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DISSERTATION

ALLYLSILANES. SYNTHESIS OF ENANTIOPURE HETEROCYCLES.

Submitted by

Michael D. Groaning

Department of Chemistry

In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 2000

COLORADO STATE UNIVERSITY

September 5, 2000

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY MICHAEL D. GROANING ENTITLED ALLYLSILANES. SYNTHESIS OF ENANTIOPURE HETEROCYCLES BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Adviser

Department Head

ABSTRACT OF DISSERTATION

ALLYLSILANES. SYNTHESIS OF ENANTIOPURE HETEROCYCLES.

Chiral, non-racemic bicyclic lactams have been shown to undergo stereoselective processes from which diastereomerically pure products were obtained. The application of allylsilane additions to the bicyclic lactam have been investigated. The annulation reaction employing allyldimethyltritylsilane has offered access to cyclobutane-fused pyrrolidines which lead to the examination of other addition reactions. Subsequently, the Sakurai reaction was examined and a heretofore unseen steric effect was discovered involving the addition of allyltrimethylsilane to α,β-unsaturated bicyclic lactams. Following this study, the addition of allyltrimethylsilane to the *N,O*-acetal of the [3.3.0]bicyclic lactam was explored and lead to an efficient method for the construction of indolizidines (including (+)-coniceine) and the key precursor to Danishefsky's synthesis of indolizomycin.

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road and in the mountains (Moab, the Colorado Trail "a.k.a. the Groaning Death March," Fruita and Canada). I will never forget the conversations Dan Poon and I had at work. They were many and often very thought provoking (sometimes too thought provoking). Over the past four years I have been fortunate enough to meet a few people outside of the Chemistry building. They have provided me with some balance and helped me control the tunnel vision of graduate school. I will start with the guys at EPIC. Special thanks have to go out to Sherold and Mike for making my time playing at EPIC extremely enjoyable. To Dale and Brian for letting me take part in teaching someone about the sport I love. I thank the entire 1999-2000 peewee B team, the kids and their parents. They let me be a part of their family during the past couple years. I learned and grew more from my interactions with them than they will ever know. To Anca, Dave and Lawrence for taking me under their wings on the walls and cracks of Vedawoo. Jon and "Tush" for the climbs at Horsetooth and the Monastery. I have to thank Mike Hillier for the workouts at Pulse and all the stories we shared. To Alex for all the weekend hikes and to Al for being Al. He is probably one of the most lovable guys that has come through this group since I started. Finally, to the secretaries that I have had the honor of knowing. Jo, you were always so damn efficient and great to talk to. Penni, you never seemed to be in a bad mood. Last, but not least, Julie, I couldn't think of a better person to end my time with at CSU. I have to thank you for allowing me to join you and Jim on the golf course. Before I leave, I'll have to let you take me out for those "oysters."

Dedicated to the memory of my father:

Carl Glenn Groaning (March 8, 1923 – August 19, 1996)

"A challenge is not an adversary to be engaged, an opponent to be conquered. It is an opportunity for growth placed by an Omniscient Benefactor. Some so compelling as to beckon more than a mere attempt, we apprehend them with a zealot's intent. The exhilaration and insight we are blessed with in the process only serves to bring us closer to our Mentor unseen. The Wellspring of all that is good and perfect. And from which, we return, not haughty, but humbled."

- R. H. Burgess

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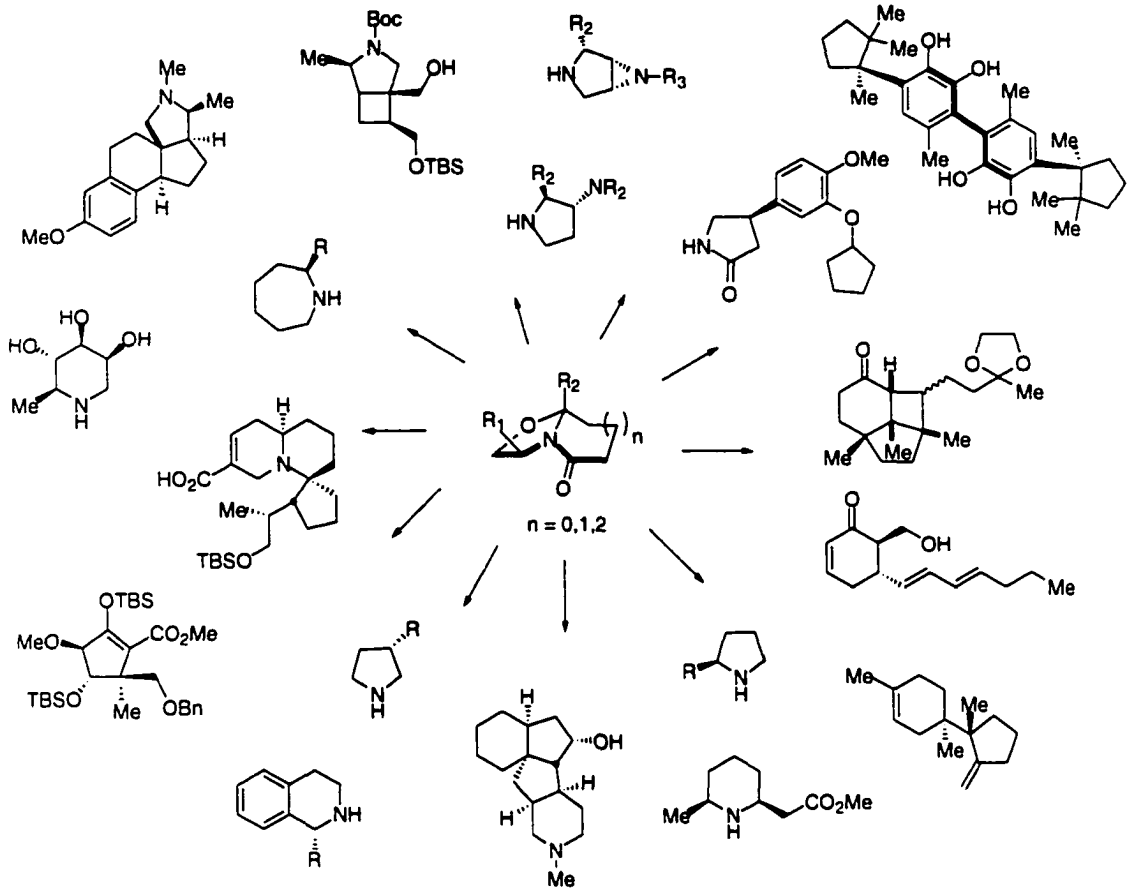
CHAPTER I. REVIEW OF BICYCLIC LACTAM CHEMISTRY

I.1. Introduction.

The bicyclic lactam has proven to be an exceptional chiral template for the construction of a wide variety of optically pure carbocycles and heterocycles (Figure 1.1). Since the first review describing the chiral non-racemic bicyclic lactam system, over 100 papers have appeared addressing its application to the construction of a variety of quaternary carbon compounds with excellent control over the absolute stereochemistry. Applications to total syntheses have effectively illustrated that the lactams can provide access to a wide variety of structural features in addition to stereogenic quaternary centers.

Figure 1.1



As a testament to its potential, notable advances continue to be made, many dealing with heterocyclic systems containing multiple stereogenic centers. The purpose of the current review is to communicate further developments of this system since it was last summarized in 1991.[1a] A short, non-comprehensive survey of bicyclic lactams was also presented in 1997.[1b]

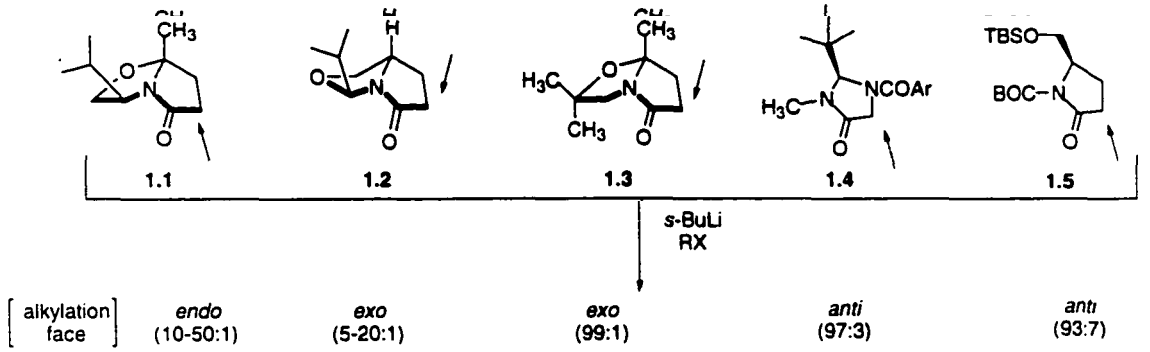
I.2. Enolate Alkylation Studies. Stereoelectronic and Steric Effects.

I.2.A. Introduction.

Diastereoselective alkylations of the chiral non-racemic bicyclic lactam have provided a method for the construction of a wide variety of optically pure carbocycles and heterocycles. Detailed examples of these alkylations and their applications toward a variety of natural products have been described in a previous review.[1] A detailed mechanistic understanding of the observed diastereoselectivity, briefly addressed in the first review, has benefited greatly from extensive studies conducted over the past ten years.[2]

It has been reported that various related bicyclic (**1.1-1.3**) and monocyclic systems (**1.4, 1.5**) provide high diastereofacial selectivity in alkylation reactions (Figure 1.2).[3] Although this trend has been observed for some time, investigations into its origin had not been described heretofore. Concurrent studies by others[4] revealed that the facial selectivity in the alkylation of [3.3.0] bicyclic lactams could be reversed by changing the structure of the chiral auxiliary. These observations initiated the search for the origin of the counterintuitive *endo* (α) selectivity obtained in the parent bicyclic lactam system **1.1**.

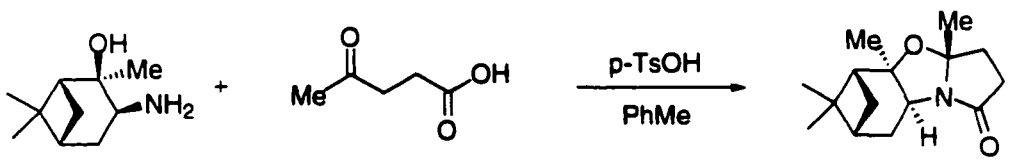
Figure 1.2



I.2.B. Reversal of Alkylation Facial Selectivity.

Condensation of the pinene derivative **1.6** with levulinic acid furnished the bicyclic lactam **1.7** which afforded solely the *exo* alkylation products **1.8** (Scheme 1.1).[4]

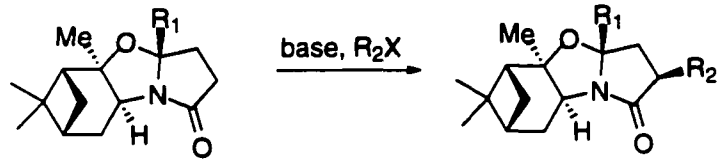
Scheme 1.1



1.6 **1.7**

As illustrated in Table 1.1, alkylations leading to **1.8a**, **1.8b** occured with high *exo* facial selectivity which likely arises from a strong steric effect. The α-face of the enolate generated from **1.7a**, **1.7b** appears to be fully blocked by either the bridging *gem*-dimethyl groups of the pinene ring system or the methyl (axial) in the α-face adjacent to the ring oxygen in **1.7**, thus accounting for the high *exo*-

selectivity at ambient temperatures (entry 2). This dramatic reversal in selectivity, when compared to the alkylation of **1.1**, led to a study of the structural features of other related systems and how those features might predictably affect the alkylations.



R_1 = Ph, **1.7a**
= Me, **1.7b**

R_1 = Ph ,**1.8a**
= Me, **1.8b**

Table 1.1 Alkylation of Pinene Derived Bicyclic Lactam 1.7.

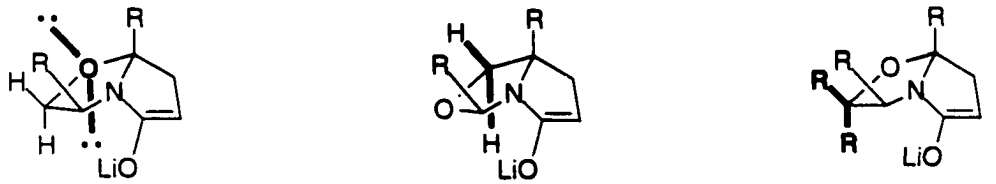
entry	R_1	R_2	R_3	base	*T* (°C)	*exo:endo*
1	Ph	Me	H	*s*-BuLi	-80	96:4
2	Ph	Me	H	LDA	25	92:8
3	Me	Me	H	*s*-BuLi	0	97:3

Other lactams have demonstrated a similar *exo*-selectivity, most notably, the bicyclic lactam **1.2** derived from pyroglutamic acid.[5] It is important to note the subtle differences between lactams **1.1** and **1.2**. The key features that seem to effect the selectivity originate in the oxazolidine ring in the bicyclic system, where the size of the group being projected into the concave face is the determining factor (these groups are highlighted in bold in structures **1.9-1.11**, Figure 1.3). Crude models of these bicyclic lactam enolates suggest that the *endo* alkylation pathway in **1.10** is inhibited by the pseudoaxial hydrogen projecting in the

concave region. On the other hand, enolate **1.9** has an oxygen in place of the methylene and therefore only projects a lone pair of electrons. These electrons may not provide sufficient steric bulk to inhibit the *endo* entry to **1.9**, which was, indeed, found to be the major pathway.

The addition of a large substituent on the amino alcohol moiety, as in lactam **1.3**, had the same effect as that of the methylene hydrogen in lactam **1.2**. Condensation of levulinic acid and the appropriate chiral aminoalcohol provided **1.3** which was subjected to subsequent metalation/alkylation affording **1.12** as a single *exo* diastereomer.

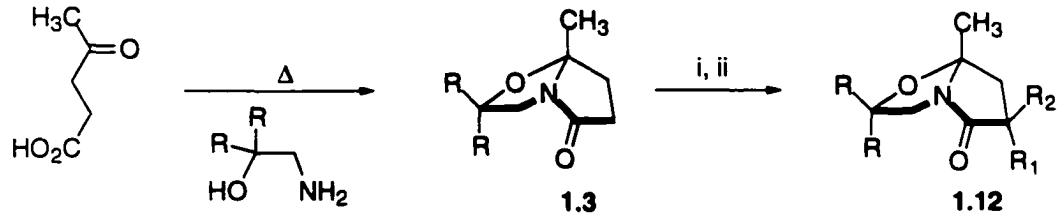
Figure 1.3



1.9 **1.10** **1.11**

(R = Alkyl, H, Aryl, etc.)

As seen in Table 1.2, lactams containing *gem*-dimethyl, *gem*-diisopropyl, and *gem*-diphenyl all gave 94-99% of the *exo* alkyl products in the second alkylation step (the first alkylation also le d to a 94:6 *exo/endo* ratio).



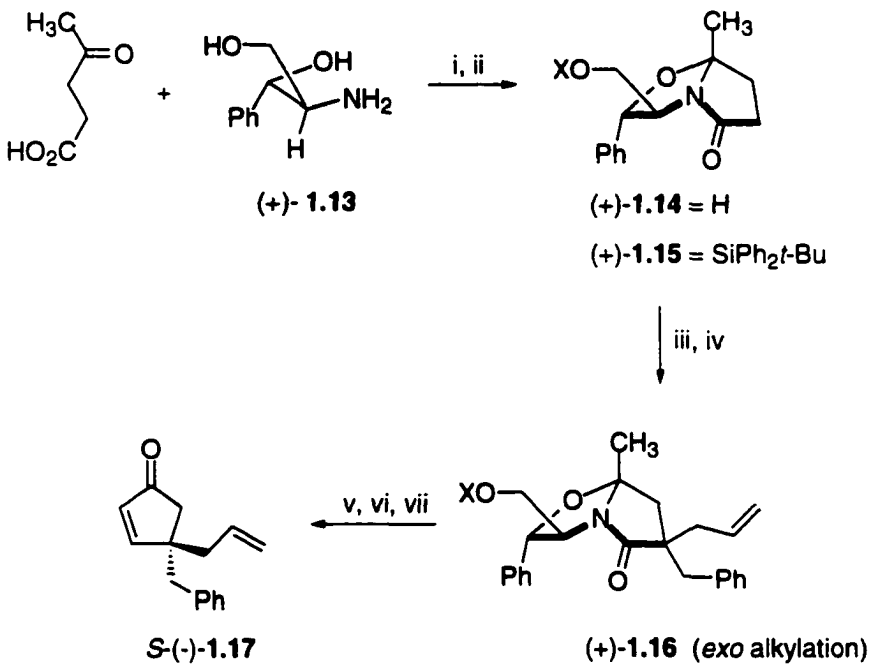
i. *s*-BuLi, R_1X; ii. *s*-BuLi, R_2X

Table 1.2. Alkylation of Racemic Bicyclic Lactams 1.3.

entry	R	R_1	R_2	*T* (°C)	% yield	*exo:endo*
1	Me	Bn	allyl	-78	89	99:1
2	Me	Bn	allyl	0	88	99:1
3	i-Pr	H	Bn	-78	91	96:4
4	i-Pr	Bn	allyl	-78	93	99:1
5	i-Pr	Bn	allyl	0	90	99:1
6	Ph	H	Bn	-78	94	94:6
7	Ph	Bn	allyl	-78	95	99:1
8	Ph	Bn	allyl	0	90	99:1

These results, using racemic lactams possessing alkyl groups on the α-face of lactams **1.3**, were consistent with the preliminary model and were confirmed by condensing the commercially available amino diol **1.13** with levulinic acid providing bicyclic lactam **1.14** (Scheme 1.2). The hydroxyl group was first protected as its *tert*-butyldiphenyl silyl ether (+)-**1.15**. Sequential metalation-alkylation with benzyl bromide and allyl bromide gave **1.16** with greater than 98% *exo*-facial selectivity.

Scheme1.2



(+)- **1.13**

(+)-**1.14** = H

(+)-**1.15** = $SiPh_2t$-Bu

S-(-)-**1.17**

(+)-**1.16** (*exo* alkylation)

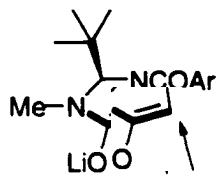
i. PhMe, Δ; ii. TBDPS-Cl, imid.; iii. *s*-BuLi, $PhCH_2Br$;
iv. s-BuLi, allylBr; v. Red-Al; vi. $Bu_4NH_2PO_4$; vii, KOH/EtOH

Conversion of the bicyclic lactam **1.16** to the 4, 4-disubstituted cyclopentenone *S*-(-)-**1.17** and comparison with that obtained *via* a similar process from a valinol derived bicyclic lactam further confirmed that they possessed opposite stereochemistry.[6] ***It may therefore be concluded that the presence of an alkyl or aryl group in the concave face of the oxazolidine ring completely reversed the diastereofacial selectivity.***

Up to this juncture, steric arguments were always proposed to explain the *endo* selectivity in the alkylation of these rigid bicyclic systems. However,

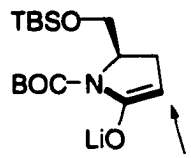
analysis of the alkylation reactions of monocylic lactams **1.4** and **1.5** suggested other factors might be influencing the stereochemical outcome.

Figure 1.4



1.4a

97% anti-alkylation



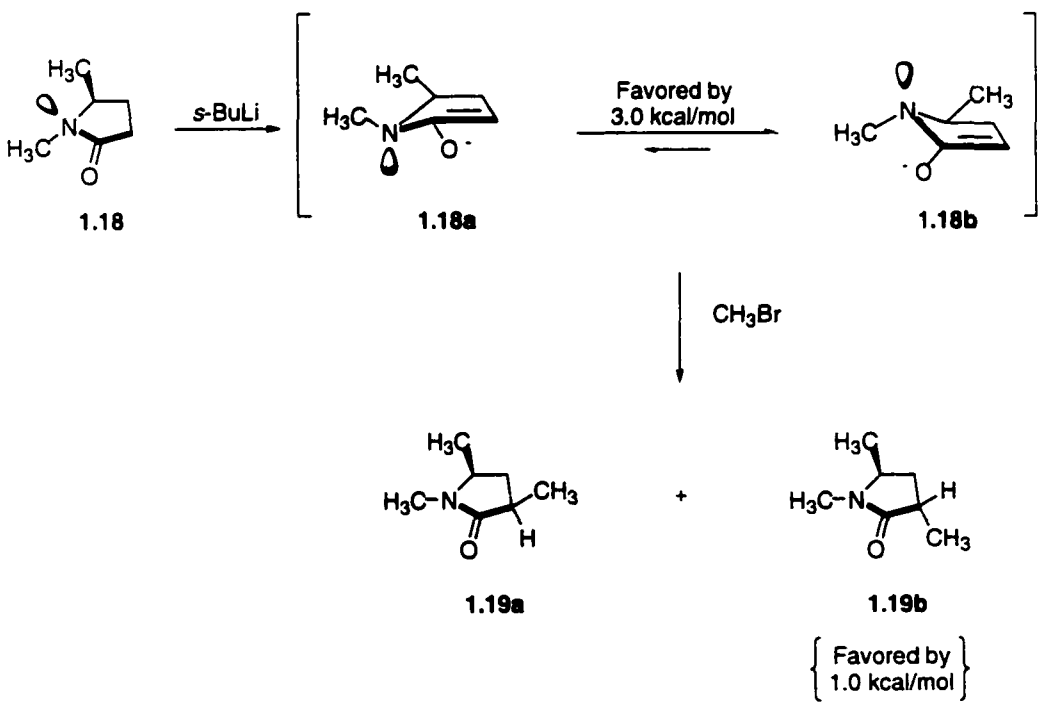
1.5a

93% anti-alkylation

The *monocyclic* enolates derived from imidazolidinones **1.4a**[3a] and 2-pyrrolidinones **1.5a**[3b] are devoid of any polycyclic concave/convex faces, yet exhibited high degrees (>95%) of facial selectivity when their enolates were alkylated (Figure 1.4). In each of these cases, alkylation took place *anti* to a relatively large substituent, which could be due to steric factors. Seebach[3a] has suggested a stereoelectronic effect in **1.4a**, based on the slight pyramidalization of the enolate β-carbon. Additionally, there has been a report[7] on lactam alkylations where the stereochemical result was due to the bulk created by chelation of the metal ion on the enolate to the ligands present in the lactam. Furthermore, the notion that the lone pair on nitrogen exhibited some electronic effect on the diastereofacial selectivity has been suggested by several authors, with no supporting evidence.[8]

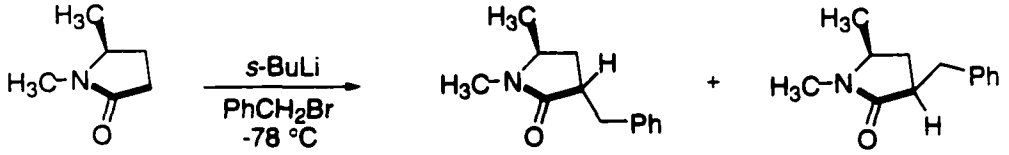
In order to isolate the potential electronic aspect of lactam alkylations, *ab initio* calculations were conducted on the simple pyrrolidinone system **1.18** (Scheme 1.3). It was determined that of the two lowest energy enolates **1.18a/1.18b**, the latter was favored by 3 kcal/mol based upon the strong 1, 2-interaction of the two methyl groups in **1.18a**.[9] Determination of the S_N2 transition state energies for alkylation of enolate **1.18b** with methyl bromide revealed that anti-facial entry was favored over syn-facial entry by 0.99 kcal/mol. Thus, **1.19b** was predicted to be the preferred product of alkylation over **1.19a** by a ratio of 5.3:1 (25 °C). Additionally, it was evident by inspection of the HOMO that the larger coefficient found on the π-bond was *anti* to the nitrogen lone pair, and therefore lay on the α-face of the lactam enolate.

Scheme 1.3



For further support of the stereoelectronic effect, previously observed, the commercially available (±)-1,5-dimethylpyrrolidinone **1.18** was converted to its enolate (*s*-BuLi, THF, -78 °C) and treated with benzyl bromide to give the *anti* alkylated product **1.20a** in >99:1 anti/syn ratio (Scheme 1.4), thus providing further experimental support for the *ab initio* calculations mentioned above.

Scheme 1.4

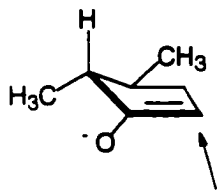


1.18 **1.20a** (99% anti) **1.20b** (1% syn)

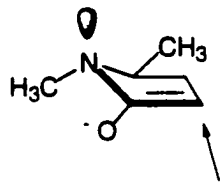
The combination of experimental and computational studies that were performed indicated that the observed *endo* selectivity may originate from a heretofore undetected electronic effect of the nitrogen lone pair perturbing the HOMO of the enolate. However, this relatively small stereoelectronic effect could apparently be overcome by steric and/or other undetectable factors. One of these other possible factors, as suggested by Houk,[2d] could be torsional and steric effects. Houk has shown that the stereoselectivity may be influenced by torsional strain and steric interactions.[9] He has also shown that distortions of π-orbitals can result from torsional effects,[10] and has performed similar calculations on *trans*-2,3-dimethylcyclopentanone **1.21** as those done in the author's

laboratory on lactam **1.18b** (Figure 1.5). In this molecule, where the nitrogen has been replaced by carbon, *ab initio* calculations predicted a 1.0 kcal/mol preference for α-attack on the enolate. This difference is in accord with torsional strain differences in allylic carbon-hydrogen bonds.

Figure1.5



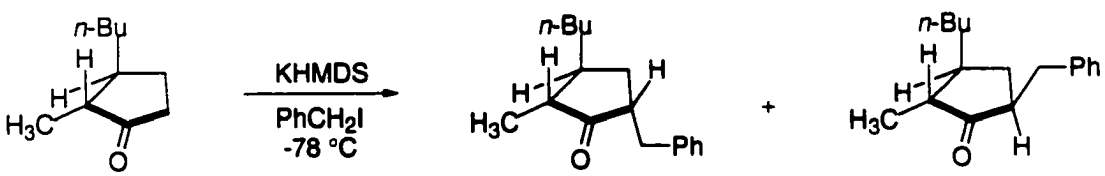
1.21



1.18b

In order to find experimental support for this prediction, *trans*-3-butyl-2-methylcyclopentanone **1.22** was synthesized, subjected to kinetic enolate generation and quenched with benzyl iodide.[2d] ^{1}H NMR analysis revealed that the *endo* product **1.23a** was favored (85:15) which was in agreement with Houk's computational prediction (Scheme 1.5).[2d]

Scheme 1.5



1.22

1.23a

(85% anti)

1.23b

(15% syn)

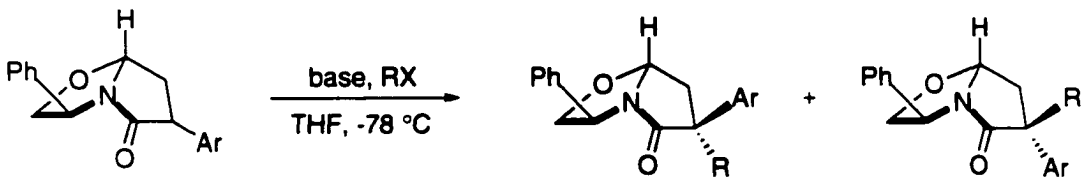
Although these diastereofacial selectivity studies on the alkylation of mono- and bicyclic lactams have provided some insight into the subtleties that influence the stereocontrol of enolate alkylations, further studies are still necessary. Stereoelectronics, torsional angles and sterics all influence this process with varying degrees of stereocontrol. Even though none of these effects has been found solely responsible for the high selectivity, their effects are certainly not mutually exclusive.

I.2.C. Alkylation of Angular Hydrogen Bicyclic Lactams.

Studies on the alkylation of the angular hydrogen bicyclo[3.3.0] system revealed that the selectivity was significantly lower when compared to the angular methyl derivative. Since the nature of the leaving group in the electrophile had previously received little attention, alkylations of **1.24** with other methyl and allyl electrophiles were examined.[11] The selectivity increased from ~6:1 to >20:1 when the electrophile was changed to methyl trifluoromethanesulfonate (Table 1.3, entries 1-3). The allyl derived electrophiles had an equally significant increase in selectivity (from ~5:1 to 10:1) when the bromide leaving group was exchanged with *p*-toluenesulfonate (Table 1.3, entries 4, 5).

This change in selectivity may be explained by a better match between the hardness of the lithium or potassium enolate and the electrophile. Alternatively,

the presence of the Lewis basic oxygens in the sulfonate moiety may act as a ligand for preorganization of the lithium or the potassium enolate with the electrophile prior to bond formation, thus increasing selectivity.



1.24
Ar = *p*-MeO(C_6H_4)-

R = Me
R = Allyl

R = Me
R = Allyl

Table 1.3. Alkylations of Angular Hydrogen Lactam 1.24.

entry	base	RX	time	yield (%)	*endo* / *exo*
1	LHMDS	MeI	1 h	94	86 / 14
2	LHMDS	MeOTf	20 min	99	95 / 5
3	LHMDS	MeOTs	14 h	74	94 / 6
4	KHMDS	AllylBr	15 min	99	83 / 17
5	KHMDS	AllylOTs	30 min	97	90 / 10

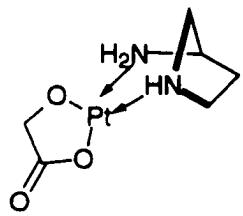
I.3. Conjugate Additions.

The first report on conjugate additions to the bicyclic lactams[1, 12] included cyclopropanations *via* the addition of sulfoxonium ylides. Since then, conjugate additions to these systems have been extended to include several other reaction types summarized below.

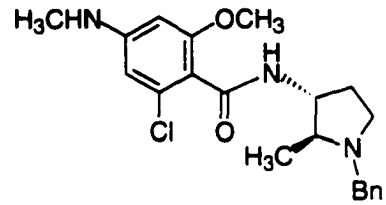
I.3.A. Amines.

Additions of amines to the α,β-unsaturated lactam **1.27** were found to occur with high facial selectivity (Scheme 1.6). These additions were directed toward several 3-aminopyrrolidines found in various biologically significant compounds (Figure 1.6, **1.25** and **1.26**).[13]

Figure1.6



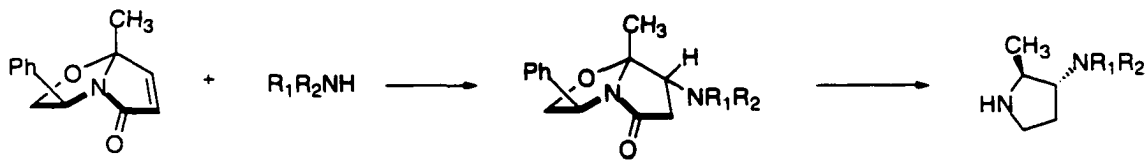
1.25



1.26

Two key features were found to be necessary for efficient amine addition: (a) the presence of water was essential in order to drive the amine addition to completion, and (b) complete reaction required 8 equivalents of the amine.

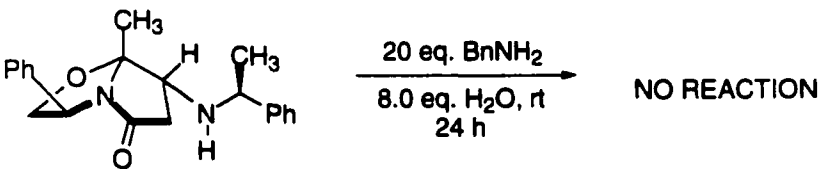
Scheme 1.6



1.27 **1.28** **1.29**

It was also found that the product of the amine addition to the lactam appeared to be kinetically controlled and highly resistant to reversal. Thus, thermodynamic factors were not involved. This was further shown when no amine exchange took place when **1.30** was subjected to scrambling conditions.

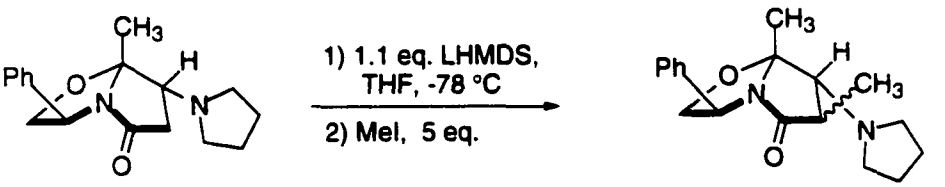
Scheme 1.7



1.30

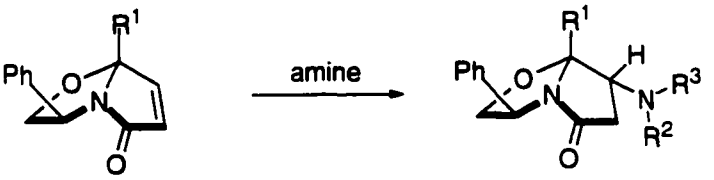
In order to ascertain whether a specifically generated enolate would result in reversal of the amine addition, pyrrolidino lactam **1.31** was subjected to lithium hexamethyldisilazide (-78 °C) and treated with excess iodomethane (Scheme 1.8). Only the methylated lactam **1.32** was formed in a 2:1 mixture of α- and β-diastereomers in the 2-position.

Scheme 1.8



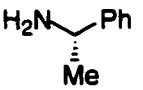
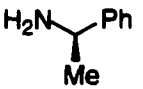
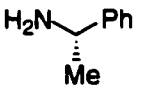
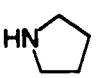
1.31 **1.32**

As the steric bulk of the amine was increased (changing to a secondary amine), the selectivity of *endo-exo* addition increased from 19:1 to >98:2 (Table 1.4). Thus, bulkier nucleophiles were seemingly sensitive to facial selectivity (Entries 1, 5). Similarly, when the angular substituent of the lactam was changed from methyl to phenyl (Entries 2, 4), the selectivities from the reaction with the same primary amine changed from 19:1 to >98:2.



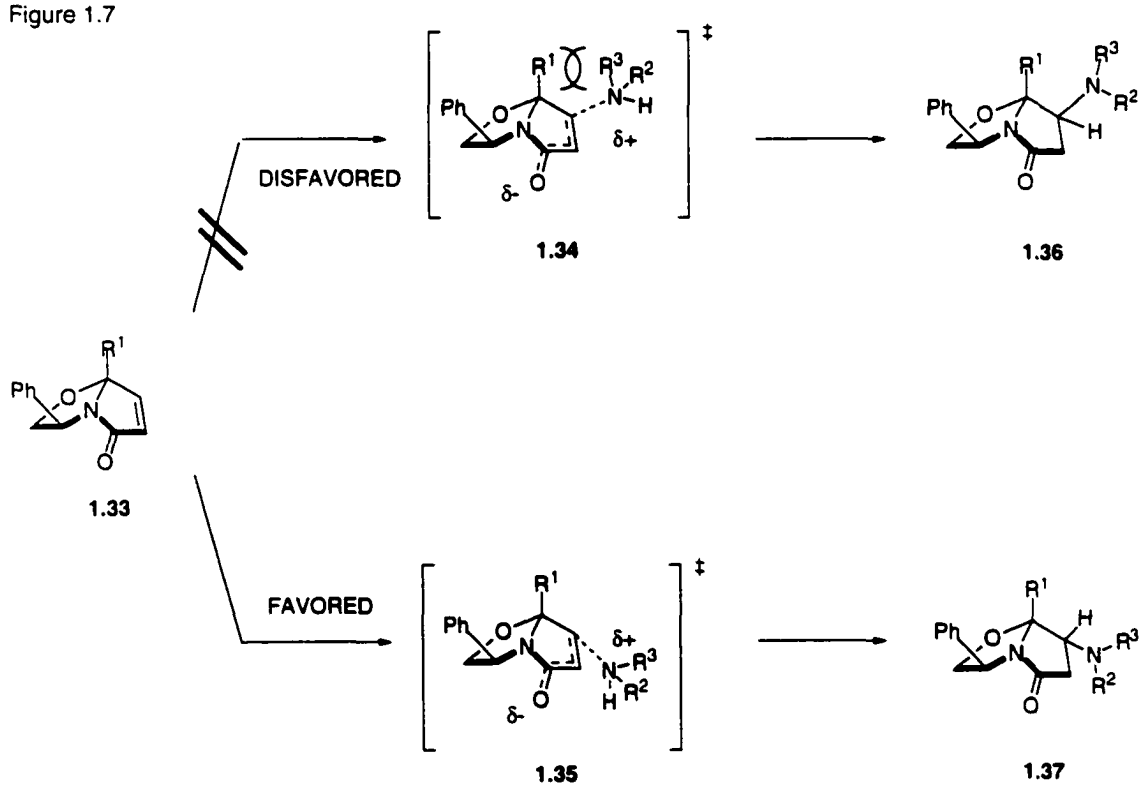
1.33 **1.37**

Table 1.4. Conjugate Addition of Amines to Unsaturated Bicyclic Lactams 1.33.

Entry	R^1	Amine	Yield (%)	Product	d.r.
1	Me	$PhCH_2NH_2$	84	**1.37a**	95:5
2	Me		83	**1.37b**	95:5
3	Me		85	**1.37c**	95:5
4	Ph		89	**1.37d**	>98:2
5	Me		89	**1.37e**	>98:2

Increasing the size of the angular substituent (R^1) resulted in increased interaction with the incoming amine component on the *exo* face. On the other hand, increasing the steric bulk of the amine (R^2 or R^3) also caused increased steric interaction with the angular substituent on the *exo* face thus favoring *endo* entry. That these steric effects were so critical to the stereochemical outcome suggested strongly that the addition process leading to the amino lactams may have proceeded through a late (product-like) transition state (Figure 1.7).

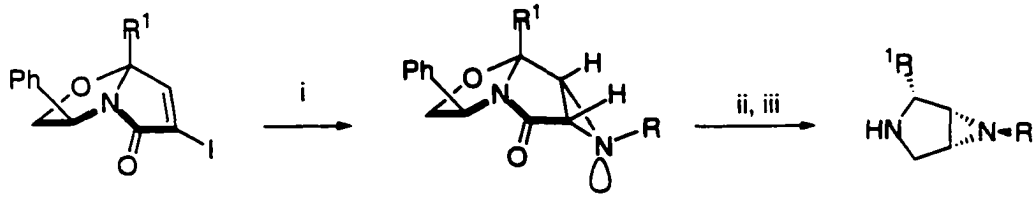
Figure 1.7



I.3.B. Aziridinations.

The amine conjugate addition, described above, was extended to construct the aziridine moiety with high efficiency.[14] Simply modifying the α,β-unsaturated bicyclic lactam **1.33** to include a leaving group at the α-carbon, i.e. iodide, provided an intramolecular reaction pathway for formation of the aziridine. This α-iodo-α,β-unsaturated lactam **1.38** was treated with a primary amine furnishing the aziridine **1.39** in good to excellent yields. The aziridinolactams **1.39** were readily reduced to their corresponding chiral 2-alkyl-3,4-aziridinopyrrolidines **1.40** (Scheme 1.9). It was also observed that the 2-substituent of the product **1.41** had been stereochemically modified (inverted) from its original position in the aziridinolactam **1.39**. This was attributed to the presence of the aziridine ring hindering attack of hydride from the underside of **1.39**.

Scheme1.9



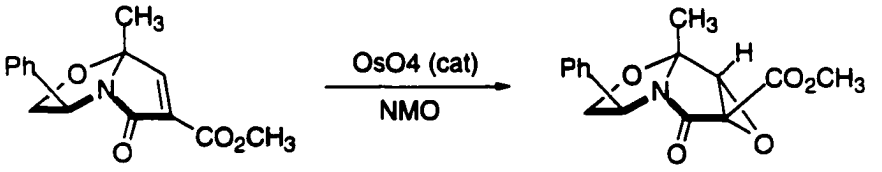
1.38 **1.39** **1.40**

i. RNH_2; ii. AlH_3; iii. $Pd(OH)_2$, H_2

I.3.C. Epoxidations.

The addition of oxygen to the α,β-unsaturated lactam **1.41** was also described using tertiary amine *N*-oxides.[15] Using the Upjohn process for the dihydroxylation of unsaturated systems (catalytic OsO_4, *N*-methylmorpholine oxide), the α-epoxide **1.42** was isolated in high yield rather than the expected diol (Scheme 1.10). Again, the stereochemical outcome of this reaction was consistent with the substituents present on the β-face blocking approach and favoring α-face entry.

Scheme 1.10



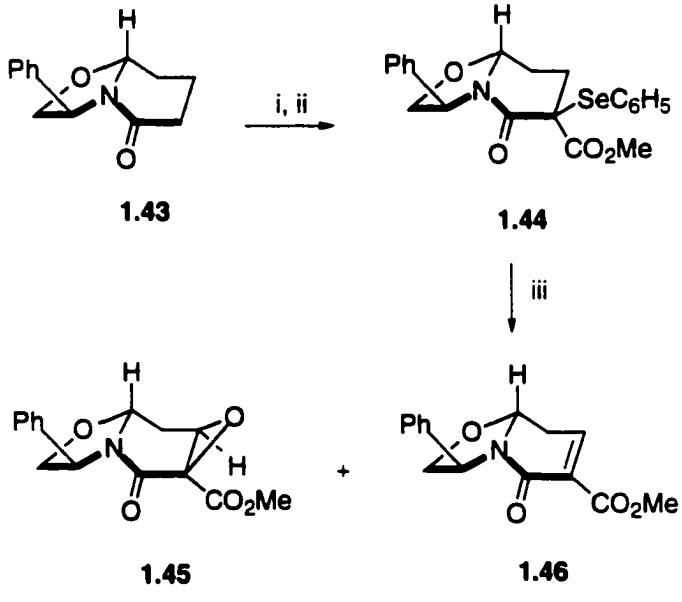
1.41 **1.42**

It was found that osmium tetroxide was unnecessary and NMO could be substituted with trimethylamine-*N*-oxide.[16] The α-facial epoxidation was successful only with a variety of doubly activated α,β-unsaturated bicyclic lactams with yields ranging from 90-99%.

Epoxidation of the α,β-unsaturated lactam has not been limited to the bicyclo[3.3.0] system. Amat[17] has shown that one can use the [4.3.0] bicyclic

lactam **1.43** to obtain the α,β-epoxy lactam **1.45** by treatment of the α–selenyl bicyclic lactam **1.44** with mCPBA (Scheme 1.11).

Scheme 1.11



1.43 **1.44** **1.45** **1.46**

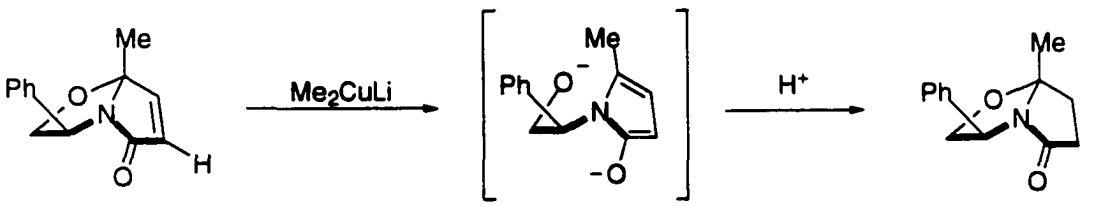
i. LiHMDS, $ClCO_2Me$; ii. $BrSeC_6H_5$; iii. *m*-CPBA

The epoxidation presumably resulted from the formation of the selenoxide of **1.44** which eliminated to the α,β-unsaturated lactam **1.46**. This was followed by epoxidation of this unsaturated system with *m*-CPBA. Here again, the angular substituent seems to dictate the facial selectivity. The presence of an angular hydrogen allowing for β-epoxidation where the oxidation of the intermediate selenide was accomplished with ozone, only the corresponding α,β-unsaturated lactam **1.46** was isolated.

I.3.D. Organocuprates.

The implementation of cuprate additions to electrophilic olefins has only been rarely utilized in a chiral sense. Attempts at addressing this task involved the addition of organocuprates, in a diastereoselective fashion, to the bicyclic lactam **1.47**. Initial attempts to add simple Gilman-type cuprates[19] to the bicyclic lactam resulted in rapid reduction of the enone system furnishing the saturated lactam **1.48** (Scheme 1.12).

Scheme 1.12



1.47 **1.48**

Previous studies[20] from this laboratory described Diels-Alder cycloaddition to **1.47** as being unsuccessful. Only when a carboalkoxy group was introduced in the α-position did reaction occur. It was subsequently found that the standard "Gilman reagent" added to lactam **1.49** providing the β-substituted lactam **1.50** in a 3:1 *trans/cis* diastereomeric ratio. Further efforts showed that the addition of a lower order cyanocuprate produced a >95:5 ratio of diastereomers (Table 1.5). The dominant *endo* addition by the cuprate may be attributed to the presence of

the angular methyl group which interferes with the approach of the cuprate on the β-face.

1.49 **1.50 a-d**

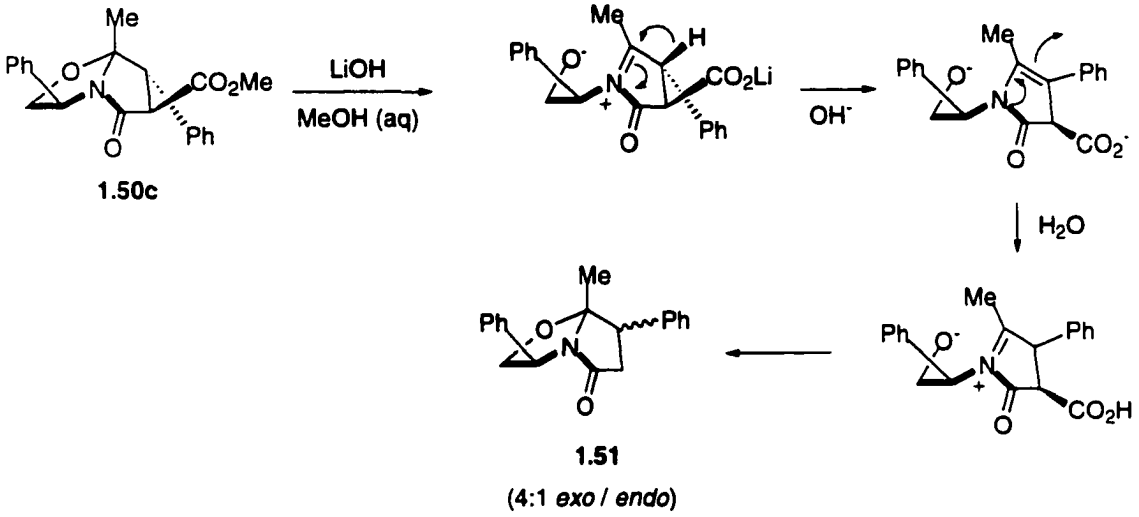
Table 1.5. Conjugate Additions of Organocuprates to 1.49.

product	R'	yield (%)[a]
1.50a	Me	84
1.50b	vinyl	84
1.50c	phenyl	76
1.50d	*n*-butyl	80

[a] The d.r. of all the products was >95:5 as determined by ^{1}H NMR.

The obvious disadvantage of using a carbomethoxy group in **1.49** as a "conjugate addition activator" was its removal after the addition. When alkaline hydrolysis was employed to decarboxylate **1.50c**, rapid epimerization was noted. A plausible route to the destruction of the stereogenic center in **1.51** is illustrated in Scheme 1.13.

Scheme 1.13



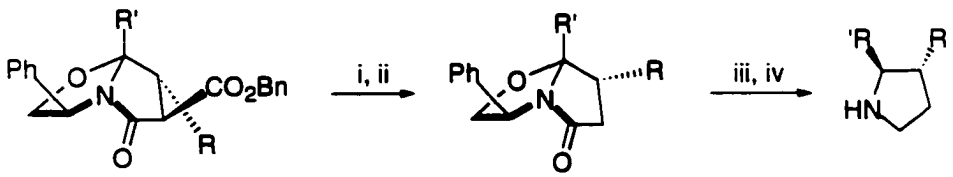
1.50c

1.51

(4:1 *exo* / *endo*)

The base induced pathway leading to epimerization was ultimately prevented by changing to a benzyl ester, which could be easily removed *via* hydrogenolysis, then decarboxylation to **1.53** in refluxing toluene (Scheme 1.14). All that remained to reveal the pyrrolidine system **1.54** was reductive removal of the auxiliary.

Scheme 1.14

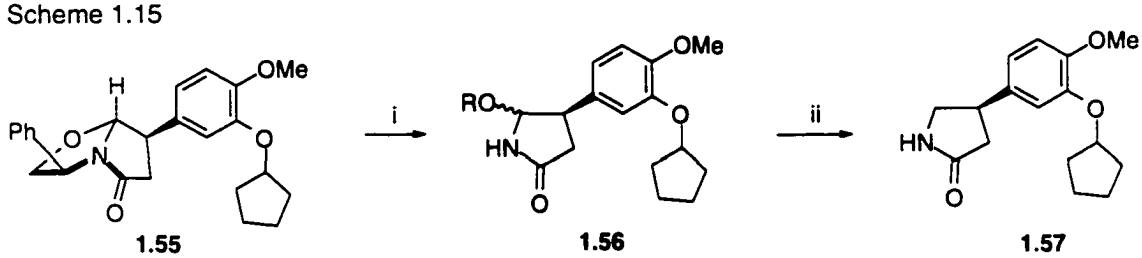


1.52 **1.53** **1.54**

i. Pd/C, H_2; ii. Δ; iii. AlH_3; iv. NH_4HCO_2, Pd/C

This sequence was then applied to the synthesis of the antidepressant and phosphodiesterase inhibitor, Rolipram® **1.57** (Scheme 1.15).[21] The synthetic route included the conjugate addition of the appropriate arylcuprate and removal of the ester to form **1.55**. This was followed by reductive removal of the chiral auxiliary to afford the carbinolamide **1.56** which was converted to Rolipram® **1.57**.

Scheme 1.15



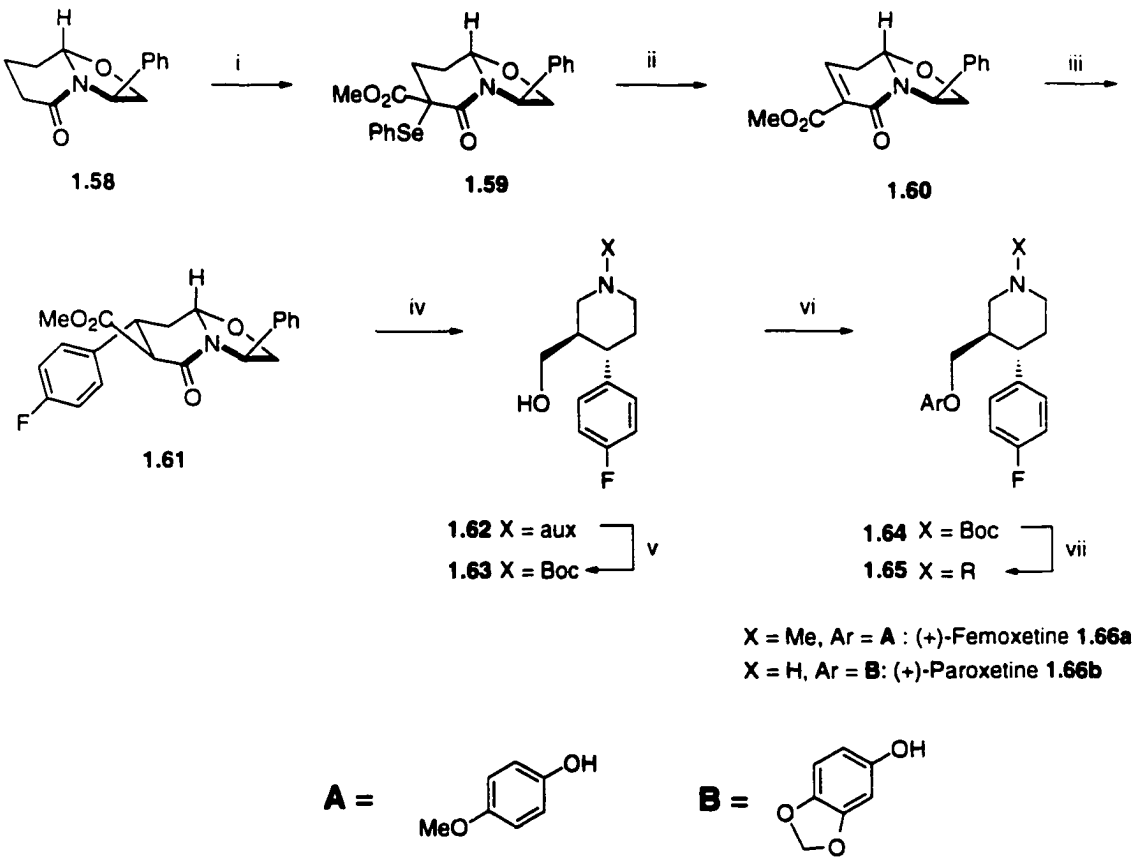
1.55 **1.56** **1.57**

i. $Ca{\bullet}NH_3$; ii. $NaCNBH_3$

Biologically important piperidines have also been constructed using the chiral bicyclic lactam template. The total synthesis of (+)-femoxetine **1.66a** and (+)-paroxetine **1.66b** was realized by the addition of the appropriate cuprate to an α,β-unsaturated [4.3.0]-bicyclic lactam **1.60** (Scheme 1.16).[22] In order to access the more electrophilic Michael acceptor, an electron-withdrawing substituent was installed. The requisite arylcuprate was added to the crude mixture to afford the Michael addition product **1.61** in excellent diastereoselectivity (97:3). Reduction with alane gave the piperidine **1.62** which was converted to the *t*-butyl carbamate **1.63** *via* hydrogenolysis of the auxiliary with *in situ* protection. Femoxetine **1.66a** and paroxetine **1.66b** were obtained by mesylation of the hydroxymethyl group

and displacement with the appropriate benzyl alkoxide. Treatment of the carbamate with lithium aluminum hydride furnished femoxetine **1.66a** and treatment of the corresponding precursor with trifluoroacetic acid produced paroxetine **1.66b**.

Scheme 1.16

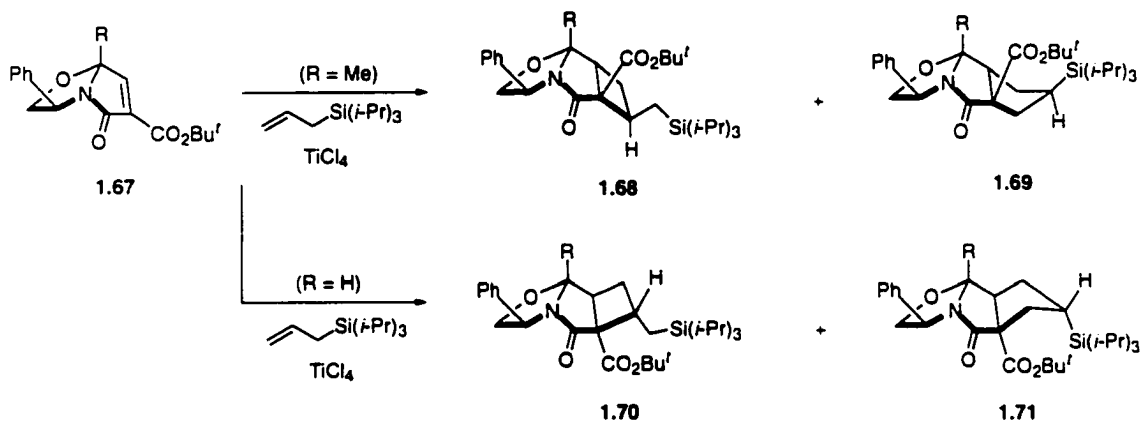


(i) LHMDS, $ClCO_2Me$, PhSeBr ; (ii) a. O_3, CH_2Cl_2, ; b. O_2, ; (iii) ArCu(CN)Li; (iv) $AlCl_3$, $LiAlH_4$;
(v) H_2, $(Boc)_2O$, 20% $Pd(OH)_2$; (vi) a. MsCl, b. NaH, Ar-OH (**A** or **B**), (vii) For R = Me, $LiAlH_4$; For R = H, TFA

I.3.E. Allylsilanes (Cyclobutannulation and Cyclopentannulation).

The use of simple allylsilanes in cyclopentane annulations is a relatively new area of research in organic chemistry.[23, 24] Allylsilanes have been primarily utilized in Lewis acid mediated Sakurai reactions with both aldehydes and electron deficient olefins.[25] Bicyclic lactam investigations in this area utilized the Lewis acid mediated addition of allyltriisopropylsilane to an α,β-unsaturated system**1.67** (Scheme 1.17).[26]

Scheme 1.17

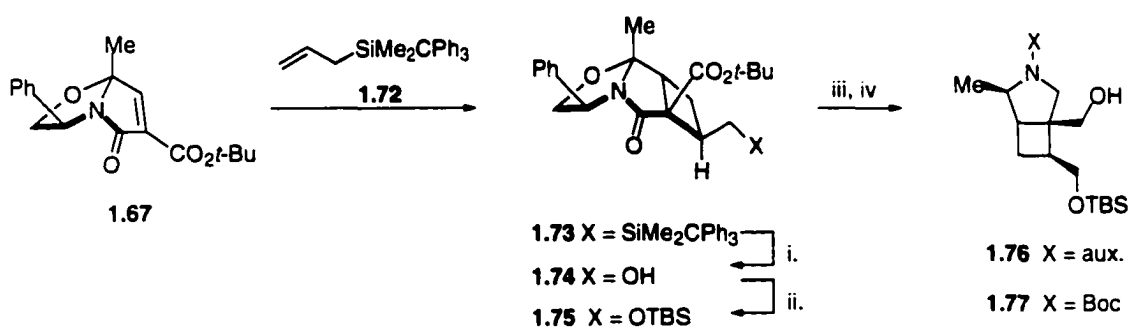


Although the existence of a [2+2] pathway under these reaction conditions has been questioned, cyclobutane products (**1.68**, **1.70**) were unambiguously identified through two dimensional NMR experiments and X-ray crystallography. These results were the first *confirmed* examples of allylsilanes undergoing Lewis acid mediated cyclobutannulation with electron deficient olefins.

In order to extend this technique and exploit the dual reactivity of the allylsilanes, the use of the silicon atom as a hydroxyl surrogate was investigated.[27]

A novel allylsilane **1.72** to satisfy the above conditions, was employed in the construction of optically pure heterocycles using the bicyclic lactam template (Scheme 1.18). Addition to the α,β-unsaturated bicyclic lactam **1.67** occurred under Lewis acid mediated conditions to provide the cyclobutane adduct **1.73** in moderate yield. Tamao-Fleming oxidation occurred in moderate yield to furnish alcohol **1.74**, which was protected as its *tert*-buyl dimethylsilyl ether **1.75**. Lactam **1.75** was then reduced with diisobutylaluminum hydride and protected to provide a single diastereomer of the conformationally constrained cyclobutane-fused pyrrolidine **1.77**.

Scheme 1.18



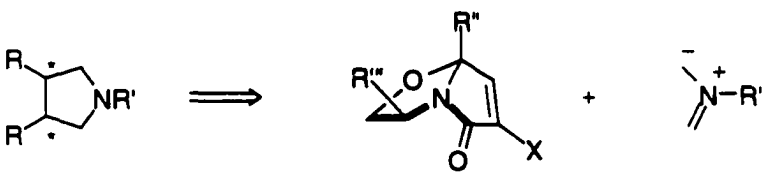
i. Bu_4NOH, H_2O_2, THF/MeOH; ii. TBSCl, imid, DCM; iii. DIBALH; iv. H_2, $Pd(OH)_2$, Boc_2O.

I.4. Pericyclic Reactions.

I.4.A. Azomethine Ylide [3+2]Cycloadditions.

The 1,3-dipolar cycloaddition reactions of azomethine ylides **1.80** have been extensively reviewed,[28] and the basic reaction has been studied as both it's racemic and asymmetric variants.[29] The use of the chiral bicyclic lactam **1.79** as a chiral dipolarophile has also proved to be quite versatile (Figure 1.8).

Figure 1.8



1.78 **1.79** **1.80**

It was found[30] that the size of the angular substituent (Table 1.6, R_1, **1.79**) exhibited a significant effect on the *endo/exo* selectivity in the cycloaddition. This was in agreement with previous studies[13, 17, 23] of other cycloadditions (Diels-Alder) and conjugate additions on these lactams.

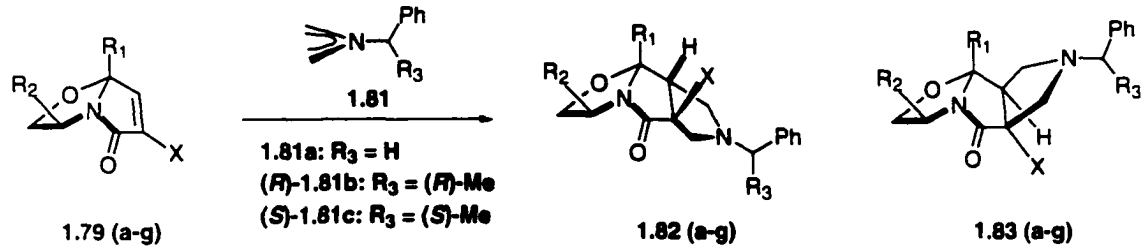


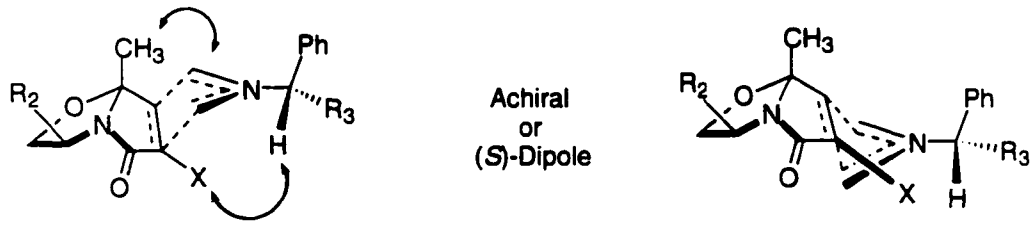
Table 1.6. Effect of Structure on Facial Selectivity.

	lactam 1.79				ylide 1.81a	ylide (*R*)- 1.81b	ylide (*S*)- 1.81c
entry	R_2	R_1	X	lactam	**1.82:1.83**	**1.82:1.83**	**1.82:1.83**
1	*i*-Pr	Me	H	**1.79a**	91:9	94:6	91:9
2	Ph	Me	H	**1.79b**	94:6	91:9	92:8
3	Ph	H	H	**1.79c**	17:83	19:81	16:84
4	*i*-Pr	Me	CO_2Me	**1.79d**	71:29	87:13	59:41
5	*i*-Pr	Me	CO_2t-Bu	**1.79e**	72:28	92:8	51:49
6	*i*-Pr	Ph	CO_2Me	**1.79f**	74:26	87:13	69:31
7	Ph	Me	Br	**1.79g**	96:4	>98:2	91:9

Table 1.6 illustrates the existence of a steric effect with respect to the substituent α to the carbonyl in the dipolarophile (lactams **1.79a-g**). As seen in entries 1 and 2, there was very little difference in selectivity when the azomethine ylide was achiral or derived from the optically pure α-methyl benzylamine. Entries 4-6 demonstrate that the selectivity is very sensitive to the presence of α-substituents (R_1) larger than hydrogen where substantial matched and mismatched double diastereoselectivity was observed. Based on these data, experimental and computational studies of other azomethine ylide cycloaddition

reactions, a predictive model was developed which assisted in further optimization of the selectivity (Figure 1.9).

Figure 1.9

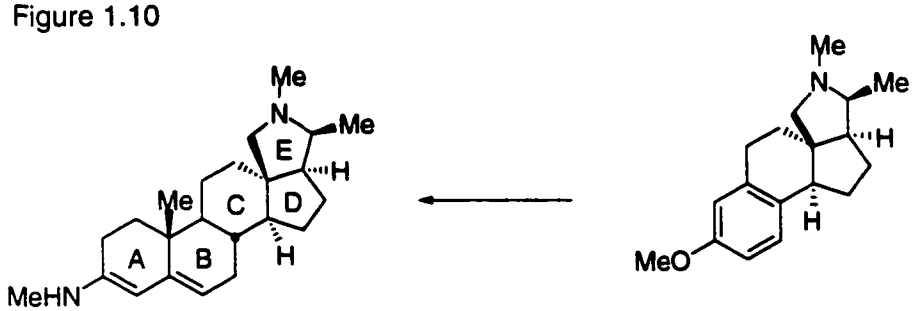


Unfavored
β-approach

Favored
α-approach

The steric model developed provided insight for the rational control of stereoselection in the dipolar cycloadditions of simple azomethine ylides to a structurally variable chiral template. This reaction route was employed in the formal synthesis of (+)-conessine **1.84**, a steroidal alkaloid possessing significant biological activity (Figure 1.10).[31]

Figure 1.10

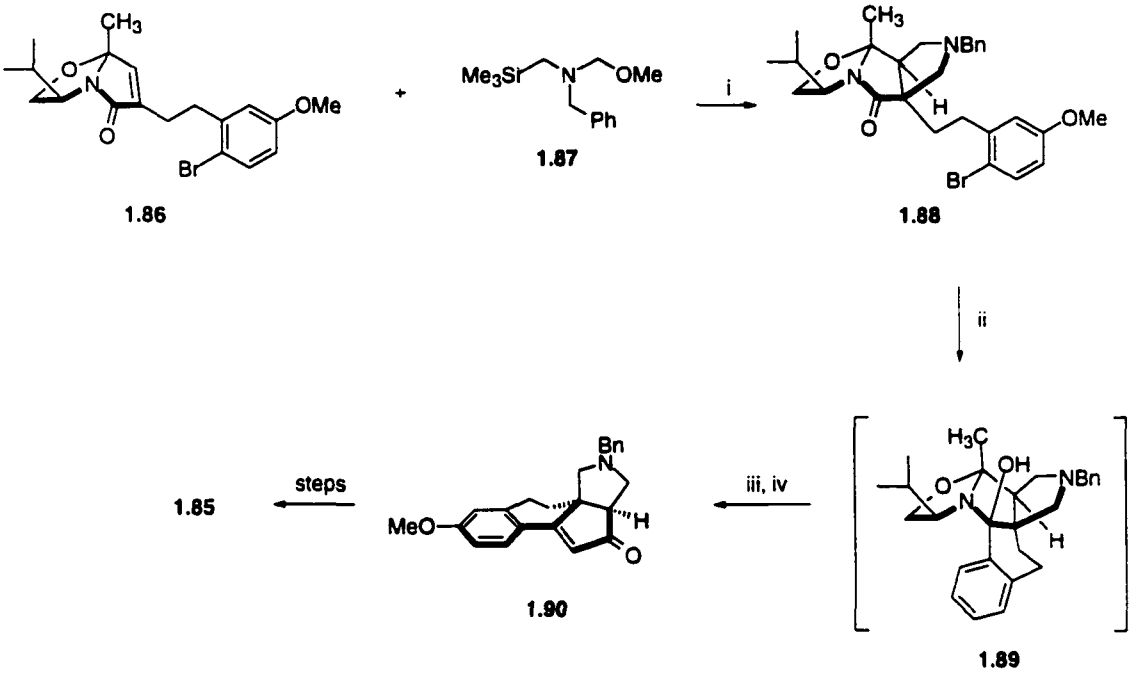


Conessine, **1.84**

1.85, (+)-benzohydrindan precursor

The synthesis of **1.85** is outlined in Scheme 1.19

Scheme 1.19



i. 0.01% TFA, 180 °C; ii. *t*-BuLi; iii. H^+, NaOEt; iv. NaOEt

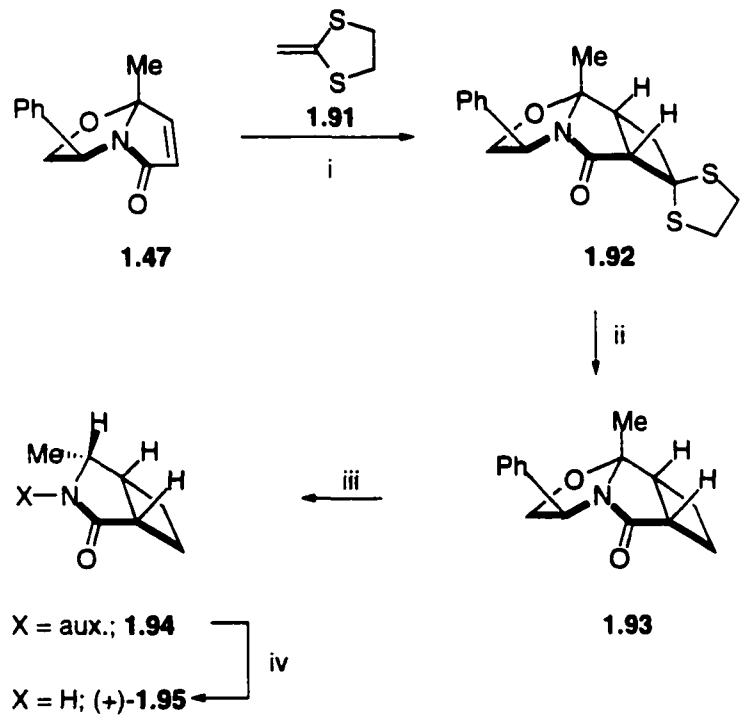
I.4.B. [2+2] Cycloadditions. Synthesis of the Core of (-)-Lintenone.

Pericyclic reactions employing the bicyclic lactam as a chiral dienophile or dipolarophile have proven very successful in the construction of carbocycles and heterocycles as seen above. Chiral cyclobutanes were readily obtained by Lewis acid mediated addition of dithioketals to unsaturated bicyclic lactams or by photochemical manipulation of the lactam produced compounds.

The dithioketal, methylenedithiolane **1.91** proved to be an excellent cycloaddition partner for the [2+2] reaction.[32] Treatment of lactam **1.47** with

dimethylaluminum chloride and dithiolane **1.91** gave 92% of the cyclobutane adduct **1.92** as a single diastereomer (Scheme 1.20). Raney-nickel reduction afforded the cyclobutano lactam **1.93** which was converted to the optically pure cyclobutano γ-lactam **1.95** in two steps.

Scheme 1.20

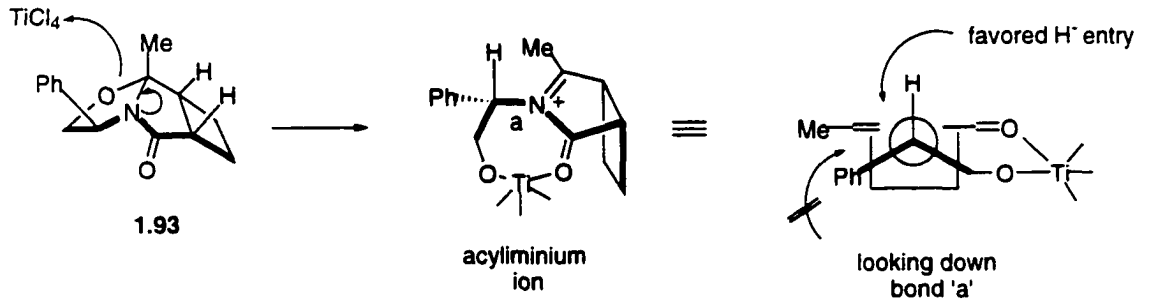


i. Me_2AlCl, toluene; ii. Raney-Ni; iii. Et_3SiH, $TiCl_4$; iv. Na, NH_3

Rationalization for the unusual stereochemical outcome in the reduction may be represented by the structures shown in Figure 1.11. The configuration of the phenylglycinol moiety, the complexation of the oxophilic titanium salt, and the presence of the *endo*-fused cyclobutane ring all appear to block the α-face to

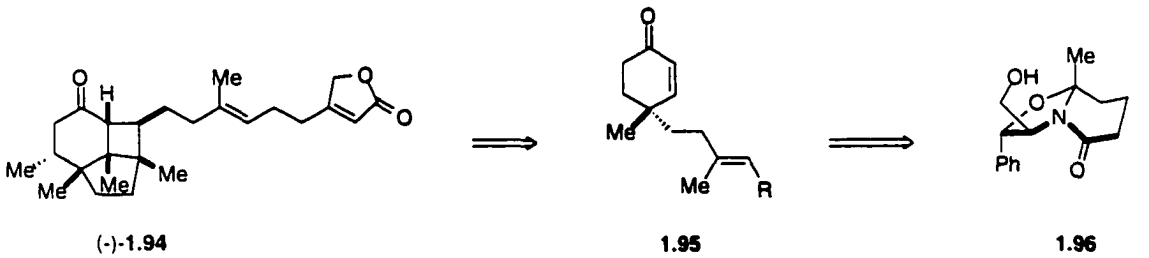
nucleophilic hydride delivery. Thus, entry of hydride from the β-face provides the inverted position taken by the methyl group which was confirmed by X-ray data.

Figure 1.11



The [4.3.0] bicyclic lactam **1.96** was also employed to construct an optically pure 4,4-disubstituted cyclohexenone **1.95** which underwent an intramolecular photochemical [2+2] cycloaddition reaction to construct the tricyclic carbon skeleton of (-)-lintenone **1.94**,[33] (Figure 1.12).

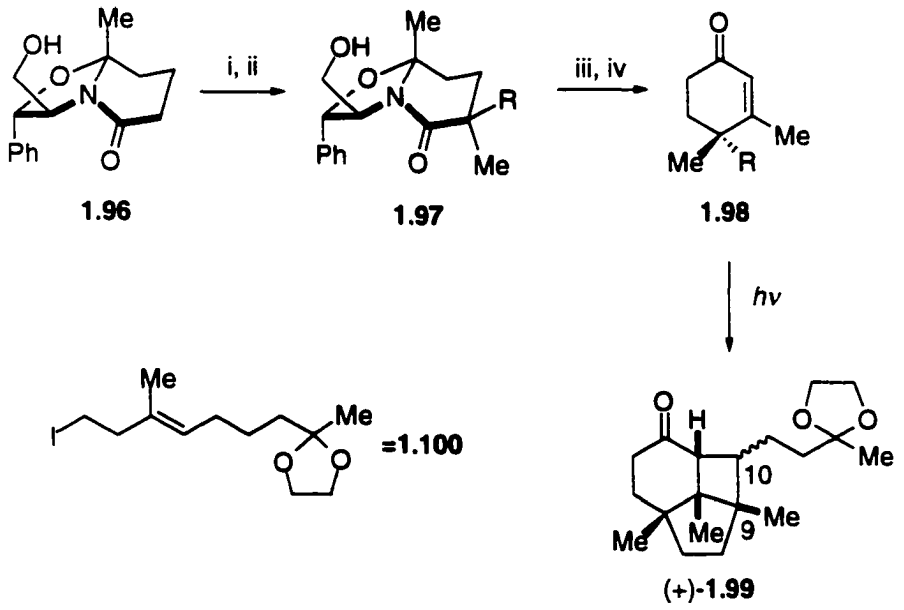
Figure 1.12



Synthesis of the requisite chiral, non-racemic cyclohexenone **1.95** was accomplished by dialkylation of bicyclic lactam **1.96** affording a 7:1 mixture of

alkylated products **1.97** with *endo* entry at each alkylation step being the predominant pathway (Scheme 1.21). The chiral auxiliary was removed by addition of methyllithium to the lactam carbonyl then hydrolysis under anhydrous conditions to provide the 4,4-disubstituted cyclohexenone **1.98**. Cyclohexenone **1.98** was irradiated to produce the photo [2+2] adduct (+)-**1.99**. The cycloaddition proceeded in high yield albeit in low diastereoselectivity at C-10 (1.4:1). Cycloadditions in similar systems lacking the C-9 methyl goup led to much higher selectivity (up to 9:1). It was concluded that the stereochemical outcome of the cyclization must be strongly perturbed by the presence of the C-9 methyl group.

Scheme 1.21

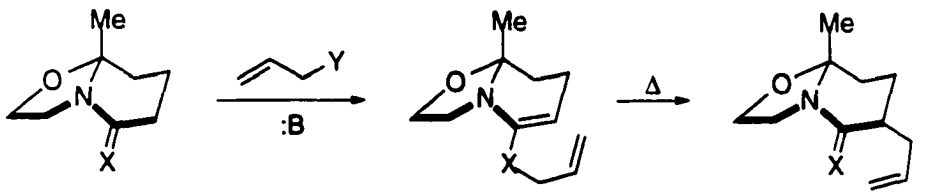


i. LDA/ **100**; ii. LDA/MeI, 7:1 d.r.;
iii. MeLi; iv. $NBu_4H_2PO_4$, anh. EtOH

I.4.C. Thio-Claisen [3,3] Rearrangements. Synthesis of (-)-Trichodiene.

The thio-Claisen rearrangement (**1.102b→1.103b**), although potentially a powerful synthetic tool, has garnered relatively little attention compared to its well-known oxygen analog (**1.102a →1.103a**) (Scheme 1.22).[34] Conversion of the bicyclic lactam **1.101a** to the thio-lactam **1.101b** was accomplished by treatment with either Belleau's or Lawsson's reagent.[35]

Scheme 1.22



1.101a, X = O
1.101b, X = S

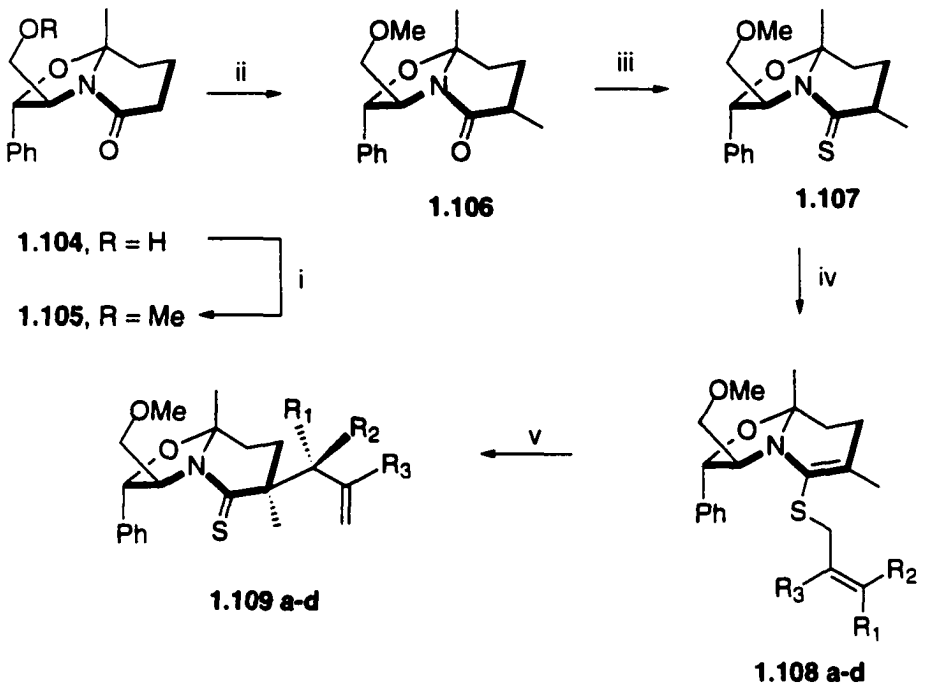
1.102a, X = O
1.102b, X = S

1.103a, X = O
1.103b, X = S

S-Alkylation was accomplished by trapping the thioenolate of **1.107** with the appropriate allylic halide followed by stirring at ambient temperatures or heated in an appropriate solvent (Scheme 1.23). The stereochemistry of the rearrangement was confirmed by single crystal X-ray analysis of **1.109b** obtained from the crotyl thioether **1.108b** (Table 1.7). The X-ray study clearly indicated that the allyl groups in **1.109** had entered from the *exo* (β) face of the bicyclic system. This stands in contrast to earlier studies, wherein enolate-based alkylation on the amide preferred the *endo* (α) face. In addition to rearrangement

on the *exo* face, the product stereochemistry in the allylic position appeared to be the result of a chair transition state, **1.111** (Figure 1.13).

Scheme 1.23



i. KH, MeI; ii. LDA, MeI; iii. $(ArPS_2)_2$; iv. LDA, **1.110**; v. Δ

1.110 =

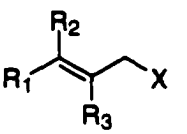
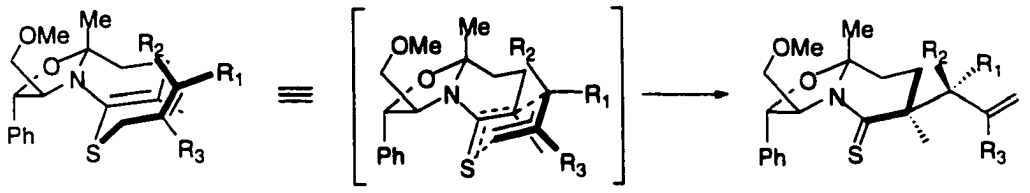


Table 1.7. Diastereoselective Thio-Claisen Rearrangements (1.108 → 1.109)

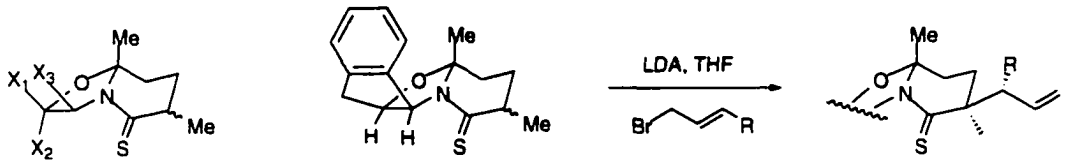
	allyl halide **1.110**						
entry	R_1	R_2	R_3	X	*T* (°C)	% **1.109**	dr
a	H	H	Me	Cl	25	71	3:1
b	Me	H	H	Br	25	79	91:9
c	Ph	H	H	Br	140	49	>99:1
d	Me	Me	H	Br	149	68	>99:1

Figure 1.13



1.108 1.111 1.109

In order to gain insight into the origin of this stereochemical outcome, a variety of other auxiliaries were investigated (**1.112a-d**, Table 1.8) as well as the introduction of Lewis acids.[34d-e] An interesting remote steric effect was observed in the reactions with various chiral auxiliaries. The original thio-Claisen rearrangement was performed on bicyclic lactam **1.112a** which places the phenyl substituent in the concave (*endo*) face of the oxazolidine. Two other auxiliaries (**1.112b** and **1.112d**, Table 1.8) which lack the substituent in the concave face (nor-ephedrine and aminoindanol) provided very poor diastereoselectivity.



1.112a : X_1 = H, X_2 = Ph, X_3 = CH_2OMe
1.112b: X_1 = Ph, X_2 = H, X_3 = Me
1.112c: X_1 = Me, X_2 = Me, X_3 = Ph

1.112d

1.113a-d

Table 1.8. Thio-ClaisenRearrangement on Various Bicyclic Lactams 112.

1.112	X_1	X_2	X_3	R	T (°C)	yield	additive	d.r. (1.113)
a	H	Ph	CH_2OMe	Me	140	48	-	99:1
b	Ph	H	Me	Me	65	70	-	64:36
c	Me	Me	Ph	Ph	110	52	-	>95:5
d	-	-	-	Me	65	40	-	50:50
a	H	Ph	CH_2OMe	Me	25	58	$Pd_2(dba)_3$	82:18
a	H	Ph	CH_2OMe	Me	25	58	$NiCl_2(PPh_3)_2$	80:20

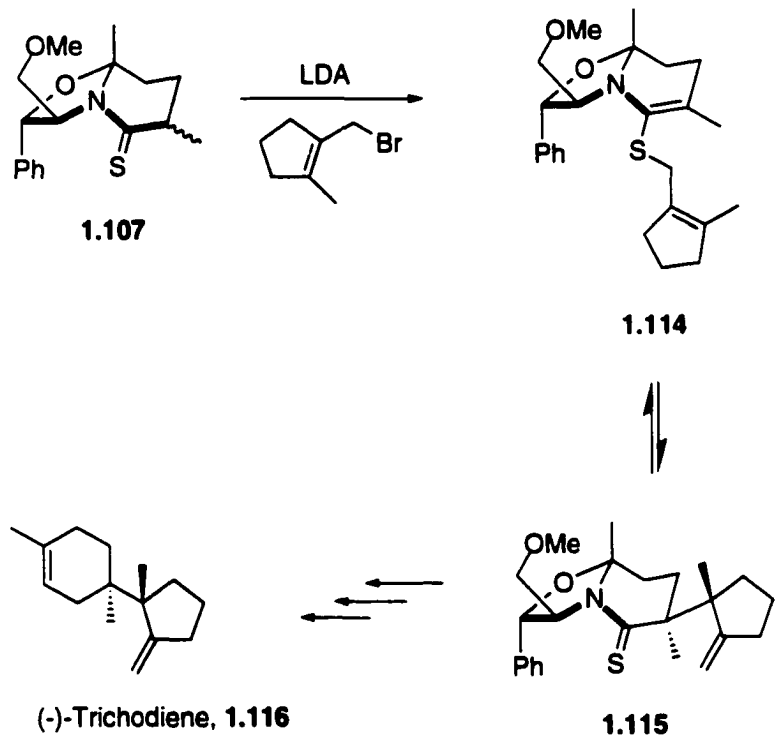
Based on the data obtained from these various auxiliaries, it is believed that the key steric factor in determining the selectivity is the group X_2 in the concave face of **1.112**. If X_2 = H, the diastereoselectivity quickly falls to nearly 1:1.

Transition metal catalysis provided a mild entry into the desired rearrangement product. Addition of palladium(II) salts (10 mol%) to the *N,S*-ketene acetal **1.112c** gave the rearranged product at room temperature with a much higher isolated yield than the original reaction conditions.[34e]

The thio-Claisen reaction was applied to the synthesis of several cyclohexenone derivatives including the first synthesis of the sesquiterpene, trichodiene[34b] (**1.116**) in enantiomerically pure form. The latter contains the

difficultly accessible vicinal quaternary stereogenic center (Scheme 1.24). The key transformation in this synthesis was the installation of the vicinal quaternary centers in a single operation *via* *S*-alkylation and subsequent thio-Claisen rearrangement.

Scheme 1.24



1.107

1.114

(-)-Trichodiene, **1.116**

1.115

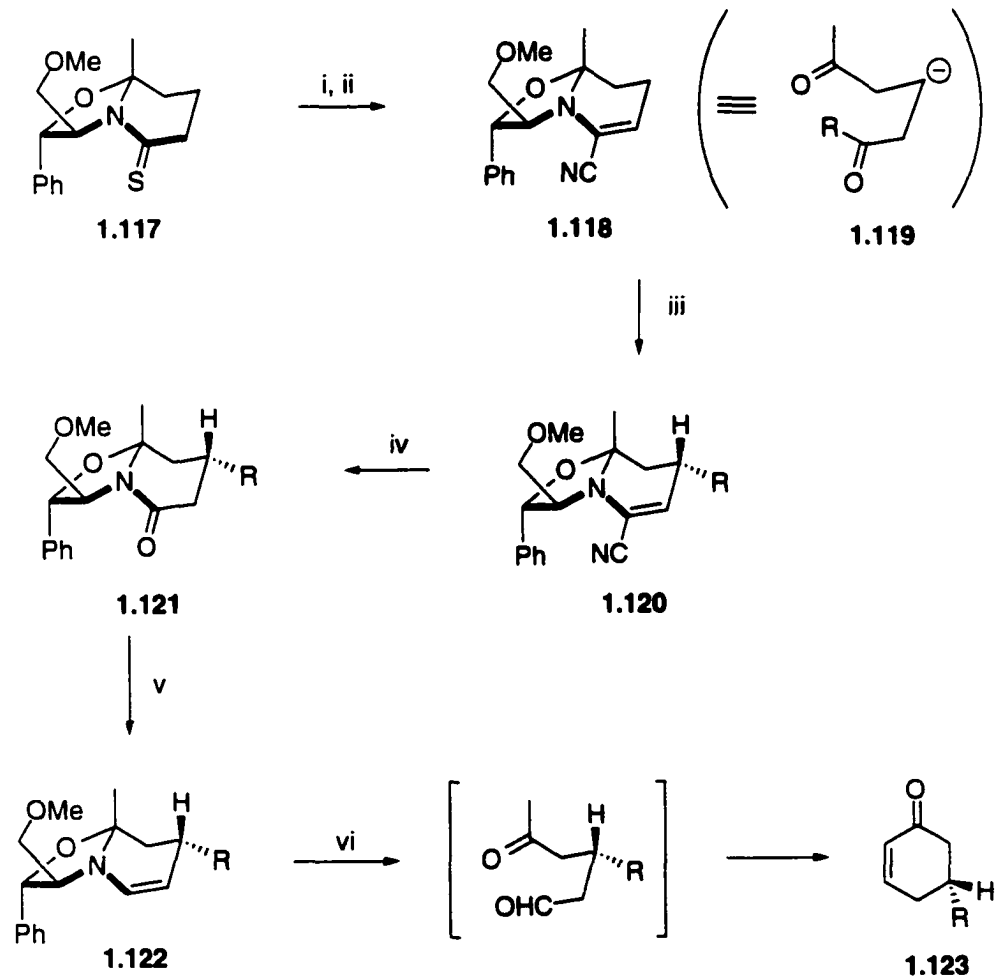
I.5. Chiral Bicyclic Thiolactams

The bicyclic thiolactam has also been used in at least two other reaction manifolds that have provided access to optically pure heterocycles and carbocycles. In the first case, the bicyclic lactam may exhibit properties of a bis-homoenolate **1.119**.

I.5.A. Cyano-enamine Alkylations. Synthesis of (-)-Penienone.

Conversion of bicyclic lactam **1.117** to the *N,S*-ketene acetal followed by treament with potassium cyanide and cuprous iodide furnished the bicyclic cyano-enamine **1.118** (Scheme 1.25). A metalation/alkylation sequence followed by acid hydrolysis led to the alkylated product **1.121** in high yield with excellent facial stereocontrol (>95:5).[36]

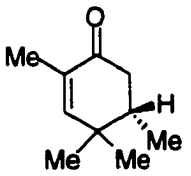
Scheme 1.25



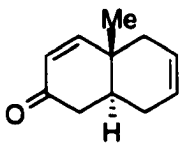
i. Et_3OBF_4; ii. KCN, CuI, cat. I_2; iii. LiTMP, R-X; iv. HCl, THF/H_2O; v. DIBALH•*n*-BuLi; vi. H_3O

This sequence was employed to construct a variety of carbocycles including the major constituent of iris essential oil **1.128**,[37] the "Woodward ketone" **1.129** (Figure 1.14)[38] and (-)-penienone **1.127** (Scheme 1.26).[39]

Figure 1.14



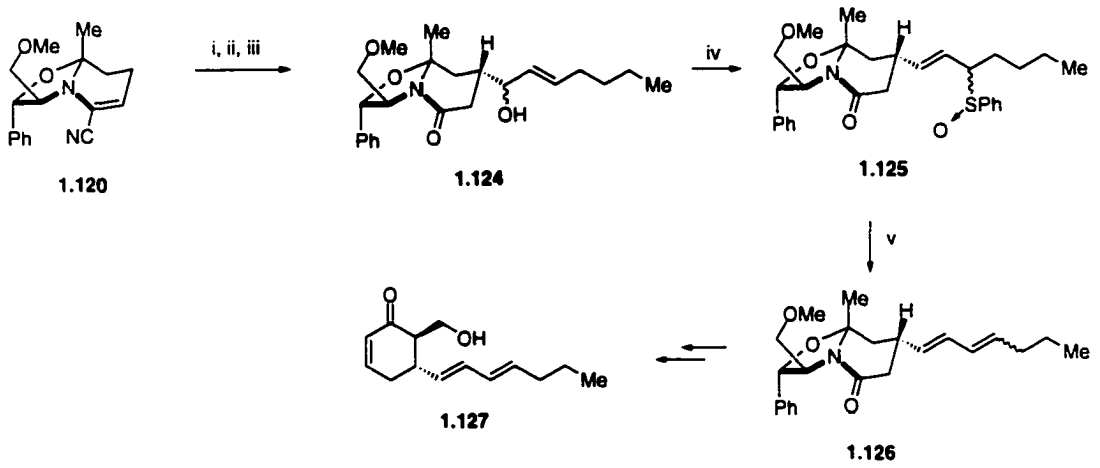
1.128



1.129

In the (-)-penienone synthesis, the key transformation was the addition of *trans*-2-heptenal to the cyano-enamine **1.120** which afforded the requisite seven carbon side chain in **1.124** as a single diastereomer (*endo*). Subsequent [3,2] rearrangement of the sulfoxide in **1.125** and elimination gave **1.126** which produced **1.127** after hydrolysis, cyclization and hydroxymethylation.

Scheme 1.26

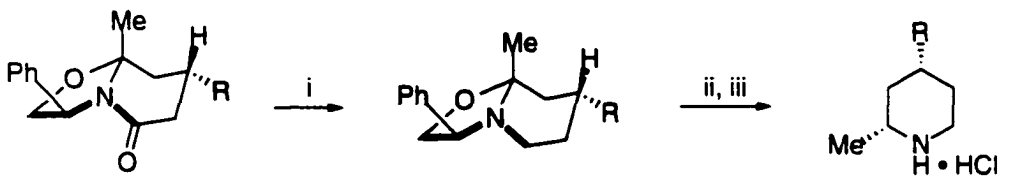


1.120 1.124 1.125 1.127 1.126

i. LiTMP, HMPA, THF, -78 °C; ii. *trans*-heptenal, -78 °C; iii. THF/HCl, 25 °C; iv. PhSCl, Et_3N, THF, 25 °C; v. THF, 65 °C

Cyanoenamine alkylations were reported to construct the 2,4-*cis* disubstituted piperidines **1.132** by using the phenylglycinol based auxiliary.[40] Alkylation, followed by hydrolysis, gave lactam **1.130** (Scheme 1.27), which was reduced to the bicyclic oxazolidine **1.131**. Hydrogenolysis of the auxiliary produced the piperidine **1.132** as a single diastereomer.

Scheme 1.27



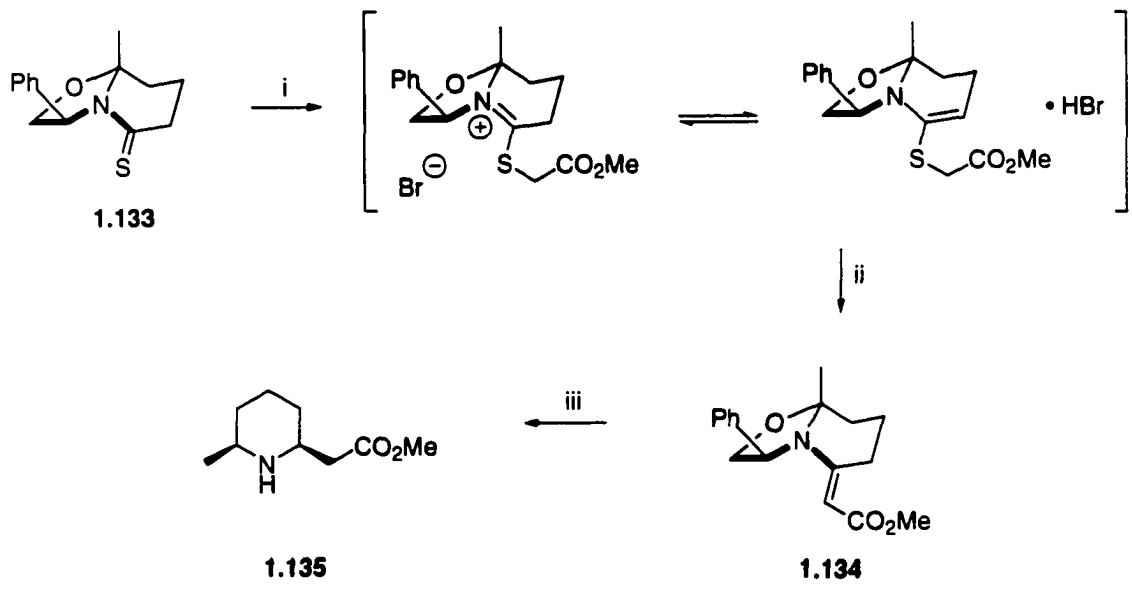
1.130 1.131 1.132

i. Red-Al; ii. $Pd(OH)_2$, H_2, MeOH; iii. HCl

I.5.B. 2,6-Disubstituted Piperidines.

Thiolactams (e.g. **1.133**) were also utilized to access the 2,6-disubstituted *cis*-piperidines **1.135** *via* the Eschenmoser contraction.[41] Thus, reaction of thio-lactam **1.133** with methyl α-bromoacetate in the presence of trimethylphosphite furnished the vinylogous urethane **1.134** which was easily reduced to the piperidine, **1.135**.

Scheme 1.28



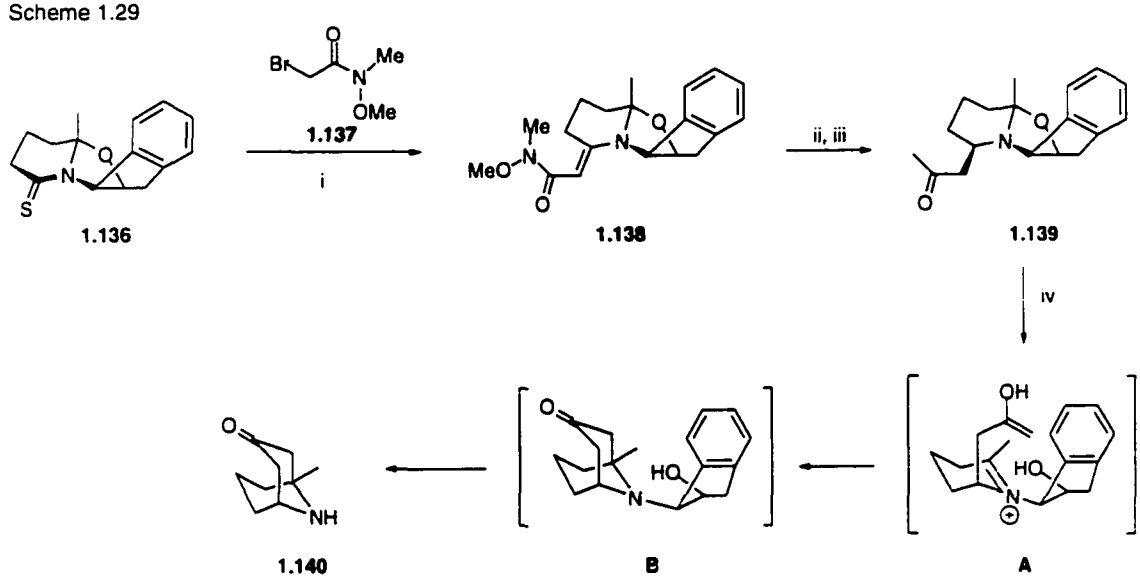
1.133 **1.135** **1.134**

i. 2-bromomethylacetate, triethylamine; ii. $P(OMe)_3$; iii. $Pd(OH)_2$, H_2

A variation of this sequence was employed in tandem with an intramolecular Mannich reaction to reach the homotropane (+)-euphococcinine, **1.140** (Scheme 1.29).[42] The Weinreb amide **1.137**[43] was simultaneously introduced into the thio-lactam **1.136** to afford the vinylogous urea **1.138**.

Addition of methyl lithium provided the keto-oxazolidine **1.139** which was directly converted to the homotropane **1.140** *via* intramolecular Mannich cyclization.

Scheme 1.29

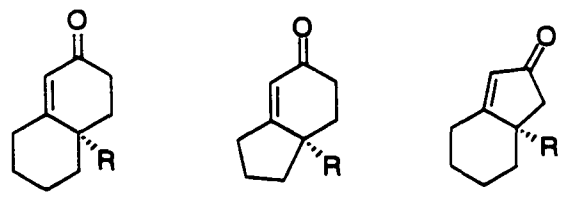


i. triethylamine, $P(OMe)_3$; ii. H_2, Pt/C; iii. MeLi; iv. NH_4OAc, HOAc.

I.6. Chiral Ketones

Although there are known routes[44] to chiral nonracemic ring systems represented by **1.141**, **1.142**, and **1.143** (Figure 1.15), the bicyclic lactam has also provided an efficient general entry into these bicyclic systems.

Figure 1.15

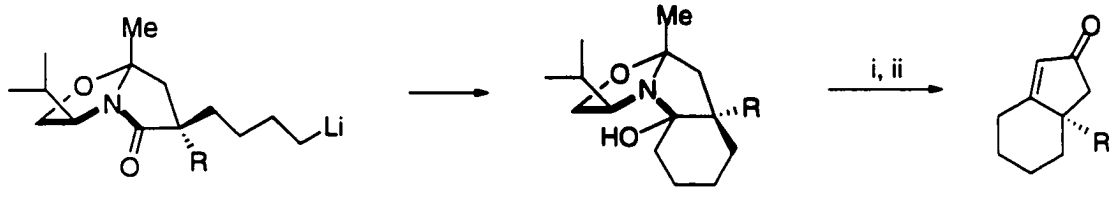


1.141 **1.142** **1.143**

I.6.A. Hydrinden-2-ones. Synthesis of the Core to (+)-Magellanine.

One of the key useful chemical features of the bicyclic lactam is the ketonic nature of the lactam carbonyl. Given the unexpectedly high electrophilic nature of the carbonyl, intramolecular nucleophilic addition to this center produces the intermediate carbinolamine **1.144** which was converted, after hydrolysis, to the corresponding hydrinden-2-one, **1.143** (Scheme 1.30).[45]

Scheme 1.30

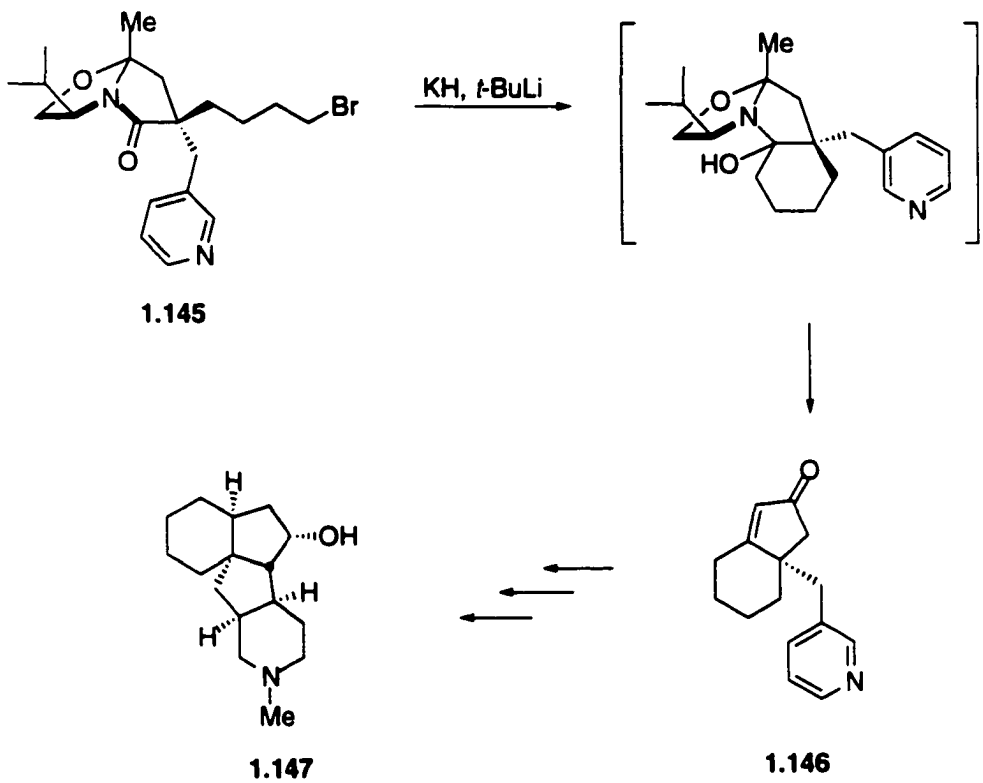


1.144 **1.143**

i. $Bu_4NH_2PO_4$, EtOH; ii. KOH, EtOH

This sequence was employed to construct the tetracyclic carbon skeleton **1.147** of the *Lycopodium* alkaloid Magellanine containing all six required contiguous stereogenic centers.[46] The key transformation in this sequence was the intramolecular addition of the alkyllithium derived from **1.145** to the bicyclic lactam carbonyl to access the appropriately substituted hydrinden-2-one **1.146**. Subsequent synthetic manipulations led ultimately to the tetracyclic system **1.147** (Scheme 1.31).

Scheme 1.31

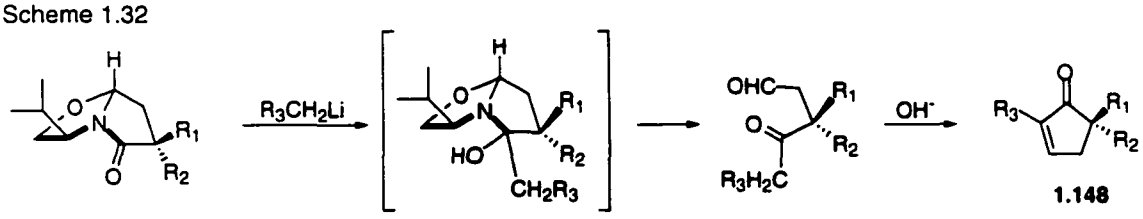


1.145 1.146 1.147

I.6.B. 5,5-Disubstituted 2-cyclopentenones.

In addition to constructing the bicyclic system of hydrindenones, heavily substituted cyclopentenones **1.148** with different substitution patterns were also obtained by addition of alkyl lithiums to the electrophilic carbonyl present in bicyclic lactams (Scheme 1.32).[47] Following hydrolysis and base catalyzed aldol cyclization the trisubstituted cyclopentenones **1.148**, possessing a stereogenic quaternary center, were obtained.

Scheme 1.32

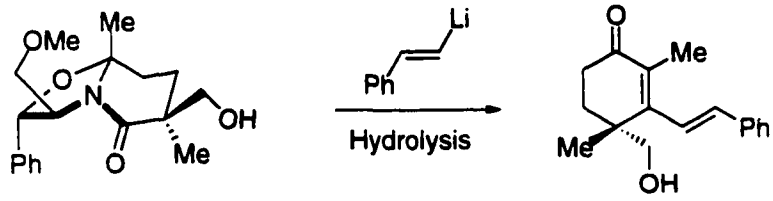


1.148

I.6.C. Addition of Vinyl Anions to Bicyclic Lactams.

Through 1998, all the carbanions that had been added to the bicyclic lactam carbonyl were derived from sp^3 alkyl halides.

Scheme 1.33

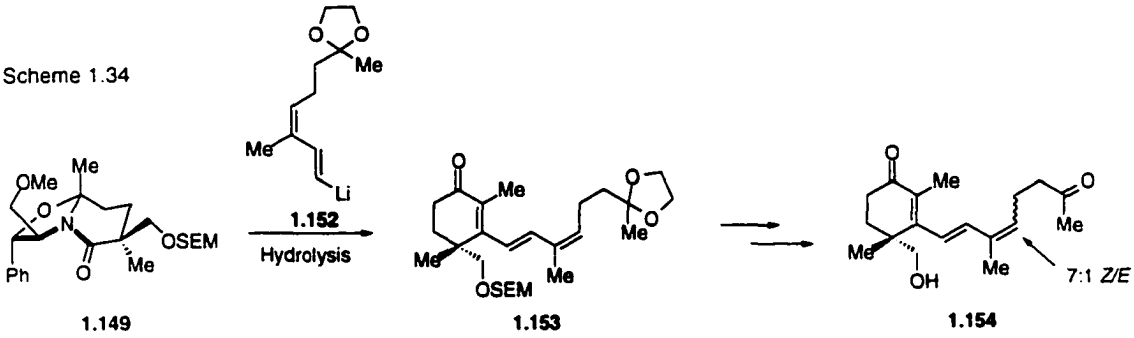


1.149 **1.150**

The addition of sp^2 anions (e.g. from β–bromostyrene) to the α,α-disubstituted bicyclic lactam **1.149** furnished cyclohexenone **1.150** after hydrolysis (Scheme 1.33).

This process was applied toward the highly convergent total synthesis of trisporol B (Scheme 1.34, **1.154**).[48]

Scheme 1.34



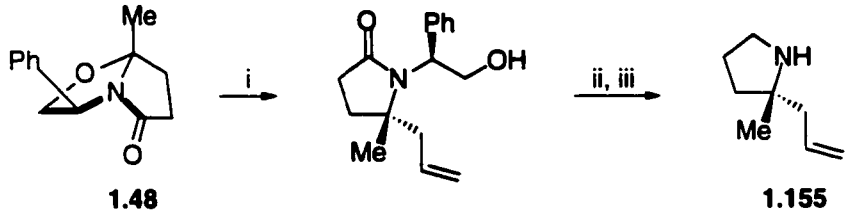
Addition of the vinyl anion **1.152** to the SEM-containing lactam **1.151** afforded the protected trisporol **153** in excellent yield as a single olefin diastereomer. During attempts to remove the protecting group an inseparable mixtures of olefin isomers **1.154** resulted.

I.7. Asymmetric Construction of Alkaloids

I.7.A. Pyrrolidines.

The addition of allylsilane to the angular position in the [3.3.0] bicyclic lactam **1.48** followed by two successive reductions furnished the conversion to a 2,2-disubstituted pyrrolidine **1.155** (Scheme 1.35).[49]

Scheme 1.35

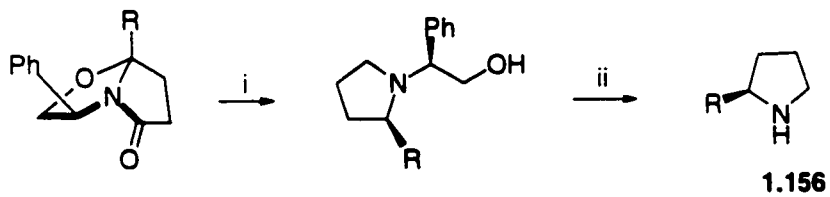


1.48 **1.155**

i. allyltrimethylsilane, $TiCl_4$, CH_2Cl_2; ii. Li, NH_3, EtOH; iii. $LiAlH_4$

This work was followed by the construction of enantiomerically pure 2- and 3-monosubstituted pyrrolidines **1.156** and **1.157** by reduction of angular alkyl or monoalkylated bicyclic lactams respectively (Scheme 1.36).[50]

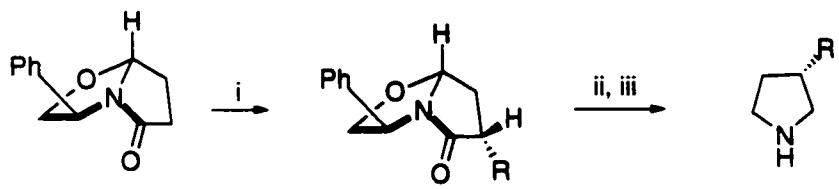
Scheme 1.36



1.156

R = CH_3, Bn, *n*-butyl, Ph,

i. $LiAlH_4$, $AlCl_3$; ii. HCO_2NH_4, Pd / C



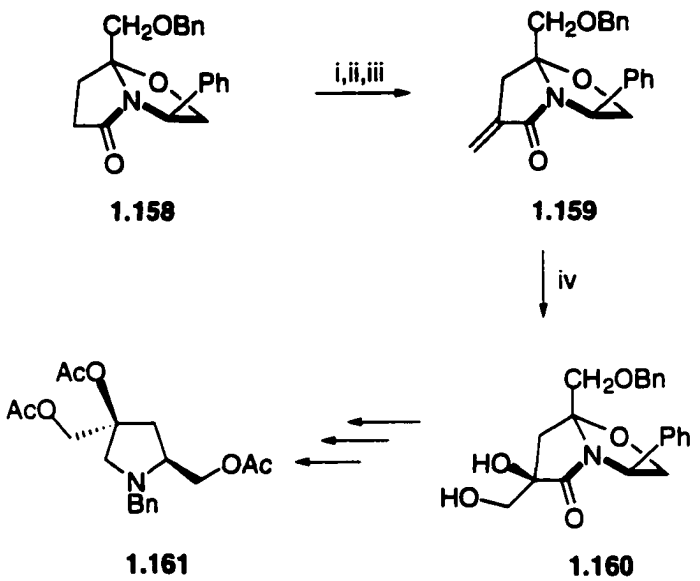
1.157

R = CH_3, Bn

i. LiHMDS, RX; ii. $LiAlH_4$; iii. H_2, Pd / C

Polyhydroxylated pyrrolidines have been implicated in a variety of biologically important processes as a result of their ability to mimic carbohydrates. The [3.3.0] bicyclic lactam was employed as a template from which these optically pure compounds could be constructed (Scheme 1.37). Bicyclic lactam **1.158** was phosphonylated in the α-position followed by condensation with formaldehyde to afford the α-methylene derivative, **1.159**. Treatment of the latter with osmium tetroxide gave the vicinal diol **1.160** as a 7:1 diastereomeric mixture which was reductively cleaved. Protection of the resulting triol **1.160** as the peracetate furnished pyrrolidine **1.161** in excellent overall yield. It appears that the rigid [3.3.0] bicyclic lactam template possessed sufficient diastereoselective bias in the approach of the osmium to the *exo* methylene to afford the selectivity observed.[51]

Scheme 1.37



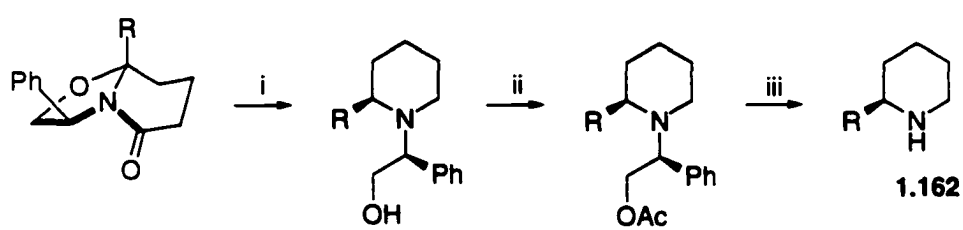
1.158 **1.159** **1.161** **1.160**

i. LDA, $ClP(OEt)_2$; ii. air; iii. NaH, $(CH_2O)_n$; iv. OsO_4

I.7.B. Piperidines.

The above route to asymmetric pyrrolidines was extended to the piperidine series by use of the [4.3.0] bicyclic lactam, offering a general and efficient route to a variety of piperidine deriviatives **1.162** (Scheme 1.38).[52]

Scheme 1.38



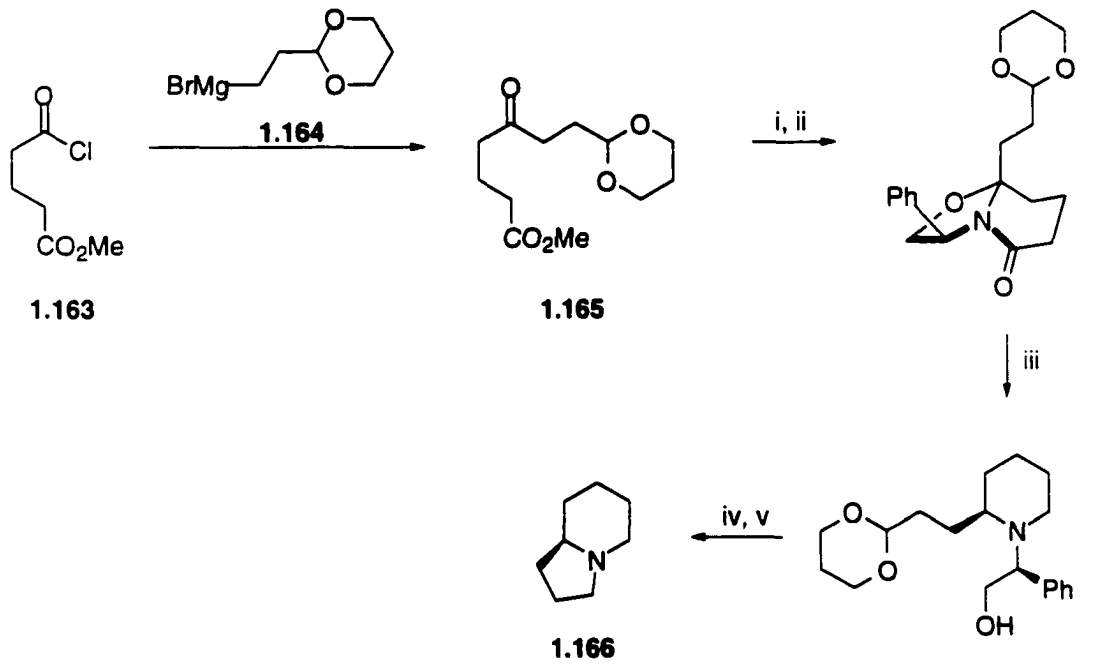
1.162

R = Me, *n*-Pr

i. Red-Al, THF, Δ; ii. Ac_2O, DMAP, CH_2Cl_2; iii. $Pd(OH)_2$ / H_2

In order to make this route more general, an efficient procedure for constructing a variety of keto acids was developed. Thus, treatment of the commercially available acid chloride **1.163** with Grignard reagent **1.164** gave the desired keto acids (e.g. **1.165**). (-)-Coniceine **1.166**[52] was synthesized in three steps using this methodology which further demonstrated the synthetic utility of the appropriatedly substituted bicyclic lactam in alkaloid synthesis (Scheme 1.39).

Scheme 1.39

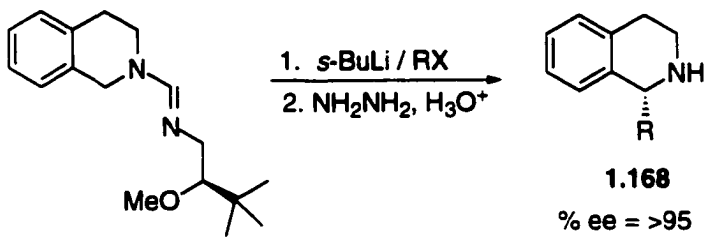


i. KOH; ii. (S)-phenylglycinol; iii. Red-Al; iv. HCl, THF, Δ; v. Pd / C, H_2

I.7.C. Tetrahydroisoquinolines.

The chiral bicyclic lactam and its reductive cleavage to *N*-heterocycles was also applied to the efficient construction of tetrahydroisoquinoline alkaloids **1.168** (Scheme 1.40).[53] Tetrahydroisoquinoline alkaloids **1.168** had previously been synthesized in these laboratories enantiomerically pure form using the formamidine **1.167**[54] as a directing group for the diastereoselective alkylation of a tetrahydroisoquinoline.

Scheme 1.40



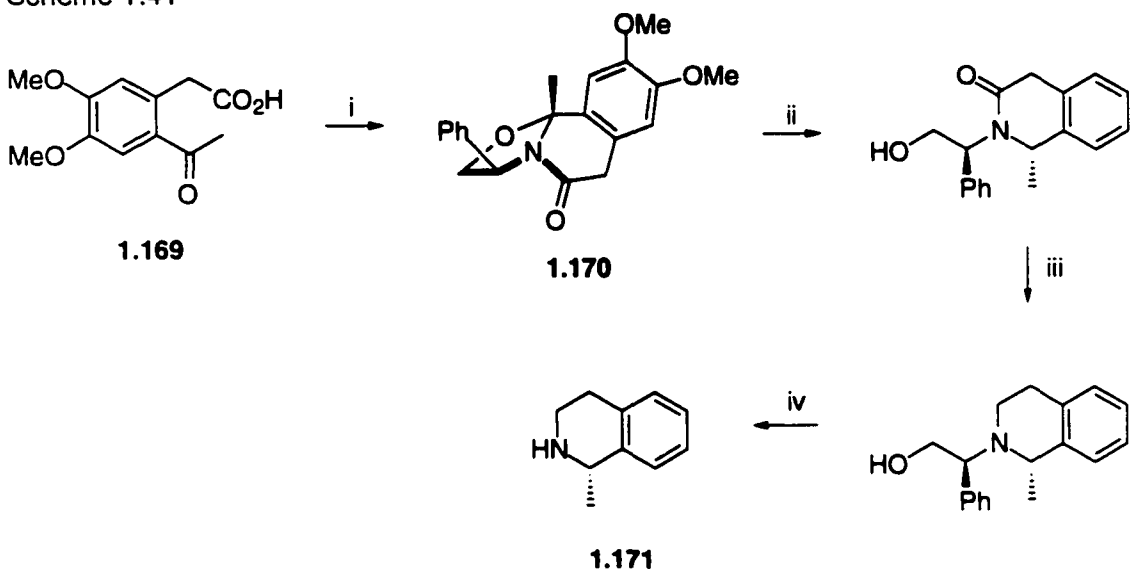
1.167

1.168

% ee = >95

Similarly substituted tetrahydroisoquinolines were also obtained using the appropriately benzo-fused bicylic lactams **1.170**, following the reduction protocol previously described for the piperidine formation. The simple *ortho*-acyl phenylacetic acid **1.169** was condensed with phenylglycinol and reduced to give (-)-salsolidine **1.171**[55] in three steps with high selecitivity (Scheme 1.41).

Scheme 1.41

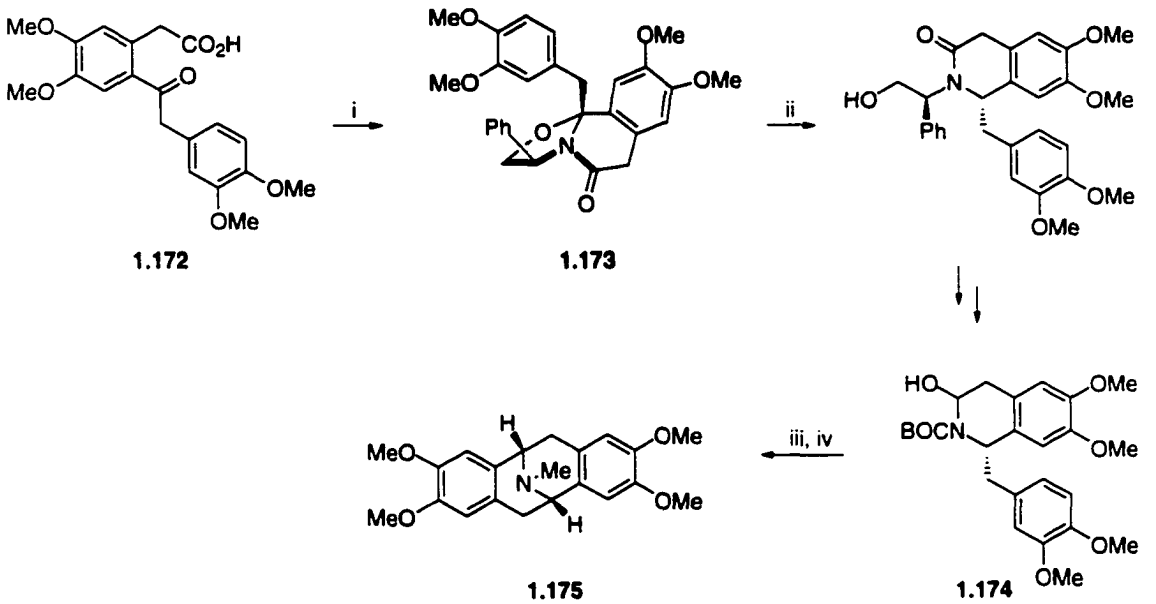


1.169 1.170 1.171

i. (S)-phenylglycinol; ii. Red-Al; iii. $LiAlH_4$; iv. Pd / C, H_2

This sequence was further employed in the asymmetric synthesis of 1,3-disubstituted tetrahydroisoquinolines and the first asymmetric route of (-)-argemonine **1.175** (Scheme 1.42).[56] The key transformation exhibited by the diastereoselective intramolecular Pictet-Spengler cyclization of the carbinolamine **1.174**.

Scheme 1.42



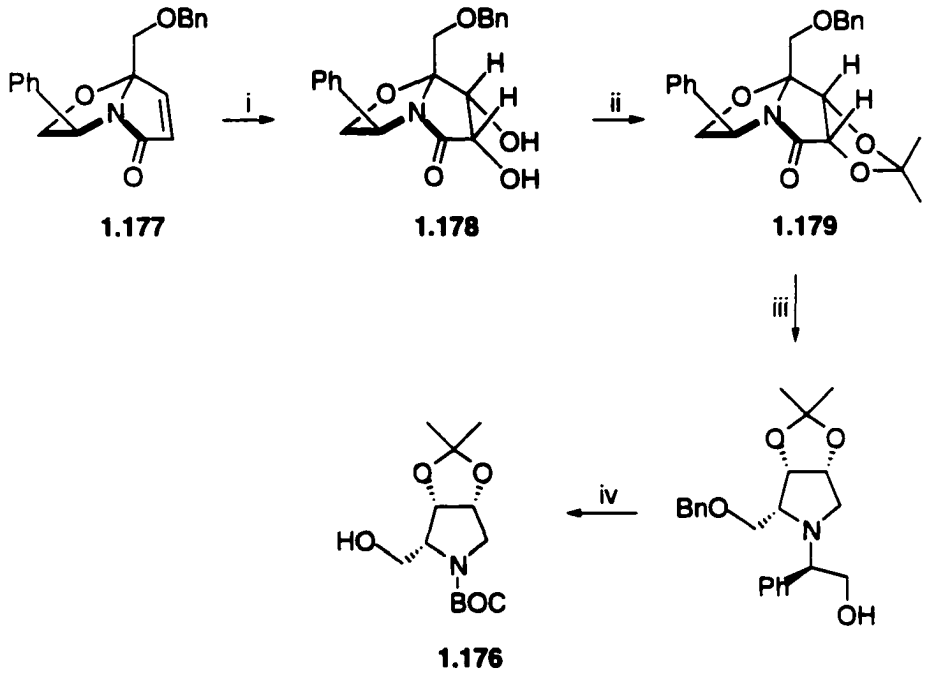
1.172 1.173 1.174 1.175

i. (*S*)-phenylglycinol; ii. Red-Al; iii. TBSOTf, CH_2Cl_2; iv. H_2CO, $NaBH_4$

I.7.D. Azasugars.

Azasugars, an important class of biologically active targets, have also been synthesized in a rapid and efficient manner by using the bicyclic lactam template.[57] These laboratories first investigated the use of the [3.3.0] bicyclic lactam in the formal synthesis of 1,4-dideoxy-1-4-imino-D-lyxitol **1.176** (Scheme 1.43).[58] Dihydroxylation of the α,β-unsaturated bicyclic lactam **1.177** produced the diol **1.178** as a 7:1 mixture of diastereomers. This was protected as its acetonide **1.179** to provide an additional "steric control element", which aided in the stereoselective reduction of the angular position. This general method afforded nonracemic azasugars from non-sugar starting materials, offering the ability to construct a wide variety of structural derivatives.

Scheme 1.43



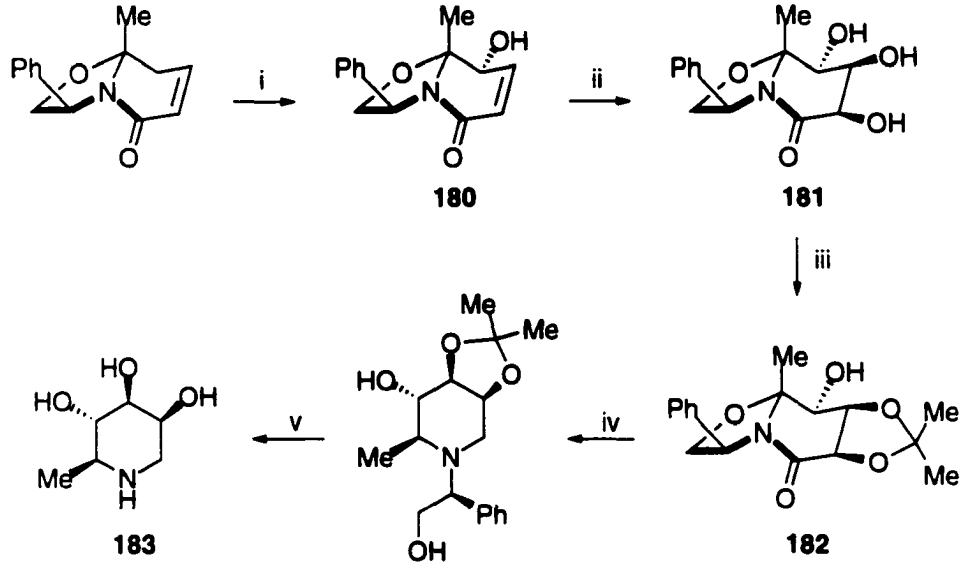
1.177 **1.178** **1.179** **1.176**

i. NMO, cat. OsO_4; ii. dimethoxypropane; iii. 9-BBN; iv. H_2 / BOC_2O, $Pd(OH)_2$

A similar approach was also taken to achieve the synthesis of L-*rhamno*-1-deoxynojirimycin **1.183** (Scheme 1.44), as well as other piperidine based derivatives.[59] Oxidation of the α,β-unsaturated lactam with selenium dioxide surprisingly furnished the allylic alcohol **1.180** as a single diastereomer. The angular alkyl group present in the lactam appears to have been responsible for this strong steric effect, which directed the oxidation in an *anti* fashion. Once the allylic hydroxyl was in place, the subsequent dihydroxylation to **1.181** occured with complete stereocontrol. This observation, previously discussed by Kishi,[60]

wherein the oxidation proceeds anti to an allylic hydroxyl group appears to be due to the donation of electrons from the C-O σ bond to the π* of the olefin.

Scheme 1.44



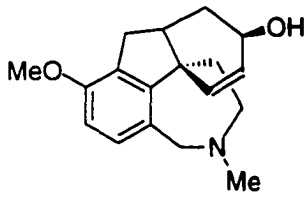
i. SeO_2, dioxane; ii. OsO_4 / NMO; iii. $(CH_3)_2C(OMe)_2$, CH_2Cl_2, pTSA; iv. BH_3•THF; v. H_2 / Pd, MeOH, then TFA

I.7.E. Chiral Non-Racemic [5.3.0] Bicyclic Lactams. Synthesis of Perhydro- and Benzo-fused Azepines.

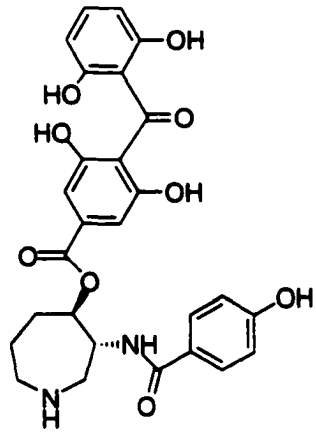
Azepines are constituents in a variety of compounds with interesting pharmacological properties,[61] i.e. galanthamine[62] **1.184**(analgesic properties), cephalotaxane[63] **1.186** (antileukemia) and balanol[64] **1.185** (protein kinase C inhibitor) (Figure 1.16). Construction of a [5.3.0] bicyclic lactam presented a reasonable template for the synthesis of this important class of alkaloids. The

two effective routes developed to access these bicyclic lactams were the usual cyclodehydration of a keto-acid containing a conformational constraint in its backbone or *via* ring closing metathesis[65] of the appropriately substituted *N*-acyl oxazolidine.

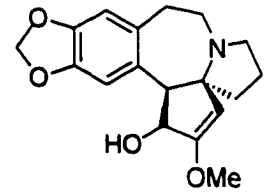
Figure 1.16



1.184



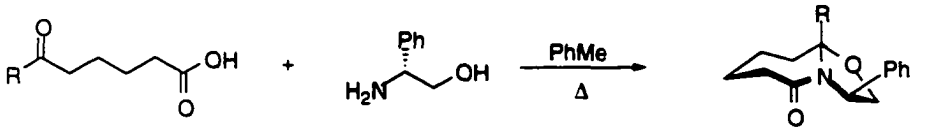
1.185



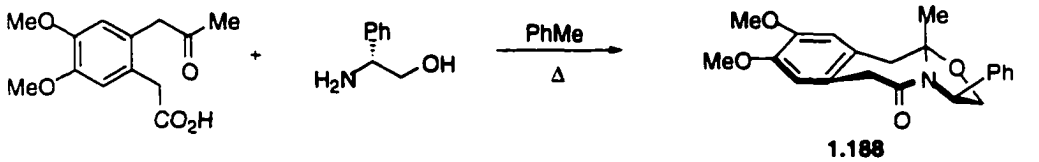
1.186

Unfortunately, cyclodehydration afforded the angular methyl **1.187a**, ethyl **1.187b** and benzofused **1.188** [5.3.0] bicyclic lactams in low diastereoselectivity (Scheme 1.45). These lactams (after separation *via* chromatography) were stereoselectively reduced to furnish 2-substituted perhydroazepines (**1.190**, **1.191**) with good enantiomeric excess (84-94%).[66] The rationale for the high selectivity was similar to that in past reductions of the [4.3.0] and [3.3.0] bicyclic lactam systems.[55] Thus, coordination of aluminum to the oxazolidine oxygen with concomitant delivery of the hydride to the *N,O*-acetal, furnished the monocyclic azepine **1.189** with retention of stereochemistry (Scheme 1.46).

Scheme 1.45

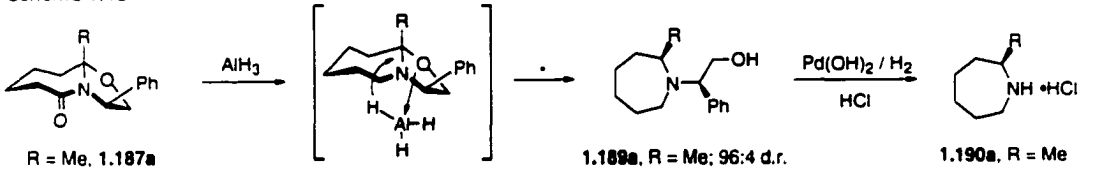


1.187a, R = Me; 40%, 2:1 d.r.
1.187b, R = Et; 40%, 2: 1 d.r.



1.188
65-87%, 1.5:1 d.r.

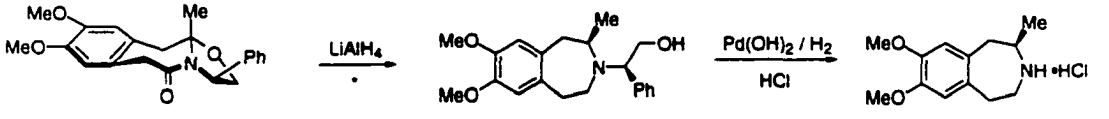
Scheme 1.46



R = Me, **1.187a**
R = Et, **1.187b**

1.189a, R = Me; 96:4 d.r.
1.189b, R = Et; 92:8 d.r.

1.190a, R = Me
1.190b, R = Et



1.188

95:5 d.r.

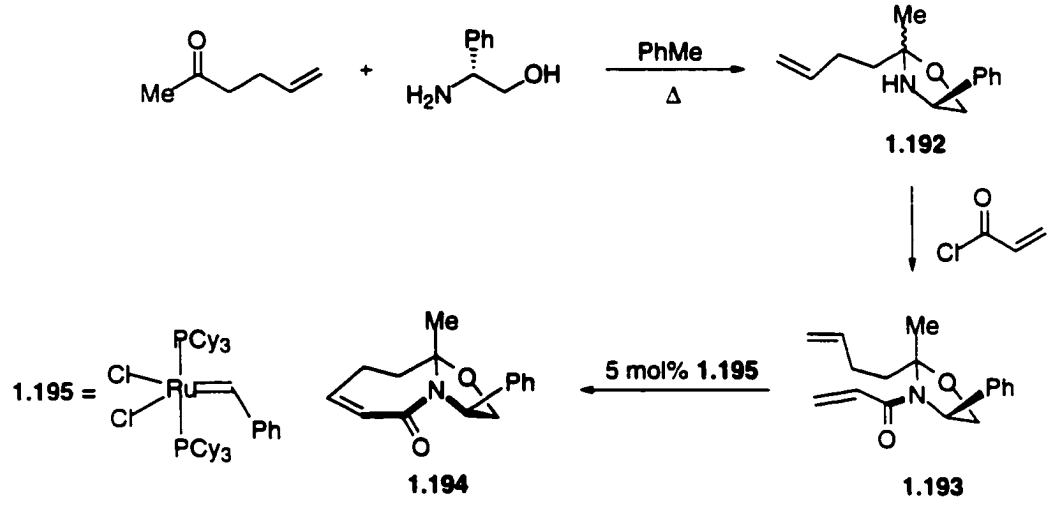
1.191

* = Proceeds with retention

The ring closing metathesis process was employed to access the α,β-unsaturated [5.3.0] bicyclic lactam **1.194** (Scheme 1.47).[66b] Routine formation of the oxazolidine ring **1.192** was followed by acylation and separation of the 3:1

diastereomeric mixture of acrylamides **1.193**. Ring closing metathesis and reduction of **1.194** then gave the desired bicyclic lactam **1.187a** in good overall yield (>50% yield).

Scheme 1.47

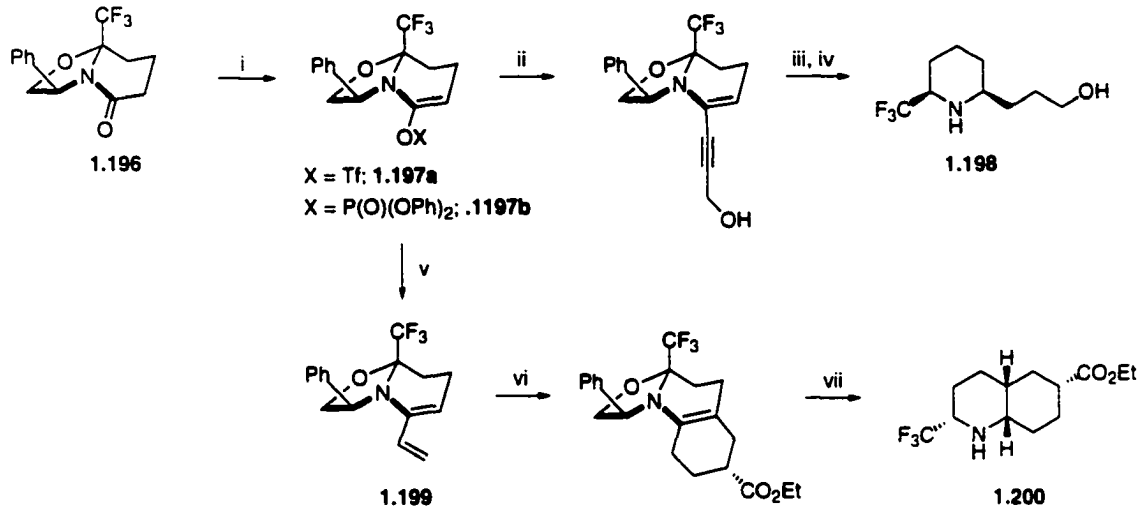


I.7.F. Triflurомethyl-Substituted Piperidines and Decahydroquinolines.

The incorporation of the trifluoromethyl group in the bicyclic lactam system imparts dramatic effects on subsequent chemical transformations.[67] Contrary to the chemistry performed on the perhydro-lactam, the enolate of the trifluoromethyl substituted bicyclic lactam was trapped with the Commins reagent[68] to afford the vinyl triflate **1.197a** (Scheme 1.48). A variety of transition metal catalyzed reactions were reported to occur with this substrate to give triflurомethyl substituted piperidines **1.198**.[69] Conversion of the vinyl phosphate

1.197b to the diene **1.199** was followed by Diels-Alder cycloaddition to give decahydroquinolines **1.200**.

Scheme 1.48



i. **1.197a**: KHMDS, N-(5-chloro-2-pyridinyl)triflimide; **1.197b**: KHMDS, $(PhO)_2P(O)Cl$;
ii. propargyl alcohol, $PdCl_2(PPh_3)_2$, CuI; iii. PtO_2 / H_2, toluene; iv. $Pd(OH)_2$ / H_2, EtOH;
v. tributyl(vinyl)tin, LiCl, $Pd(PPh_3)_4$; vi. ethylacrylate; vii. $Pd(OH)_2$ / H_2, EtOH

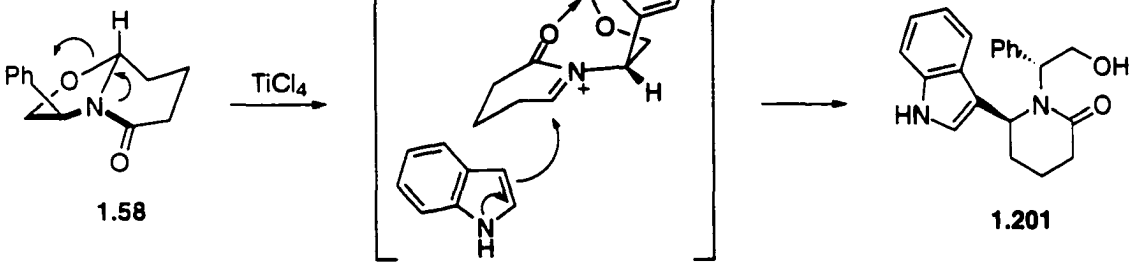
I.8. Additions to *N*-Acyliminium Ions.

I.8.A. Friedel-Crafts Additions.

The *N,O*-acetal carbon of the bicyclic lactam can function as an electrophilic center upon treatment with a strong Lewis acid. The electrophilic nature of this carbon was exploited by addition of various nucleophiles. For example, when bicyclic lactam **1.58** was treated with an equivalent of titanium tetrachloride in the presence of indole, 6-indoyl-2-piperidones **1.201** were

formed.[70] The stereochemical rationale was based upon a chelation control model as illustrated in **1.202** (Scheme 1.49).

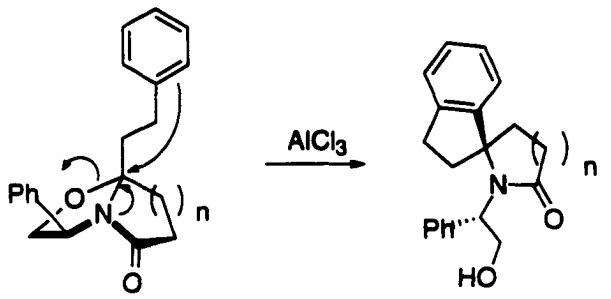
Scheme 1.49



1.58 **1.202** **1.201**

An intramolecular variant of this Mannich-type reaction has also been performed. An aryl group tethered to the angular position reacted in the presence of a Lewis acid to afford spiro pyrrolidinones and piperidones **1.203** (Scheme 1.50).[71]

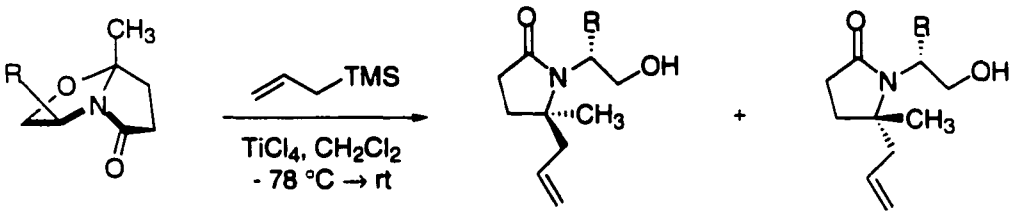
Scheme 1.50



n = 1, 2 **1.203**

I.8.B. Allysilanes.

Most of the work regarding additions to an *N*-acyl iminium ion have been focused on the additions of allylsilanes (Table 1.9). These additions to a bicyclic lactam disclosed an interesting stereochemical trend.[49a] The stereochemistry of the Lewis-acid mediated allylsilane alkylation could be controlled by changing the nature of the auxiliary group from small (methyl) to large (*tert*-butyl).



1.204a-d **1.205a** (retention) **1.205b** (inversion)

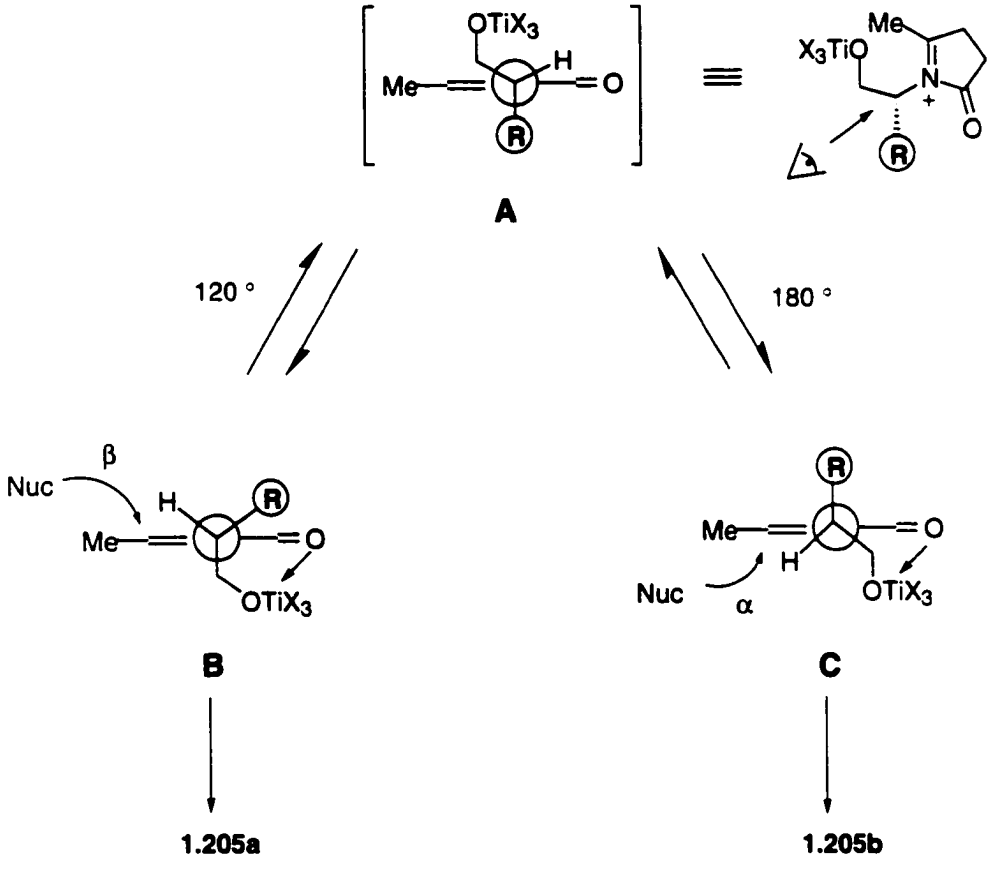
Table 1.9. Allylsilane Additions to 1.204a-d.

1.204	R	d.r (1.205a: 1.205b)
a	methyl	8:1
b	phenyl	5:1
c	*iso*-propyl	1:2
d	*tert*-butyl	1:11

An explanation was proposed for the stereochemical outcome observed for **1.205a/1.205b** (Scheme 1.51). A model was based upon a combination of the Felkin-Ahn model, allylic 1,3-strain and chelation effects. The initially formed

N-acyliminium ion **A**, is capable of bond rotation. Allylic 1,3-strain would force a rotation to either 120 or 180° to minimize conjestion around the olefinic center. From the model of Felkin-Ahn ,**C**, entry by the allylsilane would occur from the face opposite the large group to generate the product (α-entry) of inversion **1.205b**.

Scheme 1.51

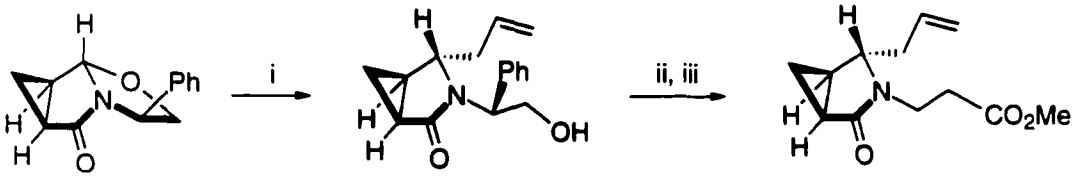


Alternatively, the alkoxytitanium moiety assumes the role of the large group, occupies the gauche position (**B**), thus directing a β-entry to generate the product of retention **1.205a**. Finally, and perhaps of equal significance, the existance of a

seven-membered-ring chelate in **B** and **C** derived from the alkoxytitanium and the carbonyl oxygen could impart added preference for either outcome.

This process of reductive ring cleavage was utilized in the asymmetric construction of the bicyclic precursor to (-)-indolizomycin **1.207** (Scheme 1.52).[72] The key transformation was the addition of allyltrimethylsilane to the cyclopropyl lactam **1.206** which occurred with complete stereocontrol at the reacting center.

Scheme 1.52

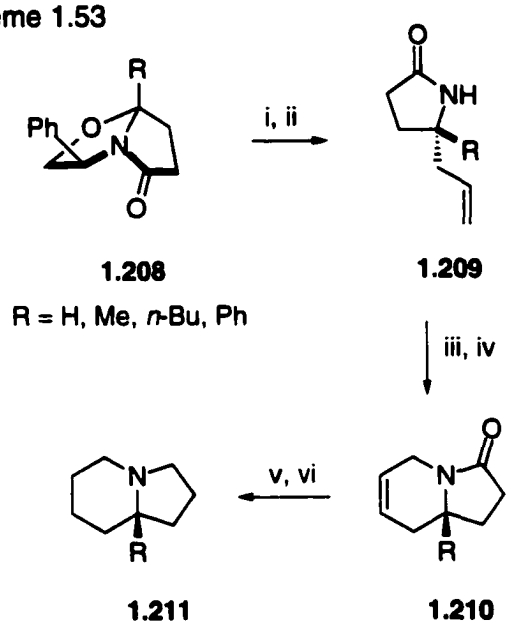


1.206 (+)-**1.207**

i. allyltrimethylsilane, $TiCl_4$; ii. Ca / NH_3; iii. KH, 3-bromo methyl propionate

A general route to indolizidines was developed from this methodology and applied to the synthesis of (-)-coniceine **1.211** (Scheme 1.53).[73] Allyltrimethylsilane was added to a variety of bicyclic lactams **1.208** in the presence of Lewis acids. Reductive cleavage of the benzylic carbon-nitrogen bond gave the 5-allyl pyrrolidinone **1.209**. Addition of allylbromide to the amide nitrogen followed by ring closing metathesis furnished the 1-azabicyclo[4.3.0]nonenones **1.210**. Reduction of the amide carbonyl and double bond yielded the indolizidines **1.211** in an efficient manner.

Scheme 1.53



1.208

R = H, Me, *n*-Bu, Ph

1.209

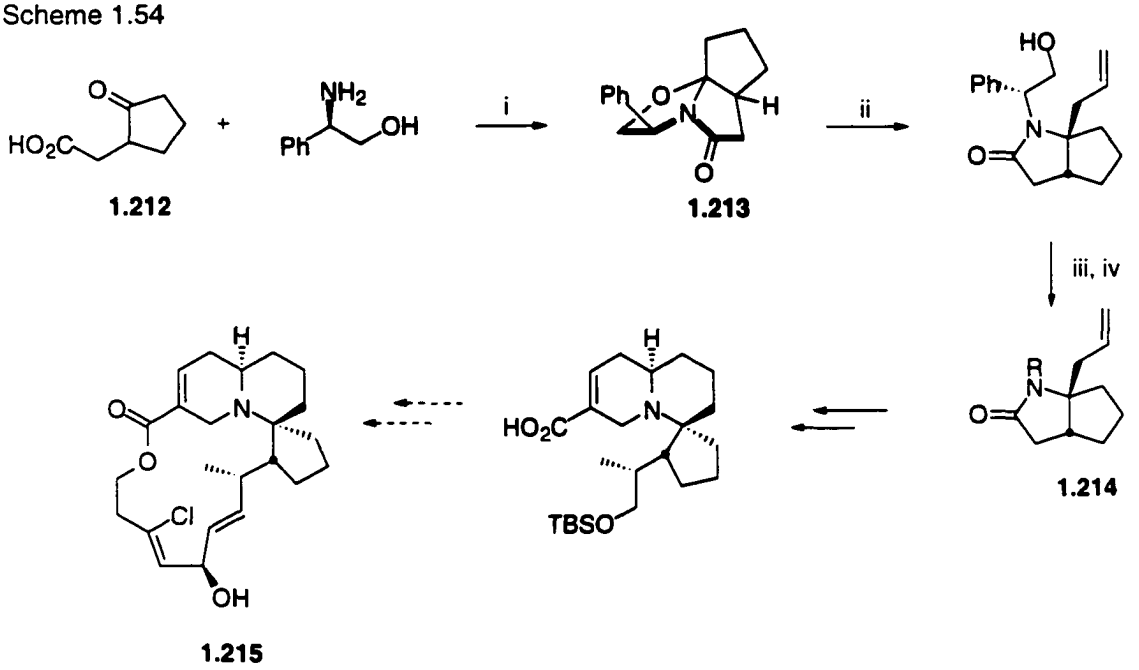
1.211

1.210

i. allyltrimethylsilane, $TiCl_4$; ii. Ca / NH_3; iii. NaH / allylbromide
iv. $(PCy_3)RuCl_2(CHPh)$ 10 mol%.; v. H_2 / $Pd(OH)_2$; vi. $LiAlH_4$

Danishefsky[74] employed this method in his asymmetric construction of spiroquinolizidine subunit **1.215** of halichlorine (Scheme 1.54). Condensation of the keto acid **1.212** with (-)-phenylglycinol followed by Lewis acid mediated addition of allyltrimethylsilane and reductive removal of the auxiliary gave the pyrrolidinone **1.214**, which was converted to **1.215** after a number of synthetic steps.

Scheme 1.54

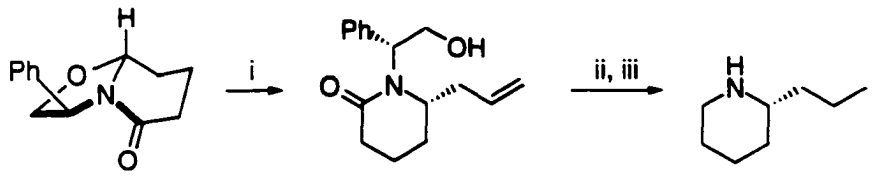


1.212 1.213 1.214 1.215

i. PhMe, Δ; ii. allyltrimethylsilane, $TiCl_4$; iii. (R = H) Na, NH_3; iv. Boc_2O, DMAP.

Using the [4.3.0] bicyclic lactam, a similar sequence was utilized to construct the piperidine alkaloid (-)-coniine.[75] Addition of allyltrimethylsilane to the [4.3.0] bicyclic lactam **1.58** afforded a >9:1 mixture of diastereomeric 6-allyl piperidone **1.216**. The mixture was separated and ultimately converted to *R*-(-)-coniine **1.217** (Scheme 1.55).

Scheme 1.55

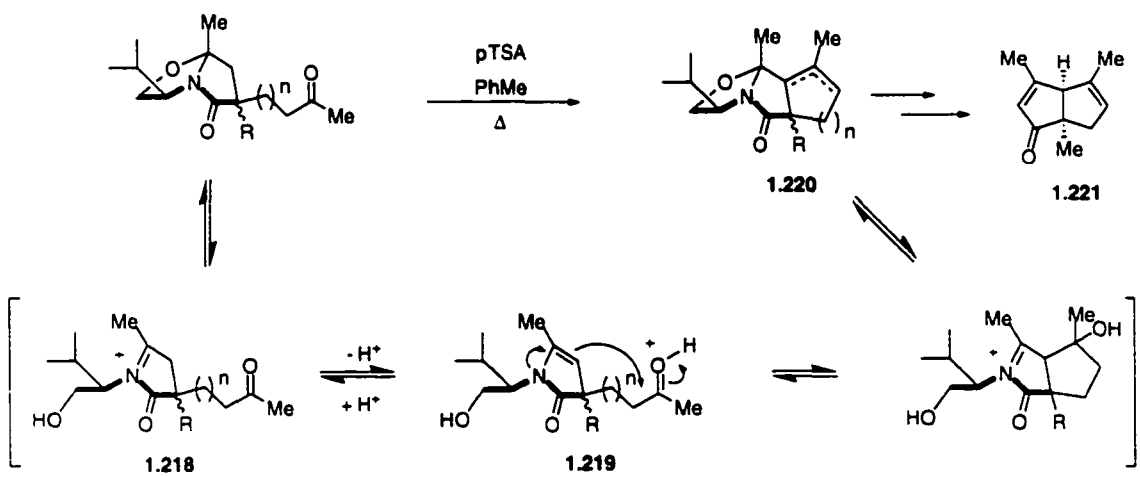


1.58 1.216 *R*-(-)-1.217

i. allyltrimethylsilane, $TiCl_4$; ii. $LiAlH_4$; iii. H_2 / Pd-C

Another pathway was uncovered which appeared to proceed through equilibration of the acyliminium ion **1.218** with the acyl-enamide **1.219** (Scheme 1.56).[76] This novel process was responsible for cyclization to the tricylic lactam **1.220** which was converted to the bicyclic [3.3.0] octenone **1.221**.

Scheme 1.56



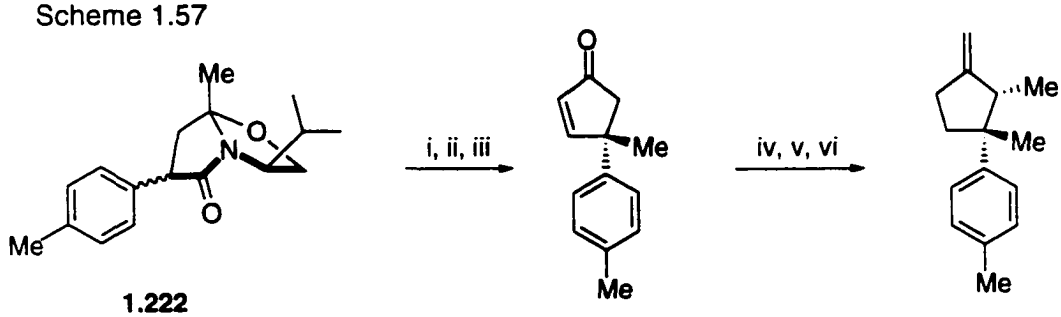
I.9. Syntheses of Complex Chiral Non-Racemic Compounds.

I.9.A. Laurene.

The bicyclic lactam system has been employed to construct (+)-laurene **1.224**[77] which possesses the difficultly accessible vicinal tertiary and quaternary centers (Scheme 1.57). The inconsequential mixture of α-aryl bicyclic lactams **1.222** was alkylated in >95:5 (*endo:exo*) diastereomeric ratio and converted to the optically pure cyclopentenone **1.223**. The latter was alkylated with methyl iodide to afford an epimeric mixture(8:1) at the tertiary stereogenic center.

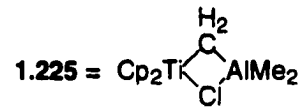
Methylenation of the carbonyl using Tebbe's reagent **1.225** gave laurene with no erosion of the 8:1 epimeric mixture of **2.224**.

Scheme 1.57



1.222 **1.223** **1.224**

i. LDA, MeI; ii. Red-Al; iii. $Bu_4NH_2PO_4$, followed by KOH;
iv. LDA, MeI; v. H_2, Pd / C; vi. **1.225**

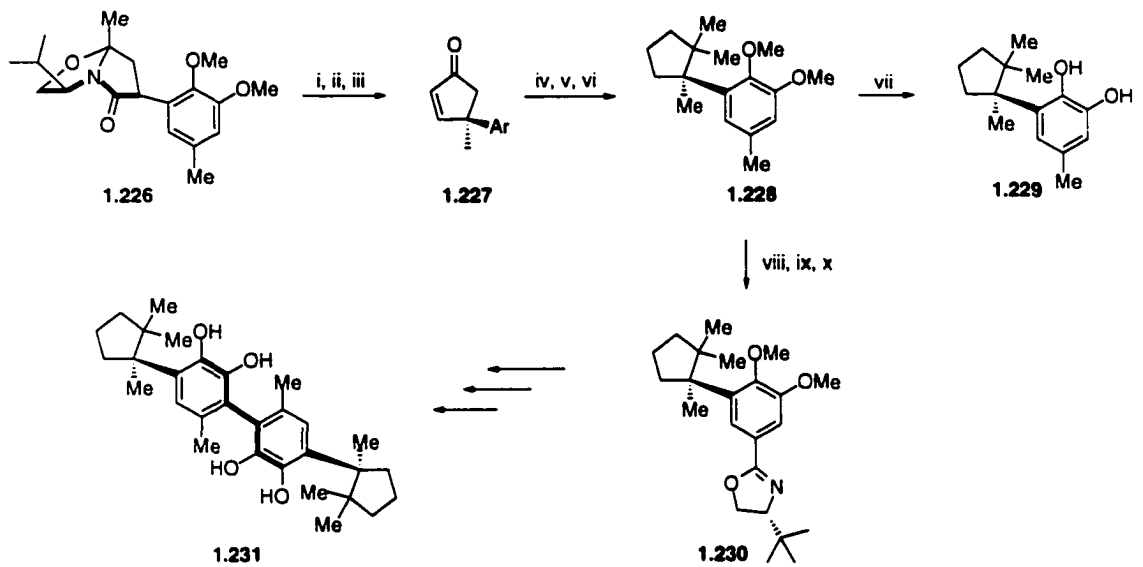


I.9.B. (-)-Herbertenediol and (-)-Mastigophorene A and B.

A similar alkylation strategy as described above was used to construct the cyclopentane natural product herbertenediol **1.229** and its two dimeric atropisomers mastigophorenes A and B **1.231** (Scheme 1.58).[78] The featured step in this transformation was the construction of a quaternary stereogenic center with complete sterecontrol. Alkylation of the mixture of α-aryl bicylic lactams **1.226** afforded the single quaternary stereocenter in the cyclopentane core **1.227** after reduction and hydrolytic cleavage. The cyclopentane was subsequently converted to cyclopentane **1.228** containing the required vicinal

quaternary centers. Methoxyl cleavage led to herbertenediol **1.229**, whereas transformation of **1.228** to the aryl-oxazoline **1.230** led to each of the atropisomers of **1.231** after asymmetric aryl-aryl coupling.[79]

Scheme 1.58

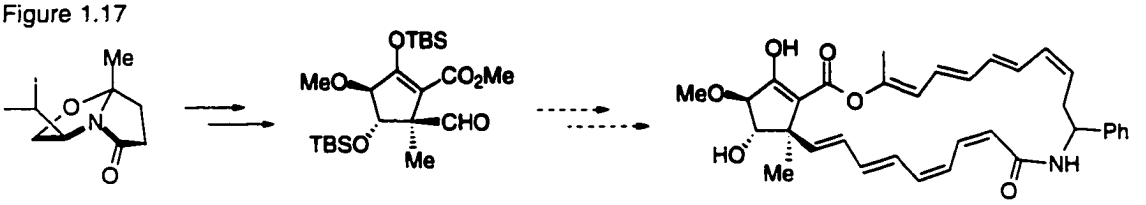


i. LDA, MeI; *ii.* Red-Al; *iii.* a. NaH_2PO_4, b. NaOH; iv. NaH, MeI; v. $(ArPS_2)_2$; vi. Raney Ni, H_2; vii. BBr_3; viii. Br_2, CH_2Cl_2; ix. $Co(OAc)_2$, O_2; x. a. $(COCl)_2$, b. *tert*-leucinol, c. $SOCl_2$, d. K_2CO_3

I.9.C. The Core Cyclopentane of Viridenomycin.

Continued efforts to apply the bicyclic lactam template to the construction of optically pure carbocycles and heterocycles opened a route to the highly oxygenated cyclopentane core (**1.232**) of viridenomycin **1.233** (Figure 1.17).[80]

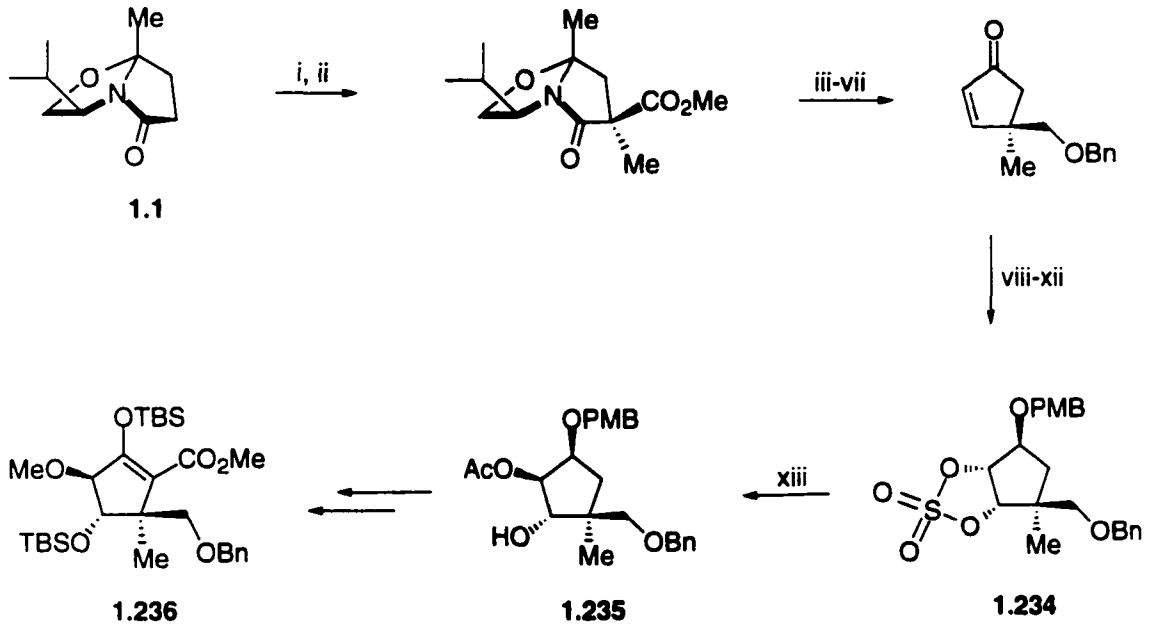
Figure 1.17



1.1 **1.232** **1.233**

The cyclopentenone equivalent **1.232** was reached by alkylation of the [3.3.0] bicyclic lactam **1.1** with methyl iodide followed by acylation with methylchloroformate (Scheme 1.59). Interestingly, the *acylation* proceeded with *complete exo selectivity*. This trend of sp^2 hybridized electrophiles approaching the enolate of **1.1** with high *exo*-selectivity has been observed in other systems.[48] The origin of this reversal in diastereofacial selectivity remains an unanswered question although initial *O*-acylation should be considered. The introduction of the *trans* diol moiety in the cyclopentenone, was accomplished by formation of the cyclic sulfate **1.234** followed by opening with cesium acetate. This afforded the *trans* diol **1.235** which was then converted to the cyclopentene derivative **1.236**, a close, useful precursor to **1.232**.

Scheme 1.59



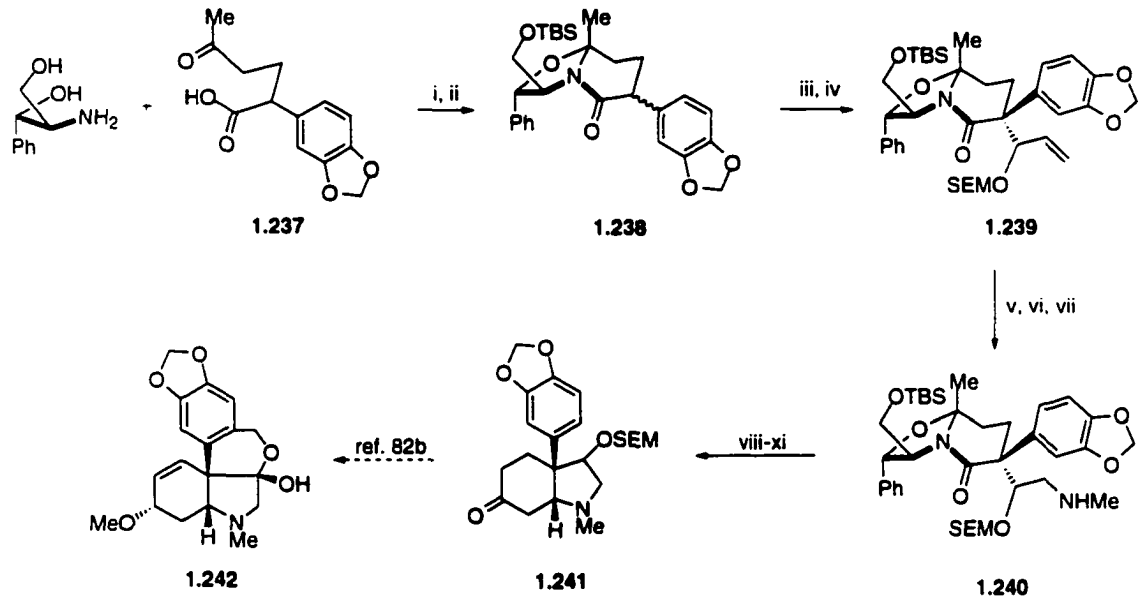
i. LDA, MeI; ii. LDA, $ClCO_2Me$; iii. $NaBH_4$; iv. NaH, BnCl; v. Red-Al;
vi. $NBu_4H_2PO_4$; vii. KOH, THF;viii. DIBALH; ix. KH, PMBCl;
x. $K_2OsO_4 \cdot H_2O$, NMO; xi. $SOCl_2$, Et_3N; xii. $RuCl_3 \cdot H_2O$, $NaIO_4$; xiii. a. CsOAc, b. H_2SO_4

I.9.D. The Hydroindolone Core of Amaryllidaceae Alkaloids.

Using similar sequences as those employed in the synthesis of mesembine,[81] the core (**1.241**) of the amaryllidaceae alkaloids was constructed (Scheme 1.60).[82] The requisite keto acid **1.237** was condensed with the amino propanediol to afford a mixture of diastereomers of the [4.3.0] bicyclic lactams **1.238**. Alkylation with acrolein and protection yielded **1.239** as a single diastereomer at the α-position (1:1 mixture at the allylic center). Lemieux-Johnson[83] oxidation, followed by reductive amination, afforded the protected

amino alcohol **1.240** which was converted to the hydroindolone **1.241**, the latter of which, is known to furnish the amaryllidaceae alkaloids.[82b]

Scheme 1.60



1.237 **1.238** **1.239** **1.240** **1.241** **1.242**

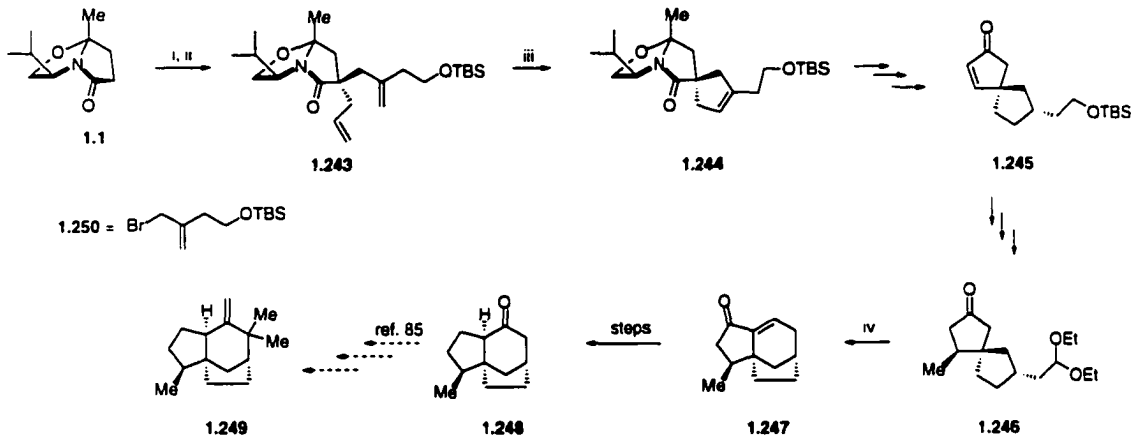
i. PhMe, Δ; ii. TBSCl, imid.; iii. LDA, acrolein; iv. SEMCl, $^{i}Pr_2NEt$; v. OsO_4 (cat), NMO; vi. $NaIO_4$; vii. $MeNH_2$, $NaCNBH_3$; viii. TBAF; ix. RedAl; x. $Bu_4NH_2PO_4$; xi. NaOH.

I.9.E. Zizaene.

The simple bicyclic lactam **1.1** was utilized along with the ring closing metathesis reaction to access the core of the tricyclic sesquiterpene zizaene, **1.249** (Scheme 1.61).[84] Sequential alkylation of **1.1** furnished the bis-olefin **1.243** which was subjected to the ring closing metathesis conditions yielding the spiro product **1.244**. Reduction of the olefin was followed by the reduction/hydrolysis/aldol sequence to give the spirocyclopentenone **1.245**. Cyclopentane **1.246** was subjected to acid catalyzed intramolecular aldol

conditions to afford the tricyclic core of zizaene **1.247**. Transposition of the carbonyl intercepted the advanced intermediate **1.248** reported by Coates' [85] in the racemic synthesis of zizaene.

Scheme 1.61



i. LDA ,1. 250; ii. LDA, allylbromide; iii. Grubbs' cat. (5 mol%); iv.TsOH.

I.10. Summary

The chiral non-racemic bicyclic lactam has proven to be an exceptionally versatile chiral template for the asymmetric construction of a variety of optically pure compounds. Those lactams derived from keto acids have been applied to the synthesis of a host of natural products and pharmacologically interesting heterocycles and carbocycles. A variety of mechanistic questions regarding facial stereocontrol have been investigated using the chiral template as the key probe. However, further elucidation of the subtle mechanistic principles involved await further study.

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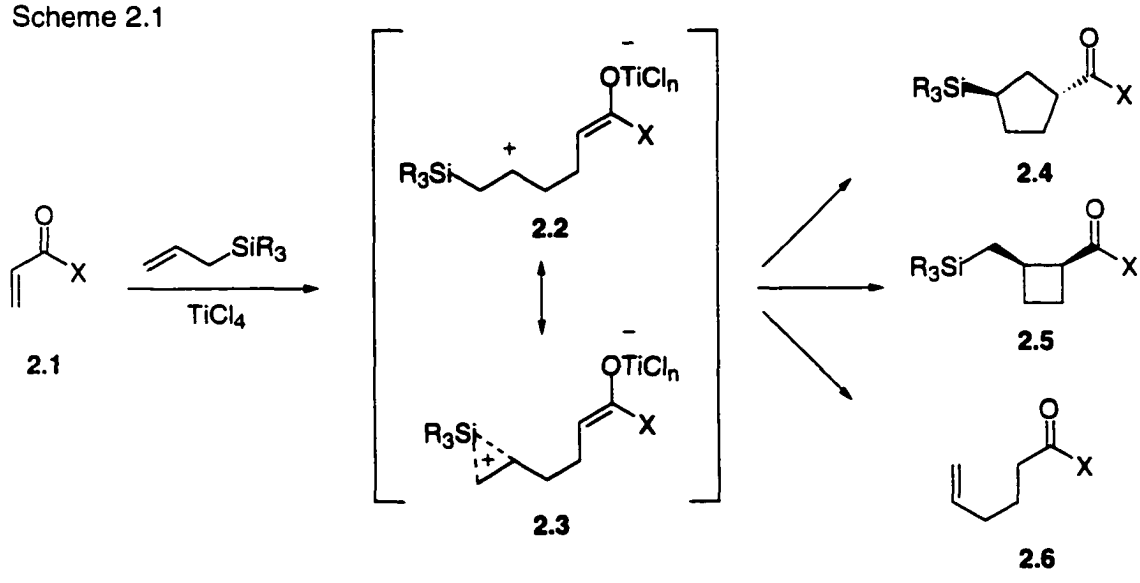
CHAPTER II. ALLYLSILANES. SYNTHESIS OF ENANTIOPURE HETEROCYCLES.

II.1. Background and Significance

The use of allylsilanes in organic synthesis has enjoyed a long history with many advances highlighting the versatility of this reagent (Scheme 2.1).[1,2,3] Sakurai and Hosomi[4] took advantage of the increased nucleophilicity[5] of allylsilanes by utilizing them in Lewis acid-mediated conjugate additions to α,β-unsaturated enone systems as an alternative to organocuprate additions.

Scheme 2.1

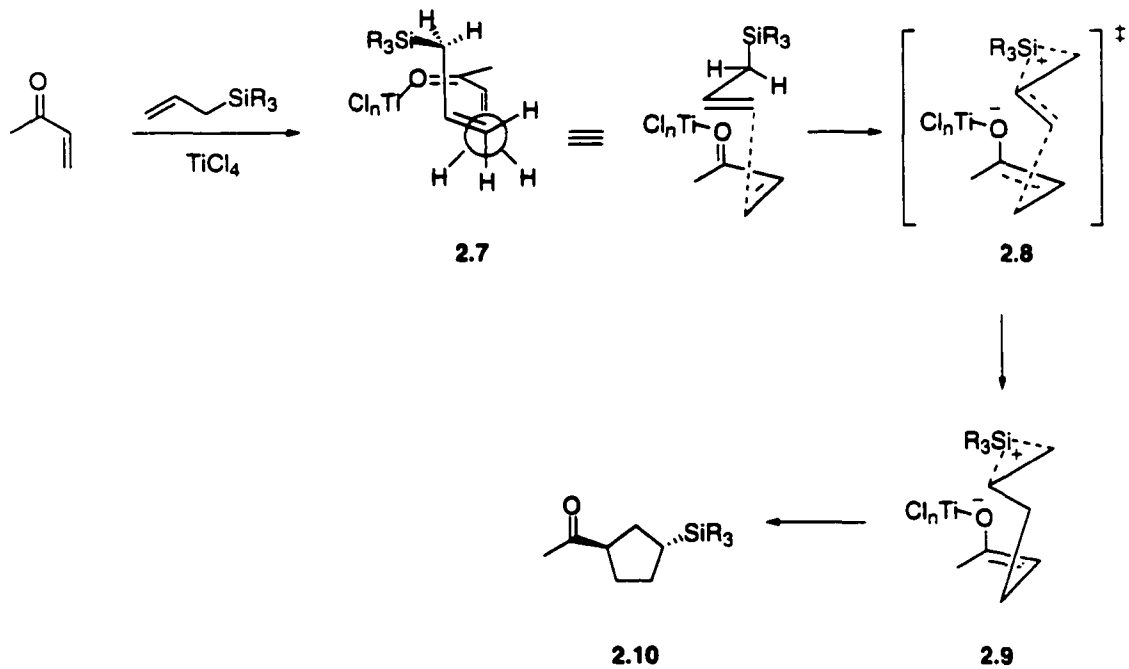


Nearly 25 years later, allylsilanes have become ubiquitous reagents in organic synthesis with a wide variety of applications. Derivatives of this original reaction ranging from the use allenylsilane[6] to propargylsilanes[7] have also been investigated. One of the unique reaction properties of this substrate is its ability to behave as a 1,3-dipole and a "[2+2]" reaction partner. These alternative reaction manifolds were observed early on[8] and evolved into the active field that currently exists. All three reaction manifolds proceed through a common intermediate (**2.2**, **2.3**). Addition of the terminal carbon of the allylsilane to the β-carbon of the enone system results in the β-silicon-stabilized carbenium intermediate (**2.2**). This intermediate can also be represented by the non-classical "siliranium" intermediate (**2.3**). At this juncture, the reaction can advance through three possible pathways. First, halide from the Lewis acid (usually titanium (IV) tetrachloride) may add to the silicon resulting in its displacement effecting net allyl transfer (**2.6**). Second, the intermediate metalloenolate may add intramolecularly to the siliranium intermediate (**2.3**) through a *4-endo* process to afford the cyclobutane adduct (**2.5**). Finally, this same metalloenolate intermediate may add *via* a *5-exo* pathway to yield the cyclopentane (**2.4**). Majetich[9] took advantage of the annulation reaction manifold by performing the conjugate addition in an *intramolecular* sense wherein the allylsilane was tethered to the enone system. Despite the extensive investigation[10] of *intermolecular* annulation of allenylsilanes to produce cyclopentene products by Danheiser throughout the 1980s , it wasn't until

Knölker's work[11] in 1990 that first optimized the annulation of allylsilanes onto enones.

Another useful feature of the allylsilane annulation is the predictable stereochemistry of the annulated products (Scheme 2.2). The cyclopentane products form with a high propensity for the carbonyl group to be *trans* to the trisubstituted silyl moiety (**2.10**). It has been suggested by various groups[12] that this stereochemical outcome arises from a preference for a synclinal transition state (**2.7**), in accord with the general topological rule for Michael additions proposed by Seebach and Golinski.[13]

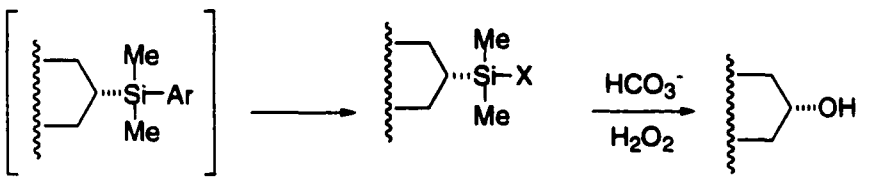
Scheme 2.2



During this same period, Tamao[14] and Fleming[15] independently discovered a synthetically useful property of the silicon moiety, the oxidative conversion of

the silicon-carbon bond into a oxygen-carbon bond (Scheme 2.3). Silicon's ability to act as a hydroxyl surrogate has increased its versatility and puissance in synthetic organic chemistry. Analogous to the well-known oxidation of borane to an alcohol by alkaline hydrogen peroxide, the oxidation of the silane has two manifestations. The first, introduced by Tamao, uses a silyl moiety (**2.12**) that contains a nucleofugal group such as a halogen, oxygen or nitrogen substituent. These silyl groups are usually quite reactive and require oxidation shortly after they are introduced. The second, introduced by Fleming, uses a silyl group containing only carbon ligands wherein at least one must be aromatic (**2.11**). These silyl groups are much more robust and can be carried through several synthetic steps before being unmasked as a hydroxyl group. The oxidation is initiated by protodesilylation of the aromatic moiety which then proceeds through the same reaction pathway as the Tamao oxidation.

Scheme 2.3



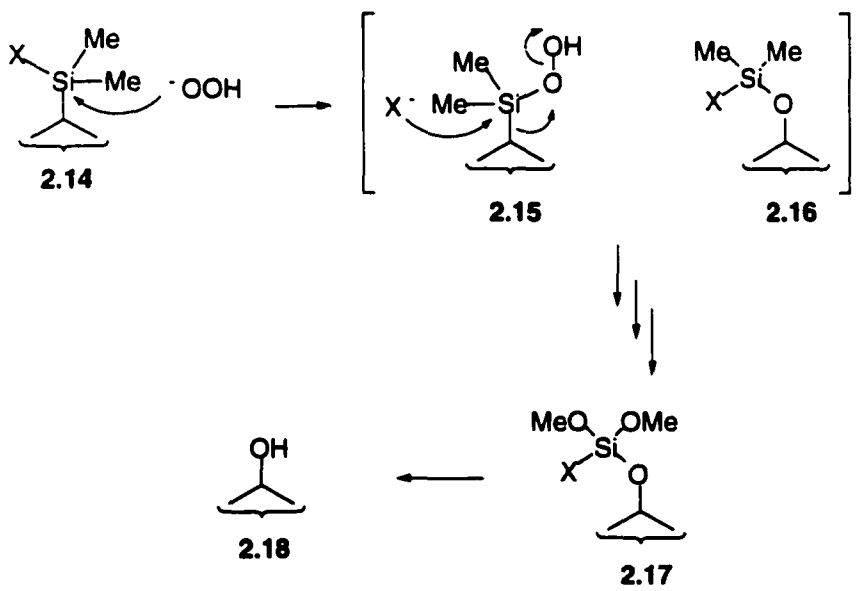
2.11 **2.12** **2.13**

X = H, halide, NR_2, OR

Both of these methods were inspired by the work of Buncel and Davies[16] who reported that basic perbenzoic acid oxidized chlorodimethylphenylsilane to dimethyl(phenoxy)silyl benzoate. Rearrangements of silyl peroxides, especially

phenyl migration, was studied by Yablokov.[17] Unlike borane, which contains a low-energy empty *p*-orbital, silicon must possess a substituent that can assist in the addition of the peroxide, a nucleofugal group (**2.14**) (Scheme 2.4). Hydroperoxide anion easily displaces the halide, oxygen, nitrogen ion from the silicon atom producing a silyl hydroperoxide (**2.15**). The remaining steps are completely analogous to the borane series in that migration of one of the carbon substituents to the neighboring oxygens must occur (**2.16**). Repetition of this sequence then affords the trialkoxysilane (**2.17**), or some similar intermediate that is then easily hydrolyzed to the alcohol (**2.18**).

Scheme 2.4



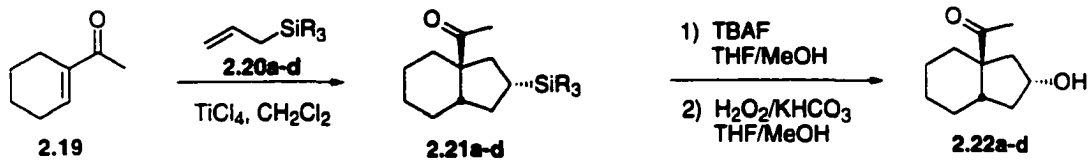
This added property of the silane allows one to exploit the nucleophilicity of the allylsilanes along with the annulation reaction manifold to access a variety of functionalized cyclobutanes and cyclopentanes. Unlike their cyclohexane

cousins, the cyclobutanes and cyclopentanes are much more difficult to construct.[18] Many groups have taken advantage of allylsilanes over the past ten years to construct functionalized carbocycles[19] and heterocycles such as oxetanes,[20] tetrahydrofurans,[21] azetidines and pyrrolidines.[22] Work in this group[23] has focused first on the construction of an allylsilane that maximized both the annulation reaction as well as the Tamao-Fleming oxidation. To this end, allydimethyltritylsilane was synthesized and applied to the construction of cyclopentanols, oxetanes and tetrahydrofurans.

II.2. Achiral Annulations with Allyldimethyltritylsilane.

The development of allyldimethyltritylsilane originated after examining several trends noted in the literature as well as observations made in these laboratories.[24] For example, allylmethyldiphenylsilane (**2.20a**) has been shown by Knölker[25] to undergo annulation (Table 2.1) with 1-acetylcyclohexene (**2.19**) followed by oxidative conversion to the alcohol (**2.22**). This interesting and useful transformation, however, suffered from a poor yield in the annulation step, while the oxidative removal *via* the Tamao method proceeded well to give **2.22a**. We found that allyltriisopropylsilane (**2.20b**) underwent similar annulations with excellent yields but we were unable to convert the silyl adduct to the carbinol (**2.22**). The other end of the reactivity spectrum is illustrated by allyltriphenylsilane (**2.20c**) which underwent annulations to **2.21c** with poor yields but was converted to the carbinol (**2.22**) in excellent yield (Table 2.1).

Table 2.1. Allyl Silane Annulations-Oxidation to Fused Cyclopentanols



2.19 2.21a-d 2.22a-d

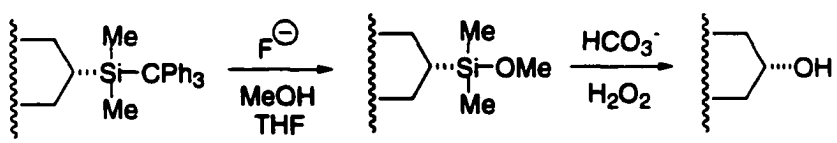
Silane, R_3	%2.21	%2.22
2.20a, $SiMePh_2$	26	80
2.20b, Si (i-Pr)$_3$	94	0
2.20c, $SiPh_3$	51	97
2.20d, $SiMe_2CPh_3$	80	70

It is apparent from these data that at least two alkyl groups on the silicon atom are required to effect efficient addition-annulation and a fluoride-labile group is necessary for efficient oxidation. This delicate balance between addition reactivity and oxidative silicon removal was fortunately achieved by use of allyldimethyltritylsilane (**2.20d**). These laboratories have reported preliminary results on the use of allyldimethyltritylsilane (ADTS) to annulate several enone systems.[26] When enone **2.19** was treated with ADTS under Lewis acid conditions, the annulation occurred in 80% yield and more importantly, the oxidative desilylation proceeded in 67-70% yields. The large trityl group, the necessary alkyl groups and ease of oxidative removal of the silicon all contributed to a successful solution to the problem at hand.

II.2.a Synthesis of 3-Substituted, 3,3-Disubstituted and 3,4-Disubstituted Cyclopentanols. When 1.5 equivalents of allyldimethyltritylsilane (ADTS) (**2.20d**) is added to a premixed solution of the electron deficient olefin (Table 2.2)

and titanium (IV) chloride in dichloromethane at -78 °C, the cyclopentyldimethyltritylsilanes are obtained in moderate to high yield (40-85%). The various olefins annulated in Table 2.2 exhibit the versatility of the silane addition as well as the diastereoselectivity of the process. In almost every case, except in entry f, we were unable to observe any other stereoisomer. The silylcyclopentanes were subsequently converted to their respective cyclopentanol derivatives by a modified Tamao oxidation. The tritylsilane was first converted to the methoxysilane (**2.24**) by reaction with tetrabutylammonium fluoride or cesium fluoride in a MeOH-THF solution (Scheme 2.5). Treatment of the crude methoxysilane (**2.24**) with basic hydrogen peroxide in a MeOH/THF solution furnished the cyclopentanols in consistently good yields (67-93%) (Table 2.2). It is noteworthy that little or no epimerization of carbonyl containing compounds occurred during the transformation of the silyl group to the hydroxyl.

Scheme 2.5

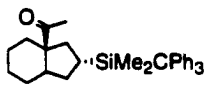
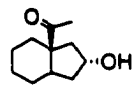
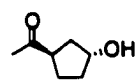
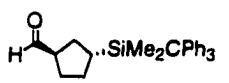
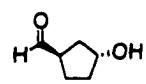
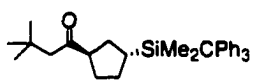
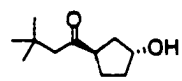
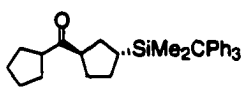
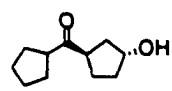
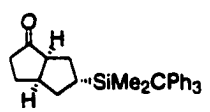
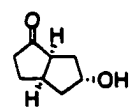
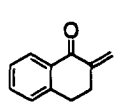
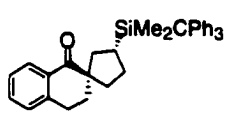
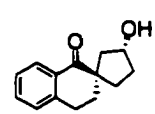


2.23 **2.24** **2.25**

The stereochemical assignments were based on comparison to spectral data of known or analogous compounds. It is also important to mention that the mild oxidation conditions showed only a slight loss of the diastereomeric integrity in only two cases (entries b, c). In the cases where epimerization was not a

concern, Tamao oxidation could be achieved in one pot by a combination of tetrabutylammonium hydroxide and hydrogen peroxide in THF. The examples depicted in Table 2.2 demonstrate the advantages of ADTS when compared to earlier allylsilanes utilized in annulations.

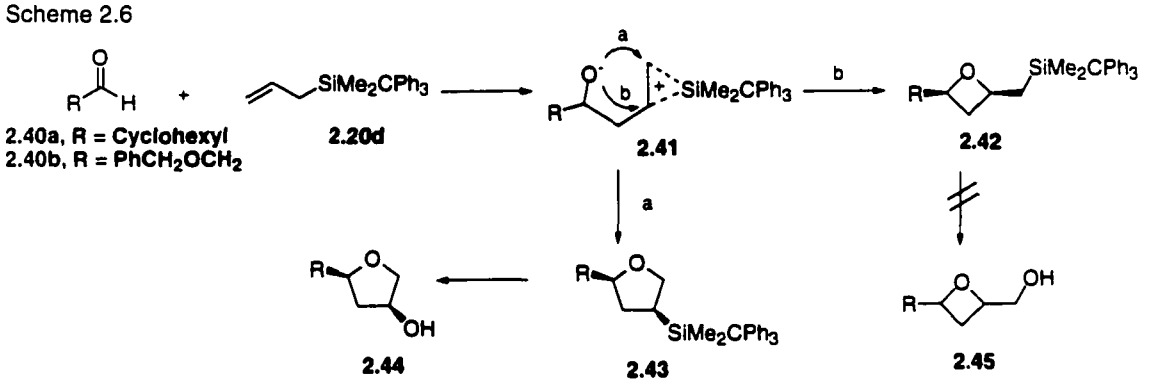
Table 2.2. Stereoselective Cyclopentanol Synthesis using ADTS, 2.20d

Entry	Olefin	Silylcyclopentane	% Yield (*d.r.*)[a]	Cyclopentanol	% Yield (*d.r.*)
a)		 **2.26**	85 (*>97:3*)	 **2.33**	67 (*>97:3*)
b)		 **2.27**	78 (*>97:3*)	 **2.34**	69 (*8:1*)
c)		 **2.28**	40 (*>97:3*)	 **2.35**	78 (*7:1*)
d)		 **2.29**	55 (*>97:3*)	 **2.36**	82 (*>97:3*)
e)		 **2.30**	63 (*>97:3*)	 **2.37**	73 (*>97:3*)
f)		 **2.31**	46 (*9:1*)	 **2.38**	93 (*9:1*)
g)		 **2.32**	68 (*>97:3*)	 **2.39**	85 (*>97:3*)

[a] Diastereomeric ratios were determined by 300 MHz ^{1}H NMR of the crude reaction mixture.

II.2.b Synthesis of 2,4-Disubstituted Oxetanes and Tetrahydrofurans. In addition to the carbocycle formation seen above, ADTS was found to smoothly undergo cycloadditions to aldehydes (**2.40**). There are two reaction pathways which may occur and therefore offer the option to form oxetane (**2.42**) or tetrahydrofuran (**2.43**). For example, if the intermediate alkoxide (**2.41**) undergoes a *4-endo* mode of attack (path b) the oxetane is formed, whereas *5-exo* attack (path a) leads to the tetrahydrofuran (Scheme 2.6).

Scheme 2.6

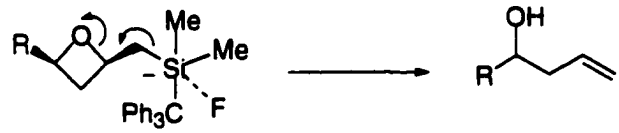


In contrast to the carbocycle formation where temperature dictates whether a 4- or a 5-membered ring will form,[24] changing the nature of the Lewis acid affects ring size in the heterocycle formation. Thus, when benzyloxyacetaldehyde (**2.40b**) is added to a mixture of ADTS and zirconium (IV) chloride at -20° C, oxetane (**2.42b**) is obtained exclusively in 88% yield after 30 min. In contrast, when benzyloxyacetaldehyde is added to a solution of $BF_3 \cdot OEt_2$ and ADTS at -78 °C, the tetrahydrofuran (**2.43b**) is the only product obtained in

72% yield after 12 h. The stereochemistry of **2.42** and **2.43** was assigned based on literature precedent for similar annulations with other allylsilanes.

In order to demonstrate that ADTS may serve as a hydroxyl equivalent, attempts were made to convert the silylmethyl oxetanes (**2.42**) to the hydroxymethyl oxetanes (**2.45**). However, after some effort no oxetane product was obtained. This failure was attributed to the facile β-cleavage of the oxetane during the Tamao oxidation. In an attempt to determine which step in the oxidation was causing the ring opening, an effort was made to isolate the intermediate fluoro or methoxy silane from **2.46**.

Scheme 2.7



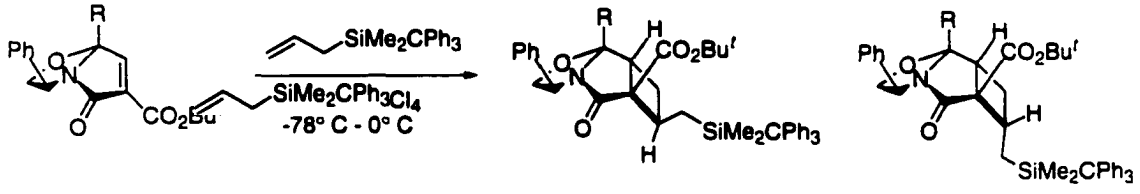
2.46 **2.47**

A solution of the silylmethyl oxetane **2.42a** was added to a solution of tetrabutylammonium fluoride in THF at -20 °C. After 45 minutes the oxetane was completely converted to the homoallylic alcohol (**2.47**) (Scheme 2.7). Solvolysis of **2.42a** with tetrabutylammonium hydroxide and protodesilylation were both unsuccessful as well. However, in the case of the silyl tetrahydrofurans (**2.43**), the ring cleavage should not be a competing pathway and their corresponding hydroxytetrahydrofurans (**2.44**) were expected to form. In the event, the

conversion of the 4-silyltetrahydrofuran (**2.43b**) to the 4-hydroxytetrahydrofuran (**2.44b**) proceeded cleanly in 86% yield.

II.2.c Annulations to α,β-Unsaturated Chiral Bicyclic Lactams. In order to assess the versatility and scope of the annulations above, a study to determine whether the chiral bicyclic lactams (**2.48**), reported earlier[23] to give either 4 or 5-membered ring annulation, would respond to the allyldimethyltritylsilane. The annulations previously performed using triisopropylallyl silanes were incapable of generating the alcohols. The bicyclic lactams (**2.48**) were treated with titanium (IV) tetrachloride in dichloromethane at -78 °C, and after addition of the allylsilane the reaction mixture allowed to warm to 0 °C. A 50-75% yield of cyclobutane adducts (**2.49, 2.50**) was exclusively obtained as a mixture of *exo-endo* silyl substituent with the major product in each instance being the *exo*-products (**2.49a-c**). It is noteworthy to mention that no cyclopentane products (i.e. **2.52**) were observed as was previously described[23] when warming the

Scheme 2.8

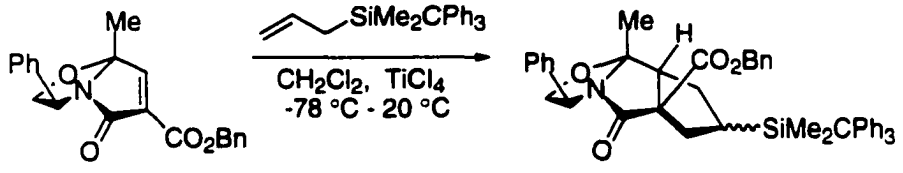


2.48a, R = Ph
2.48b, R = Me
2.48c, R = H

2.49a (90:10) **2.50a**
2.49b (87:13) **2.50b**
2.49c (83:17) **2.50c**

triisopropyl adducts to 0 °C in the presence of $TiCl_4$. Furthermore, the rates of reaction were qualitatively slower with ADTS when compared to those exhibited by allyl TIPS additions, presumably due to slightly less inductive stabilization by the methyl and trityl groups. Titanium (IV) tetrachloride mediated rearrangement of the initially formed cyclobutane from **2.49** to cyclopentane products **2.52** were attempted by warming the reaction mixture to 20-25 °C but thermal decomposition of both the product and starting materials became quite noticeable and the cyclopentane was indeed formed in poor yield and with loss of stereochemical integrity (Scheme 2.9). Thus, **2.52** was obtained in 21% yield, but with only a diastereomeric ratio of 78:22, indicating the rearrangement took place with poor stereochemical integrity.

Scheme 2.9



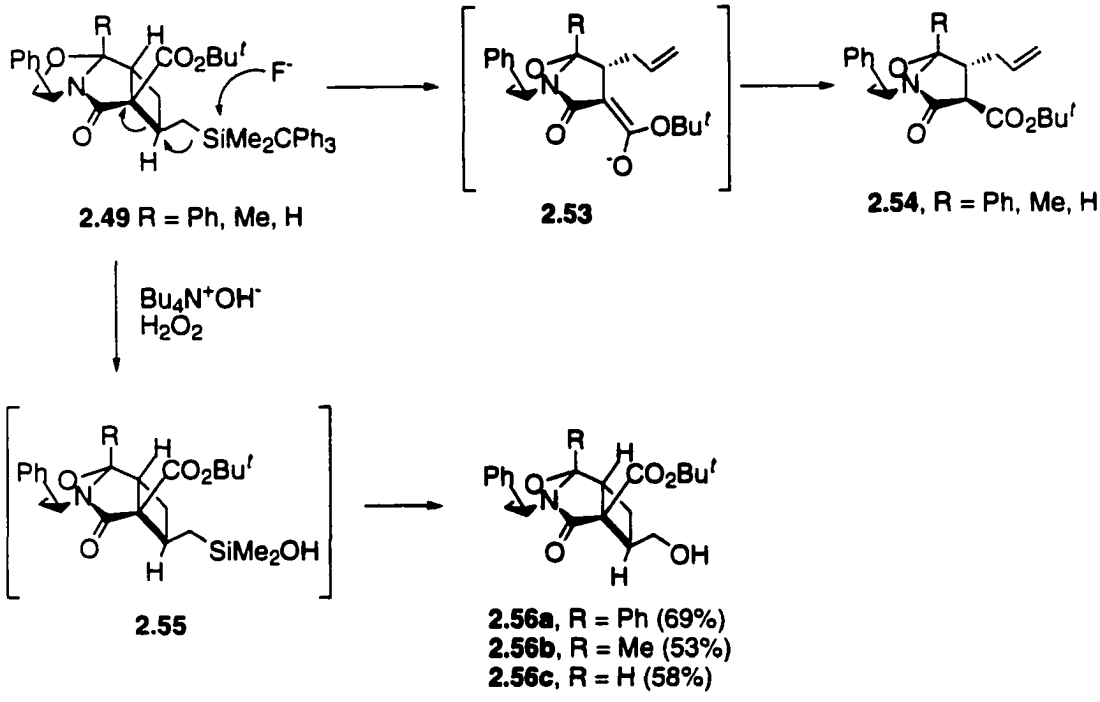
2.51b

2.52a, (*exo*)
2.52b, (*endo*)

Attempts to oxidize the silane **2.49** to the corresponding carbinol using standard Tamao conditions resulted in formation of the Sakurai product (**2.54**) (Scheme 2.10). This was considered to be a result of nucleophilic attack on the silicon by the fluoride ion and subsequent elimination to the alkene (**2.53**). If fluoride ion is indeed responsible for this fragmentation, then omitting it from the

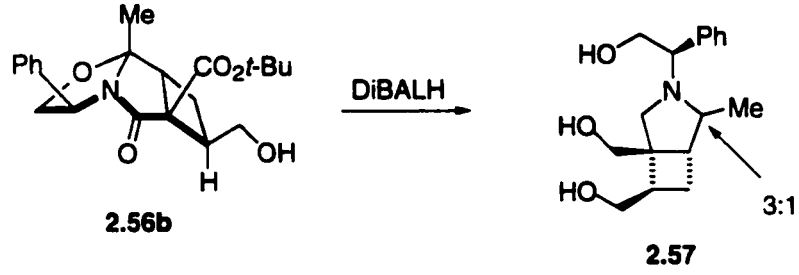
silyl-trityl solvolysis should avoid the problem. Thus, treating the cyclobutanes (**2.49**) with only tetrabutylammonium hydroxide in the presence of hydrogen peroxide produced the solvolyzed intermediate **2.55** which was readily oxidized to the primary alcohols (**2.56a-c**) in moderate yields.

Scheme 2.10



Initial attempts to remove the auxiliary began with diisobutylaluminum hydride reduction to afford a 3:1 inseparable mixture of diastereomers **2.57** at the angular position (Scheme 2.11).[27] Other reducing agents (Red-Al, BH_3, AlH_3, 9-BBN, L-Selectride) were investigated with equally poor diastereoselectivity.

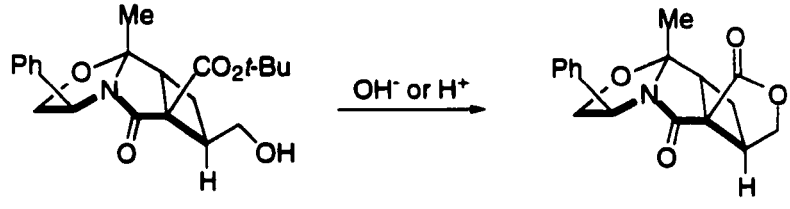
Scheme 2.11



2.56b **2.57**

Concurrent studies on these cyclobutane adducts revealed that the free hydroxymethyl group had a high propensity to lactonize onto the vicinal ester to form **2.58** under both acidic and basic conditions (Scheme 2.12). It was postulated that the first step in the reduction process was formation of the lactone which adversely effected the stereochemical outcome of the subsequent reductions.

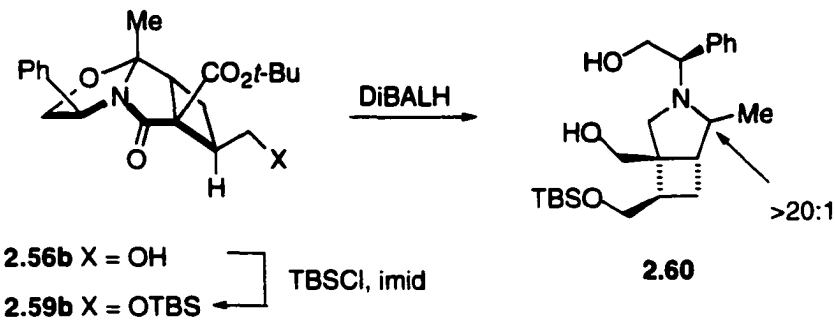
Scheme 2.12



2.56b **2.58**

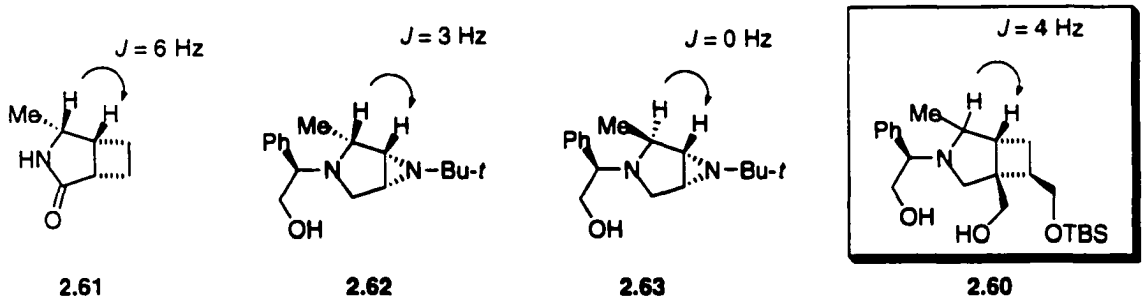
In an effort to test this hypothesis, the hydroxymethyl group was protected as its *tert*-butyldimethylsilyl ether (**2.59**) and subjected to the orginal reduction conditions (Scheme 2.13). The reduction proceeded with excellent selectivity, producing only one detectable diastereomer (**2.60**).

Scheme 2.13



Assignment of the newly formed stereogenic center was initially attempted with ^{1}H NMR using previously reported[28] reductions of tricyclic lactam systems (**2.61-2.63**) as models (Scheme 2.14). Their assignments were resolved comparing the coupling constants of the vicinal hydrogens and later confirmed by X-ray crystallography.

Scheme 2.14

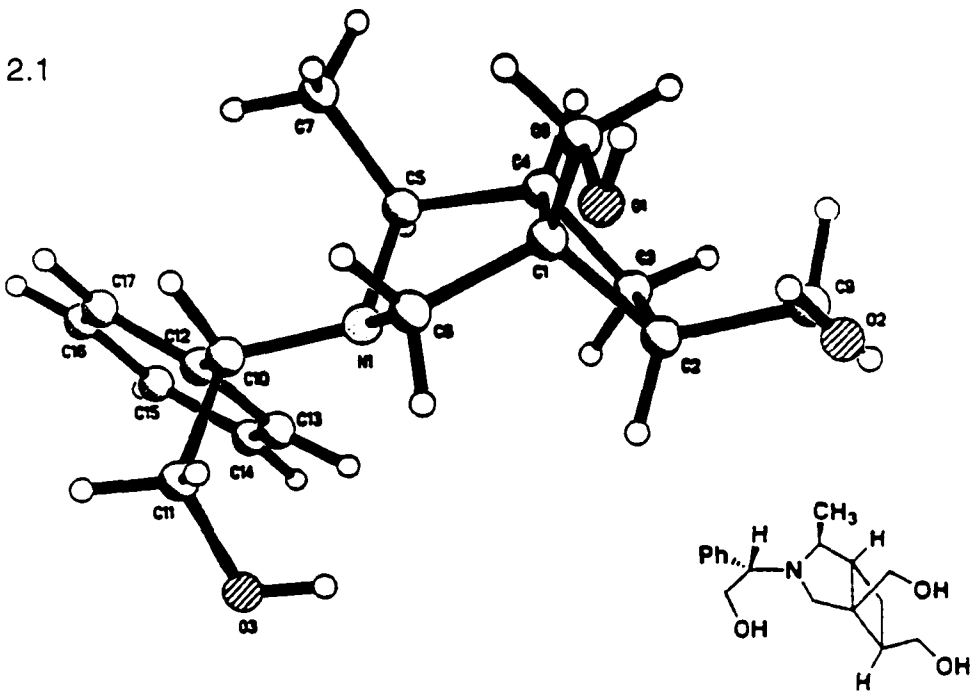


2.61 **2.62** **2.63** **2.60**

Based on these data, it would appear that the stereochemical assignment should be that of reduction with inversion. However, after analysis of the dihedral angles in models of the two possible products, the coupling constants were predicted to be ~7 Hz for the *cis* isomer and ~3 Hz for the *trans* isomer. It was neccesary to confirm the structure by X-ray crystallography to eliminate any

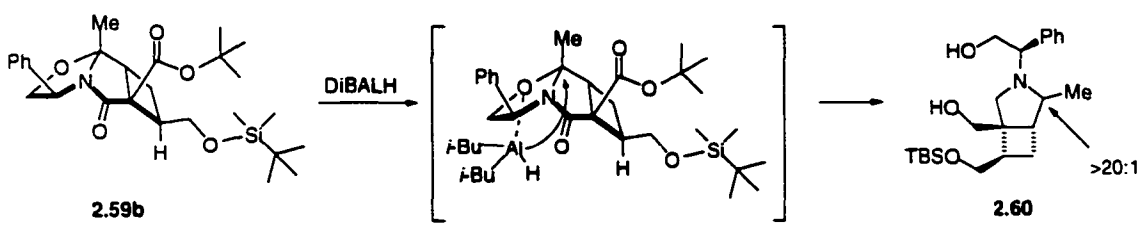
doubt. Removal of the *tert*-butyldimethylsilyl ether using tetrabutylammonium fluoride, afforded the triol **2.61** as a colorless solid with X-ray quality crystals. X-ray analysis revealed that the reduction occurred with *retention* of stereochemistry at the angular position (Figure 2.1).

Figure 2.1



This seemingly anomolous result could be rationalized by the abundance of steric bulk on the convex (*exo*) face of the tricyclic system, forcing the delivery of the hydride to occur from the concave (*endo*) face of the tricyclic lactam.

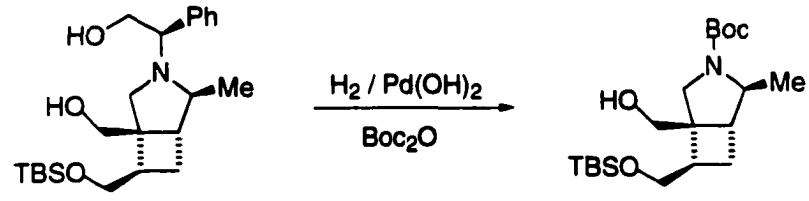
Scheme 2.15



2.59b **2.60**

With the stereochemistry of the cyclobutanopyrrolidine unequivocally established, all that remained was the hydrogenolysis of the benzylic carbon-nitrogen bond. This was accomplished by treatment of pyrrolidine **2.60** with palladium (II) hydroxide under an atmosphere of hydrogen with *in situ* protection as its *tert*-butyl carbamate (**2.62**) (Scheme 2.16).

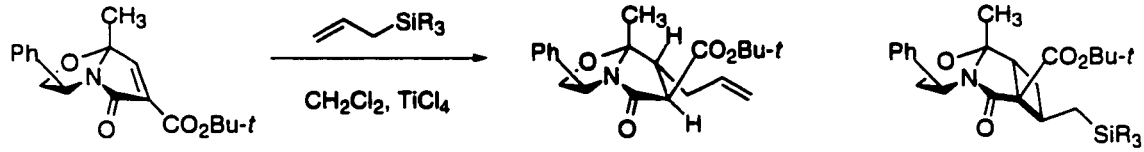
Scheme 2.16



2.60 **2.62**

II.2.d Remote Steric Effect in the Sakurai Addition onto Bicyclic Lactams.

In an effort to expand the scope of allylsilane additions to the bicyclic lactam, several other allylsilanes were investigated. It was found that various allylsilanes provided mixtures of the annulated and Sakurai products, Table 2.3.



2.48b **2.63** **2.64**

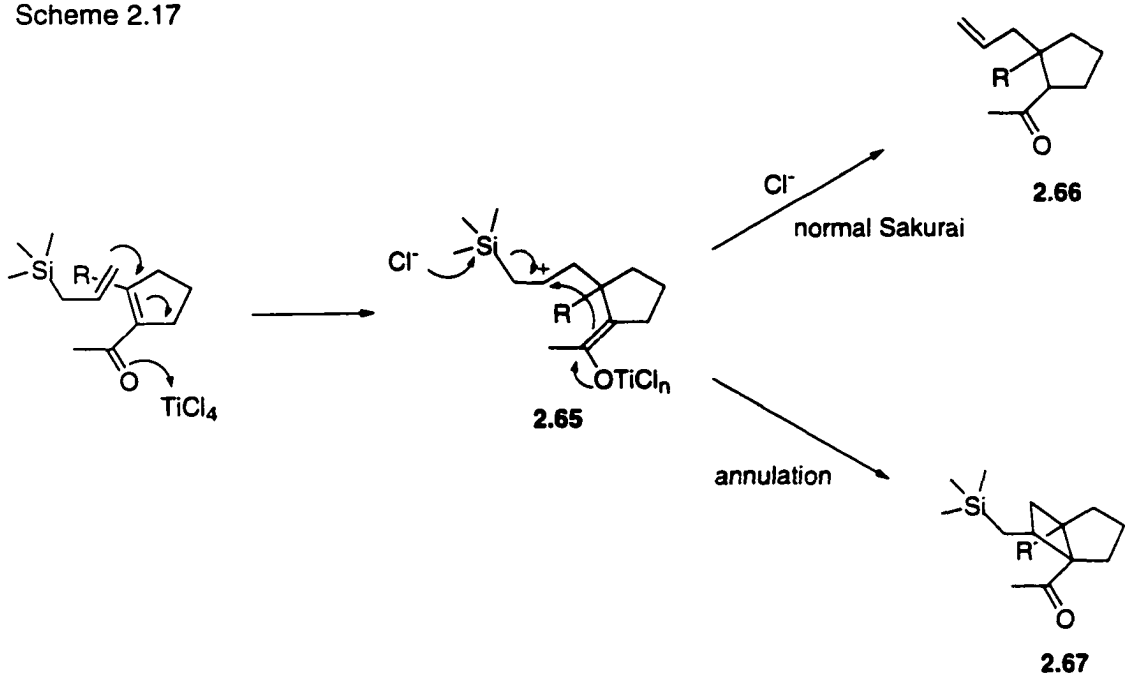
Table 2.3. Allylsilane Additions to Bicyclic Lactam 2.48b

entry	R_3	%2.63	%2.64
1	Me_3	>90	0 (45)[a]
2	Me_2Ph	86	0(53)[a]
3	$Me_2N(Pr\text{-}i)_2$	89	0
4	$(Pr\text{-}i)_3$	0	83
5	Me_2CPh_3	0	79

[a] Reaction temperatures below –50 °C afforded the annulated product **2.64**.

It is noteworthy to mention that the allylsilanes employed in entries 1 and 2 provided the annulated product (**2.64**) at temperatures below –50 °C. The isolation of these cyclobutane adducts using allyltrimethylsilanes has been the subject of controversy for several years (Scheme 2.17). As previously mentioned, this "[2+2]" adduct had been reported as early as 1976[4] wherein the structure was assigned based on spectroscopic data.

Scheme 2.17



This cyclobutane product was later reported by several other groups[8] until the assignment was challenged in 1990.[11] Danheiser[29] demonstrated that there was a steric dependence on the Sakurai/annulation ratio with allyltriisopropylsilane giving the annulation product predominately whereas allyltrimethylsilane gave the expected Sakurai product which we also observed in the bicyclic lactam series. Our earlier studies in this area involved the addition of allyltriisopropylsilane to α,β-unsaturated bicyclic lactams **2.48** to obtain silylcyclobutanes and silylcyclopentanes. During that study we found that the reaction produced silylcyclobutanes as the kinetic product and upon warming gave the more thermodynamically stable silylcyclopentane. It was believed, based on the current literature, that the duality in the reaction occured only when

bulky substituents were present on the silane and standard Sakurai products were observed when allyltrimethylsilane was utilized.

During this investigation of the Sakurai reaction with the bicyclic lactam an unexpected remote steric effect involving the addition of allyltrimethylsilane was discovered. It was observed that at low temperatures (i.e. -78 °C) the allyltrimethylsilane was *producing only the cyclobutane* (**2.68**). It has been postulated by other groups[8b,c] that the initially formed product in the Sakurai reaction is the cyclobutane adduct which irreversable decomposition to the traditional allylated product. However, this cyclobutane was only appearing in substrates where the α-alkoxycarbonyl group was large (Scheme 2.18). In order to investigate this steric effect, a series of alkoxycarbonyl bicyclic lactams (**2.48b**, **2.65** and **2.66**) were subjected to identical Sakurai conditions and the products were isolated as illustrated (Table 2.4).

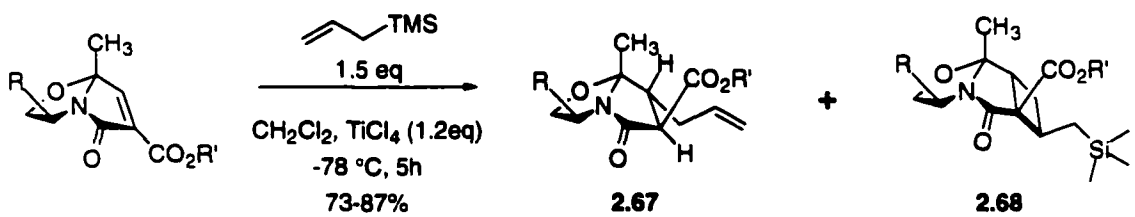
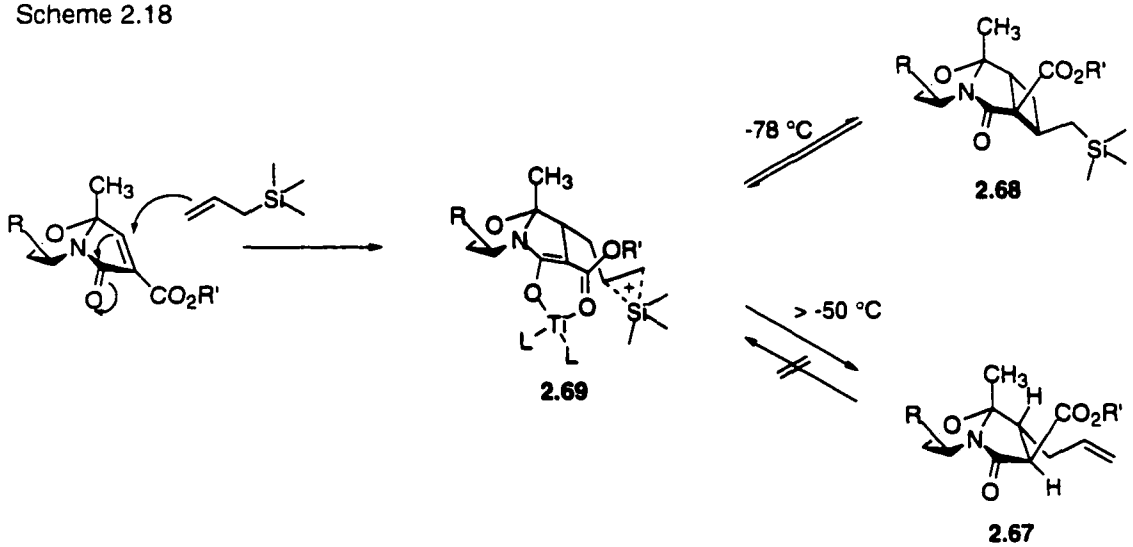


Table 2.4. Remote Steric Effect

R	R'	2.67(%)	2.68(%)
2.65 *i*-Pr	Me	>95	<5
2.66 Ph	*i*-Pr	33	67
2.48b Ph	*t*-Bu	<5	>95

Again, it should be noted that all three esters (**2.48b**, **2.65** and **2.66**) provide the normal Sakurai product (**2.67**) upon warming above -50 °C. It appears that the siliranium ion intermediate (**2.69**) (Scheme 2.18) is in close proximity to the titanium enolate, minimizing charge separation, and intermolecular nucleophilic attack by Cl^- is inhibited by the bulky ester substituent. As a result, the annulation product (**2.68**) predominates but the cyclobutane adduct was seen to revert to the siliranium intermediate (**2.69**) and eliminate to the Sakurai product (**2.67**) upon warming and in the presence of $TiCl_4$. When the reaction temperature rises above -50 °C, the process irreversibly produces the normal Sakurai product (**2.67**).

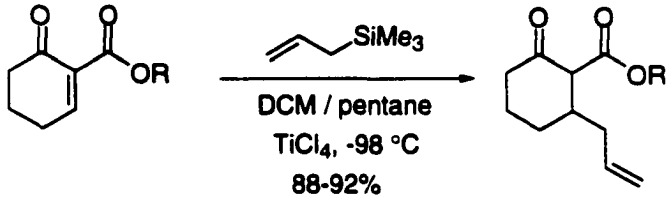
Scheme 2.18



To further probe the generality of this duality in mechanism, alkyl 6-oxo-1-cyclohexane carboxylates (**2.70a,b**) were subjected to the Sakurai reaction conditions (Scheme 2.19).[30] The increased electrophilicity of the β-carbon upon

addition of the α-ester resulted in a large increase in the reaction rate. As observed in the bicyclic lactam series, the smaller α-methoxycarbonyl provided the Sakurai product (**2.71a**) exclusively. When the larger *t*-butoxycarbonyl (**2.70b**) was submitted to the same reaction conditions at -78 °C, the starting material was consumed in 10 min providing only the allyl transfer product (**2.71b**). The cyclohexenone and allylsilane were dissolved in a 1:1 mixture of DCM/pentane, cooled to -98 °C and subjected to the same conditions. Again, the reaction was completed within 15 minutes and provided **2.71b** exclusively. It is conceivable that in the more complex environment of the bicyclic lactams (**2.48b**, **2.65** and **2.66**) the steric inhibition to chloride ion attack is more important, while in the simpler cyclohexenone systems the chloride ion is not prevented from attack on silicon by remote alkyl groups on the ester group.

Scheme 2.19



2.70a = CH_3
2.70b = *t*-Bu

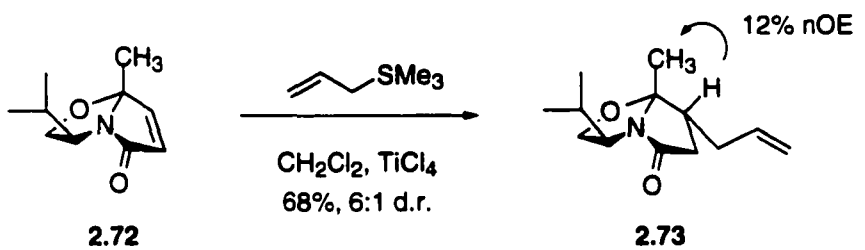
2.71a = CH_3
2.71b = *t*-Bu

In summary, a novel remote steric effect in the addition of allylsilanes to α,β-unsaturated bicyclic lactam systems has been observed. With careful control of the reaction conditions and substrate size, as opposed to altering the alkyl

substituents on the silane, it is possible to exploit the dual reactivity of allylsilanes.

At this point, the investigation of the Sakurai reaction was further explored and applied toward the construction cyclopentenones and ultimately pyrrolidines. Addition to the simple α,β-unsaturated bicylclic lactam (**2.72**) was the main focus of this study as it offers a wider range of options for further elaboration after the first transformation (Scheme 2.20). Optimal conditions gave the β-allyl bicyclic lactam (**2.73**) in 68% yield as a 6:1 mixture of separable isomers.

Scheme 2.20



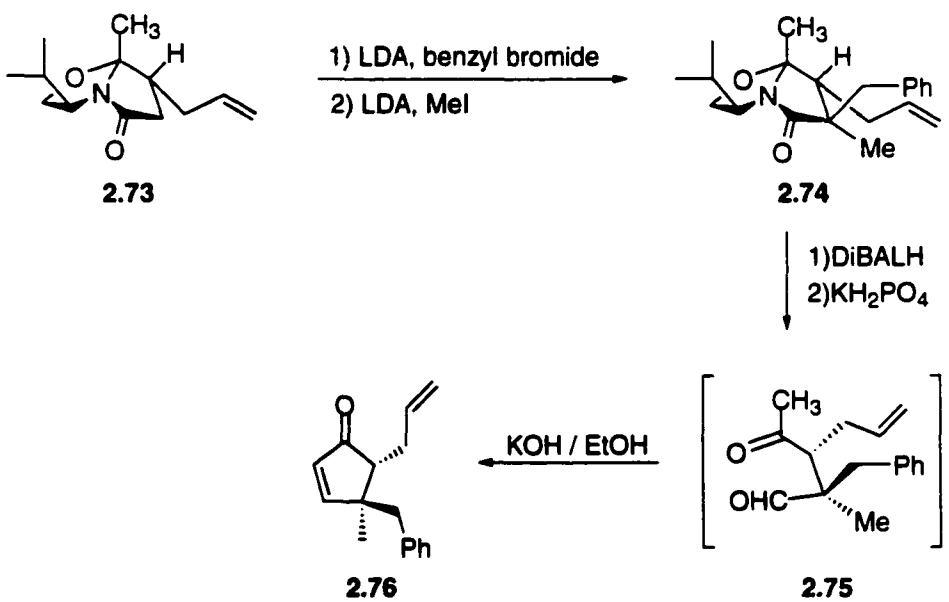
2.72 **2.73**

This reaction was determined to have occurred with *endo* addition as observed in other conjugate addition reactions. A strong nOE was recorded between the angular methyl group and the axial hydrogen in the β-position. In order to ascertain applicability of this method towards the synthesis of carbocyclic natural products, the α-position was quaternized and the lactam was converted to the cyclopentenone (Scheme 2.21).

Sequential alkylation of the β–allyl lactam with benzyl bromide and methyl iodide afforded the dialkylated lactam (**2.74**) as a 10:1 mixture of separable diastereomers. The major diastereomer was determined to be the *endo*-

alkylated product *via* ^{1}H NMR analysis of the angular methyl group. It has been consistently documented in these laboratories that the α-benzyl group resides in a conformation that shields the angular methyl position such that the signal is shifted upfield from 1.5 ppm to 0.6 ppm. This is consistent with the alkylations of the [3.3.0] bicyclic lactam with sp^3 hybridized electrophiles and suggests that the β-allyl moiety has little effect on the diastereofacial selectivity. The lactam was then reduced to the carbinol amine, hydrolyzed to the keto-aldehyde (**2.75**) and converted to the cyclopentenone (**2.76**) *via* based catalyzed intramolecular aldol condensation.

Scheme 2.21

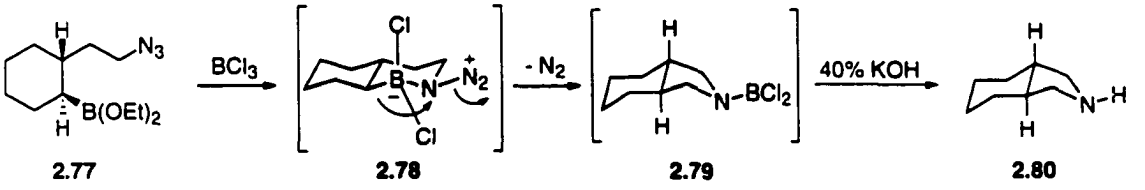


2.73 **2.74** **2.76** **2.75**

This series of reactions proved that this sequence of Sakurai/bis-alkylation could offer access to a variety of carbocyclic compounds. We were interested in utilizing this method for the construction of alkaloids and shifted our efforts

toward this end. A bis-Sakurai sequence would be investigated wherein the first addition would be performed in a 1,4-fashion followed by 1,2-addition into the angular position (Scheme 2.23). This di-olefin (**2.82**) could be subjected to ring closing metathesis giving us access to *trans*-hexahydroindoline (**2.81**) whose stereoselective synthesis has been met with very limited success. The most successful method was developed in the Brown[31] laboratories wherein dichloroboranes (**2.78**) are reacted with an intramolecular source of azide to afford the *trans*-hexahydroindoline (**2.81**) (Scheme 2.22). Although this method allows stereoselective access to the target compounds, it doesn't provide them in optically pure form.

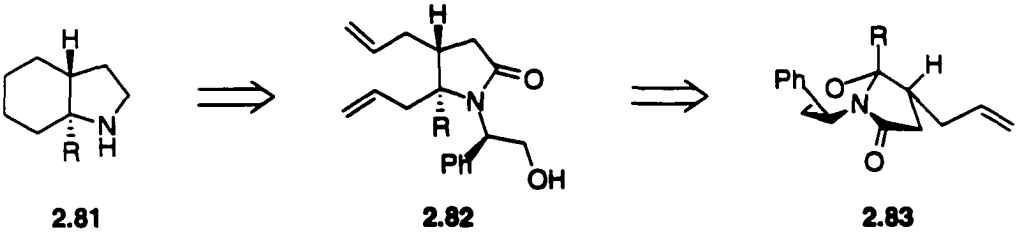
Scheme 2.22



2.77 **2.78** **2.79** **2.80**

Using the bicyclic lactam template, we believed that we could access these alkaloids in enantiomerically enriched form using the Sakurai chemistry described above.

Scheme 2.23

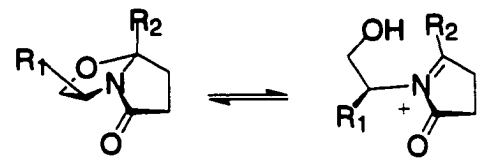


2.81 **2.82** **2.83**

II.3 Addition of Allylsilanes to the *N,O*-Acetal of the Bicyclic Lactam.

The electrophilicity of the *N,O*-acetal carbon of the bicyclic lactam has been noted for several years. Under Lewis acidic conditions, it is believed the equilibrium between the closed bicyclic system (**2.84**) and the *N*-acyl iminium ion (**2.85**) lies further toward the *N*-acyl iminium (Scheme 2.24).

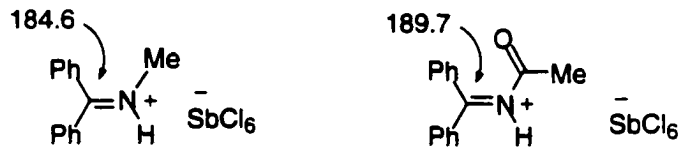
Scheme 2.24



2.84 **2.85**

The presence of the electron withdrawing group on the iminimum ion greatly increases its reactivity. Comparing ^{13}C NMR spectra[32] of different iminium salts (**2.86**, **2.87**) reveals that the imino carbon is shifted downfield by about 5 ppm suggesting that the acyliminium species is more electrophilic (Figure 2.2).

Figure 2.2



2.86 **2.87**

This property of the bicyclic lactam was probed by the addition of allyltrimethylsilane in the presence of titanium tetrachloride.[33] The addition to the phenylglycinol derived bicyclic lactam proceeded with 5:1 selectivity with the major isomer being the result of inversion at the imino carbon. Varying the amino

alcohol from which the bicyclic lactam was derived revealed an interesting trend in selectivity that was attributed to allylic 1,3-strain. It was discovered that the relative control of addition could be varied from complete addition with inversion using the alanol derived bicyclic lactams to complete addition with retention using the *tert*-leucinol derived bicyclic lactam (Table 2.5).

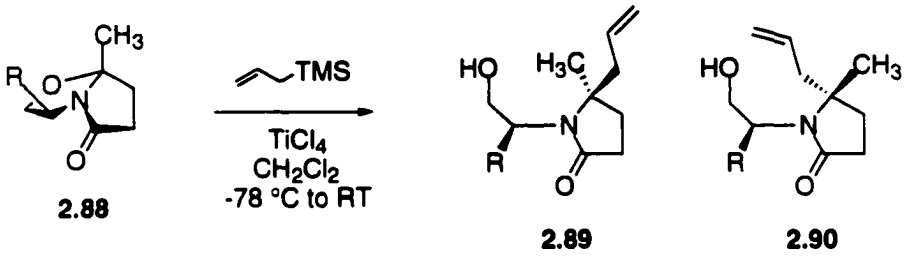


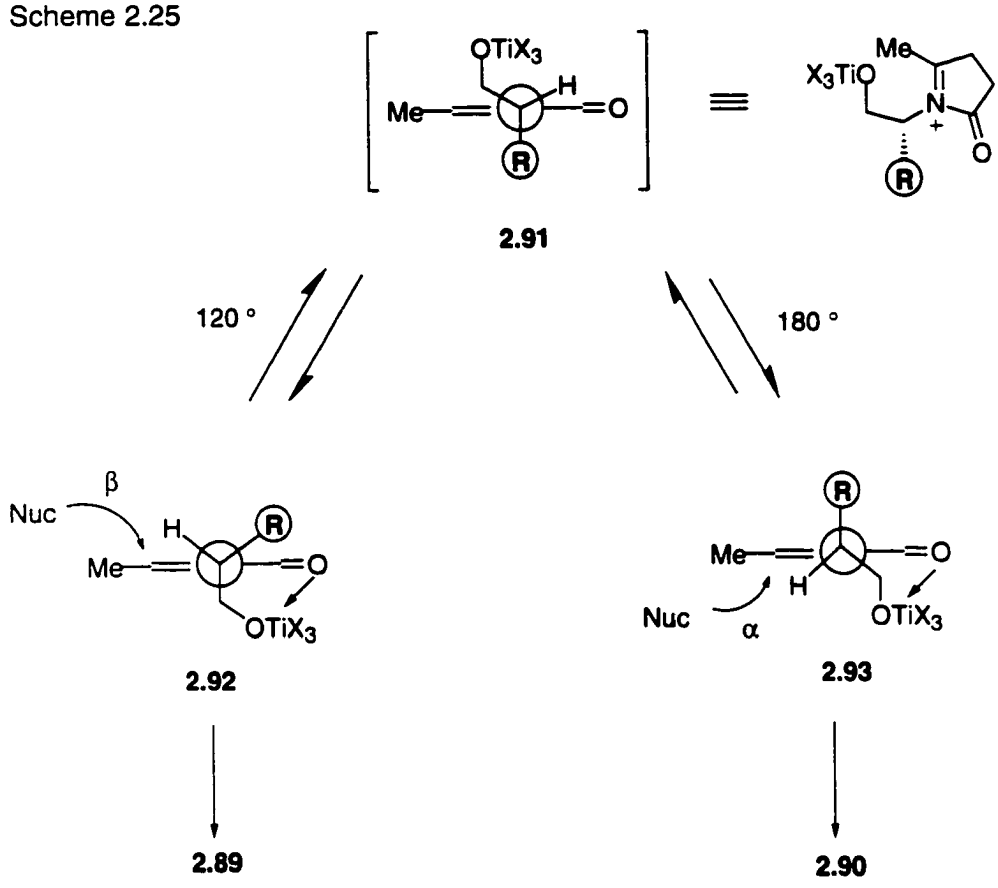
Table 2.5. Additions to the *N*-Acyliminium Ion.

R	d.r. **2.89**:**2.90**
methyl	8:1
phenyl	5:1
isopropyl	1:2
tert-butyl	1:11

A mechanistic picture emerged that involved a combination of the Felkin-Ahn model for nucleophilic addition, allylic 1,3-strain, and chelation effects. If one considers the initially formed N-acyliminium ion (**2.91**), in which R is the alkyl group derived from the various amino alcohol auxiliaries, then according to allylic 1,3-strain, a 120° rotation to **2.92** or a 180° rotation to **2.93** should minimize this strain by directing the small hydrogen atom toward the congested olefinic center.

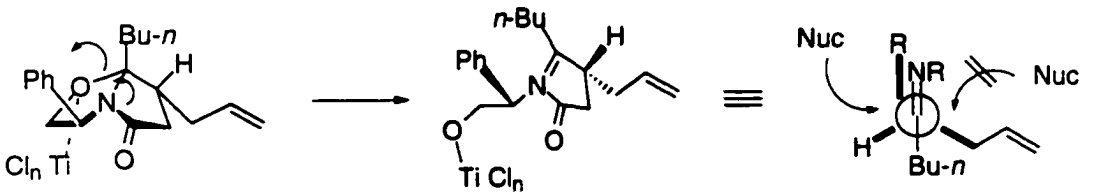
From the model of Felkin and Ahn, when R is a large group (i.e. *tert*-butyl and isopropyl), entry by silane occurs from the face opposite this large group (**2.93**) to generate the product of inversion (**2.90**). Alternatively, when R is the smaller group (methyl or phenyl), the alkoxytitanium assumes the role of the large group and occupies the antiperiplanar position (**2.92**), thus directing the entry from the β-face to afford the product of retention (**2.89**). That study illustrated how the stereochemistry of Lewis acid-allylsilane alkylations could be altered (inversion or retention at the electrophilic carbon) by simply changing the nature of the auxiliary group from small (methyl) to large (*tert*-butyl), rather than altering the stereochemistry of the chiral auxiliary.

Scheme 2.25



Based on this information, it seemed that the bis-Sakurai should yield the di-olefin in high stereoselectivity. The study commenced with the addition of allyltrimethylsilane to lactam (**2.94a**) with >20:1 diastereoselectivity (Scheme 2.27). The origin of the high levels of selectivity were attributed to the strong 1,2-interaction of the allyl moiety (**2.95**) with the incoming nucleophile onto the *N*-acyliminium ion (Scheme 2.26).

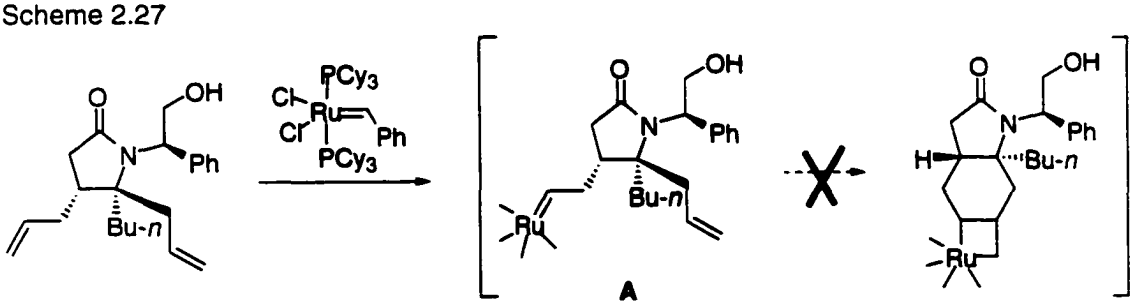
Scheme 2.26



2.94a **2.95**

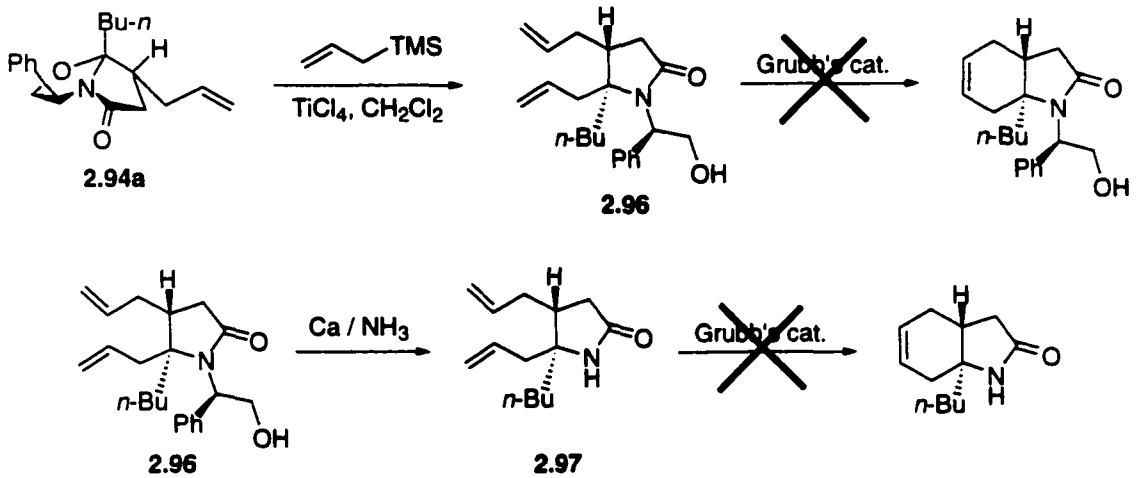
The di-olefin was subjected to catalytic ring-closing metathesis using Grubb's catalyst. Use of a variety of conditions including catalyst loading, solvents and reaction temperature afforded no reaction. It was thought that the presence of the Lewis basic lactam carbonyl and free hydroxyl group could be the source of the problem by sequestering the catalyst preventing any reaction. In order to investigate this possibility, the auxiliary was removed *via* dissolving metal reduction and a variety of conditions were tried again. Despite the removal of the free hydroxyl group, the RCM reaction did not occur. Addition of a more oxophilic metal (titanium (IV) isopropoxide) as reported by Fürstner[34] to assist catalysis in lactam systems was also unsuccessful (Scheme 2.28). At this point it was believed that the *trans* orientation restricted the conformation such that one of the olefins could never become close enough to the ruthenium carbene intermediate **A** to allow for successful metathesis (Scheme 2.27).

Scheme 2.27



A

Scheme 2.28

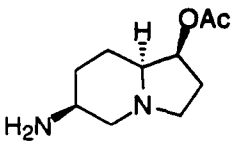


The 1,2-addition of the allylsilane is such a successful transformation that we decided to shift our focus toward the construction of indolizidine alkaloids by altering the substitution pattern on the pyrrolidinone which would be more amenable to the ring closing metathesis.

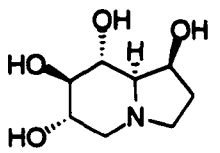
II.3.a Concise Synthesis of Indolizidines: Total Synthesis of (-)-Coniceine

Our efforts were now aimed at the construction of indolizidines which represent an important class of biologically active compounds, including such alkaloids as slaframine (**2.98**), castanospermine (**2.99**) (a potent glycosidase inhibitor) and a number of poisonous-frog alkaloids typified by pumiliotoxin B (**2.100**),[35] (Figure 2.3). Development of a general method to access these 1-azabicyclo[4.3.0]nonanes would provide a useful tool in studying a host of derivatives.

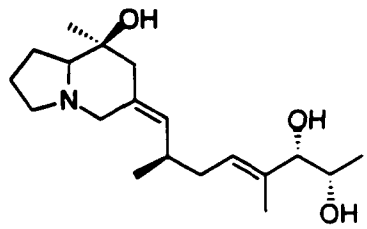
Figure 2.3



Slaframine
2.98



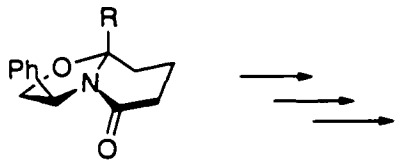
Castanospermine
2.99



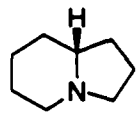
Pumiliotoxin B
2.100

The construction of optically pure heterocycles using the bicyclic lactam template has been of great interest in our group, and over the years we have published[36] applications of the [4.3.0] bicyclic lactam to construct a variety of alkaloids (e.g. 1-deoxy-6-epicastanospermine and coniceine) (Figure 2.4).

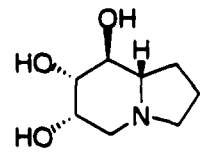
Figure 2.4



2.101



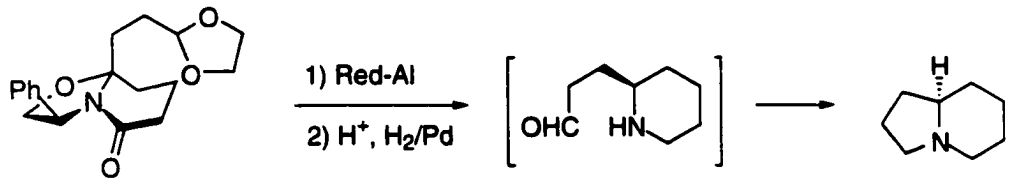
(-)-coniceine
2.102



1-deoxy-6-epicastanospermine
2.103

The synthesis of coniceine (**2.102**) was originally completed in these laboratories using the [4.3.0] bicyclic lactam (**2.104**) (Scheme 2.29). With the appropriate substitution at the angular position in place, reduction to the *N*-benzyl piperidine was followed by hydrogenolysis to the aldehyde intermediate (**2.105**). This intermediate quickly formed the imine that was reduced to coniceine (**2.102**).

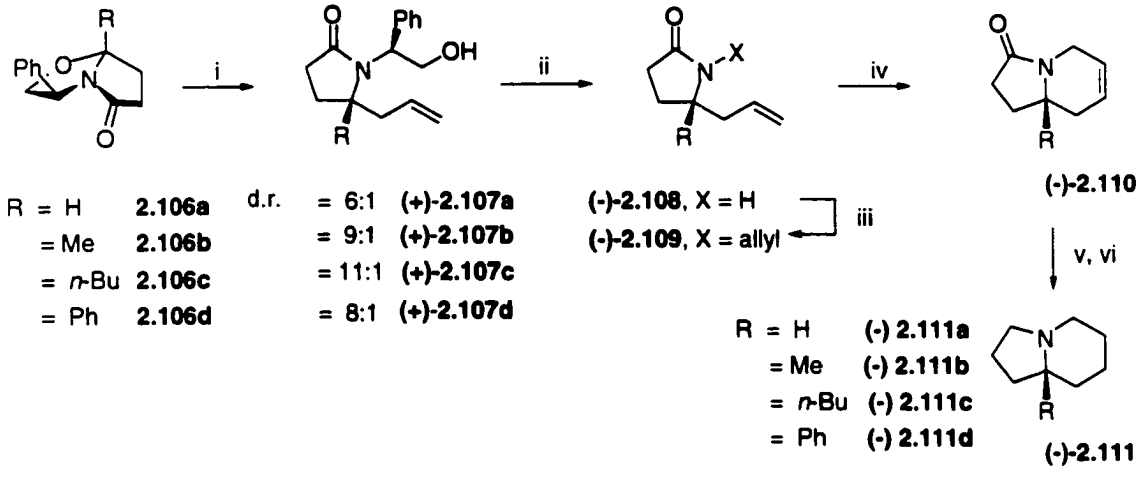
Scheme 2.29



2.104 **2.105** **2.102**

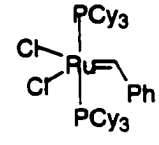
We now wish to report a general protocol utilizing bicyclic lactams **2.106a-d** for the construction of a variety of enantiomerically pure indolizidines (Scheme 2.30) including the naturally occuring parent ring system, (-)-coniceine (**2.111a**).

Scheme 2.30



i. allyltrimethylsilane, $TiCl_4$, 68-79% 6:1-11:1 d.r.; ii. Ca / NH_3, 73-89%; iii. NaH / allylbromide, 81-92%; iv.cat. **2.112** (10 mol%), 89-93%; v. H_2, $Pd(OH)_2$, 92-96%; vi. $LiAlH_4$, 83-89%

2.112 =



The synthetic route to the 1-azabicyclic systems (**2.111**) began by the addition of allyltrimethylsilane to a dichloromethane solution of the

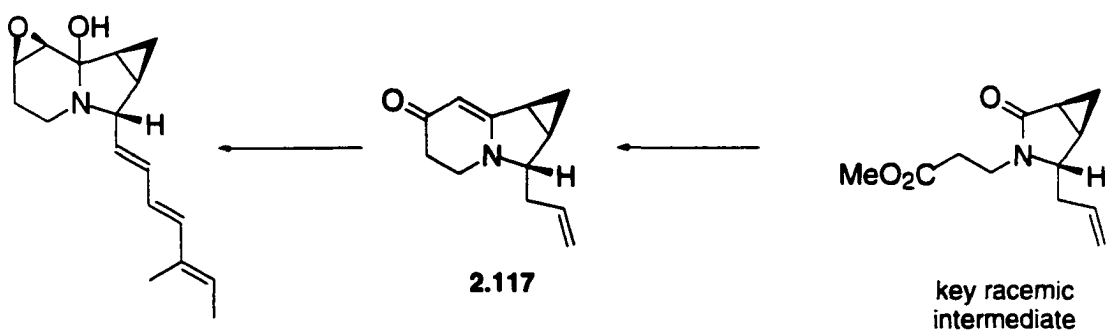
enantiomerically pure bicyclic lactam and titanium tetrachloride to furnish the 5-substituted pyrrolidinone (**2.107**) with diastereomeric ratios ranging from 6:1 to 11:1. After the diastereomers in **2.107** were separated (silica gel column chromatography) the chiral auxiliary was removed by dissolving metal reduction using calcium metal (NH_3, -78° to -30°C over 4h) affording **2.108**. It is noteworthy that in the case containing two possible benzylic cleavage sites (**2.108d**), only the exocyclic *N*-benzyl bond was cleaved. Introduction of the *N*-allyl group to give **2.109** proceeded smoothly by addition of allyl bromide to the sodium salt of the pyrrolidinone (**2.108**). The bis-olefin (**2.109**) was subjected to a ring-closing-metathesis (10 mol% **2.112**, 25 °C, dichloroethane) to afford the indolizidinones **5** in excellent yields.[37] Hydrogenation of the olefinic bond and reduction of the lactam carbonyl provided the target compounds (**2.111a-d**) in 32-51% overall yield. In the case where R = H, the reaction sequence provided a 49% overall yield of (-)-coniceine, which was identical with the data previously reported from these laboratories.

In summary, a general method for the construction of a variety of optically pure indolizidines using the chiral non-racemic [3.3.0] bicyclic lactams (**2.106a-d**) in combination with ring-closing-metathesis has been illustrated. The utility of this method is exemplified by the synthesis of (-)-coniceine with excellent stereocontrol and overall yield.

II.3.b. An Asymmetric Synthesis of the Key Precursor to (-)-Indolizomycin

Indolizomycin (**2.116**) is a bioengineered antibiotic obtained from the protoplast fusion of *Streptomyces tenjimariensis* and *Steptomyces grisline* (Figure 2.5).[38] This novel strategy for the generation of mutant natural products was reported by Umezawa. Umezawa co-joined two inactive (i.e. non-antibiotic-producting) strains to produce a particularly active one termed SK2-52 which furnished indolizomycin. Although the antibacterial properties are not exceptional, the structural complexity enticed Danishefsky to undertake its racemic synthesis.[39] Analysis of the route that Danishefsky employed revealed a wonderful opportunity for us to apply recently developed methodology toward an early intermediate in this synthesis (**2.118**). Additionally, the investigation has the potential for us to further understand the effects structural changes in the bicyclic lactam have on the stereochemical outcome of allylsilane additions.

Figure 2.5



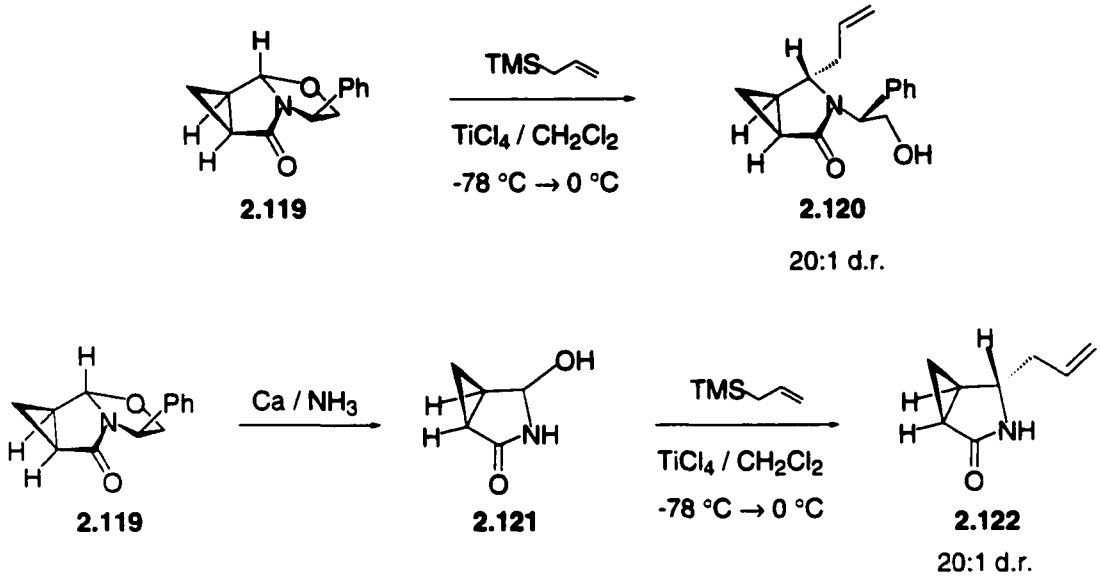
(±)-indolizomycin
2.116

2.117

key racemic intermediate
(±) - **2.118**

The construction of the requisite unsaturated bicyclic lactam (**2.127**) was accomplished by heating (*R*)-phenylglycinol with succinic anhydride affording the imide (**2.125**) in good yield (Scheme 2.33). The imide was selectively reduced with ethanolic sodium borohydride and subsequent acidification produced bicyclic lactam (**2.126**) in excellent yield. Introduction of the unsaturation required in **2.127** was accomplished *via* treatment of the potassium enolate of **2.126** with methylphenylsulfinate followed by heating in toluene as described previously.[40] Treatment of bicyclic lactam **2.127** with dimethylsulfoxonium methylide[41] provided the cyclopropyl substituted bicyclic lactam (**2.119**) in 80% yield as a 20:1 mixture of diastereomers. The *exo* entry of the methylene group to **2.127** was in agreement with earlier reports which showed the *exo* cycloaddition products predominates when the angular substituent is hydrogen.[42] The reverse (*endo* entry) was found when angular substituents were larger (e.g. methyl, phenyl). Cyclopropyl derivative **2.119** was treated with allyltrimethylsilane in the presence of stoichiometric $TiCl_4$ to effect addition at the angular position providing **2.120** in 83% yield as a 20:1 mixture of diastereomers.[33] This is a noticeable improvement from the simple cyclopropanation reported previously. In order to determine which factors had the greatest influence on the stereochemical outcome, the chiral auxiliary was removed *via* dissolving metal reduction to afford the carbinol-amide (**2.121**). Lewis acid mediated addition of allyltrimethylsilane to the bicyclic carbinol-amide proceeded with equal stereoselectivity (Scheme 2.31).

Scheme 2.31

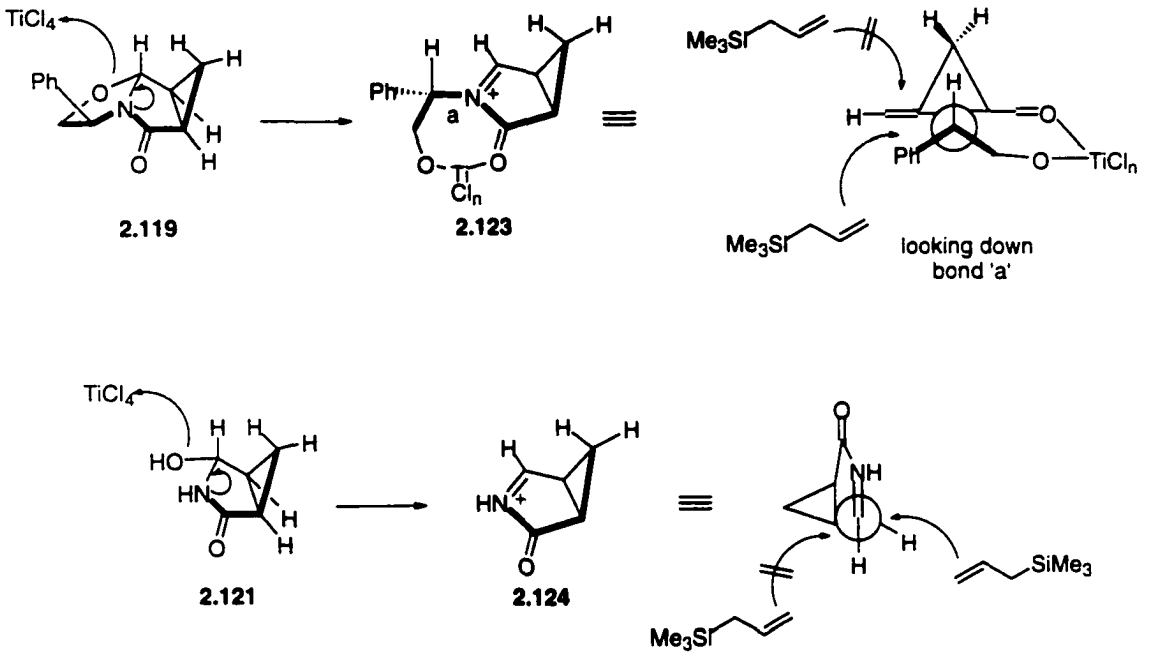


2.119 → **2.120** (20:1 d.r.)

2.119 → **2.121** → **2.122** (20:1 d.r.)

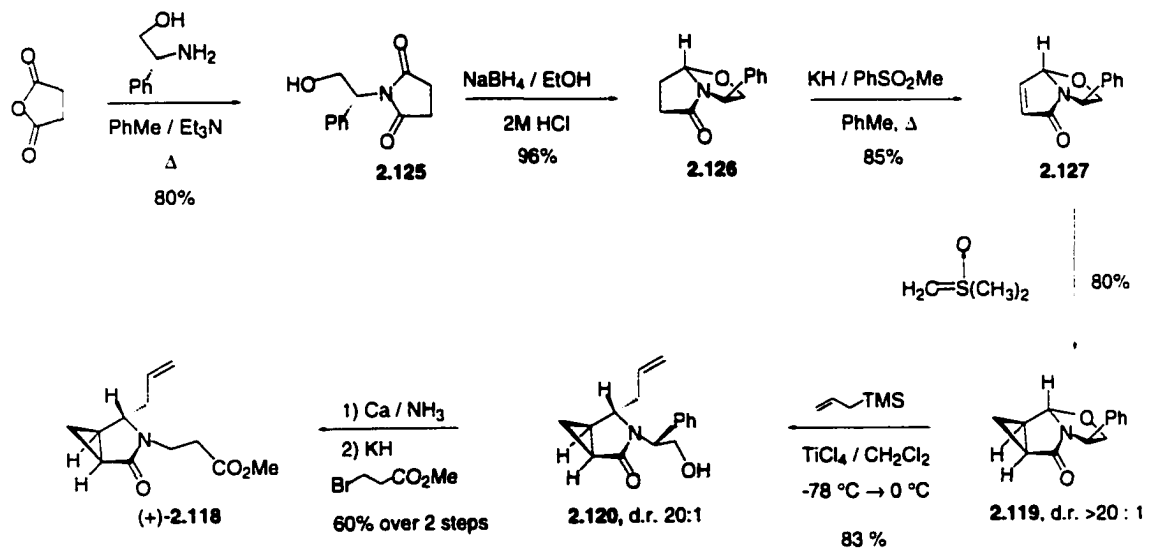
This experiment suggests that the majority of the stereochemical influence comes from the strong 1,2-interaction between the incoming nucleophile and the cyclopropyl moiety adjacent to the *N*-acyliminium ion (**2.123**, **2.124**) (Scheme 2.32).

Scheme 2.32



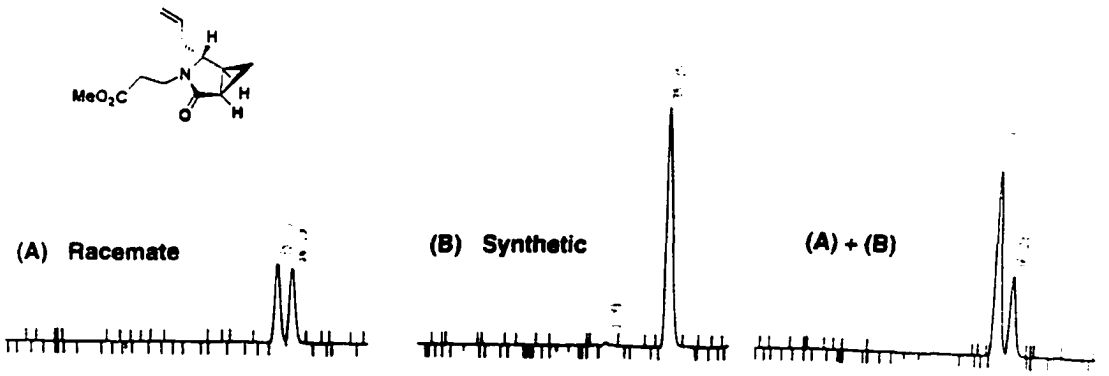
The synthesis was completed by the reductive removal of the auxiliary with Ca/NH_3 followed by *N*-alkylation (KH, methyl 3-bromopropionate) to afford (+)-**2.118** in 60% overall yield from **2.120**.

Scheme 2.33



The optical purity of substituted lactam (+)-**2.118** was determined using chiral GLC (Chiraldex G-PN, 30 m, 170 °C isotherm, Figure 2.6) and was found to be >99% e.e. by comparison to a racemic sample. All physical and spectral data were identical to those reported earlier.[43]

Figure 2.6



Two key observations were made during this work: 1) the cyclopropyl moiety in **2.119** appears to be a very important steric determinant in the stereoselectivity of allylsilane addition to the angular position and, 2) the mildness of the calcium metal reductive debenzylation of lactam **2.120** in the presence of other reducible groups, proved to be very efficient for accessing the *N*-unsubstituted pyrrolidinone. This reduction has previously been employed in our laboratories for the preparation of (-)-Rolipram where it was observed that use of the sodium, lithium, or potassium-ammonia system consistently provided lower yields.[44]

In summary, we have completed an asymmetric synthesis of the key precursor (**2.118**) to (-)-indolizomycin, extending the utility of the Sakurai additions to conformationally constrained bicyclic lactams.

II.4. Summary

In summary, the application of allylsilane additions to the bicyclic lactam have been investigated. The annulation reaction employing allyldimethyltritylsilane has offered access to cyclobutane-fused pyrrolidines which lead to the examination of other addition reactions. During the examinations of the Sakurai reaction a heretofore unseen steric effect was discovered involving the addition of allyltrimethylsilane to α,β-unsaturated bicyclic lactams. The addition of allyltrimethylsilane to the *N*,*O*-acetal of the [3.3.0]bicyclic lactam was explored and lead to an efficient method for the construction of indolizidines (including (+)-coniceine) and the key precursor to Danishefsky's synthesis of indolizomycin.

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II.6. EXPERIMENTAL SECTION

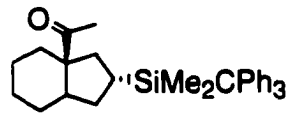
General Methods: All ^{1}H NMR spectra were recorded on a Varian Unity 300 MHz spectrometer. Data are reported as follows: chemical shifts, in parts per million downfield of internal tetramethylsilane (TMS), (multiplicity, coupling constat(s), number of protons). ^{13}C NMR spectra were recorded at 75 MHz and were also obtained on a Varian Unity 300 MHz instrument. Chemical shifts are referenced to the central peak of the deuteriochloroform triplet (77.0 ppm). Fourier transrom infrared absorption spectra were recorded on a Perkin-Elmer model PE 1600 spectrophotometer. Optical rotations were determined with a Rudolph Research Autopol III instrument and are referenced to the D-line of sodium. Melting points were measured in open pyrex capillary tubes on a MEL-TEMP melting point apparatus. Melting points are uncorrected. Elemental analyses were obtained from Atlantic Microlabs of Norcross, GA. Thin layer chromatography and flash chromatography were performed with E. Merck or Amicon Matrix silica gel (230-400 mesh). All non-aqueous reactions were conducted under an argon atmosphere in a flame dried apparatus. All reagents were purchased from Aldrich and used without purification unless otherwise noted. Grubbs' catalyst was purchased from Strem Chemicals and used without further purification. Dichloromethane and toluene were dried via distillation from calcium hydride prior to use. Tetrahydrofuran and diethyl ether were dried via

distillation from sodiumbenzophenone ketyl. Concentrations were performed under reduced pressure with a Buchi rotary evaporator. Low resolution mass spectral data were obtained on a Hewlett-Packard 5890 GC-MS/HP 5970 MSD, and high resolution mass spectral analyses were performed on a VG Autospec (Fisons Instruments) by Colorado State University staff. X-ray analysis of triol **2.61** was performed by Suzie Miller at Colorado State University.

Allyldimethyltritylsilane (ADTS), 2.20d. To a solution of bromodimethyl(triphenylmethyl)silane (6.06 g, 15.9 mmol) in dry THF (110 mL), was added a solution of allylmagnesium chloride (2.0 M in THF, 47.7 mmol, 24 mL). The resulting mixture was brought to reflux and stirred for 12 h. After cooling to rt, the reaction mixture was slowly poured into a separatory funnel containing cold sat. aq. NH_4Cl and Et_2O. The layers were separated and the aqueous layer was washed with Et_2O. The organic layers were combined, washed with brine and dried over $MgSO_4$. Filtration and rotary evaporation then gave a crude brown solid which was purified *via* flash chromatography (elution with hexane) to afford the allylsilane as a colorless solid (4.22 g, 77% yield), mp 87-89 °C (Et_2O/Hex). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 6H), 1.58 (d, J = 8.2 Hz, 2H), 4.74-4.83 (m, 2H), 5.58-5.72 (m, 1H), 7.00-7.04 (m, 6H), 7.14-7.28 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.7, 24.8, 53.9, 113.7, 125.5, 127.9, 130.1,

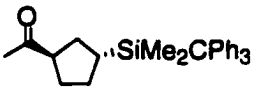
135.1, 146.3; IR (neat) 3052, 700 cm^{-1}; HRMS (EI), (M+) Calcd for $C_{24}H_{26}Si$: 342.1804, found: 342.1806.

General Method for Cyclopentannulation. To a solution of the electron deficient olefin (0.30 mmol) in CH_2Cl_2 (3 mL) at -78 °C was added titanium (IV) chloride (0.36 mmol, 1.0 M solution in dichloromethane) dropwise *via* syringe. After 5 min of vigorous stirring, allyltrityldimethylsilane (0.12 g, 0.36 mmol) was added dropwise as a solution in CH_2Cl_2. The reaction temperature was slowly allowed to reach 0 °C (approximately 4 h). The reaction was monitored *via* TLC (1:4 EtOAc/Hex) and quenched by the addition of sat. aq. NH_4Cl, resulting in a colorless mixture. The layers were separated and the aqueous layer was washed with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *via* rotary evaporation to yield the crude product which was purified via flash chromatography (9:1 Hex/EtOAc) and analyzed as shown below.

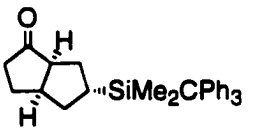


***trans*-1-Acetyl-8-(dimethyltritylsilyl)bicyclo[4.3.0]nonane 2.26.** Colorless solid (0.11 g, 85% yield), mp 152-153 °C (EtOAc/Hex): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.17 (s, 3H), 0.21 (s, 3H), 1.09-1.60 (m, 12H), 1.69-1.76 (m, 1H), 1.93 (s, 3H), 2.21-2.29 (m, 1H), 7.01-7.27 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -1.8, -0.7, 22.0, 23.3, 24.2, 25.3, 26.6, 31.4, 33.6, 38.6, 40.7, 54.1, 58.0, 125.5, 127.9,

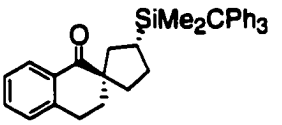
130.2, 146.4, 212.9; IR (neat) 1698 cm^{-1}; HRMS (FAB), (M+) Calcd for $C_{32}H_{38}OSi$: 466.2692, found: 466.2676.



***trans*-1-Acetyl-3-(dimethyltritylsilyl)cyclopentane 2.27.** Colorless oil (80 mg, 78% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.16 (s, 3H), 0.18 (s, 3H), 1.01-1.25 (m, 2H), 1.71-1.79 (m, 1H), 1.98 (s, 3H), 2.73-2.76 (m, 1H), 7.04-7.06 (m, 6H), 7.13-7.26 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -1.7, -1.0, 27.1, 28.4, 29.4, 30.6, 31.7, 52.3, 54.1, 125.5, 127.9, 130.2, 146.4, 210.7; IR (neat) 1707 cm^{-1}.



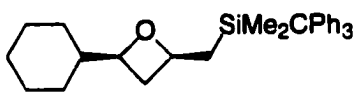
2-Oxo-7-(dimethyltritylsilyl)bicyclo[3.3.0]octane 2.31. Colorless oil (70 mg, 46% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.31 (s, 3H), 0.32 (s, 3H), 0.86-1.13 (m, 1H), 1.15-1.32 (m, 1H), 1.60-1.72 (m, 1H), 1.94 (app q, J = 8.1Hz, 1H), 2.09-2.23 (m, 2H), 2.28-2.41 (m, 2H), 2.64 (app t, J = 10.1Hz, 1H), 2.85-2.88 (m, 1H), 7.17-7.48 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -1.8, -0.7, 25.6, 27.3, 34.3, 38.1, 39.5, 40.3, 52.0, 54.3, 125.5, 127.9, 130.2, 146.3, 223.1; IR (neat) 1651 cm^{-1}.



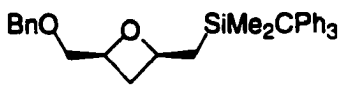
Spiro silyl ketone 2.32. Colorless oil (50 mg, 68% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.31 (s, 3H), 0.32 (s, 3H), 0.86-1.13 (m, 1H), 1.15-1.32 (m, 1H), 1.60-

1.72 (m, 1H), 1.94 (app q, J = 8.1 Hz, 1H), 2.09-2.23 (m, 2H), 2.28-2.41 (m, 2H), 2.64 (app t J = 10.1 Hz, 1H), 2.85-2.88 (m, 1H), 7.17-7.48 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -1.8, -0.7, 25.6, 27.3, 34.3, 38.1, 39.5, 40.3, 52.0, 54.3, 125.5, 127.9, 130.2, 146.3, 223.1; IR (neat) 1651 cm^{-1}; HRMS (EI), (M+) Calcd for $C_{35}H_{36}OSi$: 500.2535, found: 500.2537.

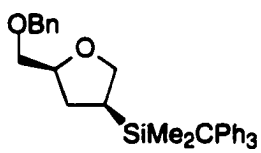
General Procedure for Annulation to Aldehydes. To a solution of aldehyde (0.18 mmol) and **1d** (0.27 mmol) in toluene (1.0 mL) was added zirconium (IV) chloride (0.19 mmol) at -20 °C. After stirring at -20 °C for 30 min, the reaction was treated with sat. aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude products were purified *via* flash chromatography eluting with EtOAc/Hex (1:9).



***cis*-2-Cyclohexyl-4-(dimethyltritylsilyl)methyl oxetane 2.45a.** Colorless oil (110 mg, 55% yield): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.39 (s, 3H), 0.41 (s, 3H), 1.18-2.1 (m, 13H), 3.58-3.82 (m, 1H), 4.22-4.35 (m, 1H), 6.95-7.05 (d, J = 9 Hz, 6H), 7.12 (m, 9H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.1, 1.3, 24.2, 25.1, 26.2, 27.8 , 28.9, 29.2, 39.8, 46.5, 54.1, 59.8, 72.6, 125.6, 128.0, 130.1, 146.3; IR (neat) 3051, 850 cm^{-1}.



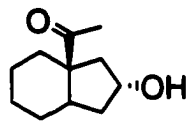
***cis*-2-Benzyloxymethyl-4-(dimethyltritylsilyl)methyl oxetane 2.45b.** Colorless oil (220 mg, 88% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.16 (s, 3H), 0.19 (s, 3H), 1.03-1.28 (m, 2H), 1.46-1.68 (m, 2H), 3.14-3.24 (m, 1H), 3.29-3.38 (m, 1H), 3.91-4.04 (m, 1H), 4.16-4.28 (m, 1H), 4.42 (app t, *J* = 9 Hz, 2H), 6.86-6.91 (m, 6H), 7.02-7.28 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.1, 1.3, 29.2, 39.8, 42.5, 54.1, 59.8, 68.7, 72.6, 74.4, 125.6, 126.9, 128.0, 130.1, 137.5, 146.3; IR (neat) 3063, 845 cm^{-1}; HRMS (CI), (MNH_4^+) Calcd for $C_{33}H_{40}O_2NSi$: 510.2828, found: 510.2828.



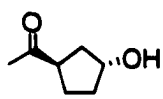
***cis*-2-Benzyloxymethyl-4-(dimethyltritylsilyl)tetrahydrofuran 2.43.** To a solution of aldehyde (0.18 mmol) and allylsilane (0.27 mmol) in toluene (1.0 mL) was added BF_3•OEt_2 (0.19 mmol) at -78 °C. After stirring at -78 °C for 12 h, the reaction was allowed to warm to rt and was treated with sat. aq NH_4Cl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with EtOAc/Hex (1:9) to afford the oxetane as a colorless oil (200 mg, 83% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.16 (s, 3H), 0.19 (s, 3H), 1.03-1.28 (m, 2H), 1.46-1.68 (m, 2H), 3.14-3.24 (m, 1H), 3.29-3.38 (m, 1H), 3.91-4.04 (m, 1H), 4.16-4.28 (m, 1H), 4.42 (app t, *J* = 9 Hz, 2H), 6.86-6.91 (m, 6H), 7.02-7.28 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.1, 1.3, 25.2, 40.8, 43.5, 53.1, 60.8, 68.7, 72.6, 74.4, 125.6, 125.9,

128.0, 130.1, 137.5, 146.3; IR (neat) 3041, 863 cm^{-1}; HRMS (CI), (MNH_4^+) Calcd for $C_{33}H_{40}O_2NSi$: 510.2828, found: 510.2825.

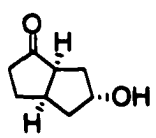
General Procedure for Oxidative Removal of Silicon. A single-neck, round-bottomed flask, equipped with a Teflon stirbar, was charged with cesium fluoride (0.13 g, 0.87 mmol) and the flask was heated under vacuum with a heat gun. After cooling to rt, the flask was filled with argon. Anhydrous MeOH (0.5 mL) and THF (2.5 mL) were added to the flask and the silyl adduct (0.17 mmol) was added as a solution in THF (1.0 mL) *via* syringe. The reaction was stirred at rt for 4 h, then was partitioned between water and CH_2Cl_2, the layers separated, and the aqueous layer was washed with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was dissolved in THF (2.5 mL) and MeOH (1.0 mL), and sequentially treated with $KHCO_3$ (30 mg, 0.29 mmol), 30% H_2O_2 (9.79 M in H_2O, 3.92 mmol, 0.40 mL), and tetrabutylammonium fluoride (1.0 M in THF, 0.25 mmol, 0.25 mL). The reaction mixture was vigorously stirred at rt for 5 h and then partitioned between water and CH_2Cl_2. The layers were separated and the aqueous layer was washed with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude products were purified by flash chromatography eluting with EtOAc/Hex (1:9).



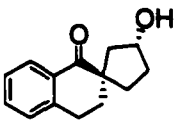
***trans*-1-Acetyl-8-hydroxybicyclo[4.3.0]nonane 2.33.** Colorless oil (30 mg, 67% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15-1.23 (m, 1H), 1.33-1.77 (m, 8H), 1.82-1.89 (m, 1H), 1.98-2.16 (m, 2H), 2.09 (s, 3H), 2.31-2.36 (m, 1H), 4.29-4.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 22.9, 25.4, 26.1, 30.0, 38.2, 39.3, 44.4, 57.7, 71.2, 212.7; IR (neat): 3420 cm^{-1}; HRMS (FAB), (M^+) Calcd for $C_{11}H_{18}O_2$: 183.1385, found: 183.1387.



***trans*-1-Acetyl-3-hydroxycyclopentane 2.34.** Colorless oil (34 mg, 69% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57-2.10 (m, 6H), 2.15 (s, 3H), 3.16 (dddd, J = 9.5, 7.0, 5.5, 4.2 Hz, 1H), 4.38 (dddd, J = 8.5, 7.0, 3.5, 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.1, 29.1, 34.9, 37.8, 49.8, 73.6, 210.7; IR (neat) 3390 cm^{-1}.

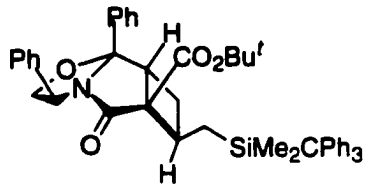


Hydroxy Ketone 2.38. Colorless oil (71 mg, 93% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17-1.29 (m, 1H), 1.34-1.80 (m, 7H), 1.82-1.92 (m, 1H), 2.01-2.14 (m, 2H), 2.29-2.33 (m, 1H), 4.24-4.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.1, 31.3, 39.2, 40.3, 44.4, 56.7, 73.2, 192.7; IR (neat) 3392 cm^{-1}.

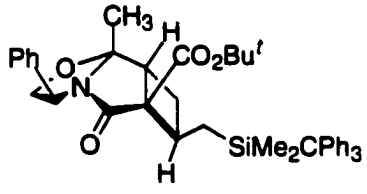


Spiro Hydroxy Ketone 2.39. Colorless oil (61 mg, 78% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15-1.32 (m, 1H), 1.60-1.72 (m, 1H), 1.94 (app q, *J* = 8.1 Hz, 1H), 2.09-2.23 (m, 2H), 2.28-2.41 (m, 2H), 2.64 (app t, *J* = 10.1 Hz, 1H), 2.85-2.88 (m, 1H), 7.17-7.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.6, 29.7, 32.8, 34.9, 36.4, 44.0, 52.5, 74.1, 126.6, 128.1, 128.6, 131.3, 133.1, 143.7, 201.7; IR (neat) 3399 cm^{-1}; Anal. Calcd for $C_{14}H_{16}O_2$: C 77.75, H 7.46, found: C 77.83, H 7.52.

General Method for Cyclopentannulation onto Bicyclic Lactam 2.48. To a solution of the bicyclic lactam **2.48** (1.2 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added titanium (IV) chloride (1.2 mmol, 1.0 M solution in CH_2Cl_2) dropwise *via* syringe. After 5 min of vigorous stirring, allyltrityldimethylsilane (600 mg, 1.75 mmol) was added as a solution in CH_2Cl_2 dropwise. The reaction temperature was allowed to rise to 0 °C over 4 h. The reaction was monitored *via* TLC (4:1 Hex/EtOAc) then treated with sat. aq. NH_4Cl, resulting in a colorless mixture. The layers were separated and the aqueous layer was washed with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the crude products **2.49** and **2.50**. The crude products were purified by flash chromatography on SiO_2 eluting with EtOAc/Hex (1:1).

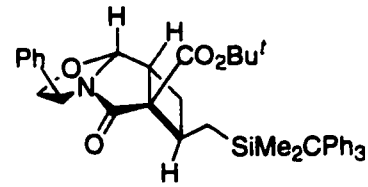


Bicyclic Lactam 2.49a. Colorless solid (0.59 g, 68% yield), mp 180 °C (EtOAc/Hex). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.11 (s, 3H), 0.14 (s, 3H), 0.83 (app t, *J* = 14.1 Hz, 1H), 1.10 (dd, *J* = 13.9, 3.0, Hz, 1H), 1.19 (s, 9H), 1.68 (ddd, *J* = 12.6, 9.0, 3.5, Hz, 1H), 2.55-2.65 (m, 1H), 2.74-2.82 (m, 1H), 3.23 (dd, *J* = 8.8, 7.3 Hz, 1H), 3.95 (app t, *J* = 9.1 Hz, 1H), 4.73 (dd, *J* = 8.8, 7.7 Hz, 1H), 5.12 (app t, *J* = 8.3, 1H), 6.95-7.34 (m, 25H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.4, 1.3, 19.9, 25.0, 27.8, 37.9, 44.5, 53.8, 59.5, 64.4, 75.2, 81.8, 100.1, 125.5, 127.2, 127.6, 128.0, 128.2, 128.4, 129.9, 138.0, 142.2, 165.8, 176.1; IR (neat) 1736, 1717 cm^{-1}. $[\alpha]_D^{23}$ = - 11.5 (c = 0.80, CH_2Cl_2).

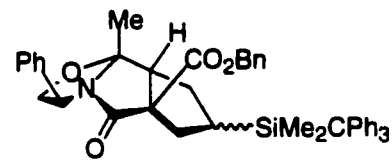


Bicyclic Lactam 2.49b. Colorless solid (0.15 g, 75% yield), mp 140-143 °C (EtOAc/Hex). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.13 (s, 6H), 0.81 (app t, *J* = 14.2 Hz, 1H), 1.22-1.26 (m, 1H), 1.30 (s , 9H), 1.48 (s, 3H), 1.49-1.60 (m, 1 H), 2.28-2.38 (m, 1H), 2.64-2.71 (m, 1H), 3.23 (app t, *J* = 8.2 Hz, 1H), 4.18 (dd, *J* = 8.7, 7.8 Hz, 1H), 4.74 (app t, *J* = 8.7 Hz, 1H), 5.13 (app t, *J* = 7.8 Hz, 1H), 6.98-7.35 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.4, 1.5, 19.8, 24.0, 24.8, 28.0, 37.7, 43.5, 54.0, 57.6, 65.1, 75.2, 82.0, 98.1, 125.6, 125.7, 127.6, 128.1, 128.8, 130.0, 139.4, 146.3, 166.7, 174.5; IR (neat) 1735, 1712 cm^{-1}; Anal. Calcd for

$C_{39}H_{53}NO_4Si$: C 76.67, H 7.20, found C 76.70, H 7.24; $[\alpha]_D^{23}$ = +32.3 (c = 0.86, CH_2Cl_2).



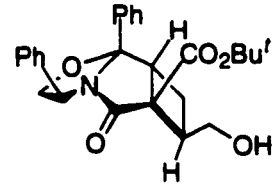
Bicyclic Lactam 2.49c. Colorless solid (100 mg, 50% yield), mp 82-85 °C (EtOAc/Hex). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.11 (s, 3H), 0.14, (s, 3H), 0.83 (app t, *J* = 14.1 Hz, 1H), 1.30 (s, 9H), 1.40 (dd, *J* = 14.2, 2.7 Hz, 1H), 2.00-2.18 (m, 2H), 2.74-2.83 (m, 1H), 3.18 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.78 (dd, *J* = 8.6, 7.1 Hz, 1H), 4.47 (app t, *J* = 8.3 Hz, 1H), 4.92 (s, 1H), 5.14 (app t, *J* = 7.5 Hz, 1H), 6.96-7.36 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.3, 1.2, 21.7, 28.0, 30.4 35.7, 40.6, 53.7, 58.9, 60.8, 73.0, 82.0, 96.1, 125.6, 126.1, 127.7, 128.0, 128.8, 129.9, 139.8, 146.1, 166.4, 177.9; IR (neat) 1744, 1712 cm^{-1}; Anal. Calcd for $C_{41}H_{45}NO_4Si$: C 76.48, H 7.04, found: C 76.30, H 7.09; $[\alpha]_D^{23}$ = +90.6 (c = 0.64, CH_2Cl_2).



Bicyclic Lactam 2.51. Colorless oil (50 mg, 21% yield) as an inseparable mixture of diastereomers. Major diastereomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.13 (s, 6H), 0.79-0.88 (m, 1H), 1.28 (s, 3H), 1.39-1.50 (m, 1H), 1.89 (dd, *J* = 9.3 Hz, 1H), 2.28-2.38 (m, 1H), 2.41-2.48 (m, 1H), 2.83 (d, *J* = 8.2 Hz, 1H), 3.9 (dd, *J* = 8.7, 7.8 Hz, 1H), 4.24 (app t, *J* = 8.7 Hz, 1H), 4.73 (app t, *J* = 7.8 Hz, 1H), 5.1 (s,

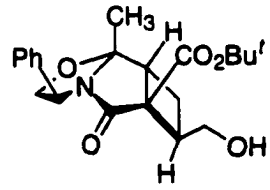
2H), 6.98-7.35 (m, 25H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.4, 1.3, 19.9, 25.0, 27.8, 37.9, 44.5, 53.8, 59.5, 64.4, 75.2, 81.8, 100.1, 126.5, 127.2, 127.6, 128.0, 128.2, 128.4, 131.9, 138.0, 142.2, 165.8, 176.1; IR (neat) 1748, 1716 cm^{-1}.

General Procedure for the Oxidative Removal of Silicon. To a solution of the silylcyclobutane **2.49** (0.47 mmol) in 10 mL of THF at 0 °C, was added tetrabutylammonium hydroxide (0.94 mL, 1.0 M in MeOH). Hydrogen peroxide (1.40 mL, 30% solution in water) was added and the reaction was stirred vigorously for 24 h, and then diluted with CH_2Cl_2 and water. The layers were separated and the aqueous layer was washed with CH_2Cl_2. The combined layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a crude oil. The crude products were purified by flash chromoatography eluting with EtOAc/Hex (1:1) to yield the hydroxymethylcyclobutane **2.56**.

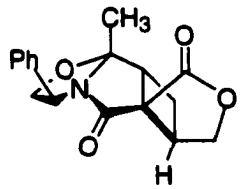


Bicyclic Lactam 2.56a. Viscous oil/foam (50 mg, 63% yield). ^1H NMR ($CDCl_3$, D_2O wash, 300 MHz) δ 1.40 (s, 9 H), 2.03 (ddd, *J* = 13.2, 9.3, 4.1 Hz, 1H), 2.58 (ddd, *J* = 12.9, 9.4, 6.8 Hz, 1H), 2.80 (m, 1H), 3.27 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.72 (dd, *J* = 12.1, 6.0 Hz, 1H), 3.85 (dd, *J* = 12.0, 3.8 Hz, 1H), 3.96 (app t, *J* = 9.0 Hz, 1H), 4.73 (br, s, HOD), 4.78 (dd, *J* = 9.0, 7.8 Hz, 1H), 5.17 (app t, *J* = 8.1 Hz, 1H), 7.09-7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 27.8, 41.7, 47.5, 59.1,

62.0, 63.0, 74.7, 83.3, 100.6, 125.8, 126.9, 127.6, 128.3, 128.5, 138.0, 141.9, 168.1, 176.6; IR (neat) 1731 cm^{-1}. HRMS: (FAB), (M+H) Calcd for $C_{26}H_{29}NO_5$: 436.2124, found: 436.2130; $[\alpha]_D^{23}$ = +19.1 (c = 0.68, CH_2Cl_2).

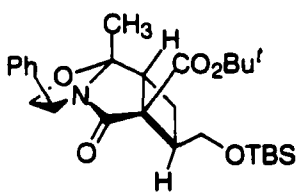


Bicyclic Lactam 2.56b. Viscous oil/foam (33 mg, 53% yield). ^1H NMR ($CDCl_3$, D_2O wash, 300 MHz) δ 1.48 (s, 3H), 1.51 (s, 9H), 1.80 (ddd, *J* = 13.0, 9.3, 3.6 Hz, 1H), 2.33 (ddd, *J* = 13.1, 9.5, 7.2 Hz, 1H), 2.70 (m, 1H), 3.20 (dd, *J* = 9.2, 7.4 Hz, 1H), 3.78 (dd, *J* = 11.8, 6.3 Hz, 1H), 3.88 (dd, *J* = 11.7, 3.8 Hz, 1H), 4.22 (dd, *J* = 8.8, 7.3 Hz, 1H), 4.76 (br. s, HOD), 4.81 (app t, *J* = 8.7 Hz, 1H), 5.18 (app t, *J* = 7.6 Hz, 1H), 7.20-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 24.6, 28.0, 41.1, 46.6, 56.9, 62.5, 63.4, 75.3, 83.1, 98.4, 125.3, 127.5, 128.7, 168.6, 174.4; IR (film) 3478, 1734, 1710 cm^{-1}. HRMS: (FAB), (M+H) Calcd for $C_{21}H_{27}NO_5$: 374.1967, found: 374.1969; $[\alpha]_D^{23}$ = +103.1 (c = 1.3, CH_2Cl_2).



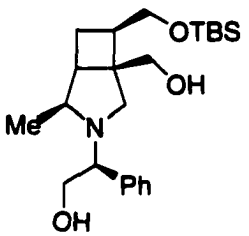
Lactone 2.58. To a flame-dried round bottom flask was added bicyclic lactam **2.56b** (400 mg, 1.07 mmol) followed by 5 mL of dichloromethane. PTSA (5 mg) was added at room temperature and the reaction was stirred under an argon atmosphere for 2 h. The reaction mixture was concentrated under reduced

pressure to afford a pale yellow residue. The crude mixture was purified *via* chromatography (SiO_2, 4:1 Hex/EtOAc) to give a colorless solid (291 mg, 91%), mp = 112-114 °C (EtOAc/Hex), $[\alpha]_D^{23}$ = 24° (*c* = 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.42 (s, 3H), 2.07 (ddd, *J* = 3, 8, 11 Hz, 1H), 2.83 (ddd, *J* = 6, 8, 12 Hz, 1H), 3.17-3.28 (m, 2H), 4.24 (dd, J = 7, 9 Hz, 1H), 4.36 (J = 5, 10 Hz, 1H), 4.70 (app. t, J = 8 Hz, 1H), 4.83 (app. t, J = 8Hz, 1H), 5.26 (app. t, J = 8 Hz, 1H), 7.23-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75MHz) δ = 23.2, 25.4, 36.5, 44.5, 56.7, 57.6, 74.1, 74.3, 97.9, 125.2, 127.5, 128.7, 139.0, 172.4, 172.9; IR (film) 1769, 1708 cm^{-1}.



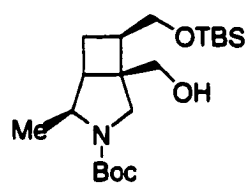
Lactam 2.59b. To a dichloromethane solution of **2.56b** (128 mg, 0.34 mmol) was added imidazole (22 mg, 1.1 equiv) follwed by *tert*-butyldimethylsilyl chloride (56 mg, 1.1 equiv). A voluminous colorless precipitate formed and after 1 h the reaction mixture was partitioned between dichloromethane and water. The aqueous layer was washed with dichloromethane, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to a colorless oil. The residue was chromatographed (SiO_2, 4:1 Hex/EtOAc) to afford a colorless oil (165 mg, 89%). $[\alpha]_D^{23}$ = 73 (c = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.13 (s, 3H), 0.14 (s, 3H), 0.98 (s, 9H), 1.56 (s, 9H), 1.62 (s, 3H), 1.95 (ddd, *J* = 12, 9, 3 Hz, 1H), 2.33 (ddd, *J* = 12, 9, 8 Hz, 1H), 2.70 (ddd, *J* = 9, 6, 2 Hz, 1H), 3.30

(dd, J = 9, 8 Hz, 1H), 3.77 (dd, J = 10, 3 Hz, 1H), 4.16 (dd, J = 10, 4 Hz, 1H), 4.28 (dd, J = 9, 7 Hz, 1H), 4.87 (app. t, J = 8 Hz, 1H), 5.23 (app. t, J = 8 Hz, 1H), 7.23-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = -5.5, -5.3, 18.3, 19.1, 24.6, 25.9, 28.2, 41.2, 46.3, 57.1, 62.1, 62.4, 75.2, 81.7, 98.7, 125.5, 127.5, 128.7, 139.6, 166.7, 174.95; IR (film) 1742, 1711 cm^{-1}; Anal. calcd for $C_{31}H_{41}NO_5Si$: C 66.49, H 8.47, found: C 66.57, H 8.48.



Pyrrolidine 2.60. A THF solution of **2.59b** (130 mg, 0.24 mmol) was cooled to –78 °C and DIBALH(0.9 mL, 10 equiv) was added dropwise *via* syringe. The reaction mixture was allowed to warm to room temperature over 8 hours at which time the reaction was cooled to –78 °C and MeOH was slowly added until the evolution of hydrogen stopped. The solution was warmed to room temperature, an equal volume of 10% KOH was added and vigorously stirred for 1 hour. The mixture was partitioned between dichloromethane and water. The layers were separted, the aqueous layer was washed with dichloromethane, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to a colorless oil. Crude ^1H NMR analysis revealed a single methyl doublet at 0.85 ppm, therefore the d.r. was determined to be >20:1. The residue was chromatographed (SiO_2, Et_2O) to afford a colorless oil (85 mg, 84%) $[\alpha]_D^{23}$ = -6 (c

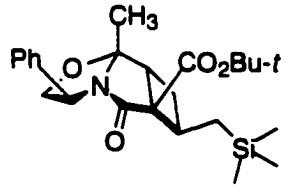
= 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 300MHz) δ = 0.13 (s, 3H), 0.14 (s, 3H), 0.85 (d, J = 9 Hz, 3H), 0.92 (s, 9H), 1.52 (ddd, J = 12, 9, 7 Hz, 1H), 1.76 (ddd, J = 11, 9, 8 Hz, 1H), 1.87 (dd, J = 11, 8 Hz, 1H), 2.36 (ddd, J = 10, 8, 7 Hz, 1H), 2.81 (ddd, J = 11, 7, 6 Hz, 1H), 2.90-3.03 (m, 2H), 3.39 (d, J = 11 Hz, 1H), 3.67 (dd, J = 10, 7 Hz, 1H), 3.80-3.92 (m, 4H), 4.09 (d, J = 11 Hz, 1H), 7.29-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = -5.6, -5.4, 14.2, 18.2, 23.5, 25.8, 41.4, 43.1, 50.5, 58.3, 63.8, 64.7, 65.4, 127.7, 128.4, 128.8; IR (film) 3360, 2957 cm^{-1}. Anal. calcd for $C_{24}H_{41}NO_3Si$: C 68.7, H 9.8, found: C 68.76, H 9.73.



Pyrrolidine 2.62. To an ethanol solution of *N*-benzyl pyrrolidine **2.60** (50 mg, 0.12 mmol) was added $Pd(OH)_2$ and di-*tert*-butylpyrocarbonate (50mg, 1.5 equiv) and stirred under an atmosphere of hydrogen. After 10 h, the reaction solution was purged with argon, filtered through a plug of celite and concentrated to a colorless oil. Column chromatography (SiO_2, 10% MeOH/$CHCl_3$) yielded the pyrrolidine as a colorless oil (43 mg, 91%): $[\alpha]_D^{23}$ = -13 (c = 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.09 (s, 6H), 0.88 (s, 9H), 1.05 (d, J = 11 Hz, 3H), 1.48 (s, 9H), 1.51-1.62 (m, 3H), 1.63-1.79 (br. m, 1H), 1.92-2.1 (br. m, 1H), 2.27-2.41 (br. m, 1H), 3.29-3.41 (m, 2H), 3.63 (dd, J = 11, 9 Hz, 1H), 3.67-3.82 (m, 3H), 3.9-4.11 (br. m, 2H); -5.6, -5.4, 18.2, 19.3, 23.5, 25.8, 28.6, 40.8, 43.3, 56.8, 59.6,

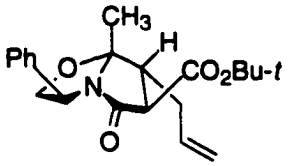
64.6, 65.3, 79.2, 100.1, 154.6; IR(film) 3456, 1692 cm^{-1}. Anal. calcd for $C_{21}H_{41}NO_4Si$: C 63.1, H 10.3, found: C 63.04, H 10.39.

General procedure for steric effect study: To a flame dried round bottomed flask was added dichloromethane and cooled to -78 °C. The bicyclic lactam was added followed by 1.5 equivalents of allyltrimethylsilane. The solution was stirred for ca. 15 min. prior to the addition of 1.2 equivalents of $TiCl_4$. The reaction was stirred at -78 °C for 5 h. then quenched by the addition of aq. NH_4Cl. The layers were separated, the aqueous layer was washed with dichloromethane, the combined organic layers were dried over Na_2SO_4 and concentrated to an oil under reduced pressure. The crude reaction mixture was analyzed by ^1H NMR and GC to determine the ration of Sakurai vs. cyclobutane products. Column chromatography (20% Et_2O in Hexane) provided the products as colorless oils/solids.

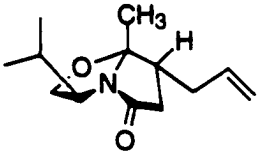


Trimethylsilylmethylcyclobutane 2.68c colorless solid (130 mg, 87%), mp = 99-101 °C (EtOAc/Hex); $[\alpha]_D^{23}$= 24° (*c* = 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.02 (s, 9H), 0.75 (app. t, *J* = 11 Hz, 2H), 1.15 (dd, *J* = 3, 8 Hz, 1H), 1.51 (s, 9H), 1.51 (s, 3H), 1.63 (ddd, *J* = 9, 7, 3 Hz, 1H), 2.48 (ddd, *J* = 9, 6, 3 Hz, 1H), 2.78 (ddd, *J* = 7, 6, 3 Hz, 1H), 3.38 (app. t, *J* = 7 Hz, 1H), 4.25 (dd, *J* = 9, 8

Hz, 1H), 4.81 (app. t, J = 8 Hz, 1H), 5.2 (app. t, J = 9 Hz, 1H), 7.23-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -0.84, 19.48, 23.99, 24.89, 28.22, 37.46, 43.77, 57.45, 75.13, 82.04, 125.64, 127.53, 128.76, 139.60, 174.34; IR (film) 1711cm^{-1}. Anal. calcd for $C_{24}H_{35}NO_4Si$: C 67.1, H 8.2, found: C 67.13, H 8.18.

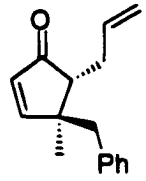


Bicyclic lactam 2.67. colorless solid (98 mg, 84%), mp = 88-89 °C (EtOAc/Hex); $[\alpha]_D^{23}$ = 16° (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.48 (s, 3H), 1.53 (s, 9H), 2.14 (ddd, J = 8, 7, 4 Hz, 1H), 2.61 (ddd, J = 8, 6, 3 Hz, 1H), 2.82 (ddd, J = 7, 6, 3 Hz, 1H), 3.31 (d, J = 8 Hz, 1H), 4.15 (dd, J = 9, 8 Hz, 1H), 4.63 (app. t, J = 8 Hz, 1H), 5.2-5.3 (m, 3H), 5.72-5.9 (m. 1H), 7.23-7.48 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.48, 23.99, 24.89, 28.22, 37.46, 43.77, 57.45, 75.13, 82.04, 95.6, 108.9, 125.64, 127.53, 128.76, 159.60, 174.34; IR (film) 1717, 1692 cm^{-1}. Anal. calcd for $C_{21}H_{27}NO_4$: C 70.6, H 7.6, found: C 70.64, H 7.56.



Lactam 2.73. To a dichloromethane solution of lactam (1.12g, 6.2 mmol) **2.72** was added allyltrimethylsilane (5 mL) and cooled to – 78 °C. A dichloromethane

solution of $TiCl_4$ was slowly added *via* syringe and the reaction was allowed to warm to room temperature over 6 h. The reaction was quenched with an aqueous solution of NH_4Cl, the mixture was partitioned between dichloromethane and water, the layers were separated, the aqueous layer was washed with dichloromethane, the combined organic layers were dried over sodium sulfate, filtered and concentrated to an oil. The residue was chromatographed (SiO_2, 4:1 Hex/EtOAc) to provide 940 mg (68 %) of **2.73** as a colorless oil. $[\alpha]_D^{23} = 58°$ (*c* = 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.91 (d, *J* = 7 Hz, 3H), 1.08 (d, *J* = 7 Hz, 3H), 1.5 (s, 3H), 1.63-1.73 (m, 1H), 1.88 (t, *J* = 10 Hz, 1H), 2.11-2.21 (m, 1H), 2.38 (dd, *J* = 9, 7 Hz, 1H), 2.56-2.70 (m, 1H), 2.88-3.02 (m, 1H), 3.62 (ddd, J = 9, 8, 7 Hz, 1H), 3.88 (dd, J = 9, 8 Hz, 1H), 4.19 (dd, J = 9, 8 Hz, 1H), 5.05-5.13 (m, 2H), 5.70-5.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 18.9, 20.4, 24.7, 33.3, 34.6, 41.1, 43.6, 60.9, 65.6, 70.7, 97.3, 116.6, 135.2, 178.5; IR (film) 1692 cm^{-1}. Anal. calcd for $C_{13}H_{21}NO_2$: C 69.92, H 9.48, found: C 69.26, H 9.34.

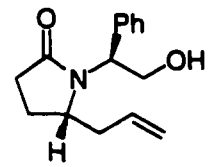


Cyclopentenone 2.76. To a THF solution of bicyclic lactam (250mg,0.76 mmol) **2.74** was added DiBALH (0.8 mL) at – 78 °C and stirred for 1 h. The reaction was quenched with methanol followed by 10% KOH and stirred for 1 h. The reaction mixture was partitioned between dichloromethane and water. The aqueous layer was washed with dichloromethane and the combined organic

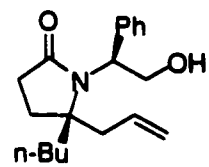
layers were concentrated to an oil. The residue was dissolved in ethanol and an aqueous solution of potassium phosphate was added. The mixture was stirred for 12 h at which time the reaction mixture was partitioned between dichlormethane and water. The layers were separated and the aqueous layer was washed with dichloromethane. The combined organic layers were concentrated to an oil which was dissolved in ethanol and treated with solid KOH. After 1 h, the mixture was again partitioned between dichloromethane and water. The layers were separated, the aqueous layer was washed with dichloromethane, the combined organic layers were dried over sodium sulfate, filtered and concentrated to an oil. The residue was chromatographed (SiO_2, 5:1 Hex/EtOAc) to provide 111 mg (65%) of **2.76** as a colorless oil. $[\alpha]_D^{23}$ 108 (c = 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3H), 2.18 (dd, *J* = 7, 6 Hz, 1H), 2.38 (dd, *J* = 12, 7 Hz, 1H), 2.48 (dd, *J* = 12, 6 Hz, 1H), 2.62 (d, *J* = 12 Hz, 1H), 2.92 (d, *J* = 12 Hz, 1H), 5.08-5.12 (m, 2H), 5.70-5.86 (m, 1H), 5.91 (d, *J* = 8 Hz, 1H), 7.11-7.23 (m, 5H), 7.52 (d, *J* = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 12.3, 20.1, 25.7, 30.5, 32.8, 51.8, 53.3, 90.5, 118.8, 123.9, 127.5, 128.9, 131.5, 212.3; IR(film) ν 1710 cm^{-1}. Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 7.07. Found: C, 83.89; H, 7.21.

General procedure for allyl γ-lactam 2.107a-d. A dichloromethane solution of the bicyclic lactam **2.106** (5.48 mmol) was cooled to -78 °C and $TiCl_4$ (9 ml of 1.0 M soltion in dichloromethane, 1.6 equiv) was slowly added *via* syringe followed by allyltrimethylsilane (1.3 mL, 1.5 equiv). The solution was stirred under an

argon atmosphere and allowed to warm to rt over a 4h period. A solution of saturated NH_4Cl (50 mL)was added in one portion and the layers were separated. The aqueous layer was washed with dichloromethane (3 X 50 mL), the combined organic layers were dried over Na_2SO_4 and concentrated to an oil. ^1H NMR analysis of the crude material was used to analyze the diastereomeric ratio. Column chromatography (SiO_2, EtOAc) provided **2.107**.

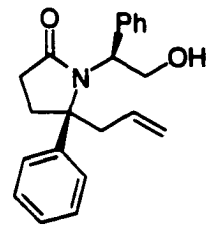


2.107a (68%) 1.01g, colorless solid: mp 75 °C (EtOAc/Hex); $[\alpha]_D^{23}$ -123 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.93-2.16 (m, 4H), 2.53 (t, *J* = 9 Hz, 2H), 4.03-4.39 (m, 4H), 4.65-5.04 (m, 3H), 5.41 (dddd, *J* = 17, 13, 10, 7, 1H), 7.21-7.58 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 28.3, 31.1, 38.7, 43.8, 61.3, 64.5, 67.2, 68.7,199.0, 126.3, 128.8, 128.9, 133.3, 138.1, 179.6; IR(film) ν 1651, 3340 cm^{-1}. Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.49; H, 7.73.



2.107c (76%) 1.25g, colorless solid: mp 98 °C (EtOAc/Hex); $[\alpha]_D^{23}$ -177 (c 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7 Hz, 3H), 1.26-1.45 (m, 4H), 1.58-1.71 (m, 2H), 1.89-2.06 (m, 4H), 2.49 (t, *J* = 9 Hz, 2H), 4.08-4.27 (m, 3H), 4.70-4.97 (m, 3H), 5.36 (dddd, *J* = 17, 13, 10, 7, 1H), 7.24-7.43 (m, 5H); ^{13}C

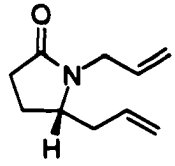
NMR (75 MHz, $CDCl_3$) 14.0, 22.9, 25.5, 27.6, 30.4, 37.7, 44.7, 60. 3, 65.5, 68.2, 199.0, 127.2, 127.7, 128.2, 132.3, 139.1, 177.4; IR(film) ν 1658, 3351 cm^{-1}. Anal. Calcd. for $C_{18}H_{27}NO_2$: C, 75.71; H, 9.03. Found: C, 75.44; H, 9.03.



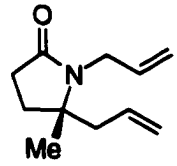
2.107d (79%) 986 mg, colorless solid: mp 112 °C (EtOAc/Hex); $[\alpha]_D^{23}$ -187 (c 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.93-2.11 (m, 4H), 2.39 (t, J = 7 Hz, 2H), 4.07-4.19 (m, 3H), 4.63-4.81 (m, 3H), 5.26 (dddd, J = 15, 12, 9, 7, 1H), 7.15-7.52 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) 22.6, 30.4, 37.7, 44.7, 60.3, 65.5, 68.2, 72.3, 118.7, 122.4, 124.7, 126.5, 127.7, 127.9, 128.2,129.6, 132.6, 138.1, 175.9; IR(film) ν 1662, 3331 cm^{-1}. Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21. Found: C, 78.53; H, 7.16.

General procedure for pyrrolidinone 2.109. To a flame dried round bottomed flask was added pyrrolidinone 2.107 (1.2 mmol) followed by cooling to –78 °C. Ammonia was then condensed into the flask (~10 mL) and calcium metal was added (~800 mg). Vigorous stirring resulted in the formation of a deep blue color. The mixture was stirred at –78 °C for 8 h at which time the bath was removed and solid NH_4Cl was added. After the ammonia boiled off, the mixture was washed with ether and filtered through a plug of celite. After the solution

was concentrated to an oil, the residue was dissolved in THF, cooled to –78 °C and successively treated with sodium hydride and allylbromide. The reaction was stirred for 12h at which time it was quenched with methanol and partitioned between dichloromethane and water. The layers were separated, the aqueous layer was washed with dichloromethane, the combined organic layers were dried over sodium sulfate, filtered and concentrated to a colorless oil. The residue was chromatographed (SiO_2, EtOAc) to provide **2.109**.

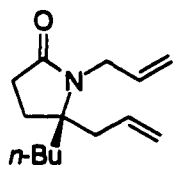


2.109a. (81%) 720mg, colorless oil; $[\alpha]_D^{23}$ -33 (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.93-2.16 (m, 4H), 2.53 (m, 2H), 4.03-4.39 (m, 4H), 4.65-5.92 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 31.1, 38.7, 43.8, 61.3, 64.5, 119.0, 123.3, 124.8, 179.6; IR(film) ν 1641, 3085 cm^{-1}. Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.59; H, 9.23.

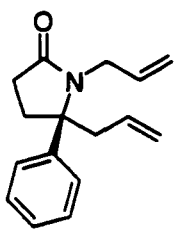


2.109b. (89%) 340mg, colorless oil; $[\alpha]_D^{23}$ -27 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.89-2.18 (m, 6H), 2.48-2.53 (m, 2H), 4.11-4.42 (m, 4H), 4.59-5.72 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3, 29.3, 32.1, 37.3, 44.1, 60.3, 65.5, 117.0,

119.3, 122.8, 178.6; IR(film) ν 1648, 3062 cm^{-1}. Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.79; H, 9.52.



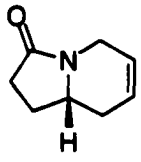
2.109c. (92%) 320mg, colorless oil; $[\alpha]_D^{23}$ -18 (c 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.37-2.18 (m, 8H), 2.30-2.42 (m, 2H), 4.10-4.45 (m, 4H), 4.59-5.88 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5., 15.4, 21.5, 25.4, 27.3, 33.1, 36.7, 42.1, 65.3, 67.5, 112.1, 124.1, 124.9, 174.6; IR(film) ν 1650, 3062 cm^{-1}. Anal. Calcd. for $C_{14}H_{23}NO$: C, 75.97; H, 6.33. Found: C, 75.90; H, 6.23.



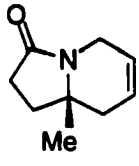
2.109d. (90%) 260mg, colorless oil; $[\alpha]_D^{23}$ -32 (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32-2.18 (m, 8H), 4.10-4.45 (m, 2H), 4.59-5.88 (m, 4H), 7.12-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.1, 36.7, 42.1, 65.3, 67.5, 112.1, 121.5, 123.2, 124.1, 124.9, 132.4, 174.6; IR(film) ν 1647, 3072 cm^{-1}. Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.50; H, 7.99.

General procedure for indolizidinone 2.110. A dichloroethane solution of the bis-olefin (0.9 mmol) **2.109** was added to a solution of the catalyst **2.112** (74mg,

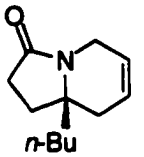
10 mol%). The purple solution slowly changed to a brown color. After 6h the reaction was concentrated *in vacuo* to an oil and chromatographed (SiO_2, EtOAc) to provide **2.110**



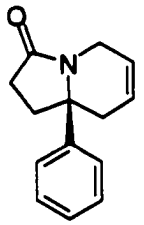
2.110a (126 mg, 93%) as a colorless solid: mp 73 °C (EtOAc/Hex); $[\alpha]_D^{23}$ -38 (c 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.08-2.31 (m, 4H), 2.36-2.58 (m, 2H), 3.45 (d, J = 9Hz, 1H), 4.42 (d, J = 9Hz, 1H), 5.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 26.4, 28.3, 33.3, 35.8, 37.8, 62.1, 123.8, 125.2, 174.2; IR(film) ν 1687 cm^{-1}. Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08. Found: C, 70.09; H, 8.01.



2.110b (196 mg, 89%) as a colorless solid: mp 71 °C (EtOAc/Hex); $[\alpha]_D^{23}$ -42 (c 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 2.12-2.32 (m, 3H), 2.41-2.52 (m, 2H), 3.51 (d, *J* = 8Hz, 1H), 4.41 (d, *J* = 7Hz, 1H), 5.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 27.3, 28.4, 29.3, 31.5, 36.7, 37.9, 63.2, 123.8, 124.8, 175.5; IR(film) ν 1696 cm^{-1}. Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67. Found: C, 71.41; H, 8.73.



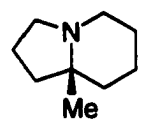
2.110c (179mg, 92%) as a colorless solid: mp 63 °C (EtOAc/Hex); $[\alpha]_D^{23}$ -58 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7 Hz, 3H), 1.12-1.39 (m, 4H), 1.48-1.82 (m, 3H), 2.01-2.21 (m, 3H), 2.38-2.53 (m, 2H), 3.40 (d, *J* = 9Hz, 1H), 4.38 (d, *J* = 9Hz, 1H), 5.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1, 23.1, 25.9, 27.8, 29.9, 30.3, 36.0, 38.4, 60.0, 122.8, 123.8, 173.5; IR(film) ν 1692 cm^{-1}. Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91. Found: C, 74.51; H, 9.98.



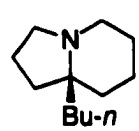
2.110d (136mg, 90%) as a colorless solid: mp 117 °C (EtOAc/Hex); $[\alpha]_D^{23}$ -149 (c 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.13-2.29 (m, 3H), 2.36-2.47 (m, 3H), 3.46 (d, *J* = 9 Hz, 1H), 4.18 (d, *J* = 9 Hz, 1H), 5.68 (m, 2H), 7.21-7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.9, 27.8, 29.9, 30.3, 36.0, 38.4, 60.0,122.8, 123.8, 125.6, 126.7, 131.1, 173.5; IR(film) ν 1692 cm^{-1}. Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.81; H, 7.15.

Geneal procedure for indolizidine 2.111. To a flame dried round bottom flask charged with indolizidinone **2.110** (0.5 mmol) was added methanol followed by palladium (II) hydroxide. The mixture was stirred under an atmosphere of

hydrogen for 8 h. The reaction mixture was purged with argon and filtered through a plug of celite. The colorless solution was concentrated to an oil and dissolved in anhydrous THF. The solution was cooled to –78 °C and lithium aluminum hydride was added. The mixture was stirred for 3 h at which time the reaction was quenched with methanol. When the effervesence subsided, 3 mL of 10% KOH was added and the mixture was vigorously stirred for 1 h. The mixture was partitioned between water and dichloromethane. The layers were separated, the aqueous layer was washed with dichloromethane, the combined layers were dried over $MgSO_4$, filtered and concentrated to a colorless oil. The residue was chromatographed (SiO_2, 10% MeOH / $CHCl_3$) to give **2.111**.

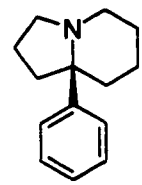


2.111b 47 mg (76%) colorless oil. $[\alpha]_D^{23}$ -12 (c 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.2 (s, 3H), 1.66-1.93 (m, 3H), 2.01-2.32 (m, 4H), 2.39-2.63 (m, 3H), 3.11 (t, J = 6Hz, 2H), 3.23 (t, J = 7Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.1, 26.3, 28.4, 29.4, 31.7, 35.5, 37.3, 58.1, 61.4, 62.5; IR(film) ν 1449 cm^{-1}. Anal. Calcd. for $C_9H_{17}N$: C, 77.64; H, 12.31. Found: C, 77.58; H, 12.40.

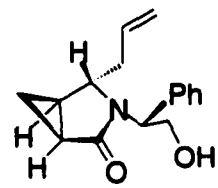


2.111c 66 mg (71%) colorless oil. $[\alpha]_D^{23}$ -28 (c 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7 Hz, 3H), 1.12-1.56 (m, 6H), 1.60-1.87 (m, 5H), 2.01-2.21

(m, 3H), 2.38-2.53 (m, 2H), 3.21 (t, J = 7Hz, 2H), 3.32 (t, J = 8Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1, 20.5, 23.1, 25.9, 27.8, 29.9, 30.3, 36.0, 38.4, 57.8, 60.0, 62.5; IR(film) ν 1204 cm^{-1}. Anal. Calcd. for $C_{12}H_{23}N$: C, 79.5; H, 12.8. Found: C, 79.44; H, 12.87.

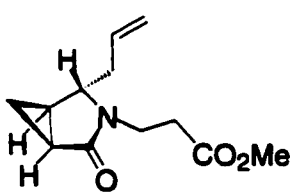


2.111d 39 mg (83%) colorless oil. $[\alpha]_D^{23}$ -31 (c 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.60-1.87 (m, 5H), 2.01-2.21 (m, 3H), 2.38-2.53 (m, 2H), 3.09-3.26 (m, 4H), 7.14-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.9, 27.8, 29.9, 30.3, 36.0, 38.4, 57.8, 60.0, 123.4, 125.5, 131.7; IR(film) ν 3018, 1408 cm^{-1}. Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.46; H, 9.61.



Allyl Lactam (-)-2.120. To a round bottomed flask was added 13 mL of $TiCl_4$ (1.0M in CH_2Cl_2) under an argon atmosphere and the solution was cooled to -78 °C. A CH_2Cl_2 solution of **2.119** (1.05 g, 4.8 mmol in 15 mL) was added *via* syringe followed by a CH_2Cl_2 solution of allyltrimethylsilane (3.24 mL, 20.4 mmol in 10 mL). The reaction was slowly allowed to warm to rt over a period of 5 h at which time solid $NaHCO_3$ was carefully added. The mixture was partitioned

between H_2O and CH_2Cl_2, the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to a oil. ^1H NMR of crude product showed a 20:1 mixture of addition products by integration of the methine proton α to the lactam nitrogen (δ major: 3.38 ppm, minor: 3.63 ppm). Column chromatography (50% ether/hexane) of the residue provided 1.02 g of **2.120** (83%) as a colorless solid: mp 63-64 °C (Et_2O/Hex); $[\alpha]_D^{23}$ = -85 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.64 (app dd, *J* = 4, 8 Hz, 1H), 1.09 (ddd, *J* = 5, 8, 13 Hz, 1H), 1.73 (ddd, *J* = 4, 6, 7 Hz, 1H), 2.00 (dddd, *J* = 2, 3, 5, 8 Hz, 1H), 2.12-2.23 (m, 1H), 2.30-2.40 (m, 1H), 3.38 (ddd, *J* = 3, 5, 10 Hz, 1H), 4.04 (dd, *J* = 4, 11 Hz, 1H), 4.29 (dd, *J* = 9, 11 Hz, 1H), 4.67 (dd, *J* = 4, 9 Hz, 1H), 5.04-5.15 (m, 2H), 5.67 (dddd, *J* = 8, 10, 14, 16 Hz, 1H), 7.29-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.2, 137.6, 132.3, 128.7, 126.0, 118.9, 64.4, 61.9,61.1,39.6, 20.4, 16.2, 12.2; IR (film) 3380, 1664 cm^{-1}. Anal.Calcd for $C_{16}H_{19}NO$: C, 74.68 H, 7.44 N, 5.44. Found: C, 74.73 H, 7.42 N, 5.44; HRMS found 258.1506 (M+) requires 258.1494 (M+).



(1α,2α,5α)-(-)-2-(2-Propenyl)-4-oxo-3-azabicyclo[3.1.0]hexane-3-propanoic Acid Methyl Ester (+)-2.118. Into a round bottomed flask was condensed ca. 20 mL of NH_3 at -78 °C. Calcium metal (2.0 g) was added and the mixture was vigorously stirred until a deep blue color formed (ca. 30 min). To this solution was

slowly added **2.120** (1.02 g, 3.99 mmol in 5 mL of THF). The reaction was warmed to -40 °C over a 2 h period and held at that temperature for 12 h at which time solid NH_4Cl was added and the mixture was allowed to warm to room temperature. After removal of NH_3, the solid residue was washed with Et_2O and the etheral solution was concentrated *in vacuo* to provide a colorless oil. Column chromatography (ether) of the residue provided 507 mg of (1α,2α,5α)-(-)-2-(2-propenyl)-4-oxo-3-azabicyclo[3.1.0]hexane (93%) as a colorless oil: $[\alpha]_D^{23}$ = 67° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.68 (app dd, *J* = 4, 8 Hz, 1H), 1.10 (ddd, *J* = 5, 8, 13 Hz, 1H), 1.76-1.84 (m, 2H), 2.30 (app t, *J* = 8 Hz, 2H), 3.54 (app t, *J* = 6 Hz, 1H), 5.11-5.19 (m, 2H), 5.79 (dddd, *J* = 7, 10, 14, 16 Hz, 1H) 6.52 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.1, 132.9, 118.5, 55.1, 41.5, 19.7, 19.2, 12.6; IR (film) 3237, 1688 cm^{-1}; HRMS found 138.0924 (M+) ($C_8H_{11}NO$ (M^+) requires 138.0919). To a THF solution of the above azabicyclohexane (82 mg in 2 mL) was added potassium hydride (24 mg) under an argon atmosphere at 0 °C. After 15 min methyl 3-bromopropionate was added and the mixture was allowed to warm to rt over 2 h. To this solution was carefully added H_2O and the reaction mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was washed with CH_2Cl_2 (3 x 10 mL), the organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* to provide a colorless oil. Column chromatography (ether) of the residue provided 78 mg of (+) – **2.218** (65%) as a colorless oil: $[\alpha]_D^{23}$ = 24° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.48 (ddd, *J* = 3.3, 4.4, 4.5 Hz, 1H), 1.03 (ddd, *J* = 5, 7, 8 Hz, 1H), 1.69 (ddd, *J* = 4, 6, 8 Hz, 1H), 1.85-1.93 (m, 1H), 2.29 (dt, *J* = 8, 14 Hz, 1H), 2.46-2.66, (m, 3H), 3.18 (dt, *J*

= 7, 14 Hz, 1H), 3.61 (dddd, J = 2, 3, 5, 7 Hz, 1H), 3.71 (s, 3H), 3.81 (dt, J = 6, 12 Hz, 1H), 5.16-5.25 (m, 2H), 5.72-5.88 (m, 1H) ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 132.3, 119.0, 60.3, 59.2, 37.9, 36.0, 32.4, 20.9, 16.2, 14.2,12.0; IR (film) 1735, 1682 cm^{-1}; HRMS found 224.1287, ($C_{12}H_{17}NO_3$ (M^+) requires 224.1293). Chiral GLC analysis (Chiraldex G-PN, 30 m, isothermal (170 °C) with a head pressure of 10 psi.) proved the sample of (+)-**2.118** to be >99% enantiomerically pure when compared to a sample of racemic **2.118** exhibiting the following retention times: 35.38 min and 36.19 min. The sample from the present study appeared at 35.35 min with no visible trace of the other enantiomer. Further mixing of the two samples gave only the peaks at 35.36 (enhanced) and 36.21 min.

Appendix
X-ray Data

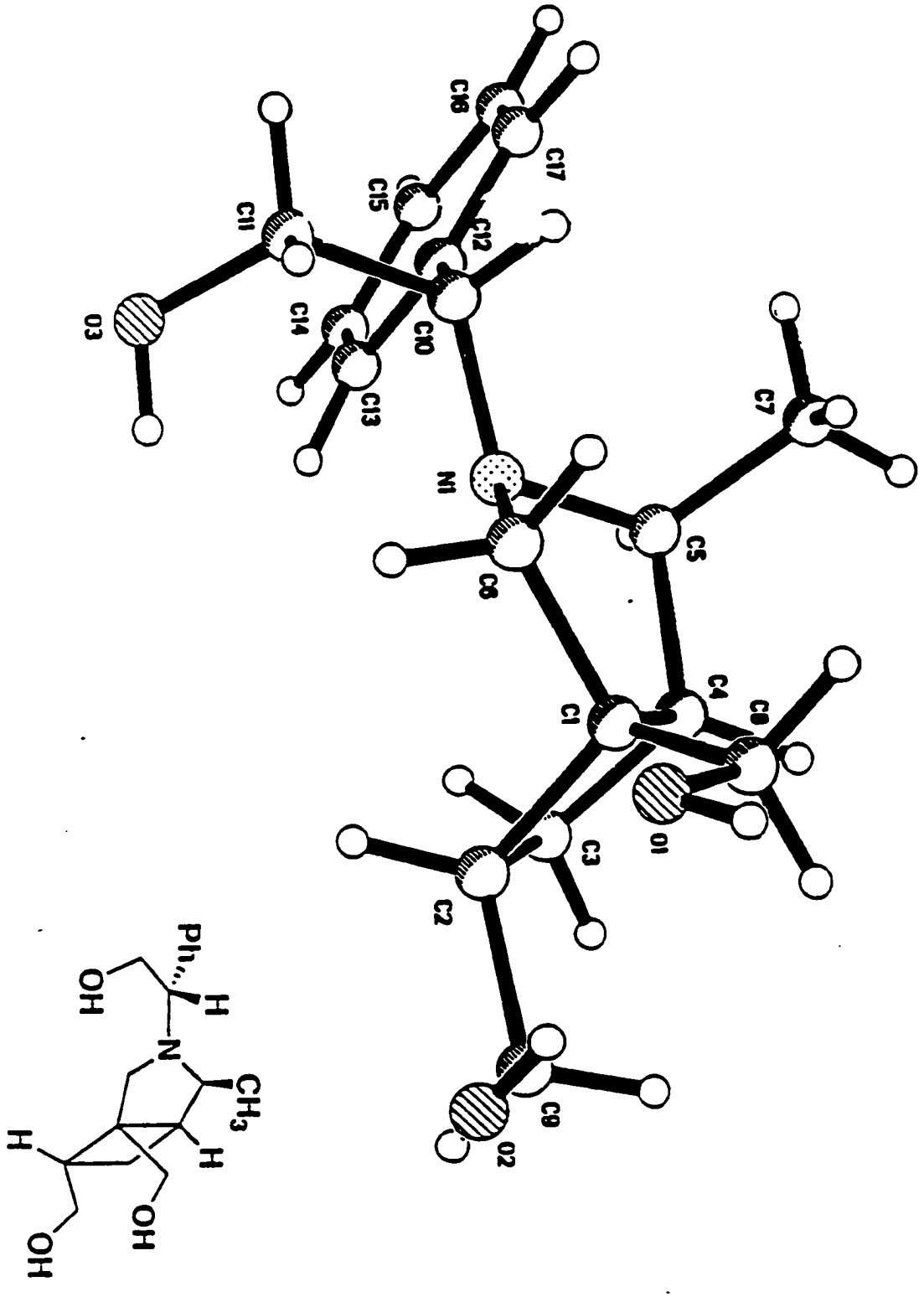


Table 1. Crystal data and structure refinement for 1.

Identification code	amccd20(Groaning/Meyers)
Empirical formula	$C_{17}H_{25}NO_3$
Formula weight	291.38
Temperature	169(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 9.5479(9) Å alpha = 90° b = 6.6836(7) Å beta = 98.070(2)° c = 12.5238(13) Å gamma = 90°
Volume, Z	791.29(14) $Å^3$, 2
Density (calculated)	1.223 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	316
Crystal size	0.02 x 0.20 x 0.40 mm (Very thin plate)
θ range for data collection	1.64 to 28.38°
Limiting indices	$-12 \le h \le 9$, $-8 \le k \le 8$, $-13 \le l \le 16$
Reflections collected	5174
Independent reflections	3488 (R_{int} = 0.0946)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3488 / 1 / 191
Goodness-of-fit on F^2	0.998
Final R indices [$I>2\sigma(I)$]	R1 = 0.1116, wR2 = 0.2685
R indices (all data)	R1 = 0.1968, wR2 = 0.3068
Absolute structure parameter	2(4)
Extinction coefficient	0.043(13)
Largest diff. peak and hole	0.394 and -0.395 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	7857(5)	5476(9)	7876(4)	25(1)
O(1)	12062(4)	5565(8)	9906(4)	33(1)
O(2)	12957(5)	2296(7)	8820(4)	35(1)
O(3)	5803(4)	2625(7)	8750(4)	30(1)
C(1)	10391(7)	5392(12)	8229(6)	28(2)
C(2)	10713(7)	3286(12)	7776(6)	30(2)
C(3)	10009(7)	3983(12)	6649(6)	35(2)
C(4)	9884(7)	6083(11)	7053(5)	29(2)
C(5)	8352(7)	6821(11)	7072(6)	32(2)
C(6)	9046(6)	5360(13)	8783(5)	28(2)
C(7)	8298(8)	9041(11)	7315(6)	37(2)
C(8)	11501(7)	6500(11)	8880(6)	32(2)
C(9)	12276(7)	2737(13)	7754(6)	35(2)
C(10)	6480(7)	6010(11)	8184(6)	31(2)
C(11)	6049(6)	4660(11)	9072(6)	26(2)
C(12)	5346(6)	6051(10)	7196(6)	25(2)
C(13)	5255(7)	4493(11)	6461(6)	29(2)
C(14)	4181(7)	4520(12)	5586(6)	37(2)
C(15)	3259(7)	6118(13)	5420(6)	39(2)
C(16)	3373(7)	7681(13)	6145(6)	35(2)
C(17)	4432(6)	7664(12)	7031(6)	30(2)

Table 3. Bond lengths [Å] and angles [°] for 1.

N(1)-C(10)	1.465(8)	N(1)-C(5)	1.476(9)
N(1)-C(6)	1.491(7)	O(1)-C(8)	1.441(8)
O(2)-C(9)	1.431(8)	O(3)-C(11)	1.429(8)
C(1)-C(8)	1.511(9)	C(1)-C(6)	1.543(9)
C(1)-C(4)	1.554(9)	C(1)-C(2)	1.564(10)
C(2)-C(9)	1.541(9)	C(2)-C(3)	1.547(11)
C(3)-C(4)	1.503(10)	C(4)-C(5)	1.546(9)
C(5)-C(7)	1.517(11)	C(10)-C(12)	1.525(9)
C(10)-C(11)	1.533(10)	C(12)-C(17)	1.384(10)
C(12)-C(13)	1.384(10)	C(13)-C(14)	1.393(9)
C(14)-C(15)	1.381(11)	C(15)-C(16)	1.379(11)
C(16)-C(17)	1.392(9)		

C(10)-N(1)-C(5)	114.6(5)	C(10)-N(1)-C(6)	115.3(5)
C(5)-N(1)-C(6)	105.6(5)	C(8)-C(1)-C(6)	112.7(6)
C(8)-C(1)-C(4)	118.6(6)	C(6)-C(1)-C(4)	105.2(5)
C(8)-C(1)-C(2)	117.6(6)	C(6)-C(1)-C(2)	111.7(6)
C(4)-C(1)-C(2)	88.6(5)	C(9)-C(2)-C(3)	110.7(6)
C(9)-C(2)-C(1)	117.4(6)	C(3)-C(2)-C(1)	88.7(5)
C(4)-C(3)-C(2)	91.1(5)	C(3)-C(4)-C(5)	115.0(6)
C(3)-C(4)-C(1)	90.7(5)	C(5)-C(4)-C(1)	104.5(5)
N(1)-C(5)-C(7)	115.8(7)	N(1)-C(5)-C(4)	102.1(5)
C(7)-C(5)-C(4)	111.9(6)	N(1)-C(6)-C(1)	104.4(5)
O(1)-C(8)-C(1)	112.5(6)	O(2)-C(9)-C(2)	110.3(6)
N(1)-C(10)-C(12)	110.6(5)	N(1)-C(10)-C(11)	113.0(5)
C(12)-C(10)-C(11)	111.5(6)	O(3)-C(11)-C(10)	113.9(6)
C(17)-C(12)-C(13)	120.5(6)	C(17)-C(12)-C(10)	119.8(6)
C(13)-C(12)-C(10)	119.8(6)	C(12)-C(13)-C(14)	119.0(7)
C(15)-C(14)-C(13)	120.8(8)	C(16)-C(15)-C(14)	119.8(6)
C(15)-C(16)-C(17)	120.0(7)	C(12)-C(17)-C(16)	119.9(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
N(1)	8(2)	35(4)	32(3)	5(3)	4(2)	-3(2)
O(1)	15(2)	46(3)	36(3)	1(3)	-4(2)	-8(2)
O(2)	23(3)	30(3)	53(3)	-2(3)	5(2)	0(2)
O(3)	14(2)	28(3)	49(3)	-3(3)	6(2)	1(2)
C(1)	20(3)	28(4)	37(4)	4(4)	6(3)	-7(3)
C(2)	17(3)	37(5)	39(4)	-9(3)	8(3)	-5(3)
C(3)	17(4)	48(5)	44(5)	-18(4)	14(3)	1(3)
C(4)	15(3)	38(4)	33(4)	-3(3)	2(3)	-5(3)
C(5)	12(3)	38(5)	44(4)	2(4)	-6(3)	-4(3)
C(6)	13(3)	40(4)	30(4)	0(3)	3(3)	-2(3)
C(7)	25(4)	38(5)	48(5)	9(4)	5(3)	-5(3)
C(8)	18(3)	34(4)	44(4)	-2(4)	5(3)	-7(3)
C(9)	16(3)	46(5)	42(5)	-5(4)	5(3)	-5(3)
C(10)	19(4)	33(4)	38(4)	-5(3)	-2(3)	-1(3)
C(11)	11(3)	35(4)	33(4)	-1(3)	12(3)	6(3)
C(12)	9(3)	27(4)	43(4)	5(3)	16(3)	4(3)
C(13)	13(3)	31(4)	45(5)	1(4)	10(3)	2(3)
C(14)	24(4)	46(5)	42(5)	-4(4)	6(3)	-3(4)
C(15)	11(3)	63(6)	44(5)	12(4)	7(3)	0(3)
C(16)	23(4)	38(5)	47(5)	3(4)	8(3)	13(3)
C(17)	16(3)	31(4)	46(5)	3(4)	8(3)	-2(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(1A)	12733(4)	6226(8)	10241(4)	50
H(2A)	12916(5)	3303(7)	9216(4)	53
H(3A)	6544(4)	2140(7)	8565(4)	45
H(2B)	10173(7)	2190(12)	8078(6)	37
H(3B)	10636(7)	3867(12)	6086(6)	42
H(3C)	9085(7)	3338(12)	6412(6)	42
H(4A)	10518(7)	7075(11)	6764(5)	34
H(5A)	7785(7)	6558(11)	6351(6)	39
H(6A)	8993(6)	4111(13)	9201(5)	33
H(6B)	9029(6)	6518(13)	9275(5)	33
H(7A)	7313(8)	9449(11)	7318(6)	55
H(7B)	8702(8)	9795(11)	6760(6)	55
H(7C)	8844(8)	9311(11)	8023(6)	55
H(8A)	12406(7)	6563(11)	8462(6)	38
H(8B)	11300(7)	7889(11)	9003(6)	38
H(9A)	12334(7)	1558(13)	7284(6)	42
H(9B)	12766(7)	3866(13)	7453(6)	42
H(10A)	6565(7)	7401(11)	8479(6)	37
H(11A)	6803(6)	4698(11)	9700(6)	31
H(11B)	5177(6)	5204(11)	9306(6)	31
H(13A)	5915(7)	3421(11)	6553(6)	35
H(14A)	4080(7)	3425(12)	5097(6)	44
H(15A)	2549(7)	6140(13)	4807(6)	47
H(16A)	2729(7)	8770(13)	6041(6)	42
H(17A)	4528(6)	8756(12)	7521(6)	37

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
0	-8	0	0	24	1
1	-8	0	76	61	30
2	-8	0	42	19	41
3	-8	0	102	58	25
4	-8	0	33	5	33
1	-7	0	0	33	1
2	-7	0	87	36	27
3	-7	0	61	33	38
4	-7	0	0	12	1
5	-7	0	0	7	1
6	-7	0	38	42	37
7	-7	0	20	40	20
0	-6	0	165	145	13
1	-6	0	181	171	8
2	-6	0	79	71	12
3	-6	0	48	39	48
4	-6	0	63	69	29
5	-6	0	0	35	1
6	-6	0	55	31	35
7	-6	0	49	36	49
8	-6	0	0	21	1
9	-6	0	75	83	23
1	-5	0	80	83	8
2	-5	0	71	64	10
3	-5	0	128	130	8
4	-5	0	67	54	19
5	-5	0	91	92	15
6	-5	0	42	43	42
7	-5	0	57	59	20
8	-5	0	36	58	36
9	-5	0	65	75	23
10	-5	0	27	6	26
0	-4	0	111	110	10
1	-4	0	186	173	15
2	-4	0	48	37	28
3	-4	0	50	38	12
4	-4	0	52	55	16
6	-4	0	179	180	10
7	-4	0	145	154	11
8	-4	0	49	61	18
9	-4	0	107	120	13
10	-4	0	29	41	29
1	-3	0	42	21	22
2	-3	0	147	127	33
3	-3	0	261	260	6
4	-3	0	134	133	4
5	-3	0	25	19	24
6	-3	0	22	27	22
7	-3	0	59	57	12
8	-3	0	65	69	11
9	-3	0	0	30	1
10	-3	0	58	54	58
11	-3	0	83	70	24
0	-2	0	232	222	9
1	-2	0	152	169	7
2	-2	0	253	272	6
3	-2	0	122	115	4
4	-2	0	89	80	7
5	-2	0	89	101	4
6	-2	0	165	151	9
7	-2	0	148	146	7
8	-2	0	76	81	10
9	-2	0	46	54	16
10	-2	0	86	90	21
11	-2	0	0	10	1
12	-2	0	34	65	33
1	-1	0	157	149	3
2	-1	0	413	362	9
3	-1	0	263	265	6
4	-1	0	160	149	3
5	-1	0	41	42	3
6	-1	0	97	86	3
7	-1	0	57	62	10
8	-1	0	141	118	7
9	-1	0	77	74	18
10	-1	0	105	99	16
11	-1	0	91	95	20
1	0	0	60	49	3
2	0	0	37	14	5
3	0	0	23	8	16
4	0	0	74	69	6
5	0	0	282	216	8
6	0	0	58	61	8
7	0	0	19	20	18
8	0	0	156	134	13
9	0	0	92	101	13
10	0	0	40	43	39
11	0	0	0	1	1
12	0	0	39	57	39
1	1	0	174	149	4
2	1	0	412	361	11
3	1	0	270	266	11
4	1	0	163	149	9
5	1	0	40	42	22
6	1	0	99	86	11
7	1	0	49	62	23
8	1	0	138	118	12
9	1	0	70	74	20
10	1	0	94	99	15
11	1	0	94	95	15
0	2	0	226	222	9
1	2	0	168	169	4
2	2	0	276	272	7
3	2	0	119	115	5
4	2	0	87	80	6
5	2	0	89	101	4
6	2	0	162	151	6
7	2	0	145	146	6
8	2	0	71	81	8
9	2	0	40	54	40
10	2	0	80	90	16
11	2	0	19	10	19
12	2	0	58	64	27
1	3	0	30	21	8
2	3	0	127	127	4
3	3	0	275	260	9
4	3	0	141	133	6
5	3	0	39	19	9
6	3	0	31	26	24
7	3	0	56	57	9
8	3	0	73	69	8
9	3	0	13	30	13
10	3	0	57	54	19
11	3	0	52	70	25
0	4	0	117	110	9
1	4	0	189	173	5
2	4	0	43	37	7
3	4	0	38	38	10
4	4	0	50	55	9
5	4	0	23	25	23
6	4	0	174	180	7
7	4	0	143	154	7
8	4	0	50	61	11
9	4	0	113	120	8
10	4	0	0	61	1
11	4	0	72	72	21
1	5	0	84	83	8
2	5	0	67	64	11
3	5	0	135	130	7
4	5	0	57	54	18
5	5	0	89	92	11
6	5	0	50	43	20
7	5	0	63	59	17
8	5	0	46	58	29
9	5	0	64	75	22
0	6	0	148	165	11
1	6	0	180	171	7
2	6	0	67	71	11
3	6	0	46	39	15
4	6	0	66	69	18
5	6	0	0	35	1
6	6	0	19	31	18
7	6	0	0	36	1
9	6	0	76	83	20
1	7	0	0	33	1
2	7	0	34	36	34
3	7	0	31	33	31
4	7	0	0	12	1
6	7	0	8	42	8
7	7	0	0	40	1
0	8	0	0	24	1
1	8	0	47	61	20
2	8	0	16	19	15
3	8	0	62	58	34
-4	-8	1	18	16	18
-3	-8	1	71	58	39
-2	-8	1	64	48	64
-1	-8	1	70	47	40
0	-8	1	20	12	19
1	-8	1	0	15	1
2	-8	1	71	23	44
3	-8	1	58	41	58
4	-8	1	0	24	1
-7	-7	1	68	29	32
-6	-7	1	0	7	1
-5	-7	1	45	21	45
-4	-7	1	54	35	54
-3	-7	1	30	26	30
-2	-7	1	109	79	17
-1	-7	1	134	105	11
0	-7	1	14	18	14
1	-7	1	0	19	1
2	-7	1	64	15	20
3	-7	1	40	13	40
4	-7	1	42	27	42
5	-7	1	48	52	67
6	-7	1	48	52	48
7	-7	1	39	28	39
-9	-6	1	14	7	14
-8	-6	1	65	62	28
-7	-6	1	58	57	33
-6	-6	1	35	26	34
-5	-6	1	89	79	19
-4	-6	1	44	16	44
-3	-6	1	74	57	17
-2	-6	1	78	59	11
-1	-6	1	61	28	15
0	-6	1	78	69	11
1	-6	1	42	43	37
2	-6	1	110	85	11
3	-6	1	80	70	23
4	-6	1	100	81	17
5	-6	1	20	14	19
6	-6	1	60	50	31
7	-6	1	16	10	16
8	-6	1	0	10	1
9	-6	1	82	84	21
-10	-5	1	48	37	67
-9	-5	1	41	51	40
-8	-5	1	64	71	21
-7	-5	1	106	117	13
-6	-5	1	65	73	18
-5	-5	1	0	26	1
-4	-5	1	67	58	26
-3	-5	1	150	134	8
-2	-5	1	70	71	10
-1	-5	1	106	110	8
0	-5	1	34	31	30
1	-5	1	116	108	8
2	-5	1	81	82	10
3	-5	1	103	100	8
4	-5	1	114	109	15
5	-5	1	68	72	17
6	-5	1	112	119	13
7	-5	1	71	62	17
8	-5	1	49	63	32
9	-5	1	127	126	14
10	-5	1	49	67	27
-9	-4	1	65	58	14
-8	-4	1	63	55	31
-7	-4	1	93	105	12
-6	-4	1	42	49	29
-5	-4	1	54	59	22
-4	-4	1	32	53	32
-3	-4	1	163	162	6
-2	-4	1	63	53	8
-1	-4	1	79	79	7
0	-4	1	209	176	10
1	-4	1	73	71	8
2	-4	1	95	87	7
3	-4	1	52	52	9
4	-4	1	65	73	9
5	-4	1	48	65	18
6	-4	1	57	55	18
7	-4	1	102	111	10
8	-4	1	37	27	37
9	-4	1	75	90	15
10	-4	1	74	68	17
-10	-3	1	0	64	1
-9	-3	1	36	25	35
-8	-3	1	31	36	31
-7	-3	1	11	20	10
-6	-3	1	55	58	11
-5	-3	1	73	66	8
-4	-3	1	85	78	5
-3	-3	1	78	98	5
-2	-3	1	111	112	18
-1	-3	1	256	249	7
0	-3	1	308	307	16
1	-3	1	85	79	8
2	-3	1	132	134	4
3	-3	1	107	110	4
4	-3	1	57	58	9
5	-3	1	49	50	10
6	-3	1	63	63	8
7	-3	1	89	95	8
8	-3	1	70	64	11
9	-3	1	36	40	30
10	-3	1	0	19	1
11	-3	1	0	64	1
-12	-2	1	66	61	43
-11	-2	1	72	65	24
-10	-2	1	40	24	39
-9	-2	1	8	38	8
-8	-2	1	179	163	8
-7	-2	1	135	130	7
-6	-2	1	31	48	16
-5	-2	1	182	182	17
-4	-2	1	38	57	6
-3	-2	1	91	110	4
-2	-2	1	123	72	12
-1	-2	1	483	492	13
0	-2	1	214	229	6
1	-2	1	194	182	6
2	-2	1	89	83	3
3	-2	1	162	156	3
4	-2	1	51	52	5
5	-2	1	8	7	7
6	-2	1	59	63	9
7	-2	1	154	147	7
8	-2	1	185	181	14
9	-2	1	36	35	35
10	-2	1	30	21	30
11	-2	1	20	39	20
12	-2	1	0	32	1
-12	-1	1	53	9	52
-11	-1	1	51	66	40
-10	-1	1	98	96	15
-9	-1	1	126	120	13
-8	-1	1	70	74	10
-7	-1	1	60	58	9
-6	-1	1	320	283	25
-5	-1	1	171	166	3
-4	-1	1	389	403	11
-3	-1	1	165	138	36
-2	-1	1	582	560	15
-1	-1	1	85	88	2
0	-1	1	870	832	22
1	-1	1	180	177	4
2	-1	1	169	153	4
3	-1	1	417	389	9
4	-1	1	307	284	5
5	-1	1	32	33	5
6	-1	1	145	131	3
7	-1	1	193	165	7
8	-1	1	121	110	7
9	-1	1	59	27	29
10	-1	1	121	106	17
11	-1	1	72	73	24
12	-1	1	32	7	31
-12	0	1	16	45	16
-11	0	1	42	56	42
-10	0	1	0	7	1
-9	0	1	20	28	20
-8	0	1	67	71	17
-7	0	1	81	49	12
-6	0	1	130	116	6
-5	0	1	84	63	7
-4	0	1	471	403	13
-3	0	1	97	37	96
-2	0	1	219	243	13
-1	0	1	292	284	34
0	0	1	253	296	5
1	0	1	91	84	2
2	0	1	301	273	8
3	0	1	356	273	14
4	0	1	310	265	11
5	0	1	237	184	7
6	0	1	162	135	7
7	0	1	46	42	13
8	0	1	0	16	1
9	0	1	99	90	15
10	0	1	113	125	16
11	0	1	62	74	30
12	0	1	64	75	31
-12	1	1	0	9	1
-11	1	1	57	66	24
-10	1	1	81	96	15
-9	1	1	112	120	13
-8	1	1	71	76	16
-7	1	1	57	58	16
-6	1	1	306	283	14
-5	1	1	144	166	10
-4	1	1	368	403	15
-3	1	1	189	138	8
-2	1	1	557	560	22
-1	1	1	87	88	5
0	1	1	881	832	22
1	1	1	189	176	4
2	1	1	173	153	5
3	1	1	438	389	12
4	1	1	315	284	9
5	1	1	26	33	14
6	1	1	140	131	10
7	1	1	167	163	6
8	1	1	116	110	12
9	1	1	23	27	22
10	1	1	108	107	16
11	1	1	53	73	30
12	1	1	42	7	[illegible]
-12	2	1	44	61	28
-11	2	1	56	65	22
-10	2	1	0	24	1
-9	2	1	17	38	17
-8	2	1	163	163	10
-7	2	1	124	130	11
-6	2	1	42	48	24
-5	2	1	180	182	10
-3	2	1	109	110	6
-2	2	1	73	72	12
-1	2	1	489	492	12
0	2	1	224	229	10
1	2	1	192	182	4
2	2	1	94	83	3
3	2	1	170	156	5
4	2	1	46	52	3
5	2	1	19	7	19
6	2	1	72	63	7
7	2	1	147	147	7
8	2	1	189	181	11
9	2	1	35	35	34
10	2	1	27	20	26
11	2	1	0	39	1
-10	3	1	67	64	16
-9	3	1	33	25	32
-8	3	1	0	36	1
-7	3	1	11	19	10
-6	3	1	61	58	9
-5	3	1	75	66	7
-4	3	1	83	78	6
-3	3	1	86	98	40
-2	3	1	124	112	6
-1	3	1	260	249	6
0	3	1	310	307	12
1	3	1	86	79	3
2	3	1	137	134	4
3	3	1	113	110	4
4	3	1	60	58	7
5	3	1	44	50	10
6	3	1	59	63	8
7	3	1	82	95	7
8	3	1	56	64	10
9	3	1	25	40	24
10	3	1	0	19	1
11	3	1	55	64	23
-10	4	1	63	83	18
-9	4	1	66	58	12
-8	4	1	53	55	12
-7	4	1	97	105	9
-6	4	1	53	49	11
-5	4	1	69	59	8
-4	4	1	49	53	10
-3	4	1	160	161	7
-2	4	1	66	53	5
-1	4	1	82	79	4
0	4	1	186	176	6
1	4	1	74	71	4
2	4	1	96	87	4
3	4	1	67	52	6
4	4	1	80	73	8
5	4	1	64	65	8
6	4	1	45	55	13
7	4	1	112	111	7
8	4	1	15	27	16
9	4	1	73	90	13
10	4	1	77	68	16
11	4	1	0	33	1
-9	5	1	56	51	22
-8	5	1	56	[illegible]	24
-7	5	1	110	117	13

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
7	-1	3	210	185	6
8	-1	3	165	150	8
9	-1	3	58	57	17
10	-1	3	51	43	43
11	-1	3	99	118	16
12	-1	3	61	76	25
-11	0	3	177	179	15
-10	0	3	240	228	22
-9	0	3	261	316	15
-8	0	3	210	246	6
-7	0	3	30	38	7
-6	0	3	162	168	7
-5	0	3	198	210	8
-4	0	3	65	85	11
-3	0	3	316	333	7
-2	0	3	181	181	8
-1	0	3	189	178	9
0	0	3	135	123	6
1	0	3	130	119	6
2	0	3	278	229	13
3	0	3	101	79	9
4	0	3	53	57	28
5	0	3	15	14	15
6	0	3	92	78	19
7	0	3	98	108	18
8	0	3	58	70	18
9	0	3	165	134	13
10	0	3	98	110	11
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-10	1	3	141	171	10
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-8	1	3	251	278	11
-7	1	3	269	274	12
-6	1	3	223	213	16
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-4	1	3	123	129	5
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-1	1	3	212	185	12
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3	1	3	39	62	39
4	1	3	38	39	11
5	1	3	65	58	24
6	1	3	79	108	22
7	1	3	122	150	7
8	1	3	298	321	13
9	1	3	192	192	9
10	1	3	167	159	6
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-10	2	3	170	170	6
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-8	2	3	95	95	6
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-6	2	3	100	100	7
-5	2	3	108	79	14
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-3	2	3	52	31	22
-2	2	3	126	118	11
-1	2	3	0	36	0
0	2	3	31	20	31
1	2	3	30	30	11
2	2	3	125	117	11
3	2	3	49	31	16
4	2	3	0	0	0
5	2	3	177	177	9
6	2	3	182	183	6
7	2	3	173	162	6
-11	3	3	210	185	6
-10	3	3	165	150	8
-9	3	3	58	57	17
-8	3	3	51	43	43
-7	3	3	99	118	16
-6	3	3	61	76	25
-5	3	3	177	179	15
-4	3	3	240	228	22
-3	3	3	261	316	15
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-1	3	3	30	38	7
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1	3	3	198	210	8
2	3	3	65	85	11
3	3	3	316	333	7
4	3	3	181	181	8
5	3	3	189	178	9
6	3	3	135	123	6
7	3	3	130	119	6
8	3	3	278	229	13
9	3	3	101	79	9
10	3	3	53	57	28
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-10	4	3	92	78	19
-9	4	3	83	108	18
-8	4	3	58	70	18
-7	4	3	165	134	13
-6	4	3	98	110	11
-5	4	3	171	183	13
-4	4	3	141	171	10
-3	4	3	98	83	8
-2	4	3	251	278	11
-1	4	3	269	274	12
0	4	3	223	213	16
1	4	3	167	176	7
2	4	3	123	129	5
3	4	3	167	164	5
4	4	3	160	185	11
5	4	3	212	185	12
6	4	3	152	150	13
7	4	3	61	57	20
8	4	3	37	34	38
9	4	3	39	62	39
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-11	5	3	65	58	24
-10	5	3	79	108	22
-9	5	3	122	150	7
-8	5	3	298	321	13
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-5	5	3	165	155	6
-4	5	3	170	170	6
-3	5	3	104	98	6
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1	5	3	108	79	14
2	5	3	58	66	17
3	5	3	52	31	22
4	5	3	126	118	11
5	5	3	0	36	0
6	5	3	31	20	31
7	5	3	30	30	11
-11	6	3	125	117	11
-10	6	3	49	31	16
-9	6	3	0	0	0
-8	6	3	177	177	9
-7	6	3	182	183	6
-6	6	3	173	162	6
-5	6	3	177	177	9
-4	6	3	182	183	6
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0	6	3	173	162	6
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3	6	3	173	162	6
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7	6	3	177	177	9
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9	6	3	173	162	6
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-4	7	3	173	162	6
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-4	8	3	177	177	9
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-2	8	3	173	162	6
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0	9	3	173	162	6
1	9	3	177	177	9
2	9	3	182	183	6
3	9	3	173	162	6
4	9	3	177	177	9
5	9	3	182	183	6
6	9	3	173	162	6
7	9	3	177	177	9
8	9	3	182	183	6
9	9	3	173	162	6
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3	12	3	173	162	6
4	12	3	177	177	9
5	12	3	182	183	6
6	12	3	173	162	6
7	12	3	177	177	9
8	12	3	182	183	6
9	12	3	173	162	6
10	12	3	177	177	9

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
2	-8	6	29	17	29
-6	-7	6	74	38	25
-5	-7	6	120	66	16
-4	-7	6	94	86	22
-3	-7	6	0	24	1
-2	-7	6	0	20	1
-1	-7	6	35	15	34
0	-7	6	47	35	22
1	-7	6	21	16	21
2	-7	6	37	38	36
3	-7	6	15	18	14
4	-7	6	40	24	40
5	-7	6	12	33	12
-8	-6	6	0	11	1
-7	-6	6	46	17	45
-6	-6	6	92	10	14
-5	-6	6	89	86	[illegible]
-4	-6	6	[illegible]	45	5
-3	-6	6	56	31	22
-2	-6	6	2	28	2
-1	-6	6	47	24	20
0	-6	6	45	53	18
1	-6	6	41	21	20
2	-6	6	43	36	22
3	-6	6	48	47	19
4	-6	6	59	39	23
5	-6	6	0	24	1
6	-6	6	15	36	14
7	-6	6	60	21	27
-9	-5	6	39	47	39
-8	-5	6	32	64	31
-7	-5	6	111	75	15
-6	-5	6	14	26	14
-5	-5	6	112	113	16
-4	-5	6	105	120	13
-3	-5	6	26	42	25
-2	-5	6	0	22	1
-1	-5	6	51	46	12
0	-5	6	107	117	10
1	-5	6	31	53	31
2	-5	6	86	88	8
3	-5	6	54	42	17
4	-5	6	71	58	10
5	-5	6	0	22	1
6	-5	6	34	27	33
7	-5	6	0	15	1
8	-5	6	57	43	22
-8	-4	6	9	38	8
-7	-4	6	55	51	23
-6	-4	6	76	66	18
-5	-4	6	26	31	26
-4	-4	6	88	93	15
-3	-4	6	138	118	11
-2	-4	6	75	57	20
-1	-4	6	36	35	36
0	-4	6	71	70	9
1	-4	6	58	64	9
2	-4	6	46	48	13
3	-4	6	75	78	9
4	-4	6	35	30	19
5	-4	6	139	144	7
6	-4	6	29	48	29
7	-4	6	40	38	25
8	-4	6	54	70	29
9	-4	6	43	45	42
-11	-3	6	67	13	48
-10	-3	6	175	44	17
-9	-3	6	136	8	18
-8	-3	6	39	27	33
-7	-3	6	11	17	10
-6	-3	6	214	222	8
-5	-3	6	135	155	10
-4	-3	6	83	64	9
-3	-3	6	90	93	5
-2	-3	6	25	22	24
-1	-3	6	111	106	6
0	-3	6	111	118	7
1	-3	6	43	66	8
2	-3	6	130	133	6
3	-3	6	99	94	6
4	-3	6	70	67	5
5	-3	6	79	82	5
6	-3	6	84	56	6
7	-3	6	122	119	7
8	-3	6	37	19	24
9	-3	6	14	20	13
10	-3	6	40	40	39
-12	-2	6	75	67	33

h	k	l	10Fo	10Fc	10s
-11	-2	6	149	108	19
-10	-2	6	184	34	12
-8	-2	6	63	68	13
-7	-2	6	87	91	7
-6	-2	6	117	144	16
-5	-2	6	91	54	26
-4	-2	6	14	16	14
-3	-2	6	79	71	7
-2	-2	6	136	151	14
-1	-2	6	191	187	6
0	-2	6	129	142	5
1	-2	6	97	101	6
2	-2	6	69	77	7
3	-2	6	72	79	5
4	-2	6	[illegible]	181	5
5	-2	6	104	106	5
6	-2	6	[illegible]	62	6
7	-2	6	64	[illegible]	7
8	-2	6	40	2	22
9	-2	6	52	37	19
10	-2	6	74	56	13
-12	-1	6	126	86	20
-11	-1	6	143	53	17
-10	-1	6	124	60	15
-8	-1	6	45	21	28
-7	-1	6	145	136	12
-6	-1	6	80	98	6
-5	-1	6	152	146	17
-4	-1	6	109	110	6
-3	-1	6	157	148	10
-2	-1	6	74	84	8
-1	-1	6	126	118	8
0	-1	6	75	83	7
1	-1	6	209	229	6
2	-1	6	192	199	6
3	-1	6	159	166	6
4	-1	6	104	94	5
5	-1	6	91	93	5
6	-1	6	92	87	5
7	-1	6	81	74	7
8	-1	6	41	18	24
9	-1	6	29	34	27
10	-1	6	59	64	23
-12	0	6	97	43	20
-11	0	6	154	50	12
-10	0	6	92	32	25
-8	0	6	0	24	1
-7	0	6	34	5	34
-6	0	6	26	6	25
-5	0	6	22	14	22
-4	0	6	139	138	6
-3	0	6	76	76	6
-2	0	6	65	56	8
-1	0	6	75	99	7
0	0	6	9	4	9
1	0	6	74	77	9
2	0	6	194	202	4
3	0	6	180	199	6
4	0	6	91	92	4
5	0	6	90	82	4
6	0	6	150	147	4
7	0	6	69	64	6
8	0	6	46	36	10
9	0	6	78	54	18
10	0	6	39	24	39
-11	1	6	132	53	14
-10	1	6	115	60	16
-8	1	6	52	21	19
-7	1	6	137	137	10
-6	1	6	78	98	10
-5	1	6	138	146	13
-4	1	6	119	110	5
-3	1	6	167	148	9
-2	1	6	74	84	8
-1	1	6	125	118	7
0	1	6	79	83	4
2	1	6	200	199	9
3	1	6	163	166	8
4	1	6	95	94	8
5	1	6	101	93	9
6	1	6	81	87	11
7	1	6	77	74	13
8	1	6	40	18	38
9	1	6	31	34	22
10	1	6	62	64	24
-11	2	6	155	109	15
-10	2	6	133	34	[illegible]
-8	2	6	49	68	[illegible]

h	k	l	10Fo	10Fc	10s
-7	2	6	84	91	11
-6	2	6	133	144	9
-5	2	6	73	54	11
-4	2	6	0	16	1
-3	2	6	81	71	3
2	2	6	71	77	7
3	2	6	70	79	8
4	2	6	180	181	6
5	2	6	109	106	9
6	2	6	61	68	13
7	2	6	64	66	13
8	2	6	44	21	37
9	2	6	75	37	16
10	2	6	69	54	23
-11	3	6	90	13	[illegible]
-10	3	6	174	44	1
-9	3	6	0	9	1
-7	3	6	21	17	21
-6	3	6	214	222	11
-5	3	6	150	155	9
-4	3	6	82	64	12
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-2	3	6	26	22	26
1	3	6	48	66	10
2	3	6	123	133	4
3	3	6	96	94	6
4	3	6	60	67	8
5	3	6	84	82	7
6	3	6	79	86	10
7	3	6	134	120	11
8	3	6	0	20	1
9	3	6	17	20	17
10	3	6	61	40	20
-10	4	6	117	100	12
-9	4	6	110	32	40
-7	4	6	72	51	30
-6	4	6	66	66	12
-5	4	6	63	31	14
-4	4	6	94	92	11
-3	4	6	120	118	12
-2	4	6	61	57	12
-1	4	6	30	35	18
0	4	6	63	70	10
1	4	6	57	64	9
2	4	6	35	48	18
3	4	6	75	78	7
4	4	6	20	30	20
5	4	6	142	144	6
6	4	6	50	48	14
7	4	6	56	38	16
8	4	6	73	70	14
9	4	6	58	65	21
-9	5	6	63	47	33
-8	5	6	86	64	21
-7	5	6	80	75	17
-6	5	6	0	26	1
-5	5	6	122	113	12
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-2	5	6	8	22	7
-1	5	6	44	46	24
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1	5	6	58	53	11
2	5	6	77	88	14
3	5	6	52	42	25
4	5	6	57	57	24
5	5	6	0	22	1
-8	6	6	0	11	1
-7	6	6	0	17	1
-5	6	6	89	84	14
-4	6	6	64	45	20
-3	6	6	15	30	14
-2	6	6	26	28	25
-1	6	6	10	24	9
0	6	6	74	53	15
1	6	6	26	21	25
2	6	6	27	36	27
3	6	6	46	47	46
4	6	6	40	39	40
5	6	6	37	24	36
6	6	6	79	36	19
-6	7	6	16	38	16
-5	7	6	78	66	20
-4	7	6	82	84	15
-3	7	6	25	24	24
-2	7	6	0	20	1
-1	7	6	0	15	1
0	7	6	0	35	1

h	k	l	10Fo	10Fc	10s
1	7	6	0	16	1
2	7	6	0	38	1
3	7	6	34	18	34
4	7	6	0	24	1
5	7	6	28	33	27
-3	8	6	39	25	39
-2	8	6	57	48	26
-1	8	6	10	15	10
0	-8	7	96	26	27
1	-8	7	56	25	34
-6	-7	7	100	57	18
-5	-7	7	0	32	1
-4	-7	7	76	42	31
-3	-7	7	39	33	39
-2	-7	7	67	43	38
-1	-7	7	28	38	25
0	-7	7	[illegible]	38	22
1	-7	7	[illegible]	27	27
2	-7	7	30	37	29
3	-7	7	41	27	[illegible]
4	-7	7	48	6	47
-8	-6	7	107	75	22
-7	-6	7	105	53	20
-6	-6	7	38	30	38
-5	-6	7	0	19	1
-4	-6	7	82	69	25
-3	-6	7	0	32	1
-2	-6	7	91	87	18
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0	-6	7	55	46	18
1	-6	7	37	32	36
2	-6	7	65	66	11
3	-6	7	27	27	26
4	-6	7	56	51	16
5	-6	7	29	34	23
6	-6	7	26	50	26
-9	-5	7	59	34	23
-8	-5	7	62	40	26
-7	-5	7	75	52	20
-6	-5	7	53	62	53
-5	-5	7	88	82	17
-4	-5	7	44	61	44
-3	-5	7	57	62	21
-2	-5	7	59	57	20
-1	-5	7	66	56	10
0	-5	7	72	80	9
1	-5	7	55	55	11
2	-5	7	42	34	15
3	-5	7	51	43	13
4	-5	7	88	91	9
5	-5	7	66	52	19
6	-5	7	65	49	30
7	-5	7	12	26	12
-8	-4	7	90	80	14
-7	-4	7	81	76	17
-6	-4	7	130	127	15
-5	-4	7	39	65	38
-4	-4	7	56	22	17
-3	-4	7	66	67	16
-2	-4	7	26	41	26
-1	-4	7	55	55	12
0	-4	7	0	14	1
1	-4	7	43	25	15
2	-4	7	134	129	7
3	-4	7	120	114	9
4	-4	7	84	93	8
5	-4	7	13	15	13
6	-4	7	41	27	40
7	-4	7	41	33	27
8	-4	7	33	40	32
-11	-3	7	185	33	20
-10	-3	7	237	55	15
-8	-3	7	64	46	16
-7	-3	7	93	106	14
-6	-3	7	122	132	7
-5	-3	7	133	139	19
-4	-3	7	58	43	10
-3	-3	7	73	79	5
-2	-3	7	43	44	10
-1	-3	7	114	112	8
0	-3	7	43	39	11
1	-3	7	62	62	9
2	-3	7	83	77	7
3	-3	7	200	219	7
4	-3	7	129	134	7
5	-3	7	74	81	6
6	-3	7	42	46	9
7	-3	7	85	88	8

h	k	l	10Fo	10Fc	10s
8	-3	7	41	39	16
9	-3	7	50	45	19
-11	-2	7	190	35	11
-9	-2	7	66	42	46
-8	-2	7	77	90	15
-7	-2	7	69	88	10
-6	-2	7	82	80	8
-5	-2	7	94	84	13
-4	-2	7	90	87	7
-3	-2	7	21	36	21
-2	-2	7	108	100	10
-1	-2	7	82	86	7
0	-2	7	156	177	5
1	-2	7	247	239	7
2	-2	7	83	86	7
3	-2	7	0	2	1
4	-2	7	118	125	4
5	-2	7	54	[illegible]	[illegible]
6	-2	7	35	44	[illegible]
7	-2	7	[illegible]	44	13
8	-2	7	57	48	14
9	-2	7	0	14	1
10	-2	7	40	36	40
-11	-1	7	186	82	12
-9	-1	7	35	49	35
-8	-1	7	87	100	13
-7	-1	7	50	49	17
-6	-1	7	159	192	16
-5	-1	7	97	95	10
-4	-1	7	68	62	8
-3	-1	7	95	88	6
-2	-1	7	39	47	15
-1	-1	7	143	142	8
0	-1	7	144	160	8
1	-1	7	148	151	8
2	-1	7	18	19	18
3	-1	7	147	146	7
4	-1	7	180	179	7
5	-1	7	91	89	5
6	-1	7	108	96	6
7	-1	7	58	47	9
8	-1	7	28	15	28
9	-1	7	83	74	16
10	-1	7	58	55	31
-11	0	7	156	27	13
-9	0	7	62	69	14
-8	0	7	121	124	12
-7	0	7	169	191	10
-6	0	7	26	5	26
-5	0	7	69	62	9
-4	0	7	63	62	8
-3	0	7	229	223	7
-2	0	7	31	18	19
-1	0	7	32	10	16
0	0	7	149	135	8
1	0	7	83	95	8
2	0	7	0	3	1
3	0	7	72	82	4
4	0	7	112	119	4
5	0	7	141	135	4
6	0	7	53	69	7
7	0	7	90	92	5
8	0	7	46	50	18
9	0	7	62	58	22
10	0	7	25	36	24
-11	1	7	169	82	12
-9	1	7	65	49	18
-8	1	7	100	100	12
-7	1	7	40	49	25
-6	1	7	177	192	11
-5	1	7	113	95	14
-4	1	7	71	62	7
-3	1	7	99	87	10
-2	1	7	40	47	15
-1	1	7	138	142	4
0	1	7	161	160	4
1	1	7	139	151	4
3	1	7	140	146	8
4	1	7	159	179	9
5	1	7	94	89	9
6	1	7	107	96	10
7	1	7	50	47	17
8	1	7	7	15	7
9	1	7	73	74	10
10	1	7	47	55	47
-11	2	7	189	35	10
-9	2	7	66	42	40
-8	2	7	73	90	14

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
-7	2	7	90	88	13
-6	2	7	89	88	13
-5	2	7	101	86	12
-4	2	7	97	87	6
-3	2	7	39	36	6
-2	2	7	107	100	4
-1	2	7	115	125	8
0	2	7	45	57	15
1	2	7	64	62	17
2	2	7	55	64	20
3	2	7	55	48	18
4	2	7	33	14	32
5	2	7	45	36	45
6	2	7	188	133	12
7	2	7	124	55	15
8	2	7	31	46	30
-7	3	7	108	106	11
-6	3	7	125	132	10
-5	3	7	158	139	11
-4	3	7	80	63	15
-3	3	7	102	79	11
-2	3	7	52	44	17
-1	3	7	57	61	12
0	3	7	84	77	10
1	3	7	209	219	10
2	3	7	134	134	6
3	3	7	79	81	9
4	3	7	17	46	16
5	3	7	74	88	12
6	3	7	33	39	23
7	3	7	51	45	24
8	3	7	219	29	12
-7	4	7	83	76	20
-6	4	7	125	127	11
-5	4	7	57	65	17
-4	4	7	65	22	16
-3	4	7	89	67	13
-2	4	7	57	61	10
-1	4	7	30	55	30
0	4	7	21	14	20
1	4	7	0	25	1
2	4	7	114	116	10
3	4	7	92	93	7
4	4	7	15	15	15
5	4	7	26	27	26
6	4	7	52	55	22
7	4	7	15	22	15
8	4	7	76	34	29
-7	5	7	32	39	32
-6	5	7	89	52	26
-5	5	7	65	42	22
-4	5	7	97	82	16
-3	5	7	69	61	14
-2	5	7	65	62	16
-1	5	7	57	57	19
0	5	7	56	56	17
1	5	7	80	80	11
2	5	7	55	55	13
3	5	7	37	34	37
4	5	7	56	43	22
5	5	7	91	91	16
6	5	7	52	52	20
7	5	7	51	54	51
8	5	7	30	30	16
-7	6	7	19	19	1
-6	6	7	89	89	16
-5	6	7	32	32	30
-4	6	7	87	87	13
-3	6	7	26	26	9
-2	6	7	21	46	20
-1	6	7	86	86	15
0	6	7	37	42	37
1	6	7	26	33	26
2	6	7	35	43	35
3	6	7	13	38	13
4	6	7	36	37	35
5	6	7	27	24	0
6	6	7	26	25	1
7	6	7	32	1	2
8	6	7	9	8	3
-7	7	7	0	17	1
-6	7	7	78	77	27
-5	7	7	1	5	2
-4	7	7	37	38	9
-3	7	7	64	62	7
-2	7	7	39	13	39
-1	7	7	87	86	17
0	7	7	33	17	21
1	7	7	36	36	17
2	7	7	110	110	36
3	7	7	45	58	0
4	7	7	0	38	38
5	7	7	38	43	17
6	7	7	43	38	31
7	7	7	37	49	37
8	7	7	69	69	29
-7	8	7	39	39	14
-6	8	7	21	21	17
-5	8	7	21	16	21
-4	8	7	0	36	17
-3	8	7	35	35	15
-2	8	7	22	22	10
-1	8	7	0	0	0
0	8	7	111	111	10
1	8	7	22	22	10
2	8	7	16	16	16
3	8	7	30	30	16
4	8	7	28	28	16
5	8	7	24	24	6
6	8	7	28	28	28
7	8	7	16	16	16
8	8	7	0	0	0
-7	9	7	0	0	0
-6	9	7	0	0	0
-5	9	7	0	0	0
-4	9	7	0	0	0
-3	9	7	0	0	0
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1	9	7	0	0	0
2	9	7	0	0	0
3	9	7	0	0	0
4	9	7	0	0	0
5	9	7	0	0	0
6	9	7	0	0	0
7	9	7	0	0	0
8	9	7	0	0	0
-7	10	7	0	0	0
-6	10	7	0	0	0
-5	10	7	0	0	0
-4	10	7	0	0	0
-3	10	7	0	0	0
-2	10	7	0	0	0
-1	10	7	0	0	0
0	10	7	0	0	0
1	10	7	0	0	0
2	10	7	0	0	0
3	10	7	0	0	0
4	10	7	0	0	0
5	10	7	0	0	0
6	10	7	0	0	0
7	10	7	0	0	0
8	10	7	0	0	0

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
0	1	9	88	102	5
1	1	9	53	56	7
2	1	9	49	58	7
3	1	9	47	49	9
4	1	9	80	83	5
5	1	9	47	52	7
6	1	9	0	11	1
7	1	9	77	81	6
8	1	9	28	31	18
9	1	9	24	28	23
-9	2	9	89	89	16
-8	2	9	0	21	1
-7	2	9	94	84	18
-6	2	9	8	30	8
-5	2	9	49	23	30
-4	2	9	46	39	21
-3	2	9	105	82	16
-2	2	9	149	147	5
-1	2	9	69	75	5
0	2	9	30	39	14
1	2	9	80	71	6
4	2	9	91	100	9
5	2	9	55	58	11
6	2	9	31	39	31
7	2	9	69	61	14
8	2	9	44	44	10
9	2	9	14	16	14
-9	3	9	0	29	1
-8	3	9	130	121	17
-7	3	9	125	126	12
-6	3	9	103	84	17
-5	3	9	76	45	31
-4	3	9	66	54	20
-3	3	9	121	104	6
-2	3	9	91	85	6
5	3	9	34	41	21
6	3	9	52	61	16
7	3	9	60	36	21
8	3	9	16	11	15
-9	4	9	46	13	45
-8	4	9	24	28	24
-7	4	9	117	112	16
-6	4	9	88	85	18
-5	4	9	28	42	27
-4	4	9	0	19	1
-3	4	9	45	30	45
-2	4	9	114	78	12
0	4	9	52	61	12
5	4	9	31	13	30
6	4	9	0	35	1
7	4	9	55	39	21
-8	5	9	0	24	1
-7	5	9	71	45	21
-6	5	9	0	16	1
-5	5	9	28	15	28
-4	5	9	55	60	22
-3	5	9	41	26	27
-2	5	9	54	73	15
-1	5	9	30	26	29
-6	6	9	64	47	24
-5	6	9	45	47	45
-4	6	9	67	71	20
-3	6	9	52	40	22
-2	6	9	31	23	31
-1	6	9	0	6	1
-4	7	9	0	17	1
-3	7	9	27	21	26
-2	7	9	0	7	1
-6	-6	10	66	22	41
-5	-6	10	0	21	1
-4	-6	10	0	26	1
-3	-6	10	13	32	13
-2	-6	10	34	8	34
-1	-6	10	30	27	30
0	-6	10	17	13	17
1	-6	10	20	20	20
2	-6	10	46	38	19
3	-6	10	52	48	18
4	-6	10	58	19	26
-8	-5	10	59	44	38
-7	-5	10	47	56	46
-6	-5	10	40	21	39
-5	-5	10	0	18	1
-4	-5	10	19	18	18
-3	-5	10	59	6	23
-2	-5	10	26	31	26
-1	-5	10	53	62	25
0	-5	10	40	35	20

h	k	l	10Fo	10Fc	10s
1	-5	10	0	26	1
2	-5	10	42	34	17
3	-5	10	32	51	31
4	-5	10	34	33	34
5	-5	10	0	20	1
-7	-4	10	42	38	42
-6	-4	10	0	15	1
-5	-4	10	40	13	40
-4	-4	10	55	53	20
-3	-4	10	85	94	17
-2	-4	10	37	25	37
-1	-4	10	38	32	16
0	-4	10	67	66	10
1	-4	10	68	64	11
2	-4	10	26	34	25
3	-4	10	61	60	10
4	-4	10	64	51	11
5	-4	10	40	29	22
6	-4	10	0	26	1
-10	-3	10	0	35	1
-9	-3	10	86	75	22
-8	-3	10	42	55	41
-7	-3	10	76	83	13
-6	-3	10	75	53	12
-5	-3	10	51	32	17
-4	-3	10	20	40	19
-3	-3	10	73	68	14
-2	-3	10	50	55	28
-1	-3	10	40	25	40
0	-3	10	30	35	29
1	-3	10	40	42	16
2	-3	10	94	100	7
3	-3	10	0	16	1
4	-3	10	34	22	33
5	-3	10	16	15	16
6	-3	10	92	77	9
7	-3	10	68	46	20
8	-3	10	70	61	15
-10	-2	10	0	51	1
-9	-2	10	7	39	7
-8	-2	10	58	28	22
-7	-2	10	69	56	21
-6	-2	10	89	87	10
-5	-2	10	125	113	9
-4	-2	10	118	111	9
-3	-2	10	60	55	24
-2	-2	10	90	88	14
-1	-2	10	73	78	12
0	-2	10	103	106	10
1	-2	10	46	41	25
2	-2	10	127	126	11
3	-2	10	66	66	14
4	-2	10	60	58	17
5	-2	10	28	27	27
6	-2	10	54	39	23
7	-2	10	66	54	11
8	-2	10	37	31	37
-10	-1	10	36	27	36
-9	-1	10	57	66	28
-8	-1	10	53	61	26
-7	-1	10	59	36	27
-6	-1	10	98	60	18
-5	-1	10	22	54	22
-4	-1	10	66	60	13
-3	-1	10	100	104	11
-2	-1	10	38	20	37
-1	-1	10	58	36	18
0	-1	10	160	160	10
1	-1	10	111	109	11
2	-1	10	86	93	11
3	-1	10	64	68	12
4	-1	10	25	25	25
5	-1	10	28	18	28
6	-1	10	0	22	1
7	-1	10	21	26	20
8	-1	10	46	25	26
-10	0	10	69	96	24
-9	0	10	0	32	1
-8	0	10	25	18	25
-7	0	10	43	45	42
-6	0	10	36	9	35
-5	0	10	96	79	10
-4	0	10	32	39	31
-3	0	10	0	4	1
-2	0	10	74	71	11
-1	0	10	26	21	25
0	0	10	114	128	9
1	0	10	105	111	9

h	k	l	10Fo	10Fc	10s
2	0	10	0	22	1
3	0	10	64	58	12
4	0	10	40	48	27
5	0	10	34	45	33
6	0	10	42	17	42
7	0	10	30	18	30
8	0	10	25	4	25
-10	1	10	15	27	15
-9	1	10	47	66	47
-8	1	10	61	61	26
-7	1	10	37	36	36
-6	1	10	96	60	25
-5	1	10	66	54	22
-4	1	10	59	60	10
-3	1	10	126	104	11
-2	1	10	0	20	1
-1	1	10	21	36	21
0	1	10	174	160	10
1	1	10	109	109	5
2	1	10	90	93	6
3	1	10	58	68	7
4	1	10	38	28	11
5	1	10	27	18	15
6	1	10	0	22	1
7	1	10	44	25	9
8	1	10	40	25	13
-10	2	10	54	51	53
-9	2	10	64	39	34
-8	2	10	23	28	23
-7	2	10	79	56	21
-6	2	10	100	87	17
-5	2	10	157	113	14
-4	2	10	152	111	14
-3	2	10	68	55	9
-2	2	10	92	88	11
-1	2	10	81	78	6
0	2	10	116	106	5
1	2	10	38	41	11
2	2	10	132	126	5
3	2	10	58	66	10
4	2	10	52	58	8
5	2	10	25	27	26
6	2	10	38	39	10
7	2	10	53	56	9
8	2	10	37	31	13
-10	3	10	51	35	36
-9	3	10	78	75	26
-8	3	10	62	55	36
-7	3	10	79	83	23
-6	3	10	80	53	25
-5	3	10	46	32	46
-4	3	10	67	40	22
-3	3	10	87	68	18
-2	3	10	49	55	9
-1	3	10	19	25	19
6	3	10	85	77	11
7	3	10	62	46	21
8	3	10	79	61	14
-9	4	10	76	50	37
-8	4	10	63	52	34
-7	4	10	0	38	1
-6	4	10	61	15	37
-5	4	10	41	13	41
-4	4	10	71	53	23
-3	4	10	120	94	13
-2	4	10	64	25	26
6	4	10	42	26	27
7	4	10	51	48	18
-5	5	10	47	18	20
-4	5	10	38	18	37
-3	5	10	0	6	1
-2	5	10	0	31	1
-1	5	10	57	62	16
-5	6	10	0	21	1
-4	6	10	41	26	41
-3	6	10	15	32	15
-2	6	10	0	8	1
-5	-6	11	0	5	1
-4	-6	11	40	15	39
-3	-6	11	51	8	50
-2	-6	11	28	17	27
-1	-6	11	58	48	21
0	-6	11	41	36	41
1	-6	11	26	32	23
2	-6	11	39	37	39
3	-6	11	32	23	31
-7	-5	11	19	39	19
-5	-5	11	20	29	19

h	k	l	10Fo	10Fc	10s
-4	-5	11	40	10	40
-3	-5	11	9	30	8
0	-5	11	18	21	18
1	-5	11	34	54	33
2	-5	11	41	21	26
3	-5	11	0	28	1
4	-5	11	29	30	28
5	-5	11	7	17	7
-7	-4	11	0	31	1
-6	-4	11	38	28	37
-5	-4	11	21	8	21
-4	-4	11	54	26	28
-3	-4	11	56	65	26
-2	-4	11	64	68	32
-1	-4	11	29	24	24
0	-4	11	44	52	17
1	-4	11	22	35	21
2	-4	11	61	28	16
3	-4	11	25	32	24
4	-4	11	26	26	26
5	-4	11	20	28	20
6	-4	11	59	48	37
-9	-3	11	0	35	1
-8	-3	11	48	44	48
-7	-3	11	0	23	1
-6	-3	11	33	20	32
-5	-3	11	55	57	17
-4	-3	11	56	55	11
-3	-3	11	33	42	33
-2	-3	11	0	23	1
-1	-3	11	67	35	37
0	-3	11	96	91	14
1	-3	11	39	37	38
2	-3	11	83	67	13
3	-3	11	0	19	1
4	-3	11	51	43	15
5	-3	11	63	44	14
6	-3	11	69	58	17
7	-3	11	67	33	31
-10	-2	11	76	44	28
-9	-2	11	68	76	38
-8	-2	11	61	61	38
-7	-2	11	0	12	1
-6	-2	11	57	69	16
-5	-2	11	81	71	12
-4	-2	11	44	55	18
-3	-2	11	56	66	24
-2	-2	11	47	28	33
-1	-2	11	0	19	1
0	-2	11	119	123	11
1	-2	11	80	79	13
2	-2	11	0	33	1
3	-2	11	25	23	24
4	-2	11	0	26	1
5	-2	11	42	28	42
6	-2	11	34	15	33
7	-2	11	69	39	48
-10	-1	11	95	76	24
-9	-1	11	68	41	48
-8	-1	11	48	18	48
-7	-1	11	31	14	30
-6	-1	11	116	101	16
-5	-1	11	62	56	14
-4	-1	11	54	48	15
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-2	-1	11	65	57	17
-1	-1	11	93	94	12
0	-1	11	77	84	16
1	-1	11	16	13	16
2	-1	11	94	98	12
3	-1	11	24	7	23
4	-1	11	29	34	28
5	-1	11	17	18	16
6	-1	11	63	35	42
7	-1	11	55	63	24
8	-1	11	17	27	17
-9	0	11	34	43	34
-8	0	11	27	15	26
-7	0	11	87	51	25
-6	0	11	169	123	15
-5	0	11	65	63	18
-4	0	11	62	55	12
-3	0	11	36	35	36
-2	0	11	50	36	22
-1	0	11	111	80	13
0	0	11	80	76	12
1	0	11	0	34	1
2	0	11	35	16	35

h	k	l	10Fo	10Fc	10s
3	0	11	37	38	34
4	0	11	0	1	1
6	0	11	56	42	22
7	0	11	49	26	15
8	0	11	0	27	1
-10	1	11	76	76	29
-9	1	11	26	42	26
-8	1	11	65	18	44
-7	1	11	10	14	10
-6	1	11	132	101	15
-5	1	11	82	54	21
-4	1	11	43	48	28
-3	1	11	105	106	11
-2	1	11	60	57	14
-1	1	11	84	94	12
0	1	11	87	84	12
1	1	11	[illegible]	13	30
2	1	11	97	98	6
3	1	11	12	7	13
4	1	11	31	34	19
5	1	11	25	18	24
6	1	11	26	35	26
7	1	11	28	63	22
8	1	11	27	27	26
-9	2	11	99	76	23
-8	2	11	69	61	25
-7	2	11	54	12	53
-6	2	11	96	69	38
-5	2	11	100	71	18
-4	2	11	74	55	18
-3	2	11	79	66	10
-2	2	11	26	28	26
-1	2	11	21	19	20
0	2	11	121	123	6
1	2	11	77	79	6
2	2	11	34	33	14
3	2	11	63	23	11
4	2	11	31	26	17
5	2	11	36	28	14
6	2	11	23	15	23
7	2	11	35	39	14
-9	3	11	56	35	56
-8	3	11	46	44	45
-7	3	11	73	23	28
-6	3	11	0	20	1
-5	3	11	56	57	36
-4	3	11	71	55	25
-3	3	11	57	42	24
-2	3	11	16	23	16
-1	3	11	39	35	12
0	3	11	94	91	6
1	3	11	43	36	10
2	3	11	65	67	8
6	3	11	52	58	9
7	3	11	67	33	28
-8	4	11	61	46	61
-7	4	11	75	31	28
-6	4	11	43	28	42
-5	4	11	31	8	31
-4	4	11	64	26	30
-3	4	11	55	45	38
-2	4	11	84	68	20
-1	4	11	6	24	5
-4	5	11	60	10	17
-3	5	11	43	30	39
-2	5	11	32	30	32
-4	6	11	0	15	1
-3	6	11	0	8	1
-6	-5	12	0	18	1
-5	-5	12	63	15	41
-4	-5	12	32	22	31
-3	-5	12	45	19	45
-2	-5	12	20	9	20
-1	-5	12	71	70	17
0	-5	12	43	42	22
1	-5	12	0	3	1
2	-5	12	40	43	22
3	-5	12	2	16	2
-7	-4	12	0	33	1
-6	-4	12	57	30	48
-5	-4	12	0	17	1
-4	-4	12	32	22	32
-3	-4	12	0	11	1
-2	-4	12	37	37	36
-1	-4	12	0	18	1
0	-4	12	0	36	1
1	-4	12	0	22	1
2	-4	12	39	15	23

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
3	-4	12	16	25	15
4	-4	12	29	28	28
5	-4	12	0	13	1
-8	-3	12	66	61	31
-7	-3	12	11	10	11
-6	-3	12	68	59	16
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-4	-3	12	95	83	11
-3	-3	12	50	56	31
-2	-3	12	82	74	16
-1	-3	12	46	44	31
0	-3	12	50	52	33
1	-3	12	3	12	3
2	-3	12	28	23	28
3	-3	12	36	37	36
4	-3	12	51	26	33
5	-3	12	72	49	21
6	-3	12	0	38	1
-9	-2	12	33	19	33
-8	-2	12	59	46	47
-7	-2	12	72	66	30
-6	-2	12	101	85	14
-5	-2	12	0	16	1
-4	-2	12	0	15	1
-3	-2	12	14	27	14
-2	-2	12	43	65	43
-1	-2	12	64	77	16
0	-2	12	110	96	13
1	-2	12	0	16	1
2	-2	12	43	41	31
3	-2	12	20	13	20
4	-2	12	40	30	39
5	-2	12	63	55	27
6	-2	12	68	46	29
7	-2	12	33	25	33
-9	-1	12	0	6	1
-8	-1	12	0	26	1
-7	-1	12	54	62	54
-6	-1	12	46	25	45
-5	-1	12	76	73	13
-4	-1	12	38	26	37
-3	-1	12	73	67	16
-2	-1	12	124	112	11
-1	-1	12	53	49	19
0	-1	12	79	73	13
1	-1	12	73	76	13
2	-1	12	82	75	13
3	-1	12	0	15	1
4	-1	12	32	16	32
5	-1	12	33	21	32
6	-1	12	25	24	24
7	-1	12	34	36	34
-8	0	12	54	7	54
-7	0	12	0	8	1
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-2	0	12	37	19	36
-1	0	12	33	40	32
0	0	12	110	108	11
1	0	12	0	3	1
2	0	12	35	37	34
3	0	12	41	13	26
4	0	12	49	1	22
7	0	12	44	22	44
-9	1	12	49	6	48
-8	1	12	39	26	39
-7	1	12	43	42	43
-6	1	12	32	25	31
-5	1	12	99	73	18
-4	1	12	25	26	25
-3	1	12	82	67	15
-2	1	12	129	112	11
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0	1	12	84	73	11
1	1	12	72	76	14
2	1	12	78	75	14
3	1	12	0	15	1
4	1	12	38	16	37
5	1	12	7	21	6
6	1	12	66	24	18

h	k	l	10Fo	10Fc	10s
7	1	12	34	36	34
-9	2	12	43	19	42
-8	2	12	64	46	63
-7	2	12	102	66	27
-6	2	12	127	85	19
-5	2	12	0	16	1
-4	2	12	10	15	10
-3	2	12	0	27	1
-2	2	12	69	65	15
-1	2	12	60	77	16
0	2	12	109	96	6
1	2	12	24	16	24
2	2	12	41	41	12
3	2	12	0	13	1
4	2	12	22	30	21
5	2	12	35	55	35
6	2	12	41	45	13
-8	3	12	68	61	44
-7	3	12	78	10	3
-6	3	12	94	59	2
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-2	3	12	83	76	16
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0	3	12	36	52	13
1	3	12	26	12	25
2	3	12	31	23	22
3	3	12	21	37	20
4	3	12	35	26	16
5	3	12	60	49	10
-6	4	12	10	30	10
-5	4	12	66	17	66
-4	4	12	10	22	10
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-6	-4	13	34	8	33
-5	-4	13	36	37	36
-4	-4	13	61	50	26
-3	-4	13	28	24	27
-2	-4	13	0	23	1
-1	-4	13	0	23	1
0	-4	13	21	38	20
1	-4	13	21	27	21
2	-4	13	24	19	24
3	-4	13	46	24	46
-8	-3	13	37	40	37
-7	-3	13	20	25	19
-6	-3	13	66	33	24
-5	-3	13	43	27	39
-4	-3	13	67	57	15
-3	-3	13	44	18	43
-2	-3	13	35	31	35
-1	-3	13	26	18	26
1	-3	13	49	43	27
2	-3	13	0	25	1
3	-3	13	6	16	6
4	-3	13	0	17	1
5	-3	13	19	24	19
-8	-2	13	61	55	50
-6	-2	13	28	20	28
-5	-2	13	17	29	17
-4	-2	13	69	56	15
-3	-2	13	39	35	39
-2	-2	13	68	77	25
-1	-2	13	48	38	22
1	-2	13	39	35	38
2	-2	13	34	32	33
3	-2	13	24	24	23
4	-2	13	0	15	1
5	-2	13	91	70	17

h	k	l	10Fo	10Fc	10s
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-7	-1	13	0	11	1
-6	-1	13	75	58	25
-5	-1	13	27	58	27
-4	-1	13	0	7	1
-3	-1	13	30	53	30
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1	-1	13	53	31	28
2	-1	13	26	25	25
3	-1	13	56	31	21
4	-1	13	50	45	27
5	-1	13	0	10	1
6	-1	13	48	16	29
-8	0	13	0	10	1
-7	0	13	174	107	25
-6	0	13	49	21	49
-5	0	13	32	[illegible]	[illegible]
-4	0	13	19	33	19
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-2	0	13	109	103	16
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0	0	13	0	17	1
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6	0	13	18	9	18
-8	1	13	99	64	29
-7	1	13	0	11	1
-6	1	13	82	58	23
-5	1	13	60	58	28
-4	1	13	21	7	21
-3	1	13	90	53	18
-2	1	13	70	58	20
-1	1	13	40	30	34
1	1	13	0	31	1
2	1	13	52	25	23
3	1	13	37	31	36
4	1	13	50	45	21
5	1	13	34	10	33
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-7	2	13	35	10	35
-6	2	13	53	20	52
-5	2	13	62	29	45
-4	2	13	70	56	20
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2	2	13	37	32	15
3	2	13	22	24	22
4	2	13	22	15	22
5	2	13	72	70	8
-7	3	13	38	25	38
-6	3	13	53	33	52
-5	3	13	32	27	32
-4	3	13	81	57	25
-3	3	13	30	18	29
-2	3	13	0	31	1
-1	3	13	10	18	10
0	3	13	39	26	15
1	3	13	34	63	34
2	3	13	25	25	24
3	3	13	42	16	12
4	3	13	47	17	15
-6	4	13	61	9	60
-5	4	13	56	37	55
-4	4	13	103	51	25
-3	4	13	27	24	26
-2	4	13	0	23	1
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1	4	13	28	27	27
2	4	13	20	19	19
3	4	13	22	24	22
0	5	13	44	20	16
1	5	13	39	27	19
-5	-4	14	0	11	1
-4	-4	14	69	17	48

h	k	l	10Fo	10Fc	10s
-3	-4	14	28	36	27
-2	-4	14	34	38	33
-1	-4	14	0	23	1
0	-4	14	37	9	36
1	-4	14	17	39	16
-6	-3	14	0	47	1
-5	-3	14	52	18	25
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3	-3	14	0	16	1
-7	-2	14	59	27	59
-6	-2	14	49	38	49
-5	-2	14	24	33	24
-4	-2	14	20	26	19
-3	-2	14	0	11	1
-2	-2	14	69	59	25
-1	-2	14	33	30	33
0	-2	14	0	9	1
1	-2	14	31	12	30
2	-2	14	0	22	1
3	-2	14	18	33	18
4	-2	14	68	42	24
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-6	-1	14	50	6	49
-5	-1	14	0	19	1
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-3	-1	14	0	24	1
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-1	-1	14	62	47	22
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2	-1	14	28	31	28
3	-1	14	0	25	1
4	-1	14	43	10	42
-7	0	14	0	38	1
-6	0	14	44	24	44
-5	0	14	25	8	24
-4	0	14	116	81	17
-3	0	14	138	110	14
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-1	0	14	44	50	44
0	0	14	28	23	28
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2	0	14	35	11	34
3	0	14	26	41	25
4	0	14	0	23	1
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-3	1	14	21	24	21
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-1	1	14	43	47	42
0	1	14	45	36	29
1	1	14	10	10	9
2	1	14	44	31	36
3	1	14	0	26	1
4	1	14	0	10	1
-7	2	14	62	27	62
-6	2	14	73	38	68
-5	2	14	0	33	1
-4	2	14	34	26	34
-3	2	14	42	11	42
-2	2	14	77	59	19
-1	2	14	13	30	12
0	2	14	21	9	20
1	2	14	30	12	30
2	2	14	26	23	25
3	2	14	60	33	39
4	2	14	0	42	1
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-5	3	14	61	18	60
-4	3	14	61	63	43
-3	3	14	0	10	1
-1	3	14	61	52	23
0	3	14	41	33	41
1	3	14	56	49	13
2	3	14	0	5	1

h	k	l	10Fo	10Fc	10s
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-4	4	14	34	17	33
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-2	4	14	64	38	37
0	4	14	18	9	17
1	4	14	50	39	13
2	4	14	16	15	16
-5	-3	15	55	32	23
-4	-3	15	30	34	30
-3	-3	15	0	26	1
-2	-3	15	42	41	41
-1	-3	15	14	17	13
0	-3	15	11	8	10
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-4	-2	15	40	23	39
-3	-2	15	4	17	4
-2	-2	15	63	34	36
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1	-2	15	56	41	27
2	-2	15	21	30	21
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-5	0	15	0	15	1
-4	0	15	25	10	24
-3	0	15	0	5	1
-2	0	15	29	49	29
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0	0	15	11	11	11
1	0	15	35	13	34
2	0	15	0	8	1
3	0	15	0	3	1
-6	1	15	0	15	1
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0	1	15	2	17	2
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-4	2	15	0	23	1
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0	2	15	0	9	1
1	2	15	54	41	26
2	2	15	43	30	42
-5	3	15	45	32	45
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0	3	15	0	8	1
1	3	15	41	25	40
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0	-1	16	45	14	44
-4	0	16	36	43	36
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-2	0	16	0	14	1
-1	0	16	0	3	1
0	0	16	40	6	39
1	0	16	0	0	1
-2	1	16	50	39	49
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0	1	16	38	14	37
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