Tetrahedron Vol 46, Nos 13/14, pp 4951–4994, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

DIASTEREOSELECTIVE CYCLOPROPANATIONS OF CHIRAL BICYCLIC LACTAMS LEADING TO ENANTIOMERICALLY PURE CYCLOPROPANES. APPLICATION TO THE TOTAL SYNTHESIS OF CIS-(1S, 3R)-DELTAMETHRINIC ACID AND R-(-)-DICTYOPTERENE C'†

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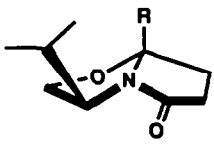
(*Received in UK* 18 *April* 1990)

Abstract - A novel diastereoselective cyclopropanation based on readily available chiral bicylic lactams (**1b-c, 6a-b**) has provided a number of enantiomerically pure cyclopropanes. Cyclopropanations of unsaturated lactams (**10a-h, 12-14**) were performed using sulfur ylides as well as a 3+2 cycloaddition-photolysis sequence and furnished the desired cyclopropane adducts (**16, 17, 19, 22**) in fair to excellent yields. In all cases involving sulfur ylides, cyclopropanations proceeded with a high degree of exo/endo diastereoselectivity (>90%). However, the mode of addition, exo vs endo, was found to be highly dependent on the angular substituent of the unsaturated lactam. In the case of diazoalkane cycloadditions, high regioselectivity was observed in all cases although exo/endo selectivity was governed by the diazoalkane employed. Diazoisopropane, being more reactive than diazomethane, normally led to lower diastereomeric ratios. Minor diastereomers could be readily removed by chromatography or in most cases by a single recrystallization to provide diastereomerically pure cyclopropyl bicyclic lactams (**16, 17, 19, 22**). Applications of this methodology to compounds of biological significance was exemplified by an asymmetric, total synthesis of cis-(1S, 3R)-deltamethrinic acid (**34**) and R-(-)-dictyopterene C' (**42**) in high enantiomeric purity.

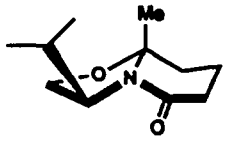
Over the past several years, a number of reports from these laboratories have demonstrated the synthetic utility of chiral bicyclic lactams **1-3**. These systems have provided access to a number of enantiomerically pure materials bearing quaternary carbon centers including cyclobutanes,[1a] cyclopentenones,[1b] cyclohexanes,[1c] and cyclohexenones·[1d] Furthermore, this methodology has been exploited in both formal and total syntheses of an array of natural products including (+)-

† This paper is dedicated to Professor W. David Ollis on the occasion of his 65th birthday.

aspidospermine,[2a] (-)-abscisic acid,[2b] and (+)-$\Delta^{9(12)}$-capnellene.[2c] In addition, a novel asymmetric synthesis of cyclopropanes[3a] based on these versatile templates was utilized in the synthesis of cis-(1S, 3R)-deltamethrinic acid[3b] and R-(-)-dictyopterene C'. We now wish to disclose a detailed account of this cyclopropanation methodology and other related studies.



1a: R = Ph
b: R = Me
c: R = H



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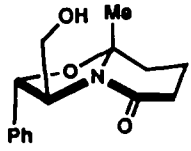

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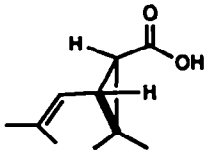
The dual importance of devising stereoselective transformations to deliver enantiomerically pure cyclopropanes can be attributed to the numerous naturally occuring substances which contain this ring system and the ability of the cyclopropane nucleus to undergo a number of interesting and useful rearrangements to provide more complex systems. Examples of the former include the potent insecticide precursor chrysanthemic acid **4**[4] and the sex attracting substance sirenin **5**[5] while examples of the latter include the vinyl cyclopropane rearrangement[6] and the divinyl cyclopropane-Cope rearrangement.[7] To date, only relatively few general synthetic approaches exist for the procurement of enantiomerically pure cyclopropanes.[8] For these reasons, the need for viable routes to these systems becomes apparent.



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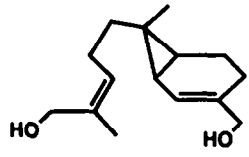

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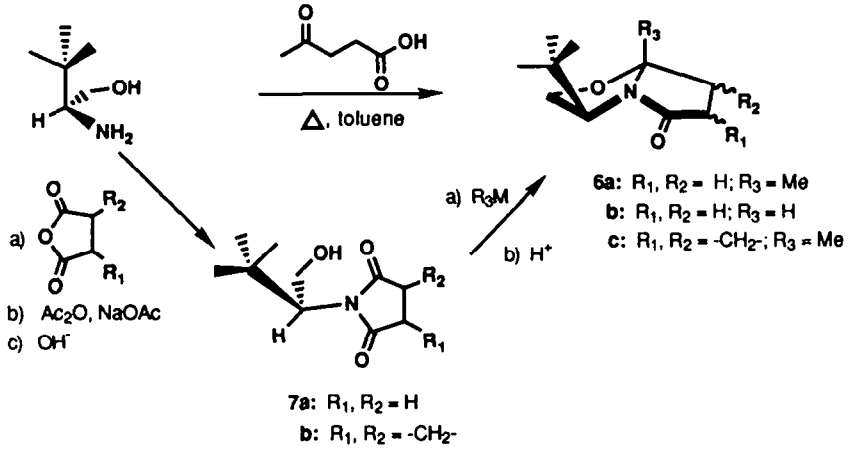
Formation of Bicyclic Lactams (4-oxa-1-azabicyclo[3.3.0]nonan-8-ones)

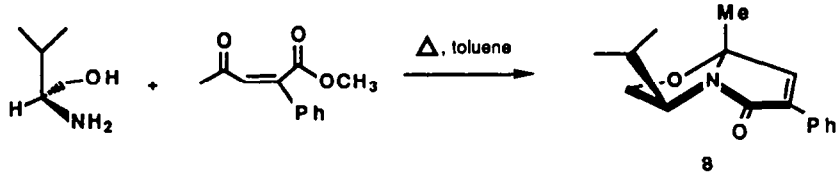
The chiral bicyclic lactam **1b** used in this study was readily formed by cyclodehydration of equimolar amounts of levulinic acid with (L)-valinol as previously described.[9] In a similar fashion the tert-leucinol derived bicyclic lactam **6a** was prepared in 92% yield from levulinic acid and (L)-tert-leucinol. This bicyclic lactam, unlike **1b** was a crystalline compound and the presence of the t-butyl group greatly simplified the ^{1}H-NMR spectrum as compared to the (L)-valinol derived lactam.

The angular hydrogen lactam **1c** was formed by the fusion-reduction-cyclization sequence which has been previously described.[10] However in the case of the (L)-tert-leucinol derived lactam, the fusion reaction led to large amounts of polymeric material. Recourse to the stepwise imide formation described by Mukaiyama[11] followed by the usual reduction-cyclization sequence

provided the desired angular hydrogen bicyclic lactam **6b** in 71% overall yield. This sequence also allowed direct entry into the angular methyl cyclopropyl lactams **6c** by use of cis-1,2-dicarboxy cyclopropyl anhydride. This procedure led to a 1:1 mixture of exo/endo cyclopropyl lactams **6c** which provided sufficient material to allow characterization of the minor diastereomers obtained by cyclopropanation methods (vide infra) and therefore accurate diastereomeric ratio determination was possible.



The α-phenyl unsaturated lactam **8** was obtained in 60% yield from the cyclodehydration of methyl-4-oxo-2-phenyl-pent-2-enoate with (L)-valinol.[12]



Unsaturated Bicyclic Lactams

The α-carbomethoxy and α,α-dithiomethyl bicyclic lactams (**9c-f**) were prepared by metalation followed by acylation or sulfenylation using methyl chloroformate and dimethyl disulfide, respectively (Table I). The unsubstituted and α-carbomethoxy lactams were then converted to the α,β-unsaturated derivatives **10** by a metallation-selenation-oxidative elimination sequence[13] and proceeded in good overall yields. For the lactams **9d-e**, conversion to the α-thiomethyl unsaturated lactams **10d-e** was accomplished using cuprous triflate-benzene complex.[14]

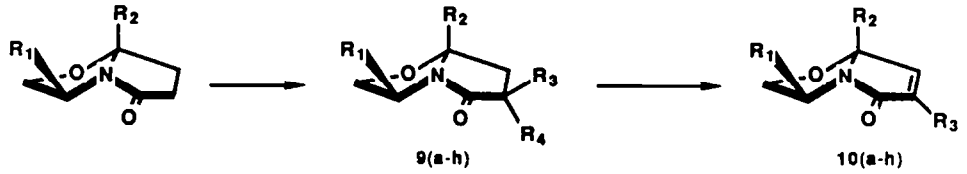
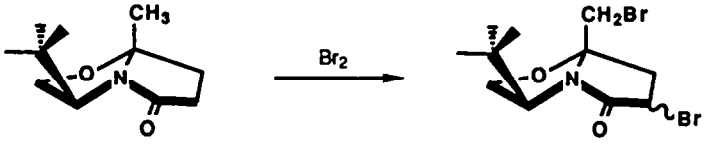


Table I. α,β-Unsaturated Bicyclic Lactams **10**

	R_1	R_2	R_3	R_4	% yield, overall	$[\alpha]_D$ (deg)	mp (°C)	methods
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**

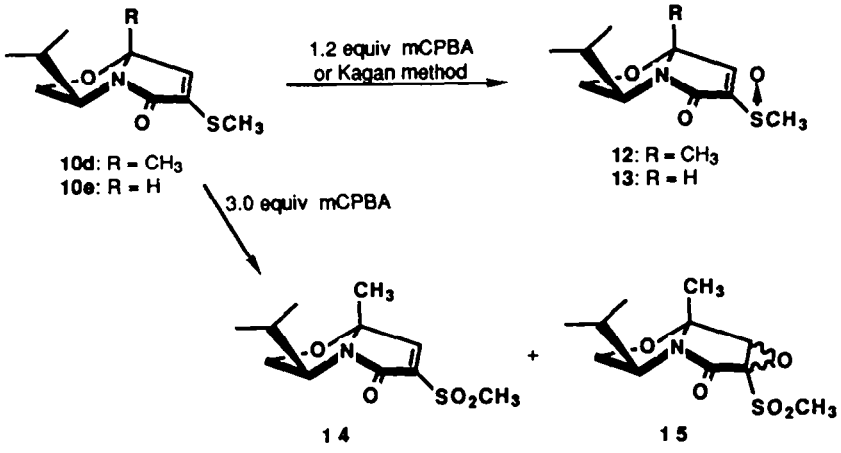
Methods: **A)** LDA/THF/-78°C; PhSeBr/THF/-78°C. **B)** H_2O_2/py./CH_2Cl_2/0°C -> RT. **C)** LDA/THF/-78°C; MeI/THF/-78°C. **D)** s-BuLi/THF/-78°C; $ClCO_2CH_3$/THF/-78°C; AcOH. **E)** O_3/CH_2Cl_2/diisopropyl amine/-78°C -> RT. **F)** LDA/THF/-78°C; CH_3SSCH_3/THF/ 0°C; $[Cu_2C_6H_6(CF_3SO_3)_2]$/diisopropylethylamine/C_6H_6/reflux.

Although other methods to introduce the unsaturation were considered and attempted including bromination or iodination followed by elimination, these methods proved to be less satisfactory. In the case of bromination of the bicyclic lactam **6a**, bromine was introduced at both the α-position and angular methyl position to give the dibrominated lactam **11**. This result is not unusual in view of the acyl iminium intermediates which are known to arise from these bicylic lactams.[15]



Oxidation of the α-thiomethyl unsaturated lactams **10d** and **10e** to the α-sulfoxide derivatives was carried out in two fashions. First, oxidation with 1.2 equiv. of meta-chloroperbenzoic acid (mCPBA) provided the α-sulfoxides **12** and **13** as 1:1 mixtures of diastereomers at sulfur in nearly quantitative yield. Alternatively, asymmetric oxidation of **10d** according to the method of Kagan[16] provided a 9:1 ratio of sulfoxide diastereomers **12** in 61% yield. The α-sulfonyl

unsaturated lactam **14** was obtained by treatment of the α-thiomethyl lactam **10d** with 3.0 equiv. of mCPBA. However, this lactam was obtained as a 2:1 ratio containing the epoxides **15** as a 3:1 ratio of endo/exo diastereomers.



Cyclopropanations with Trimethylsulfoxonium Ylide

With the requisite α,β-unsaturated lactams **8, 10** in hand, the diastereoselectivity of cyclopropanations with trimethylsulfoxonium ylide was studied using procedures described by Corey.[17] To our delight, all cyclopropanations proceeded with high diastereoselectivity and in fair to good yields (Table II). *However, it is important to note that a simple change of angular substitutent (R_2) in the lactam from methyl to hydrogen leads to a complete reversal in endo-exo (16:17) selectivity.* The asymmetry at sulfur (entries **d** and **g**) had no bearing on the diastereoselectivity observed.

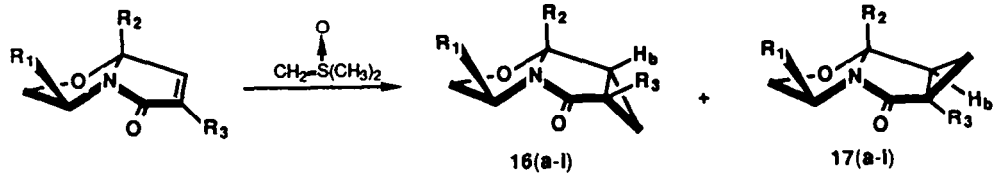


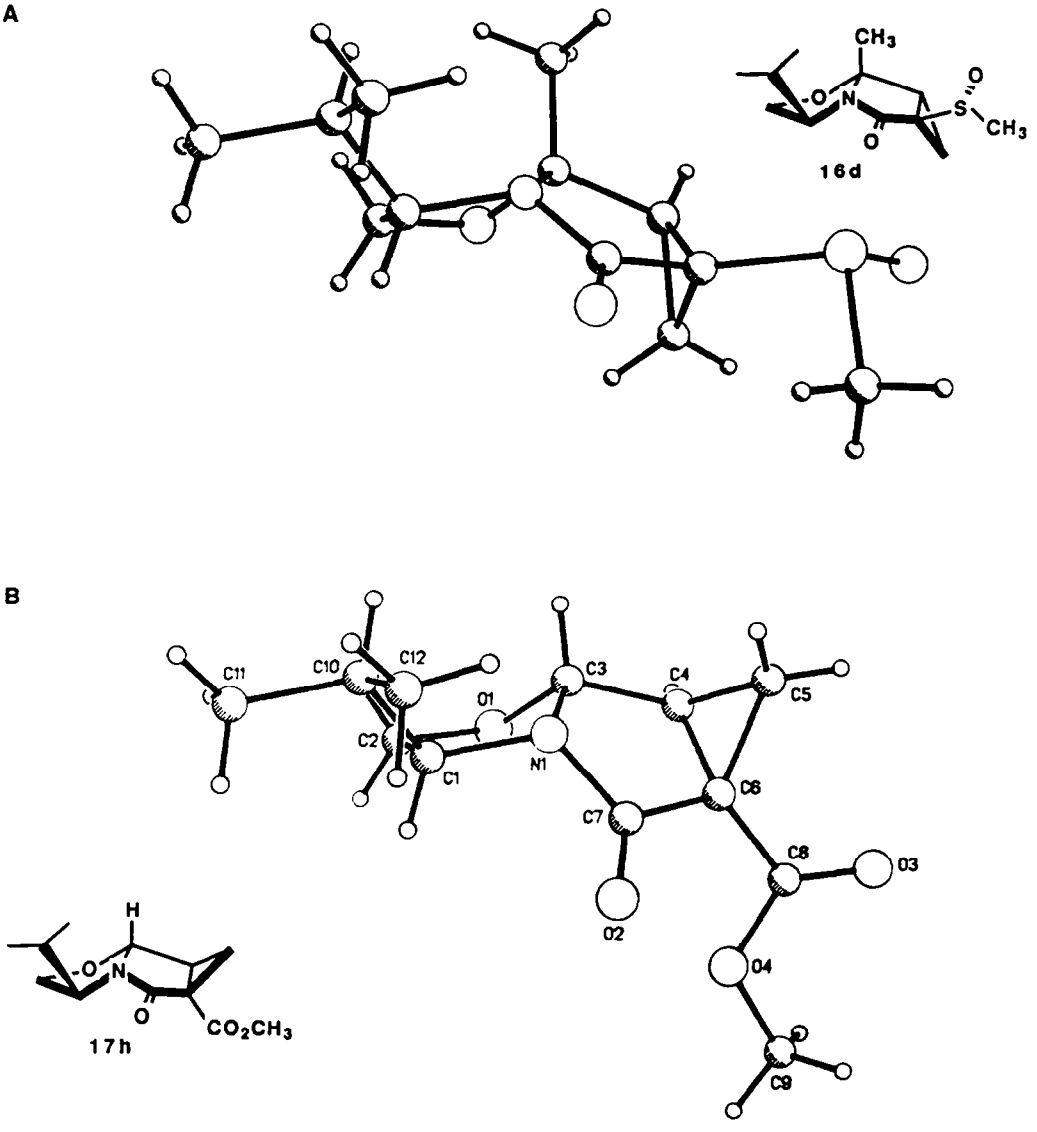
Table II. Cyclopropyl Lactams **16,17** From Trimethylsulfoxonium Ylide

	R_1	R_2	R_3	% yield	16:17	% de	mp (°C)[a]	$[\alpha]_D$[a,b] (deg)
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. [b]Concentration and solvents for rotation data are provided in the experimental.

Single crystal X-ray analysis of the cyclopropyl adduct **16d** (Figure 1A) confirmed that endo entry of the sulfoxonium ylide was favored for the angular methyl lactams (**16a-f**). Further support for endo entry in cyclopropyl adduct **16f** was gathered by conversion of this compound into R-(-)-Dictyopterene C' (vide infra). The ^{1}H-NMR spectra of the cycloadducts derived from the unsaturated lactams **10e-f, h** showed small coupling (^{3}J 0-1.3 Hz) between the angular hydrogen (H_a; R_2=H_a) and the β-proton (H_b) of the lactam ring (~90° dihedral angle; judging from models) as expected for the exo adducts **17**. Had endo entry predominated to give the endo adducts **16**, a larger coupling constant (^{3}J 6-8 Hz, ~0° dihedral angle) would be observed. This was confirmed by synthesis of the endo cyclopropyl lactam **17i** by addition of diazomethane to the unsaturated bicyclic lactam **10h** followed by photolysis. This sequence provided a 1:1 ratio of exo/endo cyclopropane adducts (Table III; entry **h**). A larger coupling constant (^{3}J 5.3 Hz) was clearly visible in the ^{1}H NMR for the isolated endo adduct **17i**. The exo stereochemistry was also confirmed by single crystal X-ray analysis in the case of the α-carbomethoxy cyclopropyl adduct **17h** (Figure 1B).

Figure 1. X-ray structures of cyclopropyl lactams **16d** (A) and **17h** (B).



3+2 Cycloadditions of Diazoalkanes and α,β-Unsaturated Bicyclic Lactams/Photolysis of Pyrazolines

The 3+2 cycloaddition of diazoalkanes and α,β-unsaturated bicyclic lactams was also investigated. Both diazomethane[18] and diazoisopropane[19] underwent cycloaddition and provided pyrazolines **18** with high regiochemistry but varying amounts of stereochemical control (Table III).

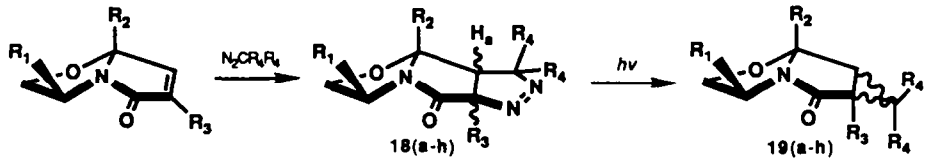


Table III. Cycloadducts **18, 19** From Lactams **10, 12**

					18	**19 (photolysis)**			
	R_1	R_2	R_3	R_4	% yield	% yield	% de	mp (°C)[a]	$[\alpha]_D$ (deg)[a,b]
a	i-Pr	CH_3	$SOCH_3$	H	91	dec	-	-	-
b	i-Pr	CH_3	SCH_3	H	55 (28% sm)	95	90	83-85	- 21.1
c	i-Pr	CH_3	CH_3	H	46 (45% sm)	93	90	oil	+36.7
d	i-Pr	CH_3	CH_3	CH_3	no reaction	-	-	-	-
e	i-Pr	CH_3	SCH_3	CH_3	-[c]	67	90	71-73	+9.9
f	t-Bu	CH_3	H	CH_3	~100	88	0[d]	-	-
g	t-Bu	CH_3	H	H	~100	59	>98[e]	72-72.5	+72.9
h	t-Bu	H	H	H	~100	50	0[f]	-	-

[a] Physical data are for pure, major diastereomers. [b] Concentrations and solvents for rotation data are provided in the experimental. [c] No pyrazoline was isolated. The cyclopropyl adduct was formed directly under the reaction conditions. [d] Spectral data for exo-**19f**: ^{1}H NMR ($CDCl_3$,300MHz) δ: 0.91 (s, 9H), 1.16 (s, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 1.87 (d, 1H, J=6.0 Hz), 2.11 (d. 1H, J=5.9 Hz), 3.69-3.81 (m, 2H), 4.05 (t,1H, J=7.1 Hz); IR (neat) 1721 cm^{-1}. [e] Identical in all respects to the cyclopropyl adduct obtained using trimethyl sulfoxonium ylide (Table II, Entry **16f**). [f] Physical and spectral data for endo-**19h**: mp 67-70°C; ^{1}H NMR ($CDCl_3$,300MHz) δ: 0.92 (s, (H), 0.99-1.04 (m, 1H), 1.91-1.98 (m, 1H), 2.11-2.17 (m, 1H), 3.45 (dd, 1H, J=6.6, 7.8 Hz), 3.90 (dd, 1H, J=6.5, 9.0 Hz), 4.12 (app t, J=8.5 Hz), 5.38 (d, 1H, J=5.0 Hz); ^{13}C NMR (300MHz) δ: 9.7, 13.8, 24.9, 26.1, 34.2, 62.7, 70.7, 91.8; IR (film) 1702 cm^{-1}.

In the cycloaddition of diazomethane and diazoisopropane with the unsaturated lactam **10g**, the exo/endo diastereoselectivity of the cycloaddition changed from >99% to 0%, respectively (Table III, entries f and g). In the case of diazomethane a single regio- and stereoisomer was formed. The regiochemical assignment was based on the ^{1}H-NMR splitting pattern of H_a (ddd) in **18g** indicating an adjacent methylene group. The opposite regiochemistry would certainly result in a different splitting pattern (d) for H_a. The stereoselectivity was determined to be endo by conversion to the cyclopropane adduct **19g** which was found to be identical to the cyclopropane adduct obtained using trimethylsulfoxonium ylide (Table II; entry **16f**).

The regioselectivity as well as the difference in stereoselectivity observed between diazomethane and diazoisopropane is readily rationalized by frontier molecular orbital theory.[20] The magnitude of the orbital coefficients for the dipole and dipolarophile explain the observed regioselectivity and is the normal mode of addition of diazoalkanes to electron deficient dipolarophiles (Figure 2). Dialkyl diazo compounds are known to be much more reactive 1,3 dipoles due to the electron donating ability of the alkyl groups resulting in a raising of the energy of

the HOMO. Since the important orbitals for this 3+2 cycloaddition are the LUMO of the dipolarophile and the HOMO of the dipole and $\Delta E_1 > \Delta E_2$ (Figure 3), this results in an acceleration of reaction rate and thus in a lowering of the selectivity observed in the case of diazoisopropane in comparison to diazomethane.

Figure 2. Orbital coefficients for the dipole HOMO and the dipolarophile LUMO.

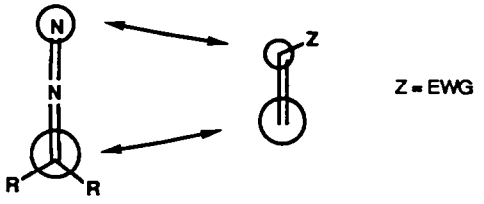
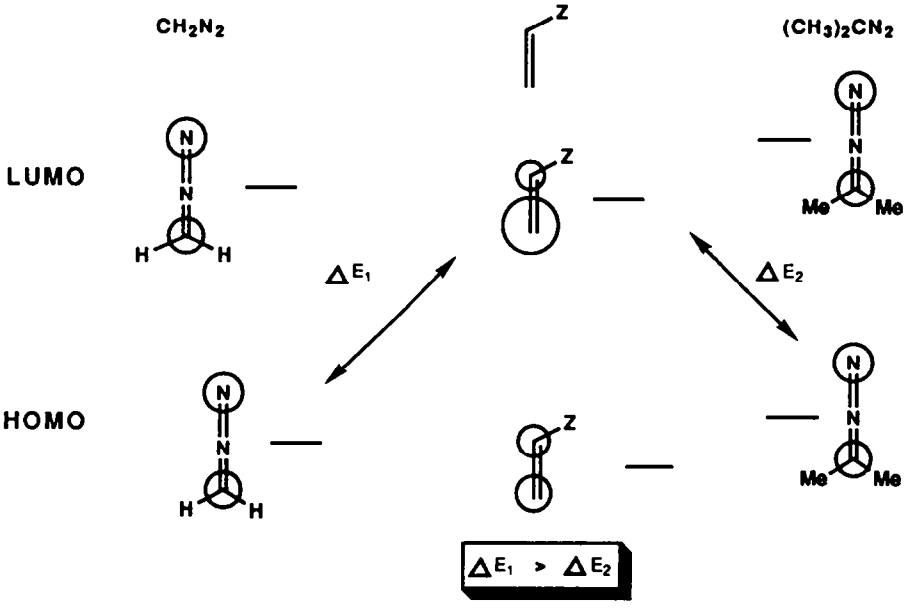
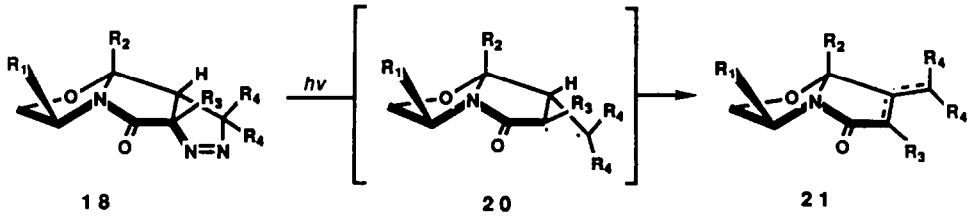


Figure 3. Frontier oribtals for a dipole-HOMO controlled reaction.



Photolysis of the pyrazoline adducts **18** provided the cyclopropyl bicyclic lactams in fair to excellent yields. In some cases, significant amounts of unsaturated lactams **21** were obtained in addition to the desired cyclopropanes. This may result from 1,2-hydrogen atom migration in the intermediate diradical species **20**.[21]

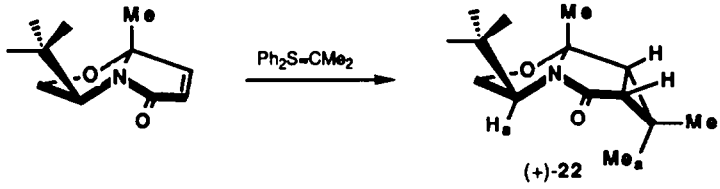


18 20 21

Thermolysis of the pyrazolines **18** was also attempted but in most cases this method led to greater quantities of the unsaturated lactams **21**. Thermolytic decomposition of diazomethane derived pyrazolines has been reported to give good yields of β-methyl unsaturated enones.[22]

Cyclopropanation With Diphenyl Sulfonium Isopropylidene

Cyclopropanation of the unsaturated lactam **10g** was also performed with diphenylsulfonium isopropylidene[23] and gave the gem-dimethyl cyclopropane adduct (+)-**22** in 94% yield and >99% de (vpc). Stereochemical assignment was easily made from homonuclear NOE experiments. Irradiation of the syn methyl group (Me_a) showed enhancement of the oxazolidine ring proton H_a which would be expected for the endo cyclopropyl adduct but not the exo isomer. Other sulfonium ylides have been utilized in cyclopropanations of these unsaturated lactams and results of these studies will be described in future reports.

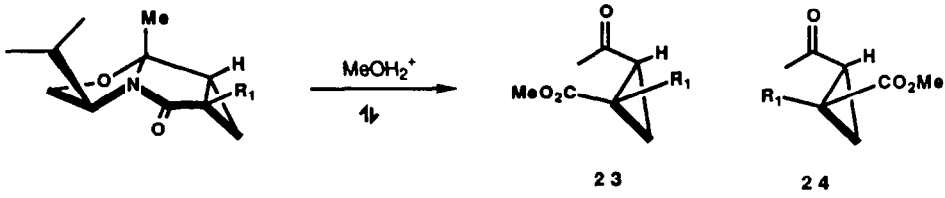


(+)-22

Removal of Chiral Auxiliary-Formation of Chiral Cyclopropanes

Chiral auxiliary removal from the cyclopropyl bicylic lactam adducts was carried out in each of two manners. First, hydrolysis in 10% sulfuric acid-methanol led to the cyclopropyl methyl esters **23** in good yields (Table IV). However, 96 h were required for completion in all cases and in one case (entry **a**) the epimer **24a** was isolated as a minor component. The quantity of **24a** produced was dependent on reaction time and complete epimerization was realized upon re-exposing **23a** to the reaction conditions for 5 days.

Table IV. Cyclopropane Esters **23, 24**

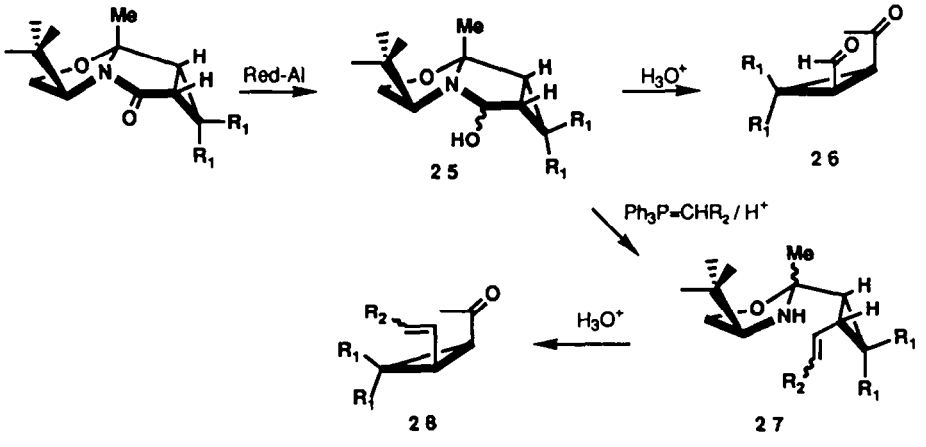


23 **24**

	R_1	% yield	$[\alpha]_D$[a] (deg)	mp
a	H	88	+48.7	oil
b	CO_2Me	86	-149.7	72-73 °C
c	C_6H_5	81	-175.7	oil

[a] All rotations taken as *c* 1-4 in THF.

The second method to remove the chiral auxiliary involved reduction of the lactam to the carbinolamine **25** using Red-Al followed by mild acid hydrolysis to give the ketoaldehydes **26**. Alternatively, the carbinolamine could be subjected to Wittig reaction conditions to give the intermediate oxazolidines **27** which on hydrolysis provided the cyclopropyl keto olefins **28**. These latter methods will be discussed further in the context of the synthesis of cis-(1S, 3R)-deltamethrinic acid and dictyopterene C' (vide infra).



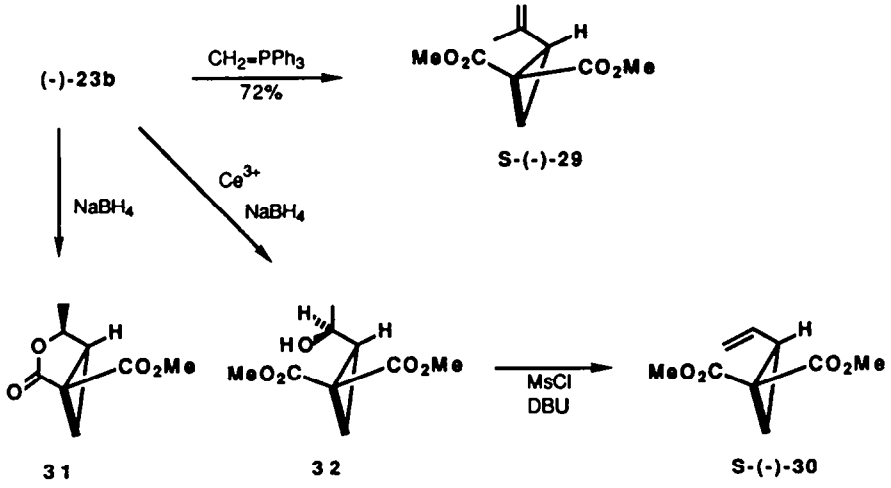
25 **26** **27** **28**

Asymmetric Synthesis of Vinyl Cyclopropanes

In order to ascertain the optical purity of the above cyclopropanes the known vinyl cyclopropanes **29** and **30** were prepared. These useful chiral synthons were employed in the total synthesis of (-)-methyl jasmonate,[24] (+)-confertin,[25] (-)-norgestrel,[26] and (+)-estrone.[27]

Furthermore, the absolute configuration of **29** and **30** is firmly established by X-ray crystallography techniques.

Wittig olefination of the the methyl ketone **23b** gave S-(-)-**29**, the opposite antipode of that reported by Quinkert,[25a] in 72% yield. Isolation and purification, however, proved difficult due to reaction by-products and the sensitivity of **29** to silica. This is revealed in the rotation value (-119° compared to Quinkert's[25a] values of +128°) however, this value is consistent with high optical purity (93% ee). The diastereomeric purity of the precursor (-)-**16b** (>99%; NMR and HPLC) provides a more reliable source of optical purity of the final product S-(-)-**29** compared to the rotation values obtained from the polarimeter. However, we do not imply that Quinkert's compound is of lower optical purity. It simply means we were not able to match his rotation data which is probably due to our polarimeter reliability. It should be noted that the opposite rotation confirms that cyclopropanation of the α, β-unsaturated bicylic lactam **10c** occurs from the endo face.

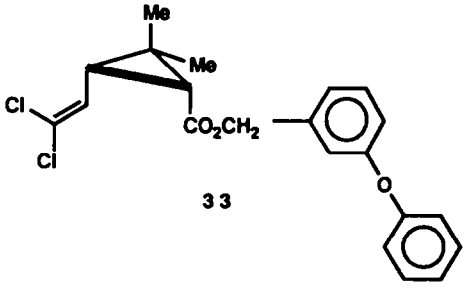


Formation of the vinyl cyclopropane **30** was not straightforward. Treatment of the methyl ketone **23b** with $NaBH_4$ in methanol provided the lactone **31** as a single diastereomer in 89% yield rather than the desired carbinol **32**. Attempts to open the lactone ring to the vinyl derivative were unsuccesful. Whereas lithium diisopropylamide returned the lactone unchanged, use of tert-butyl lithium resulted in decomposition. It was subsequently found that lactone formation could be circumvented during the reduction step by adding cerium trichloride to the reaction mixture. Conditions reported by Luche[28] (water-ethanol, 1.5:1) gave alcohol **32** in five fold excess over the lactone. Importantly, omission of cerium with the same solvent system delivered only the lactone **31**. Upon reversing the aqueous to organic solvent ratio, the lactone could no longer be detected by 270 MHz ^1H NMR and thus provided the alcohol **32** in 99% yield. The stereochemistry of the reduction was the same as the lactone **31** by interconvertive comparison.

With the desired carbinol **32** in hand, methods for conversion of the carbinol to the vinyl cyclopropane **30** were studied. Burgess' reagent is an exceptionally mild dehydrating agent and one example has been reported that removes water adjacent to a cyclopropane ring.[29] Admixture of the Burgess reagent with **32** in refluxing benzene produced a 1:1 mixture of the desired urethane and lactone **31**, and thus could not be employed. Phosporous oxychloride and pyridine, which proceeds through an E_2 elimination pathway, did not yield any product as might be anticipated from the rather harsh conditions. Mitsunobu type reaction[30] using triphenyl phosphine, diethyldiazodicarboxylate, and diazabicycloundecane (DBU) was more fruitful giving **30** in 40% yield. However, due to the extensive chromatography that is required for purification, another method was sought. Efforts to activate **32** as its tosylate failed under standard conditons. Recourse to the more reactive sulfene generated from methane sulfonyl chloride and triethylamine afforded a 99% yield of the corresponding mesylate. Elimination was accomplished utilizing DBU[31] as base to provide vinyl cyclopropane **30** in 48% overall yield from methyl ketone **22b**. Due to the volatility of **30** solvent removal was difficult and thus the rotation ($[\alpha]_D$ -46.1°) when compared to Quinkert's value[25a] ($[\alpha]_D$ +54.6°) was low.

Asymmetric Synthesis of cis-(1S, 3R)-Deltamethrinic Acid

Pyrethroids constitute an important class of insecticides due to their photodegradability and low mammalian toxicity.[32] Two such pyrethroids, cypermethrin **33** and deltamethrin **35**, are in wide commercial use owing to their superior insecticidal activity and photostability.[33] The greatest insecticidal activity of deltamethrin **35** is exhibited by the cis-(1R, 3S) cyclopropyl isomer.



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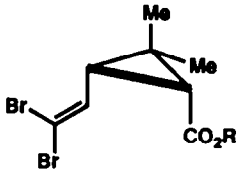
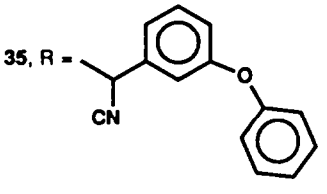


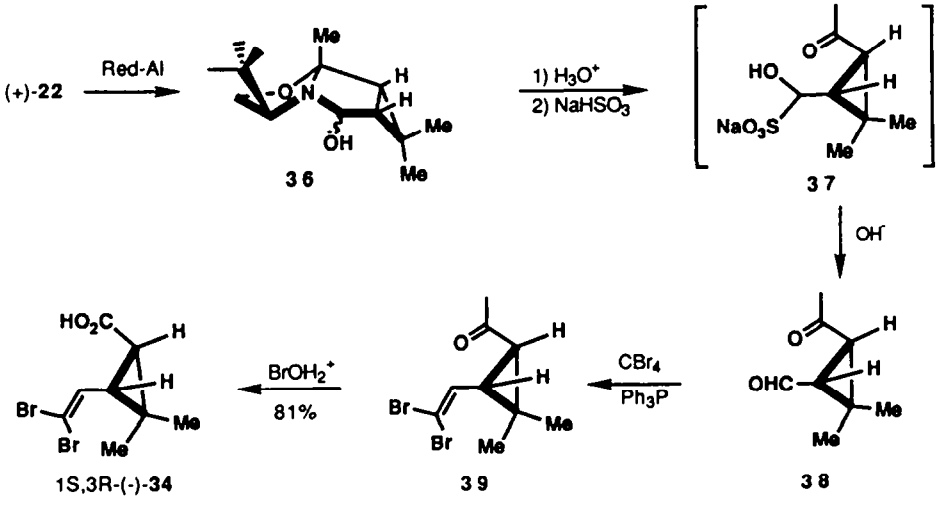
34, R = H



The requisite gem-dimethyl cyclopropyl adduct (+)-**22** for the asymmetric synthesis of these pyrethroids was obtained in high diastereomeric purity with diphenylsulfonium isopropylidene (>99% de, vide supra). This level of diastereoselectivity was determined by vpc based on

comparison with the 1:1 exo/endo ratio obtained using diazoisopropane (Table III, entry **f**). With these results, an efficient entry into a representative example of these insecticidal substances was investigated in order to further demonstrate the utility of this methodology. For this purpose, deltamethrinic acid **34**, the immediate precursor of deltamethrin **35**, was chosen as a target. The cyclopropyl adduct (+)-**22** possesses the desired cis configuration for the synthesis of **34**. Although several synthetic methods[32b] exist to obtain deltamethrinic acid **34**, with most methods employing a cyclopropanation reaction as the key step, only very few are enantioselective[32b,34] or asymmetric.[35]

Initial studies to remove the chiral auxiliary from the cyclopropyl adduct (+)-**22** were directed towards acid hydrolysis to give the corresponding cyclopropyl keto acid. However, this led to decomposition undoubtedly due to the tertiary carbocation readily formed on protonation of the lactam carbonyl and cyclopropane ring opening. A more fruitful approach involved lactam reduction with Red-Al. The reaction was quenched prior to complete consumption of (+)-**22** or a deficiency of hydride was used in order to prevent overreduction and thus yields are based on recovered cyclopropyl adduct (+)-**22**. The intermediate carbinolamine **36** was then subjected to hydrolytic conditions using a biphasic solution of aqueous tetrabutylammonium dihydrogen phosphate and methylene chloride. This sequence provided the volatile keto aldehyde **38** which was handled in either of two fashions. For characterization purposes, the ketoaldehyde could be isolated pure by conversion to its sodium bisulfite adduct **37** and after extraction with ether to remove any organic byproducts, the ketoaldehyde was re-extracted from the aqueous phase after adjusting the pH to 9.[36] However, for preparative purposes the crude ketoaldehyde **38** was directly converted to the dibromoolefin **39** by treatment of the hydrolysis mixture with the orange triphenyl phosphine-carbon tetrabromide reagent reported by Ramirez.[37] In this manner the dibromoolefin **39** was isolated pure in 42% overall yield from the gem-dimethyl cyclopropyl adduct (+)-**22**.



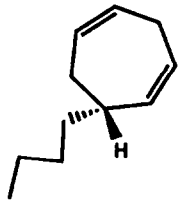
Transformation of the dibromoolefin **39** to deltamethrinic acid **34** was carried out using standard haloform conditions[38] and provided pure cis-(1S, 3R)-deltamethrinic acid in 81% yield after sublimation ($[\alpha]_D^{22}$ -16.8°). Comparison with an authentic sample obtained from Roussel-Uclaf ($[\alpha]_D^{22}$ 17.3°) indicated that the pyrethroid precursor had been obtained in high optical purity (97% ee). A single diastereomer (+)-**22** (>99% de, *via* vpc) was used in this synthetic sequence and thus a more accurate measure of optical purity is based on the diastereomeric purity rather than the optical purity as determined by the polarimeter. It should be noted that the sign of rotation of our product confirms that the diphenyl sulfonium isopropylidene entered in an endo fashion during the cyclopropanantion step. Due to the use of L-(S)-tert-leucinol, the optical antipode of the most biologically active enantiomer was obtained. It may be assumed that use of D-(R)-tert-leucinol would provide the desired enantiomer.

Asymmetric Synthesis of Dictyopterenes C and C'

The dictyopterenes are a class of non-isoprenoid C_{11} odoriferous hydrocarbons first isolated by Moore[39] from *Dictyopteris plagiogramma* and *D. australis*, two species of brown seaweed found on the sublittoral reef flats surrounding the Hawaiian islands. Due to heavy surf, large amounts of the seaweed are deposited on the shores in the summer months and the odor of *Dictyopteris* can be detected in the air around the beaches. In Hawaii, the freshly chopped seaweed, known as *limu lipoa* (meaning "seaweed gathered from the deep"), is used as a condiment with raw fish and other foods. The essential oil of these brown seaweeds consists of two interesting dialkenylcyclopropanes, dictyopterenes A **40** and B **43** (major constituents) and two related cycloheptadienes dictyopterenes C' **42** and D' **44** (minor constituents). Dictyopterene C **41**, a compound not found in the essential oil, is the proposed biogenic precursor of dictyopterene C' **42**.[40] These compounds which are released by the eggs of Dictyopteris species exhibit remarkable physiological activity including their sperm attracting ability.[41] Recently, dictyopterene C' was detected in a freshwater lake[42] and in a *dictyopteris* species found in Japan.[43]

40

41



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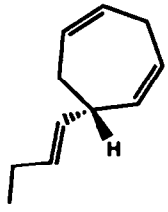
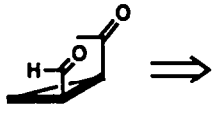


44

Although a number of syntheses of dictyopterene C' have been reported[44], only two have led to enantiomerically enriched products. Genet and Colobert[45a] employed a chiral Pd (0) coupling while Jaenicke, et. al.[45b] relied on a resolution of the intermediate cyclopropyl lactone **45** in their synthesis. At the outset, it was thought that this lactone could be intercepted starting from the cyclopropyl lactam (+)-**16f**. However, it was found that the ketoaldehyde **46** obtained by Red-Al reduction and hydrolysis of the lactam **16f**, was quite volatile and as a result could only be isolated in very low yields. Immediate reduction of the crude ketoaldehyde with sodium borohydride led to low yields of the diol **48**. Attempted Wittig reaction of the crude ketoaldehyde also led to disappointing yields (~10%) of the desired cyclopropyl olefin **49** along with ~8% of competing aldol reaction products.

45



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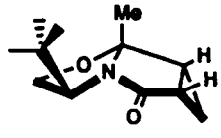
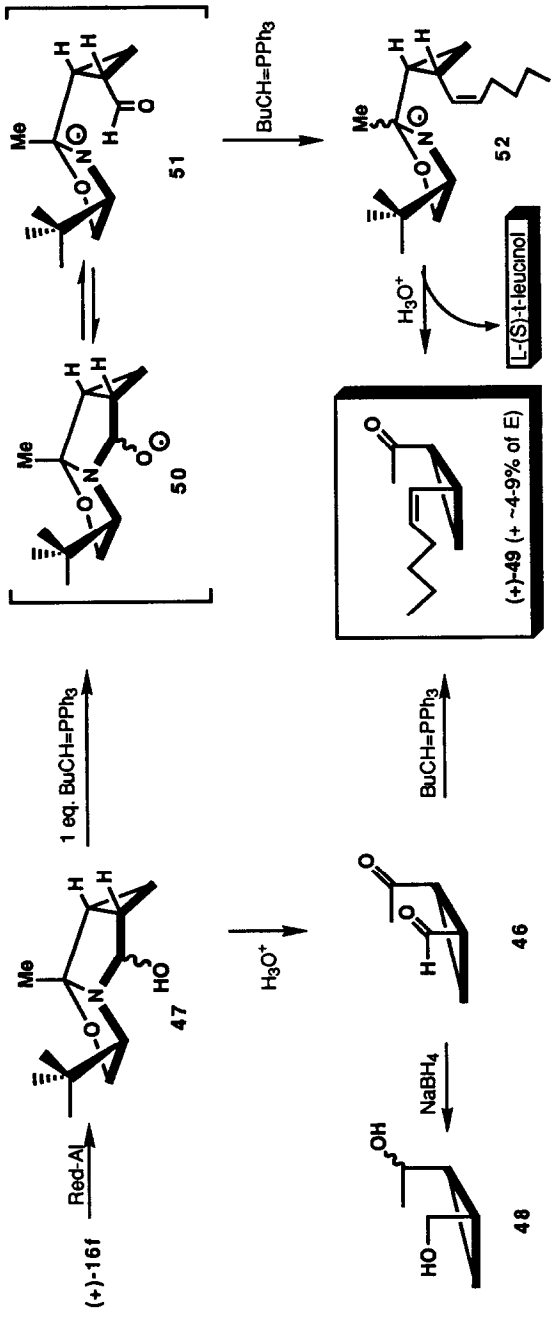


(+)-16f

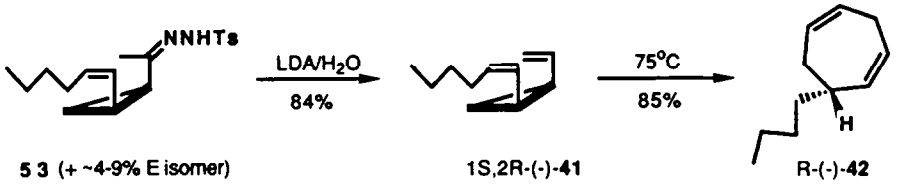
It was anticipated that direct Wittig reaction on the carbinolamine **47** would circumvent both the volatility problem and competing aldol processes which led to low yields of the desired olefin **49**. Wittig reactions have been carried out on both lactols[46] and carbinolamines[47] and have led to good yields of olefination products. The only requirement for such a process to be succesful is that an appreciable concentration of the ring-opened aldehyde **51** be present after deprotonation of the alcohol with the first equivalent of phosphorane. This process was indeed brought to fruition. Treatment of the carbinolamines **47**, obtained by Red-Al reduction of the lactam **16f**, with 2.2 equiv.


(+)-16f
Red-Al
47
1 eq. BuCH=PPh3
50
51
BuCH=PPh3
52
H3O+
L-(S)-t-leucinol
H3O+
46
BuCH=PPh3
(+)-49 (+ ~4-9% of E)
NaBH4
48

of a "salt-free" preparation of pentenyl triphenylphosphonium ylide[48] provided the oxazolidines **52**. This indicates that a significant concentration of the aldehyde **51** exists even at 0°C. This may be attributed to the inherent strain imposed by the tricyclic system which favors the ring-opened aldehyde **51**. That a mixture of epimeric oxazolidines **52** was obtained is undoubtedly due to the facile ring opening-ring closure of the oxazolidine nucleus. The oxazolidine intermediates were not isolated but subjected directly to hydrolytic conditions with aqueous tetrabutylammonium dihydrogen phosphate. In this manner, the cyclopropyl olefin **49** was obtained pure in 51% overall yield (3 steps) from the cyclopropyl lactam **16f** after micro-distillation. However, vpc analysis indicated the presence of 9% of the E isomer while ^{1}H NMR integration of the vinyl protons indicated 4% of the E isomer. These values are within instrumental limits of detection and error.

A temperature study was performed to determine if the Z/E ratio could be further increased. However, it was found that the Wittig reaction on **50-51** only took place at an appreciable rate when performed at 0°C. Temperatures lower than -10°C resulted in no reaction after 2h, and reaction at -10°C proceeded only slowly. Direct *in situ* treatment of the aluminated carbinolamines (from Red-Al reduction) with the phosphonium ylide occured only when warmed to room temperature and as a result led to a lower Z/E ratio of geometrical isomers (83:17 respectively, vpc).

Having obtained the desired olefin **49** in good yield and with a Z/E ratio of 93:7±2%, a method for conversion of the methyl ketone functionality to Dictyopterene C **41** was next considered. The Shapiro reaction was found to be an efficient method to perform this task. Extensive experimentation with various bases including n-butyl lithium,[50] methyl lithium,[51] and lithium diisopropylamide[52] indicated the latter to be the best base for effecting this transformation. In the event, conversion of the keto olefin **49** to its tosyl hydrazone **53** (85% isolated yield) followed by base catalyzed elimination with excess LDA at room temperature gave the known dictyopterene C **41** in 84% yield and in 83% ee ($[\alpha]_D^{20}$ -104°; lit. $[\alpha]_D^{25}$ -117.6° for 97:3 Z/E olefin ratio[45b, 49]). Although a single cyclopropyl bicyclic lactam diastereomer (+)-**16f** was utilized in this sequence, due to the Wittig reaction approximately 4-9% of the E olefin isomer was carried through to dictyopterene C **41**. Thus the lower rotation value obtained is due to contamination from the E isomer rather than the other enantiomer.



53 (+ ~4-9% E isomer) 1S,2R-(-)-**41** R-(-)-**42**

Cope rearrangement[45b] of dictyopterene C **41**, which is known to proceed stereospecifically via a cis-endo transition state,[53] gave, as reported, R-(-)-dictyopterene C' **42** in 85% isolated yield. However, varying amounts (~5-10%) of **41** were present even after prolonged heating (8h).[54] The range of rotation values obtained over several runs (-20.4° to -25.1°) when compared to literature

values (-12° and -16.5°) reflects the presence of **41** since the rotation value of the latter is much higher than dictyopterene C' **42**. The effect of this contamination is that a larger rotation value was obtained for the final product. That no epimerization had occured during the reaction sequence to give dictyopterene A **40** (which requires 115°C to effect Cope rearrangement) was proven by examination of the ^{1}H NMR. A quartet for the cyclopropyl proton of the unrearranged material was visible at δ0.5 rather than δ0.65 as would be expected for the trans divinyl cyclopropane.[44a]

EXPERIMENTAL

General

Microanalyses were performed by Desert Analytics, Tucson, AZ. Vpc analyses were performed on a crosslinked 5% phenyl methyl silicone capillary column (SE-52) with dimensions of 0.2 mm x 25 m and a flow rate of 30 cm/ sec. All ^{1}H NMR spectra were taken with tetramethylsilane as internal standard. Tetrahydrofuran (THF) and 1,2-Dimethoxyethane (DME, Aldrich, <1% water content) were distilled immediately prior to use from sodium-benzophenone ketyl radical. Ethyl acetate and hexane were distilled prior to use. Methylene chloride was distilled from phosphorous pentoxide prior to use. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride. Diethyl ether (Mallinckrodt) was used without purification. Brine refers to a saturated aqueous solution of sodium chloride. Flash column chromatography was performed on Aldrich-951-58μm SiO_2 on all compounds except angular hydrogen biyclic lactams which required 60Å (20-45 μm) Amicon Matrex™ SiO_2 due to decompositon on purification. Thin layer chromatography was performed on aluminum backed silica gel $60F_{254}$ (0.2 mm thickness, Art. 5554). Melting points were obtained using a Fisher-Johns melting point apparatus and are uncorrected. Unsaturated bicyclic lactams were prepared using diphenyldiselenide (Aldrich), freshly sublimed phenylselenenyl bromide (Aldrich), and freshly prepared phenylselenenyl bromide (by the method of Reich, et. al.[13]). However, the reagent prepared by the latter method is the safest, least expensive, and highest yielding for this conversion. Trimethylsulfoxonium iodide (Aldrich) was recrystallized from water, washed with acetone, and dried under high vacuum in a dessicator prior to use. Silver tetrafluoroborate was purchased from Lancaster Synthesis, Ltd. p-Tosyl hydrazide (Aldrich) was recrystallized from 60% methanol-water and dried in a vacuum dessicator before use. All other reagents were purchased from Aldrich and utilized without further purification unless otherwise noted.

L(S)-tert-leucinol

To a 2000 mL, 3-neck round-bottomed flask equipped with a stir bar, reflux condenser, and drying tube (calcium chloride pellets) was added 15.5 g (0.41 mol) of lithium aluminum hydride and 700 mL of dry THF. The mixture was heated to reflux and 33.0 g (0.25 mol) of L(S)-tert-leucine was added over a 1.5 h period. The mixture was allowed to reflux with stirring for 3 h and then stirred at room temperature overnight. The reaction was quenched by carefully adding 15 mL of water and

30 mL of 12% sodium hydroxide. The slurry was transferred to a 2000 mL erlenmeyer flask with 500 mL of ether and stirred vigorously at room temperature for 1h. After this time, 60 mL of water was added and the solids were removed by vacuum filtration. The solution was concentrated and the residue was taken up in methylene chloride and dried (Na_2SO_4). The product was purified by short-path vacuum distillation to afford 22.3 g (76%) of L(S)-tert-leucinol as a colorless oil which solidified on cooling to 0°C: bp 90-92°C, 20 torr; $[\alpha]_D^{22}$ +35.3° (*c* 3.05, EtOH); Degussa: $[\alpha]_D^{22}$ 38.7° (c 3, EtOH); IR (neat) 3550-2700 (br), 2956, 1592 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.90 (9H, s), 1.85-2.35 (br s), 2.51 (1H, dt, J = 4.0, 7.8 Hz), 3.21 (1H, dt, J = 3.9, 10.2 Hz), 3.69 (1H, J = 3.6, 5.4 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 26.2, 33.1, 61.6, 62.3.

Note: Private communication with Degussa (Dr. Krauz and Dr. Lotter) has confirmed that the L(S)-tert-leucine employed was > 99.9 % ee as determined by chiral phase gas chromatography. Previous Pirkle analysis of L(S)-valinol (napthyl urea derivative) obtained by lithium aluminum hydride reduction of L(S)-valine has shown that the reduction occurs without racemization.[55]

Bicyclic lactam 6a

In a 1000 mL one-neck round-bottomed flask equipped with a stir bar, Dean Stark trap, reflux condenser, and drying tube ($CaCl_2$) was added 12.686 g (0.108 mol) of L(S)-tert-leucinol and 13.2 g (0.108 mol) of levulinic acid. The solids were dissolved in 500 mL of toluene and the mixture was heated to reflux with azeotropic removal of water. After 26 h, the mixture was cooled to rt and concentrated *in vacuo*. The resulting light brown oil was purified by short-path distillation to give 20.208 g (95%) of bicyclic lactam **6a** as a pale yellow, crystalline solid which was >95% pure by ^{1}H-NMR. If purer samples were required, the product was recrystallized from hexanes at 0°C to give colorless needles: R_f 0.15 (30% ethyl acetate/hexane); mp 59.0-60.0°C; bp 99-100°C (1.8 mm Hg); $[\alpha]_D^{22}$ 114° (c 1.13, EtOH); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.95 (9H, s), 1.50 (3H, s), 2.14-2.21 (2H, m), 2.45 (1H, ddd, J = 16.6, 7.5, 4.2 Hz), 2.79 (1H, ddd, J = 16.7, 7.5, 4.2 Hz), 3.69 (1H, apparent t, J = 8.3Hz), 3.94 (1H, apparent t, J = 8.7 Hz), 4.15 (1H, dd, J = 8.5, 8.5 Hz); IR (film) 2965, 1715 cm^{-1}; MS *m/z* (relative intensity) 198 (M^++1, 1), 197 (M^+, 9), 140 (86), 32, (26), 28 (100); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 25.0, 27.1, 33.1, 33.5, 35.3, 65.0, 68.4, 100.4, 180.0.

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 67.23; H, 9.80.

L-(S)-tert-leucinol succinimide 7a

L(S)-tert-leucinol (0.50g, 4.27 mmol) and succinic anhydride (0.43g, 4.27 mmol) were dissolved in 50 mL of dry toluene under an argon atmosphere. The mixture was heated to reflux and after 1.5 h, 1.5 mL of triethylamine in 3.5 mL of toluene was added. The reaction was continued at reflux for 21h. The mixture was concentrated *in vacuo*, acetic anhydride (20 mL) and sodium acetate (0.33 g) were added, and the mixture was heated at 100°C for 3h. The excess acetic anhydride was removed by short-path distillation (atmospheric pressure) and the residue was passed through a short plug of silica gel with ethyl acetate to provide a light brown oil. The oil was submitted to saponification with methanolic 1N HCl for 2h followed by neutralization with solid sodium bicarbonate. After additon of 20 mL of water, the mixture was extracted with diethyl ether (3

x 75 mL), washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to provide 0.608 g (71%) of succinimide **7a** as a pale yellow oil which was >95% pure by ^1H NMR. In most runs, this material was carried on directly to the reduction/ cyclization sequence without further handling however, an analytical sample could be prepared by recrystallization from ethyl acetate to yield a pale yellow crystalline solid: $[\alpha]_D^{25}$ -1.0° (c 2.2, $CHCl_3$); ^1H-NMR ($CDCl_3$, 300MHz) δ 0.98 (9H, s), 3.83 (1H, J = 3.8 11.5 Hz), 4.02 (1H, dd, J = 3.9, 9.8 Hz), 4.42 (1H, dd, J = 9.8, 11.4 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 27.9, 28.0, 28.1, 58.5, 63.0, 178.7, 179.1.

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.34; 8.64; N, 6.96.

cis-1,2-Dicarboxycyclopropyl anhydride

Prepared according to the method of McCoy[56] to give colorless crystalline plates after recrystallization from diethyl ether: mp 56-57°C (lit. mp 58-60°C); IR (CCl_4) 1727 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.65 (2H, t, J = 4.3 Hz), 2.77 (2H, dd, J = 4.0, 7.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 17.1, 21.7, 167.6.

L-(S)-tert-Leucinol cyclopropyl succinimide 7b

cis-1,2-Dicarboxycyclopropyl anhydride (0.50 g, 4.46 mmol) was dissolved in 8 mL of dry THF and, under an argon atmosphere,was added L(S)-tert-leucinol (0.523 g, 4.46 mmol) as a THF solution (4 mL) *via* cannula at rt. The mixture was stirred at rt for 1h. The mixture was concentrated *in vacuo* to give a colorless foam. After addition of 20 mL acetic anhydride and 0.33 g sodium acetate, the mixture was heated at 100°C for 3h. The excess acetic anhydride was removed by short-path distillation (atmospheric pressure) and the residue diluted with 25 mL of methanolic 1N HCl and heated to reflux for 2h. The mixture was neutralized by addition of solid sodium bicarbonate followed by addition of 20 mL of water. The mixture was extracted with ethyl acetate (3 x 75 mL) and the organics were combined and washed with brine then dried ($MgSO_4$) and concentrated *in vacuo* to provide a yellow viscous oil. Purification by flash column chromatography (gradient elution; hexane-> 10%->20%->50% ethyl acetate/hexane) provided 721 mg (76%) of a colorless viscous oil which slowly crystallized on standing. An analytical sample was prepared by sublimation to provide a waxy solid (~1:1 mixture of syn/anti conformers *via* ^1H and ^{13}C-NMR): R_f 0.47 (ethyl acetate); mp 78-79°C; $[\alpha]_D^{22}$ 2.7° (c 0.99, $CHCl_3$); IR (CCl_4) 3467 (br), 1694 cm^{-1};^1H-NMR ($CDCl_3$) δ 0.92 (9H, s), 0.97 (9H, s), 1.43-1.59 (4H, m), 2.41-2.57 (4H, m), 3.70-3.91 (4H, m), 4.22 - 4.37 (2H, overlapping t, J =); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 19.8, 19.9, 20.0, 20.1, 20.3, 20.6, 27.6, 28.0, 29.5, 34.1, 35.2, 57.0, 59.4, 61.4, 62.7, 176.0, 176.4, 176.9, 177.2.

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11; N, 6.63. Found: C, 62.71; H, 8.06; N, 6.49.

Bicyclic lactam 6b

L-(S)-tert-Leucinol succinimide **7a** (6.77g, 0.34 mmol) was dissolved in 30 mL absolute ethanol and 12.9 g of sodium borohydride (0.34 mmol, 10 equiv) was added at 0°C with stirring. After 1h, 2M HCl (in ethanol) was added slowly *via* syringe (Caution: exothermic with gas evolution) to acidify to pH ~1-3 (~150 mL required). The mixture was allowed to stir at rt for 10-12 h. After

pouring the mixture into 100 mL aqueous saturated sodium bicarbonate, the mixture was extracted with chloroform (3 x75 mL). The organics were combined, washed with brine, dried (K_2CO_3), and concentrated *in vacuo* to give a yellow oil. The oil was diluted with methylene chloride (50 mL) and added over a 5 min period to a solution of trifluoroacetic acid (26 mL, 0.34 mol, 10 equiv) in 500 mL of methylene chloride maintained at 0°C. The mixture was allowed to warm to rt and then stirred an additional 2h. After neutralization with solid sodium bicarbonate, 20 mL of water was added and the mixture was extracted with methylene chloride (2 x 100 mL). The combined organics were washed with brine, dried (K_2CO_3) and concentrated *in vacuo* to afford 6.5 g (~100%) of the angular hydrogen bicyclic lactam **6b** as a light brown oil. This material, which was ~ 95% pure by ^{1}H-NMR, was not handled further on most runs but used in subsequent reactions in this form since much material was lost due to decomposition on attempted purification by flash column chromatography or distillation. Analytical sample purified by flash column chromatography.: $[\alpha]_D^{22}$ 78.5° (c 10.1, $CHCl_3$); R_f 0.38 (50% ethyl acetate/hexane); IR (neat) 1718 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.93 (9H, s), 1.96-2.08 (1H, m), 2.29-2.42 (1H, m), 2.44-2.55 (1H, m), 2.59-2.72 (1H, m), 3.73-3.82 (2H, m), 4.02-4.11 (1H, m), 5.06 (1H, dd, J = 2.0, 6.2 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 24.1, 26.1, 31.1, 33.7, 64.1, 68.0, 92.9, 180.3.

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.42; H, 9.33; N, 7.72.

Cyclopropyl bicyclic lactams 6c (*endo*/*exo*)

The imide **7b** (0.273 g, 1.29 mmol) was dissolved in 15 mL of dry THF and, under an argon atmosphere, 1.29 mL of methyl magnesium bromide (3.88 mmol, 3.0 equiv, 3.0 M in diethyl ether) was added dropwise over a 4 min period at rt. This produced a cloudy colorless solution. The mixture was stirred at rt for 3h and then quenched by addition to 20 mL of aqueous saturated ammonium chloride. The mixture was extracted with diethyl ether (3 x 30 mL). The organics were combined and washed with brine then dried ($MgSO_4$) and concentrated *in vacuo* to provide a pale yellow oil. The crude material was taken up in methylene chloride and added to a solution of trifluoroacetic acid (0.30 mL; 3.88 mmol; 3.0 equiv) in 50 mL of methylene chloride maintained at 0°C. The mixture was allowed to warm to rt and stirred at this temperature for 21h. The mixture was poured into 20 mL aqueous saturated sodium bicarbonate, the layers were separated, and the aqueous phase was extracted with diethyl ether (2x 30 mL). The organics were combined, washed with brine, then dried ($MgSO_4$) and concentrated *in vacuo* to provide a yellow oil. Purification by flash column chromatography (10% ethyl acetate/hexane) after preadsorption onto silica gel from ethyl acetate provided 37 mg of the *exo* cyclopropane adduct **6c** as a colorless crystalline solid and 51 mg of a 3.3:1 mixture (*via* vpc) of *endo*/*exo* cyclopropane adducts **6c** (31% total yield; ~1:1 *endo*/*exo* ratio).

***exo*-6c**: R_f 0.48 (50% ethyl acetate/ hexane); mp 65-66°C; IR (CCl_4) 1727 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 9H), 1.04-1.09 (m, 1H), 1.21-1.31 (m, 1H), 1.46 (s, 3H), 1.96-2.04 (m, 1H), 2.31-2.38 (m, 1H), 3.66 (apparent t, 1H, J = 8.5 Hz), 3.83 (apparent t, 1H, J = 8.9 Hz), 4.11 (apparent t, 1H, J = 8.6 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 14.9, 21.2, 22.0, 27.0, 28.8, 32.6, 66.6, 66.9, 99.2, 184.9.

***endo*-6c**: This compound was identical in all respects to that obtained by the sulfur ylide or diazomethane/photolysis sequences (vide infra).

α-Phenyl Lactam 8: (*Z* and *E*) Methyl-4-oxo-2-phenyl-2-pentenoate

In 75 mL of THF was placed 2.50 mL (18.1 mmol) of methyl-2-oxopropyl phosphonate. The solution was cooled to -78°C and 10.2 mL (18.1 mmol) of n-BuLi was added followed by 2.57 mL (18.1 mmol) of methyl phenyl-glyoxylate. The reaction was allowed to warm to 25°C and quenched with water. After extraction with ether, concentration, and chromatography 3.06 g (83%) of the desired *Z*-olefin and 0.485 g (13%) of the *E*-olefin was obtained. Physical and spectral data for *Z*-olefin: mp 79-80°C; IR ($CHCl_3$) 2950, 1730, 1690, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 2.30 (3H, s), 3.90 (3H, s), 6.75 (1H, s), 7.2-7.5 (5H, m).

A solution of 50 mL of dry toluene, 0.876 g (4.29 mmol) of methyl-4-oxo-2-phenyl-2-pentenoate, and 0.443 g (4.29 mmol) of L-(S)-valinol was heated to reflux with azeotropic removal of water for 16 h. Concentration and chromatography gave 0.522 g (60% based on recovered starting material) of the unsaturated lactam **8**: mp 59-61°C (pentane); IR (neat) 2960, 2860, 1715, 1490 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.95 (3H, d, J = 6.6 Hz), 1.14 (3H, d, J = 6.6 Hz), 1.62 (3H, s), 1.80 (1H, m), 3.62 (1H, m), 4.11 (1H, dd, J = 6.4, 8.8 Hz), 4.37 (1H, dd, J = 7.4, 8.8 Hz), 7.12 (1H, s), 7.25 - 7.84 (5H, m).

***Endo* and *exo* α-methyl lactam 9b (R_3, R_4 = Me, H)**

To a stirred solution of lactam **1b**[9a] (2.50 g, 13.7 mmol) in 40 mL of THF at -78°C was added 10.2 mL (15.0 mmol) of s-BuLi. The solution was stirred for 1 h and then quenched with 1.02 mL (16.4 mmol) of methyl iodide. The reaction mixture was stirred at -78°C for 1 h and allowed to warm to rt over 3 h. The solution was poured into saturated aqueous ammonium chloride and extracted with ether. The combined organics were washed with water, brine, and dried ($MgSO_4$). Concentration and purification by flash column chromatography (50% ethyl acetate/hexane) gave 2.40 g (89%) of a 7:1 mixture of *endo* and *exo* α-methyl lactams **9b**. The *endo/exo* isomers could be separated by gravity column chromatography (25% ethyl acetate/hexane).

***endo*-9b:** IR (neat) 2980, 1720, 1380 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.89 (3H, d, J = 6.6 Hz), 1.02 (3H, d, J = 6.5 Hz), 1.19 (3H, d, J = 7.3 Hz), 1.47 (3H, s) 1.66 (1H, d sept, J = 9.9, 6.5 Hz), 1.77 (1H, brt, J = 12.0 Hz) 2.42 (1H, dd, J = 8.4, 12.5 Hz), 2.89 (1H, dq, J = 8.4, 7.3 Hz), 3.59 (1H, dt, J = 6.8, 9.9 Hz), 3.86 (1H, dd, J = 6.3, 8.8 Hz), 4.15 (1H, dd, J = 7.3, 8.8 Hz).

***exo*-9b:** ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.89 (3H, d, J = 6.6 Hz), 1.05 (3H, d, J = 6.6 Hz), 1.32 (3H, d, J = 7.5 Hz), 1.49 (3H, s), 1.67 (1H, d sept, J = 10.5, 6.6 Hz), 1.81 (1H, dd, J = 13.7, 4.0 Hz), 2.47 (1H, dd, J = 13.7, 10.1 Hz), 2.66 (1H, m), 3.58 (1H, dt, J = 10.4, 7.5 Hz), 3.78 (1H, dd, J = 6.8, 8.6 Hz), 4.18 (1H, dd, J = 7.9, 8.6 Hz).

***Endo* and *exo* α-carbomethoxy lactam 9c (R_3, R_4 = CO_2Me, H)**

To a solution of LDA at -78°C [2.0 equiv, prepared from diisopropylamine (4.82 mL, 34 mmol) and 23.76 mL of s-BuLi (1.38 M in hexanes) in 100 mL of THF at 0°C] was added dropwise lactam

1b (3 g, 16.4 mmol) dissolved in 75 mL of the same solvent. After 30 min of stirring, methyl chloroformate (1.4 mL, 18.0 mmol) was added with continued stirring for 3.5 h before quenching with saturated aqueous ammonium chloride solution. The aqueous phase was extracted with ether, and the combined organic layers washed with brine and dried ($MgSO_4$). Concentration gave an oil 3.95 g (100%) as an inseparable 1:1 mixture of the *endo/exo* lactams **9c**: IR (neat) 2920, 2905, 1740 (br), 1690 (br) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.87-1.05 (12H, m), 1.50 (3H, s), 1.57 (3H, s), 1.64-1.71 (2H, m), 2.56-2.63 (4H, m), 3.59-3.65 (2H, m), 3.79 (6H, s), 3.81-3.94 (4H, m), 4.19-4.27 (2H, m). MS *m/z* (relative intensity): 241 (8), 226 (59), 198 (21), 166 (100), 128 (32).

α, α-dithiomethyl lactam 9d

A THF solution of LDA was prepared by addition of 7.50 mL (12.5 mmol) of n-BuLi (1.66 M) to diisopropylamine (2.0 mL, 14.0 mmol) in THF at 0°C. After 20 min, the LDA solution was cooled to -78°C and a THF solution of the lactam **1b** (1.83 g, 10.0 mmol) was added to the LDA *via* cannula at -78°C. After stirring for 20 min at -78°C, the reaction mixture was warmed to 0°C and a THF solution of methyl disulfide (2 mL, 22.0 mmol) was added *via* cannula. The mixture was stirred for 10 minutes at this temperature and then acidified with 1N HCl and concentrated. The residue was diluted with ether, washed with saturated sodium bicarbonate, water, brine and dried ($MgSO_4$). Concentration *in vacuo* and purification by flash column chromatography to provide 1.24 g (45%) of the dithiomethyl lactam **9d** and a mixture of starting material and mono thio lactam. This mixture was resubmitted to the reaction conditions and gave an additional 0.84 g (total yield - 72%) of product **9d** as a crystalline solid: mp 67.5-68.5°C; ^{1}H-NMR ($CDCl_3$ 270 MHz) δ 0.89 (3H, d, J = 6.6 Hz), 1.06 (3H, d, J = 6.6 Hz), 1.59 (3H, s), 1.64 (1H, m), 2.12 (3H, s), 2.24 (3H, s), 2.45, 2.69 (2H, ABsystem, J = 14.1 Hz), 3.61 (1H, m), 3.83 (1H, dd, J = 6.9, 8.7 Hz), 4.24 (1H, dd, J = 7.8, 8.7 Hz).

α, α-dithiomethyl lactam 9e

Prepared as above for **9c** with 0.168 g (10.0 mmol) of lactam **1c** gave 1.23 g (47%) of lactam **9e**, 0.50 g of α-monothiomethyl lactams, and 0.20 g (12%) of recovered starting material **9e** after purification by flash column chromatography (ethyl acetate/hexane): ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, J = 6.7 Hz), 1.02 (3H, d, J = 6.6 Hz), 1.71 (1, m), 2.15 (3H, s), 2.23 (3H, s), 2.45 (1H, dd, J = 3.5, 14.4 Hz), 2.69 (1H, dd, J = 5.9, 14.4 Hz), 3.72 (2H, m), 4.24 (1H, m), 5.12 (1H, dd, J = 3.5, 5.9 Hz).

***Endo* and *exo* α-carbomethoxy lactams 9f (R_3, R_4 = CO_2Me, H)**

Prepared as above for **9c** with 1.72 g (10.8 mmol) of lactam **1b** to afford 2.08 g (90%) of lactam **9f** as a 1:1 mixture of *endo/exo* isomers: IR (neat) 2860, 1770, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.89-1.01 (12H, m), 1.60-1.77 (2H, m), 2.21-2.79 (4H, series of m), 3.60-3.85 (12H, m), 4.21-4.26 (2H, m), 5.11-5.17 (2H, m).

General Procedure for Selenation-Oxidation-Elimination Sequence. Unsaturated Lactams 10

A THF solution of LDA was prepared fresh by the addition of 2.1 equiv (for α-unsubstituted lactams **10a, g,** and **h**) or 1.1 equiv (for α-monosubstituted lactams **10b, c,** and **f**) of n-butyllithium to a THF solution of 2.1 or 1.1 equiv of dry diisopropylamine at 0°C under an argon atmosphere. After stirring for 1 h, the solution was cooled to -78°C and the bicyclic lactam (1.0 equiv) was added *via* cannula as a THF solution. The mixture was stirred for 1 h and phenylselenyl bromide (1.2 equiv) was added slowly *via* cannula as a cooled (-78°C) THF solution. After addition was complete, the mixture was stirred at -78°C for 1 h and quenched by addition of saturated aqueous ammonium chloride. The mixture was warmed to rt and concentrated *in vacuo*. Water was added and the aqueous residue was extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in methylene chloride and the oxidation-elimination was performed by method A for the angular methyl bicyclic lactams (**10a-c, g**) and method B for the angular hydrogen lactams (**10e, f, h**).

Method A: The methylene chloride solution was cooled to 0°C and then pyridine (2.5 equiv) was added followed by the dropwise addition of 3.0 equiv of a 30% solution of hydrogen peroxide. The mixture was allowed to warm to rt slowly overnight with stirring **(Caution: During large scale preparations a violent exotherm was observed, therefore, the reaction must be allowed to warm to rt slowly.)** The reaction mixture was concentrated and the residue dissolved in ether and washed with aqueous 5% HCl (two portions), water, and brine before drying ($MgSO_4$). Concentration *in vacuo* and purification afforded the unsaturated lactams **10**.

Method B: Diisopropylamine (1.2 equiv) was added to the methylene chloride solution and the mixture was cooled to -78°C. Ozone was bubbled through the solution until a blue color persisted. The solution was purged with argon and allowed to warm to rt for 1 h. The mixture was concentrated *in vacuo* and the residue was taken up in ether. The ether solution was washed with 5% HCl, water, and brine before drying ($MgSO_4$). Concentration *in vacuo* and purification provided the unsaturated lactams **10**.

Unsaturated lactam 10a

Prepared according to general procedure (using freshly sublimed phenyl selenenyl bromide) with 439 mg (2.4 mmol) of lactam **1b** to afford 355 mg (81%) of the unsaturated lactam **10a** and 5.75 mg (1.3%) of recovered starting material. Physical and spectral data for **10a**: mp 38-40°C; $[\alpha]_D$ 21.4° (c 0.51, THF); IR (CCl_4) 2885, 1720, 1540 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.89 (3H, d, J = 6.7 Hz), 1.05 (3H, d, J = 6.7 Hz), 1.52 (3H, s), 1.75 (1H, m), 3.45 (1H, ddd, J = 10.1, 7.2, 6.1 Hz), 4.04 (1H, dd, J = 8.9, 6.0 Hz), 4.26 (1H, dd, J = 8.8, 7.3 Hz), 5.97 (1H, d, J = 5.8 Hz), 6.99 (1H, d, J = 5.8 Hz).

Unsaturated Lactam 10b

Prepared according to the general procedure (using diphenyl diselenide) with 2.41 g (12.2 mmol) of a 7:1 *endo/exo* mixture of α-methyl lactams, **9b**. This provided 1.55 g (65%) of

unsaturated lactam **10b** and 0.516 g (21%) of recovered starting material after purification by flash column chromatography (10% ethyl acetate/hexane). Recrystallization from pentane at -30°C gave colorless needles: mp 46-47°C; $[\alpha]_D^{25}$ 41.3° (c 1.0, hexane); IR ($CHCl_3$) 2880, 1705, 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, J = 6.6 Hz), 1.09 (3H, d, J = 6.7 Hz), 1.52 (3H, s), 1.76 (1H, d sept, J = 10.0, 6.7 Hz), 1.85 (3H, d, J = 1.7 Hz), 3.49 (1H, dt, J = 10.0, 6.7 Hz), 4.05 (1H, dd, J = 6.4, 8.9 Hz), 4.32 (1H, dd, J = 7.4, 8.8 Hz), 6.65 (1H, q, J = 1.7 Hz).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 67.6; H, 8.7; N, 7.2. Found: C, 67.1; H, 8.5; N, 7.1.

Unsaturated lactam 10c

Prepared according to general procedure (using freshly sublimed phenyl selenyl bromide) with 910 mg (3.78 mmol) of epimeric mixture of lactams **9c**. This afforded 831 mg (92%) of unsaturated lactam **10c** as an oil after purification by flash column chromatography (10% ethyl acetate/methylene chloride): $[\alpha]_D$ 13.5° (c 2.0, EtOH); IR (neat) 2835, 1740, 1450 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, J = 6.6 Hz), 1.09 (3H, d, J = 6.6 Hz), 1.57 (3H, s), 1.74-1.78 (1H, m), 3.59-3.84 (1H, m), 3.86 (3H, s), 4.08 (1H, dd, J = 8.9, 6.0 Hz), 4.32 (1H, dd, J = 8.9, 7.5 Hz), 7.67 (1H, s); MS *m/z* (relative intensity): 239 (2.7), 224 (18.5), 196 (29.8), 177 (27.5), 164 (56.3).

Unsaturated lactam 10f

Prepared according to general procedure (using freshly sublimed phenyl selenyl bromide) with 480 mg (2.11 mmol) of epimeric α-carbomethoxy lactams **9f**. This gave 391 mg (82%) of unsaturated lactam **10f** as an oil after purification by flash column chromatography (10% ethyl acetate/methylene chloride): $[\alpha]_D$ 18.9° (c 1.14, EtOH); IR (neat) 2940, 1750, 1715, 1425 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.95 (3H, d, J = 6.7 Hz), 1.05 (3H, d, J = 6.7 Hz), 2.65-2.78 (1H, m), 3.66-3.84 (2H, m), 3.87 (3H, s), 3.94 (1H, dd, J = 8.8 Hz), 4.41 (1H, dd, J = 8.8, 7.3 Hz), 5.43 (1H, d, J = 1.3 Hz), 7.74 (1H, d, J = 1.4 Hz); MS *m/z* (relative intensity): 225 (1.5), 182 (16.6), 163 (13.1), 150 (39.2).

Unsaturated lactam 10g

Prepared according to general procedure (using freshly prepared phenyl selenyl bromide) with 15.622 g (79 mmol) of lactam **6a**. The intermediate α-phenyl seleno lactams **9g** were purified by flash column chromatography (gradient elution; 0% - 50% ethyl acetate/hexane) and gave 22.23 g (80%) of *endo/exo* α-selenides as a yellow viscous oil. Treatment of 12.861 g (36 mmol) of the α-selenides according to the general procedure for oxidation-elimination afforded 7.065 g (99%) of the unsaturated lactam **10g** as a pale yellow crystalline solid after purification by flash column chromatography (gradient elution; 0% - 20% ethyl acetate/hexane). The product was recrystallized from hexanes at 0°C and provided colorless needles: R_f 0.25 (3/7, ethyl acetate/hexane); mp 54.5-55.5°C; $[\alpha]_D^{22}$ 68.4° (c 1.08, EtOH); IR (KBr pellet) 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.96 (9H, s), 1.51 (3H, s), 3.54 (1H, t, J = 8.6 Hz), 4.14 (1H, t, J = 9.1 Hz), 4.33 (1H, dd, J = 8.3, 9.3), 5.94 (1H, d, J = 5.7 Hz), 6.99 (1H, d, J = 5.8 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 21.8, 26.8, 32.9, 65.2,

71.3, 100.9, 127.9, 150.6, 178.7; MS *m/z* (relative intensity): 196 (M+1, 1), 195 (M, 4), 139 (30), 138 (90), 28 (100).
Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.32; H, 8.89.

Unsaturated lactam 10h

Prepared according to general procedure (using freshly prepared phenyl selenyl bromide) with 460 mg (2.51 mmol) of lactam **6b** to give 393 mg (86%) of unsaturated lactam **10h** as a pale yellow oil after purification by flash column chromatography (gradient elution; 0% - 10% ethyl acetate/hexane) as a pale yellow oil: R_f 0.52 (50% ethyl acetate/hexane); IR (neat) 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 9H), 3.66 (apparent t, 1H, J = 7.3 Hz), 4.09 (dd, 1H, J = 6.9, 9.1 Hz), 4.33 (dd, 1H, J = 7.8, 9.0 Hz), 5.43 (d, 1H, J = 1.4 Hz), 6.14 (d, 1H, J = 5.8 Hz), 7.10 (dd, 1H, J = 1.5, 5.8 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 26.0, 33.7, 63.2, 72.6, 93.8, 131.0, 145.2, 176.5.

α-Thiomethyl unsaturated lactam 10d

The α,α-dithiomethyl lactam **9d** (1.18 g, 4.3 mmol) in 5 mL of THF was added to a benzene solution (50 mL) of 5.4 g (10.2 mmol) of cuprous triflate-benzene complex **14b** and 2.1 mL (12.0 mmol) of diisopropylethylamine. The mixture was heated to reflux for 2 h and then cooled to rt, filtered, and concentrated. The residue was purified by flash column chromatography (5:1 - 2:1, hexane/ethyl acetate) and afforded 0.785 g (80%) of the unsaturated lactam **10d** as a colorless crystalline solid: mp 56-57°C; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, J = 6.6 Hz), 1.08 (3H, d, J = 6.7 Hz), 1.56 (3H, s), 1.76 (1H, m), 2.34 (3H, s), 3.51 (1H, m), 4.06 (1H, dd, J = 8.9, 6.5 Hz), 4.36 (1H, dd, J = 8.9, 7.5 Hz), 6.35 (1H, s).
Anal. Calcd for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16. Found: C, 58.14; H, 7.65; N, 6.07.

α-Thiomethyl unsaturated lactam 10e

Procedure as above for unsaturated lactam **10d** with 1.23 g (4.7 mmol) of α, α-dithiomethyl lactam **9e**, 3.7 g (7.4 mmol) of cuprous triflate-benzene complex, and 2.8 mL (16.0 mmol) of diisopropyl ethylamine with overnight reflux. The product was purified by flash column chromatography (10:1, hexane/ethyl acetate) and gave 701 mg (70%) of the unsaturated lactam **10e** as a colorless oil: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.94 (3H, d, J = 6.7 Hz), 1.05 (3H, d, J = 6.7 Hz), 1.75 (1H, m), 2.37 (3H, s), 3.61 (1H, m), 3.91 (1H, dd, J = 7.1, 8.8 Hz), 4.44 (1H, dd, J = 7.3, 9.0 Hz), 5.40 (1H, d, J = 1.9 Hz).

Dibromo bicyclic lactam 11

To a stirred solution of 0.11 mL (2.09 mmol) of Br_2 in 10 mL of CCl_4 (yellow colored solution) is added a CCl_4 solution (5 mL + 1 mL rinse) of 0.206 g (1.04 mmol) of bicyclic lactam **6a** under an argon atmosphere at ambient temperature. After 2h, the yellow solution had faded to clear and the reaction was quenched by addition of 1 mL water. The mixture was concentrated *in vacuo* and the aqueous residue was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford a yellow oil. Purification by flash column

chromatography (5% EtOAc/ CH_2Cl_2) afforded 0.065 g (18%) of dibrominated bicyclic lactam **11**. The remaining fractions contained starting material and the two epimeric mono-α-bromo lactams (0.245 g). The dibrominated product had the following spectral charactersitics: ^{1}H-NMR δ: 0.95 (9H, s, t-butyl), 2.91 (1H, dd), 3.20-3.55 (2H, m), 3.85 (1H, apparent t), 3.95 (2H, apparent t), 4.23 - 4.39 (2H, m); MS *m/z* (relative intensity) 357 (M^++4, 0.5), 355 (M^++2, 1.1), 353 (M^+, 0.6), 299 (18.0), 298 (13.0), 180 (99.7).

(R, S)-α-Sulfoxymethyl unsaturated lactams 12

To a stirred solution of α-thiomethyl unsaturated lactam **10d** (168 mg, 0.74 mmol) in methylene chloride was added dropwise at 0°C an 85% solution of m-chloroperbenzoic acid (mCPBA) in methylene chloride (150 mg, 0.87 mmol). The mixture was stirred for 0.5 h at 0°C and then quenched by addition of a 10% aqueous solution of sodium metabisulfite. The layers were separated and the aqueous phase extracted with ether. The combined organics were washed with water and brine before drying ($MgSO_4$). Concentration *in vacuo* and purification by flash column chromatography (5:1, hexane/ethyl acetate) provided 153 mg (85%) of α-sulfoxymethyl unsaturated lactam **12** as a 1:1 mixture of diastereomers at sulfur: ^{1}H-NMR ($CDCl_3$, 270 MHz, of diastereomeric mixture) δ 0.92 (6H, d, J = 6.5 Hz), 1.08 (6H, d, J = 6.7 Hz), 1.62 (3H, s), 1.63 (3H, s), 1.77 (2H, m), 2.93 (3H, s), 2.94 (3H, s), 3.51 (2H, m), 4.11 (2H, m), 4.40 (2H, m), 7.52 (1H, s), 7.53 (1H, s).

(R, S)-α-Sulfoxymethyl unsaturated lactam 13

Procedure as described above for unsaturated lactam **12** using 395 mg (1.8 mmol) of α-thiomethyl unsaturated lactam **10e** and mCPBA (400 mg) with a reaction time of 1.5 h at 0°C. Purification by flash column chromatography yielded 402 mg (95%) of the α-sulfoxymethyl unsaturated lactams **13** as a 1:1 mixture of diastereomers at sulfur: ^{1}H-NMR ($CDCl_3$, 270 MHz, of diastereomeric mixture) δ 0.95 (6H, d, J = 6.7 Hz), 1.05 (6H, d, J = 6.7 Hz), 1.74 (2H, m), 2.93 (3H, s), 2.95 (3H, s), 3.63 (2H, m), 3.99 (2H, m), 4.48 (2H, m), 5.49 (3H, s), 5.51 (3H, s), 7.60 (2H, s).

(R, S)-α-Sulfoxymethyl unsaturated lactams 12 (Kagan Method)

To a stirred solution of 0.15 mL (0.5 mmol) of Ti (Oi-Pr)$_4$ and 0.17 mL (1.0 mmol) of (+)-(R, R)-diethyl tartrate in 9 mL of methylene chloride was added 9 mL (0.5 mmol) of water at rt under argon. Stirring was maintained until the yellow solution became homogeneous (~20 min.) and 0.11 g (0.5 mmol) of the α-thiomethyl lactam **10d** was added as a methylene chloride solution. The reaction mixture was cooled to -20°C and 0.5 mL of a methylene chloride solution of t-butyl hydrogen peroxide (90 mg, 1.0 mmol) was introduced *via* syringe. The solution was maintained at -20°C for 36 h. The reaction was concentrated, extracted with ether, and purified by flash column chromatography (1:2, ethyl acetate/hexane) to afford 74 mg (61%) of α-sulfoxymethyl unsaturated lactams **12** as a 9:1 (^{1}H-NMR) mixture of diastereomers at sulfur. The major diastereomer was purified by chromatography and had the following physical and spectral characteristics: $[\alpha]_D$ 107° (c 2.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.93 (3H, d, J = 6.7 Hz), 1.09 (3H, d, J = 6.7 Hz), 1.63

(3H, s), 1.78 (1H, m), 2.94 (3H, s), 3.50 (1H, m), 4.13 (1H, dd, J = 9.1, 6.6 Hz), 4.44 (1H, dd, J = 9.1, 7.7 Hz), 7.49 (1H, s).

α-(Sulfonylmethyl) unsaturated lactam 14

The α-thiomethyl unsaturated lactam **10d** (280 mg, 1.2 mmol) was treated with mCPBA (630 mg, 3.6 mmol) for 2 h at rt according to the procedure described for α-sulfoxymethyl unsaturated lactam **12** above. Purification by radial chromatography (gradient elution; 10:1 - 3:1 hexane/ethyl acetate) afforded 166 mg (53%) of the desired unsaturated lactam **14** and 85 mg of the epoxides **15** as a 3:1 (^{1}H-NMR) mixture of *endo/exo* diastereomers.

14: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.91 (3H, d, J = 6.7 Hz), 1.07 (3H, d, J = 6.6 Hz), 1.60 (3H, s), 1.72 (1H, m), 3.18 (3H, s), 3.53 (1H, m), 4.10 (1H, dd, J = 6.6, 9.0 Hz), 4.39 (1H, dd, J = 7.6, 9.0 Hz), 7.69 (1H, s).

15 (major diastereomer): ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, J = 6.7 Hz), 1.05 (3H, d, J = 6.7 Hz), 1.62 (3H, s), 1.70 (1H, m), 3.28 (3H, s), 3.50 (1H, m), 3.99 (1H, dd, J = 4.6, 8.6 Hz), 4.19 (1H, dd, J = 70, 8.6 Hz), 4.33 (1H, s).

15 (minor diastereomer): ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.89 (3H, d, J = 6.7 Hz), 1.01 (3H, d, J = 6.7 Hz) 1.56 (3H, s), 3.62 (3H, s), 3.60 (1H, m), 3.91 (1H, dd, J = 6.9, 8.8 Hz), 4.35 (1H, dd), 4.55 (1H, s).

General Procedure for Cyclopropanations with Trimethyl Sulfoxonium Ylide. Cyclopropyl Bicyclic Lactams 16, 17

In a dry round-bottomed flask was placed sodium hydride (1.0-2.0 equiv., 50% dispersion in mineral oil) under an argon atmosphere. The oil was removed by three washings with dry hexanes *via* cannula. The sodium hydride was dried under high vacuum and finely ground trimethyl sulfoxonium iodide (1.0-2.0 equiv.) was added as a solid. DMSO (X mL added to make final concentration of unsaturated lactam **10** ~0.15 - 0.20 M) was added slowly with stirring *via* syringe. After hydrogen gas evolution had ceased and the cloudy slurry became a clear homogeneous solution (~1 h), the unsaturated lactam **10** was added *via* cannula as a DMSO solution (5-10 mL). After varying reaction times and temperatures (vide infra) the solution was poured into an aqueous saturated ammonium chloride solution. The mixture was extracted exhaustively with ether and the combined organics were washed with water (2x) and brine before drying ($MgSO_4$). Concentration *in vacuo* and purification provided the cyclopropyl lactams **16, 17**.

Cyclopropyl lactams 16a, 17a

Prepared according to general procedure at rt for 2.5 h with 315 mg (1.74 mmol) of unsaturated lactam **10a**, 200 mg (2.09 mmol) of sodium hydride, and 460 mg (2.09 mmol) of trimethyl sulfoxonium iodide. Concentration *in vacuo* and purification by flash column chromatography (8% ethyl acetate/methylene chloride) gave 200 mg (64%) of cyclopropyl lactams **16a, 17a** as a 40:1 *endo/exo* diastereomeric ratio and 36 mg (20%) recovered **10a**. Recrystallization from ether-pentane (1:1) gave a colorless crystalline solid: mp 47-48°C; $[\alpha]_D$ +58.3° (c 1.33, THF); IR (KBr pellet) 2960, 1700, 1380 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.83 (3H,

d, J = 6.5 Hz), 0.87-0.90 (1H, m), 1.02 (3H, d, J = 6.7 Hz), 0.97-1.05 (1H, m), 1.60 (3H, s), 1.58-1.67 (1H, m), 1.74-1.80 (1H, m), 2.10-2.17 (1H, m), 3.25-3.31 (1H, m), 3.87 (1H, dd, J = 8.8, 6.5 Hz), 4.52 (1H, dd, J = 8.7, 8.0 Hz); MS *m/z* (relative intensity): 195 (2.7), 180 (41.7), 160 (3.6), 152 (100), 134 (8.5).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.95; H, 9.04.

Cyclopropyl lactams 16b, 17b

Prepared according to general procedure at rt for 2.5 h with 500 mg (2.09 mmol) of unsaturated lactam **10c**, 506 mg (2.29 mmol) of trimethyl sulfoxonium iodide, and 220 mg (2.29 mmol) of sodium hydride. Concentration of the organic extracts gave 340 mg (65%) of a colorless solid: mp 98-99°C (ether, clear prisms); $[\alpha]_D$ -69.0° (c 2.96, THF); IR (KBr pellet) 2900, 1730 (br), 1695, 1450 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.84 (3H, d, J = 6.5 Hz), 1.05 (3H, d, J = 6.6 Hz), 1.38 (1H, t, J = 5.0 Hz), 1.57-1.63 (1H, m), 1.82 (1H, dd, J = 7.7, 5.1 Hz), 2.31 (1H, dd, J = 7.8, 5.0 Hz), 3.32-3.40 (1H, m), 3.79 (3H, s), 3.86 (1H, dd, J = 8.8, 6.8 Hz), 4.26 (1H, t, J = 8.2 Hz); MS *m/z* (relative intensity): 253 (1.3), 238 (20.1), 210 (24.4), 178 (19.6), 170 (6.7), 113 (10.8).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.69; H, 7.55; N, 5.52.

After recrystallization, the mother liquor was found to contain a trace of an isomeric material (~1%), however contamination with residual starting material (**10c**) prevented characterization.

Cyclopropyl lactams, 16c, 17c.

Prepared according to general procedure at rt for 2.5 h with 139 mg (0.54 mmol) of unsaturated lactam **8**, 143 mg (0.65 mmol) of trimethyl sulfoxonium iodide, and 64 mg (0.65 mmol) of sodium hydride. Concentration of the organic extracts and purification by flash column chromatography (6% ethyl acetate/methylene chloride) gave 86 mg (58%) of **16c** and 3 mg (2%) of **17c**; diastereomeric ratio 29:1. Recrystallization of the major diastereomer from ether gave a colorless crystalline solid: mp 105.5-108°C; $[\alpha]_D$ -77.5° (c 1.2, THF); IR (KBr pellet) 2860, 1705, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.89 (3H, d, J = 6.6 Hz), 1.06 (3H, d, J = 6.7 Hz), 1.34-1.44 (2H, m), 1.68 (3H, s), 1.65-1.72 (1H, m), 2.11 (1H, dd, J = 7.3, 4.2 Hz), 3.39-3.45 (1H, m), 3.93 (1H, dd, J = 8.8, 6.8 Hz), 4.33 (1H, dd, J = 8.7, 7.9 Hz), 7.26-7.43 (5H, m); MS *m/z* (relative intensity): 271 (10.8), 256 (10.7), 228 (35.2), 205 (3.3), 188 (4.2), 159 (3.6), 144 (46.4).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80. Found: C, 75.27; H, 7.92.

Cyclopropyl lactams 16d, 17d

Prepared according to general procedure at 0-5°C for 2.5 h with THF as cosolvent, 147 mg (0.60 mmol) of unsaturated lactam **12** (as a 1:1 mixture of diastereomers at sulfur), 29 mg (0.60 mmol) of sodium hydride, and 66 mg (0.60 mmol) of trimethyl sulfoxonium iodide. Purification by flash column chromatography (1:5 - 1:2, ethyl acetate/hexane) afforded 101 mg (65%) combined yield of diastereomeric (1:1, at sulfur) cyclopropyl lactams **16d** (exclusively *endo* by ^{1}H-NMR). Recrystallization provided crystalline solids: (1) mp 81-82.5°C; $[\alpha]_D$ +33.2° (c 4.0, acetone); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.86 (3H, d, J = 6.6 Hz), 1.04 (3H, d, J = 6.6 Hz), 1.29 (1H, dd, J = 4.4, 8.2

Hz), 2.84 (3H, s), 3.29 (1H, m), 3.92 (1H, dd, J = 7.0, 9.0 Hz), 4.34 (1H, dd, J = 7.8, 9.0 Hz). (2) mp 115-116.5°C; $[\alpha]_D$ -11.4° (c 1.25, acetone); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.86 (3H, d, J = 6.6 Hz), 1.05 (3H, d, J = 6.6 Hz), 1.46 (1H, dd, J = 4.5, 5.7 Hz), 1.56 (1H, dd, J = 5.8, 8.0 Hz), 1.67 (3H, s), 3.38 (1H, dd, J = 4.5, 8.0 Hz), 2.87 (3H, s), 3.34 (1H, m), 3.91 (1H, dd, J = 7.0, 9.0 Hz), 4.33 (1H, dd, J = 7.8, 9.0 Hz).

Cyclopropyl lactams 16e, 17e

Prepared according to general procedure at 0-5°C for 2.5 h with THF as cosolvent, 62 mg (0.24 mmol) of unsaturated lactam **14**, 60 mg (0.26 mmol) of trimethyl sulfoxonium iodide and 14 mg (0.29 mmol) of sodium hydride. Purification provided 46 mg of cyclopropyl lactam **16e** (homogeneous by ^{1}H-NMR): ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.86 (3H, d, J = 6.6 Hz), 1.07 (3H, d, J = 6.7 Hz), 1.52 (1H, dd, J = 4.9, 5.7 Hz); 1.68 (3H, s), 1.80 (1H, dd, J = 5.7, 8.2 Hz), 2.66 (1H, dd, J = 4.9, 8.2 Hz), 3.25 (3H, s), 3.31 (1H, m), 3.92 (1H, dd, J = 7.0, 9.0 Hz).

Cyclopropyl lactams 16f, 17f

Prepared according to the general procedure for 30 min at rt followed by 10-12 h at 50-60°C using 0.719 g (3.68 mmol) of unsaturated lactam **10g**, 1.621 g (7.36 mmol, 2.0 equiv) of trimethylsulfoxonium iodide, and 0.294 g (7.36 mmol, 2.0 equiv.) of sodium hydride. Purification by flash column chromatography (gradient elution, 10%-30% ethyl acetate/hexane) gave 0.622 g (81%) of a 19:1 (*via* vpc) mixture of diastereomers (**16f:17f**, respectively). The minor diastereomer **17f** was readily removed by recrystallization from hexanes at 0°C to provide pure (homogeneous by vpc) **16f** as colorless plates: mp 72.0-72.5°C; $[\alpha]_D^{22}$ 72.9° (c 1.41, THF); R_f 0.60 (50% ethyl acetate/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.87-0.92 (1H, m), 0.94 (9H, s), 0.96-1.04 (1H, m), 1.62 (3H, s), 1.75-1.82 (1H, m) 2.12-2.19 (1H, m), 3.35 (apparent t, 1H, J = 8.5 Hz), 3.95 (apparent t, 1H, J = 9.1 Hz), 4.22 (1H, dd, J = 8.3 Hz, 9.3 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 178.5, 99.0, 69.9, 65.3, 33.0, 27.1, 26.1, 24.9, 20.2, 10.1; IR (CCl_4) 1719 (C=O); MS *m/z* (relative intensity): 209 (M^+, 1.1), 194 (M^+-15, 9.3), 152 (72.9), 124 (11.6), 55.1 (21.5), 40 (26.7), 32 (100), 28 (100).
Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.95; H, 9.17; N, 6.61.

Cyclopropyl lactams 16g, 17g

Prepared according to general procedure at 0°C for 3 h using 0.38 g (1.66 mmol) of unsaturated lactams **13** (as a 1:1 mixture of diastereomers at sulfur), 0.42 g (1.91 mmol) of trimethyl sulfoxonium iodide, and 0.092 g (1.92 mmol) of sodium hydride with THF as cosolvent. Purification by flash column chromatography (1:5 - 1:2, ethyl acetate/hexane) afforded 0.20 g (50%) of *exo* cyclopropyl adducts **16g** (exclusively *exo* by ^{1}H-NMR), diastereomeric at sulfur (1:1): (1) mp 110-111°C; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.89 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.7 Hz), 1.38 (1H, t, J = 4.9 Hz), 1.55 (1H, m), 2.07 (1H, dd, J = 4.9, 9.4 Hz), 2.80 (1H, dd, J = 5.0, 9.4 Hz), 2.81 (3H, s), 3.26 (2H, m), 4.27 (1H, m), 4.81 (1H, s). (2) mp 109-110°C; $[\alpha]_D$ 178.5° (c 1.2, acetone); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.88 (3H, d, J = 6.7 Hz), 0.94 (3H, d, J = 66 Hz), 1.57 (1H, dd, J = 4.9, 5.1 Hz),

1.58 (1H, m), 1.90 (1H, dd, J = 5.1, 9.3 Hz), 2.63 (3H, s), 2.88 (1H, d, J = 4.9, 9.3 Hz), 3.63 (2H, m), 4.23 (1H, m), 4.83 (1H, s).

Cyclopropyl lactams 16h, 17h

Prepared according to general procedure at rt for 2.5 h using 90 mg (0.40 mmol) of unsaturated lactam **10f**, 106 mg (0.48 mmol) of trimethyl sulfoxonium iodide, and 22 mg (0.48 mmol) of sodium hydride. Recrystallization from ether gave 55 mg (50%) of a colorless crystalline solid: (single *exo* cyclopropane diastereomer **17h** by ^{1}H-NMR); mp 94-95°C; $[\alpha]_D$ 152° (c 1.2, THF); IR (KBr pellet) 2870, 1720, 1445 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.84 (3H, d, J = 6.7 Hz), 0.91 (3H, d, J = 6.7 Hz), 1.46-1.55 (2H, m), 1.99 (1H, dd, J = 9.0, 4.6 Hz), 2.81 (1H, dd, J = 9.0, 5.5 Hz), 3.55 (1H, dd, J = 8.5, 7.1 Hz), 3.68 (1H, q, J = 8.3 Hz), 3.76 (3H, s), 4.17 (1H, dd, J = 8.1 Hz), 4.68 (1H, s); MS *m/z* (relative intensity): 238 (5.5), 209 (19.2), 196 (49.7), 181 (17.6), 164 (54.4). **Anal.** Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16. Found: C, 60.15; H, 7.17.

Cyclopropyl lactams 16i, 17i.

Prepared according to general procedure at rt for 6 h using 96 mg (0.53 mmol) of unsaturated lactam **10h**, 223 mg (1.06 mmol, 2.0 equiv) of trimethyl sulfoxonium iodide, and 42 mg (1.06 mmol) of sodium hydride. Purification, by passing through a silica gel plug (10% ethyl acetate/hexane), yielded 41 mg (40%) of **17i** (single diastereomer by ^{1}H-NMR) as a colorless oil: $[\alpha]_D^{22}$ 149° (c 0.93, $CHCl_3$); R_f 0.45 (50% ethyl acetate/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.86 (9H, s), 1.00-1.07 (1H, m), 1.20-1.28 (1H, m), 1.95-2.02 (1H, m), 2.31 (1H, ddd, J = 4.5, 5.4, 8.5 Hz), 3.68-3.76 (2H, m), 4.04-4.12 (1H, m), 4.76 (1H, d, J = 1.3 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 14.4, 20.2, 22.5, 26.0, 33.3, 63.6, 67.9, 92.5, 182.3.

General Procedure for 3+2 Cycloaddition of Diazomethane to the Unsaturated Lactams 10, 12

Diazomethane was generated using the mini-Diazald apparatus according to the method described in Aldrich Technical Information Bulletin #AL-180. Excess diazomethane (~10 equiv) was codistilled with ether directly into an ether solution of the unsaturated lactams **10, 12** at rt. Reaction progress was monitored by TLC and when all starting material had been consumed, the excess diazomethane was quenched with glacial acetic acid until the solution was colorless and nitrogen gas evolution had ceased. The ether solution was diluted with heptane and concentrated *in vacuo*. The residue was purified by flash column chromatography.

General Procedure for 3 + 2 Cycloaddition of Diazoisopropane to the Unsaturated Lactams 10

Diazoisopropane was generated according to the procedure of Andrews, et. al.[19] and an excess was added to an ether solution of the unsaturated lactam **10** at -78°C. The mixture was allowed to warm to rt and after reaction was complete as judged by TLC, the mixture was

concentrated and either purified by flash column chromatography or submitted directly to the photolysis step.

General Procedure for Photolysis of Pyrazolines 18

The crude or purified pyrazolines were dissolved in benzene, transferred to a KIMAX test tube and sealed. The mixture was irradiated with a medium pressure Hanovia lamp (Pyrex cooling sleeve) until no pyrazoline was detected by TLC. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography.

Pyrazoline 18a

Treatment of a 1:1 diastereomeric mixture (at sulfur) of the α-sulfoxy unsaturated lactams **12** (15 mg, 0.06 mmol) with diazomethane (16 h) gave 16 mg (91%) of the pyrazolines **18a** (1:1, diastereomeric at sulfur) as a colorless oil after purification by flash column chromatography (10:1, hexane/ethyl acetate): ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.85 (6H, d, J = 6.6 Hz); 1.0 (3H, d, J = 6.2 Hz), 1.06 (3H, d, J = 6.2 Hz), 1.56 (3H, s), 1.58 (3H, s), 1.66 (1H, m), 3.01 (2H, m), 3.18 (3H, s), 3.19 (3H, s), 3.48 (1H, m), 3.80 (1H, m), 4.16 (1H, m), 4.78-5.01 (2H, m), 5.12-5.24 (2H, m).

Pyrazoline 18b

Treatment of the unsaturated lactam **10d** (80 mg, 0.35 mmol) with diazomethane (16 h) gave 52 mg (55%) of the pyrazoline **18b** and 22 mg (38%) of unreacted starting material **10d** after purification by radial chromatography (10:1, hexane/ethyl acetate): mp 119-121°C; $[\alpha]_D$ -101° (c 2.0, acetone); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.86 (3H, d, J = 6.6 Hz), 1.07 (3H, d, J = 6.7 Hz), 1.55 (3H, s), 1.67 (1H, m), 2.37 (1H, dd, J = 5.0, 9.6 Hz), 2.54 (3H, s), 3.50 (1H, m), 3.81 (1H, apparent t, J = 8.0 Hz), 4.15 (1H, apparent t, J = 8.0 Hz), 4.74-5.01 (2H, AB system, J = 18.8, 9.8 Hz).

Pyrazoline 18c

Treatment of the unsaturated lactam **10b** (200 mg, 1.02 mmol) with diazomethane (16 h) gave 90 mg (45%) of unreacted starting material **10b** and 112 mg (46%) of pyrazoline **18c** as a colorless crystalline solid: mp 88-89°C; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.86 (3H d, J = 6.6 Hz), 1.06 (3H, d, J = 6.7 Hz), 1.51 (3H, s), 1.66 (1H, m), 1.74 (3H, s), 2.30 (1H, dd, J = 4.1, 9.6 Hz), 3.51 (1H, m), 3.78 (1H, apparent t, J = 7.2 Hz), 4.08 (1H, apparent t, J = 7.8 Hz), 4.74 (1H, dd, J = 9.6, 18.8 Hz), 5.06 (1H, dd, J = 4.1, 18.8 Hz).

Pyrazoline 18g

Treatment of the unsaturated lactam **10g** (147 mg, 0.75 mmol) with diazomethane (~14 equiv.; 1.5 h) gave 191 mg (100%) of the pyrazoline **18g** which could be recrystallized from ethyl acetate/hexane to provide a colorless crystalline solid which slowly decomposed on standing: R_f 0.40 (50% ethyl acetate/hexane); mp 101-102°C; $[\alpha]_D^{22}$ 480° (c 0.57, $CHCl_3$); IR (neat) 1714 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.96 (9H, s), 1.55 (3H, s), 2.66 (1H, apparent dt, J = 4.9, 9.7 Hz), 3.58

(1H, apparent t, J = 8.8 Hz), 3.88 (1H, apparent t, J = 9.2 Hz), 4.10 (1H, dd, J = 8.3, 9.0 Hz), 4.75 (1H, ddd, J = 2.5, 10.0, 18.7 Hz), 5.02 (1H, ddd, J = 2.5, 4.8, 7.3 Hz), 5.91 (1H, dd, J = 2.2, 9.2 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 27.2, 27.5, 33.0, 39.5, 66.0, 67.7, 79.8, 97.7, 98.0, 173.2.

Anal. Calcd for $C_{12}H_{19}N_3O_2$: C, 60.73; H, 8.07; N, 17.71. Found: C, 60.94; H, 8.25; N, 17.75.

Endo and Exo Cyclopropyl lactams, 19h

Treatment of the unsaturated lactam **10h** (100 mg; 0.55 mmol) with diazomethane (~8 equiv., 4 h) gave 124 mg (~100%) of an ~1:1 mixture (^{1}H-NMR) of *endo/exo* pyrazolines which were found to be unstable to silica gel. A sample of the 1:1 mixture of pyrazolines (20 mg, .09 mmol) was photolyzed and purification by flash column chromatography (gradient elution, 0%-20% ethyl acetate/hexane) afforded 3 mg of ***exo*-19h**, 4 mg of ***endo*-19h** (40% total yield), and 6 mg (34%) of unsaturated lactams **21** (R_1=t-Bu; R_2, R_3, R_4=H).

***endo*-19h**: This compound was identical to the cyclopropyl adduct **16h** (vide infra) obtained by the sulfur ylide method.

***exo*-19h**: Physical and spectral data can be found in the text (Table III).

Cyclopropyl Lactam 19e

Cycloaddition of diazoisopropane with lactam **10d** (240 mg, 1.06 mmol) required 3 days for complete reaction and additional portions of diazoisopropane were added each day. After two sequential purifications by flash column chromatography (gradient elution 5% - 10% ethyl acetate/hexane) 190 mg (67%) of the cyclopropyl lactam **19e** and 88 mg (31%) of the β-ispropyl-α,β-unsaturated lactam **21** (R_1=i-Pr; R_2, R_4=CH_3; R_3=SCH_3) were isolated pure.

19e: mp 71-73°; $[\alpha]_D$ 9.9° (c, 2.6); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.87 (3H, d, J = 6.5 Hz), 1.07 (3H, d, J = 6.7 Hz), 1.15 (3H, s), 1.32 (3H, s), 1.54 (1H, s), 1.56 (3H, s), 1.62 (1H, m), 2.25 (3H, s), 3.43 (1H, m), 3.89 (1H, dd, J = 7.4, 8.8 Hz), 4.35 (1H, dd, J = 8.0, 8.8 Hz), ^{13}C ($CDCl_3$, 270 MHz) δ 174.94, 97.99, 72.81, 59.88, 49.46, 38.44, 34.88, 32.82, 26.95, 23.67, 20.66, 18.78, 18.44, 15.11.

21: ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.90 (3H, d, J = 6.6 Hz), 1.08 (3H, d, J = 6.6 Hz), 1.26 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 7.0 Hz), 1.55 (3H, s), 1.71 (1H, m), 2.49 (3H, s), 2.90 (1H, dq, J = 7.0, 7.2 Hz), 3.47 (1H, m), 3.99 (1H, dd, J = 6.4, 8.8 Hz), 4.27 (1H, dd, J = 7.5, 8.8 Hz).

Cyclopropyl Lactam 19f

Cycloaddition of diazoisopropane with the unsaturated lactam **10h** (98 mg, 0.50 mmol) required 19 h for completion. Photolysis of the crude pyrazolines and purification (gradient elution, 3% - 7% ethyl acetate/hexane) gave 105 mg (88%) of a 1:1 mixture (vpc) of *endo/exo* cyclopropyl lactam adducts **19f**. Purification by preparative thin layer chromatography (1 mm SiO_2, 0.5% ethyl acetate/hexane, 3 elutions) provided pure samples of the *exo* and *endo* diastereomers.

***endo*-19f**: This compound was identical to the cyclopropyl adduct **(+)-22** (vide infra) obtained by the sulfur ylide method.

***exo*-19f**: Spectral data can be found in the text (Table III).

Gem-dimethy cyclopropyl lactam (+)-22

To a stirred solution of 1.55 g (5.12 mmol. 2.0 equiv) of ethyl diphenylsulfonium tetrafluoroborate (prepared by addition of diphenyl sulfide to an equimolar amount of triethyloxonium tetrafluoroborate in methylene chloride, rt, 24h), 328 μL (5.12 mmol, 2.0 equiv) of dry methylene chloride, and 50 mL of freshly distillled DME was added lithium diisopropylamide (LDA , 1.5 M in cyclohexane, Aldrich) under an argon atmosphere at -70°C (dry ice/ ethanol bath) until the yellow-green color persisted. At this point, 3.75 mL (5.63 mmol, 2.2 equiv) of LDA was added. The clear yellow-green solution became cloudy after 5 min. The mixture was stirred at -70° for 30 min and 335 μL (5.38 mmol, 2.1 equiv) of methyl iodide was added (passed through basic alumina immediately prior to use) which caused the yellow-green color to fade and caused the formation of a colorless precipitate after 5 min. After stirring for 2h between -70 and -50°C an additional 3.75 mL (5.63 mmol) of LDA was added which immediately produced a bright orange colored soultion. The solution was stirred for 1.5 h at -70°C and 0.495 g (2.56 mmol, 1.0 equiv) of the unsaturated bicyclic lactam **10g** was added as a DME solution (7 mL). The solution was stirred for 3 h while maintaining the temperature between -70° and -20°C. The colorless mixture was quenched with 10 mL of aqueous saturated ammonium chloride, allowed to warm to ambient temperature, concentrated in vacuo, and extracted with diethyl ether (3 x 75 mL). The organics were combined, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography (10% ethyl acetate/hexane) afforded 0.574 g (94%) of *endo* gem-dimethylcyclopropane bicyclic lactam **(+)-22** as a colorless crystalline solid. The *exo* diastereomer could not be detected (*via* vpc) and the limits of detection were estimated at 0.6%. The product was further purified by recrystallization from hexanes at 0°C to provide colorless prisms: mp 76.0-77.0°C ; $[\alpha]_D^{20}$ 100.9° (c 1.12, EtOH); IR (KBr pellet) 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.93 (9H, s), 1.06 (3H, s), 1.12 (3H, s), 1.55 (3H, s), 1.44 (1H, d, J = 6.0 Hz), 2.07 (1H, d, J = 5.9 Hz), 3.47 (1H, apparent t, J = 8.7 Hz), 3.96 (1H, apparent t, J = 9.2 Hz), 4.21 (1H, apparent t, J = 9.0 Hz); ^{13}C-NMR ($CDCl_3$, 270 MHz) δ: 176.1, 99.9, 70.0, 63.4, 38.7, 33.1, 30.9, 27.4, 27.2, 26.7, 25.5, 17.0; MS *m/z* (relative intensity) 239 (M^++2, 0.2), 238 (M^++1, 1.2), 237 (M^+, 6.1), 222 (M^+-15, 37.8), 180 (53.9), 142.0 (30.0), 96 (30.8), 84 (87.0), 28 (100.0).
Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77. Found: C, 70.76; H, 9.98.

General Procedure for Acid Hydrolysis. Cyclopropanes 23, 24

The cyclopropyl lactam **16** was dissolved in 10% sulfuric acid/methanol and heated at reflux for 4 days. After cooling to rt, the reaction mixture was partially neutralized with solid sodium carbonate and extracted with ether. The combined organics were washed with a saturated aqueous solution of sodium bicarbonate, brine, and then dried ($MgSO_4$).

Cyclopropyl methyl ester, 23a.

Hydrolysis performed according to the general procedure using 140 mg (0.718 mmol) of cyclopropyl lactam **16a** in 7 mL of 10% sulfuric acid/methanol to give 89 mg (88%) of the cyclopropyl methyl ester **23a** as an oil: $[\alpha]_D$ 48.7° (c 0.79, THF); IR (neat) 2940, 1700, 1440 cm^{-1};

^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.18-1.26 (1H, m), 1.66-1.72 (1H, m), 2.06-2.25 (2H, m), 2.26 (3H, s), 3.67 (3H, s); MS *m/z* (relative intensity): 142 (4.7), 127 (100), 111 (28.9), 110 (26.7), 100 (12.7), 99 (10.3), 68 (29.2).

Prolonged heating in the acidic hydrolysis medium gave the epimerized product **24a** as a minor component: $[\alpha]_D$ 254° (c 0.68, THF); IR (neat) 2850, 1735, 1705, 1390 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.39-1.45 (2H, m), 2.14-2.21 (1H, m), 2.30 (3H, s), 2.45-2.47 (1H, m), 3.69 (3H, s).

Cyclopropyl methyl diester, 23b

Hydrolysis performed according to the general procedure using 570 mg (2.25 mmol) of cyclopropyl lactam **16h** in 25 mL 10% sulfuric acid/methanol to give 389 mg (86%) of cyclopropyl methyl diester **23b** as colorless prisms (recrystallized from ether): mp 72-73°C; $[\alpha]_D$ -149.7° (c 4.67, THF); IR (neat) 2930, 1720 (br), 1690, 1420 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.64 (1H, dd, J = 8.6, 4.4 Hz), 1.98 (1H, t, J = 2.5 Hz), 2.36 (3H, s), 2.86 (1H, dd, J = 8.4, 6.8 Hz), 3.73 (3H, s), 3.77 (3H, s). MS *m/z* (relative intensity): 200 (1.6), 185 (53.5), 169 (24.6), 153 (18.5), 140 (10.9), 126 (15.3).
Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 54.16; H, 6.09.

Cyclopropylmethyl ester, 23c

Hydrolysis performed according to the general procedure using 58 mg (0.214 mmol) of the cyclopropyl lactam **16c** in 6 mL of 10% sulfuric acid/methanol to give 38 mg (81%) of the cyclopropyl methyl ester **23c** as an oil: $[\alpha]_D$ 176° (c 1.5, THF); IR (neat) 2980, 1750, 1710, 1445 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.52 (1H, dd, J = 8.3, 4.8 Hz), 2.13 (1H, dd, J = 6.1, 4.7 Hz), 2.37 (3H, s), 2.46 (1H, dd, J = 8.1, 6.4 Hz), 3.62 (3H, s), 7.28-7.42 (5H, m); MS *m/z* (relative intensity): 218 (0.3), 186 (9.2), 159 (51.7), 144 (6.2), 131 (5.1), 115 (23.4).

Vinyl Cyclopropane S-(-)-29

Methyl triphenylphosphonium bromide (580 mg, 1.63 mmol) was stirred in THF (20 mL) at rt and 0.87 mL of n-butyllithium (1.87 M in hexanes) was added (turns yellow). After being stirred for 45 min., methyl ketone **23b** (250 mg, 1.25 mmol) dissolved in 5 mL of the same solvent was introduced with continued stirring for 3 h. The reaction mixture was quenched with water, and the aqueous phase extracted with ether. The combined organic layers were washed with brine and dried (Na_2SO_4). Concentration gave 114 mg (72%) of S-(-)-**29** as a clear liquid: $[\alpha]_D$ -119.6° (c 1.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.47 (1H, dd, J = 3.9, 1.9 Hz), 1.80 (3H, s), 1.87 (1H, dd, J = 8.1, 5.0 Hz), 2.49 (1H, t, J = 8.5 Hz), 3.68 (3H, s), 3.75 (3H, s), 4.71 (1H, s), 4.87 (1H, s).

Cyclopropyl lactone, 31

The ketone **23b** (70 mg, 0.35 mmol) was dissolved in methanol (10 mL) and cooled to 0°C. Sodium borohydride (13.4 mg, 0.35 mmol) was added in two equal portions one hour apart. The reaction mixture was stirred a total of 2.5 h and quenched by the addition of water (1 mL). The solution was extracted with ether, and the organic extracts washed with brine and dried. Concentration gave 62.4 mg (89%) of cyclopropyl lactone **31** as a solid: mp 97.5-99°C; $[\alpha]_D$ -56.8°

(c 1.1, THF); IR (KBr pellet) 2995, 1780, 1440, cm^{-1}; ^1H-NMR ($CDCl_3$, 270 MHz) δ 1.38-1.42 (1H, m), 1.44 (3H, d, J = 6.4 Hz), 2.04 (1H, dd, J = 8.0 Hz, 4.5 Hz), 2.52 (1H, dd, J = 7.8, 5.3 Hz), 3.82 (3H, s), 4.43 (1H, q, J = 6.4 Hz); MS *m/z* (relative intensity): 170 (8.9), 155 (86.1), 139 (23.8), 126 (39.9). **Anal.** Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.56; H, 5.99.

Cyclopropyl alcohol, 32

Ketone **23b** (38 mg, 0.18 mmol) was dissolved in ethanol (2.9 mL). $CeCl_3$-$7H_2O$ (78 mg, 0.21 mmol) and water (1.7 mL) were added and stirred until dissolved. After being cooled to -15°C (Salt - ice bath), sodium borohydride (10 mg, 0.26 mmol) was added in portions over 10 min. The reaction mixture was stirred 0.5 h and quenched by the addition of acetone (1mL). The solution was extracted with ether, and the organic extracts washed with brine and dried. Concentration gave 35 mg (99%) of cyclopropyl alchohol **32** as an oil: $[\alpha]_D$ -19.3° (c 1.38, THF); IR (neat) 3480 (brd), 2940, 1730, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.25 (1H, dd, J = 7.4, 5.2 Hz), 1.32 (3H, d, J = 6.3 Hz), 1.53 (1H, dd, J = 9.2, 5.0 Hz), 1.89-1.98 (1H, m), 2.50 (1H, br s), 3.15-3.24 (1H, m), 3.72 (3H, s), 3.80 (3H, s).

Vinyl cyclopropane, S-(-)-30

Alcohol **32** (53 mg, 0.26 mmol) and triethylamine (0.146 mL, 1.10 mmol) were dissolved in dichloromethane (3 mL) and cooled to 0°C. Methane sulfonyl chloride (0.041 mL, 0.52 mmol) was added dropwise with stirring for 15 min. Water (1 mL) was added and the aqueous phase extracted with ether. The combined organic layers were washed with dilute acid (5% HCl), saturated sodium carbonate solution, and brine before drying over $MgSO_4$. Concentration gave 73 mg (99%) of the mesylate as an oil. The mesylate (70 mg, 0.25 mmol) was dissolved in 4 mL of benzene. DBU (0.19 mL, 1.25 mmol) and DMAP (5 mg) were added and the reaction mixture brought to reflux for 48 h. After cooling to rt the reaction mixture was concentrated and directly applied to a column of SiO_2. Elution with 30% ethyl acetate/hexane gave 22.6 mg of the vinyl cyclopropane S-(-)-**30** as an oil: $[\alpha]_D$ -46.1° (c 0.33, CCl_4); ^1H-NMR ($CDCl_3$, 270 MHz) δ 1.58 (1H, dd, J = 9.1, 4.9 Hz), 1.72 (1H, dd, J = 7.5, 4.9 Hz), 2.59 (1H, q, J = 8.0 Hz), 3.74 (6H, s), 5.12 - 5.43 (3H, m).

Cyclopropyl ketoaldehyde 38

Note: Method A provided pure ketoaldehyde which allowed determination of spectral characteristics. However, in most runs, Method B was followed and the crude hydrolysis mixture containing mostly the desired ketoaldehyde and starting material **(+)-22** was submitted directly to the dibromoolefination reaction.

Method A: To a stirred solution of 0.164 g (0.68 mmol, 1.0 equiv) of the *endo* gem-dimethyl cyclopropane adduct in 10 mL of dry THF was added 0.22 mL (0.75 mmol, 1.1 equiv) of sodium bis-(2-methoxyethoxy) alumino hydride (3.4 M solution in toluene, Aldrich) at 0°C under an argon atmosphere. After 15 min, the ice bath was removed and the mixture was allowed to warm to rt. After 24h, the reaction was quenched with 0.5 mL of methanol and the reaction mixture was

concentrated *in vacuo*. Addition of 10 mL of aqueous 5% sodium hydroxide was followed by extraction with diethyl ether (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. The crude intermediate carbinolamine was submitted directly to hydrolytic conditions by addition of 10 mL of methylene chloride and 10 ml of aqueous 1M $Bu_4NH_2PO_4$. The biphasic solution was stirred vigorously at rt for 96h. The layers were separated, after diluting the methylene chloride phase with 50 mL diethyl ether (this was necessary due to the solubility of $Bu_4NH_2PO_4$ in CH_2Cl_2) and the aqueous phase was then extracted with diethyl ether (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) then carefully concentrated *in vacuo* (with a cold water bath to keep the distilling flask cold during solvent removal) to provide a yellow oil. The combined organics were then washed with an aqueous 10% sodium bisulfite solution to form the bisulfite adduct **37**. The ether layer contained mostly unreacted cyclopropane adduct **(+)-22**. This was purified by flash column chromatography (1% ethyl acetate/methylene chloride) to provide 70 mg of recovered starting material **(+)-22**. The sodium bisulfite extract was cooled in an ice/water bath and then the pH was adjusted to 9 with aqueous 10% sodium hydroxide solution at which point the bisulfite solution went from clear to cloudy. The bisulfite extract was kept cold and extracted with diethyl ether (4 x 50 mL). The combined organics were washed with brine then dried ($MgSO_4$). Careful removal of solvent by rotary evaporation *in vacuo* using a cold water bath afforded the desired product as a yellow oil: IR (CCl_4) 1704 (br), 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.32 (3H, s), 1.46 (3H, s), 1.89 (1H, dd, J = 8.3, 6.3 Hz), 2.31 (3H, s), 2.46 (1H, d, J = 8.4 Hz), 9.77 (1H, d, J = 6.3 Hz); ^{13}C-NMR ($CDCl_3$, 270 MHz) δ 204.3, 199.9, 45.4, 43.2, 31.7, 30.3, 29.6, 28.4, 14.5.

Method B: Reduction-hydrolysis performed as in Method A with 91 mg (0.378 mmol) of gem-dimethyl cyclopropane adduct **(+)-22** in 10 mL of dry THF, 0.08 mL (0.265 mmol) of sodium bis-(2-methoxyethoxy) alumino hydride (3.4 M solution in toluene, Aldrich), 10 mL of methylene chloride, and 10 ml of aqueous 1M $Bu_4NH_2PO_4$. The crude product consisting of the ketoaldehyde **38** and starting material **(+)-22** was submitted directly to the dibromoolefination reaction.

Cyclopropyl dibromoolefin 39

To a stirred solution of 0.398 g (1.52 mmol, 2.0 equiv) of carbon tetrabromide in 5 mL of dry methylene chloride cooled to 0°C under an argon atmosphere was added 0.260 g (0.784 mmol. 1.0 equiv) of triphenylphosphine. This immediately produced a dark orange colored solution. After 10 min, the ketoaldeyde was added as a methylene chloride solution (6 mL) *via* cannula. After 10 min, the reaction was quenched by the addition of 5 mL of aqueous 20% sodium thiosulfate solution. The phases were separated and the aqueous phase was extracted with methylene chloride (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$), then concentrated *in vacuo* to afford a viscous brown oil. Purification by flash column chromatography (gradient elution: methylene chloride -> 30% ethyl acetate/methylene chloride) provided 47 mg of recovered *endo* gem-dimethyl cyclopropyl bicyclic lactam **(+)-22** and 23 mg (42%, based on recovered starting material, over 3 steps) of the desired dibromoolefin as a colorless solid: mp 40.5-41.5°C; $[\alpha]_D^{20}$

24.0° (c 0.92, $CHCl_3$); IR (CCl_4) 1698, 1550 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.18 (3H, s), 1.25 (3H, s), 2.01 (1H, t, J = 8.4 Hz), 2.16 (1H, d, J = 8.2 Hz), 2.24 (3H, s), 6.81 (1H, d, J = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 270 MHz) δ 14.6, 28.7, 33.0, 38.6, 39.6, 88.9, 133.6, 167.2; MS *m/z* (relative intensity) 296 (M^++2, 0.3), 279 (M^+-15, 0.4), 215.1 (20.6), 174 (38.5), 172 (40.7), 93 (79.9), 91 (36.8), 77.1(32.0), 32 (100), 28 (100).

Anal. Calcd for $C_9H_{12}OBr_2$: C, 36.52; H, 4.09. Found: C, 36.87; H, 4.02.

cis-(1S,3R)-Deltamethrinic acid (-)-34

A sodium hypobromite solution was prepared by dropwise addition of 11 μL (0.21 mmol, 3.3 equiv) of Br_2 to a stirred solution of 33 mg (0.83 mmol, 13 equiv) of sodium hydroxide in 0.92 mL of water maintained at 0°C with an ice/water bath. To the resulting yellow solution was added 180 μL of cold dioxane. A solution of the cyclopropyl methyl ketone was prepared by addition of 260 μL of water and 880 μL of dioxane to 19 mg (0.064 mmol, 1.0 equiv) of the methyl ketone **39**. This solution was cooled to 0°C and then the sodium hypobromite was added to the methyl ketone *via* cannula. The mixture was kept below -10°C for 4h, quenched with 2 mL of aqueous 20% sodium thiosulfate solution, and heated at reflux for 15 min. The reaction mixture was cooled slightly and then acidified to pH 5 with aqueous 1N HCl at which time a solid precipitated out of solution. The mixture was concentrated *in vacuo*, 5 mL of water was added and the mixture was extracted with ethyl acetate (3 x 60 mL). The combined organics were washed with brine, dried ($MgSO_4$), then concentrated *in vacuo* to afford 20 mg (~100%) of a yellow crystalline solid. Purification by sublimation (100-110°C, 0.7 mm Hg) afforded 15.0 mg (81%) of cis-(1S, 3R)-deltamethrinic acid (-)-**34** as a white waxy solid in 97% ee: mp 129-130°C; $[\alpha]_D^{22}$ -16.8° (c 1.50, $CHCl_3$); authentic sample from Roussel-Uclaf gave mp 129-132°C, $[\alpha]_D^{22}$ -17.3° (c 1.50, $CHCl_3$) ; IR (CCl_4) 3400-2700, 1698 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.27 (3H, s), 1.29 (3H, s), 1.85 (1H, d, J = 8.4 Hz), 2.04 (1H, t, J = 8.5 Hz), 6.73 (1H, d, J = 8.6 Hz), 11.0-12.4 (1H, br s); MS *m/z* (relative intensity) 300 (M^++4, 0.3), 298 (M^++2, 0.6), 296 (M^+, 0.2), 93 (10.9), 91 (17.0), 44 (31), 32 (27), 28 (100).

Anal. Calcd for $C_8H_{10}O_2Br_2$: C, 32.25; H, 3.38. Found: C, 32.12; H, 3.53.

Salt-free triphenylphosphonium pentylidene

The "salt-free" ylide solution was prepared according to the procedure of Bestman.[48] Treatment of a THF slurry of pentenyl triphenyl phosphonium bromide (5.0 g, 12.1 mmol) with 14.3 mL (12.1 mmol) of sodium hexamethyldisilazide (0.89 M in THF) produced a deep orange-colored solution with concurrent sodium bromide precipitation. The mixture was stirred for 1h at rt and then 1h at reflux. After cooling, the THF was distilled by short-path distillation and the hexamethyl disilazane was removed under high vacuum at ~100°C. The resulting bright orange residue was taken up in 44 mL of dry THF.

Cyclopropyl olefin 49

The solid cyclopropane adduct **(+)-16f** (1.119 g, 5.35 mmol) was dissolved in 30 mL of dry THF in a dry 100 mL round-bottomed flask. To this solution was added 1.10 mL (3.74 mmol, 0.7

equiv) of Red-Al (3.4 M in toluene, Aldrich) dropwise over 2 min with stirring at rt under an argon atmosphere. After stirring for 17h at rt, the solution was quenched with 0.2 mL of methanol (gas evolution) and concentrated *in vacuo*. The residue was taken up in 80 mL of ethyl acetate and washed with 10% aqueous sodium hydroxide solution (10 mL), brine (5 mL), and then dried ($MgSO_4$) and concentrated *in vacuo*. After removal of residual water by azeotropic distillation with benzene (3 x 20mL), the crude carbinolamines **47** were diluted in 100 mL of dry THF and cooled to 0°C (Cryocool) under an argon atmsophere. To this solution was added 27.2 mL (13.38 mmol, 2.2 equiv) of a 0.492 M solution of salt-free triphenylphosphonium pentylidene precooled to 0°C. The resulting orange mixture was stirred at 0°C for 24 h and then allowed to warm to rt overnight. The crude oxazolidines **52** were hydrolyzed by addition of 50 mL of aqueous 1M $Bu_4NH_2PO_4$ directly into the reaction flask (immediate fading from orange to colorless) followed by vigorous stirring at rt for 15h. The mixture was concentrated *in vacuo* and the aqueous layer was diluted with 10mL of H_2O and extracted with diethyl ether (3 x 75 mL). The ethereal extracts were washed with brine (10 mL) and then dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was preadsorbed onto silica gel from diethyl ether and then applied as a dry powder to the top of a silica gel column which had been eluted with hexanes. Gradient elution (hexane->5%->10%->20% ethyl acetate/hexane) provided 482 mg of olefin isomers plus traces of triphenylphosphine oxide. The product was further purified by micro-distillation to provide 452 mg (51% over 3 steps from **16f**) of the cyclopropyl olefin **49** as a colorless, odoriferous (terpene-like) oil (91:9 Z/E, *via* vpc; 96:4 Z/E *via* ^{1}H-NMR): R_f 0.30 (10% ethyl acetate/hexane); bp 73-75°C (0.5 mm Hg); $[\alpha]_D^{22}$ -390° (c 1.54, $CHCl_3$); IR (neat) 1698 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300MHz) δ 0.90 (3H, t, J=6.8 Hz), 1.14-1.21 (1H, m), 1.26-1.40 (4H, m), 2.04-2.33 (4H, m), 2.22 (3H, s), 5.15-5.23 (3H, m), 5.40-5.49 (2H, m); ^{13}C-NMR ($CDCl_3$, 300MHz) δ 13.8, 15.0, 21.9, 22.2, 27.2, 28.9, 31.5, 31.7, 125.8, 132.1, 205.8.
Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.35; H, 11.00.

Cyclopropyl hydrazone 53

To a dry 10 mL round-bottomed flask containing 395 mg (2.37 mmol) of the cyclopropyl methyl ketone **49** was added 463 mg (2.49 mmol; 1.05 equiv) of p-tosyl hydrazide. A minimum amount of ethanol was added to dissolve the hydrazide and the mixture was stirred at rt for 24h. A colorless crystalline precipitate formed after 3h. The flask was cooled to 0°C and the solid was collected by vacuum filtration and washed with small portions of cold ethanol to provide 593 mg of tosyl hydrazone **53** as a colorless crystalline solid. The remaining filtrate was concentrated and the residue was dissolved in a minimum amount of hot ethanol. Recrystallization at 0°C provided an additional 80 mg (85% total isolated yield): R_f 0.54 (50% ethyl acetate/hexane); mp 133-135°C dec; $[\alpha]_D^{22}$ -791° (c 1.05, $CHCl_3$); IR (CCl_4) 3215, 1741, 1576 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.88 (3H, brt, J = 6.9Hz), 0.93-1.00 (1H, m), 1.14-2.20 (1H, m), 1.26-1.32 (4H, m), 1.73-1.85 (1H, m), 1.77 (3H, s), 1.87-1.93 (1H, m), 2.42 (3H, s), 4.20 (1H, dd, J = 9.7, 10.9 Hz), 5.05 (1H, dt, J = 7.4, 10.9 Hz), 7.10 (1H, br s), 7.30 (1H, d, J = 8.1 Hz), 7.82 (2H, d, J=8.3Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 11.4, 13.9, 17.2, 18.2, 21.6, 22.2, 25.8, 27.2, 31.8, 126.6, 128.2, 129.5, 131.0, 136.0, 144.0, 170.5.
Anal. Calcd for $C_{18}H_{26}N_2O_2S$: C, 64.63, H, 7.84, N, 8.38. Found: C, 64.64; H, 7.93; N, 8.20.

1S, 2R-Dictyopterene C (-)-41

In a 15 mL round-bottomed flask containing 181 mg (0.54 mmol) of tosyl hydrazone **53** was added 3 ml of dry THF followed by dropwise addition of 5.0 equiv of freshly prepared LDA (from addition of 1.93 mL (2.71 mmol, 5.0 equiv) of n-butyl lithium (1.40 M in hexanes) to 0.40 mL of diisopropylamine (2.84 mmol, 5.05 equiv) in 1 mL of THF at 0°C) at rt. Addition of LDA was accompanied by immediate color changes from colorless to yellow to burnt orange and finally after ~ 1h, a dark brown-red color. After stirring at rt for 6h, the reaction was quenched by the addition of 5 mL of water which caused an immediate color change from dark brown-red to light yellow. The reaction mixture was taken up in 50 ml of pentane and the organic layer was washed with water (5x10mL), aqueous 1M NaH_2PO_4 (2x10mL), dilute aqueous NH_4OH (1x10mL), and brine. The organics were dried through $MgSO_4$ and concentrated *in vacuo* to provide a light yellow oil. Purification by gravity column chromatography on silica gel (pentane) provided 68 mg (84%) of the known dictyopterene C **9** as a colorless oil in 83% ee: R_f 0.70 (10% ethyl acetate/hexane); $[\alpha]_D^{20}$ -104° (c 3.3, CCl_4);lit.[45b] $[\alpha]_D^{25}$ -125.1° (c 2.4 $CHCl_3$) corrected for 100% ee; IR (neat) 3072, 3002, 2857-2957, 1636 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.50 (1H, apparent dd, J = 6.0, 10.7Hz), 0.83 (3H, t, J = 7.0 Hz), 1.08 (1H, apparent dt, J = 4.8, 8.3 Hz), 1.24-1.34 (4H, m, 1.62-1.67 (1H, m), 1.74-1.79 (1H, m), 2.04-2.11 (2H, m), 4.90-5.08 (3H, m), 5.37 (1H, dt, J = 7.1, 11.1 Hz), 5.43-5.99 (1H, m); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 13.9, 14.7, 17.2, 22.3, 27.3, 29.7, 31.8, 114.2, 128.4, 131.1, 138.1.

R-(-)-Dictyopterene C' (-)-42

In a thick-walled, rounded glass tube (dimensions: ~2mm x 3mm) was placed 68 mg (0.45 mmol) of dictyopterene C **9** as a pentane soultion. After removal of the pentane *in vacuo*, the tube was cooled with liquid nitrogen and sealed with a torch. The tube was completely submersed in a 75°C oil bath for 5h. Purification by gravity column chromatography (pentane) on silica gel provided 54 mg (85%) of R-(-)-dictyopterene C' **5** as a colorless oil containing ~5-10% of unrearranged Dictyopterene C **41**(further heating (3h) did not change product:starting material ratio): $[\alpha]_D^{22}$ -25.1° (c 1.91, $CHCl_3$) ; lit.[45b] $[\alpha]_D^{25}$ -16.5° (c 1.74, $CHCl_3$) corrected for 100%ee; R_f 0.45 (pentane); IR (neat) 2856-3012, 1654 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.90, (3H, t, J = 6.5 Hz), 1.22-1.41 (6H, m), 2.05-2.26 (2H, m), 2.40-2.53 (1H, m), 2.69 (1H, dt, J = 19.1, 5.1 Hz), 2.91-2.98 (1H, m), 5.56-5.74 (4H, m); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 14.1, 22.9, 28.3, 29.4, 32.9, 36.0, 37.2, 127.2, 128.1, 129.9, 136.9.

ACKNOWLEDGEMENT

The authors are grateful to the National Institutes of Health for financial support of this work. An NSF Predoctoral Fellowship (to DR), a Merck Sharp and Dohme Postdoctoral Fellowship (to JLR), and a Fullbright Grant (to WM) are also gratefully acknowledged. The authors extend thanks to Professor A. Krief (Namur) for spectral data of **34** for comparison and to Dr. J-O Demoute

(Roussel-Uclaf) for a sample of **34**. Generous quantities of (L)-tert-leucine were obtained from Dr. K. Krauz and Dr. H. Lotter of DeGussa A.G., Hanau, West Germany and are greatly appreciated.

REFERENCES

1. a) Meyers, A. I., Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306. b) Meyers, A. I.; Garland, R. J. *J. Am. Chem. Soc.* **1984**, *106*, 1146. Meyers, A. I.; Wanner, K. T. *Tetrahedron Lett.* **1985**, *26*, 2047. c) Meyers, A. I.; Busacca, C. A. *Tetrahedron Lett.* **1989**, *30*, 6973. Meyers, A. I.; Busacca, C. A. *Tetrahedron Lett.* **1989**, *30*, 6977. d) Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *57*, 1936. Meyers, A. I.; Lefker, B. A. *Tetrahedron Lett.* **1987**, *28*, 1745.
2. a) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673. b) Meyers, A. I.; Sturgess, M. A. *Tetrahedron Lett.* **1989**, *30*, 1741. c) Meyers, A. I.; Bienz, S. *J. Org. Chem.* **1990**, *55*, 791.
3. a) Meyers, A. I.; Romine, J. L.; Fleming, S. A. *J. Am. Chem. Soc.* **1989**, *110*, 7245. b) Meyers, A. I.; Romo, D. *Tetrahedron Lett.* **1989**, *30*, 1745.
4. Elliot, M.; Janes, N.J. "Pyrethrum, the Natural Insecticide"; Casida, J. E., Ed.; Academic Press: New York-London, **1973**; pp 55-100.
5. a) Machlis, L.; Nutting, W. H.; Williams, M. W.; Rapoport, H. *Biochem.* **1966**, *5*, 2147. b) Machlis, L.; Nutting, W. H.; Rapoport, H. *J. Am. Chem. Soc.* **1968**, *90*, 1674. c) Nutting, W. H.; Rapoport, H. ; Machlis, L. *J. Am. Chem. Soc.* **1968**, *90*, 6434.
6. For reviews see: a) Ramaiah, M. *Synthesis* **1984**, 529. b) Hudlicky, T.; Kutchan, T. M.; Naqui, S. M. *Org. React.* **1985**, *33*, 247.
7. Wong, H.N.C.; Hon, M-Y; Tse, C-W; Yip, Y-O; Tanko, V.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.
8. For a review see: Salaun, J. *Chem. Rev.* **1989**, *89*, 1247.
9. a) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663. b) Meyers, A. I.; Wallace, R. H.; Harre, M..; Garland, R.*J. Org. Chem.* , in press.
10. Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243.
11. Mukaiyama, T.; Yamashita, H.; Asami, M. *Chem. Lett.* **1983**, 385.
12. Meyers, A. I.; Fleming, S. A., unpublished results.
13. Reich, H. J.; Renga, J.M.; Reich, I.L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
14. a) Cohen, T.; Mura, A.J., Jr.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *J. Org. Chem.* **1976**, *41*, 3218. b) Kochi, J. K.; Salomon, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3300.
15. Meyers, A. I.; Bienz, S.; Busacca, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 1907.
16. Kagan, H. B.; Pitchen, P. *Tetrahedron Lett.* **1984**, *25*, 1049.
17. Corey,E. J.; Chaykovsky, M. J. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
18. Black, T. H. *Aldrichimica Acta* **1983**, *16*(1), 3.
19. Andrews, S. D.; Day, A. C.; Raymond, P.; Whiting, M. C. *Org. Syn.* **50**, 27.

20. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, **1976**, pp 148-153.
21. Bateson, J. H.; Southgate, R.; Tyler, J. H.; Fell, S. C. M. *J. Chem. Soc. Perkin Trans. I* **1986**, 973.
22. a) Hanessian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170. b) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982**, *17*, 311.
23. a) Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, 2325-2328. b) Corey, E. J.; Jautelat, M. *J. Am Chem. Soc.* **1967**, *89*, 3912.
24. 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.; Adam, F.; Durner, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 856.
25. a) Quinkert, G.; Schmalz, H.-G.; Walzer, E.; Kowalczyk-Przewolka, T.; Duner, G.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 61. b) Quinkert, G.; Schmalz, H.-G.; Walzer, E.; Gross, S.; Durner, G.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 732.
26. Quinkert, G.; Durner, G.; Baier, J. *Helv. Chim. Acta* **1985**, *68*, 1054.
27. a) Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 637. b) Quinkert, G.; Schwartz, U. ; Stark, H.; Weber, W.-D.; Adam, F.; Baier, H.; Durner, G.; Frank, J. *Liebigs Ann. Chem.* **1982**, 1999.
28. Luche, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
29. Burgess, E. M.; Atkins, G. M., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4744.
30. Mitsunobu, O. *Synthesis* **1981**, 1.
31. Oediger, H.; Maller, F.; Eiter, K. *Synthesis* **1972**, 591.
32. 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.
33. 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. d) Elliot, M.; Farnham, A.; Janes, N. F.; Needham, R.; Pulman, D. *Nature* **1974**, *248*, 710.
34. For recent advances in enantioselective syntheses derived from (+)-3-carene, see: Mandel, A. K. et al. *Tetrahedron*, **1986**, *42*, 5715.
35. For some recent asymmetric syntheses see: a) Kleschick, W. A.; Reed, M. W. Bordner, J. *J. Org. Chem.* **1987**, 52, 3168. b) Krief, A.; Dumont, W.; Pasau, P. *Tetrahedron Lett.* **1988**, *9*, 1073.
36. March, J. *Advanced Organic Chemistry*, 3rd ed., John Wiley & Sons: New York, **1985**, pp. 795-796.
37. Ramirez, F.; Desai, N. B.; Mckelvie, N. *J. Am Chem. Soc.* **1962**, *84*, 1745.
38. Sandborn, L. T.; Bousquet, E. W. *Org. Syn. Coll. Vol.1* , 526.
39. For reviews in this area see: a) Moore, R.E. *Acct. of Chem. Res.* **1977**,*10*, 40. b) Jaenicke, L. ; Muller, D.G. *Fortschr, Chem. Org. Naturst.* **1973**, *30*, 61. c) Moore, R. E. In "Marine Natural Products," P.J. Scheuer. Ed., Academic Press: New York, 1978, chapter 2.

40. Pettus, J. A. , Jr.; Moore, R. E. *J. Am Chem. Soc.* **1971**, *93*, 3088.
41. Muller, D. G. *Science* **1981**, *212*, 1040.
42. Juettner, F.; Wurster, K. *Limnol. Oceanogr.* **1984**, *29*, 1322.
43. Kajiwara, T.; Kodama, K.; Hatanaka, A. *Nippon Suisan Gakkaishi.* **1980**, *46*, 771.
44. For some racemic syntheses see: (a) Ohloff, G.; Pickenhagen, W. *Helv. Chim Acta.* **1969**, *52*, 880. (b) Billups, W.E.; Chow, W. Y.; Cross, J.H. *J. Chem. Soc., Chem. Comm.* **1974**, *7*, 252. (c) Das, K.C.; Weinstein, B. *Tetrahedron Lett.* **1969**, *27*, 3459. (d) Schneider, M; Erben, A. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 192.
45. a) Genet, J.P.; Colobert, F. *Tetrahedron Lett.* **1985**, *26*, 2779. b) Jaenicke, L.; Boland, W.; Schotten, T. *Tetrahedron Lett.* **1986**, *27*, 2349.
46. For a leading reference see: Boland, W.; Jaenicke, L.; Ney, P. *Synthesis*, **1980**, 1015.
47. For leading references see: (a) Speckamp;, W.N.; de Boer, E.J.J. *Tetrahedron Lett.*, **1975**, *46*, 4039. (b) Wakabayashi, T.; Saito, M. *Tetrahedron Lett.*, **1977**, *48*, 93. (c) Nagasaka, T.; Yamamoto, H.; Hayashi, H.; Watanabe, M.; Hamaguchi, F. *Heterocycles*, **1989**, *29*, 155.
48. Bestmann, H.J.; Stransky, W.; Vostrowsky, O. *Chem. Ber.*, **1976**, *109*, 1694.
49. The authors in ref. 45b report a 97:3 ratio of enantiomers and this is therefore 94% ee, not 97% ee as the authors state. Thus, the 83% ee reported herein is based on optically pure **41** having $[\alpha]_D$=125°.
50. a) Shapiro, R.H.; Heath, M.J. *J. Am. Chem. Soc.*, **1967**, *89*, 5734. b) Shechter, H.; Cook, F.; Kaufmann, G.; Friedman, L.; Bayless, J. *J. Am. Chem. Soc.*, **1967**, *89*, 5736.
51. a) Shapiro, R.H.; Duncan, J.H. *Org. Syn.*, **1971**, *51*, 66. b) Dauben, W.G.; Lorber, M.E.; Vietmeyer, N.D.; Shapiro, R.H.; Duncan, J.H.; Tomer, K. *J. Am. Chem. Soc.*, **1968**, *90*, 4762.
52. Vedejs, E.; Shepherd, R.A. *J. Org. Chem.*, **1976**, *41*, 742.
53. For studies of thermal and photochemical rearrangements of cis and trans divinylcyclopropanes to cyclopheptadienes see: a) Pickenhagen, W.; Naf, F.; Ohloff, G; Muller, P.; Pelberger, J.C. *Helv. Chim. Acta.* **1973**, *56*, 1868. b) Schneider, M.' Erben, A. *Angew. Chem. Int. Ed. Engl.*, **1977**, *16*, 192. c) Jaenicke, L.; Akintobi, T.; Marner, F. J. Leibigs Ann. Chem. , 1973, 1252. d) Vogel, E. *Angew. Chem.*, **1962**, *74*, 829. e) Gajewski, J. J.; Hawkins, C. M.; Jimenez, J.I. *J. Org. Chem.* **1990**, *55*, 674.
54. The conditions of Jaenicke[45b] were employed to convert **41** into **42** and these workers reported $[\alpha]_D$-15° for **42** which was higher than the value for the natural material reported by Moore (-12°). These authors did not mention whether any **41** was present in their sample of **42**.
55. Meyers, A.I.; Dickman, D.A.; Bailey, T.R. *J. Am. Chem. Soc.*, **1985**, *107*, 7974.
56. McCoy, L.L. *J. Am. Chem. Soc.*, **1958**, *80*, 6568.