9p, 143745-68-0; **9q**, 143745-69-1; **10**, 13200-60-7; **11**, 62004-76-6; **12**, 143745-70-4; **13**, 143745-71-5; **14**, 143745-72-6; **15a**, 143745-74-8; **15b**, 143745-75-9; **16a**, 143745-76-0; **16b**, 143745-77-1; $PhNH_2$, 142-04-1; 4-$MePhNH_2$, 540-23-8; 2-$ClPhNH_2$, 137-04-2; 3-$ClPhNH_2$, 141-85-5; 4-$MeOPhNH_2$, 20265-97-8; 4-$MeSPhNH_2$, 39870-00-3; 4-EtO_2CPhNH_2, 23239-88-5; 3-O_2NPhNH_2, 33240-96-9; 4-H_2NPhNH_2, 55972-71-9; PhNHMe, 2739-12-0; $PhNHCH_2Ph$, 2290-89-3; 3-$MePhNH_2$, 638-03-9; PhSH, 12385-08-9; 2-H_2NPhSH, 137-07-5; 4-*t*-Bu-2-MePhSH, 15570-10-2; 2-MeOPhSH, 7217-59-6; 2-MePhSH, 137-06-4; 3-MePhSH, 108-40-7; 4-MePhSH, 106-45-6; 4-HOPhSH, 637-89-8; 4-H_2NPhSH, 1193-02-8; 4-HO-3,5-(*t*-$Bu)_2PhSH$, 950-59-4.

An Asymmetric Route to Enantiomerically Pure 1,2,3-Trisubstituted Cyclopropanes

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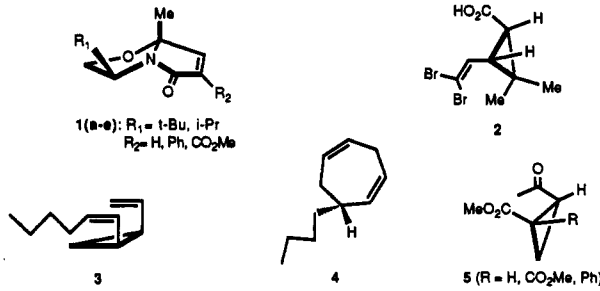
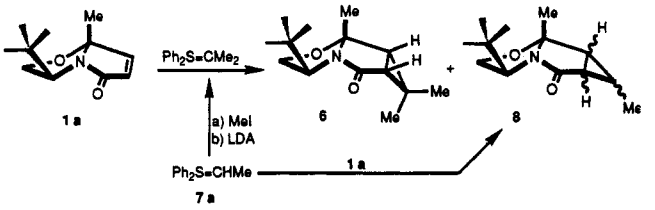
Cycloaddition of various sulfur ylides to the chiral unsaturated lactams **1a**, **1b** led to cyclopropanated products containing a monosubstituted appendage. The stereochemical outcome is such that all the products are mainly (or exclusively) the kinetically controlled *endo-syn*-**8**, -**9**, or *endo-anti*-**10**. The latter occurs by virtue of an epimerization to the thermodynamically favored product. Removal of the chiral auxiliary following Wittig reaction on the intermediate carbinol amines (**11**, **15**) gave chiral, nonracemic 1,2,3-trisubstituted cyclopropanes containing various functionalities (**13**, **16**).

Earlier cyclopropanations of unsaturated bicyclic lactams **1** have provided access to the potent insecticide precursor, *cis*-(1*S*,3*R*)-deltamethrinic acid (**2**), dictyopterene C (**3**), a proposed biogenic precursor to dictyopterene C′ (**4**), the potent seaweed sperm attractant, and various other enantiomerically pure cyclopropanes **5**.[1] It

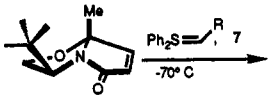


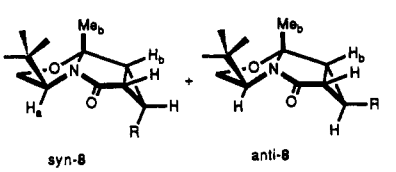
is obvious from their structures that these cyclopropyl systems possess only two stereogenic centers. We now wish to disclose extensions of this chiral cyclopropanation methodology which afford absolute stereocontrol of three centers leading to enantiomerically pure 1,2,3-trisubstituted cyclopropanes.[2]

In our earlier effort directed toward the asymmetric synthesis of deltamethrinic acid, **2**, cyclopropanation of the unsaturated lactam **1a** with diphenylsulfonium isopropylide gave mixtures of the desired *gem*-dimethylcyclopropane **6** and two diastereomeric monomethylcyclopropanes **8**. The isopropylide was generated in situ and, as a result of incomplete alkylation of the ylide **7a**, varying amounts of monomethylcyclopropanes **8** were produced. Interestingly, of the four possible stereoisomers (endo/exo and syn/anti) monomethylcyclopropanes, only two were produced, and more importantly they were produced in unequal amounts.



These findings prompted an investigation of cyclopropanation of the unsaturated lactam **1a** with diphenylsulfonium ethylide **7** (R = Me).[3] When the reaction with **1a** was performed at −70 °C followed by warming to −20 °C, the two *syn*- and *anti*-cyclopropyl adducts **8a** were obtained in 95% yield as a 3.0:1 mixture as determined by VPC analysis. The diastereomeric ratio of **8a** could be improved to 4.6:1 by maintaining the reaction temperature between −70 °C and −60 °C.





	syn	anti
8a, R = Me	4.6	1
8b, R = CH = CH_2	31.0	1
8c, R = Ph	7.0	1

The major diastereomer was determined to be the endo–syn adduct **8a** by NOE experiments which showed

(1) For earlier studies on chiral bicyclic lactams, including cyclopropanation, see a review on this subject: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *46*, 9503–9569.

(2) For recent reports of cyclopropanations providing tri- and tetrasubstituted, enantiomerically pure cyclopropanes, see: (a) Winkler, J. D.; Gretler, E. A. *Tetrahedron Lett.* **1991**, *41*, 5733. (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *50*, 7373. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (d) Sugimura, T.; Katagiri, T.; Tai, A. *Tetrahedron Lett.* **1992**, *33*, 367.

(3) Corey, E. J.; Jautelat, M. *J. Am. Chem. Soc.* **1967**, *89*, 3912.

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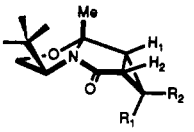
Table I. ^1H–^1H Coupling Constants (Hz) for Cyclopropyl Lactam Adducts



cyclopropane config	R_1	R_2	cis $J(H_1,H_2)$	trans $J(H_2,R_1)$	cis $J(H_2,R_2)$	trans $J(H_1,R_1)$	cis $J(H_1,R_2)$
endo[a]	CH_3	CH_3	6.0				
exo[a]	CH_3	CH_3	6.0				
endo–syn	CH_3	H	5.8		9.1		7.6
endo–anti	H	CH_3	5.6	3.1		3.3	
endo–syn	CH_2=CH_2	H	5.8		9.0		7.6
endo–anti	H	CH_2=CH_2	5.8			3.3	
endo–syn	Ph	H	6.0				7.8
endo–anti	H	Ph	7.1			3.6	
endo–anti	H	CO_2Me	6.0	3.0		3.0	

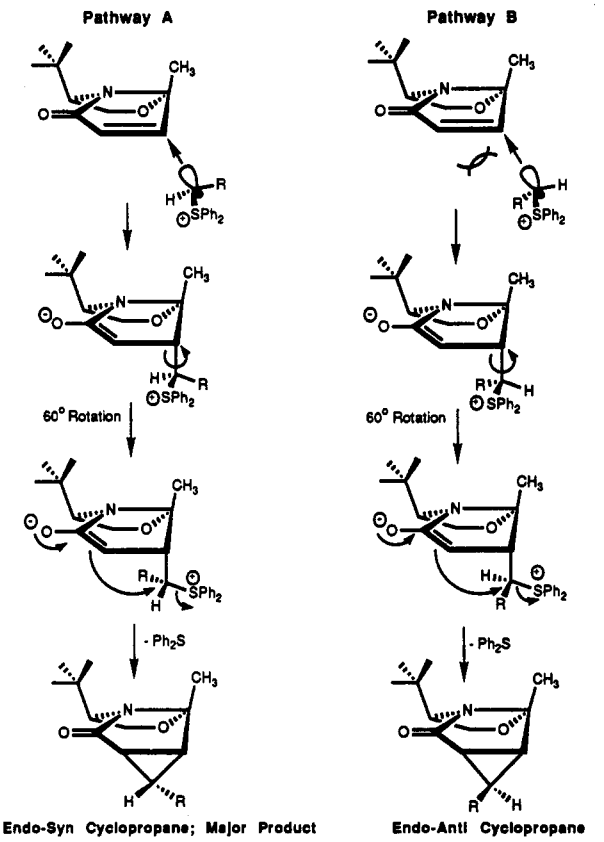
[a] From ref 1.

enhancement of H_a (5.6%) when the *syn*-methyl ($R = Me_a$) was irradiated as in the case of the *gem*-dimethyl cyclopropyl adduct **6** described above. The absence of the latter NOE enhancement as well as positive NOE enhancements observed for the angular methyl (Me_b), the β-hydrogen (H_b), and the *anti*-methyl (R = Me) confirmed the endo–anti stereochemistry for the minor diastereomer **8a**. As in *gem*-dimethyl cyclopropanation leading to **6**, no adducts from exo addition of the sulfur ylide were detectable by VPC analysis.[1]

That the *endo*-methylcyclopropyl lactam *syn*-**8** was the major diastereomer formed was at first quite surprising since this product would appear to be the thermodynamically disfavored product as a result of steric interactions between the methyl group (Me_a) and the bicyclic ring system. A rationale for the observed selectivity is presented in Scheme I for a generalized diphenylsulfonium ylide (Ph_2S=CHR). During initial approach of the sulfur ylide, the large diphenyl sulfide moiety would prefer to be directed away from the bicyclic lactam. Of the two remaining substituents, one would by necessity be under the lactam ring during approach while the other may be in a sterically less congested situation on the perimeter of the lactam ring. For this reason, the R group of the ylide being larger than a proton would prefer to be positioned away from the lactam ring as in pathway A. Pathway B is disfavored since it would lead to steric interactions between the R group and the lactam ring during conjugate addition. Displacement of diphenyl sulfide in the intermediate addition product by the enolate electrons requires a 60° rotation in order to attain proper alignment of the leaving sulfonium group in the S_N2 process. This places R of the ylide under the lactam ring. Ring closure may then occur to afford the cyclopropyl lactam as depicted in pathway A. Based on this steric argument, pathway A would be favored and lead to the *syn*-monomethylcyclopropyl lactam **8**.

In order to test the above hypothesis concerning the steric effects of the ylide addition on the syn–anti selectivity, a series of sulfonium ylides were prepared and utilized in cyclopropanations of the unsaturated lactam **1a**. Cyclopropanation with diphenylsulfonium allylide[4] produced the vinylcyclopropyl lactam *syn*-**8b** in 59% yield (79% based on recovered starting material) in excess of the diastereomer *anti*-**8b** by >31:1 as determined by ^1H-NMR. This further supports proposed pathway A in Scheme I by the fact that an increase in steric requirement

Scheme I



of the ylide leads to an increase in syn–anti selectivity.

NOE experiments once again strongly suggested that the major diastereomer possessed the endo–syn stereochemistry. This was readily seen by a 6.4% enhancement of H_a when the vinylidine proton in **8b** was irradiated. The stereochemistry was confirmed by the X-ray diffraction structure of the vinylcyclopropyl adduct *syn*-**8b**. The X-ray structure clearly shows the concave nature of these lactams as well as the near-perpendicular relationship (Scheme I) between the cyclopropyl and lactam rings. On this basis, it is not surprising to see positive NOE enhancements between the oxazolidine ring hydrogen (H_a) and the syn substituent of these cyclopropyl lactam systems.

Cyclopropanation of the unsaturated lactam **1a** with diphenylsulfonium benzylide[6] (**7**, R = Ph) afforded *syn*-

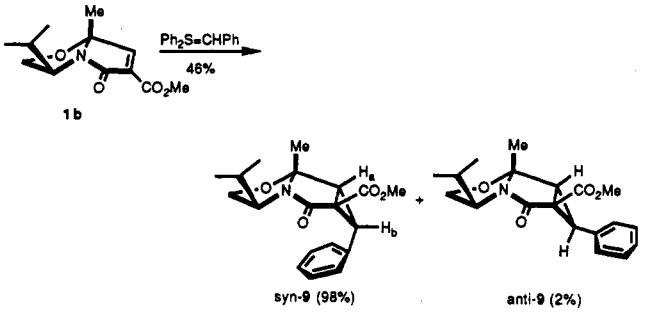
(4) LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem.* 1971, *36*, 1126.

(5) X-ray data for **8b** is in the supplementary material.

(6) Johnson, A. W.; Hruby, V. J.; Williams, J. L. *J. Am. Chem. Soc.* 1964, *86*, 918.

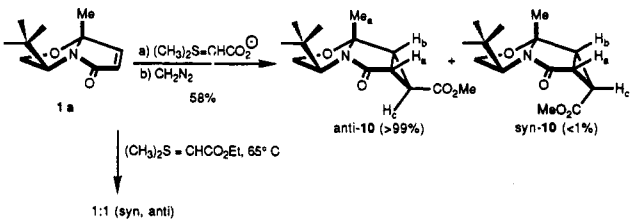
and *anti*-phenylcyclopropanes **8c** in 41% yield as a 7:1 ratio of diastereomers (Table I). The lower selectivity in the case of the benzyl ylide may be due to the severe steric interactions between the phenyl ring and the bicyclic lactam which, by necessity, occurs during cyclopropane ring closure (see Scheme I). Furthermore, this cyclopropanation was found to be capricious and irreproducible and required higher temperatures than previously employed ylides (−78 °C → rt). This is probably the result of lower reactivity of the sulfur ylide as a result of stabilization of the carbanion by the phenyl ring. This sluggishness was also observed for the allyl ylide, described above, which added to the unsaturated lactam **1a** and gave lower yields (59%) than the methyl-substituted sulfonium ylide (95%, vide supra) due to incomplete reaction. The assignment of endo–syn and endo–anti diastereomers for **8c** was initially made by comparison of the chemical shifts of the oxazolidine ring protons (vide supra). A significant downfield shift for these protons (e.g., H_a in *syn*-**8a**, R = Ph) as a result of the shielding effect of the phenyl ring was observed.

Subsequently, it was found that cyclopropanation of the α-carbomethoxy-unsaturated lactam **1b**[7] with diphenylsulfonium benzylide led to reproducible yields (47%, 56% based on recovered starting material) of the cyclopropyl adduct **9** in high diastereomeric excess (>96% de; ^{1}H-NMR). The addition proceeded efficiently at −78 °C, and this may contribute to the higher selectivity observed in comparison to the same reaction with the unsaturated lactam **1a** (vide supra). Interestingly, the ^{1}H-NMR spectrum of the cyclopropyl adduct *syn*-**9** in deuteriochloroform exhibited a singlet at 2.88 ppm for both cyclopropyl protons (H_a, H_b). However, when the spectrum was taken in benzene-d_6 the expected doublet splitting patterns were observed for the two cyclopropyl protons. This result is a consequence of second-order effects which occur when the coupling constants of two protons (e.g., H_a and H_b) are approximately equal to the difference in their chemical shift (i.e., $J_{ab} \sim \Delta\nu(\nu_a - \nu_b)$).[8] In other words, the approximate magnetic equivalence of these protons makes them virtually identical so that coupling is not observed when the spectrum is taken in deuteriocholoroform. However, when taken in benzene-d_6, a larger difference in chemical shift (magnetic unequivalence; $J_{ab} < \Delta\nu$) allows a return to first order rules and thus the expected doublets are observed.



Additional confirmation for the stereochemical assignments of these cyclopropyl adducts described herein came from examination of the coupling constants for the cyclopropyl ring protons. In general, cyclopropyl protons with a cis relationship give rise to larger couplings (~7–10 Hz) when compared to those with a trans relationship (~3–7 Hz).[9] This is a consequence of the difference in dihedral angle between the *cis*- and *trans*-cyclopropyl ring protons. An obvious pattern emerged for the coupling constants of the cyclopropyl adducts **8** and **9**, and these are summarized in Table I. The trans coupling constants were always in the range of 3.0–3.6 Hz while the cis coupling constants were in the range of 5.6–9.1 Hz.

It was desirable to extend this cycloaddition to reach a carboxyl-substituted cyclopropyl lactam since this would allow for further elaboration of the cyclopropyl substituent. Toward this end, cyclopropanation of the unsaturated lactam **1a** with dimethyl(carboethoxymethylene)sulfuran[10] was attempted. However, this ylide was unreactive toward the unsaturated lactam at 25 °C, and thus the reaction mixture was heated to 65 °C. Unfortunately, this resulted in stereorandom addition affording a ~1:1 mixture of diastereomeric (ethoxycarbonyl)cyclopropyl lactams *syn*- and *anti*-**10** (Et ester). Cyclopropanation with the more reactive sodium (dimethylsulfuranylidene)acetate (dimethylthetin anion)[10] proceeded efficiently at 25 °C to give a single carboxyl substituted cyclopropyl lactam as evidenced by ^{1}H-NMR. It should be noted that the published procedure for generation of this ylide required two separate deprotonation steps; however, it was found that dimethylthetin anion could be prepared directly by treatment of dimethyl(carboxymethylene)sulfonium bromide with 2 equiv of sodium hydride. The initially formed carboxycyclopropyl lactam was immediately treated with diazomethane to give the corresponding carbomethoxycyclopropyl adduct which was assigned the stereochemistry as shown for *anti*-**10** based on the following:



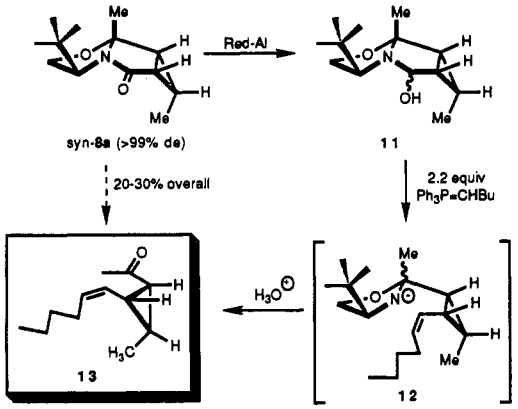
Homonuclear NOE experiments (Me_a, H_b) for the carbomethoxycyclopropyl adduct *anti*-**10** confirmed preferential endo approach of the sulfonium ylide during cyclopropanation. The assignment of stereochemistry about the cyclopropane ring was made by inspection of the cyclopropyl ring coupling constants in anti-**10** which indicated a cis–trans–cis relationship for the cyclopropyl protons (Table I). The syn diastereomer, *syn*-**10**, would have a cis–cis–cis relationship for the cyclopropyl protons. Protons H_a and H_b are, by necessity, in a cis relationship indicating that the remaining cyclopropyl proton H_c is trans to each of the former. Surprisingly, the only product obtained in the cyclopropanation was the endo–anti carboxyl cyclopropyl lactam *anti*-**10** in contrast to other sulfonium ylides described previously. This product is probably the result of thermodynamic equilibration of the initially formed endo–syn carboxylcyclopropyl adduct (corresponding to lactam *syn*-**10**) since the reaction was normally performed with excess ylide. The ylide can serve as a base to deprotonate the resulting carboxylate forming a dianion which in turn results in epimerization of the α-center to the thermodynamically more stable lactam

(7) Romo, D.; Romine, J. L.; Midura, W.; Meyers, A. I. *Tetrahedron* **1990**, *46*, 4951.
(8) Becker, E. D. *High Resolution NMR–Theory and Chemical Applications*; Academic: New York, 1980; pp 163–167.
(9) Gunther, H. *NMR Spectroscopy*; J. Wiley & Sons: New York, 1980; pp 108, 384.
(10) Casanova, J.; Rutolo, D. A. *J. Chem. Soc., Chem. Commun.* **1967**, *1224*.
(11) Adams, J.; Hoffman, L, Jr.; Trost, B. M. *J. Org. Chem.* **1970**, *35*, 1600.

anti-**10**. In this regard, treatment of the unsaturated lactam **1a** with a deficiency of ylide (0.5 equiv) led to small but detectable quantities of the *syn*-**10** cyclopropylcarboxyl adduct supporting this contention.

To demonstrate that optically pure 1,2,3-trisubstituted cyclopropanes could be reached via the present cyclopropanation employing sulfonium ylides, the chiral auxillary was removed from two of the cyclopropyl adducts by the reduction–olefination–hydrolysis sequence.[7]

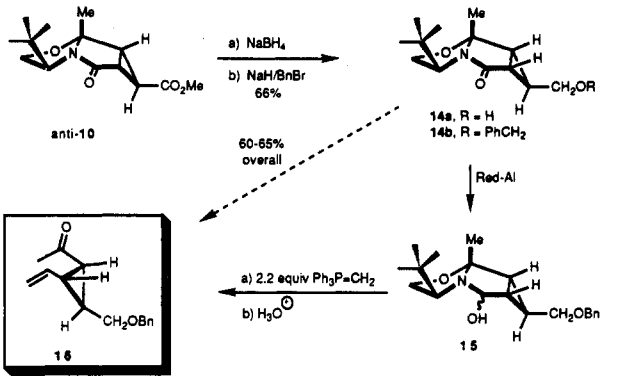
The monomethylcyclopropyl lactam *syn*-**8a** was obtained stereochemically pure after flash chromatography and the diastereomeric purity was >99% as evidenced by VPC analysis. Reduction with Red-Al afforded the carbinolamine **11** which, after aqueous workup to remove the aluminum salts, was immediately treated with 2.2 equiv of "salt-free" pentylidenetriphenylphosphorane. The intermediate oxazolidines **12** were not isolated but directly subjected to hydrolytic conditions to afford the odoriferous cyclopropane **13** in ca. 30% overall yield from the cyclopropyl lactam *syn*-**8a**. The moderate yield obtained for this three-step sequence is a direct consequence of the volatility of **13**. No major effort was expended to trap all the product. ^{1}H-NMR indicated an ~95:5 ratio of *Z*/*E* olefin isomers in **13**. Based on the diastereomeric purity of the cyclopropyl lactam precursor *syn*-**8a**, it can be safely assumed that the cyclopropyl ketoolefin **13** possesses stereogenic carbon purity greater than 99%.



The cyclopropyl lactam *anti*-**10** was also subjected to chiral auxiliary removal and was transformed to the vinylcyclopropyl ketone, **16**. To avoid complications during reduction of the lactam carbonyl with Red-Al, the carbomethoxy group in *anti*-**10** was first reduced with $NaBH_4$, and the resulting alcohol **14a** was then alkylated[12] to give the (benzyloxy)cyclopropyl lactam **14b**. The benzyl group was chosen to decrease any potential volatility of the cyclopropane **16**. Reduction of **14b** to the carbinolamine **15** was performed as described above for *syn*-**8a** and now the smaller ylide, triphenylphosphonium methylidene, was introduced since the benzyloxy substituent was expected to be sufficiently large to supress volatility. Furthermore, the use of the ethylidene Wittig reagent also precluded forming *Z*/*E* olefin isomers. Hydrolysis followed the olefination step, and the cyclopropyl ketoolefin **16** was obtained in a more satisfactory overall yield of 65% based on the benzyloxy lactam, *anti*-**10**.

In summary, the above route to chiral, nonracemic 1,2,3-substituted cyclopropanes appears to be quite efficient so long as products of minimal volatility are targeted. Of course, techniques are available to trap volatile products if the need arises.

(12) Proveknghiou, C.; Czernecki, S.; Georgoulis, C. *Tetrahedron Lett.* 1976, 3535.



Experimental Section

General. Microanalyses were performed by Desert Analytics, Tucson, AZ, and Atlantic Microlab, Inc., Norcross, GA. VPC analyses were performed on a cross-linked 5% phenyl methyl silicone capillary column (SE-52) with dimensions of 0.2 mm × 25 m and a flow rate of 30 cm/s. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME, Aldrich, <1% water content) were distilled immediately prior to use from sodium–benzophenone ketyl radical. Flash column chromatography was performed on Aldrich-951-58-μm silica gel. 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.

Monomethylcyclopropyl Lactams *syn*-8a, *anti*-8a. To a stirred solution of 1.57 g (5.19 mmol, 1.2 equiv) of diphenylethylsulfonium tetrafluoroborate,[3] 416 μL (6.50 mmol, 1.5 equiv) of dry methylene chloride, and 50 mL of freshly distilled DME was added 4.45 mL of LDA (1.46 M in cyclohexane) under an argon atmosphere at −70 °C (dry ice/ethanol bath). The clear yellow-green solution became cloudy after 5 min. After the solution was stirred at −70 °C for 30 min, 845 mg (2.27 mmol, 1.0 equiv) of unsaturated lactam[7] **1a** was added as a DME solution (10 mL). After 30 min, the reaction flask was allowed to warm to −60 °C and maintained at this temperature for 48 h. TLC analysis showed some starting material remained; therefore, an additional 0.5 equiv of the diphenylsulfonium ethylide was prepared as described above and added to the reaction mixture. After 16 h, the reaction was quenched at −60 °C by addition of 10 mL of aqueous saturated ammonium chloride solution and the aqueous phase was extracted with ether (3 × 60 mL). The combined organics were washed with brine and then dried and concentrated in vacuo to afford 930 mg (96%) of a 4.6:1 mixture (vpc) of *syn*/*anti*-cyclopropyl lactams **8a** as a pale yellow oil. Purification by flash column chromatography (gradient elution; hexane to 10% ethyl acetate/hexane by 2.5% increments; 200 mL of each concentration) gave 360 mg of pure cyclopropyl lactam *syn*-**8a** and 570 mg of a mixture of cyclopropyl lactams *syn*, *anti*-**8** (R = Me). The *endo*-cyclopropyl lactam *syn*-**8a** had the following physical and spectral characteristics: R_f 0.40 (50% ethyl acetate/hexane); $[\alpha]^{22}_D$ 92° (*c* 0.97, $CHCl_3$); IR (neat) 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 9 H), 1.13 (d, 3 H, *J* = 6.7 Hz), 1.33–1.38 (m, 1 H), 1.60 (s, 3 H), 1.63 (dd, 1 H, *J* = 5.9, 7.6 Hz), 2.30 (dd, 1 H, *J* = 5.8, 9.2 Hz), 3.51 (apparent t, 1 H, *J* = 8.5 Hz), 3.98 (apparent t, 1 H, *J* = 9.2 Hz), 4.23 (dd, 1 H, *J* = 8.4, 9.3 Hz); ^{13}C-NMR ($CDCl_3$, 75.0 MHz) δ 10.3, 19.4, 22.9, 27.2, 27.4, 31.2, 33.2, 62.5, 70.0, 100.0, 176.6.

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.90; H, 9.48; N, 6.27. Found: C, 69.66; H, 9.64; N, 6.00.

The *endo*-cyclopropyl lactam *anti*-**8a** had the following physical and spectral characteristics: R_f 0.48 (50% ethyl acetate/hexane); IR (neat) 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 75.0 MHz) δ 0.93, (s, 9 H), 1.09 (d, 3 H, *J* = 6.1 Hz), 1.22–1.29 (m, 1 H), 1.53 (dd, 1 H, *J* = 3.2, 5.6 Hz), 1.59 (s, 3 H), 1.92 (dd, 1 H, *J* = 3.1, 5.6 Hz), 3.34 (apparent t, 1 H, *J* = 8.7), 3.93 (apparent t, 1 H, *J* = 9.1 Hz), 4.20 (dd, 1 H, *J* = 8.3, 9.2 Hz); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 15.9, 18.5, 26.0, 27.1, 27.9, 32.9, 33.0, 65.0, 69.8, 99.1, 178.3.

Vinylcyclopropyl Lactam 8b. To a well-stirred slurry of 320 mg (1.02 mmol, 2.0 equiv) of diphenylallylsulfonium tetrafluoroborate[4] in 40 mL of dry THF was added 546 μL (0.608 mmol, 0.85 equiv) of *tert*-butyllithium (1.68 M in cyclohexane) under

an argon atmosphere at −78 °C. A deep orange color resulted immediately. The reaction mixture was maintained between −40 and −50 °C for 4.5 h and then cooled to −78 °C before adding 100 mg (0.51 mmol, 1.0 equiv) of the unsaturated lactam **1a** as a THF solution (5 mL) via cannula. The reaction mixture was placed in a −35 °C freezer for 72 h and then quenched at −35 °C with an aqueous saturated ammonium chloride solution (5 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 30 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford a pale yellow oil. Purification by flash column chromatography (gradient elution; methylene chloride to 5% ethyl acetate/methylene chloride) gave 71 mg (59%; 79% based on recovered starting material) of the cyclopropyl lactam **8b** (>30:1 syn/anti ratio via ^{1}H-NMR) and 28 mg of recovered starting material. Recrystallization afforded analytically pure **8b** as colorless plates: R_f 0.48 (5% ethyl acetate/methylene chloride); mp 95–96 °C; $[\alpha]^{20}_D$ 60.8° (*c* 1.58, $CHCl_3$); IR (CCl_4) 1718 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 75.0 MHz) δ 0.96 (s, 9 H), 1.62 (s, 3 H), 1.90 (dd, 1 H, *J* = 5.7, 7.5 Hz), 1.99 (dd, 1 H, *J* = 8.1, 16.4 Hz), 2.51 (dd, 1 H, *J* = 5.8, 8.9 Hz), 3.49 (apparent t, 1 H, *J* = 8.5 Hz), 3.99 (apparent t, 1 H, *J* = 9.2 Hz), 4.24 (apparent t, H, *J* = 9.2 Hz), 5.14 (dd, 1 H, *J* = 0.8, 10.0 Hz), 5.30 (dd, 1 H, *J* = 0.9, 16.8 Hz), 5.52 (1 H, ddd, *J* = 8.5, 10.2, 17.0 Hz); ^{13}C-NMR ($CDCl_3$, 75.0 MHz) δ 25.7, 27.0, 27.1, 27.8, 32.4, 33.1, 63.0, 70.0, 99.5, 117.8, 132.1, 175.8; MS *m*/*z* (relative intensity) 235.1 (M^+, 0.8), 220.1 (M^+ − 15, 15.5).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 8.99; N, 5.95. Found: C, 71.49; H, 9.05; N, 5.76.

Phenylcyclopropyl Lactams 8c. To a well-stirred, cooled (−78 °C) slurry of 270 mg (0.768 mmol, 1.5 equiv) of diphenylbenzylsulfonium tetrafluoroborate[6] in 5 mL of THF was added 0.50 mL (0.819 mol, 1.5 equiv) of *tert*-butyllithium (1.67 M in pentane) under an argon atmosphere. After 30 min, 100 mg (0.512 mmol, 1.0 equiv) of the unsaturated bicyclic lactam **1a** was added as a THF solution (3 mL) via cannula. The reaction was allowed to warm to ambient temperature overnight and then quenched with an aqueous saturated ammonium chloride solution (5 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 30 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. After two successive purifications by flash column chromatography (3% ethyl acetate/methylene chloride), 40 mg of *endo*-phenylcyclopropyl lactam *syn*-**8c**, 20 mg of a 1.7:1 mixture (via ^{1}H NMR) of syn/anti diastereomers (41% combined yield; 63% based on recovered starting material), and 34 mg of recovered starting material were obtained. The phenylcyclopropyl lactam *syn*-**8c** had the following spectral characteristics: IR (neat) 1713 cm^{-1}; ^{1}H-NMR (C_6D_6, 270 MHz) δ 0.74 (s, 9 H), 1.32 (s, 3 H), 1.35 (dd, 1 H, *J* = 6.0, 7.8 Hz), 1.99–2.23 (m, 2 H), 2.76 (apparent t, 1 H, *J* = 8.1 Hz), 3.13 (apparent t, 1 H, *J* = 8.5 Hz), 3.42 (apparent t, 1 H, *J* = 8.4 Hz), 6.97–7.16 (m, 3 H), 7.67–7.72 (m, 2 H); ^{13}C-NMR ($CDCl_3$, 62.5 MHz) δ 24.8, 27.1, 28.0, 28.5, 30.7, 32.9, 64.0, 70.1, 99.9, 126.6, 127.3, 131.1, 134.2, 175.5.

Phenylcyclopropyl Lactam 9. Prepared according to the procedure described above for phenylcyclopropyl lactams **8c** with 212 mg (0.60 mmol, 1.5 equiv) of diphenyl benzylsulfonium tetrafluoroborate,[6] 393 μL of *t*-BuLi (1.67 M in pentane), and 96 mg (0.40 mmol, 1.0 equiv) of unsaturated lactam **1b**.[7] Purification by flash column chromatography (10%–50% ethyl acetate/hexane in 10% incremental increases) gave 75 mg (47%; 56% based on recovered starting material) of the phenylcyclopropyl lactam **9** as a colorless oil and 18 mg of recovered starting material. Crystallization from hexane/ether (~10:1) at 0 °C gave colorless needles: R_f 0.47 (50% ethyl acetate/hexane); mp 133.5–136.0 °C; IR (film) 1712 (br) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, 1 H, *J* = 6.6 Hz), 1.08 (d, 1 H, *J* = 6.6 Hz), 1.59–1.67 (m, 1 H), 1.70 (s, 3 H), 2.88 (s, 2 H), 3.45 (dt, 1 H, *J* = 2.7, 7.2 Hz), 3.55 (s, 3 H), 3.92 (dd, 1 H, *J* = 1.9, 6.9 Hz), 4.34 (dd, 1 H, *J* = 0.9, 7.9 Hz), 7.26 (s, 5 H); ^{1}H-NMR (C_6D_6, 300 MHz) δ 0.55 (d, 3 H, *J* = 6.6 Hz), 1.12 (d, 3 H, *J* = 6.6 Hz), 1.27–1.34 (m, 1 H), 1.47 (s, 3 H), 2.83 (d, 1 H, *J* = 5.0 Hz), 2.96 (d, 1 H, *J* = 5.0 Hz), 3.18 (s, 3 H), 3.24–3.30 (m, 1 H), 3.47 (dd, 1 H, *J* = 1.6, 7.1 Hz), 3.85 (dd, 1 H, *J* = 0.96, 7.8 Hz); ^{13}C-NMR ($CDCl_3$, 75.0 MHz) δ 18.8, 20.6, 25.6, 31.6, 34.4, 36.6, 44.3, 52.3, 61.3, 73.1, 96.4, 127.7, 128.1, 128.9, 132.4, 165.1, 171.0; GC–MS *m*/*z* (abundance) 330 (M^+ + 1), 329 (M^+), 202, 170.

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04. Found: C, 69.11; H, 7.06.

Carbomethoxycyclopropyl Lactam *anti*-10. Sodium dimethylsulfoxonium methylide ("dimsyl sodium") was prepared by the addition of 25 mL of dry DMSO to 410 mg (10.2 mmol, 4.0 equiv) of a 60% mineral oil dispersion of NaH which had been rinsed with hexanes (3 × 10 mL). After gas evolution had ceased and the solution was homogeneous (~30 min), 1.03 g (5.12 mmol, 2.0 equiv) of dimethyl(carboxymethylene)sulfonium bromide (prepared by addition of bromoacetic acid to excess dimethyl sulfide; recrystallization from ethanol and washing with ether gave light brown crystals) was added cautiously (rapid gas evolution) as a DMSO solution via cannula.[10] The resulting turbid solution was stirred at ambient temperature with intermittent vigorous swirling until the solution was homogeneous (~30 min). To the gray solution was added 500 mg (2.56 mmol, 1.0 equiv) of unsaturated lactam **1a** as a DMSO solution (7 mL) via cannula, and the mixture was stirred at ambient temperature for 13 h. The reaction mixture was quenched by pouring into aqueous saturated ammonium chloride (40 mL). The pH was adjusted to ~1 by addition of 1 N HCl, and then the aqueous phase was extracted with ethyl acetate (4 × 50 mL). The combined organics were washed with brine and then dried ($MgSO_4$) and concentrated to give the carboxycyclopropyl lactam as the carboxylic acid, *anti*-**10** (H in place of Me) as a pale yellow solid: IR (neat) 2500–3500, 1716 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.94 (s, 9 H), 1.64 (s, 3 H), 2.01 (apparent s, 1 H), 2.33 (dd, 1 H, *J* = 2.7, 6.0 Hz), 2.70 (dd, 1 H, *J* = 2.8, 6.0 Hz), 3.36 (apparent t, *J* = 8.6 Hz), 3.96 (apparent t, 1 H, 9.2 Hz), 4.25 (apparent t, 1 H, *J* = 9.0 Hz), 7.80–8.25 (broad s, 1 H); ^{13}C-NMR ($CDCl_3$, 75.0 MHz) δ 23.5, 25.6, 27.1, 28.6, 33.0, 33.4, 65.1, 70.1, 98.5, 174.6, 175.9.

The carboxylic acid was not handled further but directly treated with excess diazomethane in ether. Purification by flash column chromatography gave 376 mg (58%) of carbomethoxycyclopropyl lactam *anti*-**10** as a colorless crystalline solid. Recrystallization from hexanes at 0 °C gave colorless plates: R_f 0.59 (50% ethyl acetate/hexane); mp 87.0–88.5 °C; $[\alpha]^{22}_D$ 47.8° (*c* 1.36, $CHCl_3$); IR (neat) 1724 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.94 (s, 9 H), 1.64 (s, 3 H), 2.02 (dd, 1 H, *J* = 3.0, 6.0 Hz), 2.29 (dd, 1 H, *J* = 2.9, 6.1 Hz), 2.64 (dd, 1 H, *J* = 3.0, 6.0 Hz), 3.35 (apparent t, 1 H, *J* = 8.9 Hz) 3.69 (s, 3 H), 3.96 (apparent t, 1 H, *J* = 9.3 Hz), 4.24 (apparent t, 1 H, *J* = 9.2 Hz); ^{13}C-NMR (C_6D_6, 75.0 MHz) δ 23.6, 25.4, 27.1, 28.6, 32.8, 33.1, 51.8, 65.2, 69.8, 98.3, 170.1, 175.2.

Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92. Found: C, 63.10; H, 8.03.

Acetylcyclopropyl Olefin 13. To a stirred THF solution (14 mL) of 313 mg (1.40 mmol) of the cyclopropyl lactam *syn*-**8a** was added 0.29 mL (0.98 mmol, 0.7 equiv) of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, Aldrich, 3.4 M in toluene) at ambient temperature under an argon atmosphere. After 24 h, the reaction was quenched by addition of 1 mL of methanol and diluted with 50 mL of ethyl acetate. The organics were washed with 10% aqueous sodium hydroxide solution, water, and then brine and dried ($MgSO_4$). The crude mixture was dried azeotropically with benzene, transferred to a dry flask, and diluted with 10 mL of dry THF. After the mixture was cooled to 0 °C, 5.97 mL of a 0.492 M solution of "salt-free" pentylidenetriphenylphosphorane[13] was added under an argon atmosphere. The resulting orange solution was stirred at this temperature for 24 h and then warmed to ambient temperature for 2 h. After this time, 14 mL of aqueous 1 M $Bu_4NH_2PO_4$ was added, and the mixture was stirred for 14 h at ambient temperature. Concentration in vacuo was followed by extraction with ether (3 × 35 mL). The combined organics were washed with brine and then dried ($MgSO_4$) and concentrated to afford a viscous yellow oil which was preadsorbed onto silica gel from ether. The dry powder was loaded onto a column which had been eluted with hexanes, and then gradient elution (hexane to 20% ethyl acetate by 2.5% increments) gave 41 mg (23%; 28% based on recovered starting material) of the ketoolefin **13** as a pale yellow oil (contaminated with ~5% of diphenylpentenylphosphine oxide) and 36 mg of recovered cyclopropyl lactam **8a**. ^{1}H-NMR showed the presence

(13) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694.

of ~5% of the *E* olefin. Further purification by microdistillation gave a colorless, odoriferous oil: R_f 0.68 (50% ethyl acetate/hexane); IR (neat) 1694 cm^{-1}; $[\alpha]^{22}_D$ −125° (*c* 0.94, $CHCl_3$); ^1H-NMR ($CDCl_3$, 300 MHz) δ 0.90 (broad t, 3 H, *J* = 6.9 Hz), 1.21 (d, 3 H, *J* = 6.5 Hz), 1.23–1.43 (m, 6 H), 1.60–1.73 (m, 1 H), 2.03–2.44 (m, 3 H), 2.23 (s, 3 H), 5.51–5.82 (m, 2 H).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.84; H, 11.11.

Cyclopropyl Lactams 14a, 14b. To a stirred solution of 486 mg (1.82 mmol) of the cyclopropyl lactam *anti*-**10** in 18 mL of absolute ethanol cooled to −5 °C was added in one portion 207 mg (5.46 mmol, 3.0 equiv) of $NaBH_4$. The slurry was maintained at −5 °C for 5 min, allowed to warm to ambient temperature for 5 h, and then heated to reflux for 17 h. The reaction mixture was transferred to a beaker and diluted with 50 mL of ethanol, and then 1.38 mL (24.0 mmol, 13.2 equiv) of acetic acid was added carefully. After concentration in vacuo, the residue was partitioned between ethyl acetate and aqueous 5% HCl. The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 75 mL). The combined organics were washed with aqueous saturated sodium bicarbonate and brine and then dried ($MgSO_4$). Concentration in vacuo gave 312 mg (72%) of the carbinol, **14a**, as a viscous colorless oil: R_f 0.14 (50%) ethyl acetate/hexane); IR (neat) 3406, 1694 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 0.93 (s, 9 H), 1.53–1.55 (m, 1 H), 1.61 (s, 3 H), 1.80 (dd, 1 H, *J* = 3.3, 5.8 Hz), 2.21 (dd, 1 H, *J* = 3.2, 5.7 Hz), 3.36 (apparent t, 1 H, *J* = 8.4 Hz), 3.52 (dd, 1 H, *J* = 6.1, 11.5 Hz), 3.62 (dd, 1 H, *J* = 5.6, 11.3 Hz), 3.94 (apparent t, 1 H, *J* = 9.1 Hz), 4.23 (apparent t, 1 H, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 75.0 MHz) δ 24.4, 25.5, 25.9, 27.1, 29.6, 33.0, 61.7, 65.0, 69.9, 99.0, 178.3.

Without further handling, the carbinol **14a** was transformed to its benzyl ether as described below. To a stirred slurry of oil-free sodium hydride in THF (5 mL) was added 312 mg (1.30 mmol) of the alcohol as a THF solution (10 mL). After 30 min, 4 mg (0.013 mmol, 0.01 equiv) of Bu_4NI was added followed by 186 μL (1.56 mmol, 1.2 equiv) of benzyl bromide. After 3 h, an additional 30 mg of sodium hydride and 90 μL of benzyl bromide were added and stirring was continued for 18 h. The mixture was quenched by addition of water (5 mL), and then concentration in vacuo was followed by extraction with ether (3 × 40 mL). The combined organics were washed with aqueous saturated sodium bicarbonate and brine and then dried ($MgSO_4$) and concentrated to afford a yellow oil. Purification by flash column chromatography (gradient elution: hexane to 10% ethyl acetate/hexane by 2.5% increments and then 20% ethyl acetate/hexane) gave 394 mg (66% overall from cyclopropyl lactam **10**) of the benzyl ether **14b** as a pale yellow, viscous oil. An analytical sample was prepared by microdistillation to afford a colorless viscous oil: R_f 0.60 (50% ethyl acetate/hexane); $[\alpha]^{22}_D$ 50.2° (*c* 1.22, $CHCl_3$); IR (neat) 1714 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 9 H), 1.45–1.55 (m, 1 H), 1.58 (s, 3 H), 1.76 (dd, 1 H, *J* = 3.3, 5.8 Hz), 2.15 (dd, 1 H, *J* = 3.3, 5.8 Hz), 3.33 (apparent t, 1 H, *J* = 8.2 Hz), 3.38 (dd, 1 H, *J* = 5.8, 10.4 Hz), 3.50 (dd, 1 H, *J* = 5.3, 10.3 Hz), 3.91 (apparent 5, 1 H, *J* = 9.2 Hz), 4.19 (dd, 1 H, *J* = 8.3, 9.3 Hz), 4.48 (apparent s, 2 H), 7.24-7.34 (m, 5 H); ^{13}C-NMR ($CDCl_3$, 75.0 MHz) δ 22.8, 24.5, 25.9, 27.1, 29.5, 32.9, 65.0, 68.4, 69.8, 72.5, 98.8, 127.6, 128.3, 137.9, 177.9.

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26. Found: C, 72.81; H, 8.27.

"Salt-Free" Triphenylphosphonium Methylidene. The "salt-free" ylide solution was prepared according to the procedure of Bestman[13] (as described above for the pentenyl ylide) with 2.038 g of methyltriphenylphosphonium bromide (5.70 mmol) and 6.28 mL (12.1 mmol, 1.1 equiv) of sodium hexamethyldisilazide (1.0 M in THF). This ylide was best prepared fresh immediately prior to use.

Acetylcyclopropyl Olefin 16. Prepared according to the method described for cyclopropyl olefin **13** (vide supra) with 117 mg (0.36 mmol) of cyclopropyl lactam **14b**, 0.08 mL (0.28 mmol, 0.8 equiv) of Red-Al (Aldrich, 3.4 M solution in toluene), 4.3 mL (0.90 mmol, 2.5 equiv) of "salt-free" methylidine triphenylphosphorane (0.21 M in THF), and 5 mL of aqueous 1 M $Bu_4NH_2PO_4$. The reaction afforded 54 mg (65%) of the optically pure cyclopropyl ketoolefin **16** as a colorless oil after purification by flash column chromatography (gradient elution: hexane to 20% ethyl acetate/hexane by 5% increments). An analytical sample was obtained by microdistillation as a colorless oil: R_f 0.45 (50% ethyl acetate/hexane); $[\alpha]^{22}_D$ −88.2° (*c* 0.84, $CHCl_3$); IR (neat) 1694 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 2.02–2.13 (m, 2 H), 2.23 (s, 3 H), 2.25 (dd, 1 H, *J* = 5.8, 8.7 Hz), 3.43 (dd, 1 H, *J* = 5.7, 10.4 Hz), 3.51 (dd, 1 H, *J* = 5.4, 10.4 Hz), 4.48, 4.53 (AB q, 2 H, *J* = 12.0, 12.0 Hz), 5.01 (dd, 1 H, *J* = 1.8, 10.3 Hz), 5.19 (dd, 1 H, *J* = 1.8, 17.1 Hz), 5.71 (ddd, 1 H, *J* = 9.0, 10.3, 19.2 Hz), 7.26–7.38 (m, 5 H); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 27.9, 31.7, 32.3, 33.6, 70.3, 72.4, 116.1, 127.5, 127.6, 128.3, 133.9, 138.0, 204.7.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.06; H, 7.89.

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Supplementary Material Available: Complete X-ray data and structure of lactam **8b** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.