Tetrahedron Vol. 47, No. 46, pp. 9503-9569, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
Pergamon Press plc

TETRAHEDRON REPORT NUMBER 302

Chiral Non-Racemic Bicyclic Lactams. Vehicles for the Construction of Natural and Unnatural Products Containing Quaternary Carbon Centers.

Daniel Romo and A. I. Meyers*

Department of Chemistry, Colorado State University
Fort Collins, CO 80523, U.S.A.

(*Received* 1 *July* 1991)

CONTENTS

I. INTRODUCTION

Considering the prominence of asymmetric centers in the majority of natural products and compounds of therapeutic relevance, an excellent opportunity has existed for the synthetic organic chemist to develop efficient and general methods for the construction of these chiral, non-racemic materials. Indeed, in the past 20 years, the field of asymmetric synthesis has experienced a virtual explosion in the number of methods available for reaching an array of molecular types in high enantiomeric purity.[1]

Most asymmetric synthetic routes take advantage of classical and modern methods for chemical bond construction but in addition, employ natural chiral sources such as amino acids[2] or carbohydrates[3] which are covalently or ionically attached to a substrate. These chiral sources are commonly referred to as chiral auxiliaries unless they are ultimately incorporated into the final product in which case they have been called chirons (chiral synthons)[3]. When covalently or ionically attached to a substrate the chiral auxiliary renders enantiotopicity or diastereotopicity to the molecule. Asymmetric induction is achieved during the stereodifferentiating step in which two or more possible routes to products differ in their energy of activation ($\Delta G^{\ddagger}$) due to steric and/or electronic effects during the transition state. The result is that one diastereomer (or enantiomer) is formed to a greater extent than the other possible stereoisomers. If the distinction in reactivity can be controlled such that the $\Delta\Delta G^{\ddagger} \geq 3$ kcal then the process becomes one of practical utility (>99% ee). Thus, new stereocenters can be produced in an absolute sense due to the stereochemical information transmitted to the new asymmetric center from the chiral auxiliary. In most cases, varying mixtures of two or more stereoisomers are produced and, in the case of a covalently attached chiral auxiliary, diastereomers rather than enantiomers are produced. The pure major diastereomer may, however, be isolated by conventional purification methods. This offers an advantage in comparison to asymmetric syntheses which employ a non-covalently attached chiral auxiliary (chiral bases or catalysts) which, if products of less than 100% optical purity are produced, lead directly to enantiomers, the separation of which is usually not conveniently accomplished by conventional means. This report will not deal with catalytic asymmetric reactions, a field which also holds highly significant potential due to efficiency of implementation, and one which many believe is the ultimate goal of reaching chiral, non-racemic substances. On the other hand, when dealing with stoichiometric asymmetric processes, efficient methods for chiral auxiliary removal must be available in order to warrant their use over classical resolution or catalytic techniques.

It is the purpose of this report to summarize the synthetic utility of one such covalently attached, chiral auxiliary which has enjoyed considerable success. This novel method for the construction of asymmetric quaternary carbon centers, first reported[4] from these laboratories in 1984, enables one to transform a prochiral substrate (a γ-keto acid or δ-keto acid) into a variety of optically pure substances including 2,2-dialkyl ketoacids, cyclopropanes, cyclobutanes, cyclopentenones, cyclohexenones, indanones, naphthalenones, 3,3-disubstituted dihydronaphthalenes, and other systems (Fig. 1.). These transformations are made possible via the chiral, non-racemic 1-aza-8-oxo-4-oxa-[3.3.0]bicyclooctanes **3**, hereafter called "bicyclic lactams," which are derived from dicarbonyl compounds **2** and chiral amino alcohols **1**. Since the first report which illustrated the potential of these bicyclic lactams for the construction of

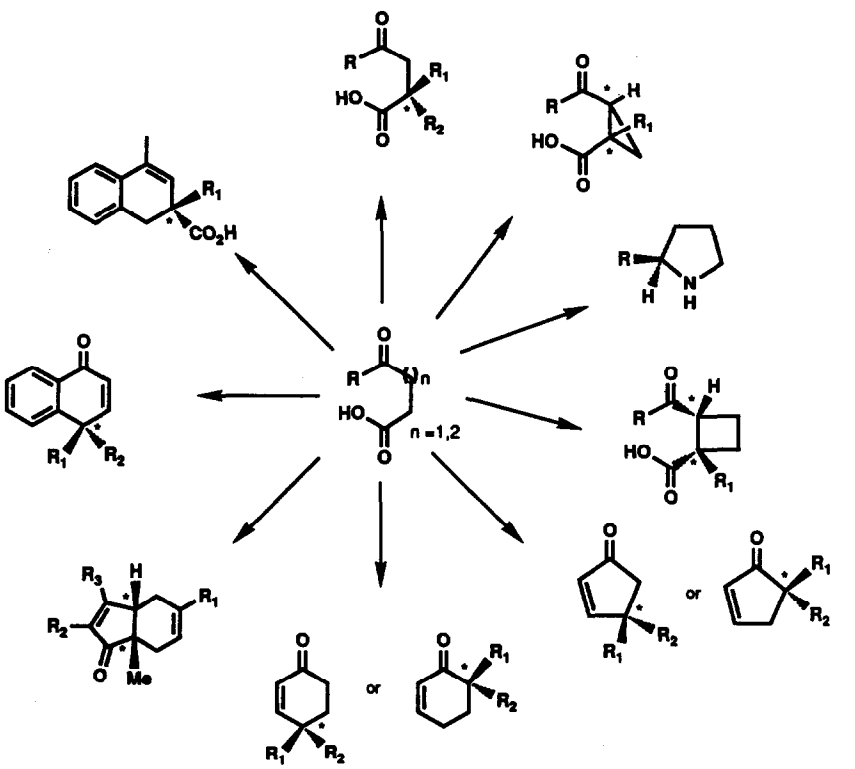
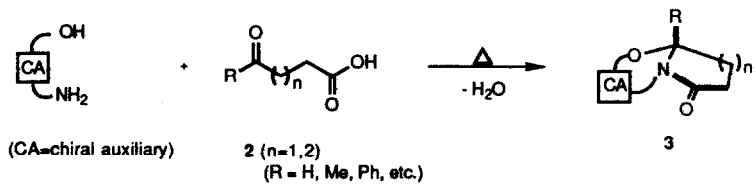


Figure 1. Optically pure quaternary carbon substances derived from keto acids by use of chiral bicyclic lactams.



1 (CA=chiral auxiliary) 2 (n=1,2) (R = H, Me, Ph, etc.) 3

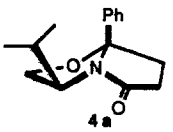
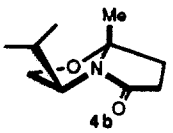
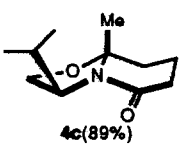
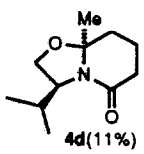
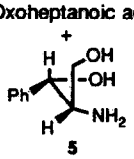
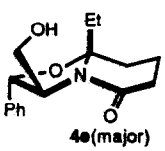
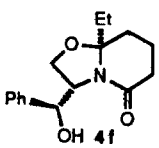
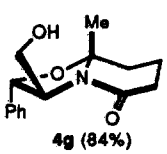
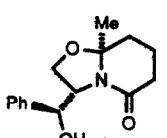
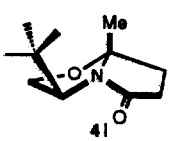
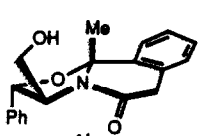
α, α-dialkylated-γ-keto acids,[4] a number of useful extensions of this methodology including cycloadditions and ring annelations have clearly demonstrated the versatility of these bicyclic lactams as templates for asymmetric synthesis.

II. PREPARATION OF CHIRAL, NON-RACEMIC BICYCLIC LACTAMS

Two general methods have been developed for the construction of the title bicyclic systems and involve condensation of an optically pure amino alcohol and a dicarbonyl compound. In the first route a cyclodehydration process was utilized between an optically pure amino alcohol **1** and a γ-ketoacid **2**. This was performed by heating the components at reflux in toluene with azeotropic removal of water. Thus, condensation of a γ-ketoacid and an amino alcohol afforded the bicyclo [3,3,0] octanes (entries 1, 2, 6) as single diastereomers (Table 1). However, the bicyclo [4,3,0] nonanes (entries 3, 4, 5, 7) are obtained as a diastereomeric mixture of lactams (approximately 10:1) with the absolute stereochemistry as shown at the angular position. In these cases, the pure diastereomer was readily obtained by recrystallization or chromatography and a number of bicyclic lactams were prepared in this manner in good to excellent yields. This approach is the most expedient since it involves a single synthetic step, and is only limited by the availability of the ketoacid. The amino alcohols employed are commercially available but can also be less expensively obtained by lithium aluminum hydride reduction of the corresponding amino acids.[5]

γ-Ketoacids substituted in the α-position have also been utilized in cyclodehydration with amino alcohols to afford the corresponding α-monosubstituted lactams **6a-c** (Table 2). Although a mixture of α-epimers was obtained in each case, subsequent alkylations performed on these bicyclic lactams, via their common planar enolate, rendered these mixtures inconsequential with

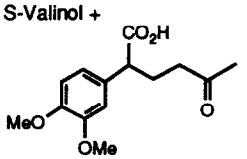
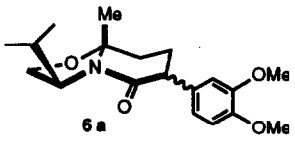
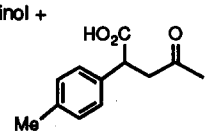
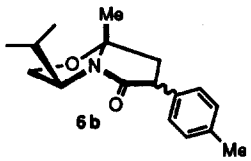
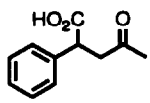
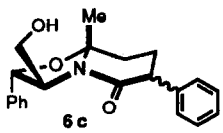
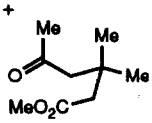
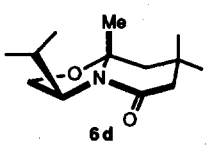
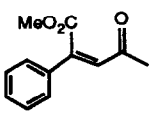
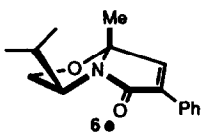
Table 1. Bicyclic Lactams **4** via Cyclodehydration of Amino alcohols and Dicarbonyl Compounds.

Entry	Dicarbonyl compound + Amino alcohol	Bicyclic lactam **4**	Yield, %[a]	Ref.
1	3-Benzoylpropionic acid + S-Valinol	 **4a**	85	4
2	Levulinic acid + S-Valinol	 **4b**	85	6
3	5-Ketohexanoic acid + S-Valinol	 **4c**(89%)  **4d**(11%)	65	7
4	5-Oxoheptanoic acid +  **5**	 **4e**(major)  **4f**	68	8
5	Levulinic acid + **5**	 **4g** (84%)  **4h** (14%) + 2% of another isomer[b]	60-65	9
6	Levulinic acid + S-tert-Leucinol	 **4i**	92	10
7	3-(2-Acetyl)phenyl-acetic acid + **5**	 **4j**	60	11

[a]The yield refers to the isolated pure major diastereomer. [b]The other isomer corresponds to bicyclic lactam **4g** with the inverted stereochemistry for the angular methyl group.

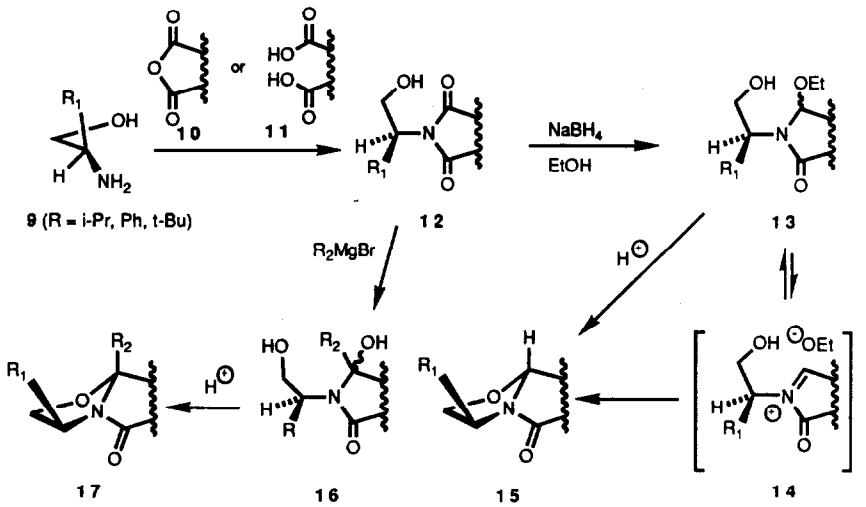
regard to further chemistry (*vide infra*). Two additional bicyclic lactams **6d-e** were also prepared directly via the cyclodehydration reaction and were utilized in specific chemical synthesis (*vide infra*).

Table 2. Functionalized Bicyclic Lactams **6** via Cyclodehydration.

Amino alcohol + Dicarbonyl compd	Bicyclic lactams **6**	Yield, %	Ref.
S-Valinol + 	 **6a**	90[a]	7
S-Valinol + 	 **6b**	91	12
5 + 	 **6c**	53[a,b]	7
S-Valinol + 	 **6d**	54	36
S-Valinol + 	 **6e**	60	10

[a]These mixtures of α-aryl diastereomers were also accompanied by varying amounts (10-20%) of isomers which were epimeric at the angular methyl group. [b]This yield includes a metalation /alkylation sequence (MeI) to provide the diastereomerically pure *endo* α-methyl-*exo* α-phenyl bicyclic lactam.

The second route developed to secure these chiral bicyclic lactams is related to the extensive work of Speckamp[14] involving N-acyliminium species. Condensation of an optically pure amino alcohol **9** with a cyclic anhydride or dicarboxylic acid afforded the imides **12** which, on addition of an alkyl Grignard or hydride, afforded the carbinolamines **16** or the ethoxy amines **13**, respectively (Scheme 1). These intermediates were directly subjected to acidic conditions resulting in ring closure, via the N-acyliminium species **14**, furnishing the bicyclic lactams **15** and **17** in fair to good overall yields (Table 3).



Scheme 1

This procedure produced good overall yields (69%) of the angular hydrogen bicyclic lactam **15b** which had been obtained in only very low yields by the alternative cyclodehydration route employing aldehydic carboxylic acids. The latter starting material was both tedious to prepare and unstable to the cyclodehydration conditions. This sequence also removes the limitation imposed by the previous method since any group (R_2) can be introduced at the angular position provided the appropriate Grignard reagent is readily available. Thus, treatment of the succinimide **12b** with methylmagnesium bromide gave the intermediate carbinolamine **16** (R_2 = Me) which was immediately treated with trifluoroacetic acid to give the angular methyl lactam **17a** in good yield.

Table 3. Succinimides **12** and Bicyclic Lactams **15** and **17**.

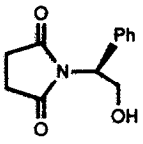
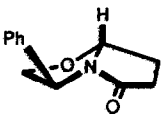
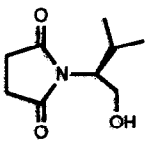
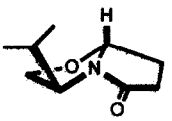
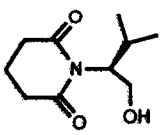
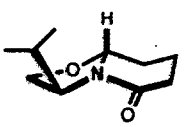
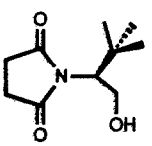
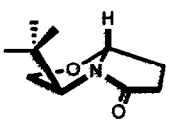
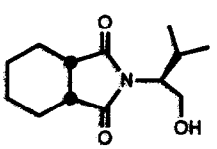
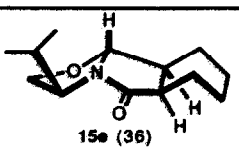
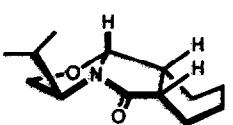
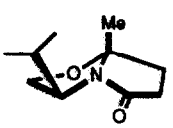
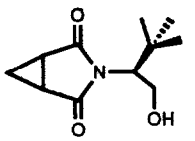
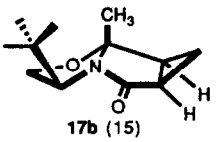
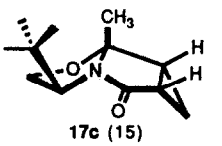
Anhydride/ Amino alcohol[a]	Imide (yield, %)	Method[b]	Bicyclic Lactam (yield, %)[c]	Method[b]	Ref.
Succinic/ S-Phenyl glycinol	 **12a** (80)	A	 **15a** (77)	D	15
Succinic/ S-Valinol	 **12b** (73)	B	 **15b** (95)	D	15
Glutaric/ S-Valinol	 **12c** (21)	B	 **15c** (77)	D	15
Succinic/ S-tert-leucinol	 **12d** (73)	C	 **15d** (99)	D	10
cis-1,2-Cyclo-hexane dicarboxylic /S-Valinol	 **12e** (95)	B	 **15e** (36)  **15f** (64)	D	15
Succinic/ S-Valinol	**12b**	B	 **17a** (73)	E	15

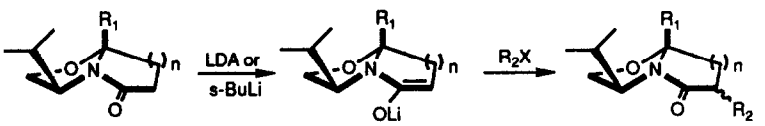
Table 3, cont'd.

cis-1,2-Cyclopropane dicarboxylic /S-tert-Leucinol	 12f (76)	C	 17b (15)  17c (15)	E	10

[a]Equimolar quantities. [b]Method A: toluene/reflux/Et_3N; Method B: Neat mixture /220°C; Method C: THF/RT, Ac_2O/NaOAc/100°C, 10% aq. NaOH/reflux; Method D: $NaBH_4$/HCl/EtOH; Method E: MeMgBr/THF/RT [c]Crude products were ~95% pure.

III. METALATIONS AND STEREODIFFERENTIAL ALKYLATIONS OF BICYCLIC LACTAMS

It was envisaged at the outset that the lactams described above when metalated and alkylated would provide the corresponding α-mono-substituted lactams **20** with some degree of diastereoselectivity. Initial studies with the bicyclic lactams **18** (R_1= Ph, Me) derived from L-valinol were rather encouraging.[4] Metalation with lithium diisopropylamide (LDA) or *sec*-butyllithium followed by alkylation with a variety of alkyl halides proceeded to **20** with good to excellent diastereoselectivity (9-32:1 ratios, Table 4).



18 (n=1, 2) **19** (n=1, 2) **20** (n=1, 2)

During the alkylation, the alkyl halide approached the lactam enolate **19** in predominantly an *endo* fashion to afford the major diastereomer of the α-methyl bicyclic lactams **20** (n = 1, R_1 = Ph, R_2 = Me). The *exo* and *endo* isomers (as determined by X-ray techniques) were in most cases readily separable by Kugelrohr distillation or recrystallization.

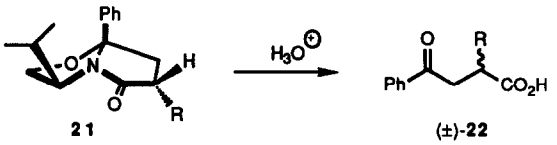
Having secured the α-alkyl lactams **21** in high diastereomeric purity, it was expected that hydrolytic removal of the chiral auxiliary would deliver a variety of chiral 2-substituted keto acids **22**. Disappointingly, all attempts to remove the chiral auxiliary in order to liberate the keto acids

Table 4. α-Alkyl Lactams **20** from Lactams **18** (n=1).

Entry	R_1	R_2X[a]	%De[b]	Yield,%[d]
a	Ph	$PhCH_2Br$	80	88
b	Ph	MeI	80	80
c	Ph	EtI	94	80
d	Me	Allyl Br	-[c]	88
e	Me	$PhCH_2Br$	-[c]	82
f	Me	MeI	82	70
g	Me	$PhCH_2Br$	82	80

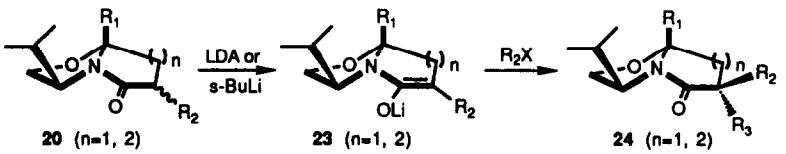
[a] Added to a solution of enolate in THF at -78°C. [b] Determined by HPLC and/or ^{1}H-NMR. [c] Not determined. [d] Combined yields of both diastereomers after chromatography.

resulted in significant racemization at the α-center (<20% ee). Interestingly, the keto acid **22** was found to be quite stable to epimerization under the wide range of acidic conditions employed; therefore, it was concluded that racemization had occurred at some intermediate stage in the hydrolysis of **21**.



21 (±)-**22**

Since quaternization of the α-center in **20** would obviate the possibility of racemization during subsequent chiral auxiliary removal, a second metalation/alkylation sequence was applied to the diastereomerically pure or to the mixture of *endo*/*exo* mono-substituted lactams **20**.



20 (n=1, 2) **23** (n=1, 2) **24** (n=1, 2)

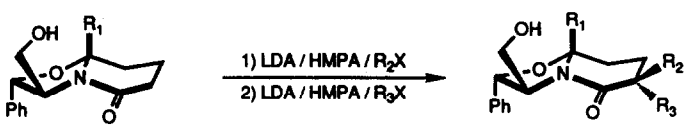
The second alkylation again proceeded with high *endo* selectivity and in many cases resulted in much higher *endo*/*exo* ratios (Table 5) than the first alkylation. The major underlying reason for preferential *endo* alkylation of these bicyclic lactams is not trivial and this aspect will be discussed in Section XIV.

Table 5. Quaternary Products **24** from Lactams **20.**

Entry	R_1	R_2	R_3[a]	% De[b]	Yield, %[c]	Ref.
a	Ph	Me	$PhCH_2$	95	75	4
b	Ph	$PhCH_2$	Me	85	74	4
c	Ph	Me	Et	76	80	4
d	Ph	Et	Me	82	75	4
e	Ph	Me	p-MeOPhCH_2	94	85	4
f	Ph	p-MeOPhCH_2	Me	86	90	4
g	Ph	Me	i-Pr	50	59	4
h	Ph	i-Pr	Me	82	49	4
i	Me	allyl	$PhCH_2$	93	77	6
j	Me	$PhCH_2$	allyl	90	63	6
k	Me	Me	$PhCH_2$	94	74	6
l	Me	$PhCH_2$	Me	46	60	-[e]
m	Me	p-Tolyl	Me	80	65[d]	12
n	Me	Et	$PhCH_2$	90	74	6
o	Me	p-Me$PhCH_2$	Me	86	90	-[e]

[a]Added to a solution of enolate in THF at -78°C. [b]Determined by HPLC and/or ^{1}H-NMR. [c]*Endo* alkylated diastereomer after two sequential alkylations and flash chromatography. [d]Reflects only methylation since the starting material was the α-(p-tolyl)-bicyclic lactam **6b**. [e]Unpublished results.

The bicyclic lactams **4e** and **4g** were likewise subjected to a double alkylation sequence. However, due to the presence of the hydroxyl group, two equivalents of base were required for enolate formation. Rationale for the use of this chiral auxiliary will be discussed below (Section VI). Moderate to high diastereoselectivity was observed during the alkylation with the major diastereomer **25a-b** resulting again from *endo* entry of the alkyl halide to the enolate (Table 6).



4e R_1=Et
g R_1=Me

25a R_1=Et
b R_1=Me

Table 6. Dialkylated Lactams **25a-b** from Lactams **4e-g.**

Entry	R_1	R_2	R_3[a]	%De[b]	Yield, %[c]	Ref.
a	Me	Ph	Me	80	53	7
b	Me	Me	$PhCH_2$	94	67	8
c	Me	$PhCH_2$	Me	46	60	8
d	Me	$PhCH_2$	allyl	64	72	8
e	Me	Me	CH_2CH_2OH[d]	72	90	7
f	Et	Me	$PhCH_2$	94	81	8

[a] Added to a solution of enolate in THF at -78°C. [b] Determined by HPLC and/or H^1NMR. [c]Pure major diastereomer. [d]Ethylene oxide was used as the electrophile.

It was determined that the pK_a of the proton α to the carbonyl was higher in this system than the corresponding proton in the L-valinol derived lactam presumably as a result of being doubly charged. However, it was found that protection of the hydroxyl group as its trimethylsilyl or methoxymethyl ether in order to circumvent dianion formation during the enolization step resulted in complete loss of diastereoselectivity during the alkylation.[7b] It was necessary, therefore, to employ HMPA as cosolvent in order to perform the deprotonation at low temperature. Alternatively, complete deprotonation could be effected by allowing the lactam to react with the base at warmer temperatures (0°C). This, however, resulted in low yields of alkylated products.

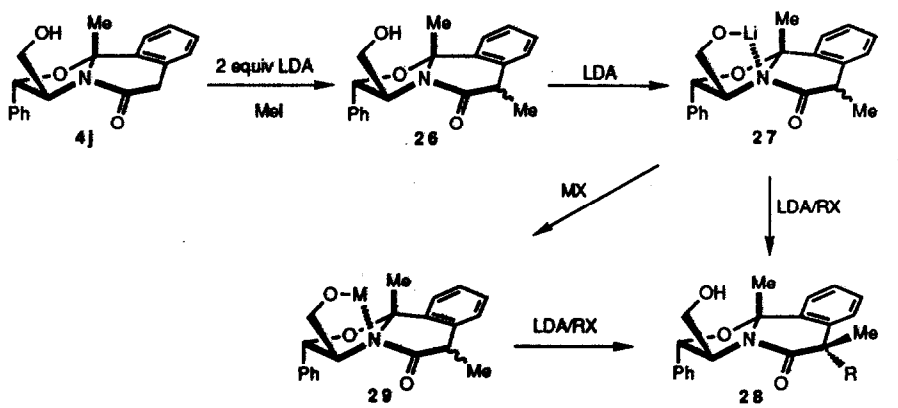
The order of addition of alkyl halides to the lactam enolates was found to be crucial to the extent of diastereoselectivity. In certain cases, the sequential addition of alkyl halides afforded very high selectivities (>20:1) whereas the reverse order of addition gave only poor selectivities. For instance, sequential alkylation with methyl iodide followed by benzyl bromide (entry k, Table 5) gave high diastereoselection while reversing the order of addition resulted in lowered selectivity (entry l, Table 5). In general, alkyl halides such as allyl and benzyl bromide gave high *endo* selectivity whereas methyl and ethyl gave moderate to low selectivities. Exceptions were noted in the case of α-aryl substituted lactams (entry m, Table 5; entry f, Table 6) where alkylation with methyl iodide occurred with good diastereoselection. These findings are consistent with the reactivity-selectivity principle[16b] which states that the less reactive the substrate, the higher the selectivity. The generality of this principle has come under scrutiny.[16a] Other studies, however, with the bicyclic lactams, including alkylations and 3+2 cycloadditions (vide infra) are consistent with this principle and thus it may be useful as a predictive tool concerning the expected stereochemical outcome of a given alkyl halide.

As can be seen in Tables 5 and 6, a number of quaternary centers with various substituents are available via the described metalation/alkylation sequence. The dialkylated products can be routinely obtained in greater than 98% de after flash chromatography on silica gel and both R and S stereoisomers are readily available by simply reversing the order of alkylation. In cases where

the selectivity was not acceptable for a given alkyl halide, it would be a simple matter to employ the optical antipode of the chiral auxiliary and perform the alkylation sequence in the reverse order to obtain the desired stereochemistry.

Single crystal X-ray analysis of three different dialkylated lactams confirmed that alkylation had occurred in predominantly an *endo* fashion and allowed assignment of the absolute configuration of the major quaternary carbon diastereomer.[6,7a,8] In addition, transformation of a number of α-disubstituted lactams into natural products of known absolute configuration (vide infra) provided further proof of the absolute stereochemistry at the quaternary center.

Some interesting insights into asymmetric enolate alkylations of these bicyclic lactams were made during alkylation studies of the benzo-fused bicyclic lactam **4j** (Scheme 2).[11] Generally poor selectivities and yields of diastereomers were obtained during the second alkylation of the enolate derived from lithio alkoxide **27** with allyl, benzyl, and ethyl halides (Table 7, entries a-b). However, longer chain alkyl halides led to acceptable diastereomeric ratios and improved yields of pure diastereomers **28** (Table 7, entries d-e). These results are again consistent with the aforementioned reactivity-selectivity rule.[16]



Scheme 2

X-ray analysis again indicated that alkylation occurred predominantly from the α-face of the molecule and also showed that the 6-membered lactam **28** was almost planar. Thus, *endo/exo* loses its meaning and the more traditional facial selectivity terms α and β were used to describe the mode of alkylation in these systems.

Table 7. Quaternary Products **28** from Benzo-Fused Lactams **26.**

Entry	RX	M	α/β Ratio[a,b]	Yield,%[c]
a	$PhCH_2Br$	Li	1.2	44
b	allyl Br	Li	3.2	55
c	EtI	Li	4.0	30
d	$H_2C{=}CH_2(CH_2)_3CH_2I$	Li	14.8	64
e	$TBSO(CH_2)_2CH_2I$	LI	53.7	65
f	$PhCH_2Br$	Cp_2ZrCl	6.3	61
g	allyl Br	Cp_2ZrCl	12.6	72
h	EtI	Cp_2ZrCl	21.5	52

[a]Determined by ^{1}H-NMR or HPLC. [b]Refers to ratio of *endo*(α) to the *exo*(β) product obtained from **27**. [c]Pure diastereomer after flash chromatography.

In an effort to increase the poor selectivities obtained with reactive halides (entries a-c), the initially formed lithio alkoxides **27** were transmetalated to afford larger metal ion systems **29** in hope of retarding alkylation from the β face of the lactam. As can be seen in Table 7 (entries f-h), addition of zirconecene dichloride gave zirconates which both increased α/β ratios and yields of pure diastereomers. In order to determine that this increase in diastereoselection was a result of blocking of the β face by the metal ion system, a variety of metals with varying steric bulk were introduced. From Table 8, it is evident that the size of the metal alkoxides shows a reasonable correlation with α/β ratios.

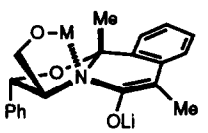
Table 8. Diastereoselective Alkylation of **29** with Benzyl Bromide as a Function of Metal Alkoxides.

Entry	MX[a]	M	α/β Ratio[b]
a	-	Li	1.2
b	$ZnBr_2$	ZnBr	2.9
c	CH_3MgI[c]	MgI	3.7
d	$Ti(i\text{-}PrO)_3Cl$	$Ti(i\text{-}PrO)_3$	5.1
e	Cp_2ZrCl_2	Cp_2ZrCl	6.3
f	$t\text{-}BuMe_2SiCl$	$t\text{-}BuMe_2Si$	0.31

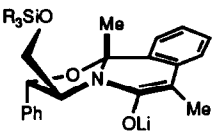
[a]Added to lithio alkoxide **27** prior to metalation to form the enolate. [b]Determined by ^{1}H-NMR or HPLC. [c]Methyl magnesium iodide was used to deprotonate the hydroxyl group of **26**.

Interestingly, the silicon substituent resulted in a reversal of the stereochemistry (Table 7, entry f). This reversal in selectivity was suggested to be due to the inability of the silyl group to complex to the nitrogen lone pair in the same way as the metal ion (depicted by intermediates **30**

and **31**) and thus is turned away, exposing the β-face of the bicyclic lactam. Thus, good diastereoselectivity can be achieved with the bicyclic lactam **4j** by employing the dilithiated lactam (for slow reacting halides) or the zirconated-lithio lactams (for more reactive halides). This transmetalation process may also prove to be useful for those bicyclic lactams derived from amino diol **5** (Table 6) which gave poor selectivity with various alkyl halides.



30

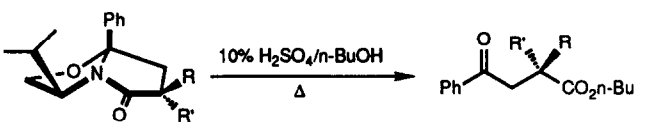


31

Having accessed a number of α-dialkylated bicyclic lactams in high diastereomeric purity, attention was turned to the important task of removal of the chiral auxiliary, and the various techniques developed for this purpose will be discussed below within the context of the final products obtained.

IV. CHIRAL α,α-DIALKYL-γ-KETOESTERS AND 3,3-DIALKYL DIHYDRONAPHTHALENES

The initial method developed for chiral auxiliary removal involved acidic hydrolysis with 10% sulfuric acid in refluxing 1-butanol.[4,17] In this manner, a number of α,α-dialkyl-γ-keto butyl esters **33** were obtained in good yields and high enantiomeric purity from dialkylated lactams **32** (Table 9).

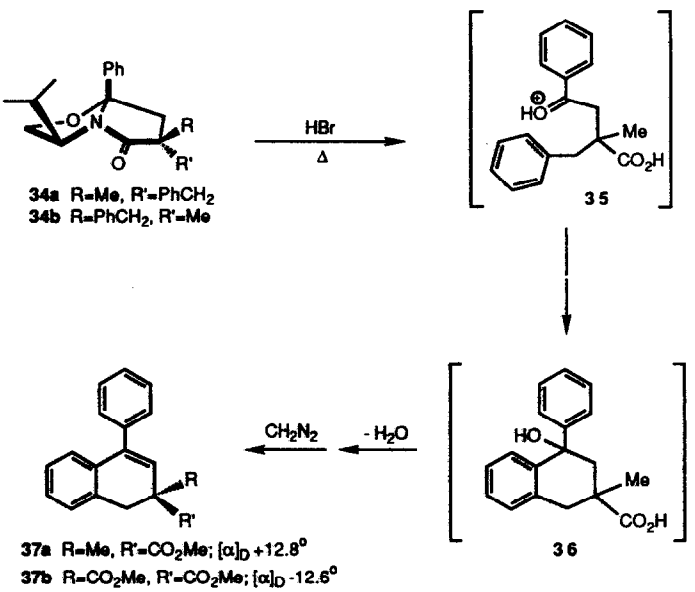


32 **33**

Hydrolysis of lactams **34a-b**, which contained an α-benzyl substituent, with aqueous 48% HBr resulted in formation of the intermediate ketoacids **35**. An *in situ* Friedel-Crafts reaction proceeded spontaneously to ultimately afford the dihydronaphthalenes **37** after esterification with diazomethane (Scheme 3). Due to the harsh conditions involved, ketoacids or esters containing sensitive functionality would not be accessible via this technique.

Table 9. α,α-Dialkylated -γ-Keto Esters **33.**

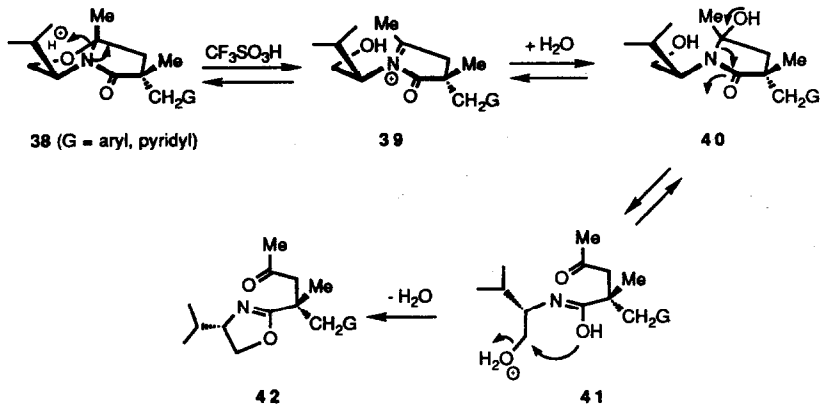
Entry	R	R'	Yield, %	$[\alpha]_D^{23}$	Conf'n
a	Me	$PhCH_2$	79	+23.9	S
b	$PhCH_2$	Me	78	-24.8	R
c	Me	Et	71	-30.0	S
d	Et	Me	87	+31.5	R
e	Me	p-$MeOPhCH_2$	88	+22.2	S
f	p-$MeOPhCH_2$	Me	92	-23.1	R



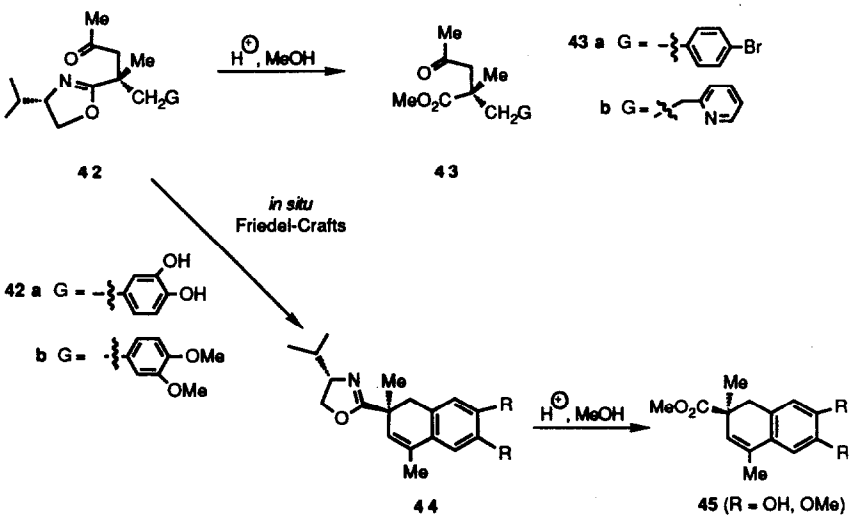
Scheme 3

A more recent hydrolytic method which employed milder conditions revealed an unprecedented formation of an oxazoline from the bicyclic lactam (Scheme 4a).[17] Heating a 1,2-dichloroethane solution of the α,α-disubstituted lactam **38** with 5.0 equiv of trifluoromethanesulfonic acid (triflic acid) resulted in 70-90% yields of the keto oxazolines **42**. The proposed mechanism invokes the fragmentation to the N-acyliminium ion **39** (vide infra) followed by skeletal rearrangement to the keto oxazoline **42**.

The α-benzyl (**42a-b**) but not α-2-pyridyl- or α-*p*-bromobenzyl substituted oxazolines (**42**; G = 2-pyridyl, G = p-bromophenyl) furnished the dihydronaphthalene oxazolines **44**, as previously observed, using 48% HBr for the hydrolysis via an *in situ* Friedel-Crafts reaction (Scheme 4b).



Scheme 4a



Scheme 4b

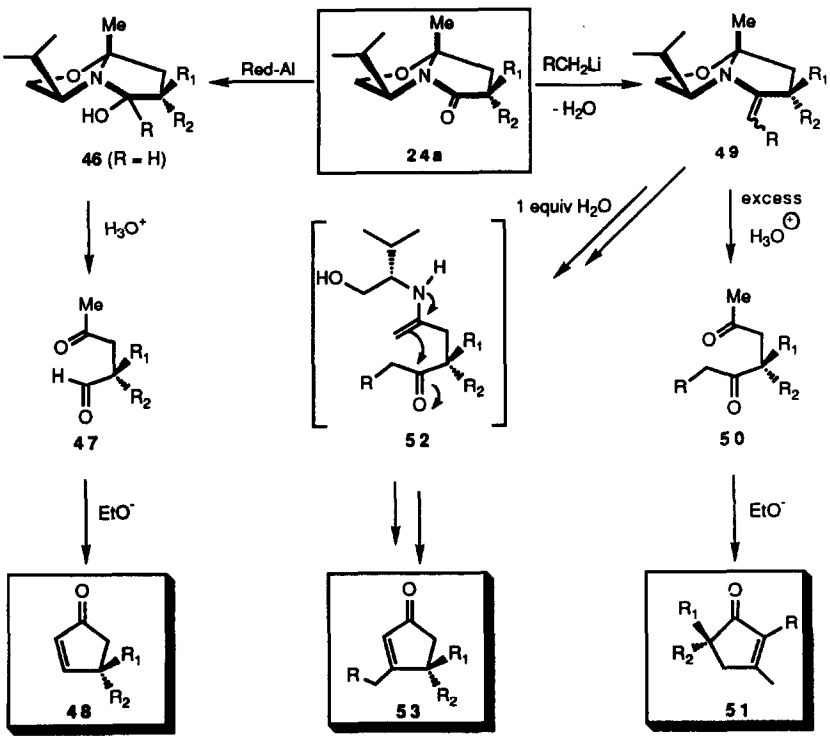
Conversion of the keto oxazolines **42** and dihydronaphthalene oxazolines **44** to the ketoesters **43** and dihydronaphthalene esters **45**, respectively, was effected using aqueous sulfuric acid and then Fischer esterification. In summary, this latter two step procedure employing triflic acid offered a milder and more general process for effecting chiral auxiliary removal to the esters **43** and **45** in comparison to the previous method which employed sulfuric acid in refluxing 1-butanol.

V. CHIRAL 4,4- AND 5,5-DIALKYLCYCLOPENTENONES

Enantiomerically pure 4,4- and 5,5-dialkylcyclopentenones **48**, **51**, and **53** were obtained from the dialkylated lactams **24a** by a three step sequence involving reduction (alkylation) of the lactam carbonyl, hydrolysis of the bicyclic system, and aldol cyclization (Scheme 5). To date, nucleophiles which have been employed for lactam carbonyl reduction or alkylation include sodium bis-2-methoxyethoxy aluminum hydride (Red-Al), lithium monoethoxyaluminum hydride, methyl lithium, n-butyllithium, and 3-butenyllithium.

The carbinolamines **46** were produced when hydride was employed as the nucleophile. However, in the case of alkyllithium additions, the enamines **49** were formed, after aqueous treatment as a result of elimination of water from the intermediate carbinolamines. The spontaneous formation of the enamines **49** may be due to the severe steric interactions caused by the vicinal quaternary centers in the carbinolamine (e.g. **46**, R=alkyl).

Hydrolysis of the carbinolamines **46** or enamines **49** was effected in a water-ethanol mixture containing tetrabutylammonium dihydrogen phosphate and furnished the dicarbonyl

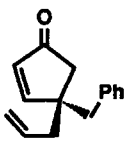
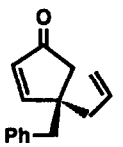
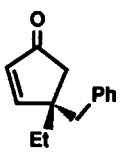


Scheme 5

compounds **47** and **50**, respectively. Base catalyzed aldol cyclization of the ketoaldehydes **47** afforded the 4,4-dialkylcyclopentenones **48** in good overall yields from the dialkylated lactams **24a** (Table 10).

Aldol cyclization of the unsymmetrical diketones **50** resulted in mixtures of the isomeric cyclopentenones **51** and **53**. However, in the presence of excess water, the 2,3,5,5-tetrasubstituted cyclopentenones **51** were the only products observed. The isomeric cyclopentenone **53** would necessarily arise from attack at the more sterically congested carbonyl.

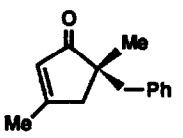
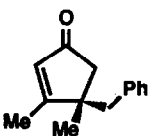
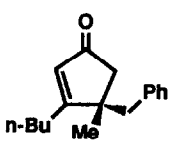
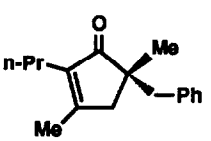
Table 10. 4,4-Dialkyl-2-Cyclopentenones **48.**

Entry	Cyclopentenone	Overall yield, %[a]	$[\alpha]_D$	Conf'n.	Ref.
a		64	-64.1°	S	6
b		69	+60.9°	R	6
c		56	-78.3°	S	6

[a]Reflects the three step sequence of reduction, hydrolysis, and aldol condensation from the dialkylated lactams **24a**.

Conditions were also found (1 equiv H_2O, slow addition via syringe pump, refluxing 1-pentanol) which allowed access to the isomeric 3,4,4-trisubstituted cyclopentenones **53** via the enamine **52** in 45% yield along with an equal amount of the isomeric cyclopentenone **51**. This finding was first made in studies involving preparation of chiral cyclohexenones (Section VI) and thus the proposed mechanism for this directed aldol condensation will be discussed below. Normally, the three step sequence involving reduction, hydrolysis, and aldol cyclization is performed without isolation of intermediates and gives good overall yields of the cyclopentenones from the diastereomerically pure dialkylated bicyclic lactams **24a**. Various optically pure tri-and tetrasubstituted cyclopentenones **53** and **51** have been obtained via alkyllithium additions to the dialkylated lactams **24a** (Table 11).

Table 11. Tri- and Tetrasubstituted Cylopentenones **53** and **51.**

Entry	Cyclopentenone	Overall yield, %[a]	$[\alpha]_D$	Conf'n.	Ref.
a		28[b]	-44.3°	R	9
b		89	+93.5°	R	9
c		45[c]	-16.0°	S	9
d		84	+96.6°	R	9

[a]Reflects the three step sequence of alkyl lithium addition, hydrolysis, and aldol cyclization from the dialkylated lactams **24a** (R_1= Me, R_2 = CH_2Ph). [b]Accompanied by 46% of the isomeric cyclopentenone **51** (entry b). [c]Accompanied by 16% of the isomeric cyclopentenone **53** (entry d).

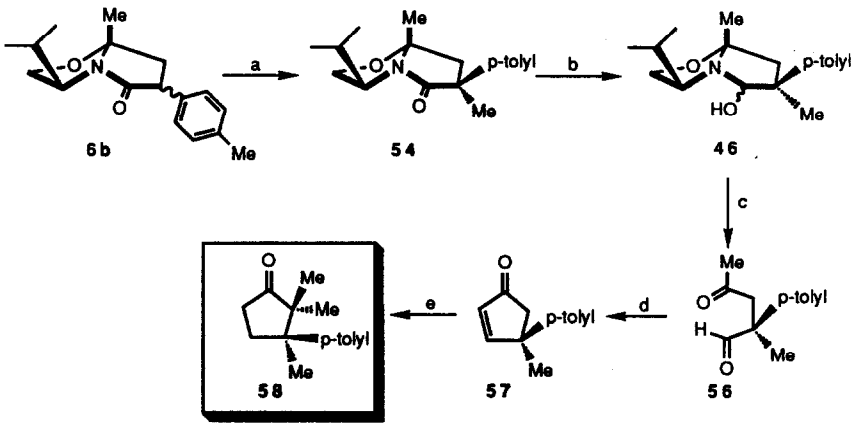
This route to optically pure cyclopentenones was subsequently employed in the asymmetric syntheses of three natural products and these are summarized in the following sections, **A - C.**

A. (-)-α-Cuparenone

(-)-α–Cuparenone is a naturally occurring sesquiterpene found as the (+)-enantiomer in the essential oil of the *Mayur Pankhi* tree.[18] The requisite α-aryl bicyclic lactam **6b** for the proposed synthesis was obtained in a single synthetic step via the cyclodehydration route(vide supra).[12] Metalation and alkylation of **6b** with methyl iodide gave a 90% yield of the *endo* α-methyl derivative **54** accompanied by 7% of the *exo* α-methyl diastereomer (Scheme 6). Recrystallization of the crude mixture afforded 60% of **54** which was determined to be >99% diastereomerically pure by HPLC analysis. Stereochemical assignments were based on the shielding effect of the *exo*-aryl group on the angular methyl group. Thus, the diastereomer which has the aryl group in the *endo* position exhibited a singlet for the angular methyl protons at 1.15 ppm whereas the diastereomer which has the aryl group positioned on the *exo* face exhibits the methyl singlet further downfield at 1.54 ppm. This shielding effect appears to be quite general and

has allowed preliminary stereochemical assignments for a number of α-aryl and α-benzyl substituted bicyclic lactams. These preliminary assignments were later confirmed by X-ray techniques or correlation to previously known compounds.

With the appropriately substituted lactam **54** in hand as a single diastereomer, the synthetic sequence towards α-cuparenone continued by reduction of lactam **54** with Red-Al to the carbinolamine **46** followed by hydrolysis and aldol cyclization to the cyclopentenone **57** via the ketoaldehyde **56**. The remaining steps, involving dimethylation and hydrogenation of the enone, proceeded in 42% overall yield to afford the unnatural enantiomer of α-cuparenone **58**. Comparison of rotation values for the synthetic material from this study (-166°) with that reported in the literature (+170°) revealed that the target had been reached in at least 97.6% optical purity which was in good agreement with the diastereomeric purity (HPLC) determined for the dialkylated lactam precursor **54**. The fact that the unnatural enantiomer was obtained confirmed that the alkylation of the α-aryl lactam **6b** with methyl iodide had proceeded in predominantly an *endo* fashion.



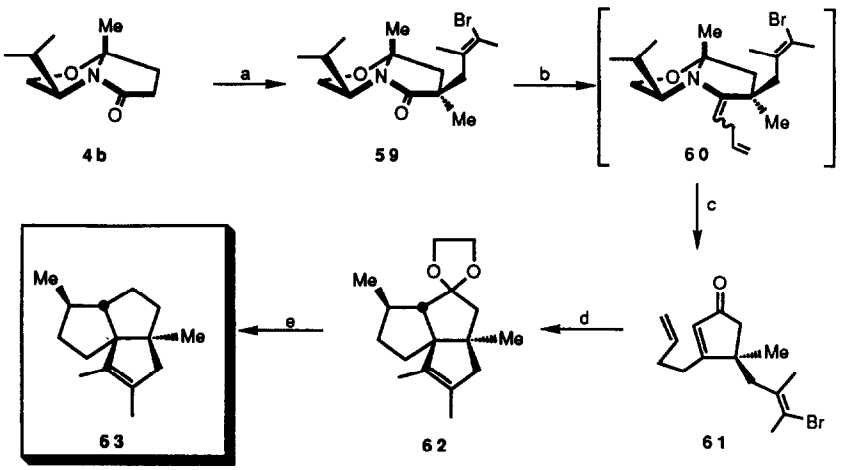
[a] Reagents: (a) LDA, MeI, 90% (94% de); (b) Red-Al, 100%; (c) 1M $Bu_4NH_2PO_4$ (aq.), EtOH, 98%; (d) 1M KOH in EtOH, 90%; (e) (i) NaH, MeI, 48%; (ii) 10% Pd/C, 3 atm H_2, 87%.

Scheme 6[a]

B. (-)Silphiperfol-6-ene

The synthesis of chiral cyclopentanones was also utilized in the first asymmetric entry[9] into (-)-silphiperfol-6-ene **63**, a tricyclic sesquiterpene isolated from the roots of *Silphium perfoliatum*.[19] The study commenced by a sequential metalation-alkylation process of the valinol derived lactam **4b** utilizing 1,3-dibromopentene and methyl iodide (Scheme 7). This produced the dialkylated lactam **59** along with 7% of the *exo* isomer as determined by both ^{1}H-NMR and

HPLC. The major diastereomer was assumed to be the lactam containing the methyl group in the *endo* position, but definite proof had to await the final product whose absolute configuration was known. After purification of **59** by flash chromatography and conversion to the enamine **60** by addition of butenyl lithium, hydrolysis furnished the intermediate diketone, **61**. Utilizing the aforementioned aldol cyclization conditions to reach 3,4,4-trisubstituted cyclopentenones, the desired cyclopentenone **61** was obtained in 45% yield in addition to 46% of the isomeric tetrasubstituted cyclopentenone. The requisite cyclopentenone **61** had been previously prepared in racemic form by Curran[20] and the product from this study was found to be identical in all respects except for chiroptical properties.



[a]Reagents: (a) (i) LDA, 1,3-dibromo-2-methylbut-2-ene, 84% (ii) LDA, MeI, 79% (86% de); (b) 3-butenyl lithium; (c) $Bu_4NH_2PO_4$, 3 equiv H_2O, 45%; (d) (i)ethylene glycol, pyridinium-p-toluenesulfonate, 90% (ii) Bu_3SnH, AIBN, 53%; (e) (i) H_2SO_4, 98% (ii) $H_2NNH_2{\cdot}H_2O$, K_2CO_3, 61%.

Scheme 7[a]

With the known precursor **61** in hand, the Curran route to racemic silphiperfol-6-ene was followed to reach the final target. After protection of the ketone as the dioxolane, radical initiated cyclization afforded the tricyclic dioxolane **62** . Deprotection of the ketone followed by Wolf-Kishner reduction gave silphiperfol-6-ene **63** with $[\alpha]_D$ -74.06°. Although this rotation deviated somewhat from that reported for the isolated natural material[19] (-92.80°), it was deemed correct based on the diastereomeric purity (~97%) of the precursor bicyclic lactam **59**. It was, therefore, concluded that the enantiomeric purity of the triquinane **63** obtained from this study was closer to 95% ee, and that specific rotations may not always serve as an accurate assessment of enantiomeric purity.

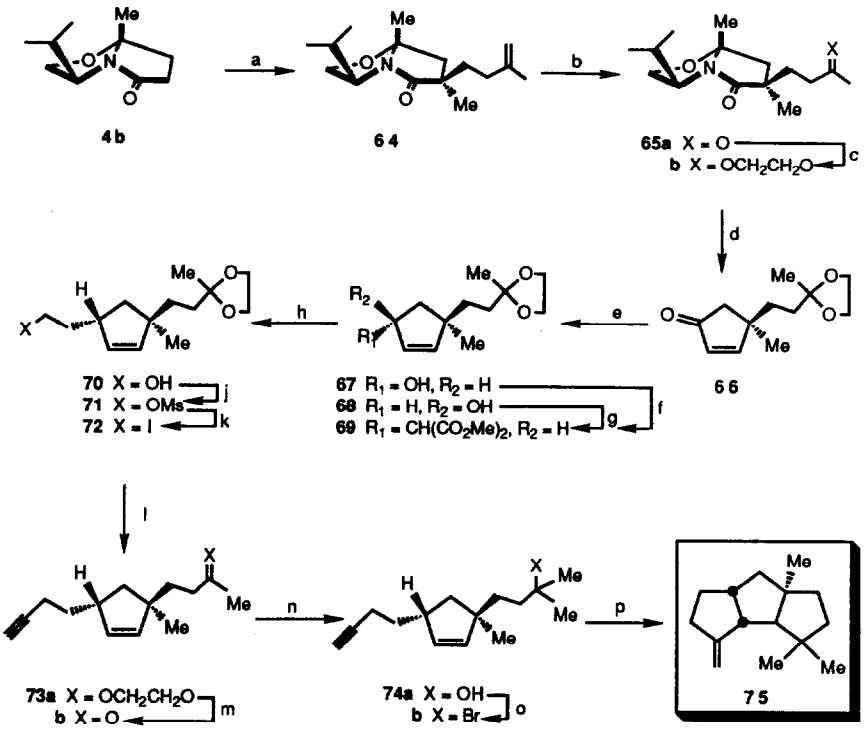
C. (+)-$\Delta^{9,12}$-Capnellene

A third application of the chiral cyclopentenone route from bicyclic lactams resulted in the first asymmetric synthesis of capnellene (as its unnatural enantiomer) which was accomplished in 14.1% overall yield (the highest yet reported) from commercially available materials.[21] This interesting linear triquinane found in the soft coral *Capnella imbricata* displays similar biological activity to the hirsutanes which possess antibacterial and antitumor properties.[22] The cyclopentene **74b** was seen as an attractive target via the bicyclic lactam methodology and this compound had been previously reached by Curran in a racemic synthesis of capnellene.[23]

The synthesis began by a sequential alkylation of the bicyclic lactam **4b** with prenyl iodide and methyl iodide in the usual manner with the exception that N,N'-dimethylpropyleneurea (DMPU) was added to the base prior to introduction of the bicyclic lactam (Scheme 8). This additive has since been commonly employed to increase yields of alkylated materials by ensuring complete deprotonation of the starting lactam and thus assisted in complete conversion of starting material to product. The second alkylation with methyl iodide proceeded to give **64** in 82% de with the major diastereomer having the methyl disposed on the *endo* face of the bicyclic lactam. The minor *exo* methyl diastereomer was easily removed by flash chromatography to afford pure dialkylated lactam **64** in 66% overall yield from the lactam **4b**. Ozonolysis of the alkene to the ketone **65a** followed by ketalization with ethylene glycol gave the dioxolane **65b** in 93% overall yield from lactam **64**. Subjecting the lactam **65b** to the standard reduction-hydrolysis-cyclization conditions furnished the cyclopentenone **66** in 78% overall yield. Based on the diastereomeric purity of the dialkylated lactam **64** as evidenced by ^{1}H-NMR and HPLC, it was safely assumed that the enantiomeric purity of the cyclopentenone **66** was also very high (>99%).

Reduction of the enone with sodium borohydride in the presence of $CeCl_3$ gave a 55:45 mixture of chromatographically separable epimeric carbinols **67** and **68** in 92% combined yield. Each of these alcohols was converted independently into the same key intermediate **69** by two different protocols. The first involved conversion of the α-carbinol **67** to the ethyl carbonate followed by retentive displacement using sodiodimethyl malonate catalyzed by Pd(0). The second protocol employed Mitsunobu conditions to invert the β-carbinol **68** to its α-carbinol epimer **67** followed by retentive displacement, as before, via the phenyl formate. Thus, both hydroxy epimers obtained from the reduction of cyclopentenone **66** were useable as precursors in the projected scheme.

The alcohol **70** was secured in 92% overall yield from diester **69** by carbodemethoxylation followed by lithium aluminum hydride reduction. Conversion of the alcohol to the iodide **72** was accomplished in 93% yield via the mesylate **71**. In order to extend the carbon chain and introduce the alkynyl unit found in Curran's intermediate,[23] the iodide **72** was displaced with lithio acetylide-ethylendiamine complex producing the alkyne **73a** in 86% yield. The remaining steps to reach the penultimate precursor to capnellene involved deblocking of the dioxolane **73a** to the ketone **73b**, methylation of the ketone with methylmagnesium chloride to the tertiary alcohol **74a**,



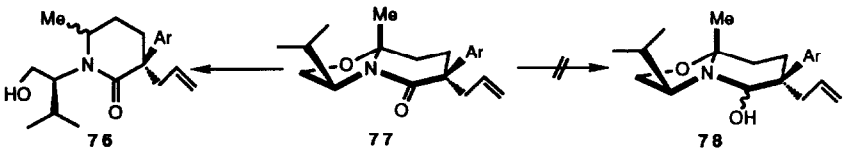
[a]Reagents: (a) (i) LDA, DMPU, prenyl iodide, 79% (ii) LDA, DMPU, MeI, 93% (82% de); (b) O_3, 98%; (c) ethylene glycol, p-TsOH, 95%; (d) (i) Red-Al (ii) 1M $Bu_4NH_2PO_4$ (iii) 1M KOH, 78%; (e) $NaBH_4$, $CeCl_3$, 94% (1.2:1 ratio of **67**:**68**); (f) (i) $ClCO_2Et$, py. (ii) $Pd(PPh_3)_4$, $CH_2(CO_2Me)_2$, 90%; (g) (i) DEAD-PPh_3, $PhCO_2H$, 85% (ii) $Pd(PPh_3)_4$, $NaCH(CO_2Me)_2$, 74%; (h) (i) NaCl, 92% (ii) LAH, 99%; (j) MsCl, py., 99%; (k) NaI, 93%; (l) lithium acetylide ethylendiamine complex, 86%; (m) p-TsOH, 89%; (n) MeMgCl, 98%; (o) TMSBr, 96%; (p) Bu_3SnH, AIBN, 58%.

Scheme 8[a]

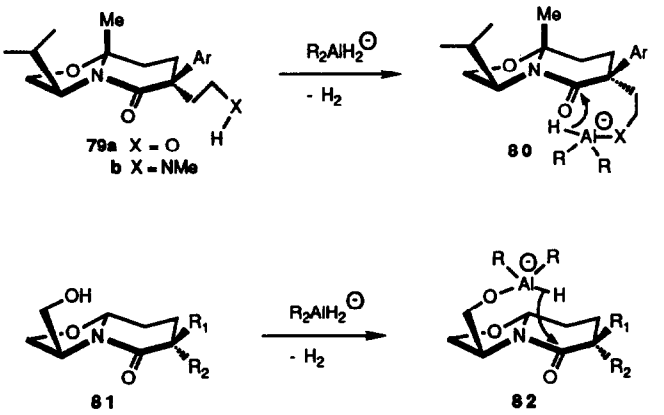
and conversion to the bromide **74b**. These steps were performed in a straightforward manner and proceeded in 85% overall yield from the dioxolane **73a**. With the cyclopentene **74b** in hand, the AIBN initiated radical cyclization afforded (+)-$\Delta^{9,12}$-capnellene **75** in 58% yield. The cyclopentene precursor **74b** and the title compound **75** were identical in all respects except for chiroptical properties with authentic racemic materials. Comparison of the rotation value for the product from this study ($[\alpha]_D$ -145°) with that reported in the literature for the natural material ($[\alpha]_D$ +149°) indicated an optical purity of at least 97% ee.

VI. CHIRAL 4,4- AND 6,6-DIALKYLCYCLOHEXENONES

The homologous [4.3.0] bicyclic lactams such as **77** exhibited very different chemical properties in comparison to their [3.3.0] bicyclic lactam counterparts (e.g. **24a**). Attempts to remove the chiral auxiliary employing conditions utilized for the [3.3.0] bicyclic lactams were not very successful. Addition of hydride did not effect reduction of the lactam carbonyl to the carbinolamine **78** as in the [3.3.0] series but resulted, instead, in reduction of the acetal center furnishing the piperidone **76** as the major product. Furthermore, in attempts at alkyllithium additions, the carbonyl group in **77** was found to be unreactive towards these reagents.

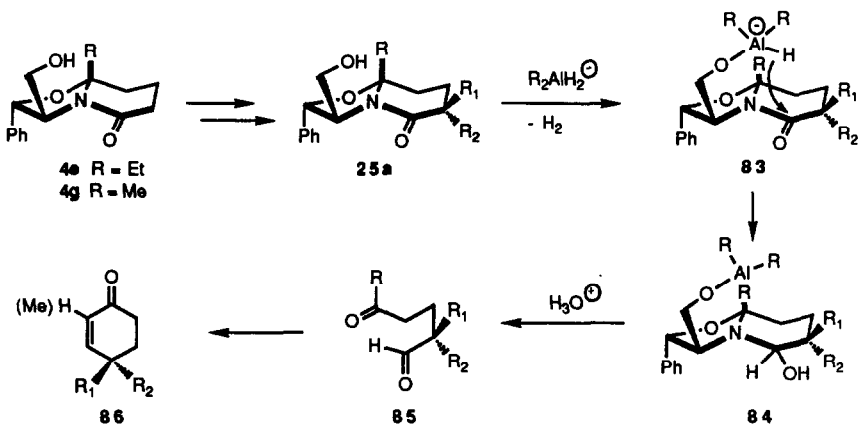


Interestingly, it was known from collateral experiments in our laboratory, that efficient additions to the carbonyl group in the [4.3.0] systems, and auxiliary removal, was indeed possible in those lactams which contained a β-amino or β-hydroxyethyl group (e.g. **79a** and **79b** respectively) on the side chain.[7] This behavior was rationalized by assuming the first equivalent of hydride removes the amine or alcohol proton resulting in an aluminum complex **80** which serves as a "tether" to deliver hydride intramolecularly and in a controlled fashion. It was further believed that if such a "tether" could be permanently incorporated into the chiral auxiliary of a bicyclic lactam (e.g. **81**) this would remove the limitation imposed by these earlier findings, and also deliver hydride (e.g. **82**).



This hypothesis led to the examination of the bicyclic lactams **4e** and **4g** which possessed a pendant hydroxyl group on the chiral auxiliary (Scheme 9).[8] It was strongly anticipated that the

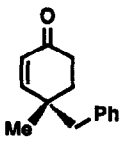
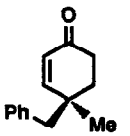
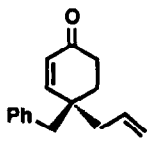
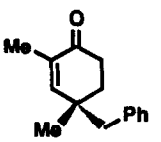
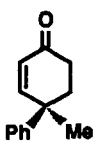
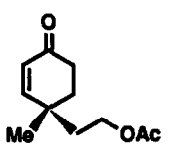
hydroxyl group would serve as the "tether" described above and effect controlled reduction of the lactam carbonyl. Indeed, this turned out to be correct as hydride addition with Red-Al led to smooth reduction of the carbonyl group (**83** to **84**). Presumably the first equivalent of hydride removes the alcohol proton and forms the aluminate complex **83** which was now in a position to deliver hydride intramolecularly. Hydrolysis ($Bu_4NH_2PO_4$-H_2O-EtOH) of the resulting carbinolamine **84** proceeded directly without the appearance of any intermediates to the 4,4-dialkylcyclohexenones **86**. Presumably the *in situ* intramolecular aldol cyclization of the intermediate ketoaldehydes **85** proceeds under the acidic conditions employed. Thus a number of optically pure cyclohexenones were prepared by this sequence in yields ranging from 47-71% (Table 12).



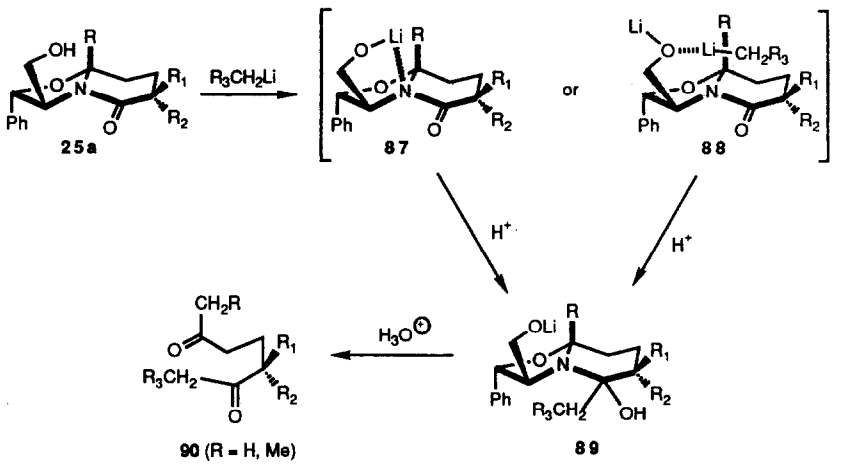
Scheme 9

As for alkyl lithium additions to doubly alkylated lactams **25a**, the carbinolamines **89** were readily accessible.[9,24] However, in contrast to the [3.3.0] bicyclic lactams, higher temperatures were required for the addition (-5°C vs -30°C). Two plausible explanations for successful alkyl lithium additions to these systems in contrast to the valinol derived counterparts **77** are depicted by lithio intermediates **87** and **88** (Scheme 10). On addition of the first equivalent of alkyl lithium, deprotonation of the alcohol proton occurs to form the lithium alkoxide. The lithium atom may then compete for electron density from the amide pi system as shown by **87** thus rendering the amide carbonyl more electrophilic. Alternatively, a second equivalent of alkyl lithium may coordinate to the lithium alkoxide **87** as depicted by intermediate **88** and in this way function as a directing group for the alkyl lithium addition (complex induced proximity effect[25]). The resulting quaternary carbinolamines **89** were then hydrolyzed in the usual manner (ethanol-aqueous 1M tetrabutylammonium dihydrogen phosphate) to afford the diketones **90**.

Table 12. 4,4-Dialkyl-2-Cyclohexenones **86.**

Entry	Cyclohexenone	Overall yield, %[a]	$[\alpha]_D$	Conf'n.	Ref.
a		53	-65.6°	R	8
b		68	+64.8°	S	8
c		47	+49.0°	R	8
d		65	-39.7°	R	8
e		47	+122.2°	R	8
f		71	-28.4°	R	7

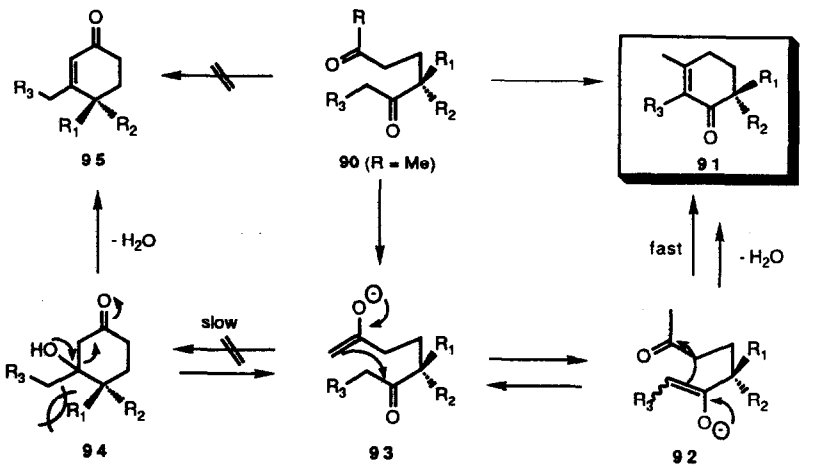
[a]Reflects a three step (two pot) sequence involving reduction, hydrolysis, and *in situ* intramolecular aldol cyclization from the dialkylated lactams **25a**.



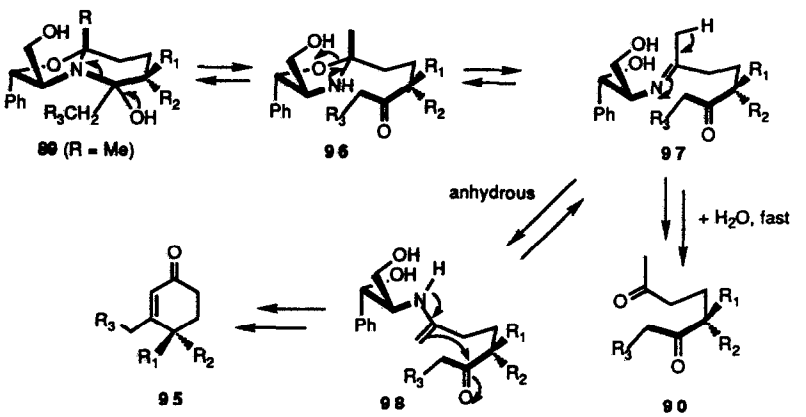
Scheme 10

Although two possible regioisomeric cyclohexenones (**91** and **95**) are possible from intramolecular aldol cyclization of the diketone **90**, the sole products observed were the 6,6-dialkylcyclohexenones **91** (e.g. entries a-b, Table 13) upon treatment of the diketone **90** with ethanolic potassium hydroxide (Scheme 11). This is undoubtedly due to attack of the enolate **92** on the less sterically demanding methyl ketone. The alternative cyclization of the presumed kinetically formed enolate **93** on the sterically congested ketone is less favorable. This latter direction of cyclization would lead to the cyclohexanone **94** containing two adjacent quaternary centers, which was not observed.

In subsequent studies, it was found that the regioisomeric cyclohexenones **95** could indeed be exclusively obtained by employing anhydrous conditions for the hydrolysis of the carbinolamines **89** (Scheme 12).[9] It was proposed that after initial ring opening to form the keto oxazolidine **96**, further ring cleavage is possible leading to the imine **97**. In the presence of water, the imine is rapidly hydrolyzed to the diketone **90** which has already been shown to give **91** exclusively. However, in the absence of water the imine **97** may undergo tautomerization to the enamine **98** allowing directed intramolecular aldol cyclization to occur at the sterically congested ketone. In this manner, a single cyclization product, **95**, is produced after dehydration and hydrolysis of the resulting iminium by the water liberated. This behavior of unsymmetrical



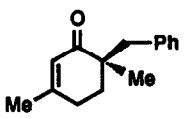
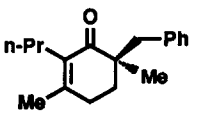
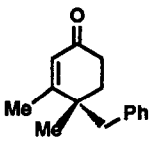
Scheme 11



Scheme 12

diketones to afford regioisomeric cyclohexenones based on the presence or absence of water had been previously observed by other workers.[26] Based on these results, either trisubstituted cyclohexenone could be obtained in good yield as single regioisomer (Table 13).

Table 13. Tri- and Tetrasubstituted Cyclohexenones **95** and **91**.

Entry	Cyclohexenone	Overall yield, %[a]	[α]D	Conf'n.	Ref.
a		56	-12.5°	R	9
b		47	+9.6°	R	9
c		67	-52.0°	R	9

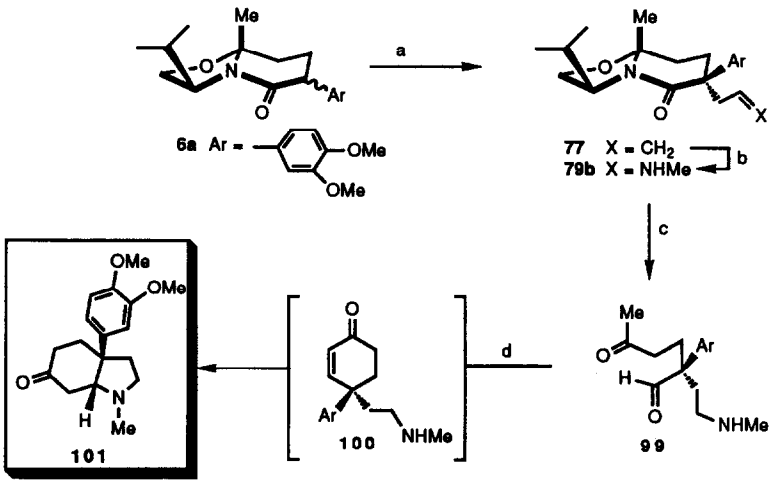
[a]Reflects a three step (two pot) sequence involving alkyl lithium addition, hydrolysis, and intramolecular aldol condensation from the dialkylated lactams **25a** (R_1=Me, R_2=CH_2Ph).

In summary, efficient routes to 4,4-dialkylated cyclohexenones **86** via the hydride reduction and hydrolysis of lactams **25a** were available while 3,4,4- and 2,6,6-trisubstituted cyclohexenones **95** and **91** via alkyl lithium additions to the lactams **25a** were also accessible. This synthetic sequence was subsequently employed in the asymmetric synthesis of the alkaloid (+)-mesembrine and in the formal synthesis of (+)-aspidospermine. This methodology was also demonstrated by the asymmetric synthesis of a number of 4,4-dialkylnaphthalenones and a formal synthesis of 9(-)-eburnamine. These studies are described in the following sections, *A* - *D*.

A. (+)-Mesembrine

The first asymmetric synthesis of the *Sceletium* alkaloid mesembrine **101** was accomplished using the route to reach chiral cyclohexenones described above.[7] The synthesis was founded on the alkylation of the previously described α-aryl substituted lactam **6a** (Table 2) with allyl bromide to afford the α-allyl derivative in >99% de. The minor components consisting of isomeric lactams epimeric at the angular methyl group resulting from initial bicyclic lactam formation were readily removed by flash chromatography. The diastereomerically pure dialkylated lactam **77** was obtained in 71% yield. Oxidation of the latter to the aldehyde followed by reductive amination with methylamine afforded the amino ethyl lactam **79b** in 72% overall yield from **77**. Reduction of the lactam carbonyl with lithium monoethoxy aluminum hydride followed by hydrolysis under the usual conditions gave the ketoaldehyde **99** and after treatment with alkali furnished the cyclohexenone **100** which spontaneously cyclized to (+)-mesembrine **101** in 60% overall yield from the lactam **79b**. Apparently, the basic conditions were suitable for

intramolecular aldol condensation as well as intramolecular Michael addition to give the final product in a one pot reaction. Comparison of rotation values of the material obtained from this study ($[\alpha]_D$ +58.5°) with those reported in the literature ($[\alpha]_D$ -55.4°, -59°) indicated that the unnatural enantiomer of mesembrine had been obtained in high optical purity and was consistent with the de of **77**. The sign of rotation (absolute configuration) also indicated that as in all previous alkylations of these lactam systems, *endo* entry of allyl bromide to the enolate of lactam **6a** had predominated.



[a]Reagents: (a) s-BuLi, allyl bromide, 71%, (>99% de); (b) (i) OsO_4, $NaIO_4$ (ii) $MeNH_2$, $NaCNBH_4$, 72%; (c) (i) $LiAl(OEt)H_3$ (ii) $Bu_4NH_2PO_4$ (iii) 4N NaOH, 60%.

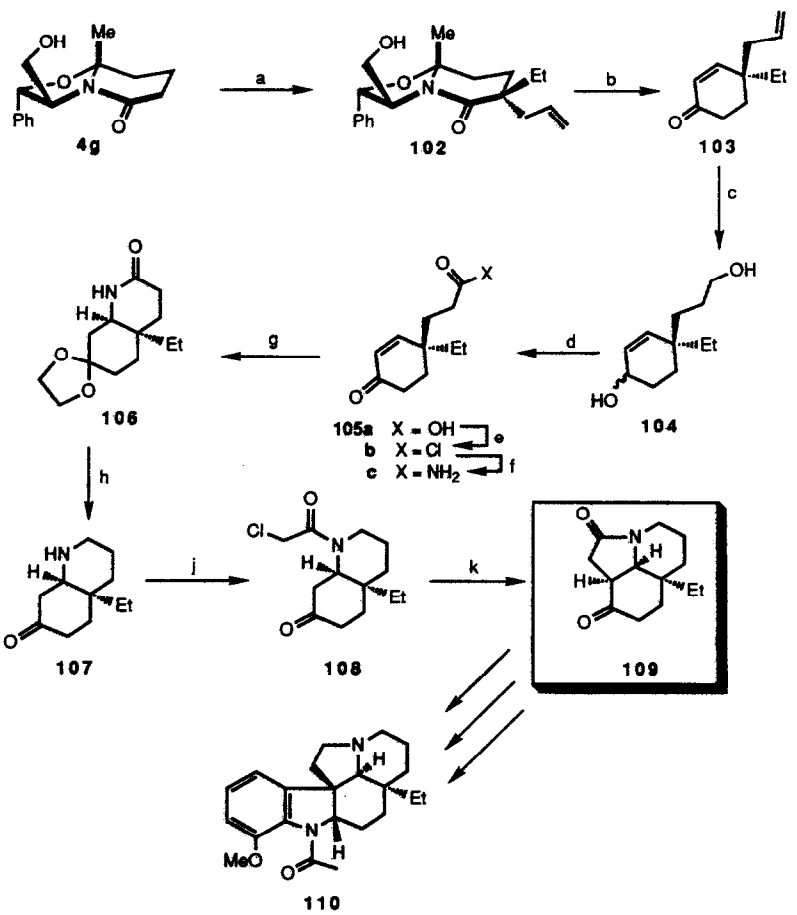
Scheme 13[a]

B. Formal Synthesis of Unnatural (+)-Aspidospermine

The tricyclic hydrolilolidone **109** has served as a key precursor for the Fischer indole synthesis of *Aspidosperma* alkaloids such as aspidospermine **110**.[27] As a further demonstration of the methodology to reach optically pure cyclohexenones, the tricyclic species **109** was targeted.[28]

Toward this end, sequential alkylation of the bicyclic lactam **4g** with ethyl iodide and allyl bromide led to the dialkylated lactam **102** in 48-50% yield as a 25:1 ratio of diastereomers. Once again, the *endo* allyl isomer was the major component. The lactam **102** was transformed to the chiral cyclohexenone **103** in 77% overall yield via the typical reaction sequence involving reduction, hydrolysis, and aldol cyclization. It should be noted that the procedure for the synthesis of the chiral cyclohexenone **103** has appeared in *Organic Syntheses*.[29]

Continuing the approach to hydrolilolidone, treatment of the cyclohexenone **103** with 9-BBN gave the diol **104** which was immediately oxidized to the keto acid **105a** with Jones reagent in 77% overall yield for the two steps. Conversion to the amide **105c** was accomplished through the acid chloride **105b** followed by treatment with ammonia. Michael addition of the amide nitrogen to the enone was effected by heating the amide **105c** and ethylene glycol in benzene



[a]Reagents: (a) (i) LDA, EtI, 92% (ii) LDA, allyl bromide; 48-50% (92% de); (b) (i) Red-Al (ii) $Bu_4NH_2PO_4$, 62-75%; (c) 9-BBN, H_2O_2; (d) Jones reagent, 70% (two steps); (e) oxalyl chloride (f) NH_3, 72.5% (two steps); (g) ethylene glycol, p-TsOH, 85%; (h) (i) LAH (ii) 1N HCl, 87.2%; (j) chloroacetyl chloride, 61%; (k) t-BuOK, 72%.

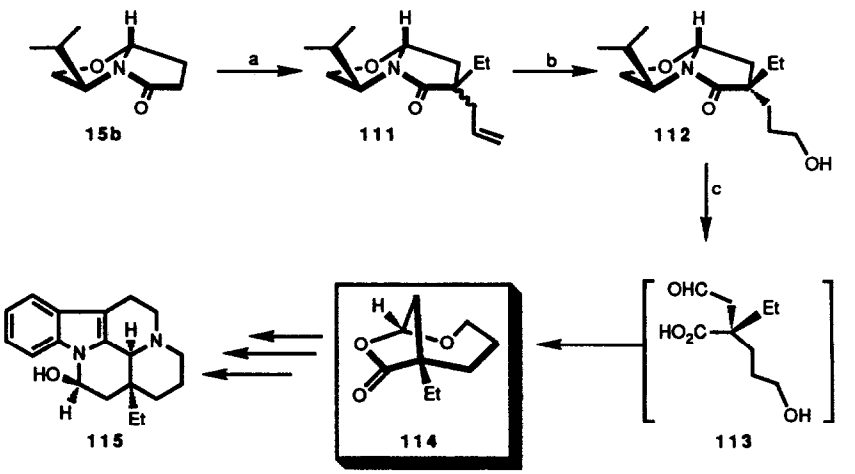
Scheme 14[a]

with catalytic acid. This gave the dioxolane **106** as a single diastereomer in 85% yield from the amide **105c**. The enantiomeric purity of dioxolane **106** was determined to be 92% by use of a chiral Pirkle solvent which was in good agreement with the diastereomeric purity of the lactam precursor **102** (25:1; 92% de).

Reduction of the amide with lithium aluminum hydride provided the aminoketone **107** in 87% yield after removal of the dioxolane. Chloroacetylation of the aminoketone by the Stork procedure[30] afforded the amide **108** in 61% yield after recrystallization. The hydrolilolidone system **109** was prepared by a previously described sequence[30] in 72% yield. The material obtained in this manner was spectroscopically consistent with racemic materials prepared by Fowler.[27]

C. Formal Synthesis of 9-(-)-Eburnamine

An additional illustration of the lactam methodology targeted the bicyclic lactone **114**[31] (Takano lactone) which had been previously employed[32] as an intermediate to reach a number of alkaloids in enantiomerically pure form, including 9-(-)-eburnamine **115**. The synthesis commenced by the sequential alkylation of the angular H lactam **15b** with ethyl iodide and allyl iodide to give the dialkylated lactams **111** in a 4.6:1 ratio of diastereomers with the major one presumed to contain the *endo* allyl group based on previous results (Scheme 15). It is important to note that alkylation of angular hydrogen lactams (i.e. **15b**) often resulted in somewhat disappointing ratios of *endo/exo* products. Compared to **4b** (Table 5) where ratios were 20-30:1, these angular H systems were not as selective. The inseparable mixture of **111** was subjected to



[a]Reagents: (a) (i) LDA, EtI, 85% (ii) LDA, allyl bromide, 99%, (64% de); (b) 9-BBN, H_2O_2, 70% (two steps); (c) 1M HCl, 62%.

Scheme 15[a]

hydroboration with 9-BBN followed by oxidation to give the alcohols **112**, which now proved to be easily separable by chromatography, and the diastereomerically pure alcohol **112** was obtained in 70% overall yield.

It should be stated here that although the diastereofacial selectivity during the alkylation of **15b** was only 4-5:1, the yield of pure diastereomer can still be quite satisfactory (~70%). Thus, one must not condemn low stereoselection as synthetically impractical if the ratios (>4:1) still provide ~80% of pure material. Interestingly, the Takano lactone **114** was ultimately obtained in 62% yield in a single step by heating the lactam **112** in 1M HCl.

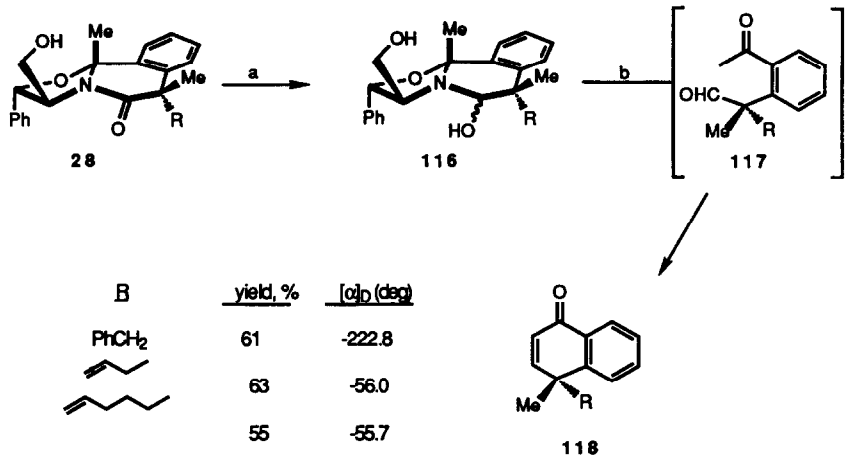
Comparison of rotation values of the final product ($[\alpha]_D$ 5.58°) with those reported in the literature ($[\alpha]_D$ 6.7° and 5.4°)indicated that the lactone **114** had indeed been obtained in high enantiomeric purity and also confirmed predominant *endo* approach of allyl bromide during the alkylation. The most accurate assessment of enantiomeric purity (>99% ee) is based on the diastereomeric purity of the lactam precursor **112** after chromatography (>99%de).

D. 4,4-Dialkyl-1-Naphthalenones

The benzo-fused dialkylated lactams **28** which were discussed in Section III were converted to 4,4-dialkyl-1-naphthalenones[11] by the reduction hydrolysis sequence employed to reach cyclohexenones (vide supra). Thus, Red-Al reduction of the diastereomerically pure lactams **28** followed by hydrolysis of the carbinolamines **116** in the usual manner directly produced the napthalenones **118** in yields ranging from 55-63% (Scheme 16). As seen in earlier studies, the intermediate ketoaldehydes **117** formed during the hydrolysis underwent *in situ* aldol condensation to the naphthalenones. Based on the diastereomeric purity of the lactam precursors **28** (>99% de after chromatography), it was assumed that the napthalenones **118** thus obtained were enantiomerically pure.

VII. PREPARATION OF AN α-KETO BICYCLIC LACTAM

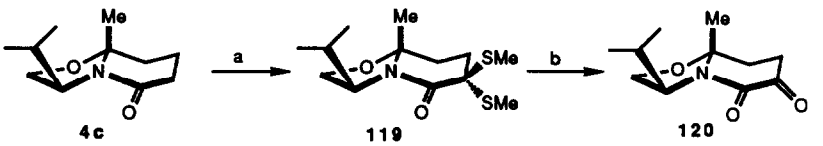
In an effort to extend the bicyclic lactam methodology to allow access to cyclohexenones containing an alkoxy group at the quaternary stereocenter, the α-keto lactam **120** was chosen as a potential precursor to reach these systems.[13] A concise two step synthesis of this valuable



[a]Reagents: (a) Red-Al; (b) $Bu_4NH_2PO_4$.

Scheme 16[a]

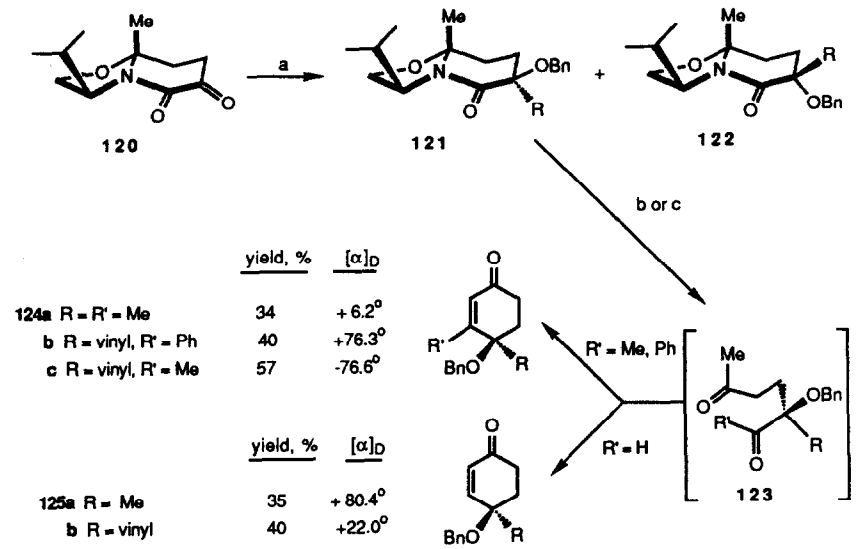
intermediate was devised via the α-dithiomethyl derivative **119**, and successfully executed to afford the keto lactam **120** in 58% overall yield from **4c.**



Reagents: (a) LDA, $MeSSO_2Me$, 70%; (b) 8.0 eq NBS, acetone, -5° C, 3 h.

A. 4-Alkoxy-4-Alkylcyclohexenones

In order to obtain the desired 4-alkoxy substituent, the keto lactam **120** was treated with methyl and vinyl Grignard reagents at -100°C furnishing the corresponding tertiary alcohols in 65-75% yields and in a 7:1 and 8:1 ratio of diastereomers, respectively (Scheme 17).[13] For purification purposes, these alcohols were transformed to the benzyl ether derivatives, the major diastereomer of which was determined to be the *endo* diastereomer **121** (NOE) and was thus consistent with the direction of alkylation of the previously studied bicyclic lactams. Conversion of the resulting tertiary alcohols to their benzyl ethers was performed in order to simplify chromatographic separation of the diastereomers and in this way the pure, major *endo* isomer **121** was obtained.



[a]Reagents: (a) RMgX, 65-75% (ii) BnBr, NaH, Bu_4NI; (b) (i) Red-Al (ii) $Bu_4NH_2PO_4$; (c) (i) R'Li (ii) anhyd. $Bu_4NH_2PO_4$.

Scheme 17[a]

Removal of the chiral auxiliary in **121** was accomplished by either of the two previously mentioned procedures (hydride reduction or alkyl lithium addition) followed by hydrolysis and aldol cyclization of the ketoaldehydes **123** (R' = H) and diketones **123** (R' = Me, Ph). In this manner, a number of cyclohexenones **124-125** bearing a tertiary alkoxy group at the quaternary stereocenter were prepared in overall yields ranging from 30-57% (from the benzyl ethers **121**).

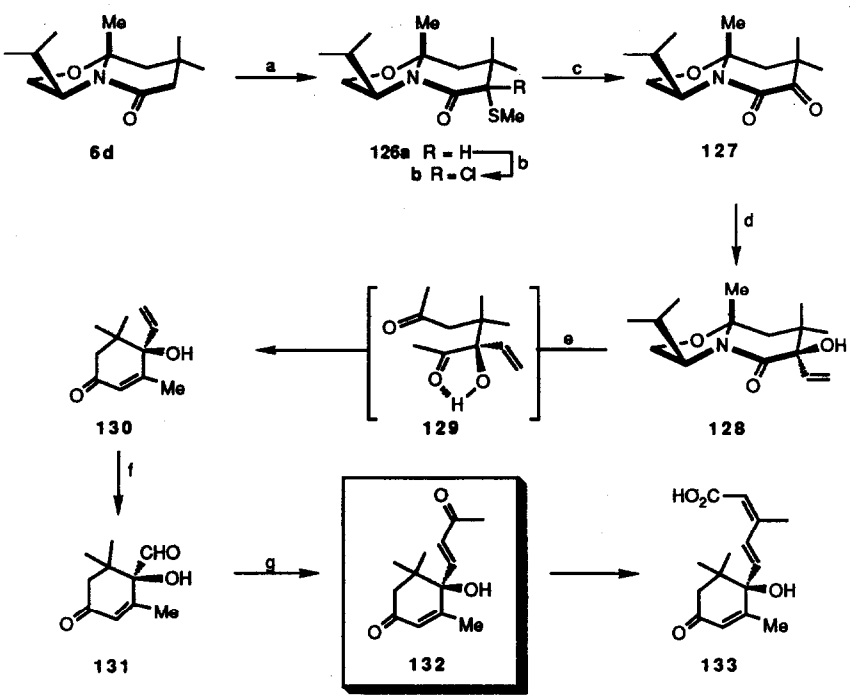
B. (-)-Dehydrovomifoliol

To further assess the value of this approach in reaching important natural products, dehydrovomifoliol **132**, the penultimate precursor[33] to (±)-abscisic acid (ABA) **133**, was considered. The importance of (+)-ABA stems from its known function as growth regulator in most plants.[34] A discrepancy in the optical purity of dehydrovomifoliol between Mori ($[\alpha]_D^{20}$ 262°)[35a] and Takasugi ($[\alpha]_D^{20}$ 159°)[35b] provided further impetus for this study.

The requisite bicyclic lactam **6d** containing the gem-dimethyl substituents, was prepared[36] in 54% yield by cyclodehydration of a keto ester (prepared from isophorone by ozonolysis and decarboxylation) and (S)-valinol as previously described (Section II, Table 2). Introduction of the α-ketone functionality was not possible via the double thiomethylation sequence[13] (e.g. **119**) presumably due to the steric bulk introduced by the adjacent gem-dimethyl group. However, a

route comparable in efficiency was found involving mono α-thiomethylation followed by chlorination and hydrolysis which gave the desired α-keto lactam **127** in 50% overall yield from lactam **6d** (Scheme 18).

The key step involving vinyl magnesium addition to the keto lactam **127**, proceeded at -100° C in 90% yield to give the *endo* vinyl lactam **128** with less than 1% of the *exo* diastereomer. The high selectivity was attributed to the increased steric bulk (axial methyl group) present on the β-face of the keto lactam **127**. Conversion of the latter to the 4-hydroxy enone **130** was achieved



[a]Reagents: (a) LDA, $MeSSO_2Me$, 65%; (b) NCS (c) $CuCl_2{\cdot}2H_2O$, 89% (two steps); (d) vinyl magnesium bromide, 90% (>98% de); (e) (i) MeLi (ii) H_3PO_4, 44%; (f) O_3, 91%; (g) $Ph_3P{=}CHC(O)CH_3$, 75%.

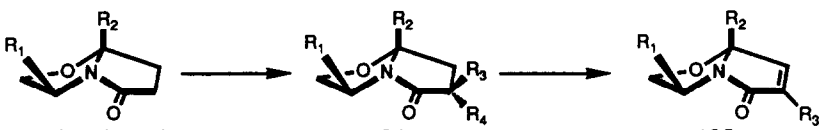
Scheme 18[a]

by the now established procedure of methyllithium addition followed by hydrolysis and *in situ* aldol cyclization. The cyclohexenone was obtained in 44% overall yield from **128**. It is interesting that only a single aldol product was observed from **128** which arose from nucleophilic attack at the most hindered carbonyl. It was postulated that, as a result of the intramolecular hydrogen bonding possible in the intermediate diketone **129**, the electrophilic nature of the more hindered carbonyl is enhanced.

To complete the synthesis, ozonolysis to the aldehyde **131** and chain extension to the target ketone **132** was performed in 68% overall yield from the cyclohexenone **130**. The material obtained in this study was found to be identical in all respects to that reported by the three previous laboratories with the exception of chiroptical properties. A negative rotation value of -219° which was intermediate between those reported by Mori (266°) and Takasugi (159°) for the natural material was obtained. In addition to confirming predominant *endo* approach of vinyl lithium to the dicarbonyl compound **127**, the sign of rotation also indicated that the dehydrovomifoliol obtained would provide unnatural (-)-ABA. From the specific rotation observed, it was clear that the discrepancy in the optical purity still remained. However, confirmatory proof that the material obtained in this study was indeed of high optical purity came from a ^{1}H-NMR chiral lanthanide shift study which indicated an enantiomeric purity for **132** of at least 95% when compared to racemic materials. Final Wittig transformation of dehydrovomifoliol **132** to (-)-ABA **133** was not performed since it was well known to give a 1:1 mixture of E:Z isomers.

VIII. PREPARATION OF α,β-UNSATURATED BICYCLIC LACTAMS

Having demonstrated that the chiral bicyclic lactams gave good to excellent diastereoselectivity during alkylation reactions, attention was focused on the use of unsaturated systems **135** to examine the extent of diastereofacial selectivity resulting from cycloadditions. The general route to these unsaturated lactams employed selenium-based methodology and allowed access to a number of derivatives (Table 14).[10] In addition, dithiomethylation of the lactams followed by elimination further provided access to the thiomethyl derivatives **135d-e**. In one example, the α-phenyl derivative (i.e. **135** R_1 = i-Pr, R_2 = Me, R_3 = Ph) could be prepared directly by the cyclodehydration reaction of (S)-valinol and the requisite α,β-unsaturated keto ester as described previously (Section II, Table 2).



4b, 4l; 15b, 15d **134** **135**

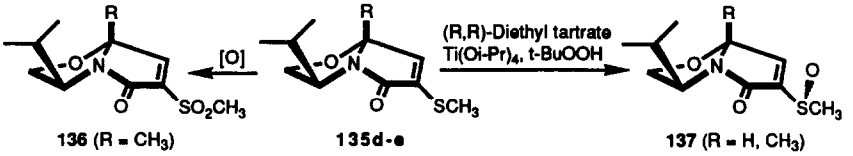
Table 14. α,β-Unsaturated Bicyclic Lactams **135.**

Entry	R_1	R_2	R_3	R_4	Yield, %[a]	[α]D	Mp (°C)	Method[b]
a	i-Pr	CH_3	H	SeC_6H_5	81	+21.4°	38-40	A,B
b	i-Pr	CH_3	CH_3	SeC_6H_5	58	+41.3°	46-47	C,A
c	i-Pr	CH_3	CO_2CH_3	SeC_6H_5	91	+13.5°	oil	D,A
d	i-Pr	CH_3	SCH_3	SCH_3	65	-	56-57	F
e	i-Pr	H	SCH_3	SCH_3	40	-	oil	F
f	i-Pr	H	CO_2CH_3	SeC_6H_5	74	+19.0°	oil	D, E
g	t-Bu	CH_3	H	SeC_6H_5	80	+68.4°	54.5-55.5	A,B
h	t-Bu	H	H	SeC_6H_5	72	+5.6°	oil	A,E

[a]Refers to an overall yield from the saturated unsubstituted lactams (**4b,l**; **15b, d**) to the unsaturated lactams **135**. [b]Methods: **A)** LDA , PhSeBr; **B)** H_2O_2, py.; **C)** LDA, MeI.; **D)** s-BuLi, $ClCO_2CH_3$; **E)** O_3, diisopropyl amine; **F)** (i) LDA, CH_3SSCH_3 (ii) $[Cu_2C_6H_6(CF_3SO_3)_2]$ / diisopropylethylamine.

The α-sulfonylmethyl and α-sulfoxymethyl lactams, **136** and **137** respectively, were obtained by simply oxidizing the α-thiomethyl lactams[10] **135d-e**. A second stereocenter at sulfur was introduced in the case of lactams **136d-e** by Kagan-Sharpless oxidation in order to observe any effect on diastereoselectivity as a result of this additional stereocenter.

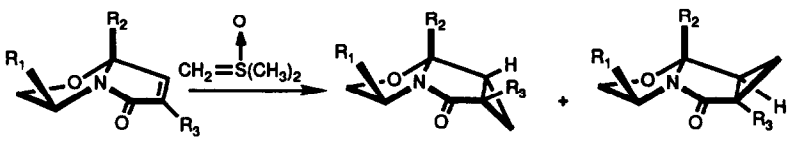
These methods allowed access to a number of unsaturated lactams which would serve as substrates for a variety of cycloaddition reactions and these will be discussed in the sections to follow.



136 (R = CH_3) **135d-e** **137** (R = H, CH_3)

IX. 2+1 CYCLOADDITIONS-CYCLOPROPANATIONS

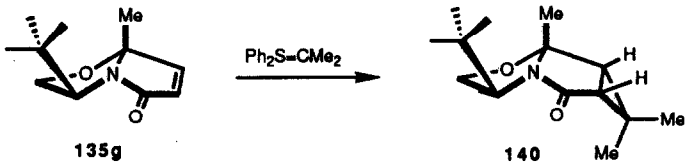
Initial studies were carried out with dimethylsulfoxonium methylide and the resulting cyclopropanations of the unsaturated lactams **135** proceeded with high diastereoselectivity (Table 15).[10, 37]



135 **138** **139**

One striking observation was the reversal in selectivity obtained between the angular methyl lactams **135a-f** and the angular hydrogen lactams **135g-l**. This was confirmed by X-ray analysis of cyclopropyl lactams **138d** and **138h**. **This simple change in angular substituents caused a reversal in selectivity from predominantly *endo* cyclopropanation in the case of the angular methyl lactams to predominantly *exo* in the case of the angular hydrogen lactams.** For the unsaturated lactam **137d** containing an asymmetric sulfur center, no effect on diastereoselectivity was observed as a result of this additional center. The major cyclopropyl adduct was obtained in diastereomerically pure form by recrystallization or in some cases by chromatography.

Sulfonium ylides, employed for cyclopropanation of the unsaturated lactam **135g**, likewise led to very high *endo*/*exo* selectivities. For example, treatment of the lactam **135g** with diphenylsulfonium isopropylidene afforded the gem-dimethyl cyclopropyl adduct **140** in 94% yield and >99%de (vpc).[39] The stereochemistry of this cycloadditon was determined by NOE experiments and by conversion of this adduct into the known deltamethrinic acid (Section IX.C).



135g 140

Table 15. Cyclopropyl Lactams **138**, **139**[10, 37].

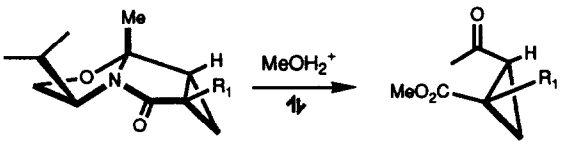
Entry	R_1	R_2	R_3	Yield, %	**138:139**	% De	Mp (°C)[a]	$[\alpha]_D$[a]
a	i-Pr	CH_3	H	64	40:1	95	47-48	+58.3°
b	i-Pr	CH_3	CO_2CH_3	65	100:1	98	98-99	-69.0°
c	i-Pr	CH_3	C_6H_5	60	>29:1	>93	106-108	-77.5°
d	i-Pr	CH_3	$SOCH_3$	90	>19:1	>90	81-82.5	+33.0°
							115-116.5	-11.0°
e	i-Pr	CH_3	SO_2CH_3	70	>19:1	>90	oil	-
f	t-Bu	CH_3	H	81	19:1	90	72-72.5	+72.9°
g	i-Pr	H	$SOCH_3$	50	>1:19	>90	110-111	+178.5°
							109-110	-
h	i-Pr	H	CO_2CH_3	50	>1:30	>93	94-95	+152°
i	t-Bu	H	H	40	>1:19	>90	oil	+149°

[a]Physical data are for pure, major diastereomers.

A. Chiral Cyclopropanes

To demonstrate the utility of this cyclopropanation process, the chiral auxiliary was removed from a number of these cyclopropyl adducts and the resulting chiral, non-racemic cyclopropanes were transformed into compounds of synthetic, biological, and agricultural interest.

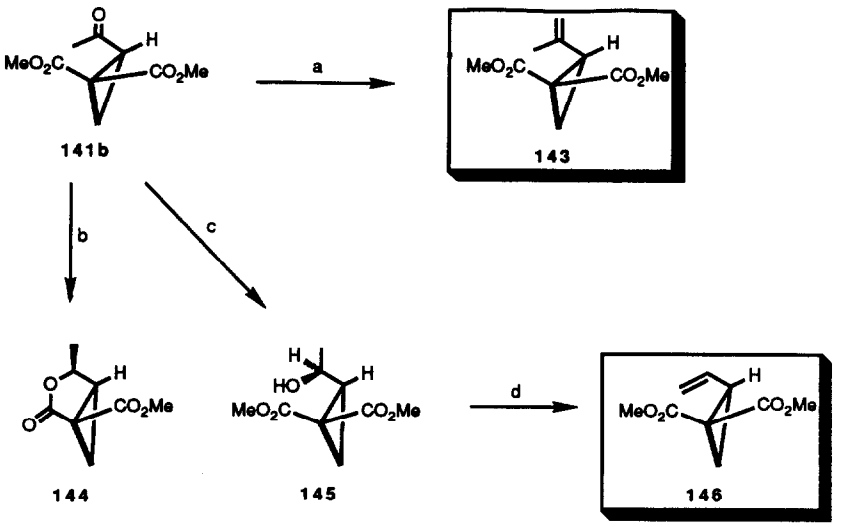
Acidic hydrolysis of the cyclopropyl adducts **138a-c** in 10% H_2SO_4-MeOH furnished the cyclopropyl methyl esters **141a-c** in good yields.[37] Epimerization of the latter was only observed after prolonged heating and only in the case of cyclopropane **141a**. The cyclopropyl diester **141b** was ultimately transformed into two chiral cyclopropane derivatives which have been elegantly utilized by Quinkert[38] in the total synthesis of a number of natural products (Scheme 19). Thus, treatment of diester **141b** with methylene triphenylphosphorane afforded the vinyl derivative **143** in 93% ee as determined by comparison of rotation values. However, it was stated that due to the errors normally associated with polarimeters, a more accurate measure of enantiomeric purity should be based on the diastereomeric purity of the cyclopropyl lactam precursor **138b** (>99% de; NMR and HPLC). The sign of rotation was consistent with *endo* cyclopropanation of the unsaturated lactam **135c**.



138a-c **141a-c**

	R_1	yield, %	$[\alpha]_D$
a	H	88	+48.7°
b	CO_2Me	86	-149.7°
c	Ph	81	-175.7°

In order to secure the chiral cyclopropane **146**, reduction of the methyl ketone **141b** was effected using $NaBH_4$. However, the lactone **144** was the sole isolated product. Since the desired vinyl cyclopropane **146** was inaccessible via this lactone under a variety of conditions, conditions were found to circumvent lactone formation which involved reduction in the presence of cerium trichloride to exclusively produce **145** in 99% yield.[37] Interestingly, complete stereoselectivity was realized under both reduction conditions. Dehydration of the alcohol was accomplished via elimination of the mesylate furnishing the vinyl derivative **146** in 48% overall yield and high optical purity.



[a]Reagents: (a) CH_2=PPh_3, 72%; (b) $NaBH_4$, 99% (>99% de); (c) $CeCl_3 \cdot 3H_2O$, $NaBH_4$, 99% (>99% de); (d) (i) MsCl; (ii) DBU, 48% (two steps).

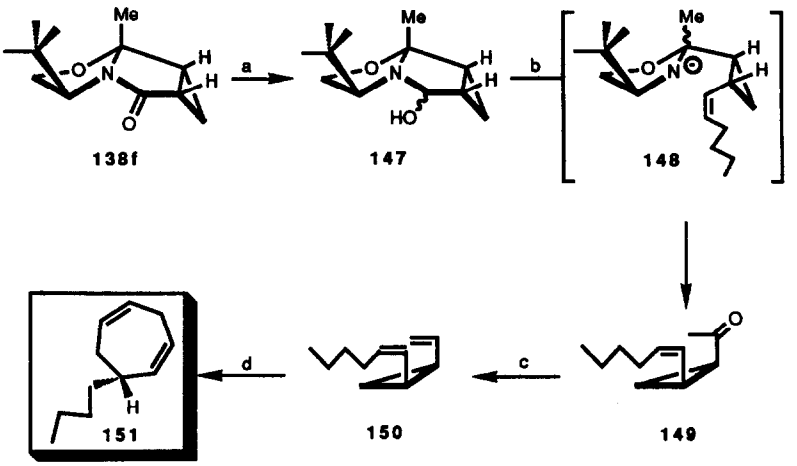
Scheme 19[a]

B. Dictyopterene C'

First isolated by Moore,[40] the dictyopterenes are a class of odoriferous C_{11} hydrocarbons found in the essential oil of *Dictyopteris plagiogramma* and *D. australis*, two species of brown seaweed found on reefs surrounding the Hawaiian islands. These compounds exhibit remarkable physiological activity related to the sexual reproduction of this species of seaweed.[41a] Dictyopterene C' **151** is a minor constituent of the essential oil of these seaweeds, however, dictyopterene C **150**, the proposed biogenic precursor of dictyopterene C', is not found in the essential oil.

Dictyopterene C' was targeted for total synthesis via the known cyclopropyl precursor dictyopterene C **150**.[10] The process began by reduction of the cyclopropyl adduct **138f** to the carbinolamine **147** followed by Wittig olefination. This led to the intermediate oxazolidine anion **148** which was directly hydrolyzed to the keto olefin **149**. Earlier attempts at reduction and hydrolysis of cyclopropanolactam **147** gave the ketoaldehyde (not shown) albeit in poor yields. It was found that the latter was quite volatile and the Wittig reaction was complicated by competing aldol condensations. Direct Wittig olefination on the carbinolamine **147** allowed the volatile intermediates to be bypassed and prevented competing aldol reactions. During the Wittig olefination, ~4-9% of the E-isomer of **149** accompanied the desired Z-isomer. Since the mixture of olefin isomers was not easily separated, the 94:6±2 mixture was carried forward to dictyopterene C'. Conversion of the methyl ketone **149** to its tosyl hydrazone followed by base

catalyzed elimination (Shapiro reaction) afforded the divinylcyclopropane **150** in 71% yield. Comparison of rotation values for cyclopropane **150** ($[\alpha]_D$ - 104°) with literature values ($[\alpha]_D$ -117.6°) indicated high optical purity (83% ee) and was consistent with the adventitious presence of 4-9% of the E-olefin.[41b] Cope rearrangement of the divinyl cyclopropane **150** gave dictyopterene C' **151** in 85% yield. Higher rotation values (-20.4° to 25.1°) were obtained for the final product compared to those reported in the literature (-12° and -16.5°), however this was found to be due to the presence of varying amounts of unrearranged divinyl cyclopropane **150** ($[\alpha]_D$ -104°).



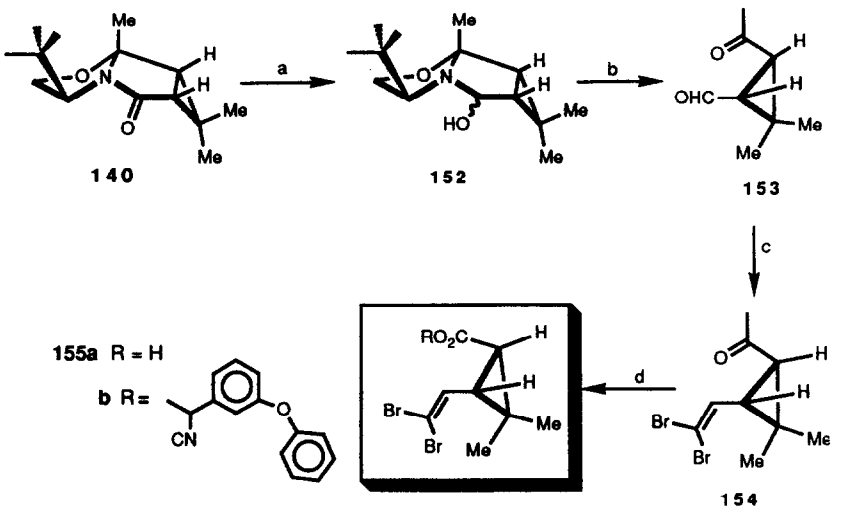
[a]Reagents: (a) Red-Al; (b) (i) $PPh_3{=}CH(CH_2)_3CH_3$; (ii) $Bu_4NH_2PO_4$, 51% (three steps); (c) (i) H_2NNHTs, 85% (ii) LDA, 84%; (d) Δ, 85%.

Scheme 20[a]

C. cis-(1S, 3R)-Deltamethrinic Acid

Due to their high insecticidal activity and low mammalian toxicity, pyrethroids are widely used for agricultural applications.[42] One prominent member of this class of insecticides is deltamethrin **155b** which to date is the most potent analog of the naturally occurring chrysanthemic acid.[43]

The immediate precursor to deltamethrin, deltamethrinic acid **155a**, was reached in an asymmetric total synthesis from the cyclopropyl adduct **140** (Scheme 21) which had been earlier obtained in excellent yield and with very high diastereoselectivity.[39] Removal of the chiral auxiliary was effected under the usual protocol involving reduction and hydrolysis. Due to the volatility of the keto aldehyde **153**, it was immediately subjected to dibromo olefination to afford the chiral cyclopropane **154** in 42% overall yield from the lactam **140**.



[a]Reagents: (a) Red-Al; (b) $Bu_4NH_2PO_4$; (c) CBr_4, Ph_3P, 42% (three steps); (d) NaOH, Br_2, 81%.

Scheme 21[a]

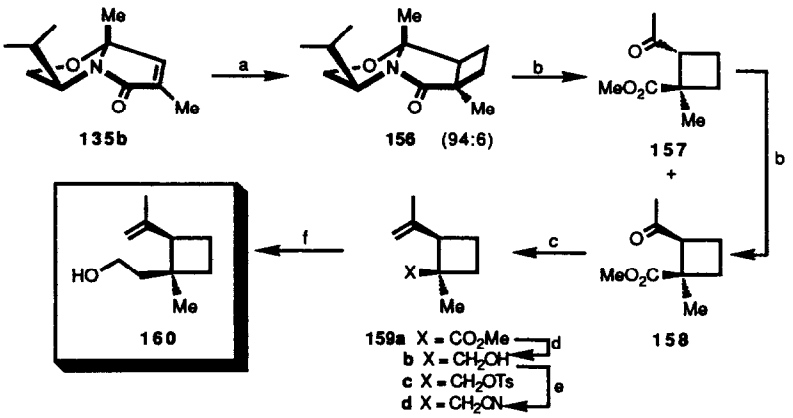
Using the haloform oxidation, deltamethrinic acid **155a** was obtained in 81% yield and 97% ee as determined by comparison of rotation values ($[\alpha]_D$ -16.8°) with authentic samples ($[\alpha]_D$ +17.3°). Although the optical antipode of the most potent enantiomer was obtained, it is clear that the opposite enantiomer could be reached by use of D-(R)-t-leucinol as the chiral auxiliary. The sign of rotation also confirms exclusive *endo* approach of the sulfur ylide to the unsaturated lactam during the cycloaddition.

X. 2+2 CYCLOADDITIONS - ((-)-GRANDISOL)

High diastereoselectivity was also realized during 2+2 photo-cycloadditions to the unsaturated lactams. Thus, a route to (-)-grandisol **160**, the major component of the boll weevil sex pheromone,[44] was achieved based on the photocycloaddition of ethylene to the α-methyl unsaturated lactam **135b**.[45] The cycloaddition to **135b** proceeded in 93% yield and 88% de (Scheme 22).

Since the cyclobutane adducts showed some instability to chromatography, the diastereomeric mixture of **156** was utilized in the subsequent experiments. Removal of the chiral auxiliary was effected by heating in 5% H_2SO_4-MeOH to generate the cyclobutanes **157-158** in 56% yield as a 45:55 mixture of epimers. It was subsequently found that pure cyclobutane **157** could be reconverted to the 45:55 mixture by resubmitting it to the hydrolysis conditions. In this fashion, both epimers **157-158** were utilized to reach the target compound. Wittig olefination of the methyl ketone **158** to the isopropylidene derivative **159a** was accomplished in 80% yield.

Following reduction to the alcohol **159b**, a one carbon homologation via displacement of the tosylate **159c** with cyanide was employed to obtain the correct number of carbons for grandisol. With the nitrile in hand, selective reduction followed by hydrolysis afforded the aldehyde which



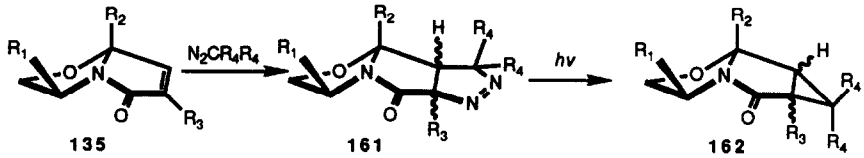
[a]Reagents: (a) ethylene, hv, acetophenone, 93% (84-86% de); (b) 5% H_2SO_4, MeOH, 56% (45:55 ratio of **158:157**); (c) $PPh_3{=}CH_2$, 80%; (d) $LiAlH_4$, 98%; (e) (i) TsCl, py. (ii) NaCN, 62% (two steps); (f) (i) $(i\text{-Bu})_2AlH$ (ii) 5% H_2SO_4 (iii) $LiAlH_4$, 63% (three steps).

Scheme 22[a]

was immediately reduced to afford grandisol **160** in 63% yield from nitrile **159d**. Although comparison of rotation values with literature values indicated that the product had been obtained in high enantiomeric purity, the Mosher ester was prepared for additional verification. On comparison with racemic Mosher ester derivatives, the product from this study was found to have an optical purity of 88%. This compares well with the mixture of cyclobutyl adducts **156** (88% de) obtained earlier in the synthesis. The sign of rotation was consistent with predominant *exo* approach of ethylene to the unsaturated lactam during the cycloaddition. **It should be noted that this (2+2) cycloaddition is the only other example, other than cyclopropanation of the angular hydrogen lactams (Section IX), of predominant *exo* entry involving these lactam systems.**

XI. 3+2 CYCLOADDITIONS - PYRAZOLINE FORMATION AND CONVERSION TO CYCLOPROPANES

In efforts directed towards the asymmetric synthesis of cyclopropanes via the bicyclic lactams, the 3+2 cycloaddition of various diazoalkanes was studied.[10] In all cases, very high **regiocontrol** was realized for pyrazolines **161** during the cycloaddition, not an unexpected



result for electron deficient dipolarophiles. However, **stereocontrol** was either excellent or very poor with regard to diastereoselectivity. The percent de for the resulting cyclopropanes **162** is presented in Table 16. The degree of stereocontrol was found to be highly dependent on both lactam structure and the diazoalkane employed. For example, in the reaction of the unsaturated lactam **135g** with diazomethane, exclusive *endo* approach of the dipole was observed (Table 16, entry g). In contrast, addition of diazoisopropane to the same substrate resulted in complete loss of stereoselection (Table 16, entry f). This change in behavior was attributed to the higher reactivity of diazoisopropane in comparison to diazomethane which would be expected to lead to lower selectivity in accord with the reactivity-selectivity principle.[16]

Table 16. Cycloadducts **161**, **162** From Lactams **135**[10].

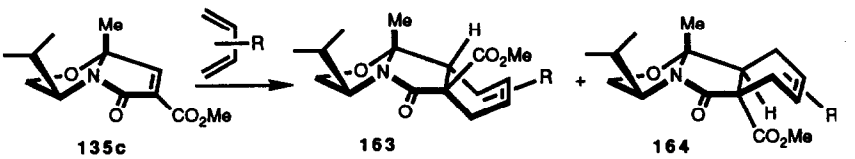
					161	**162 (photolysis)**			
Entry	R_1	R_2	R_3	R_4	Yield, %	Yield, %	% De	Mp (°C)[a]	$[\alpha]_D$[a]
a	i-Pr	CH_3	$SOCH_3$	H	91	dec	-	-	-
b	i-Pr	CH_3	SCH_3	H	55	95	90	83-85	- 21.1°
c	i-Pr	CH_3	CH_3	H	46	93	90	oil	+36.7°
d	i-Pr	CH_3	CH_3	CH_3	0	-	-	-	-
e	i-Pr	CH_3	SCH_3	CH_3	-[b]	67	90	71-73	+9.9°
f	t-Bu	CH_3	H	CH_3	~100	88	0	-	-
g	t-Bu	CH_3	H	H	~100	59	>98	72-72.5	+72.9°
h	t-Bu	H	H	H	~100	50	0	-	-

[a] Physical data are for pure, major diastereomers. [b]No pyrazoline was isolated. The cyclopropyl adduct **162** was formed directly under the reaction conditions.

Extrusion of nitrogen from the pyrazolines to cyclopropanes **162** was effected by photolytic means; however, in many cases the cyclopropanes were accompanied by unsaturated lactams arising from hydrogen migration in the intermediate diradical species. Indeed, under certain conditions, hydrogen migration, to afford α,β-unsaturated carbonyl compounds, has been observed as the major reaction pathway.[46]

XII. 4+2 CYCLOADDITIONS - ASYMMETRIC DIELS-ALDER ROUTE TO CARBOCYCLIC SYSTEMS

To further expand the synthetic prowess of these chiral unsaturated lactams, 4+2 cycloadditions were attempted and proceeded with a very high degree of diastereoselectivity (>150:1 ratios) to give the tricyclic systems **163** (Table 17).[47a] Once again, exclusive *endo* addition was the normal course of events. However, the α-carbomethoxy substituent was found to be necessary for dienophile activation to achieve stereoselective 4+2 cycloaddition. Higher temperatures were found to be necessary for the unsubstituted dienophile and resulted in stereorandom products. The stereochemical outcome was verified by X-ray crystallography of the t-butyl ester derivative of cycloadduct **163b**.

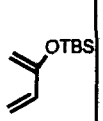
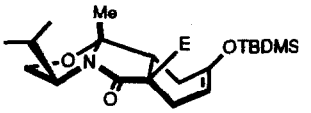
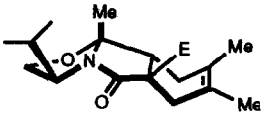
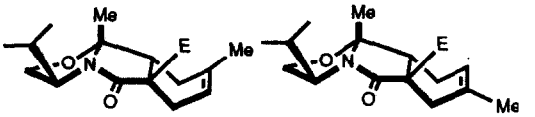
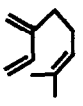
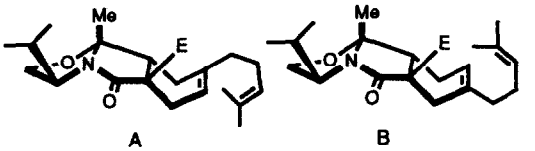
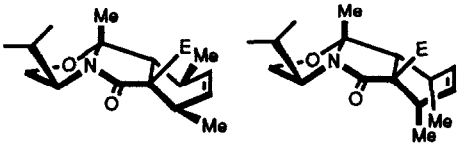


When unsymmetrical dienes were employed, varying amounts of regiocontrol were observed, depending upon the specific diene employed (Table 17, entries a, c, and e). However, in those instances where low regiocontrol was the result, the outcome could be greatly improved by the use of various Lewis acids at lower temperatures (entries d and f).

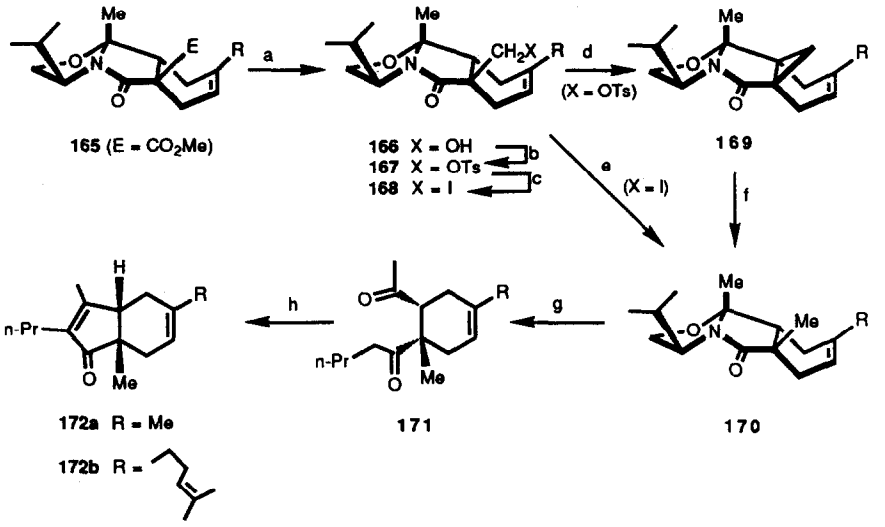
Secondary stereocontrol (Alder "*endo* selectivity") was also examined with *trans, trans*-2,4-hexadiene. In the thermal reaction, a 1.3:1 ratio of diastereomers was obtained in 87% yield (Table 17, entry g). However, the secondary control could be greatly improved by employing Lewis acids. Thus, when the cycloaddition was carried out at -60°C in the presence of catalytic $SnCl_4$, a 10:1 ratio of diastereomers was obtained (Table 17, entry i).

The synthetic potential of this asymmetric cycloaddition process was demonstrated when two cycloadducts were carried forward to optically pure bicyclic systems after removal of the chiral auxiliary.[47b] Conversion of the carbomethoxy groups to methyl groups was found desirable in order to prevent complications during chiral auxiliary removal. Thus, the cycloadducts **165** were first reduced to the alcohols **166** and the latter transformed into its tosylate **167** (Scheme 23).

Table 17. Cycloadducts **163** from Unsaturated Lactam **135c.**

Entry	Diene[a]	Cycloadducts (E = CO_2Me)	Yield, %	A:B ratio
a			95	100:0
b			89	-
c		 A B	74	2.0:1
d[b]	"	" "	71	25:1
e		 A B	70	2.3:1
f[b]	"	" "	66	15:1
g			87	1.3:1
h[c]	"	" "	87	2.2:1
i[d]	"	" "	55	10:1

[a]Ten equiv of diene were employed. [b]Performed at 0° C with 1.0 equiv of $ZnCl_2$. [c]Performed at 25°C with 1.0 equiv of $ZnCl_2$. [d]Performed at -60°C with 0.2 equiv of $SnCl_4$.



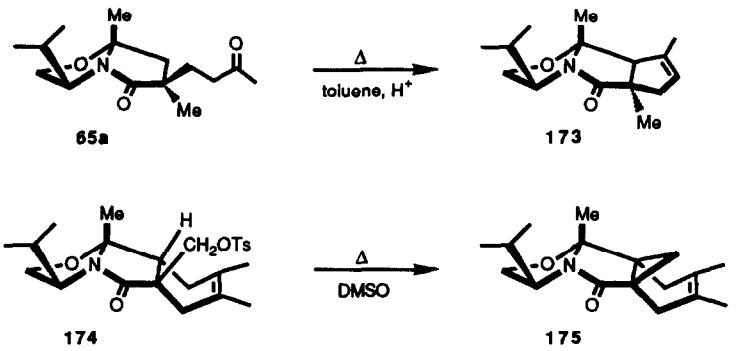
[a]Reagents: (a) $NaBH_4$, 95%; (b) TsCl, 99% (c) NaI (d) DMSO, Δ, 100%; (e) Mg, MeOH; (f) (i) TMSI (ii) Mg, MeOH, 55-60% (two steps); (g) (i) n-BuLi (ii) $Bu_4NH_2PO_4$; (h) NaOEt, 55-60% (3 steps).

Scheme 23[a]

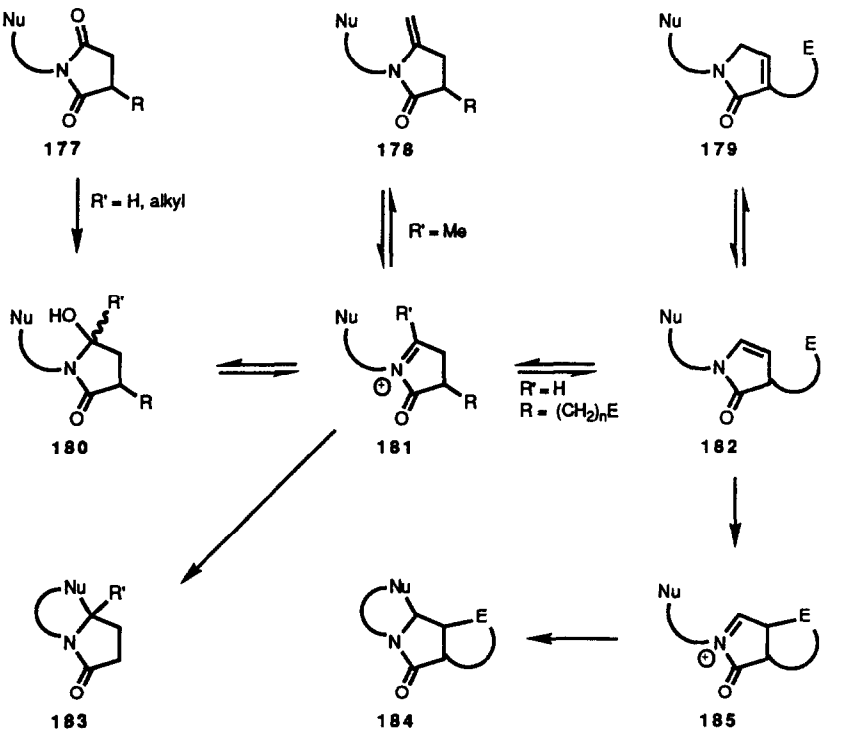
Attempted reduction of the tosylates to the methyl substituted cycloadducts **170** with $NaBH_4$-DMSO led, unexpectedly, to exclusive formation of the cyclopropyl derivatives **169**. This unusual ring annulation is believed to occur via the N-acyliminium species arising from these bicyclic lactams and will be further discussed below (Section XIII). Conversion of the methyl ester **165** to the methyl derivative **170** was, nevertheless, achieved *via* the cyclopropyl derivative **169** by cyclopropyl ring opening with trimethylsilyl iodide followed by reduction with magnesium in methanol. Alternatively, the tosylates **167** were converted to the respective iodides **168** and then reduced with magnesium in methanol to the methyl derivatives **170**. Utilizing the three-step sequence to reach cyclopentenones described above (Section V), the lactams **170** were treated with n-butyllithium and then hydrolyzed to afford the diketones **171**. The fused carbocycles **172a-172b** were then secured in 55-60% overall yield from lactams **170** by aldol cyclization of the crude diketones **171**.

XIII. A NOVEL ANNULATION VIA N-ACYLIMINIUM ION-ENAMIDE TAUTOMERS

The unexpected annulation which occurred when solutions of bicyclic lactams (e.g. **65a**, **174**) containing an α-substituent sensitive to nucleophilic attack (tosylate, carbonyl) were heated, in the presence or absence of catalytic acid, was deemed worthy of further study.[48] Thus, heating a toluene solution of the bicyclic lactam **65a** with catalytic acid produced the annulated product



173 in 80% yield as a single diastereomer. As stated above, the tricyclic species **174** bearing a primary tosylate when heated in dimethyl sulfoxide led to the cyclopropyl derivative **175** in quantitative yield. These interesting cyclizations on a seemingly unactivated carbon were rationalized by the intermediacy of an N-acyliminium ion species of the type **181, 182,** and **185** (Scheme 24). Transient intermediates of this sort have recently attracted much interest due to

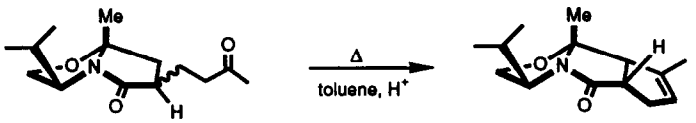


Scheme 24

their impressive synthetic utility.[14] The availability of the carbinolamides **180** via reduction of the imides **177** has opened up routes to a variety of bicyclic species **183** by nucleophilic capture of the N-acyliminium intermediate **181**. In fact, this sequence of events was the basis for one of the choice routes employed for the preparation of bicyclic lactams (**181** -> **183**; see Section II). However, the unexpected annulation observed for **65a** and **174** was proposed to proceed through a heretofore sparsely utilized intermediate, namely the enamide **182** which may arise from proton shift in the equilibrium manifold available to the acyliminium species **181**.

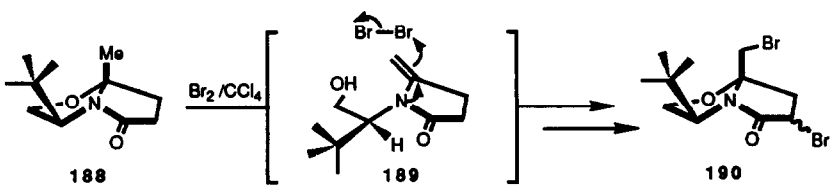
Within this scenario, the annulated tricyclic product **173** arose from nucleophilic attack on the pendant ketone (E = $(CH_2)_2C(O)CH_3$) by the enamide **182**. Subsequent dehydration leads to the cyclopentene and re-closure of the oxazolidine ring (**185** -> **184**, Nu=OH) afforded the observed product **173**. In a similar manner, nucleophilic displacement of the tosylate in lactam **174** by the enamide intermediate corresponding to **182** (E = CH_2OTs) produced the cyclopropane **175** after reclosure of the oxazolidine ring.

The possible involvement of the isomeric α,β-unsaturated lactam **179** in the equilibrium mixture (Scheme 24) was supported by the formation of a single diastereomer of the annulated product **187** when the monsubstituted lactam **186** as a mixture of α-epimers was heated in toluene. Thus, equilibration to allow for the formation of the more stable *endo* ring fused product must have passed through unsaturated lactam **179**.



186 **187**

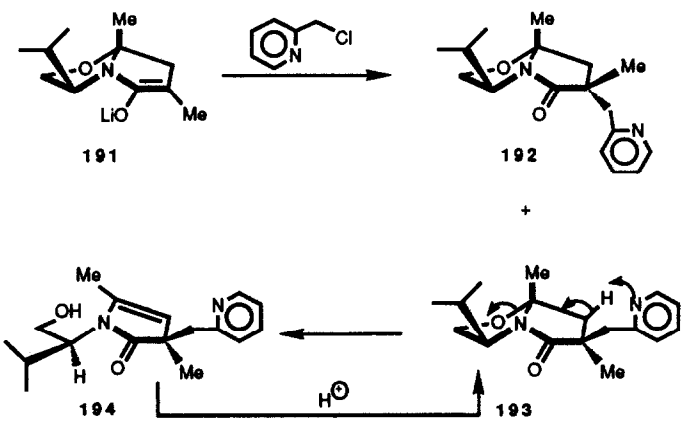
Strong evidence for the omnipresent existence of acyliminium species (**181**) arising from these bicyclic lactams was gained in a number of collateral studies. For example, attempted bromination α to the carbonyl of the bicyclic lactam **188** with bromine in carbon tetrachloride (25°C) produced the dibromide **190**, undoubtedly arising from further bromination at the angular methyl group.[10] This side reaction was attributed to bromination of the enamide **189** whose existence may be derived from double bond migration as depicted in Scheme 24 (**181** -> **178**).



188 **189** **190**

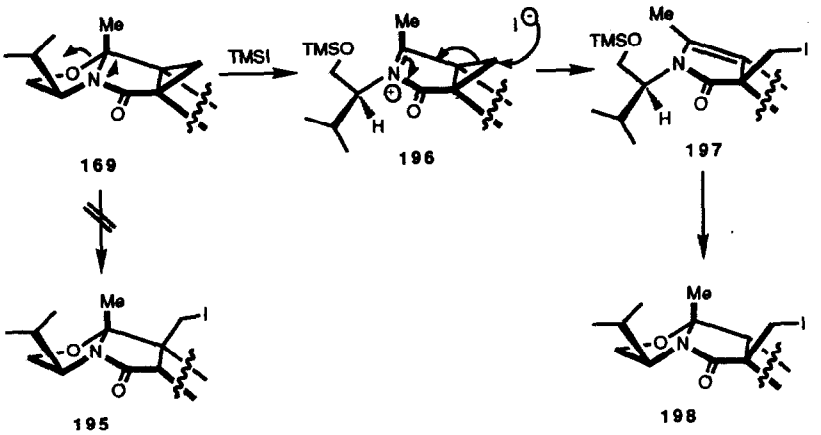
Some further interesting behavior was observed which bore on the presence of the acyliminium intermediates in these bicyclic lactams. During alkylations of the enolate **191** with 2-(chloromethyl)pyridine, in addition to the expected alkylated product **192**, the ring opened monocyclic species **194** was unexpectedly obtained (Scheme 25).[17] The appearance of the latter was based on the simultaneously formed *exo* alkylated material **193** which underwent an intramolecular elimination catalyzed by the pyridyl nitrogen. The absence of the corresponding ring-opened *endo* alkylation product was attributed to improper alignment of the adjacent proton with the departing oxazolidine ring oxygen atom necessary for ring fracture. Nevertheless, the monocyclic lactam **194** was readily converted to the bicyclic lactam **193** by treatment with trifluoroacetic acid.

Further exhibition of this facile ring-chain tautomerism of these lactams was found in the regiochemistry of trimethylsilyl iodide promoted ring opening of the cyclopropyl derivatives **169** (Scheme 26).[47b] The expected mode of ring opening based on precedent would have produced the enolate of **169** and resulted in the β-iodomethyl derivative **195**. However, the only observed product was that derived from the alternative ring opening mode giving the α-iodo methyl derivative **198**. The latter was believed to arise from the intermediacy of the N-acyliminium species **196**.



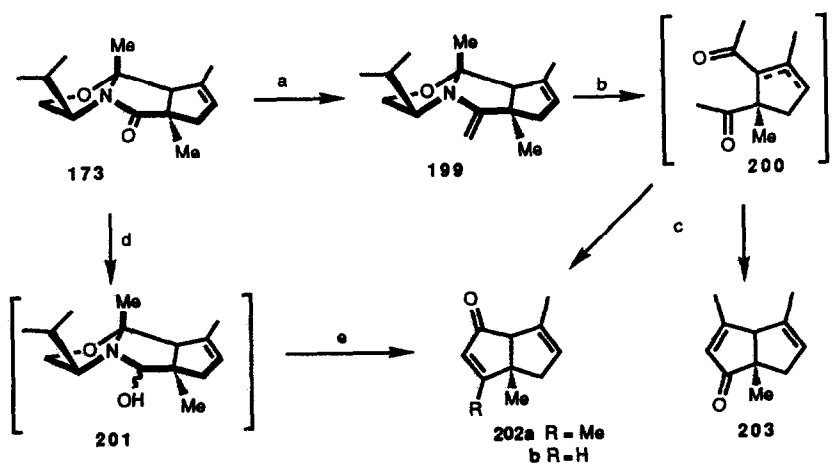
Scheme 25

Cleavage of the TMS ether **197** under the aqueous conditions then allowed for re-closure of the oxazolidine ring leading to the observed product **198**.



Scheme 26

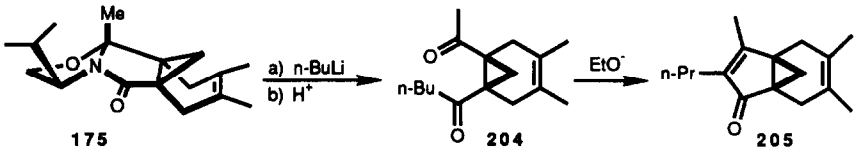
The value of this novel and efficient annulation in reaching optically pure carbocycles was shown by the conversion of **173** and **175** into cyclopentenones.[48] Thus, treatment of the tricyclic lactam **173** with methyllithium followed by hydrolysis and aldol cyclization of enamine **199** furnished the cyclopentenones **202a** and **203** as a 5:1 mixture. Alternatively, partial reduction of the tricyclic lactam **173** followed by hydrolysis led to the cyclopentenone **202b** in 26% yield accompanied by 52% of the ketoaldehyde precursor (not shown).



[a]Reagents: (a) methyllithium; (b) $Bu_4NH_2PO_4$; (c) Red-Al; (d) $Bu_4NH_2PO_4$ (26% **202b**, 52% ketoaldehyde precursor).

Scheme 27[a]

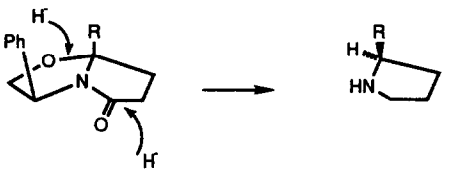
In a related manner, the cyclopropyl derivative **175** was transformed into the tricyclic species **205** by a three step sequence involving n-butyllithium addition, hydrolysis, and aldol cyclization in 89% overall yield.



175 204 205

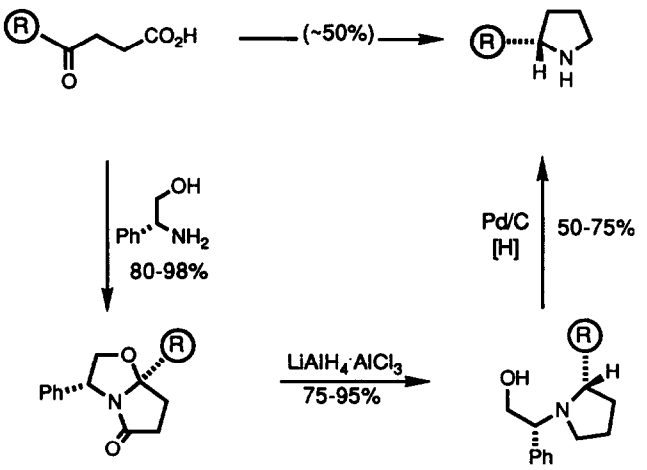
XIV. PREPARATION OF CHIRAL 2-SUBSTITUTED PYRROLIDINES

More recently, efforts have been turned to the acquisition of chiral heterocycles derived from the bicyclic lactams. For example, it should be possible to retain a portion of the bicyclic system **A** by selectively reducing the carbonyl group and the C-O bond to produce optically active 2-substituted pyrrolidine, **B**.



A B

This was indeed accomplished by the route outlined in Scheme 28.[49] The 3-step sequence delivered the titled products in ~50% overall yield from readily available 4-keto acids[50] and S-phenyl glycinol. A range of 2-substituted pyrrolidines were obtained where R = $PhCH_2$, n-heptyl, cyclopentyl, Ph, etc. This method can now take its place among others[51] which have been employed to prepare chiral 2-substituted pyrrolidines.



Scheme 28

XV. MECHANISTIC CONSIDERATIONS

A. Alkylations

A number of studies have been performed to determine the major factors responsible for preferential *endo* alkylation of the bicyclic lactams described herein. From these studies, it has become clear that there is more than a single factor involved which appears to work in concert to give preferential *endo* alkylation. Studies which have been pursued by this group and others will be presented below.

On first inspection, it would seem that the bulk associated with the chiral auxiliary (eg. isopropyl, t-butyl, etc.) and the angular substituents (Ph, Me, H) play a major role in governing the stereochemical outcome of alkylations. However, X-ray analysis of the α-benzyl lactam **20e** clearly shows that the isopropyl group occupies a pseudo-equatorial position and therefore should not present a significant steric deterrent to *exo* alkylation. This assumes, of course, that the ground state conformation of the crystalline material bears a relationship to the conformation of the enolate in solution. Although this may be a poor assumption, it is borne out by an earlier alkylation study described below. Furthermore, the concave nature of these bicyclic lactams as determined by X-ray analyses of several derivatives indicates that alkylation proceeds to the seemingly more congested concave face. This sterically concave nature is quite common in other bicyclo [3.3.0] systems and normally directs nucleophiles or electrophiles to the convex (*exo*)

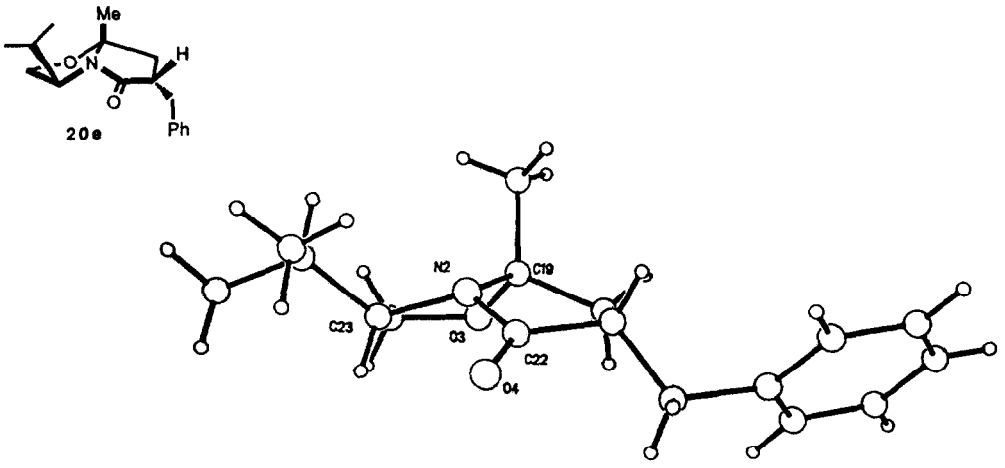
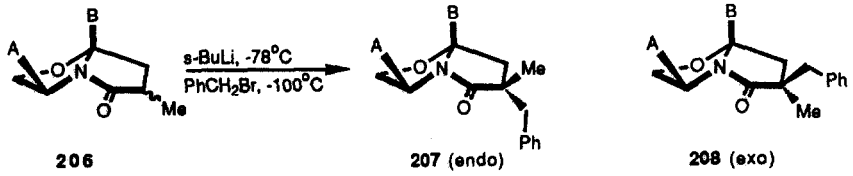


Figure 2. Single crystal X-ray structure of *endo*-benzyl bicyclic lactam **20e.**

face.[52] Thus, the question had to be addressed as to why these bicyclic lactams were prone to *endo*/entry. In order to assess the role that sterics may play on the facial selectivity of alkylations, a series of variously substituted α-methyl bicyclic lactams **206** were prepared and benzylated under a set of comparable conditions. These were chosen so the quaternary alkylated product could not epimerize and therefore would be a direct consequence of the kinetic selectivity.



The structural framework was systematically adjusted from the t-leucinol derived lactam **206a** to a perhydro bicyclic lactam **206f**. These systems were prepared by the methods described in preceding sections of this review. The results from these alkylation studies are presented in Table 18.

Table 18. Effect of Ring Substituents on *Endo/Exo* Benzylation Ratios of Lactams **206**[a].

Entry	A	B	% *Endo* (**207**)[b,c]	% *Exo* (**208**)	Ref.
a	t-Bu	Me	98	2	53
b	i-Pr	Ph	98	2	4
c	i-Pr	Me	97	3	6
d	i-Pr	H	77	23	53
e	H	Me	70	30	53
f	H	H	69	31	53

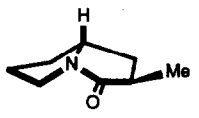
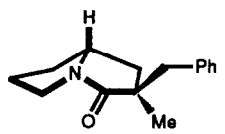
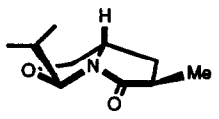
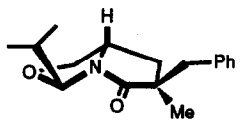
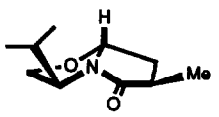
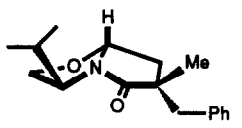
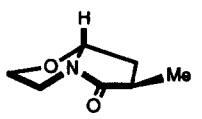
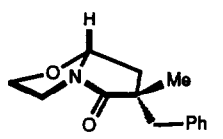
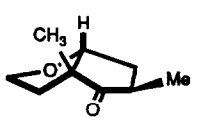
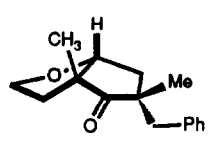
[a]Performed by metalation at -78°C and addition of benzyl bromide at -100°C. [b]Determined by HPLC analysis. [c]Yields for the benzylation reaction ranged from 81-94%.

From the table it is evident that systematic stripping of the bulky substituents from the bicyclic lactam structure led to a corresponding decrease in *endo/exo* selectivity for the benzylation. The stereochemistry of the dialkylated lactams **207-208** was based on ^{1}H-NMR employing the shielding effect of the benzyl group on the angular ring substituent which allowed determination of the relationship (*syn* vs *anti*) between these two groups. Further support for stereochemical assignments was obtained from NOE experiments.

From these results, it may be concluded *a priori* that steric effects make some contribution to the diastereoselectivities observed. However, even in the simplest lactam **206f**, a significant preference (> 2:1;corresponding to ~0.3-0.4 kcal/mol at -100°C) for *endo* alkylation remains. Therefore, other factors must be brought into play which contribute to the stereoselective alkylations of these systems.

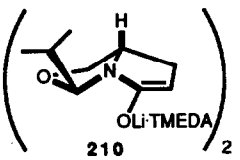
In an additional study involving several analogous bicyclo [3, 3, 0] systems **209**, which were prepared in other laboratories, an attempt was made to assess the role of the ring oxygen. A phenyl analog of **209b** (in place of isopropyl) was prepared by Thottahil[54] whereas the lactam **209a** was reported by Edwards[55a] and the alkylations studied by Eschenmoser.[55b] These systems were first alkylated with methyl iodide and then benzylated under similar conditions. Surprisingly, kinetic benzylations of these systems (entry a, b) led to mainly *exo* products (Table 19). The above mentioned valinol derived and perhydro lactams (entries c and d) are included for comparison.

Table 19. Alkylations of Analogous Bicyclo [3.3.0] Systems **209**.

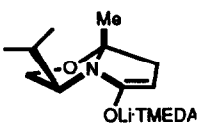
Entry	Bicyclic [3.3.0]system	Major product	% *Endo*	% *Exo*	Ref.
a			20	80	53b
b			6	94	53b
c			77	23	53b
d			70	30	53b
e			70	30	53b

The surprising observation that *exo* alkylation predominates when the oxazolidine ring oxygen atom is transposed (entry b) or completely deleted (entry a) from the bicyclic structure is immediately obvious. Furthermore, deletion of the nitrogen atom and replacement with a quaternary carbon still leads to preferential *endo* alkylation (entry e) although the question of steric factors contributed by this additional substituent (methyl) must now be considered. Thus, one may, *a priori*, conclude that the nitrogen lone pair is not a key player in determining the alkylation stereochemistry. Mention should also be made of the unusually high degree of pyramidalization of nitrogen in these lactam systems (0.22-0.31Å from the plane defined by the three attached carbon atoms as determined by X-ray analysis of five different bicyclic lactam systems). Amido nitrogens are usually trigonal (planar) due to resonance structures available to these functional groups. However, Eschenmoser[55b] has pointed out that enolates such as lactam enolate **209a** would be expected to be pyramidal in analogy to ketene-O,N-acetals and similar pyramidalization has been observed in X-ray structure analyses of lithium enolates of two N,N-dimethylamides by Seebach.[56] Eschenmoser also cites[55b] several earlier examples by others

including alkylation of an indole derivative, a chiral N-acyl sultam, and an imidazolidinone in which preferential *endo* alkylation was observed[53b] in spite of a steric disadvantage. In each of these cases, pronounced facial selectivity during alkylations has been explained in terms of the directing effect of a pyramidal nitrogen's lone pair. X-ray analysis of lactam enolate **210** which was found to exist as a dimer showed the highest degree of pyramidalization (0.494Å) for a lactam enolate to date.[57] However, alkylation of this lactam results in predominant *exo* entry (94:6); ***syn* to the nitrogen lone pair** (Table 19, entry b). This result along with entry e (Table 19), casts doubt on the extent of the directing effect of the nitrogen's lone pair during alkylations of these systems. Although the X-ray structure of the lithium enolate **211** would be exceedingly useful for comparison, the crystals obtained thus far after considerable effort were not suitable for X-ray analysis.



210

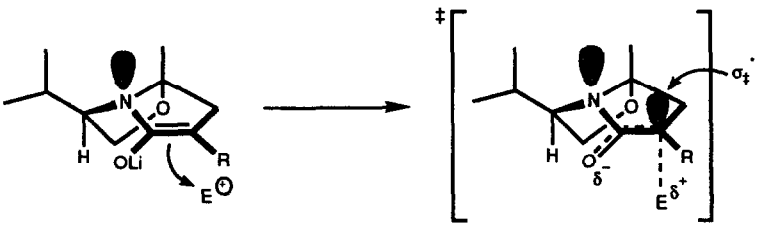


211

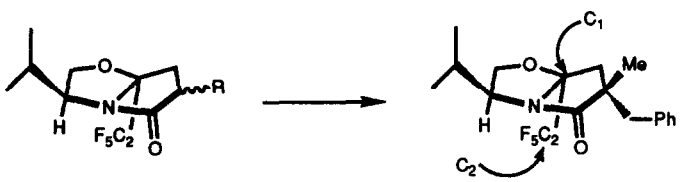
The role that the aggregation state of the enolate may have on selectivity was also considered since in many cases, this has been shown to be responsible for stereoselective alkylations.[58] A variety of aggregation levels are known for lithium species, including monomers, dimers, tetramers, and hexamers which have been observed in solution by NMR, cryoscopic measurements and in the solid state by X-ray.[59] However, in cases where enolate structure has played a role in the stereochemical outcome of an alkylation, the reaction is usually found to be sensitive to solvent polarity, concentration, and counterion. These parameters are manifested *via* chelation effects which hold the enolate in a particular conformation[60,61] or direct the electrophile[25] such that the coordination sphere about the counterion biases the two faces of the enolate. A series of experiments[62] have indicated that such counterion effects may not be responsible for the selectivity observed during alkylations of the bicyclic lactams. Addition of HMPA or TMEDA to the enolates did not affect the resulting diastereoselectivity observed. In addition, no change in diastereomeric ratios was observed when the solvent was varied from THF to diethyl ether to heptane. Finally, changing the counterion from lithium to sodium to potassium had no significant effect on the *endo/exo* ratios of the alkylations. Thus, it would appear that neither the aggregation state of the enolate nor the coordination sphere about lithium plays a major role in the observed selectivity. However, Liotta and Durkin[63] have recently described AMPAC and MOPAC (MNDO) calculations which indicate that a major portion of the selectivity in these lactam systems can be attributed to preferential *exo* solvation as a result of the favorable interactions between the lithium and the pyramidalized nitrogen. They determined that the *endo* transition state for alkylation was 0.7 kcal/mole more stable than the *exo* transition state and on

this basis there should be a preference for *endo* alkylation (88:12 at -100°C). No explanation for these different conclusions derived from experiments or computation can be offered at this time.

Another possible rationale put forward for selective *endo* alkylation invokes stereoelectronic control by the Cieplak effect.[64] As proposed by Cieplak, this effect occurs during σ bond forming reactions in the *absence* of other larger factors (sterics, other stereoelectronic effects, etc.) and involves stabilization of the developing σ* orbital by a neighboring electron rich σ bond. In this way, approach of a nucleophile or electrophile occurs antiperiplanar to the most electron rich σ bond. This proposal has been supported by experimental studies involving adamantyl[65a] and other systems[65b] which were specifically chosen since their inherent rigid structure removes other overriding stereodirecting factors. When applied to the bicyclic lactams, *endo* alkylation appears to be consistent with the Cieplak model since alkylation occurs antiperiplanar to the relatively electron rich C_1-C_2 bond (compare to the electron poor C_1-O bond).



In order to verify whether or not this effect is operative during alkylations of the bicyclic lactams, the angular pentafluoroethyl lactam **212b** was prepared.[66] It should be noted that during formation of the bicyclic lactam **212a**, the opposite stereochemistry (X-ray) at the angular carbon was obtained in contrast to all previous cases involving [3.3.0] bicyclic lactams. However, this was not expected to alter the question that was being addressed.



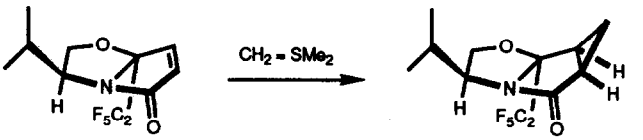
212a R= H
b R = CH_2Ph

213

The Cieplak effect was deemed not to be a major contributor to the selectivity observed with these systems since alkylation of the α-benzyl lactam **212b** with methyl iodide occurred in the same sense (*endo*) as before (predominantly antiperiplanar (97:3 *endo*/*exo* ratio) to the most electron poor σ bond; C_1-C_2 bond) and the stereochemistry of the major diastereomer **213** was verified by X-ray analysis. This result strongly implies that other, larger, stereodirecting factors are in operation in these systems, dwarfing any Cieplak effect that may be operating.

B. Cycloadditions

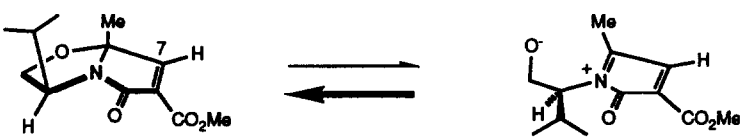
1. Cyclopropanation. Although the Cieplak effect was also investigated as a possible explanation for the high facial selectivity observed during cyclopropanations, as in the alkylations above, no directing effect was observed during cyclopropanation of the unsaturated lactam **214**.[66]



214 **215**

The normal mode of *endo* approach of the sulfur ylide occurred (X-ray verification) to give the cyclopropyl adduct **215**. This is partially due to larger stereodirecting effects, namely group bulk, which were revealed when the corresponding unsaturated **angular hydrogen lactams** (Section IX; Table 15; entries g-i) were cyclopropanated and found to give preferential *exo* cyclopropanation (>19-30:1). In this way, the predominant mode of cyclopropanation can be predicted simply based on the size of the angular substituent present in the bicyclic lactam. However, whether another stereo or stereoelectronic effect is also operating is still an open question (vide infra).

2. Diels-Alder Reaction. Once again, the facial selectivity observed for the (4+2) cycloadditions[47] using lactam **135c** must be considered as a consequence of steric effects on the β-face. However, X-ray structures of these systems, as well as NOE data, show the isopropyl group to be situated in a psuedo-equatorial position and the angular methyl group to be the only substituent close enough to the π-system to affect the steric outcome.



135c **216**

The possibility also exists that the acylimminium zwitterion **216** may be a player in the cycloadditions to **135c** since the ring chain tautomerism has been implicated in earlier studies.[48] Furthermore, this type of anti-aromatic species has been postulated to explain transformations within the pyrrole literature.[67] In the absence of additional information gathered to date, the role of **216** in this process remains uncertain.

Another aspect to consider in these cycloaddition processes which may be significant is torsional angle arguments. These proposals, set forth in convincing manner by Houk[68] and others[69] to explain facial selectivities in pericyclic reactions may be applied herein. The notion that the direction of pyramidalization is related to the direction of attack is indeed intriguing. While the pyramidalization of the olefinic C-7H in **135c** is not immediately obvious, even from usual X-ray data which, as is well known, does not set C-H bonds, it is entirely possible that it is pyramidalized to a small degree.[70] As reported by Seebach,[69] this value can be rather small (~3°). There is no question that continued efforts to assess the subtle underlying causes for the diastereofacial selectivity seen in these lactams will be desirable.

XVI. SUMMARY

The chiral bicyclic lactams have thus far proven to be useful templates for the asymmetric synthesis of a variety of natural and unnatural products. The utility of these lactam systems stems from their ability to allow elaboration of γ or δ–keto acids and γ-aldehydic acids in an asymmetric fashion. A number of chiral, non-racemic bicyclic lactams were readily prepared by condensation of an optically pure amino alcohol with a dicarbonyl compound. High levels of asymmetric induction (82-99% de) were realized when these systems are alkylated and thus this methodology provided access to a variety of quaternary substituted cyclopentenones, cyclohexenones, naphthalenones, and dihydronaphthalenes in optically pure form. In addition, a variety of cycloadditions with unsaturated bicyclic lactams proceeded with high diastereoselectivity (82-99% de) to afford an array of carbocycles ranging from cyclopropanes to cyclohexanes. A novel annulation method via N-acyliminium ion-enamide tautomers of these lactam systems also allowed access to fused carbocyclic structures. A number of methods for effecting chiral auxiliary removal from these bicyclic lactams are available and thus, the optically pure product can be liberated and further elaborated.

ACKNOWLEDGEMENT

The authors are grateful to our many coworkers whose names appear in the references, who have contributed significantly to this research effort. Finally, grateful acknowledgement is made to the National Institutes of Health which has supported this study since its inception in 1985.

REFERENCES

1. For recent surveys of asymmetric syntheses see: a) Nogradi, M. *Stereoselective Synthesis*; VCH: New York, 1987. b) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vols. 1-5.

2. Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987.

3. Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon Press: New York, 1983.

4. a) Meyers, A. I.; Harre, M.; Garland, R. *J. Am Chem. Soc.* **1984**, *106*, 1146. b) A review by S. F. Martin (*Tetrahedron* **1980**, *36*, 419) which summarized synthesis of quaternary carbon compounds, indicated the virtual lack of asymmetric routes to this class of compounds. At this writing there are now numerous routes to chiral quaternary carbon compounds and, in addition to the bicyclic lactam method described here, a listing may be found in Palazzi, C.; Poli, G.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4223; see also Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428.

5. a) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am Chem. Soc.* **1985**, *107*, 7974. b) Dickman, D.A.; Meyers, A.I.; Smith, G. A.; Gawley, R. *Org. Syn. Coll. Vol. VII*, 530.

6. Meyers, A. I.; Wanner, K. T. *Tetrahedron Lett.* **1985**, *26*, 2047.

7. a) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am Chem. Soc.* **1985**, *107*, 7776. b) Meyers, A. I.; Wanner, K. T., unpublished results.

8. Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936.

9. Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663.

10. Romo, D.; Romine, J. L.; Midura, W.; Meyers, A. I. *Tetrahedron* **1990**, *46*, 4951.

11. Wunsch, T.; Meyers, A. I. *J. Org. Chem.* **1990**, 55, 4233.

12. Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, 51, 1541.

13. Meyers, A. I.; Sturgess, M. A. *Tetrahedron Lett.* **1988**, *29*, 5339.

14. For a review of N-acyliminium cyclizations in synthesis see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

15. Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, 54, 4243.

16. a) Johnson, C. D. *Tetrahedron* **1980**, *36*, 3461. b) Johnson, C. D. *Chem. Rev.* **1975**, *75*, 755.

17. Meyers, A. I.; Wallace, R. H.; Harre, M.; Garland, R. *J. Org. Chem.* **1990**, *55*, 3137.

18. Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1964**, 3.

19. Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.

20. Curran, D. P.; Kuo, S. *J. Am Chem. Soc.* **1986**, *108*, 1106.

21. Meyers, A. I.; Bienz, S. *J. Org. Chem*. **1990**, *55*, 791.

22. Takeuchi, T.; Linuma, J.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215.

23. Curran, D.P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991.

24. Meyers, A. I.; Lefker, B. A. *Tetrahedron Lett.* **1987**, *28*, 1745.

25. The ability of a heteratom to direct an organolithium to a proximal site, through chelation, is well known. For a review of complex induced proximity effects, see: Beak, P.; Meyers, A.I. *Acc. Chem. Res.* **1986**, *19*, 3187.

26. Terashima, S.; Sato, S.; Koga, K. *Tetrahedron Lett.* **1979**, *20*, 3469.

27. a) Stevens, R.V.; Fitzpatrick, J. M; Kaplan, M; Zimmerman, R. L. *J. Chem. Soc., Chem. Comm.* **1971**, 857. b) Wu, P.-L.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1988**, *53*, 963. c) Martin, S. F.; Desai, S. R.; Philips, G. W.; Miller, A. C. *J. Am Chem. Soc.* **1980**, *102*, 3294. d) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1966**, 1311.

28. Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673.

29. Meyers, A. I.; Berney, D. *Org. Syn.* **1990**, *69*, 55.

30. Stork, B.; Dolfini, J. E. *J. Am Chem. Soc.* **1963**, *85*, 2872.

31. Meyers, A. I.; Romine, J. L.; Robichaud, A. J. *Heterocycles* **1990**, *30*, 339.

32. Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 305 and earlier references cited.

33. Roberts, D. L.; Heckman, R. A.; Hege, B. P.; Bellin, S. A. *J. Org. Chem.* **1968**, *33*, 3566.

34. Walton, D. C. In *Abscisic Acid*; Addicot, F. T., Ed.; Praeger Press: New York, 1983, Chapter 4.

35. a) Mori, K. *Tetrahedron* **1974**, *30*, 3566. b) Takasugi, M.; Anetai, M.; Katsui, N.; Masamune, T. *Chem. Lett.* **1973**, 245.

36. Meyers, A. I.; Sturgess, M. *Tetrahedron Lett.* **1989**, *30*, 1741.

37. Meyers, A. I.; Romine, J. L.; Fleming, S. A. *J. Am Chem. Soc.* **1989**, *110*, 7245.

38. a) Quinkert, G.; Schmalz, H.-G.; Dzierzynski, E. M.; Durner, G.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 992. b) Quinkert, G.; Schmalz, H.-G.; Walzer, E; Kowalczyk-Przewolka, T.; Duner, G.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 732. c) Quinkert, G.; Durner, G.; Baier, H. *Helv. Chim. Acta* **1985**, *68*, 1054. d) Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 637 and references cited.

39. Meyers, A. I.; Romo, D.*Tetrahedron Lett.* **1989**, *30*, 1745.

40. Moore, R. E.; Pettus, J.A., Jr.; Mistysyn, J. *J. Org. Chem.* **1974**, *39*, 2201.

41. a) Muller, D. G. *Science* **1981**, *212*, 1040. b) For other asymmetric routes to the Dictyopterenes see Dorsch, D.; Kunz, E.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3319 and Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron* **1991**, *47*, 1215. The latter obtains the divinyl cyclopropane **150** with >99:1 E:Z ratios.

42. For reviews in this area see: a) Arlt, D.; Jautelat, M; Lantzsch, R. *Agnew. Chem. Int. Ed. Engl.* **1981**, *20*, 703. b) Nauman, K. *Chemie der Synthetischen Pyrethroid Insektizide*, Springer Verlag: Berlin, 1981.

43. a) Elliot, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473. b) Elliot, M. *Pestic. Sci.* **1980**, *11*, 119. c) "Deltamethrine," a Rousell-Uclaf monograph, **1982**, pp. 25-66. For other recent asymmetric routes to deltamethrinic acid, see a) Krief, A.; Dumont, W.; Pasau, P. *Tetrahedron Lett.* **1988**, *29*, 1073, 1079, 1083. b) Kleschick, W. A.; Reed, M. W.; Bordner, J. *J. Org. Chem.* **1987**, *52*, 3168.

44. Tumlinson, J. H.; Gueldner, R. c.; Hardee, D. D.; Thompson, A. C.; Hedin, P. A.; Minyard, J. P. *J. Org. Chem.* **1971**, *36*, 2616. For other enantioselective syntheses of grandisol, see Hobbs, P. D.; Magnus, P. D. *J. Am. Chem. Soc.* **1976**, *98*, 4594; Mori, K. *Tetrahedron* **1978**, *34*, 915.

45. Meyers, A. I.; Fleming, S. A. *J. Am Chem. Soc.* **1986**, *108*, 306.

46. a) Hanessian, S.; Murray, P.J. *J. Org. Chem.* **1987**, *52*, 1170. b) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982**, *17*, 1311. c) Farina, F.; Martin, M.V.; Paredes, M. C. *Heterocycles* **1988**, *27*, 365. d) Feringa, B.L.; deLange, B. *Tetrahedron Lett.* **1988**, *29*, 5317.

47. a) Meyers, A. I. ; Busacca, C. A. *Tetrahedron Lett.* **1989**, *30*, 6973. b) Meyers, A. I. ; Busacca, C. A. *Tetrahedron Lett.* **1989**, *30*, 6977.

48. Bienz, S.; Busacca, C. A.; Meyers, A. I. *J. Am Chem. Soc.* **1989**, *111*, 1905.

49. Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294.

50. Bentacourt de Perez, R. M.; Fuentes, L. M.; Larson, G. L.; Barnes, C. L.; Heeg, M. J. *J. Org. Chem.* **1986**, *51*, 2039.

51. a) Tseng, C. C.; Terashima, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, *25*, 2. b) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974. c) Shiosaki, K.; Rapaport, H. *J. Org. Chem.* **1985**, *50*, 1229. d) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590. e) Arseni-Yadis, D.; Huang, P. Q.; Husson, H. P. *Tetrahedron Lett.* **1988**, *29*, 631. f) Skrinjar, M.; Wistrand, L. G. *Tetrahedron Lett.* **1990**, *31*, 1775. g) Polniziak, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. h) Ganem, B.; Liotta, L. *J. Syn. Lett.* **1990**, 503. i) Maryanoff, B. E.; McComsey, D. F. *J. Heterocyclic Chem.* **1985**, *22*, 911. j) Morlacchi, F.; Losacco, V. *J. Heterocyclic Chem.* **1976**, *13*, 165. k) Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250. l) Nordlander, J. E.; Njoroge, F. G.; Payne, M. S.; Warman, D. *J. Org. Chem.* **1985**, *50*, 3481.

52. For examples of concave systems which alkylate *exo*, see: Crimmins, M.T.; DeLoach, J.A. *J. Am. Chem. Soc.* **1986**, *108*, 8015 and references cited. For many examples of diastereofacial alkylation on 5,5-bicyclic ring systems see Evans, D. A. *Asymmetric Syntheses;* Academic, 1984; Vol. 3.

53. a) Meyers, A. I.; Ragauskas, A., unpublished results. b) Meyers, A. I.; Lefker, B. A., unpublished results. c) Meyers, A. I., Wallace, R. H., unpublished results.

54. Thottahil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140.

55. a) For the preparation of lactam **209a** see: Edwards, O. E.; Paton, J. M.; Benn, M. H.; Mitchell, R. E.; Watanatada, C.; Vohra, K. N. *Can. J. Chem.* **1971**, *49*, 1648. b) Matassa, V. G.; Jenkins, P. R.; Kumin, A.; Damm, L; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Israel J. of Chem.* **1989**, *29*, 321.

56. Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764. b) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta.* **1985**, *68*, 1373.

57. Meyers, A. I.; Williard, P. G.; Lefker, B. A., unpublished results.

58. Seebach, D. *Angew Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

59. a) Williard, P. G.; Carpenter, G. B. *J. Am Chem. Soc.* **1985**, *107*, 3345. b) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. c) Kallman, N.; Collum, D. B.*J. Am Chem. Soc.* **1987**, *109*, 7466. d) Geurink, P. J. A.; Klumpp, G. W.*J. Am Chem. Soc.* **1986**, *108*, 538. e) Jackman, L. M.; Scarmoutzos, L. M.; DeBrosse, C. W.*J. Am Chem. Soc.* **1987**, *109*, 5355. f) Jackman, L. M.; Smith, B. D.*J. Am Chem. Soc.* **1988**, *110*, 3829.

60. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am Chem. Soc.* **1982**, *104*, 1737; Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375.

61. Evans, D. A.; Britton, T. C.; Dorow, R. L; Dellaria, J. F. *J. Am Chem. Soc.* **1986**, *108*, 6395 and references cited. Also see: ref. 2, pp. 96-107.

62. Meyers, A. I.; Wallace, R. H.; Romo, D. unpublished results.

63. Liotta, D.; Durkin, K. A. *J. Am Chem. Soc.* **1990**, *112*, 8162.

64. Cieplak, A. S. *J. Am Chem. Soc.* **1981**, *103*, 4540.

65. a) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836 and references cited. b) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6691.

66. Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509.

67. Triebs, A.; Reitsam, F. *Liebigs Ann. Chem.* **1958**, *611*, 205; Cordell, G. A. *J. Org. Chem.* **1975**, *40*, 3161; Hosmane, R. S.; Hiremath, S. P.; Schneller, S. W. *J. Chem. Soc. Perkin Trans. I* **1973**, 2595.

68. Houk, K. N.; Wu, Y.; Mueller, P. H.; Caramella, P.; Paddon-Row, M. N.; Nagase, S.; Mazzochi, P. H. *Tetrahedron Lett.* **1990**, *31*, 7289 and earlier work cited.

69. a) Schleyer, P. v-R. *J. Am. Chem. Soc.* **1967**, *89*, 701. b) Huisgen, R.; Allinger, N. L.; Ooms, P. H. J.; Mingin, M. *J. Am. Chem. Soc.* **1980**, *102*, 3951. c) Seebach, D.; Zimmerman, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763.

70. For another possible example of the role of pyramidalization in facial selectivity, see Meyers, A. I.; Leonard, W. R.; Romine, J. L. *Tetrahedron Lett.* **1991**, *32*, 597.