mL). The combined organic extracts were washed with brine and saturated aqueous $CuSO_4$ and then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The processed reaction mixture was purified by flash column chromatography (2:1 v/v P.E/EtOAc) to afford an inseparable 1:1 diastereomeric mixture of the title product **99** (4.8 g, 94%) as a pale yellow oil. The ratio of the diastereomers was based on the integration of the Me proton signals at δ 1.19 and 1.23.

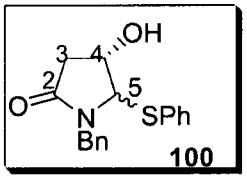
$[\alpha]_D^{25}$ +46.9° (*c* 1.44, $CHCl_3$), IR (film) 3500-3150, 3050, 3025, 1671, 1625, 1512 cm^{-1}

Discernible signals of diastereomer A : ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.02-1.08 (m, 3 H, Me), 1.19 (d, 3 H, J = 5.1 Hz, Me), 2.24 (dd, 1 H, J = 17.0, 3.3 Hz, H-3), 2.79 (dd, 1 H, J = 17.1, 7.1 Hz, H-3'), 3.24-3.57 (m, 2 H, OC*H*$_2$CH$_3$), 3.77-3.97 (m, 1 H, OH), 4.07-4.11 (m, 1 H, H-4), 4.11 (d, 1 H, J = 13.7 Hz, N-C*H*-Ph), 4.63-4.74 (ddd, 1 H, J = 10.3, 10.3, 5.1 Hz, OC(*H*)OCH$_3$) 4.79 (d, 1 H, J = 13.7 Hz, N-C*H'*-Ph), 4.76-4.90 (m, 1 H, H-5), 7.13-7.34 (m, 5 H, Ph*H*)

Discernible signals of diastereomer B: 1.08-1.14 (m, 3 H, Me), 1.23 (d, 3 H, J = 5.1 Hz, Me), 2.36 (dd, 1 H, J = 17.1, 3.1 Hz, H-3), 2.82 (dd, 1 H, J = 17.1, 7.4 Hz, H-3') 4.00-4.07 (m, 1 H, OH)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.3, 15.4, 20.3, 20.4, 36.9, 37.5, 43.4, 43.5, 60.6, 61.2, 74.7, 75.8, 87.3, 99.4, 99.7, 127.8, 128.3, 128.4, 128.9, 136.3, 172.8

(EI)-HRMS calcd for $C_{15}H_{21}NO_4$ for 279.1471, found 279.1472



(4*S*, 5*R*/*S*)-*N*-Benzyl-4-hydroxy-5-phenylthio-2-pyrrolidinone[45]

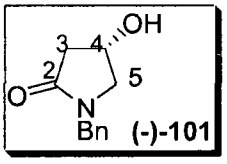
To a solution of **99** (7.00 g, 25.1 mmol) in dry CH_2Cl_2 (5 mL) at 0°C was added PhSH (5.1 mL, 50.1 mmol). The mixture was stirred for 10 min and then Mg(OTf)$_2$ (8.10 g, 27.6 mmol) was added. The reaction mixture was stirred at rt for 12 h and then by filtration through a pad of silica gel, the excess PhSH was removed using (20:1 v/v PE/Et$_2$O) and (8:1 v/v CH_2Cl_2/acetone) was used to obtain the product **100**. The product filtrate was concentrated under reduced pressure to give a viscous brown oil (6.9 g 93%), which was used in the next reaction without further purification. The ^{1}H NMR showed a

diastereomeric mixture of *cis* :*trans* ratio of 1:2 based on integration of the benzylic signals at δ 4.12 and 4.19 respectively.

IR (film) 3550-3125, 3063, 3030, 1681, 1612, 1587 cm^{-1}

Discernible signals of diastereomer A (*trans*) : ^1H NMR ($CDCl_3$, 300 MHz): δ 2.03 (dd, 1 H, J = 17.6, 5.8 Hz, H-3), 2.16 (d, 1 H, J = 17.4 Hz, H-3'), 2.97 (br s, 1 H, OH), 4.19 (d, 1 H, J = 14.9 Hz, NC*H*Ph), 4.51 (s, dd superimposed, 2 H, J = 9.5, 5.6 Hz, H-4, H-5), 5.17 (d, 1 H, J = 14.9 Hz, NC*H*'Ph), 7.10-7.44 (m, 10 H, Ph*H*) *cis* and *trans* diastereomers overlapped in aromatic region

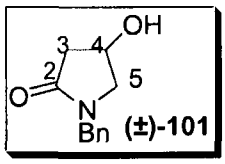
Discernible signals of diastereomer B (*cis*) : 2.18 (d, 1 H, J = 16.8 Hz, H-3), 2.58 (dd 1 H, J = 16.8, 7.5 Hz, H-3'), 4.12 (d, 1 H, J = 14.8 Hz, NC*H*Ph), 4.79 (d, 1 H, J = 6.2 Hz, H-5), 5.17 (d, 1 H, J = 14.4 Hz, NC*H*'Ph)



(–)-(4*S*)-*N*-Benzyl-4-hydroxy-2-pyrrolidinone[45]

To a solution of Bu_3SnH (0.910 mmol, 0.25 mL) in PhMe (4 mL) at 80°C was added a mixture of **100** (130.0 mg, 0.430 mmol) and AIBN (14.3 mg, 0.09 mmol) in PhMe (4 mL) via cannula. The cannula was rinsed with PhMe (2 mL) and the reaction mixture stirred at 80°C for 3 h. The PhMe was removed under reduced pressure leaving behind an oily residue to which was added 10% KF in MeOH (15 mL). The solution was stirred for 20 min, filtered and concentrated and then purified by flash column chromatography (2:1 v/v CH_2Cl_2/acetone) afford **101** (66 mg, 80%) as white crystals.

mp: 104-106°C; lit[45] 107.5-109°C ; $[\alpha]_D^{25}$ –34.2° (*c* 0.59, $CHCl_3$); lit[45] $[\alpha]_D^{20}$ –32.5° (*c* 1.3, $CHCl_3$)



(±)-*N*-Benzyl-4-hydroxy-2-pyrrolidinone

The TBDMS ether (±)-**104** (100. mg, 0.328 mmol) was dissolved in a mixture of 1:1 v/v MeOH/aqueous 1 M HCl (1 mL). The mixture was stirred at rt for 3 h. Solid $NaHCO_3$ was added till no evolution of gas was visible. The MeOH was removed under reduce pressure. The residue was re-dissolved in CH_2Cl_2 and anhydrous Na_2SO_4 added. After 1 h, the Na_2SO_4 was filtered off and the filtrate concentrated on a rotary evaporator. The concentrate was purified by flash column chromatography (2:1 v/v CH_2Cl_2/acetone) to afford (±)-**101** (50 mg, 81%) as white solids.

IR (CH_2Cl_2 film) 3375, 2924, 1669 cm^{-1}

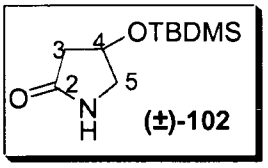
^1H NMR ($CDCl_3$, 300 MHz) δ 2.41 (dd, 1 H, J = 17.3, 2.2 Hz, H-3), 2.70 (dd, 1 H, J = 17.3, 6.6 Hz, H-3'), 3.18 (dd, 1 H, J = 10.8, 1.9 Hz, H-5), 3.44 (br s, 1 H, OH), 3.37 (dd, 1 H, J = 10.9, 5.5 Hz, H-5'), 4.38 (d, 1 H, J = 14.8 Hz, N-C*H*-Ph), 4.38-4.48 (m, 1 H, H-4) 4.49 (d, 1 H, J = 14.8 Hz, N-C*H'*-Ph), 7.10-7.30 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.0, 46.2, 55.6, 64.1, 127.6, 127.4, 128.6, 135.9, 172.9

4.2 General procedure for preparation of 4-*t*-butyldimethylsilyloxy-2-pyrrolidinone[46]

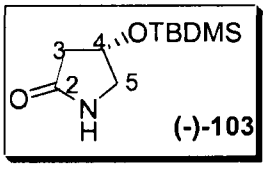
4-Hydroxy-2-pyrrolidinone (±)-**85** or (–)-**85**, imidazole and DMAP were dissolved in dry DMF after which TBDMSCl was added to the reaction mixture and the mixture stirred at 40°C overnight. EtOAc and brine were then added to the reaction mixture resulting in salt formation. The mixture was stirred for 10 min and then the aqueous layer separated from the organic layer. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the

combined organic extracts were washed with brine and then dried over anhydrous Na_2SO_4. The dried organic layer was filtered and then concentrated under vacuum to give the crude product, which was purified by flash column chromatography (2:1 v/v CH_2Cl_2/acetone) to give (±)-**102** or (–)-**103** (94%) as white solids.



(±)-4-*t*-Butyldimethylsilyloxy-2-pyrrolidinone (94%) (made from (±)-**85**)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.04 (s, 6 H, $Si(Me)_2$), 0.88 (s, 9 H, Si-*t*-Bu), 2.26 (dd, 1 H, J = 17.0, 4.1 Hz, H-3), 2.56 (dd, 1 H, J = 17.0, 6.8 Hz, H-3'), 3.25 (dd, 1 H, J = 10.1, 3.4 Hz, H-5), 3.60 (dd, 1 H, J = 10.1, 6.0 Hz, H-5'), 4.50-4.65 (m, 1 H, H-4), 6.12 (br s, 1 H, N-H)



(–)-(*S*)-4-*t*-Butyldimethylsilyloxy-2-pyrrolidinone (made from (–)-**85**)

mp: 88-90°C; $[\alpha]_D^{25}$ –5.8° (*c* 0.85, $CHCl_3$); IR (CH_2Cl_2 film) 3175, 1667cm^{-1}

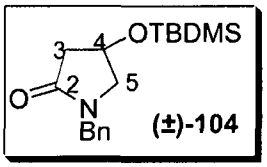
^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.02 (s, 6 H, $Si-(Me)_2$), 0.83 (s, 9 H, Si-*t*-Bu), 2.22 (dd, 1 H, J = 16.9, 4.1 Hz, H-3), 2.50 (dd, 1 H, J = 16.9, 6.8 Hz, H-3'), 3.19 (dd, 1 H, J = 10.1, 3.3 Hz, H-5), 3.54 (dd, 1 H, J = 10.1, 6.1 Hz, H-5'), 4.43-4.57 (m, 1 H, H-4), 6.78 (br s,1 H, N-H)

^{13}C NMR ($CDCl_3$, 75 MHz): δ -5.2, -5.1, 17.7, 25.4, 40.3, 51.5, 67.6, 176.4

4.3 General procedure for the preparation of (±)-*N*-benzyl-4-*t*-butyldimethylsilyloxy-2-pyrrolidinone and (*S*)-*N*-allyl-4-*t*-butyldimethylsilyloxy-2-pyrrolidinone.

The TBDMS protected 2-pyrrolidinone (±)-**102** or (–)-**103** was dissolved in dry THF (3 mL), and a few crystals of 2,2'-bipyridine was added. The mixture was cooled to –15°C and BuLi (1.55 M, 0.0930 mmol) was then added dropwise to the cooled mixture. The solution turned dark red after all of the BuLi had been added.

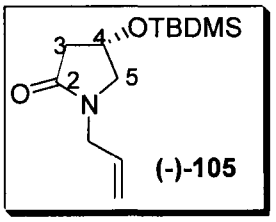
DMF was added and the mixture stirred for 3 min. BnBr or allyl bromide was added dropwise with stirring. The reaction mixture was stirred at –15°C for 15 min and then the temperature allowed to rise gradually to 0°C over 5 h by which time the reaction was judged to be complete by TLC analysis. EtOAc was added and the resulting solution washed twice with brine. The washed organic layer was dried over anhydrous Na_2SO_4, filtered, then concentrated and finally purified by flash column chromatography (2:1 v/v PE/EtOAc) and EtOAc to afford (±)-**104** (88%) and (–)-**105** (90%) both as yellow oils.



(±)-**104**

(±)-*N*-Benzyl-4-*t*-butyldimethylsilyloxy-2-pyrrolidinone (made from (±)-**102**)

^{1}H NMR ($CDCl_3$, 200 MHz) δ -0.02 (s, 3 H, Si-Me), 0.02 (s, 3 H, Si-Me'), 0.82 (s, 9 H, Si-^{t}Bu), 2.37 (dd, 1 H, J = 16.9, 3.2 Hz, H-3), 2.65 (dd, 1 H, J = 16.9, 6.4 Hz, H-3'), 3.09 (dd, 1 H, J = 10.3, 2.7 Hz, H-5), 3.42 (dd, 1 H, J = 10.3, 5.7 Hz, H-5'), 4.34 (d, 1 H, J = 14.9 Hz, N-C*H*-Ph), 4.37-4.50 (m, 1 H, H-4), 4.58 (d, 1 H, J = 14.9 Hz, N-C*H'*-Ph), 7.20-7.40 (m, 5 H, Ph*H*)



(–)-(4*S*)-*N*-Allyl-4-*t*-butyldimethylsilyloxy-2-pyrrolidinone

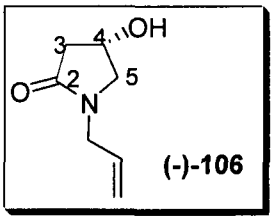
(made from (–)-**103**)

$[\alpha]_D^{25}$ –4.9° (*c* 0.515, $CHCl_3$) IR (Neat) 1699 cm^{-1}

^1H NMR ($CDCl_3$, 300MHz) δ 0.02 (s, 6 H, Si-$(Me)_2$), 0.83 (s, 9 H, Si-^{t}Bu), 2.29 (dd, 1 H, J = 16.8, 3.3 Hz, H-3), 2.56 (dd, 1 H, J = 16.8, 6.6 Hz, H-3'), 3.13 (dd, 1 H, J = 10.4, 2.9 Hz, H-5), 3.47 (dd, 1 H, J = 10.3, 5.9 Hz, H-5'), 3.73 (dd, 1 H, J =15.5, 5.8 Hz, N-C*H*-CH=CH_2), 3.91 (dd, 1 H, J = 15.8, 4.6 Hz, N-C*H'*-CH=CH_2), 4.34-4.44 (m, 1 H, H-4), 5.11 (dd, 2 H, J = 10.0, 8.6 Hz, N-CH_2-CH=C*H*$_2$) , 5.56-5.71 (m, 1 H, N-CH_2-C*H*=CH_2)

^{13}C NMR ($CDCl_3$, 75 MHz) δ –5.0, -4.9, 17.8, 25.5, 41.3, 44.5, 55.9, 65.1, 117.5, 131.9, 172.4

(CI)(NH_3)-HRMS calcd for $C_{13}H_{26}NO_2Si$ for 256.1655, found 256.1730



(–)-(4*S*)-*N*-Allyl-4-hydroxy-2-pyrrolidinone (made from (–)-**105**)

The TBDMS ether (–)-**105** was dissolved in a mixture of 1:1 v/v MeOH/aqueous 1 M HCl (1 mL). The mixture was stirred at rt for 3 h. Solid $NaHCO_3$ was added till no evolution of gas was visible. The MeOH was removed under reduce pressure. The residue was re-dissolved in CH_2Cl_2 and anhydrous Na_2SO_4 added. After 1 h, the Na_2SO_4

purified by flash column chromatography (2:1 v/v CH_2Cl_2/acetone) to afford (–)-**106** (84%) as a yellow oil.

$[\alpha]_D^{25}$ –13.3° (*c* 1.5, $CHCl_3$); 3600-3083, 1666, 1650 cm^{-1}

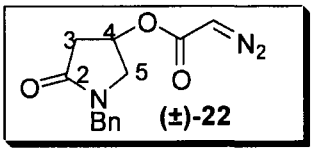
^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (d, 1 H, J = 17.3 Hz, H-3), 2.62 (dd, 1 H, J = 17.3, 6.5 Hz, H-3') 3.23, (d, 1 H, J = 10.9 Hz, H-5), 3.52 (dd, 1 H, J = 10.9, 5.6 Hz, H-5'), 3.78 (dd, 1 H, J = 16.6, 6.5 Hz, N-C*H*-CH=CH_2), 3.85 (dd, 1 H, J = 16.2, 6.2 Hz, N-C*H'*-CH=CH_2), 4.13 (br s, 1 H, OH), 4.37-4.46 (m, 1 H, H-4), 5.14 (dd, 2 H, J = 10.4, 6.9 Hz, N-CH_2-CH=C*H*$_2$), 5.57-5.74 (m, 1 H, N-CH_2-C*H*=CH_2)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.9, 44.7, 55.7, 63.8, 117.9, 131.5, 172.8

(EI)-HRMS calcd for $C_7H_{11}NO_2$ for 141.0709, found 141.0791

4.4 General Procedure for Preparation of diazoacetates[33] (±)-22, (–)-107 and (–)-108

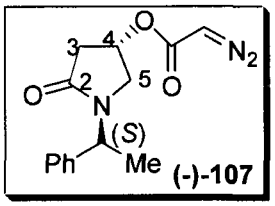
The alcohol (–)-**84**, or (±)-**101** or (–)-**106** and TsNH=NCHCOCl were dissolved in dry CH_2Cl_2, to give a clear colorless solution which was cooled to 0°C in an ice bath. To the cooled solution was added DMA resulting in a yellow solution. The reaction mixture was stirred at 0°C for 20 min and then at rt for 10 min. Reaction mixture was re-cooled to 0°C and *i*-Pr_2NEt added and the resulting mixture stirred at 0°C for 20 min and finally at rt for 20 min. CH_2Cl_2 was then added to the mixture and the resulting solution was washed with citric acid solution followed by saturated aqueous $NaHCO_3$ solution. The washed organic layer was dried over Na_2SO_4, filtered and concentrated to give a dark oil which was purified by flash chromatography (2:1 PE/EtOAc) to afford (±)-**22** (90%), and (2:1 CH_2Cl_2/acetone) to give (–)-**107** (85%) and (–)-**108** (90%), all three as yellow oils.



(±)-*N*-Benzyl-4-(α-diazoacetoxy)-2-pyrrolidinone (made from (±)-**101**)

IR (Neat) 3025, 2150, 1694 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ 2.54 (dd, 1 H, J = 17.8, 1.3 Hz, H-3), 2.84 (dd, 1 H, J = 17.8, 6.9 Hz, H-3'), 3.26 (d, 1 H, J = 11.7 Hz, H-5), 3.61 (dd, 1 H, J = 11.6, 5.7 Hz, H-5'), 4.39 (d, 1 H, J = 14.8 Hz, N-C*H*-Ph), 4.55 (d, 1 H, J = 14.8 Hz, N-C*H'*-Ph), 4.74 (s, 1 H, C*H*=N_2), 5.28-5.40 (m, 1 H, H-4), 7.10-7.40 (m, 5 H, Ph*H*)

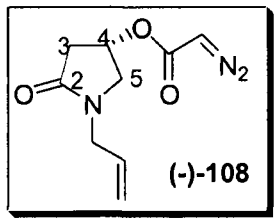


(–)-4*S*-(*N*-((*S*)-α-Methylbenzyl)-4-(α-diazoacetoxy)-2-pyrrolidinone (made from (–)-**84**)

$[\alpha]_D^{25}$ –78.1° (*c* 0.16, $CHCl_3$); IR (Neat) 3062, 2112, 1685 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ 1.51 (d, 3 H, J = 7.0 Hz, PhCH(N)*Me*), 2.52 (dd, 1 H, J = 17.7, 1.9 Hz, H-3), 2.82 (dd, 1 H, J = 17.7, 6.5 Hz, H-3'), 3.02 (d, 1 H, 11.6 Hz, H-5), 3.65 (dd, 1 H, J = 11.5, 5.4 Hz, H-5'), 4.67 (s, 1 H, C*H*=N_2) 5.30-5.40 (m, 1 H, H-4), 5.51 (q, 1 H, J = 7.0 Hz, PhC*H*(N)Me), 7.20-7.40 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9, 38.0, 48.4, 48.6, 67.3, 126.5, 127.3, 128.3, 139.4, 170.9



(–)-4*S*-*N*-Allyl-4-(α-diazoacetoxy)-2-pyrrolidinone (made from (–)-**106**)

$[\alpha]_D^{25}$ –12.5° (*c* 1, $CHCl_3$); IR (Neat) 3084, 2922, 2114, 1694 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 2.47 (dd, 1 H, J = 17.8, 2.1 Hz, H-3), 2.76 (dd, 1 H, J =17.9, 7.1 Hz, H-3'), 3.33 (dd, 1 H, J = 11.7, 1.7 Hz, H-5), 3.67 (dd, 1 H, J = 11.7, 5.9 Hz, H-5'), 3.80 (dd, 1 H, J = 15.3, 6.0 Hz, N-C*H*-CH=CH_2), 3.94 (dd, 1 H, J = 15.3, 5.6 Hz, N-C*H'*-CH=CH_2), 4.75 (s, 1 H, C*H*=N_2), 5.15 (dd, 2 H, J = 9.1, 1.4 Hz, N-CH_2-CH=C*H*$_2$) 5.30-5.38 (m, 1 H, H-4), 5.58-5.74 (m, 1 H, N-CH_2-C*H*=CH_2)

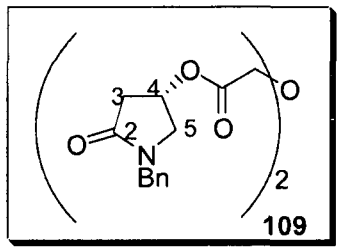
^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.8, 44.7, 52.9, 67.3, 118.1, 125.1, 129.9, 131.7, 171.3

(EI)-HRMS calcd for $C_9H_{11}N_3O_3$ for 209.0800, found 209.0792

4.5 General procedure for Rh_2(4*S*-MPPIM)$_4$ catalyzed reaction of diazoacetates (±)-22, (–)-107 and (–)-108

The catalyst was dried at 90°C under high vacuum for 1 h. After cooling to rt under vacuum, it was flushed with nitrogen and argon respectively. DCE was added to the catalyst resulting in a bluish green solution and then refluxed at 80°C. The diazoacetate was dissolved in DCE (4 mL) and the resulting solution added to the refluxing catalyst via syringe pump. The catalyst solution changed from bluish green to light yellow. The reaction mixture was refluxed for 2 h after all of the diazoacetate had been added to the catalyst. The progress of reaction was monitored with TLC. Reaction mixture was cooled

to rt, after which the DCE was removed under reduced pressure to give the crude products which were separated by flash column chromatography using the solvent mixture as indicated.

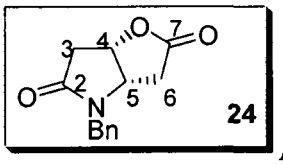


Ether dimer (made from (±)-**22**)[20c]

(1:1 v/v PE/EtOAc, yellow oil)(4.7%)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.52 (d, 1 H, J = 17.9 Hz, H-3), 2.82 (dd, 1 H, J = 17.9, 7.1 Hz, H-3'), 3.22 (dd, 1 H, J = 11.7, 1.5 Hz, H-5), 3.61 (dd, 1 H, J = 11.7, 5.9 Hz, H-5'), 4.08 (d, 1 H, 16.5 Hz, O=C-C*H*-O), 4.16 (d, 1 H, J = 16.5 Hz, O=C-C*H'*-O), 4.41 (d, 1 H, J = 14.7 Hz, N-C*H*-Ph), 4.49 (d, 1 H, J = 14.7 Hz, N-C*H'*-Ph), 5.29-5.36 (m, 1 H, H-4), 7.10-7.30 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.8, 46.4, 52.7, 67.8, 68.1, 127.9, 128.2, 128.9, 135.7, 169.2, 171.3



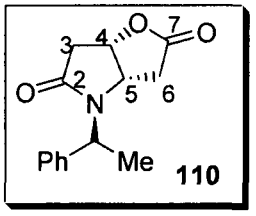
***N*-Benzylbicyclic-γ-lactam lactone** (made from (±)-**22**)[20c]

(2:1 v/v EtOAc/PE, light yellow solid)(36%)

mp: 112-114°C (lit[20c] 114-116°C) $[\alpha]_D^{25}$ –40.3° (*c* 1.18, $CHCl_3$) (lit[20c] $[\alpha]_D^{22}$ –38.9.3° (*c* 0.9, $CHCl_3$); IR (CH_2Cl_2 film) 2947, 1784, 1695 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 2.60 (dd, 1 H, J = 18.4, 6.1 Hz, H-3), 2.69 (dd, 1 H, J = 18.3, 1.7 Hz, H-3'), 2.82 (d, 2 H, J = 3.8 Hz, H-6), 4.02 (d, 1 H, J = 15 Hz, N-C*H*-Ph), 4.19 (ddd, 1 H, J = 5.9, 5.9, 1.8 Hz, H-5), 4.97 (d, 1 H, J = 15 Hz, N-C*H'*-Ph), 5.02-5.15 (m, 1 H, H-4), 7.17-7.38 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.5, 36.9, 44.4, 57.2, 75.4, 128.0, 128.6, 135.0, 171.2, 173.7



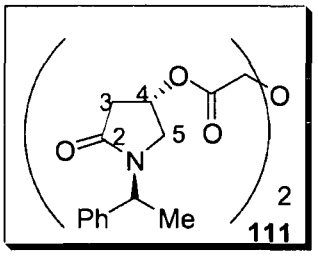
(*N*-(*S*)-α-Methylbenzyl)bicyclic-γ-lactam lactone (made from (–)-**107**)

(1:1 v/v PE/EtOAc, yellow oil)(20%)

$[\alpha]_D^{25}$ +60° (*c* 1, $CHCl_3$); IR (CH_2Cl_2 film) 1783, 1684cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) δ 1.55 (d, 3 H, J = 7.2 Hz, PhCH(N)*Me*), 1.89 (dd, 1H, J = 18.5, 1.6 Hz, H-3), 2.25 (dd, 1 H, J = 18.5, 7.2 Hz, H-3'), 2.75 (d, 2 H, J = 3.9 Hz, H-6),

^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7, 33.6, 37.1, 49.3, 55.9, 75.2, 126.8, 128.0, 128.4, 140.0, 171.4, 173.6



Ether dimer (made from (–)-**107**)

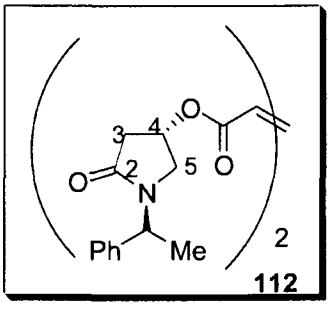
(1:1 v/v PE/EtOAc, colorless oil)(25%)

$[\alpha]_D^{25}$ +57.7° (*c* 1.3, $CHCl_3$); IR(Neat) 1748, 1684 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (d, 3 H, J = 7.1 Hz, PhCH(N)*Me*), 2.46 (dd, 1 H, J = 17.7, 2.1 Hz, H-3), 2.78 (dd, 1 H, J = 17.8, 6.8 Hz, H-3'), 2.92 (dd, 1 H, J = 11.6, 1.4 Hz, H-5), 3.61 (dd, 1 H, J = 11.7, 5.6 Hz, H-5'), 3.89 (d, 1 H, J= 16.7 Hz, O=C-C*H*-O), 3.98 (d, 1 H, J = 16.7 Hz, O=C-C*H'*-O), 5.25-5.31 (m, 1 H, H-4), 5.45 (q, 1 H, J = 7.1 Hz, PhC*H*(N)Me), 7.10-7.30 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 37.9, 48.6, 48.7, 67.8, 67.9, 126.8, 127.6, 128.5, 139.4, 168.9, 170.8

(EI)-HRMS calcd for $C_{28}H_{32}N_2O_7$ for 508.2210, found 508.2214



Alkene dimer (made from (–)-**107**)

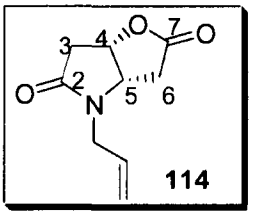
(1:1 v/v PE/EtOAc, colorless oil)(6.2%)

$[\alpha]_D^{25}$ +75° (*c* 0.7, $CHCl_3$)

^1H NMR ($CDCl_3$, 300 MHz) δ 1.49 (d, 3 H, J = 7.1 Hz, PhCH(N)*Me*), 2.50 (dd, 1 H, J = 17.8, 2.3 Hz, H-3), 2.79 (dd, 1 H, J = 17.8, 6.9 Hz, H-3'), 3.01 (dd, 1 H, J = 11.6, 1.8 Hz, H-5), 3.62 (dd, 1 H, J = 11.6, 5.8 Hz, H-5'), 5.24-5.31 (m, 1 H, H-4), 5.46 (q, 1 H, J = 7.4 Hz, PhC*H*(N)Me), 6.09 (s, 1 H, O=CC*H*=CH), 7.17-7.32 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.3, 37.8, 48.4, 48.8, 67.9, 126.8, 127.4, 128.5, 129.8, 139.5, 164.2, 170.9

(EI)-HRMS calcd for $C_{28}H_{30}N_2O_6$ for 490.2104, found 490.2099



***N*-Allylbicyclic-γ-lactam lactone** (made from (–)-**108**)

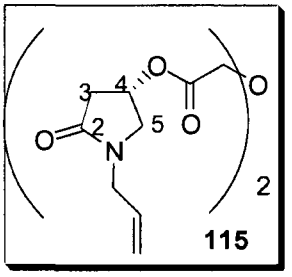
(8:1 v/v CH_2Cl_2/acetone, light pink solid)(35%)

$[\alpha]_D^{25}$ –34.1° (*c* 0.88, $CHCl_3$); IR(CH_2Cl_2) 3009, 1782, 1697cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.70-2.82 (m, 4 H, H-3 and H-7), 3.58 (dd, 1 H, J = 15.5, 7.1 Hz, N-C*H*-CH=CH_2), 4.27 (dd, 1 H, J = 15.5, 5.1 Hz, N-C*H'*-CH=CH_2), 4.39 (ddd, 1 H, J = 6.3, 4.7, 2.3 Hz, H-4), 5.06-5.13 (m, 1 H, H-8), 5.17-5.29 (m, 2 H, N-CH_2-CH=C*H*$_2$), 5.64-5.80 (m, 1 H, N-CH_2-C*H*=CH_2)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.8, 36.9, 43.4, 57.7, 75.6, 119.1, 131.4, 170.9, 173.7

(EI)-HRMS calcd for $C_9H_{11}NO_3$ for 181.0739, found 181.0739



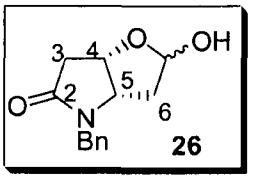
Ether dimer (made from (–)-**108**)

(2:1 v/v CH_2Cl_2/acetone, colorless oil)(8.4%)

$[\alpha]_D^{25}$ –45° (*c* 0.1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.52 (dd, 1 H, J = 17.8, 2.0 Hz, H-3), 2.83 (dd, 1 H, J = 17.9, 7.1 Hz, H-3'), 3.36 (dd, 1 H, J = 11.8, 1.7 Hz, H-5), 3.74 (dd, 1 H, 11.8, 5.9 Hz, H-5'), 3.86 (dd, 1 H, J = 15.3, 6.1 Hz, N-C*H*-CH=CH_2), 3.97 (dd, 1 H, J = 15.3, 5.9 Hz, N-C*H'*-CH=CH_2), 4.20 (d, 1 H, J = 16.6 Hz, O=C-C*H*-O), 4.26 (d, 1 H, J = 16.6 Hz, O=C-C*H'*-O), 5.22 (dd, 2 H, J = 9.7, 1.3 Hz, N-CH_2-CH=C*H*$_2$), 5.35-5.45 (m, 1 H, H-4), 5.63-5.82 (m, 1 H, N-CH_2-C*H*=CH_2)

4.6 Synthesis of (+)-(1*S*, 8a*S*)-1-hydroxyindolizidine Intermediates



(4*S*, 5*S*)-Bicyclic γ-lactam lactol. To a solution of bicyclic γ-lactam lactone **24** (236 mg, 1.03 mmol) in dry THF (10 mL) at –78°C was added a solution of Red-Al ® in PhMe (63% wt, 1 mL, 0.72 M) dropwise. The reaction mixture was stirred for 2 h at –78°C and at – 40 °C for 1 h then quenched at the same temperature with MeOH (1 mL). After warming to rt, saturated NH_4Cl (3 mL) was added, the resulting aqueous layer was separated and to this was added brine (10 mL) and NaCl. The mixture was stirred and then extracted with CH_2Cl_2 (2 x 15 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (2:1 v/v CH_2Cl_2/acetone) to afford a diastereomeric mixture of **26** (167 mg, 70%) as a white powder. The ratio of the diastereomers was 1:2.5 and is based on the integration of the benzylic proton signals at δ 4.91 and 5.11.

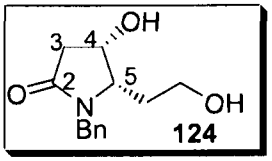
mp:131-132 °C; $[\alpha]_D^{25}$ –95° (*c* 0.5, $CHCl_3$); IR (film) 3450-3125, 3075, 1664, 1500 cm^{-1}

Discernible signals of major diastereomer: ^1H NMR ($CDCl_3$, 300 MHz): δ 178-1.88 (m), 1.95-2.06 (m), 2.28 (d, J = 14.9 Hz), 2 H, H-6), 2.57 (d, J = 17.9 Hz), 2.70 (dd, J = 17.9, 6.7 Hz), 2.78 (dd, 17.5, 5.9 Hz), 2 H, H-3), 2.89 (br d, 1 H, J = 3.9 Hz, OH), 3.93 (d, 1 H, J = 14.8 Hz, N-C*H*-Ph), 4.03-4.13 (m, 1 H, H-5), 4.72-4.78 (m, 1 H, H-4), 4.91 (d, 1 H, J = 14.8 Hz, N-C*H'*-Ph), 5.58 (m, 1 H, H-7), 7.09-7.39 (m, 5 H, Ph*H*)

Discernible signals of minor diastereomer: 4.00-4.05 (m, 1 H, H-5), 4.66-4.72 (m, 1 H, H-4), 5.11 (d, 1 H, J = 14.9 Hz, N-C*H*-Ph)

^{13}C NMR ($CDCl_3$,75 MHz): δ 36.2, 37.4, 38.3, 39.9, 44.6, 60.8, 73.8, 98.6, 99.0, 127.5, 128.2, 128.7, 135.8, 172.3, 172.6

(EI)-HRMS calcd for $C_{13}H_{15}NO_3$ for 233.1052, found 233.1045



(4*S*, 5*S*)-*N*-Benzyl-5-(2-hydroxyethyl)-4-hydroxy-2-pyrrolidinone.

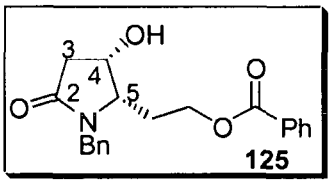
$NaBH_4$ (30.0 mg, 0.790 mmol) was added to a solution of bicyclic γ-lactam lactol **26** (20.0 mg, 0.0900 mmol) in ethanol (4 mL) at 0°C. The mixture was stirred at rt for 1 h and then quenched with three drops of acetic acid at 0°C, after which the EtOH was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 x 15 mL), the combined organic extracts were concentrated under reduced pressure and the residue purified by flash column chromatography (1:3 v/v CH_2Cl_2-acetone) to afford the title product **124** (20.2 mg, 100%) as colorless crystals.

mp: 130-132 °C; $[\alpha]_D^{25}$ –34° (*c* 0.36, MeOH); IR (film) 3500-3200, 3050, 1669, 1500 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 1.77-1.99 (m, 2 H, C*H*$_2$CH$_2$OH), 2.47 (dd, 1 H, J = 17.3, 2.8 Hz, H-3), 2.64 (dd, 1 H, J = 17.3, 6.8 Hz, H-3'), 3.21 (br s, 1 H, OH), 3.44-3.60 (m, 2 H, CH$_2$C*H*$_2$OH), 3.74 (ddd, 1 H, J = 10.2, 5.2, 3.6 Hz, H-5), 3.97 (d, 1 H, J = 15.3 Hz, N-C*H*-Ph), 4.34-4.43 (m, 1 H, H-4), 4.16 (br s, 1 H, OH), 4.88 (d, 1 H, J = 15.3 Hz, N-C*H'*-Ph), 7.12-7.35 (m, 5 H, Ph*H*).

^{13}C NMR ($CDCl_3$,75 MHz): δ 27.8, 39.0, 43.7, 58.7, 61.8, 65.7, 127.2, 127.3, 128.4, 135.9, 173.5

(EI)-HRMS calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1209.



125

(4*S*, 5*S*)-*N*-Benzyl-5-(2-benzoyloxyethyl)-4-hydroxy-2-pyrrolidinone.

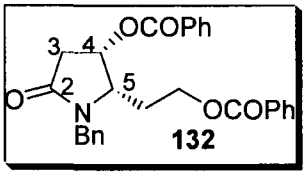
To a mixture of diol **124** (220. mg, 0.940 mmol), dry pyridine (3 mL) and dry $CHCl_3$ (7.2 mL) at 0°C was added redistilled benzoyl chloride (1.71 mmol, 0.20 mL). The mixture was stirred at rt overnight after which the solvent was removed under reduced pressure. The residue purified by flash column chromatography (2:1 v/v CH_2Cl_2-acetone) to afford **125** (150 mg, 47%) as an amber colored oil. Starting compound **124** was recovered (112 mg).

$[\alpha]_D^{26}$ –39.3° (*c* 0.89, $CHCl_3$); IR (film) 3500-3150, 3050, 3035, 1716, 1672, 1587, 1575 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.08-2.26 (m, 2 H, C*H*$_2$CH$_2$O), 2.52 (dd, 1 H, J = 17.2, 2.6 Hz, H-3), 2.71 (dd, 1 H, J = 17.2, 6.3 Hz, H-3'), 2.86 (br s, 1 H, OH) 3.58 (ddd, 1 H, J = 8.1, 5.4, 5.4 Hz, H-5) 4.00 (d, 1 H, J = 15.2 Hz, N-C*H*-Ph), 4.30-4.43 (m, 2 H, CH$_2$C*H*$_2$O), 4.43-4.51 (m, 1 H, H-4), 5.01 (d, 1 H, J = 15.2 Hz, N-C*H'*-Ph), 7.15-7.30 (m, 5 H, Ph*H*), 7.37-7.46 (m, 2 H, Ph*H*C=O), 7.57-7.59 (m, 1 H, Ph*H*C=O), 7.84-7.91 (m, 2 H, Ph*H*C=O).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.6, 40.3, 43.9, 58.9, 61.6, 65.8, 127.5, 127.7, 128.4, 128.7, 129.4, 133.2, 136.1, 166.5,173.1

(CI-NH_3)-HRMS (M+1) calcd for $C_{20}H_{22}NO_4$ for 340.1471, found 340.1546



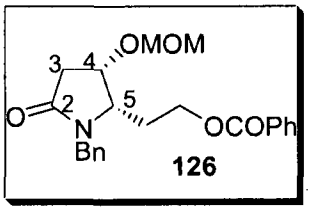
(4*S*, 5*S*)-*N*-Benzyl-4-benzoyloxy-5-(2-benzoyloxyethyl)-2-pyrrolidinone.

To a mixture of diol **124** (181 mg, 0.770 mmol) and dry pyridine (2 mL) at 0°C and under argon pressure was added redistilled benzoyl chloride (0.850 mmol, 0.14 mL). The mixture was stirred at rt for 1 h after which the solvent was removed under reduced pressure. The residue purified by flash column chromatography (2:1 v/v CH_2Cl_2-acetone) to afford **132** (211 mg, 62%) as a light yellow oil and **125** (110 mg, 42%) as an amber colored oil.

IR (film) 1718, 1699, 1654, 1602, 1584 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.13-2.31 (m, 2 H, C$H_2$$CH_2O$), 2.68 (dd, 1 H, J = 17.6, 1.8 Hz, H-3), 2.91 (dd, 1 H, J = 17.6, 6.6 Hz, H-3'), 3.94 (ddd, 1 H, J = 10.3, 8.2, 5.3 Hz, H-5), 4.14 (d, 1 H, J = 15.2 Hz, N-C*H*-Ph), 4.31 (ddd, 2 H, J = 17.1, 11.5, 5.8 Hz, CH_2CH_2O), 5.07 (d, 1 H, J = 15.2 Hz, N-C*H'*-Ph), 5.64 (ddd, 1 H, J = 9.1, 6.2, 3.4 Hz, H-4), 7.19-7.32 (m, 5 H, Ph*H*), 7.32-7.48 (m, 4 H, Ph(C=O)), 7.48-7.61 (m, 2 H, Ph(C=O)), 7.80 (d, 2 H, J = 7.2 Hz, Ph(C=O)), 7.96 (d, 2 H, J = 7.2 Hz, Ph(C=O))

^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.3, 37.9, 44.2, 57.4, 60.9, 68.5, 127.6, 127.7, 128.2, 128.4, 128.7, 129.4, 129.5, 132.9, 133.5, 135.8, 165.5, 172.3



126

(4*S*, 5*S*)-*N*-Benzyl-5-(2-benzoyloxyethyl)-4-(methoxymethoxy)-2-pyrrolidinone.

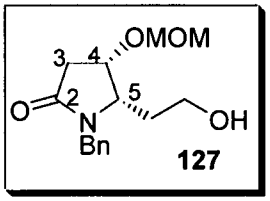
A solution of alcohol **125** (110. mg, 0.320 mmol) in dry $CHCl_3$ (6 mL) at 0°C was added dimethoxymethane (21.4 mmol, 2 mL), the mixture was stirred and then P_2O_5 (200. mg, 1.41 mmol) was added. The reaction mixture was then stirred at rt overnight. The $CHCl_3$ was separated from the solid P_2O_5 and then washed with ice cold aqueous Na_2CO_3 (1 x 15 mL). To the residual P_2O_5 was added ice cold aqueous Na_2CO_3 (7 mL) and the resulting solution was then extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5:1 v/v CH_2Cl_2-acetone) to afford the title product **126** (103 mg, 83%) as a light yellow oil. Starting alcohol **125** (6.5 mg) was also recovered.

$[\alpha]_D^{26}$ −10.4° (*c* 0.72, $CHCl_3$); IR (film) 3050, 3025, 1719, 1696, 1600, 1575 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.06-2.30 (m, 2 H, C*H*$_2$CH$_2$O), 2.60 (dd, 1 H, J = 16.9, 5.4 Hz, H-3), 2.67 (dd, 1 H, J = 16.9, 6.5 Hz, H-3'), 3.37 (s, 3 H, Me), 3.74 (ddd, 1 H, J = 9.5, 6.3, 3.7 Hz, H-5), 3.97 (d, 1 H, J = 15.1 Hz, N-C*H*-Ph), 4.31-4.45 (m, 3 H, H-4, CH$_2$C*H*$_2$O), 4.64 (d, 1 H, J = 6.9 Hz, OC*H*O), 4.69 (d, 1 H, J = 6.9 Hz, OC*H'*O), 5.11 (d, 1 H, J = 15.1 Hz, N-C*H'*-Ph), 7.17-7.31 (m, 5 H, Ph*H*), 7.38-7.47 (m, 2 H, Ph(C=O)), 7.52-7.61 (m, 1 H, Ph(C=O)), 7.87-7.93 (m, 2 H, Ph*H*C=O).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.9, 37.1, 43.7, 55.7, 56.8, 61.2, 71.0, 95.5, 127.2, 127.6, 128.0, 128.2, 128.4, 128.5, 129.2, 129.3, 129.6, 132.7, 135.8, 166.1,172.0.

(EI)-HRMS calcd for $C_{22}H_{25}NO_5$ for 383.1733, found 383.1730



(4*S*, 5*S*)-*N*-Benzyl-5-(2-hydroxyethyl)-4-(methoxymethoxyl)-2-pyrrolidinone.

To anhydrous methanol (2 mL) maintained under argon pressure and cooled to 0°C was added sodium metal (9.30 mg, 0.400 mmol). The mixture was stirred for 15 min then a solution of benzoate **126** (103 mg, 0.270 mmol) in anhydrous CH_2Cl_2 (4 mL) was added to the sodium methoxide via cannula transfer. The cannula was rinsed with anhydrous CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at 0°C for 30 min and 20 min at rt at which time the reaction was judged to be complete by TLC. The reaction was quenched with a few drops of saturated NH_4Cl at 0°C, after which MeOH was removed under reduced pressure. Brine (10 mL), NaCl and EtOAc (10 mL) was added to the resulting residue and the mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer thoroughly extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification was achieved by means of flash column chromatography (2:1 v/v CH_2Cl_2-acetone) to afford the product **127** (67 mg, 89% yield) as a colorless viscous oil.

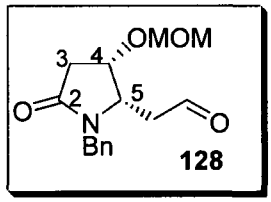
$[\alpha]_D^{25}$ –27.8° (*c* 0.36, $CHCl_3$); IR (film) 3575-3200, 3050, 3025, 1678, 1637 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 1.80-1.92 (m, 1 H, C*H*CH_2OH), 1.97-2.11 (m, 1 H, C*H'*CH_2OH), 2.34 (br s, 1 H, OH), 2.56 (dd, 1 H, J = 16.8, 5.8 Hz, H-3), 2.65 (dd, 1 H, J = 16.8, 6.6 Hz, H-3'), 3.36 (s, 3 H, Me), 3.66 (ddd, 1 H, J = 10.7, 8.0, 4.0 Hz H-5), 3.71

(t, 2 H, J = 5.9 Hz, CH_2CH_2OH) 4.01 (d, 1 H, J = 15.2 Hz, N-C*H*-Ph), 4.31 (q, 1 H, J = 6.5 Hz, H-4), 4.61 (d, 1 H, J = 6.8 Hz, OC*H*O), 4.67 (d, 1 H, J = 6.8 Hz, OC*H'*O), 4.99 (d, 1 H, J = 15.2 Hz, N-C*H'*-Ph), 7.16-7.36 (m, 5 H, Ph*H*),

^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.6, 37.3, 43.9, 55.9, 58.2, 59.2, 71.8, 95.8, 127.5, 127.7, 128.6, 136.3, 172.2

(EI)-HRMS calcd for $C_{15}H_{21}NO_4$ for 279.1471, found 279.1467



128

(4*S*, 5*S*)-*N*-Benzyl-4-(methoxymethoxyl)-5-(2-oxoethyl)-2-pyrrolidinone.

To a solution of alcohol **127** (60.0 mg, 0.220 mmol) in anhydrous DMSO (2 mL) was added anhydrous Et_3N (0.18 mL, 1.32 mmol) at rt. The resulting mixture was cooled to 0°C and a solution of SO_3.Py complex (102 mg, 0.650 mmol) in anhydrous DMSO (20 mL) was added dropwise via cannula. The mixture was stirred at rt for 16 h, then diluted with EtOAc (10 mL). The resulting mixture was washed with water (2 x 5 mL) and saturated $CuSO_4$ (1 x 5 mL). The aqueous layer was saturated with brine, NaCl and then extracted with EtOAc (2 x 5 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification was effected by means of flash column chromatography using 8:1 v/v CH_2Cl_2-acetone as eluent to afford the title product **128** (58 mg, 97%) as a colorless oil.

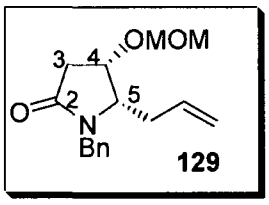
$[\alpha]_D^{26}$ +13.6° (*c* 1.1, $CHCl_3$); IR (film) 1713, 1689 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.56 (dd, 2 H, J = 17.3, 4.0, Hz, H-3, C*H*C=O), 2.71 (dd, 1 H, J = 17.1, 6.9, Hz, C*H'*C=O), 2.88 (dd, 1 H, J = 17.4, 8.9 Hz, H-3'), 3.31 (s, 3 H, Me),

4.07 (d, 1 H, J = 15.2 Hz, N-C*H*-Ph), 4.16 (ddd, 1 H, J = 10.6, 6.4, 4.3 Hz, H-5), 4.34-4.44 (m, 1 H, H-4), 4.54 (d, 1 H, J = 6.9 Hz, OC*H*O), 4.59 (d, 1 H, J = 6.9 Hz, OC*H'*O), 4.87 (d, 1 H, J = 15.2 Hz, N-C*H'*-Ph), 7.16-7.37 (m, 5 H, Ph*H*), 9.69 (s, 1 H, C*H*O).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.0, 41.2, 44.3, 55.9, 56.5, 70.6, 95.9, 127.7, 128.8, 135.9, 172.2, 199.0

(EI)-HRMS calcd for $C_{15}H_{19}NO_4$ for 277.1314, found 277.1310



(4*S*, 5*S*)-5-Allyl-*N*-benzyl-4-(methoxymethoxyl)-2-pyrrolidinone.

BuLi (0.06 mL, 0.150 mmol, 2.4 M) was added to a suspension of $MePh_3PBr$ (48.3 mg, 0.135 mmol) in anhydrous THF (2 mL) at 0°C resulting in a dark orange solution. The solution was cooled to –40°C and a solution of aldehyde **128** (25.0 mg, 0.0900 mmol) in anhydrous THF (1 mL) was then added via cannula transfer. The cannula was rinsed with anhydrous THF (1 mL) and the reaction mixture allowed to stir at the same temperature for 30 min and then at rt for 1 h at which time there was no further appreciation in product formation as judged by TLC. The reaction was quenched with a few drops of saturated NH_4Cl after which the THF was removed under reduced pressure. The residue was saturated with brine (10 mL), NaCl, and then stirred vigorously before being extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification was effected by flash column chromatography (8:1 v/v CH_2Cl_2-acetone) to afford **129** (18 mg, 72%) as a colorless oil. Starting aldehyde **128** (5 mg) was recovered.

$[\alpha]_D^{26}$ -50° (*c* 0.35, $CHCl_3$); IR (film) 3050, 3025, 1694, 1662, 1600, 1512 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.37 (dd, 1 H, J = 14.1, 6.0 Hz, C*H*'CH=CH_2), 2.47 (dd, 1 H, J = 14.9, 7.1 Hz, C*H*'CH=CH_2) 2.56 (dd, 1 H, J = 16.8, 5.6 Hz, H-3) 2.64 (dd, 1 H, J = 16.8, 6.9 Hz, H-3') 3.36 (s, 3 H, Me), 3.39 (ddd, 1 H, J = 6.3, 4.7, 3.2 Hz, H-5), 3.98 (d, 1 H, J = 15.2 Hz, N-C*H*-Ph), 4.22-4.32 (m, 1 H, H-4), 4.61 (d, 1 H, J = 6.9 Hz, OC*H*O), 4.65 (d, 1 H, J = 6.9 Hz, OC*H*'O), 5.06 (d, 1 H, J = 15.4 Hz, N-C*H*'-Ph) 5.06-5.15 (m, 2 H, CH=CH_2), 5.69-5.86 (m, 1 H, C*H*=CH_2), 7.16-7.39 (m, 5 H, Ph*H*).

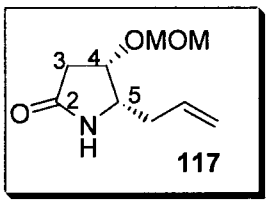
^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.4, 37.4, 43.7, 55.6, 59.6, 71.4, 95.8, 117.9, 127.2, 127.5, 128.3, 133.5, 136.1, 172.2

(CI-NH_3)-HRMS (M+1) calcd for $C_{16}H_{22}NO_3$ for 276.1521, found 276.1598

Compound **129** was also prepared from the alcohol **138** (pg 31) using either $CH_2(OMe_2)/P_2O_5$[37] or MOM-Cl, *i*-Pr_2NEt.[47] The procedures are as shown below. Both these routes gave **129** that showed identical spectroscopic and analytic data to **129** prepared from **128** as described above.

A solution of alcohol **138** (214 mg, 0.920 mmol) in dry $CHCl_3$ (4 mL) at 0°C was added dimethoxymethane (62.1 mmol, 5.5 mL), the mixture was stirred and then P_2O_5 (100. mg, 1.41 mmol) was added. The reaction mixture was then stirred at rt overnight. The $CHCl_3$ was separated from the solid P_2O_5 and then washed with ice cold aqueous Na_2CO_3 (1 x 15 mL). To the residual P_2O_5 was added ice cold aqueous Na_2CO_3 (7 mL) and the resulting solution was then extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5:1 v/v CH_2Cl_2-acetone) to afford the title product **129** (209 mg, 83%) as a light yellow oil.

Alternatively, a solution of alcohol **138** (285 mg, 1.23 mmol) in dry CH_2Cl_2 (10 mL) maintained under argon pressure and cooled to 0°C was added MOM-Cl (2.45 mmol, 0.18 mL). The mixture was stirred and then *i*-Pr_2NEt (2.45 mmol, 0.42 mL) was added. The reaction mixture was then stirred at rt overnight. The solvents were removed in vacuo and the residue washed with water (1 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5:1 v/v CH_2Cl_2-acetone) to afford **129** (302 mg, 89%) as a light yellow oil.



117

(4*S*, 5*S*)-5-Allyl-4-(methoxymethoxyl)-2-pyrrolidinone.

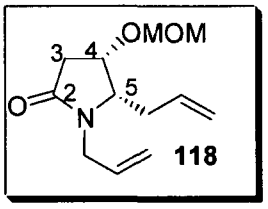
To liquid NH_3 (50 mL) at –78°C was added sodium metal (41.1 mg, 1.80 mmol). The resulting deep blue-black solution was stirred at the same temperature for 30 min after which a solution of the *N*-benzyl amide **129** (33.0 mg, 0.120 mmol) in dry THF (3 mL) was added via cannula transfer. Cannula was rinsed with dry THF (1 mL) and the reaction mixture was allowed to stir at –78°C for 3 h. The reaction mixture was quenched at –78°C with excess solid NH_4Cl and then allowed to warm slowly to rt by which time all the NH_3 had evaporated. The residue was extracted with CH_2Cl_2 (3 x 20 mL), the combined extracts were concentrated under reduced pressure and purified by means of flash column chromatography (2:1 v/v CH_2Cl_2-acetone) to afford **117** (16 mg, 73%) as colorless oil.

IR (film) 3231, 3075, 1698, 1650 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.27 (ddd, 1 H, J = 14.2, 9.2, 9.2 Hz, C*H*CH=CH_2), 2.37-2.47 (m, 1 H, C*H'*CH=CH_2), 2.39 (dd, 1 H, J = 16.5, 4.3 Hz, H-3), 2.55 (dd, 1 H, J = 16.5, 6.4 Hz, H-3'), 3.35 (s, 3 H, Me), 3.76 (ddd, 1 H, J = 10.2, 5.8, 5.8 Hz, H-5), 4.31-4.40 (m, 1 H, H-4), 4.60 (d, 1 H, J = 6.9 Hz, OC*H*O), 4.65 (d, 1 H, J = 6.9 Hz, OC*H'*O), 5.09-5.19 (m, 2 H, CH=CH_2), 5.60-5.84 (m, 2 H, C*H*=CH_2, N-H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 34.4, 38.0, 56.1, 57.6, 73.7, 96.1, 118.7, 134.4, 175.0

(CI-NH_3)-HRMS (M+1) calcd for $C_9H_{16}NO_3$ for 186.1052, found 186.1126



118

(4*S*, 5*S*)-*N*, 5-Diallyl-4-(methoxymethoxyl)-2-pyrrolidinone.

The MOM protected 2-pyrrolidinone **117** (14.0 mg, 0.0800 mmol) together with a few crystals of 2,2'-bipyridine were dissolved in dry THF (3 mL) and the solution was cooled to –15°C. Standardized BuLi (0.07 mL, 0.0800 mmol, 1.15 M) was then added to the cooled solution dropwise resulting in a deep red colored solution which was stirred for 10 min before dry DMF (0.5 mL) was added. After stirring the mixture for another 10 min, allylbromide (0.01 mL, 0.120 mmol) was added to the reaction mixture resulting in an instant discharge of the red color to yellow. The reaction mixture was stirred at –15°C for 20 min and then allowed to warm gradually to rt, by which time the reaction was complete as indicated on TLC analysis.

The reaction mixture was diluted with EtOAc (10 mL) and then washed with brine (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Purification was effected by flash column chromatography (8:1 v/v

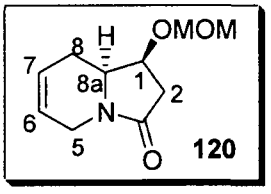
CH_2Cl_2-acetone) to afford the diallyl product **118** (16.5 mg, 91% yield) as a pale yellow non-viscous oil.

$[\alpha]_D^{26}$ –41.7° (*c* 0.24, $CHCl_3$); IR (film) 3060, 1689, 1650, 1587, 1550 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.32-2.46 (m, 2 H, C*H*$_2$CH=CH_2), 2.47 (dd, 1 H, J = 16.1, 2.3 Hz, H-3), 2.56 (dd, 1 H, J = 16.1, 6.8 Hz, H-3'), 3.35 (s, 3 H, Me), 3.50 (dd, 1 H, J = 15.7, 7.2 Hz, N-C*H*CH=CH_2), 3.69-3.77 (m, 1 H, H-5), 4.28 (dd, 1 H, J = 12.8, 6.3 Hz, H-4), 4.33 (dd, 1 H, J = 15.3, 4.5 Hz, N-C*H'*CH=CH_2), 4.60 (d, 1 H, J = 6.9 Hz, OC*H*O), 4.64 (d, 1 H, J = 6.9 Hz, OC*H'*O), 5.04-5.21 (m, 4 H, CH_2CH=C*H*$_2$, N-CH_2CH=C*H*$_2$), 5.60-5.88 (m, 2 H, CH_2C*H*=CH_2, N-CH_2C*H*=CH_2)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.9, 37.9, 43.1, 56.1, 60.6, 71.9, 96.3, 117.9, 118.4, 132.6, 134.1, 172.4

(CI-NH_3)- HRMS (M+1) calcd for $C_{12}H_{20}NO_3$ for 226.1365, found 226.1440



120

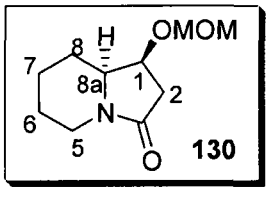
(1*S*, 8a*S*)-1-(Methoxymethoxyl)-2, 5, 8, 8a-pentahydroindolizin-3-one.

To a solution of substrate **118** (25.0 mg, 0.110 mmol) in dry CH_2Cl_2 (3 mL) at reflux was added via cannula transfer a solution of Grubbs (II) catalyst (4.72 mg, 0.00600 mmol) in dry CH_2Cl_2 (2 mL). The reaction was refluxed for 1 h by which time reaction was judged to be complete by TLC analysis. The reaction was cooled to rt and the solvent removed under reduced pressure after which the residue was purified by flash column chromatography (8:1 v/v CH_2Cl_2-acetone) to give the product **120** (18.5 mg, 88%) as an amber colored oil.

$[\alpha]_D^{26}$ –72.9° (*c* 0.24, $CHCl_3$); IR (film) 3025, 1689, 1648 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.00-2.13 (m, 1 H, H-8), 2.42 (dd, 1 H, J = 17.5, 4.2 Hz, H-2), 2.42-2.54 (m, 1 H, H-8'), 2.63 (dd, 1 H, J = 17.3, 7.2 Hz, H-2'), 3.34 (s, 3 H, Me), 3.51 (br d, 1 H, J = 17.5 Hz, H-5), 3.72 (ddd, 1 H, J = 10.7, 5.9, 4.8 Hz, H-8a), 4.25 (dddd, 1 H, J = 17.5, 3.9, 3.9, 3.9 Hz, H-5'), 4.36-4.45 (ddd, 1 H, J = 6.7, 6.7, 4.4 Hz, H-1), 4.59 (d, 1 H, J = 6.8 Hz, OC*H*O), 4.65 (d, 1 H, J = 6.8 Hz, OC*H'*O), 5.62-5.71 (m, 1 H, H-7), 5.79-5.88 (m, 1 H, H-6)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.2, 37.5, 40.1, 55.6, 56.2, 70.8, 95.8, 122.7, 124.2, 171.8

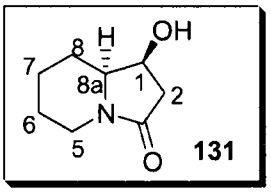


(1*S*, 8a*S*)-1-(Methoxymethoxyl)hexahydroindolizin-3-one.

To a solution of alkene **120** (30.0 mg, 0.150 mmol) in methanol (4 mL) was added Pd-C 10% wt (3.00 mg). The mixture was then subjected to hydrogen pressure of 30 psi on a Parr hydrogenator for 1 h by which time reaction was complete as per TLC analysis. The methanol was removed under reduced pressure and the residue was filtered through a short column of silica gel (2:1 v/v CH_2Cl_2-acetone) to afford the saturated product **130** (26 mg, 88%) as a colorless oil.

$[\alpha]_D^{26}$ +37.9° (*c* 0.33, $CHCl_3$); IR (film) 1766, 1684 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 1.28-1.46 (m, 2 H, H-7), 1.51-1.72 (m, 3 H, H-6, H-8), 1.88-1.97 (m, 1 H, H-8'), 2.38 (dd, 1 H, J = 17.2, 2.8 Hz, H-2), 2.50-2.64 (m, 2 H, H-2', H-5), 3.32 (s, 3 H, Me), 3.43-3.53 (m, 1 H, H-8a), 4.09 (br d, 1 H, J = 13.2 Hz, H-5'), 4.28 (ddd, 1 H, J = 9.7, 3.6, 2.9 Hz, H-1), 4.57 (d, 1 H, J = 6.8 Hz, OC*H*O), 4.63 (d, 1 H, J = 6.8 Hz, OC*H'*O).



(1*S*, 8a*S*)-1-Hydroxyhexahydroindolizin-3-one.

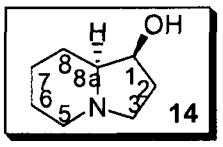
MOM ether **130** (20.0 mg, 0.100 mmol) was dissolved in 1 M HCl (aq) solution in methanol (5 mL). It was heated at 60-65°C with stirring for 100 min. It was cooled to rt and the reaction was quenched with solid Na_2CO_3. The solvent was removed under reduced pressure and the residue was redissolved in MeOH and the solvent decanted. To the residual solid was added brine and solid NaCl, stirred vigorously before being extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and then purified by flash column chromatography (15:1 v/v EtOAc-MeOH) to afford the product **131** (13 mg, 84%) as colorless crystals.

mp: 147-150 °C, lit.[26t] 149-157 °C; $[\alpha]_D^{26}$ +27.8° (*c* 0.18, acetone), (lit.[26t] $[\alpha]_D^{20}$ +26.9° (*c* 0.15, acetone); IR (film) 3500-3125, 3001, 2390, 1688 1557 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 1.25-1.46 (m, 2 H, H-7), 1.50-1.71 (m, 4 H, H-6, H-8), 1.88-1.98 (m, 1 H, H-6), 2.23 (br d, 1 H, J = 5.7 Hz, OH), 2.30 (dd, 1 H, J = 17.4, 1.3 Hz, H-2), 2.51-2.67 (m, 2 H, H-5', H-2'), 3.67 (ddd, 1 H, J = 11.3, 6.0, 6.0 Hz, H-8a), 4.05 (m, 1 H, H-5'), 4.30-4.38 (m, 1 H, H-1)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1, 23.9, 24.5, 40.1, 40.9, 61.5, 66.3, 171.9

(EI)-HRMS calcd for $C_8H_{13}NO_2$ for 155.0946 found 155.0949



(+)-(1*S*, 8a*S*)-1-Hydroxyindolizidine.

A solution of lactam **131** (10.0 mg 0.0650 mmol) in THF (1.5 mL) was added dropwise to borane methyl sulfide complex in ether (0.35 mL, 5 M). The mixture was refluxed at 80°C for 1 h, and then stirred at rt temperature overnight. The reaction mixture was cooled to 0°C and then quenched with ethanol (2 mL). The solvent was removed under reduced pressure and to the residue was added ethanol (5 mL) and the mixture brought to reflux. The reaction was monitored by TLC (1:1 v/v PE-EtOAc), and after 5 h of reflux, the less polar amine-borane complex was completely consumed and only one polar spot was detected on TLC. The reaction mixture was cooled to rt and then treated with 6 drops of concentrated HCl and after which the ethanol was removed under reduced pressure. To the white solid residue was added water (5 mL) and the washed with CH_2Cl_2 (2 x 5 mL). The aqueous solution was concentrated under reduced pressure and the residue was applied to ion exchange chromatography (Dowex 50x2-400 ion exchange resin, 200-400 mesh) using water and 5% NH_4OH solution as eluent. The fractions were combined and concentrated under reduced pressure. The residue was re-dissolved in CH_2Cl_2 (5 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the alkaloid **14** (7 mg, 78%) as a clear light yellow oil.

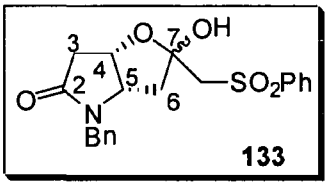
$[\alpha]_D^{26}$ +19.2° (*c* 0.13, $CHCl_3$), (lit.[26t] $[\alpha]_D^{22}$ +17.4° (*c* 0.4, $CHCl_3$), lit.[27i] $[\alpha]_D^{22}$ +16.4° (*c* 0.28, $CDCl_3$), $[\alpha]_D^{22}$ +18.1° (*c* 0.42, $CDCl_3$); IR (film) 3525-3100, 1737 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 1.10-1.31 (m, 1 H, H-7), 1.37-1.73 (m, 6 H, H-2, H-6, H-7', H-8), 1.76-2.01 (m, 3 H, H-2', H-3), 2.06-2.20 (m, 2 H, H-5), 3.01-3.14 (m, 2 H, H-5', H-8a), 3.97-4.06 (m, 1 H, H-1)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.7, 24.9, 25.1, 30.0, 52.6, 53.4, 68.7, 72.8

(EI)-HRMS calcd for $C_8H_{15}NO$ for 141.1154, found 141.1157

4.7 Preparation of (–)-slaframine Intermediates



133

(4*S*, 5*S*)-7-(Phenylsulfonylmethyl)bicyclic γ-lactam lactol.

A solution of methyl phenyl sulfone (70.8 mg, 0.170 mmol) in dry THF (1 mL) was cooled to –78°C and *n*-BuLi (0.25 mL of 1.79 M in hexanes, 0.450 mmol) was added dropwise resulting in a clear, bright yellow solution, which was stirred for 2 h, and then warmed to -40°C. The bicyclic γ-lactam lactone **24** (80.5 mg, 0.350 mmol) in dry THF (1 mL) was added dropwise via cannula, and then the cannula was rinsed with 0.5 mL dry THF. The mixture was stirred at –40°C for 1.5 h and at 0°C for 1.5 h by which time reaction was judged to be complete by TLC. The reaction mixture was cooled to -40°C, quenched with saturated NH_4Cl (2 mL) and then diluted with CH_2Cl_2 (2 mL). The aqueous layer was saturated with NaCl and brine; the resulting mixture was stirred for 30 min and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and then purified by flash column chromatography (5:1 v/v CH_2Cl_2- acetone) to give an inseparable diastereomeric mixture of **133** (107 mg, 80%) as a colorless oil. The ratio of the diastereomers was 1:2 and is based on the integration of the benzylic proton signals at δ 4.78 and 5.05.

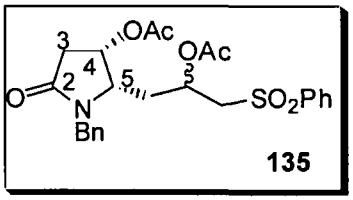
$[\alpha]_D^{26}$ +6.6° (*c* 0.38, $CHCl_3$); IR (film) 3500-3125, 3050, 1687, 1667, 1600, 1512 cm^{-1}

Discernible signals of major diastereomer: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.83 (dd, 1 H, J = 13.7, 3.5 Hz, H-6), 2.04 (d, 1 H, J = 18.1 Hz, H-3), 2.25 (dd, 1 H, J = 13.7, 7.3 Hz, H-6'), 2.52 (dd, 1 H, J= 18.1, 6.9 Hz, H-3'), 3.41 (d, 1 H, J = 14.6 Hz, C*H*SO_2Ph), 3.48 (d, 1 H, J = 14.8 Hz, C*H'*SO_2Ph), 3.90 (d, 1 H, J = 14.7 Hz, N-C*H*-Ph), 3.99-4.08 (m, 1 H, H-5), 4.61-4.71 (m, 1 H, H-4), 4.78 (d, 1 H, J = 14.7 Hz, N-C*H'*-Ph), 7.12-7.35 (m, 5 H, Ph*H*), 7.47-7.57 (m, 2 H, SO_2Ph), 7.59-7.68 (m, 1 H, SO_2Ph*H*), 7.85-7.92 (m, 2 H, SO_2Ph)

Discernible signals of minor diastereomer: 1.85 (dd, 1 H, J = 13.7, 3.5 Hz, H-6), 2.46 (d, 1 H, J = 13.9 Hz, H-6'), 2.63 (dd, 1 H, J = 18.2, 9.2 Hz, H-3), 2.70 (dd, 1 H, J = 18.2, 6.2 Hz, H-3'), 3.54 (d, 1 H, J = 14.9 Hz, C*H*SO_2Ph), 3.91 (d, 1 H, J = 15 Hz, N-C*H*-Ph), 4.61-4.67 (m, 1 H, H-4), 5.05 (d, 1 H, J = 15 Hz, N-C*H'*-Ph) Major and minor diastereomers overlapped in the aromatic region.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.8, 39.6, 40.2, 42.9, 44.7, 61.0, 61.3, 62.7, 63.0, 74.6, 103.2, 103.6, 127.6, 127.8, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 133.7, 133.9, 135.6, 140.0, 140.2, 172.0, 172.2

(EI)-HRMS calcd for $C_{20}H_{21}NO_5S$ for 387.1140, found 387.1143 (mixture of major and minor diastereomers)



135

(4*S*, 5*S*)-*N*-Benzyl-4-(acetoxy)-5-(2-acetoxy-3-phenylsulfonepropyl)-2-pyrrolidinone

$NaBH_4$ (192 mg, 5.09 mmol) was added to a solution of bicyclic γ-lactam lactol sulfone **133** (148 mg, 0.380 mmol) in ethanol (5 mL) at 0°C. The mixture was stirred at rt for 1 h and then quenched with three drops of acetic acid at 0°C, after which the EtOH was removed under reduced pressure to give a white slurry residue. CH_2Cl_2 (15 mL) was added to the residue and the resulting suspension was suction filtered through a pad of Celite® washing the residue with CH_2Cl_2 (40 mL) in the process. The filtrate was concentrated under reduced pressure to give **134** a viscous oil, which foamed when dried under high vacuum and this was used in the next reaction without further purification.

To a mixture dihydroxy sulfone **134** (124 mg, 0.320 mmol) and DMAP (3.90 mg, 0.0320 mmol) was added dry CH_2Cl_2 (5 mL). After cooling the resulting solution to 0°C, Ac_2O (0.12 mL, 1.27 mmol) was added and the mixture was stirred at the same temperature for 15 min before Et_3N (0.18 mL, 1.27 mmol) was added dropwise to the mixture. The reaction was stirred at rt for 5 h by which time reaction was complete as indicated by TLC analysis. The reaction mixture was washed with 0.5 M HCl solution (2 x 10 mL) and then with saturated $NaHCO_3$ solution (3 x 10 mL) and finally with water (1 x 10 mL). The organic solution was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification was effected by means of flash column chromatography (4:1 v/v CH_2Cl_2-acetone) to afford an inseparable diastereomeric mixture of **135** (136 mg, 85% over 2 steps) as a white foam. The diastereomeric ratio was

1:2 and is based on the integration of the signals of the methyl protons of the acetate at δ 1.63 and 1.77.

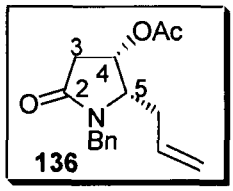
$[\alpha]_D^{25}$ –7.4° (*c* 1.01, $CHCl_3$); IR (film) 3075, 3050, 1736, 1689, 1625, 1500 cm^{-1}

Discernible signals of major diastereomer: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.77 (s, 3 H, Me), 1.97-2.21 (m, 2 H, C*H*$_2$-CH-OAc), 2.09 (s, 3 H, Me), 2.51 (dd, 1 H, J = 17.5, 3.2 Hz, H-3), 2.74 (dd, 1 H, J = 17.5, 6.7 Hz, H-3'), 3.04 (dd, 1 H, J = 14.5, 9.0 Hz, C*H*SO_2Ph), 3.27 (dd, 1 H, J = 14.6, 8.9 Hz, C*H*'SO_2Ph), 3.51-3.60 (m, 1 H, H-5), 3.99 (d, 1 H, J = 15.4 Hz, N-C*H*-Ph), 5.04 (d, 1 H, J = 15.3 Hz, N-C*H*'-Ph), 5.04-5.27 (m, 1 H, CH_2-C*H*-OAc), 5.14-5.27 (m, 1 H, H-4), 7.14-7.36 (m, 5 H, Ph*H*), 7.50-7.59 (m, 2 H, SO_2Ph), 7.61-7.69 (m, 1 H, SO_2Ph), 7.77-7.87 (m, 2 H, SO_2Ph)

Discernible signals of minor diastereomer: 1.63 (s, 3 H, Me), 2.01 (s, 3 H, Me), 2.80 (dd, 1 H, J = 17.5, 6.7 Hz, H-3), 3.11 (dd, 1 H, J = 14.9, 9.0 Hz, C*H*SO_2Ph), 3.35 (dd, 1 H, J = 14.6, 8.9 Hz, C*H*'SO_2Ph), 3.41-3.46 (m, 1 H, H-5), 3.91 (d, 1 H, J = 15.4 Hz, N-C*H*-Ph), 5.01 (d, 1 H, J = 15.5 Hz, N-C*H*'-Ph), 5.27-5.35 (m, 1 H, H-4) Major and minor diastereomers overlapped in the aromatic region.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.5, 20.7, 20.8, 31.7, 31.4, 37.7, 43.5, 43.8, 43.9, 55.5, 56.9,58.7, 59.4, 64.7, 66.0, 67.6, 67.8, 127.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.6, 128.7, 128.8, 129.0, 129.3, 133.9, 133.9, 135.5, 139.1, 169.6, 170.1, 171.9

(EI)-HRMS calcd for $C_{24}H_{27}NO_7S$ for 473.1508, found 473.1502 (mixture of major and minor diastereomers)



(4*S*, 5*S*)-5-Allyl-*N*-benzyl-4-acetoxy-2-pyrrolidinone.

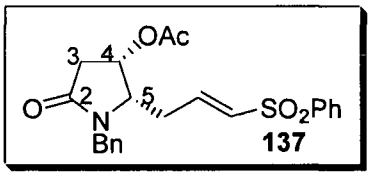
To a stirred mixture of SmI_2 (3.5 mL, 0.350 mmol, 0.1 M in THF) and HMPA (0.18 mL, 1.06 mmol) was added a solution of lactam diacetate **135** (33.4 mg, 0.0700 mmol) in THF (1 mL) via cannula transfer at rt. The reaction mixture was stirred at the same temperature for 10 min by which time the deep purple color of the reaction mixture had discharged and the reaction was judged to be complete by TLC analysis. The reaction mixture was cooled to 0°C and then quenched with 3 drops of saturated NH_4Cl solution. The THF was removed under reduced pressure and to then brine (12 mL) and aqueous NaOH (1 mL, 0.5 M) were added to the residue. The mixture was stirred at rt for 5 min and then extracted with EtOAc (3 x 20 mL) and CH_2Cl_2 (1 x 20 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by means of flash column chromatography (8:1 v/v CH_2Cl_2-acetone) afforded the desired product **136** (11.8 mg, 61%) as a colorless oil and 5.1 mg of unreacted **135**. A small amount of impure **137** (2.1 mg, 7%) was also obtained as a colorless oil. Attempted purification of **137** was unsuccessful.

$[\alpha]_D^{23}$ –19.5° (*c* 0.77, $CHCl_3$); IR (film) 3050, 3025, 3000, 1738, 1694 1687, 1612, 1512 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.06 (s, 3 H, Me), 2.38 (t, 2 H, J = 6.7 Hz,C*H*$_2$CH=CH$_2$), 2.53 (dd, 1 H, J = 17.4, 4.2 Hz, H-3), 2.75 (dd, 1 H, J = 17.3, 7.0 Hz, H-3'), 3.66-3.76 (m, 1 H, H-5), 4.02 (d, 1 H, J = 15.2 Hz, N-C*H*-Ph), 5.04 (d, 1 H, J = 15.3 Hz, N-C*H'*-Ph) 5.04-5.13 (m, 2 H, CH=C*H*$_2$), 5.26-5.34 (m, 1 H, H-4), 5.55-5.72 (m, 1 H, C*H*=CH$_2$), 7.09-7.39 (m, 5 H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7, 31.7, 37.4, 44.0, 58.9, 68.1, 118.5, 127.6, 127.7, 128.6, 132.6, 135.9, 170.1, 171.9

(CI-NH_3)-HRMS(M+1) calcd for $C_{16}H_{20}NO_3$ for 274.1365, found 274.1434

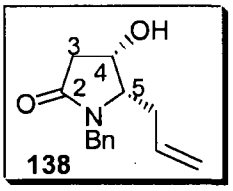


(4*S*, 5*S*)-*N*-Benzyl-4-(acetoxy)-5-(3-phenylsulfonyl-2-propenyl)-2-pyrrolidinone

Further purification of **137** using flash column chromatography was unsuccessful; however, the ^1H NMR of the impure compound showed signals related to **137**, which are quoted below:

IR (film) 1740, 1695, 1584 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 1.93 (s, 3 H, Me), 1.95-2.12 (m, 2 H, CH_2CH=C), 2.50 (dd, 1 H, J = 17.7, 5.4 Hz, H-3), 2.78 (dd, 1 H, J = 17.4, 7.5 Hz, H-3'), 3.78-3.86 (m, 1 H, H-5), 4.02 (d, 1 H, J = 15.2 Hz, N-C*H*-Ph), 4.88 (d, 1 H, J = 15.0 Hz, N-C*H'*-Ph), 5.27-5.31 (m, 1 H, H-4), 6.25 (d, 1 H, J = 15.1 Hz, C=C*H*SO_2Ph), 6.74-6.85 (m, 1 H, CH_2CH=C), 7.15-7.35 (m, 5 H, Ph*H*), 7.52-7.68 (m, 3 H, SO_2Ph), 7.78-7.90 (m, 2 H, SO_2Ph)



(4*S*, 5*S*)-5-Allyl-*N*-benzyl-4-hydroxy-2-pyrrolidinone

To a stirred mixture of SmI_2 (57.8 mL, 5.78 mmol, 0.1 M in THF) and HMPA (4 mL, 23.1 mmol) was added a solution of lactam diacetate **135** (547 mg, 1.15 mmol) in THF (1 mL) via cannula transfer at rt. The reaction mixture was stirred at the same temperature for 10 min by which time the deep purple color of the reaction mixture had discharged and the reaction was judged to be complete by TLC analysis. The reaction mixture was cooled to 0°C and then quenched with saturated NH_4Cl solution (1 mL). The THF was removed under reduced pressure and to then brine (20 mL) and aqueous NaOH (2 mL, 0.5 M) were added to the residue. The mixture was stirred at rt for 5 min and then extracted with EtOAc (3 x 20 mL) and CH_2Cl_2 (1 x 20 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

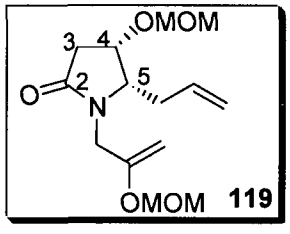
K_2CO_3 (477 mg, 3.46 mmol) was added to a solution of the crude **136** (282 mg, 1.03 mmol) in MeOH (10 mL). The mixture was stirred at rt for 1 h by which time the reaction was complete. The solvent was removed under reduced pressure and to the resulting residue was added CH_2Cl_2 (20 mL) and then the solution was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and then purified by flash column chromatography (2:1 v/v CH_2Cl_2-acetone) to afford the product **138** (294 mg, 54% over two steps) as white crystals.

mp: 64-65 °C; $[\alpha]_D^{23}$ –47.9° (*c* 0.365, $CHCl_3$); IR (film) 3500-3175, 3050, 1670, 1500 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.18 (br s, 1 H, OH), 2.35-2.48 (m, 2 H), 2.48 (dd, 1 H, J = 16.5, 1.3 Hz, H-3), 2.67 (dd, 1 H, J = 17.2, 6.6 Hz, H-3'), 3.51 (ddd, 1 H, J = 9.2, 6.9, 4.6 Hz, H-5), 4.07 (d, 1 H, J = 15.2 Hz, N-C*H*-Ph), 4.39 (ddd, 1 H, J = 9.2, 6.9, 4.6 Hz, H-4), 4.96 (d, 1 H, J = 15.2 Hz, N-C*H'*-Ph), 5.06-5.20 (m, 2 H, CH=CH_2), 5.68-5.86 (m, 1 H, C*H*=CH_2), 7.13-7.35 (m, 5H, Ph*H*)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.5, 40.1, 43.9, 60.9, 66.3, 118.3, 127.4, 127.6, 128.6, 133.7, 136.3, 173.1

(EI)-HRMS calcd for $C_{14}H_{17}NO_2$ for 231.1259, found 231.1256



(4*S*, 5*S*)-5-Allyl-4-(methoxymethoxyl)-*N*-(2-methoxymethoxyl-2-propenyl)-2-pyrrolidinone

A mixture of MOM protected 2-pyrrolidinone **117** (20.0 mg, 0.110 mmol) and a few crystals of 2,2'-bipyridine were dissolved in dry THF (5 mL) resulting in a clear colorless solution which was cooled to –15 °C under argon. BuLi (0.05 mL, 0.110 mmol, 2.03 M) was then added to the cooled solution drop wise resulting in a deep red colored solution, which was stirred for 10 min before adding DMF (0.5 mL). After stirring the mixture for another 10 min, 1-iodo-2-(methoxymethoxy)-2-propene (36.9 mg, 0.162 mmol) was added to the reaction mixture resulting in an instant discharge of the red color to yellow.

Reaction mixture was stirred at –15 °C for 20 min and then allowed to warm up gradually to rt, by which time the reaction was complete as indicated on TLC analysis.

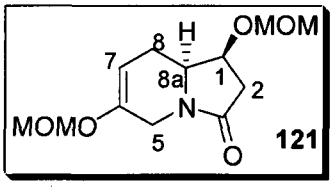
The reaction mixture was diluted with EtOAc (15 mL) and then washed with brine (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Purification was effected by flash column chromatography (5:1 v/v CH_2Cl_2-acetone) to give the product **119** (50 mg, 83%) as a pale yellow oil.

$[\alpha]_D^{26}$ –12.5° (*c* 0.20, $CHCl_3$); IR (film) 3075, 1695, 1642 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.38-2.62 (m, 2 H, C*H*$_2$CH=CH$_2$), 2.42 (dd, 1 H, J = 17.1, 6.3 Hz, H-3), 2.57 (dd, 1 H, J = 17.0, 6.9 Hz, H-3'), 3.35 (s. 3 H, Me), 3.38 (s, 3 H, Me), 3.44 (d, 1 H, J = 15.5 Hz, N-C*H*C=CH$_2$), 3.73-4.00 (m, 1 H, H-5), 4.11-4.15 (m, 1 H, H-4), 4.27 (d, 1 H, J = 7.9 Hz, OC*H*O), 4.32 (d, 1 H, J = 7.9 Hz, OC*H'*O), 4.44 (d, 1 H, J = 15.5 Hz, N-C*H'*C=CH$_2$), 4.61 (d, 1 H, J = 6.9 Hz, OC*H*O), 4.65 (d, 1 H, J = 6.9 Hz, OC*H'*O), 4.92 (s, 2 H, N-CH$_2$C=C*H*$_2$), 5.04-5.17 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.73-5.88 (m, 1 H, CH$_2$C*H*=CH$_2$)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.6, 37.6, 43.1, 55.8, 60.5, 71.7, 86.9, 93.7, 96.0, 118.0, 133.9, 154.9, 172.4

(CI-NH_3)-HRMS (M+1) calcd for $C_{14}H_{24}NO_5$ for 286.1576, found 286.1665



(1*S*, 8a*S*)-1, 6-bis(Methoxymethoxyl)-2, 5, 8, 8a-tetrahydroindolizin-3-one

To a solution of substrate **119** (40.0 mg, 0.140 mmol) in dry CH_2Cl_2 (5 mL) at reflux was added via cannula transfer a solution of Grubbs (II) catalyst (5.90 mg, 0.00700 mmol) in

dry CH_2Cl_2 (2 mL). The reaction was refluxed for 1 h by which time reaction was judged to be complete by TLC analysis. The reaction was cooled to rt and the solvent removed under reduced pressure after which the residue was purified by flash column chromatography (8:1 v/v CH_2Cl_2-acetone) to give the product **121** (26 mg, 72%) as an amber colored oil.

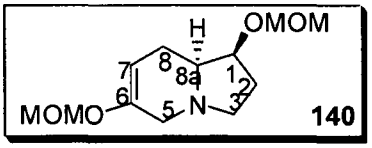
Using the same procedure, 179 mg (0.620 mmol) of **119** in anhydrous PhMe (125 mL) at 85°C was added a 3 mL solution of Grubbs II catalyst (26.6 mg, 0.0300 mmol) via cannula transfer. The reaction was stirred at the same temperature for 1 h by which time reaction was judged to be complete by TLC analysis. The reaction was cooled to rt and the solvent removed under reduced pressure after which the residue was purified by flash column chromatography (8:1 v/v CH_2Cl_2-acetone) to give **121** (133 mg, 84%) as an amber colored oil.

IR (film) 1696, 1670 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz): δ 2.04 (ddd, 1 H, J = 11.5, 6.9, 4.6 Hz, H-8), 2.44 (dd, 1 H, J = 17.3, 5.1 Hz, H-2), 2.44-2.59 (m, 1 H, H-8'), 2.66 (dd, 1 H, J = 17.2, 7.4 Hz, H-2'), 3.34 (s, 3 H, Me), 3.38 (s, 3 H, Me), 3.44 (d, 1 H, J = 17.3 Hz, H-5), 3.72 (ddd, 1 H, J = 11.5, 6.9, 4.6 Hz, H-8a), 4.26 (d, 1 H, J = 17.3 Hz, H-5'), 4.38-4.47 (m, 1 H, H-1), 4.60 (d, 1 H, J = 6.5 Hz, OC*H*O), 4.64 (d, 1 H, J = 6.5 Hz, OC*H'*O), 4.90 (d, 1 H, J = 6.5 Hz, OC*H*O), 4.94 (d, 1 H, J = 6.5 Hz, OC*H'*O), 5.06 (br d, 1 H, J = 6.7 Hz, H-7)

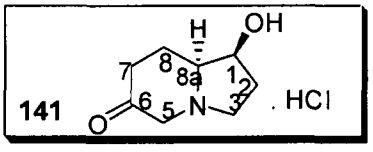
^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.3, 37.5, 40.6, 55.6, 56.4, 70.6, 93.7, 95.6, 95.8, 148.4, 171.4

(EI)-HRMS calcd for $C_{12}H_{19}NO_5$ for 257.1263, found 257.1258



(1*S*, 8a*S*)-1, 6-bis(Methoxymethoxyl)-2, 3, 5, 8, 8a-pentahydroindolizidine.

A mixture of lactam **121** (80.0 mg, 0.311 mmol) and lithium aluminum hydride (122 mg, 3.11 mmol, 95% pure) in 10 mL of THF was stirred at reflux at 80°C on an oil bath for 5 h. The mixture was cooled to 0°C and reaction quenched with 3 drops of 10% NaOH where upon Celite® was added and the mixture stirred. The THF was decanted and the solid residue extracted with 2:1 v/v CH_2Cl_2/acetone (3 x 10 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography (8:1 CH_2Cl_2/acetone) to afford **140** (61 mg, 81%) as a colorless oil.



(1*S*, 8a*S*)-1-Hydroxyhexahydroindolizin-6-one hydrochloride.

The crude MOM ether **140** (103 mg, 0.420 mmol) was dissolved in 1 M HCl (aq) solution in MeOH (5 mL). The reaction mixture was heated at 60-65°C for 3 h and then cooled to rt. The solvent was removed under reduced pressure and the residue was redissolved in EtOH (5 mL) before 5 drops of concentrated HCl was added. The mixture was allowed to stand for 5 min after which the solvent was removed in vacuo to afford the amber colored hydrochloride salt **141**, in quant recovery.

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