the procedure used for the debenzylation of the pentacyclic amide **34a**, dihydroindole **45** (11.0 mg, 0.029 mmol) was similarly debenzylated with Na/NH_3. Purification of the crude product by flash chromatography (230–400 mesh silica, 2–8% $MeOH/CH_2Cl_2$) afforded 8.6 mg (100%) of alcohol **46** as a colorless glass: ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (dd, J = 0.5, 7.4 Hz, 1 H, ArH), 7.04 (dt, J = 1.1, 7.6 Hz, 1 H, ArH), 6.75 (dt, J = 0.8, 7.4 Hz, 1 H, ArH), 6.66 (d, J = 7.7 Hz, 1 H, ArH), 5.70 (ddd, J = 1.6, 4.9, 9.9 Hz, CH=C*H*CH_2), 5.59 (dd, J = 0.8, 10.0 Hz, C*H*=$CHCH_2$), 3.61–3.72 (m, 2 H), 3.53 (dd, J = 5.8, 10.9 Hz, 1 H), 3.46 (dd, J = 4.1, 16.2 Hz, 1 H), 3.25–3.33 (m, 1 H), 2.80 (d, J = 16.1 Hz, 1 H), 2.69 (s, 1 H), 2.30–2.40 (m, 2 H), 1.55–1.78 (m, 4 H), 1.35–1.48 (m, 2 H), 1.20–1.32 (m, 2 H) ppm; MS (CI) 297 (MH); MS (EI) 296.1905 (7, 296.18885 calcd for $C_{19}H_{24}N_2O$, M), 151 (98), 144 (68), 138 (48), 137 (100), 130 (40).

(6aβ,11aβ,13bα,13aα)-11-Acetyl-13a-(2-hydroxyethyl)-2,3,5,6,11,11a,12,13,13a,13b-decahydro-1*H*-cyclopent[*ij*]indolo[2,3-*a*]-quinolizine (47). A solution of the alcohol **46** (7.0 mg, 0.024 mmol) and EtOH (1 mL) containing catalytic Pd/C (7 mg) and ammonium formate (15 mg, 0.24 mmol) was heated at reflux for 1 h. The reaction mixture was then cooled to 23 °C, filtered through a bed of Celite, washed with $CHCl_3$, and concentrated. Flash chromatography of the residue (230–400 mesh silica, 2–8% $MeOH/CH_2Cl_2$) yielded 6.9 mg (98%) of the dihydro product as a pale yellow solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 7.4 Hz, 1 H, ArH), 7.00 (dt, J = 1.1, 7.6 Hz, 1 H, ArH), 6.73 (dt, J = 0.8, 7.4 Hz, 1 H, ArH), 6.63 (d, J = 7.7 Hz, 1 H, ArH), 3.61 (td, J = 5.5, 10.4 Hz, 1 H), 3.45–3.52 (m, 2 H), 3.11 (bdd, J = 7.0, 10.3 Hz, 1 H), 3.04 (bd, J = 10.8 Hz, 1 H), 2.20–2.32 (m, 3 H), 2.04 (dt, J = 3.1, 13.8 Hz, 1 H), 1.98 (app dt, J = 2.5, 11.7 Hz, 1 H), 1.60–1.83 (m, 4 H), 1.45–1.52 (m, 3 H), 1.13–1.33 (m, 4 H), 1.00–1.16 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 135.2, 127.3, 122.7, 119.2, 110.5, 70.7, 65.3, 58.6, 53.7, 53.4, 52.8, 40.5, 38.5, 35.4, 29.7, 28.2, 24.2, 21.7 ppm; IR (KBr) 3312, 3189, 2940, 2911, 2813, 1608, 1463, 1043, 743 cm^{-1}; MS (CI) 299 (MH); MS (EI) 298.2056 (3, 298.20450 calcd for $C_{19}H_{20}N_2O$, M), 141 (10), 140 (100).

This intermediate (6.9, mg, 0.023 mmol) was acetylated as described by Ban[15] to provide, after purification by flash chromatography (230–400 mesh silica, 2%–8% $MeOH/CH_2Cl_2$), 7.0 mg (89%) of **47** as a colorless solid: ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 140.6, 138.0, 127.6, 124.3, 122.3, 118.3, 70.3, 67.9, 53.6, 52.8, 52.4, 40.3, 39.5, 35.2, 35.0, 25.8, 24.1, 23.2, 21.5 ppm; MS (CI) 341 (MH); MS (EI) 340.2148 (9, 340.21506 calcd for $C_{21}H_{28}N_2O_2$, M), 312 (9), 168 (6), 140 (100). The ^1H NMR spectra of this intermediate agreed with an authentic spectrum provided by Professor Y. Ban.

Acknowledgment. This research was supported by an NIH Javits Neuroscience Investigator Award (NS-12389) to L.E.O. NMR and mass spectral instrumentation employed in this study were purchased with the assistance of NSF Shared Instrumentation Grants. We particularly acknowledge Dr. H.-N. Lin for his early investigations in this area. We also thank Professor J. Lévy for a comparison sample of (+)-meloscine, Professor K. Bernauer for comparison spectra of natural **1** and **2**, and Professor Y. Ban for comparison spectra of **47**.

Supplementary Material Available: Experimental preparations and spectroscopic data (^1H NMR and MS) for **35b**, **36b**, and **37b** (2 pages). Ordering information is given on any current masthead page.

Synthetic Studies on Basmane Diterpenes. Enantiospecific Total Synthesis of (+)-7,8-Epoxy-2-basmen-6-one by Claisen Ring Expansion

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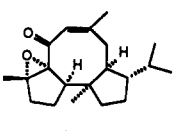
Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received August 8, 1990*

Abstract: The first synthesis of an epoxybasmenone is described. The enantiospecific pathway begins by transforming optically pure aldehyde **10** into bicyclic lactone **39**. Methylenation of **39** by means of the Tebbe reaction allows for operation of a Claisen rearrangement that proceeds almost completely by way of chair transition state **44** to give the cyclooctadienone **42**. Regiospecific cyclopentannulation with installation of four additional stereogenic centers rested upon successful introduction of a functionalized four-carbon chain as in **48**, facially controlled hydrogenation of the conjugated double bond, cyclization, and hydroxyl-directed epoxidation. Finally, Swern oxidation led to the target molecule **3**, whose three-dimensional structural features were confirmed by X-ray crystallography.

Introductory Remarks

The discovery of (+)-**1** in the sun-cured leaves of Greek tobacco (Serres) by Wahlberg et al.[1] has been important in identifying a new class of carbotricyclic diterpenes and in confirming that intramolecular proton-induced cyclization of cembranoids need not give hydrophenanthrenes exclusively.[2] The studies described herein not only were formulated to develop concise routes to basmanes, the generic name assigned to this class (see **2** for atomic numbering),[1] but were seen to have the potential for broad application toward other biologically significant targets. In this paper, we detail an enantiospecific route to (+)-7,8-epoxy-2-basmen-6-one (**3**), the first member of this group to yield to total synthesis.[3]



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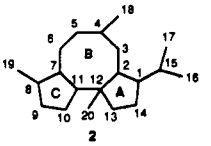

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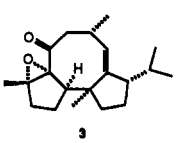

3

A third inducement to undertake this work centered about the unusual structural features of the basmenones. The 1*S* configuration is a characteristic of all known tobacco cembranoids.[4]

(1) Wahlberg, I.; Eklund, A.-M.; Nishida, T.; Enzell, C. R.; Berg, J.-E. *Tetrahedron Lett.* **1983**, *24*, 843.
(2) Dauben, W. G.; Hubbell, J. P.; Oberhausli, P.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44*, 669.
(3) Preliminary communication: Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252.
(4) (a) Colledge, A.; Reid, W. W.; Russell, R. *Chem. Ind. (London)* **1975**, 570. (b) Enzell, C. R.; Wahlberg, I. *Recent Adv. Tobacco Sci.* **1980**, *6*, 64.

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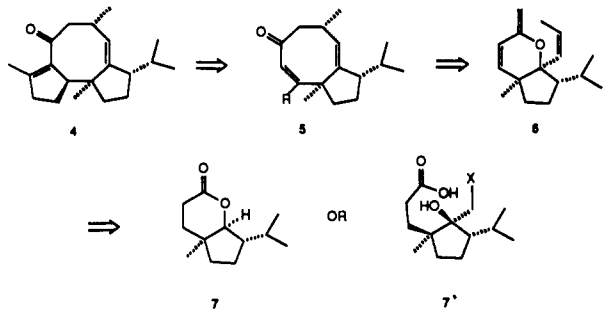
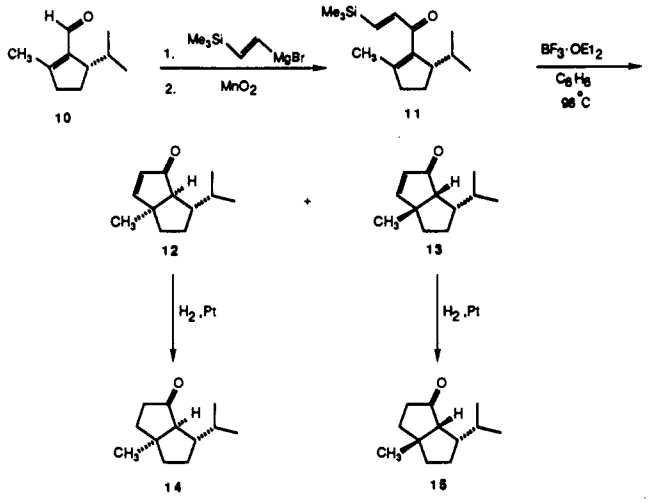
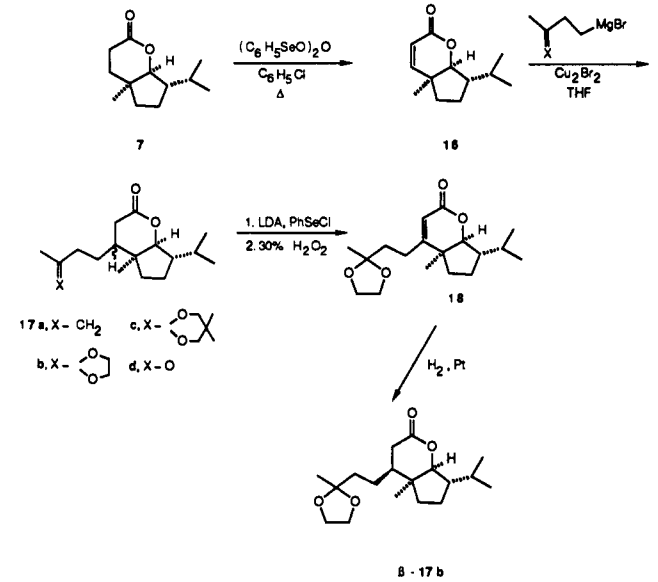
Scheme I



Scheme II



Scheme III



Furthermore, the all-cis stereochemistry of the two five-membered rings causes the central cyclooctane framework to exist in a saddlelike conformation. Other structural features, such as elongated C–C bond lengths, revealed in the case of **1** by X-ray analysis, suggest that the tricyclic basmenone ring system is very likely strained.[1]

Relevant to any synthetic attack on basmanes in general is recognition that the two five-membered rings are positioned in adjacent fashion on the cyclooctane core. Consequently, basmanes differ inherently from sester- and diterpenoids of the ophiobolin,[5,6] ceroplastol,[7,8] and fussicoccin type,[9] where a one-carbon spacer serves to distance ring A from ring C. Various strategies pertinent to these dicyclopenta[*a*,*d*]cyclooctanes have appeared with growing frequency in concert with their theoretical and biological relevance.[9]

Retrosynthetic Analysis. Our synthetic plan contemplated intermediacy of a system of type **5** in which the relative configurations of at least three stereogenic centers would have been properly arranged (Scheme I). The prospectus deliberately leaves open the specific point in time at which the substituent R, the group that is to serve as progenitor of the second five-membered ring (as in **4**), is to be set into the requisite β configuration. This stereochemical latitude opens up several options for harmonizing the construction of subunits that would not otherwise be possible to consider.

For the purpose of achieving expedient arrival at **5**, we wished to implement a ring expansion variant of the Claisen rearrangement.[10] This central element of our strategy had previously been shown to be highly utilitarian in providing ready access to precapnelladiene (**8**)[11] and the *cis*- and *trans*-lauthisans (**9a** and **9b**).[12] The surmise that **6** would be well suited to the stereospecific introduction of the alkyl groups in **5** rests on the strong likelihood that the [3,3] sigmatropic event required to reach **5** would be heavily dominated by a chairlike transition-state topography.[13]

(5) Isolation: (a) Ophiobolin A: Ishibashi, K.; Nakamura, R. *J. Agric. Chem. Soc. Jpn.* **1958**, *32*, 739. Nozoe, S.; Morisaki, M.; Tsuda, K.; Iitake, Y.; Takahashi, N.; Tamura, S.; Ishibashi, K.; Shirasaka, M. *J. Am. Chem. Soc.* **1965**, *87*, 4968. (b) Ophiobolins B and C: Nozoe, S.; Hirai, K.; Tsuda, K. *Tetrahedron Lett.* **1966**, 2211. Canonica, L.; Fiecchi, A.; Kinele, M. G.; Scala, A. *Ibid.* **1966**, 1329. Ishibashi, K. *J. Antibiot.* **1962**, *A15*, 88. (c) Ophiobolin D: Itai, A.; Nozoe, S.; Tsuda, K.; Ikuda, S.; Iitaka, Y.; Nakayama, Y. *Tetrahedron Lett.* **1967**, 4111. Nozoe, S.; et al. *Ibid.* **1967**, 4113. (d) Ophiobolin F: Nozoe, S.; Morisaki, M.; Fukushima, K.; Okuda, S. *Ibid.* **1968**, 4457. Nozoe, S.; Morisaki, M. *J. Chem. Soc. D* **1969**, 1319.

(6) Synthetic activity: (a) Das, T. K.; Gupta, A. D.; Ghosal, P. K.; Dutta, P. C. *Indian J. Chem., Sect. B* **1976**, *14B*, 238. (b) Das, T. K.; Dutta, P. C. *Synth. Commun.* **1976**, *6*, 253. (c) Das, T. K.; Dutta, P. C.; Kartha, G.; Bermassan, J. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1287. (d) Boeckman, R. K., Jr.; Bershas, J. P.; Clardy, J.; Solheim, B. *J. Org. Chem.* **1977**, *42*, 3630. (e) Dauben, W. G.; Hart, D. J. *Ibid.* **1977**, *42*, 922. (f) Baker, W. R.; Senter, P. D.; Coates, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1011. (g) Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597. (h) Paquette, L. A.; Andrews, D. R.; Springer, J. P. *Ibid.* **1983**, *48*, 1147. (i) Takeshita, H.; Kato, N.; Nakanishi, K. *Chem. Lett.* **1984**, 1495. (j) Coates, R. M.; Muskopf, J. W.; Senter, P. A. *J. Org. Chem.* **1985**, *50*, 3541. (k) Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *Ibid.* **1985**, *50*, 201. (l) Mehta, G., Krishnamurthy, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1319. (m) Rigby, J. H.; Senanayake, C. *J. Org. Chem.* **1987**, *52*, 4634. (n) Rowley, M.; Kishi, Y. *Tetrahedron Lett.* **1988**, *29*, 4909. (o) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735.

(7) Isolation: (a) Fusicoccin A: Hough, E.; Hursthouse, M. B.; Neidle, S.; Rodgers, D. *Chem. Commun.* **1968**, 1197. Ballio, A.; Brufani, M.; Casinori, C. G.; Cerrini, S.; Fedeli, W.; Pellicciari, R.; Santurbano, B.; Vaiaga, A. *Experientia* **1968**, *24*, 631. Barrow, K. D.; Barton, D. H. R.; Chain, E.; Ohnsorge, U. F. W.; Thomas, R. *J. Chem. Soc. C* **1971**, 1265. (b) Fusicoccin H: Barrow, K. D.; Barton, D. H. R.; Chain, E.; Ohnsorge, U. F. W.; Sharma, R. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1590. (c) Fusicoccin J: Barrow, K. D.; Barton, D. H. R.; Chain, E.; Bageend-Kasujja, D.; Mellows, G. *Ibid.* **1975**, 877. (d) Cotylenol: Sassa, T. *Agric. Biol. Chem.* **1972**, *36*, 2037; **1975**, *39*, 1729. (e) Ceroplastol I and ceroplasteric acid: Iitake, Y.; Watanabe, L.; Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1968**, *90*, 1092. (f) Ceroplastol II: Rios, T.; Quijano, L. *Tetrahedron Lett.* **1969**, 1317. (g) Albolic acid: Rios, T.; GOmez, F. *Ibid.* **1969**, 2929.

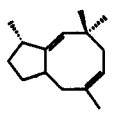
(8) Synthetic activity: (a) Kato, N.; Nakanishi, K.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1109. (b) Kato, N.; Tanaka, S.; Takeshita, H. *Chem. Lett.* **1986**, 1989. (c) Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354. (d) Kato, N.; Takeshita, H.; Kataoka, H.; Ohbuchi, S.; Tanaka, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 165. (e) Boeckman, R. K., Jr.; Arvanitis, A.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 2737.

(9) (a) Cordell, G. A. *Phytochemistry* **1974**, *13*, 2343. (b) Canonica, L.; Fiecchi, A. *Res. Prog. Org. Biol. Med. Chem.* **1970**, *2*, 49.

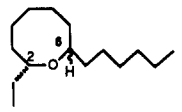
(10) (a) Rhoads, S. J.; Brandenburg, C. F. *J. Am. Chem. Soc.* **1971**, *93*, 5805. (b) Rhoads, S. J.; Watson, J. M. *Ibid.* **1971**, *93*, 5813. (c) Demole, l.; Enggist, P. *J. Chem. Soc., Chem. Commun.* **1969**, 264. (d) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 3075. (e) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6889. (f) Danishefsky, S.; Tsuzuki, K. *Ibid.* **1980**, *102*, 6891.

(11) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868; **1985**, *107*, 7352.

(12) Paquette, L. A.; Sweeney, T. J. *J. Org. Chem.* **1990**, *55*, 1703; *Tetrahedron* **1990**, *46*, 4487.



8



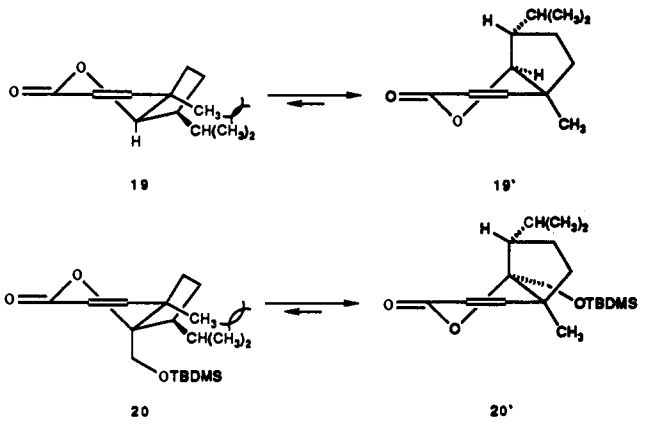
9 a, 8-(S)-
b, 8-(R)-

It was envisioned that **6** might be produced in turn from either **7** or **7'**, although it was not clear from the outset which of these would prove more accessible and serviceable. The protocol for advancement to either of these intermediates necessarily had to incorporate high resident levels of optical purity. As matters have turned out, we have been able to access both **7** and **7'** from aldehyde **10**, which is available in enantiomerically pure condition from commercially available (*R*)-(+)-limonene.[14]

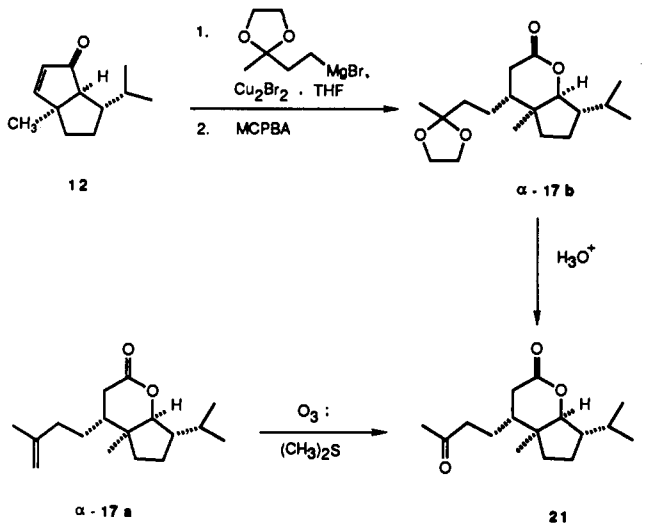
Cyclopentanone-2-propionate Approach to 7. Steric Complications. The first task in gaining access to **7** centered on proper annulation of a functionalized five-membered ring. The silicon-directed Nazarov cyclization[15] was selected for this purpose, although we were unaware at the time of its successful application in an example involving generation of a quaternary center.[16] Condensation of **10** with the Grignard reagent derived from (*E*)-(2-bromoethenyl)trimethylsilane gave the carbinol, whose oxidation with barium manganate in dry dichloromethane solution[15c,17] served to provide ketone **11** in 85% overall yield (Scheme II). The four Lewis acids $FeCl_3$, $ZnCl_2$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ were screened as possible promoters of the desired electrocyclization of **11**. With the first two, no reaction occurred in dichloromethane at room temperature under anhydrous conditions. When catalytic quantities of water or HCl were introduced, substantial levels of decomposition to tarry products were observed. Parallel findings were noted with $SnCl_4$ in the absence of moisture. In contrast, heating **11** to 98 °C with 4 equiv of boron trifluoride etherate in benzene[18] generated an 84:16 mixture of **12** and **13** (72% combined yield). These diquinane ketones proved amenable to chromatographic separation. The major isomer was assigned all-cis stereochemistry on the basis of its greater thermodynamic stability (the isopropyl group is quasi-equatorial) and the known predilection of the directed Nazarov process to be kinetically biased toward cis products.[15]

Having secured pure samples of **12** and **13**, we hydrogenated the individual isomers to arrive at **14** and **15**. On exposure of **14** to *m*-chloroperbenzoic acid in chloroform, the normal Baeyer–Villiger reaction course[19] was followed and lactone **7** was obtained without any loss of stereochemical integrity (Scheme III). Initial efforts to introduce a conjugated double bond into this intermediate as in **16** proceeded in low yield and gave product that was contaminated to the 20% level with a difficultly separable unknown impurity. This complication surfaced when recourse was made to phenylselenyl chloride or bromide, as well as diphenyl or di-2-pyridyl diselenide with subsequent oxidative elimination. Ultimately, the use of benzeneselenenic anhydride in hot chlorobenzene[20] was considered and found to be the ideal reagent. The yield of **16** following chromatographic purification was 97%.

Scheme IV



Scheme V



In order to realize attachment of a functionalized four-carbon side chain to **16** in a satisfactory way and with good control over β-face selectivity, careful attention was paid to the response of three cuprate reagents. The Grignard derived from 2-methyl-4-bromobutene was admixed with cuprous bromide in both ether and tetrahydrofuran. In THF, the organometallic proved to be marginally reactive (20% conversion) and the resultant β:α ratio was 4:1. The reactivity level is considerably enhanced in ether (64% yield), but the β:α ratio becomes inverted (1:4.7).

The Grignard reagents based on 4-bromo-2-butanone ethylene and neopentyl glycol ketals could not be satisfactorily prepared in ether or 1,2-dimethoxyethane, thereby limiting study to tetrahydrofuran. Their cuprates ultimately gave **17b** and **17c** in good yield. The β isomers were again found to dominate (β:α = 4.7:1 and 7.6:1, respectively).

To understand the obviously delicate stereochemical sensitivities to which **16** is subject, one needs only to consider its two most accessible conformations (**19** and **19'**, Scheme IV). The structural elements in conformer **19** are such that steric effects should favor topside (β) attack, while stereoelectronic factors are clearly more conducive to 1,4-addition from the α face. The situation is precisely reversed in **19'**, where the potential for substantive 1,3-diaxial steric compression is especially obvious. When the angular hydrogen was replaced by a [(*tert*-butyldimethylsilyl)oxy]methyl group as in **20** and **20'**, cuprate reagents continued to prefer β entry, and to approximately the same extent (consult ref 28). We find this difficult to reconcile with the involvement of conformers **19** and **20** in the product-forming transition states, since the ratios should be strongly affected by the added steric screening in **20**. They are not. At this point in time, therefore, our view is that conformers **19'** and **20'** are the more kinetically relevant, with

(13) (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1. (c) Bennett, G. B. *Synthesis* **1977**, 589. (d) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (e) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

(14) Lange, G. L.; Neidert, E. E.; Orrom, W. J.; Wallace, D. J. *Can. J. Chem.* **1978**, *56*, 1628.

(15) (a) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. (b) Denmark, S. E.; Jones, T. K. *Helv. Chim. Acta* **1983**, *66*, 2377, 2397. (c) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821.

(16) Prof. S. Denmark subsequently informed us that he had achieved equally good success in cases involving the generation of quaternary centers. Consult: (a) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168. (b) Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043.

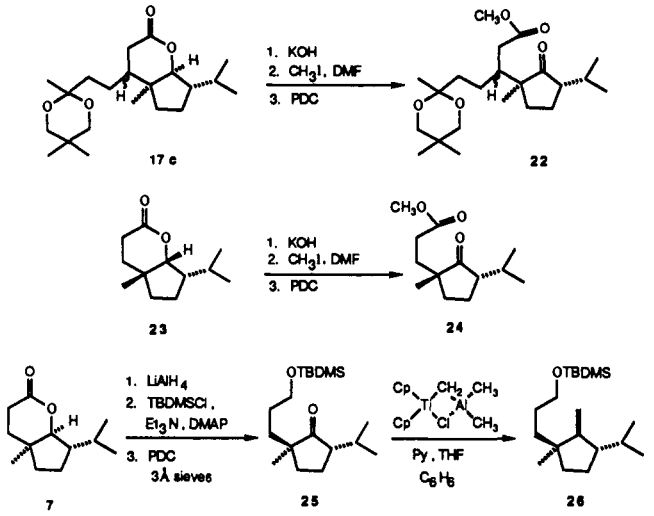
(17) Fiouzabadi, H.; Ghaderi, E. *Tetrahedron Lett.* **1978**, 839.

(18) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017.

(19) Hassall, C. H. *Org. React. (N.Y.)* **1957**, *9*, 73.

(20) (a) Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1978**, 130. (b) Barton, D. H. R.; Morzycki, J. W.; Motherwell, W. B.; Ley, S. V. *Ibid.* **1981**, 1044.

Scheme VI



adduct configuration being determined predominantly by stereoelectronic control.

While the epimers of **17a** lend themselves to chromatographic purification, comparable success was not achieved with **17b** or **17c**. Consequently, recourse was made to α-**17a** for the purpose of confirming stereochemical assignment. In line with the behavior of many diquinane systems,[21] enone **12** underwent cuprate addition to give a major adduct that can be reliably assigned as the α isomer. Its Baeyer–Villiger oxidation led to α-**17b** (Scheme V), acidic hydrolysis of which gave **21**. This keto lactone proved identical in all respects with the product of ozonolysis of α-**17a**.

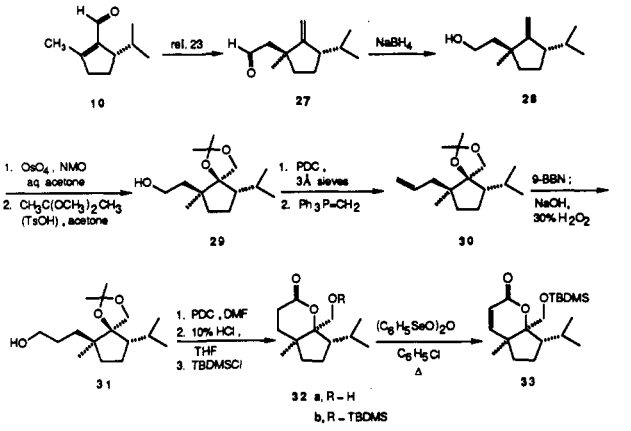
In an effort to produce β-**17b** in a stereochemically homogeneous state, oxidation of the epimeric mixture to **18** was examined. Unfortunately, **17b** proved more recalcitrant to oxidation than **7**. The maximum yield for this conversion was only 20%. We were particularly disappointed in the consistent inefficiency of this transformation since the hydrogenation of **18** did indeed afford β-**17b** exclusively (99%).

Even earlier than our observations relating to these stereochemical interrelationships was the demonstration that opening of the lactone ring in **17c** was viable. While this could not be accomplished with sodium methoxide in methanol because of a rapid recyclization rate, the following three-step sequence gave **22** in 81% overall yield. Saponification with potassium hydroxide in ethanol/water (1:1) was carried to completion, and the carboxylate anion was directly alkylated with methyl iodide in dimethylformamide.

The resultant hydroxy ester was immediately oxidized with pyridinium dichromate (Scheme VI). Disappointingly, the ketone carbonyl group in **22** proved to be too sterically blockaded to react with (*Z*)- (and (*E*))- propenylmagnesium bromide and related organometallics.

The notable unreactivity of **22** is shared by **24**, which was prepared analogously from lactone **23**. The presence of a carbomethoxy group in both **22** and **24** prevented the adaptation of forcing conditions. In order to probe this option, **7** was transformed by conventional means into **25**. This was quickly seen not to be a solution to the problem, since this ketone was also unreactive to the same Grignard reagents at more elevated temperatures. While condensation of **25** with the Tebbe reagent[22] did result in

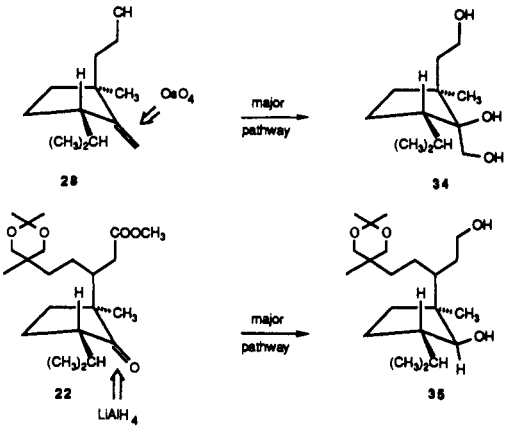
Scheme VII



conversion to **26**, the extent of reaction was only 15% and the recovered ketone had undergone extensive epimerization.

The information gained from these studies established that passage via lactone **7** was impractical and that reliance on an intermediate already carrying a functionalized carbon atom as in **7′** might effectively skirt this complication.

Arrival at the Penultimate Claisen Substance. The three-step conversion of **10** to **27** had previously been described by Mehta and Krishnamurthy.[23] The most conveniently workable one-carbon homologation[24] of **27** began with sodium borohydride reduction to **28** followed by osmylation and regioselective acetonide formation as in **29** (Scheme VII). Although the two-component mixture could not readily be separated, high-field ^{1}H NMR clearly indicated one isomer to dominate heavily. Nuclear Overhauser effect (NOE) studies at 500 MHz suggested that the tertiary C–O bond was oriented β. This assignment was ultimately corroborated by X-ray analysis of a more advanced intermediate. Accordingly, **28** experiences electrophilic attack preferentially from that direction anti to the isopropyl group to give **34** after hydrolysis. These data provide an interesting contrast to the face selectivity that is experienced by keto ester **22** during hydride reduction to **35**.[25]

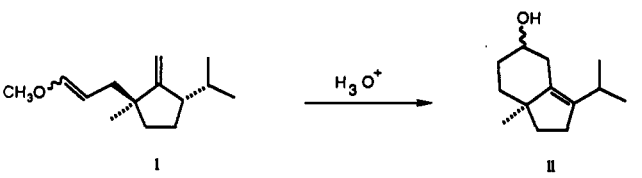


(21) (a) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Heidelberg, 1987. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (c) Paquette, L. A. *Ibid.* **1979**, *79*, 41.

(22) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *Ibid.* **1980**, *102*, 3270. (c) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, I.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733. (d) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212.

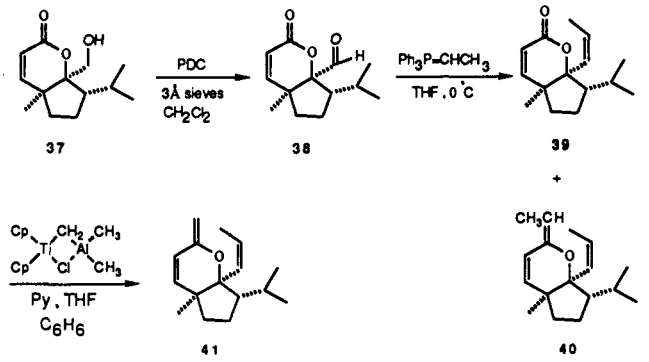
(23) Mehta, G.; Krishnamurthy, N. *Tetrahedron Lett.* **1987**, *28*, 5945.

(24) An alternative attempt to accomplish one-carbon homologation of **27** using Wittig chemistry was thwarted when enol ether i was observed to undergo cyclization to ii during acidic hydrolysis.



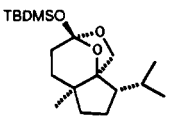
(25) Kang, H.-J. Unpublished observations.

Scheme VIII



The unstable aldehyde obtained from **29** reacted with methylenetriphenylphosphorane to give **30**.[26] Following the hydroboration of **30** with 9-BBN, alcohol **31** was recognized to be available from **27** in 62% overall yield after chromatographic purification on silica gel. Once oxidation to the carboxylic acid level had been achieved, closure to bicyclic lactone **32a** was guaranteed. The cis disposition of the propionic acid residue and tertiary hydroxyl correlates well with kinetically favorable exo-trig closure. A relevant consequence of this cyclization is proper placement of a suitably oxygenated carbon at the immediately adjacent (not tertiary) site.

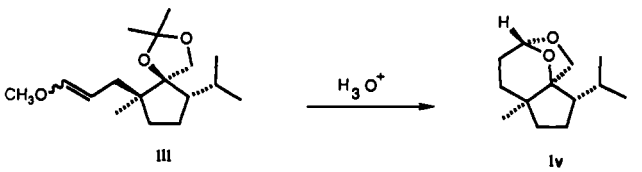
In order to exploit the structural features of **32a**, its hydroxy group was first silylated. This protection step was hardly conventional. Thus, use of the reactive *tert*-butyldimethylsilyl triflate reagent[27] in ether with triethylamine as acid scavenger led rapidly (<5 min at 20 °C) and completely to **36**, a sensitive compound.



The reactivity of **32a** toward *tert*-butyldimethylsilyl chloride (imidazole, DMF) was very appreciably abated. Although the production of **36** was again kinetically favored under these circumstances, this ortho ester was now formed reversibly and reverted back to **32a** as a consequence of the good nucleophilicity of chloride ion in this solvent system. The starting hydroxy lactone was more slowly but irreversibly transformed into **32b**.

With arrival at **33**, indirect construction of ring B in **3** was nearly completed.[28] Homologative generation of two additional sights of unsaturation, one with high stereocontrol, was now required to reach this major plateau of the synthesis. The successful route that was employed for the fully stereocontrolled elaboration of **39** is summarized in Scheme VIII. Desilylation of **33** with tetra-*n*-butylammonium fluoride in tetrahydrofuran afforded **37** in quantitative yield. Its conversion in turn to aldehyde **38** was readily accomplished with pyridinium dichromate in slurried

(26) The conversion of iii was equally efficient. Acidic hydrolysis of this intermediate delivered iv, an acetal whose oxygen atoms could not be chemically differentiated adequately well.



(27) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(28) Addition of the Grignard cuprates derived from 4-bromo-2-butanone ethylene and neopentyl glycol ketals to **20** resulted in the formation of 1,4-adducts exhibiting β:α ratios of 4.1:1 and 5.7:1, respectively.

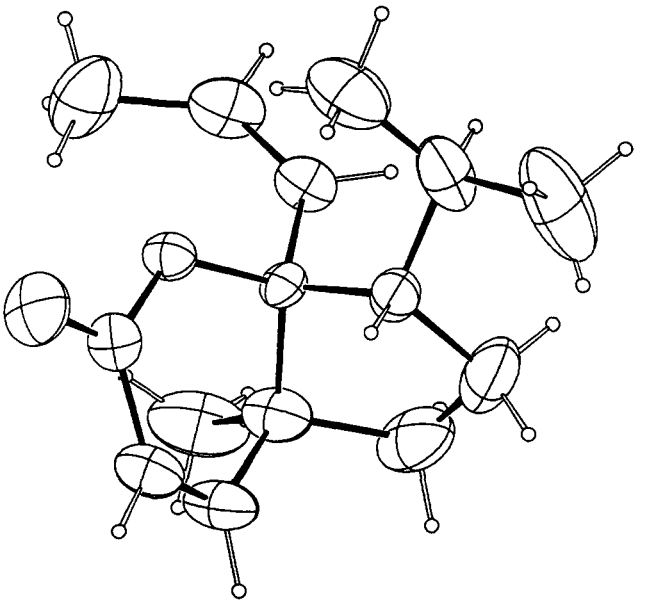
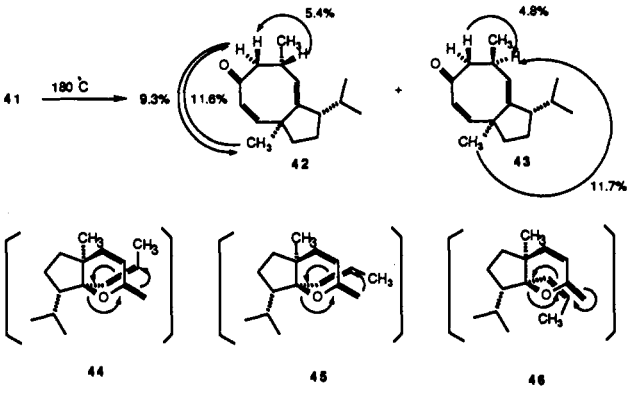


Figure 1. ORTEP drawing for **39**. The non-hydrogen atoms are represented by 30% probability thermal ellipsoids. The hydrogen atoms are drawn with an artificial radius.

Scheme IX



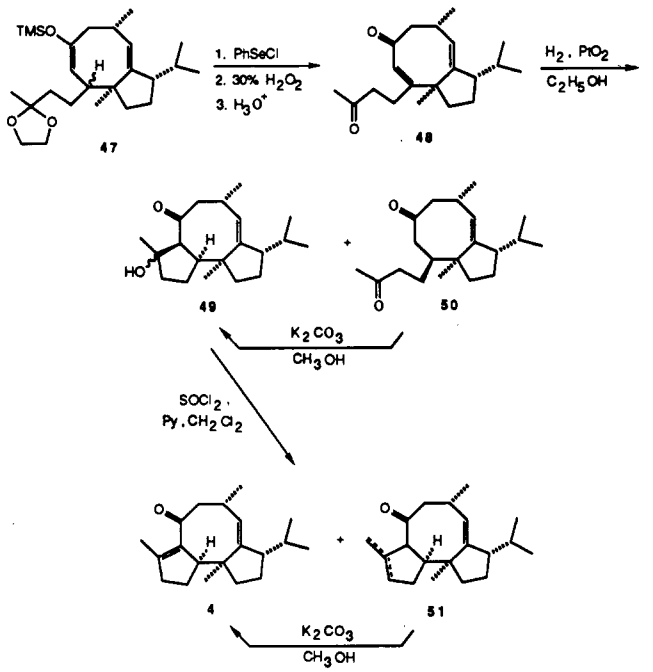
combination with powdered 3-Å molecular sieves. Without purification, **38** was brought into condensation with ethylidenetriphenylphosphorane[29] dissolved in tetrahydrofuran at 0 °C. This process provided for the routine isolation of **39** in 77% yield. The *Z* geometry of the newly introduced double bond was confirmed by X-ray crystallographic analysis of this colorless crystalline solid (Table I, supplementary material; Figure 1). When larger scale runs of this Wittig reaction were undertaken, it proved possible to isolate the minor product **40** in yields up to 5%. Once again, a single isomer was formed; however, the configuration of the exocyclic enol ether double bond has not been unequivocally established.

Some comment relating to the formation of **40** is appropriate here. Lactone carbonyls are normally unreactive toward Wittig reagents,[30] and compounds related to **32b** are no exceptions to this trend. It is interesting to surmise therefore that the conjugated double bond in a system such as **39** is conducive to activating the lactone moiety toward nucleophilic attack by the ylide.

Construction of the AB Ring System and Proper Annulation of Ring C. The conversion of **39** to **41** was accomplished by means of the Tebbe reaction.[22] As a consequence of the structural features in **41**, prototropic isomerization of the vinyl ether double bond is effectively precluded.[31] When thermally activated (180

(29) (a) Dusza, J. P. *J. Org. Chem.* **1960**, *25*, 93. (b) Schlosser, M.; Christmann, K. F. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 667. (c) Schlosser, M. *Top. Stereochem.* **1979**, *5*, 1.
(30) Murphy, P. J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1.

Scheme X

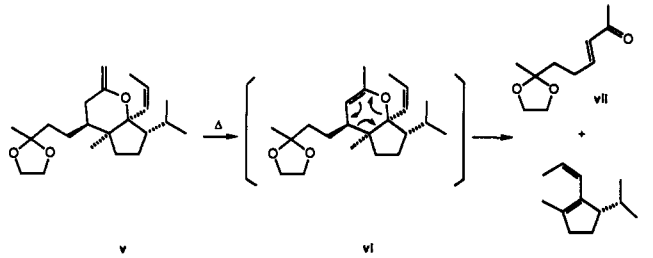


°C, 24 h, NaOH-washed Carius tubes), pure samples of **41** underwent conversion to a mixture of **42** and **43** rich in the α-4-methyl isomer (15:1, Scheme IX). These epimers could easily be distinguished spectroscopically, NOE effects being particularly diagnostic.

The Claisen step exhibited several interesting features. For example, if **41** was not well purified such that organometallic residues from the Tebbe reagent remained, **42** and **43** were formed more rapidly (conversion was usually complete in 8.5 h at 170 °C) and their ratio was now closely balanced (1:1). A modest increase in reaction yield (to ca. 60%) was also noted. Obviously, the impurities serve as Lewis acid promoters to accelerate the [3,3] sigmatropic process. Consequently, passage through chair transition state **44**, the assumed progenitor of **42**, appears to be facilitated. However, prior equilibration of (*Z*)- to (*E*)-propenyl would allow for competitive isomerization via **45** to **43**. The relative importance of boat form **46**, an alternative reaction trajectory to **43**, is not known at present.

Pure **42**, which exhibits an $[\alpha]^{19}_D$ of −2.7° in chloroform, underwent smooth condensation with the Grignard reagent derived from 4-bromo-2-butanone ethylene glycol ketal in the presence of $CuBr \cdot SMe_2$. Direct O-silylation of the regiospecifically generated enolate made accessible the homologated intermediate **47** (Scheme X). The facial control exercised by the cuprate reagent ($\beta:\alpha$ = 1:3) is not of consequence, since **47** was directly oxidized by sequential reaction with phenylselenyl chloride and 30% hydrogen peroxide. After acidic hydrolysis, **48** was isolated in 84%

(31) Internalization of the vinyl ether double bond in v manifested itself in a striking way during attempted Claisen rearrangement. When heated at



180 °C, ring expansion was not seen. Rather, retrograde Diels–Alder fragmentation to give vii was kinetically favored, this process presumably being mediated by vi.[25]

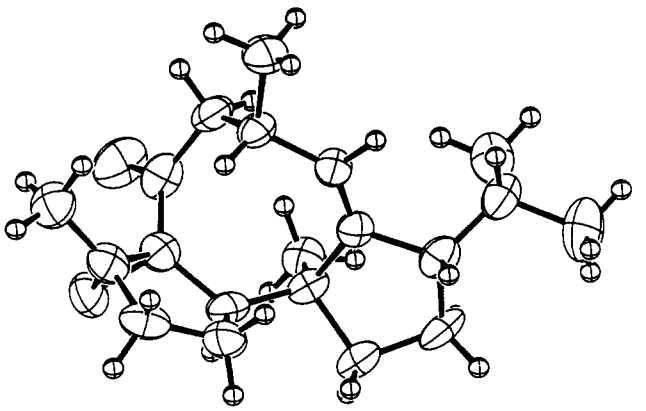
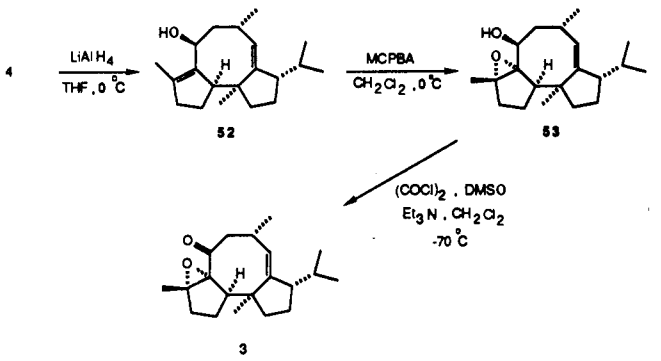


Figure 2. ORTEP drawing for **3**. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids. The hydrogen atoms are drawn with an artificial radius.

Scheme XI

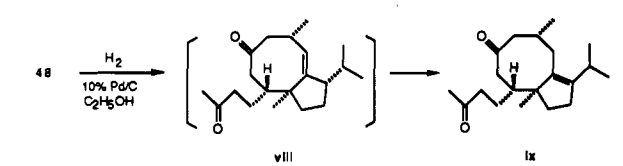


overall yield from **42**. As a consequence of the conformation adopted by **48**, hydrogenation over platinum proceeded stereoselectively from the α face.[32] A mixture of three compounds was produced. When chromatographic purification was undertaken at this stage, the aldol product **49** could be isolated in 42% yield. The second fraction consisted of a 9:1 mixture of **50** and its C-11 epimer (48%). More advisable and customary was our practice to treat the hydrogenate directly with potassium carbonate in methanol in order to complete the formation of ring C.

Once this was achieved, **49** was exposed to thionyl chloride and pyridine in dichloromethane solution in order to effect dehydration. Smooth conversion to a mixture of **4** and **51** resulted. These regioisomers were stirred in the presence of methanolic K_2CO_3 for 1 week in order to realize maximal conversion to **4** (70% after chromatography). Evidence for the stereo and positional integrity of the cyclopentene ring was founded entirely on ^1H and ^{13}C NMR data. Molecular modeling of **4** defined the compound as possessing a bowl-shaped topography with the several α substituents protruding outward from the convex surface, in line with the spectroscopic observations. Subsequent X-ray analysis of **3** corroborated this early deductive reasoning.

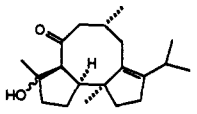
Arrival at (+)-7,8-Epoxy-2-basmen-6-one. The course of nucleophilic addition to the carbonyl group in **4** could be fully anticipated to be dictated by steric approach control. Accordingly, this tricyclic ketone was reduced with lithium aluminum hydride

(32) The use of 10% Pd/C as catalyst had very different consequences. In this instance, the nonconjugated double bond was prone to migrate to the adjacent site internal to the five-membered ring (as in viii). Enone reduction then proceeded more slowly and from the opposite surface to provide ix, where the side chain is projected to the undesired α face.[25]

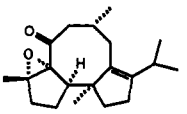


so as to produce **52** exclusively (Scheme XI). The attractiveness of the β-hydroxyl construction intensifies in the context of our desire to take advantage of the anti epoxidation mode that 3-cyclooctenols are recognized to follow.[33] In the case of **52**, the exocyclic double bond responded in entirely comparable fashion. Peracid oxidation resulted in the isolation of **53** at the 86% level. The α disposition of the oxirane ring was unambiguously confirmed by single-crystal X-ray analysis (Table I, supplementary material; Figure 2) following Swern oxidation to give **3**. This opticaly pure, solid epoxybasmenone is characterized by an $[\alpha]^{19}_D$ of +138°.

Double-Bond Migration in these Systems. In contemplating suitable extension of this methodology to the construction of conjugated enones exemplified by **1**, we undertook attempts to achieve double-bond isomerization by means of rhodium catalysis. For this to be successful, the transition metal would likely have to be able to engage in oxidative addition from the more sterically congested β (concave) face. Additionally, it was mandatory that no alternative energy minimum be accessed prior to arrival at the projected targets. As matters worked out, insertion by Rh into an allylic β C–H bond appears entirely workable. However, the kinetically favored pathway involves migration in the opposite direction! Thus, stirring **49** or **3** with 5% Rh/C in ethyl acetate under H_2 at room temperature ($RhCl_3$ in hot ethanol was ineffective) resulted in regiospecific isomerization to 54 and 55, respectively.[34] The coirradiation of **49** or **3** with thiophenol and AIBN also gave **54** and **55**. The structural assignments rest securely on their NMR features, which clearly show attachment of the isopropyl substituent to a trigonal carbon.



54



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Summary

The 7,8-epoxy-2-basmen-6-one ring system can be assembled efficiently by the Claisen ring expansion strategy reported here. This methodology would appear to hold considerable synthetic utility, different aspects of which are currently being explored in other contexts. Its particular value resides in the conciseness and efficiency with which eight-membered ring construction can be achieved from structurally simpler lactone precursors. Good topological control can be relied upon during the sigmatropic rearrangement, provided that the system is free of transition-metal impurities. This feature allows for the incorporation of reliable stereochemical predictability into the synthetic design.

Experimental Section[35]

(*E*)-1-[(5*S*)-5-Isopropyl-2-methyl-1-cyclopenten-1-yl]-3-(trimethylsilyl)-2-propen-1-one (11). A solution of (*E*)-(2-bromoethenyl)trimethylsilane (25.0 g, 140 mmol) in dry tetrahydrofuran (180 mL) was added during 30 min to a magnetically stirred suspension of magnesium turnings (3.50 g, excess) in the same solvent (40 mL). After completion of the addition, the mixture was refluxed for 1 h, cooled to −30 °C, and treated dropwise with a solution of **10** (13.0 g, 85.5 mmol) in 100 mL of dry tetrahydrofuran. The progress of reaction was monitored by TLC. When complete, the reaction mixture was warmed to 0 °C, quenched with 4% ammonium chloride solution (300 mL), and extracted with ether. The combined ethereal phases were dried and evaporated. The residue was purified by prepartive HPLC on silica gel to give 18.9 g (88%) of the carbinol as a colorless oil: IR (neat, cm^{-1}) 3600–3150 (br), 2955–2810, 1610, 1465, 1245, 870, 840; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26–5.98 (m, 2 H), 4.86 (br s, 1 H), 2.78 (m, 1 H), 2.22–2.06 (m, 2 H), 1.69–1.55 (m, 4 H), 0.95–0.92 (overlapping doublets, J = 4.6 Hz, total 3 H), 0.82 and 0.79 (two d's, J = 6.9 Hz, total 6 H), 0.11 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 147.97, 137.79, 127.73, 126.56, 71.21, 53.50, 38.68, 30.09, 22.15, 22.01, 15.93, 14.33, −1.11; MS m/z ($M^+ - H_2O$) calcd 234.1803, obsd 234.1780.

A stirred solution of the carbinol (11.2 g, 44.4 mmol) in dry dichloromethane (500 mL) was cooled to 0 °C and treated with barium manganate (115 g, 449 mmol). The mixture was allowed to warm to room temperature, and the progress of reaction was monitored by TLC. After 24 h, the excess $BaMnO_4$ was removed by filtration through a Celite pad, which was washed repeatedly with ether and acetone. After concentration of the filtrate, the residue was purified by preparative HPLC on silica gel (elution with 2% ethyl acetate in petroleum ether) to give **11** as a sensitive colorless oil (9.70 g, 97%): IR (neat, cm^{-1}) 1650; ^1H NMR (300 MHz, C_6D_6) δ 7.31 (d, J = 18.8 Hz, 1 H), 6.87 (d, J = 18.8 Hz, 1 H), 3.32–3.20 (m, 1 H), 2.25–1.97 (m, 3 H), 1.79 (s, 3 H), 1.73–1.61 (m, 1 H), 1.52–1.40 (m, 1 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.74 (d, J = 6.9 Hz, 3 H), 0.01 (s, 9 H); ^{13}C NMR (20 MHz, C_6D_6) δ 191.48, 149.13, 145.17, 142.87, 140.31, 53.90, 39.52, 30.45, 23.20, 21.18, 17.20, 16.46, −1.81; MS m/z (M^+) calcd 250.1752, obsd 250.1750; $[\alpha]^{24}_D$ +79.1° (c 0.42, $CHCl_3$).

Nazarov Cyclization of 11. A benzene solution (4 mL) of **11** (100 mg, 0.40 mmol) and boron trifluoride etherate (230 mg, 4 equiv) was placed in a pressure bottle and heated to 90 °C. After 22 h, the reaction mixture was cooled to room temperature, diluted with ether, and washed successively with sodium bicarbonate solution, water, and brine. The organic phase was dried, concentrated, and filtered through a small pad of silica gel. Final purification was realized by MPLC on silica gel (elution with 7% ethyl acetate in petroleum ether). There were obtained 42.8 mg of **12** and 8.2 mg of **13** (72% combined).

For pure **12**: IR (neat, cm^{-1}) 1706; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 5.4 Hz, 1 H), 5.96 (d, J = 5.6 Hz, 1 H), 2.14 (d, J = 3.6 Hz, 1 H), 1.80–1.47 (m, 6 H), 1.31 (s, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.98, 171.07, 130.96, 61.33, 53.58, 50.72, 36.01, 30.73, 28.99, 25.53, 21.52, 20.42; MS m/z (M^+) calcd 178.1358, obsd 178.1386; $[\alpha]^{21}_D$ −40.7° (c 2.24, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.18. Found: C, 80.97; H, 10.19.

For pure **13**: IR (neat, cm^{-1}) 2950, 2930, 2860, 1700, 1595, 1445, 1345, 1160; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 5.5 Hz, 1 H), 6.03 (d, J = 5.5 Hz, 1 H), 2.32 (d, J = 7.9 Hz, 1 H), 1.73–1.67 (m, 4 H), 1.48–1.38 (m, 1 H), 1.29 (s, 3 H), 1.13 (d, J = 5.4 Hz, 3 H), 1.12–1.00 (m, 1 H), 0.85 (d, J = 5.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.06, 170.43, 133.78, 57.86, 53.28, 52.68, 37.09, 28.99, 28.38, 25.27, 22.94, 21.98; MS m/z (M^+) calcd 178.1403, obsd 178.1353; $[\alpha]^{26}_D$ +72.7° (c 1.31, $CHCl_3$).

(3a*S*,6*S*,6a*S*)-2,3,4,5,6,6a-Hexahydro-6-isopropyl-3a-methyl-1-(3a*H*)-pentalenone (14). A solution of **12** (871 mg, 4.89 mmol) in ethanol (30 mL) containing 10 mg of platinum oxide was hydrogenated at 40 psi for 40 min, filtered through Celite, and rinsed with petroleum ether. Evaporation of the filtrate gave 868 mg (98%) of **14**: IR (neat, cm^{-1}) 1738; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (ddd, J = 18.7, 9.1, 9.1 Hz, 1 H), 2.29 (dddd, J = 18.7, 8.9, 4.6, 1.6 Hz, 1 H), 1.90–1.48 (m, 9 H), 1.17 (s, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.79, 62.88, 52.12, 48.45, 39.04, 37.36, 33.16, 32.99, 30.14, 27.16, 21.67, 20.26; MS m/z (M^+) calcd 180.1514, obsd 180.1516; $[\alpha]^{26}_D$ +104.6° (c 1.16, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.82; H, 11.29.

(4a*S*,7*S*,7a*S*)-Hexahydro-7-isopropyl-4a-methylcyclopenta[*b*]pyran-2(3*H*)-one (7). A solution of unpurified **14** (868 mg) in chloroform (50 mL) was treated with *m*-chloroperbenzoic acid (2.11 g, 12.23 mmol, 2.5 equiv) and stirred at room temperature for 2 days. Sodium sulfite solution (30 mL of 10%) was introduced, and the layers were separated after 1 h of rapid mixing. The aqueous phase was washed with saturated sodium bicarbonate solution (30 mL) and water (30 mL) prior to drying and solvent evaporation. The residue was purified by MPLC (silica gel, elution with 6:1 petroleum ether in ethyl acetate) to give 890 mg (95%) of **7** as a colorless oil: IR (neat, cm^{-1}) 1747; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (d, J = 5.7 Hz, 1 H), 2.41–2.35 (m, 2 H), 1.86–1.58 (m, 7 H), 1.35 (m, 1 H), 1.06 (s, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.29, 91.86, 55.22, 39.48, 38.24, 32.42, 31.68, 27.76, 26.28, 25.86, 21.43, 20.37; MS m/z (M^+) calcd 196.1463, obsd 196.1453; $[\alpha]^{26}_D$ −52.4° (c 2.22, $CHCl_3$).

(33) (a) Whalen, D. L.; Cooper, J. D. *J. Org. Chem.* **1978**, *43*, 432. (b) Teranishi, S.; Kanada, K.; Gitsukawa, K.; Itoh, T. *J. Am. Chem. Soc.* **1979**, *101*, 159. (c) Stark, D. J. *Tetrahedron Lett.* **1981**, *22*, 2089.

(34) For earlier related observations, see: (a) Ito, O.; Matsuda, M. *J. Org. Chem.* **1984**, *49*, 17. (b) Lunazzi, L.; Placucci, G.; Grossi, L. *J. Chem. Soc., Chem. Commun.* **1979**, 533.

(35) Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^1H NMR were recorded at 300 MHz and ^{13}C NMR spectra at 75 or 20 MHz as indicated. Mass spectra were recorded on a Kratos MS-30 instrument by Mr. Dick Weisenberger at The Ohio State University Chemical Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All MPLC separations were conducted on Merck Lobar columns (Licroprep Si-60) with the help of a Fluid Metering INC pump and a Waters Associates Model R403 differential refractometer detector. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases were dried prior to use.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.35.

(4a*S*,7*S*,7a*S*)-5,6,7,7a-Tetrahydro-7-isopropyl-4a-methylcyclopenta[*b*]pyran-2(3*H*)-one (16). To a solution of **7** (30 mg, 0.15 mmol) in chlorobenzene (2 mL) was added benzeneselenenic anhydride (65 mg, 0.18 mmol), and the mixture was refluxed overnight. An additional 65 mg of the anhydride was introduced, and heating was resumed for 24 h. The cooled reaction mixture was diluted with ether and washed with 2 N hydrochloric acid and water prior to drying. Solvent evaporation and MPLC purification (silica gel) furnished 28.8 mg (97%) of **16**: IR (neat, cm^{-1}) 1731; ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, J = 9.8, 1.1 Hz, 1 H), 5.88 (d, J = 6.9 Hz, 1 H), 4.21 (d, J = 6.9 Hz, 1 H), 1.93 (m, 1 H), 1.84–1.56 (m, 4 H), 1.39 (m, 1 H), 1.21 (s, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 161.23, 152.76, 119.41, 89.74, 52.40, 40.91, 37.03, 31.76, 24.98, 24.48, 21.00, 20.32; MS m/z (M^+) calcd 194.1306, obsd 194.1310. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.15; H, 9.62.

Conjugate Addition Reactions to 16. A. (4*S*,4a*S*,7*S*,7a*S*)-Hexahydro-7-isopropyl-4a-methyl-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclopenta[*b*]pyran-2(3*H*)-one (17b). 4-Bromo-2-butanone ethylene ketal (326 mg, 1.67 mmol) was allowed to react with magnesium turnings (200 mg) in anhydrous tetrahydrofuran (2 mL) until Grignard reagent formation was complete. This solution was added dropwise to a cold (−70 °C), magnetically stirred slurry of cuprous bromide (72 mg, 0.25 mmol) in the same solvent (2 mL). The resulting mixture was warmed to −40 °C, recooled to −78 °C, and treated with **16** (48.6 mg, 0.25 mmol). Following 1.5 h at −78 °C, the mixture was warmed to room temperature during 1.5 h and quenched with saturated ammonium chloride solution. The product was extracted into ether, and the ethereal solution was washed with water, dried, and evaporated. MPLC purification (silica gel) afforded 64 mg (82%) of a 4.7:1 mixture of β-**17b** and α-**17b**.[36]

For pure β-**17b**: IR (neat, cm^{-1}) 2950, 2870, 1740, 1465, 1380, 1270, 1150, 1060; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (d, J = 7.0 Hz, 1 H), 3.98–3.87 (m, 4 H), 2.51 (dd, J = 3.4, 16.5 Hz, 1 H), 2.11 (dd, J = 12.0, 16.5 Hz, 1 H), 1.84–1.48 (m, 9 H), 1.38–1.23 (m, 2 H), 1.30 (s, 3 H), 1.11 (s, 3 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.20, 109.66, 93.03, 64.63 (2 C), 56.96, 42.64, 40.67, 36.84, 31.86, 31.65, 31.60, 26.62, 25.63, 23.90, 23.75, 21.47, 20.31; MS m/z ($M^+ - CH_3$) calcd 295.1909, obsd 295.1951; $[\alpha]^{20}_D$ +47.6° (c 2.8, $CHCl_3$). Anal. Calcd for $C_{17}H_{22}O_4$: C, 69.64; H, 9.74. Found: C, 69.60; H, 9.79.

B. (4*S*,4a*S*,7*S*,7a*S*)-Hexahydro-7-isopropyl-4a-methyl-4-[(2,5,5-trimethyl-1,3-dioxan-2-yl)ethyl]cyclopenta[*b*]pyran-2(3*H*)-one (17c). An analogous reaction involving the neopentyl glycol ketal of 4-bromo-2-butanone (1.08 g, 4.54 mmol) and **16** (176 mg, 0.908 mmol) afforded after MPLC (silica gel) 292 mg (91%) of β-**17c** and α-**17c** as a 7.6:1 mixture of isomers: ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (d, J = 6.9 Hz, major) and 3.84 (d, J = 5.8 Hz, minor, total 1 H), 3.57 (d, J = 11.7 Hz, minor) and 3.56 (d, J = 11.2 Hz, major, total 1 H), 3.38 (d, J = 11.3 Hz, 2 H), 2.52 (dd, J = 3.3, 16.5 Hz, major) and 2.45 (dd, J = 2.8, 16.5 Hz, minor, total 1 H), 2.13 (dd, J = 12.1, 16.4 Hz, major) and 2.09 (dd, J = 12.7, 16.3 Hz, minor, total 1 H), 1.85–1.50 (m, 8 H), 1.40–1.08 (m, 3 H), 1.36 (s, minor) and 1.35 (s, major, total 3 H), 1.12 (s, 3 H), 1.04 (s, minor) and 1.02 (s, major, total 3 H), 1.00 (d, J = 6.6 Hz, major), 0.99 (d, J = 6.3 Hz, minor, total 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.86 (s, 3 H).

C. (4*S*,4a*S*,7*S*,7a*S*)-Hexahydro-7-isopropyl-4a-methyl-4-(3-methyl-3-butenyl)cyclopenta[*b*]pyran-2(3*H*)-one (17a). 2-Methyl-4-bromobutene (373 mg, 2.50 mmol) was converted to its magnesiocuprate as described and allowed to react with **16** (97 mg, 0.50 mmol) in the manner detailed in A except in ether as solvent. MPLC purification (silica gel) gave 85 mg (64%) of **17a** and 6 mg (6.5%) of recovered lactone. The β:α ratio was 1:4.7. Mutual separation of these epimers was achieved by MPLC on silica gel (elution with 7% ethyl acetate in petroleum ether).

For β-**17a**: colorless oil; IR (neat, cm^{-1}) 2950, 2870, 1745, 1650, 1465, 1270, 1200, 1060; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (s, 1 H), 4.68 (s, 1 H), 4.02 (d, J = 6.9 Hz, 1 H), 2.55 (dd, J = 3.4, 16.4 Hz, 1 H), 2.16–2.06 (m, 1 H), 2.11 (dd, J = 12.1, 16.4 Hz, 1 H), 1.98–1.49 (series of m, 7 H), 1.71 (s, 3 H), 1.37–1.10 (m, 3 H), 1.10 (s, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 170.31, 144.99, 110.77, 92.41, 57.05, 42.43, 40.05, 35.40, 32.15, 32.01, 31.68, 27.71, 26.48, 25.98, 22.32, 21.66, 20.65; MS m/z (M^+) calcd 264.2089, obsd 264.2096.

For α-**17a**: IR (neat, cm^{-1}) 2960, 2870, 1745, 1650, 1460, 1380, 1260, 1140; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (s, 1 H), 4.69 (s, 1 H), 3.86 (d, J = 6.0 Hz, 1 H), 2.48 (dd, J = 3.2, 16.4 Hz, 1 H), 2.15–1.78 (series of m, 4 H), 2.09 (dd, J = 12.9, 16.4 Hz, 1 H), 1.71 (s, 3 H), 1.69–1.54 (m, 5 H), 1.44–1.25 (m, 2 H), 1.00 (d, J = 6.6 Hz, 3 H), 0.94 (s, 3 H), 0.92 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.23, 144.70, 110.53, 91.98, 53.64, 43.05, 39.73, 37.86, 35.46, 32.14, 31.35, 27.87, 25.73, 22.18, 21.28, 20.07, 19.60; MS m/z ($M^+ - C_3H_7$) calcd 221.1541, obsd 221.1551.

(4*S*,4a*S*,7*S*,7a*S*)-Hexahydro-7-isopropyl-4a-methyl-4-(3-oxobutyl)cyclopenta[*b*]pyran-2(3*H*)-one (17d). A. Hydrolysis of 17b. A solution of **17b** (64 mg, 0.21 mmol) in tetrahydrofuran (2 mL) and 5% hydrochloric acid (1 mL) was stirred at room temperature for 4 h, diluted with ether, and washed with sodium bicarbonate solution and water. Drying, solvent evaporation, and MPLC purification (silica gel) gave 53 mg (98%) of **17d** as a 4.7:1 mixture of β and α isomers.

For β-**17d**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.01 (d, J = 7.1 Hz, 1 H), 2.58–2.32 (m, 3H), 2.14 (s, 3 H), 2.11 (dd, J = 12.2, 16.4 Hz, 1 H), 1.94–1.75 (m, 2 H), 1.71–1.50 (m, 4 H), 1.40–1.17 (m, 3 H), 1.13 (s, 3 H), 1.00 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H).

For α-**17d**: see characterization in the following text as compound **21**.

B. Hydrolysis of 17c. A solution of **17c** (62 mg, 0.17 mmol) in tetrahydrofuran (2 mL) and 5% hydrochloric acid (1 mL) was stirred overnight at room temperature. The usual workup gave **17d** (43 mg, 93%) as a 7.6:1 mixture of β and α isomers.

C. Ozonolysis of α-17a. A solution of α-**17a** (43 mg, 0.16 mmol) in dichloromethane (2 mL) was cooled to −78 °C and treated with a precooled (−78 °C) saturated solution of ozone in the same solvent (10 mL). After 15 min, dimethyl sulfide (2 mL) was introduced, and the temperature was allowed to rise to 20 °C. The reaction mixture was washed with water, dried, and evaporated to leave a residue that was purified by MPLC. There was isolated 27 mg (63%) of pure α isomer **21**; IR (neat, cm^{-1}) 1740, 1715; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (d, J = 6.0 Hz, 1 H), 2.57–2.34 (m, 3 H), 2.14 (s, 3 H), 2.08 (dd, J = 14.6, 16.3 Hz, 1 H), 1.89–1.75 (m, 3 H), 1.72–1.57 (m, 4 H), 1.43–1.30 (m, 2 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.93 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 205.46, 171.42, 91.48, 54.17, 43.21, 40.85, 40.42, 38.05, 32.35, 31.89, 29.48, 26.16, 23.80, 21.54, 20.48, 19.36; MS m/z ($M^+ - C_3H_6O$) calcd 208.1463, obsd 208.1511.

D. Access from 12. A 183-mg (0.94-mmol) sample of 4-bromo-2-butanone ethylene ketal was transformed into its magnesiocuprate in the manner described earlier. To the cuprate solution was added **12** (44.5 mg, 0.25 mmol) dissolved in 2 mL of anhydrous tetrahydrofuran. The reaction mixture was stirred for 1.5 h at −78 °C and warmed to room temperature during 1.5 h. Following quenching with saturated ammonium chloride solution, the products were extracted into ether, washed with water, and dried. Solvent evaporation followed by MPLC (silica gel) of the residue afforded 69 mg (93%) of **17b** as a 4.1:1 mixture of α and β isomers.

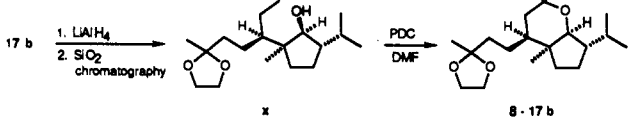
The above ketone (69 mg, 0.23 mmol) was dissolved in chloroform (4 mL), treated with *m*-chloroperbenzoic acid (100 mg, 0.58 mmol), and stirred at room temperature. After 16 h, an additional 40 mg of peracid was introduced and oxidation was allowed to proceed 46 h longer. Saturated sodium bisulfite solution (5 mL) was added, stirring was maintained for 30 min, and the usual workup was implemented.

The unpurified lactone was dissolved in tetrahydrofuran (2 mL), treated with 5% hydrochloric acid (1 mL), and stirred for 4 h. The product was extracted into ether and processed as described earlier to give 40 mg (65%) of a 1:4.1 mixture of β-**17d** and **21**.

Methyl β-[(1*S*,3*S*)-3-Isopropyl-1-methyl-2-oxocyclopentyl]-2,5,5-trimethyl-1,3-dioxane-(2*R*)-valerate (22). Lactone **17c** (248 mg, 0.704 mmol) and potassium hydroxide (42 mg, 0.74 mmol) were dissolved in 50% aqueous ethanol (6 mL), and the solution was stirred overnight at 80 °C. Solvent was evaporated, and the residue was dried in vacuo, treated with dimethylformamide (3 mL) and methyl iodide (0.5 mL), and stirred at room temperature for 6 h. The predescribed workup gave hydroxy ester, which was used directly.

To a solution of the previous material in dichloromethane (8 mL) were added pyridinium dichromate (496 mg, 1.41 mmol) and 3-Å molecular sieves (350 mg). This mixture was stirred at room temperature for 4 h, diluted with ether, and filtered through a Celite pad. The filtrate was evaporated to leave a residue that was purified by MPLC on silica gel. There was isolated 218 mg (81% overall) of a colorless oil consisting principally of **22** and 27 mg (11%) of unreacted **17c**.

(36) Pure β-**17b** was obtained by the following sequence of steps:[25]



For **22**: IR (neat, cm^{-1}) 2950, 2865, 1730, 1465, 1435, 1370, 1215, 1095, 1020, 850; ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 3 H), 3.53–3.39 (m, 4 H), 2.22–2.02 (m, 4 H), 1.97–1.88 (m, 1 H), 1.78–1.59 (m, 6 H), 1.34 (s, 3 H), 1.30–1.20 (m, 2 H), 0.98 (s, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.95 (s, 3 H), 0.90 (s, 3 H), 0.80 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.31, 172.97, 98.78, 70.12 (2 C), 56.24, 52.13, 50.87, 40.64, 37.11, 36.15, 30.69, 29.63, 27.03, 24.20, 22.67, 22.20, 20.79, 20.28, 20.17, 20.06, 18.28; MS m/z (M^+) calcd 382.2719, obsd 382.2740.

(4a*S*,7*S*,7a*S*)-Hexahydro-7-isopropyl-4a-methylcyclopenta[*b*]pyran-2(3*H*)-one (23). A solution of **13** (340 mg, 1.91 mmol) in ethanol (20 mL) containing a catalytic quantity of platinum oxide was hydrogenated for 10 min at 40 psi. The catalyst was separated by filtration, and the filtrate was evaporated to give **15**, which was used without further purification: IR (neat, cm^{-1}) 1736; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28–2.19 (m, 2 H), 2.10 (d, J = 7.0 Hz, 1 H), 1.91–1.55 (m, 8 H), 1.22 (s, 3 H), 1.07 (d, J = 5.8 Hz, 3 H), 0.86 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 218.46, 60.37, 53.58, 47.16, 40.22, 40.17, 35.98, 32.18, 29.25, 28.96, 23.27, 22.30; MS m/z ($M^+ - H_2O$) calcd 162.1409, obsd 162.1372.

The material obtained was dissolved in chloroform (20 mL), treated with *m*-chloroperbenzoic acid (824 mg, 4.78 mmol) and *p*-toluenesulfonic acid (5 mg), and then stirred at room temperature for 2 h. Saturated sodium sulfite solution (10 mL) was introduced, followed 1 h later by the usual workup. Final purification by MPLC on silica gel gave 329 mg (88%) of lactone **23**.

For **23**: IR (neat, cm^{-1}) 1742; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (d, J = 3.9 Hz, 1 H), 2.45–2.35 (m, 2 H), 1.93–1.46 (m, 8 H), 1.11 (s, 3 H), 0.98 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.44, 89.57, 52.14, 40.65, 37.68, 32.96, 28.44, 28.10, 27.99, 27.31, 21.74 (2C); MS m/z (M^+) calcd 196.1463, obsd 196.1422.

Methyl β-[(1*S*,3*S*)-3-Isopropyl-1-methyl-2-oxocyclopentyl]propionate (24). Lactone **23** (25.3 mg, 0.129 mmol) and potassium hydroxide (7.6 mg, 0.135 mmol) were dissolved in 3 mL of 1:1 ethanol/water, stirred overnight at 80 °C, and freed of solvent in vacuo. The dried solid was treated with excess methyl iodide (0.15 mL) in dimethylformamide (2 mL). The reaction mixture was stirred at room temperature for 2 h, diluted with ether, washed with water, and dried. Solvent evaporation gave the hydroxy ester, which was utilized directly.

The previous material in dichloromethane (3 mL) was treated with powdered 3-Å molecular sieves (65 mg) and pyridinium dichromate (72.7 mg, 0.19 mmol). The resulting mixture was stirred at room temperature for 2 h, diluted with ether, and filtered through a Celite pad. The filtrate was evaporated, and the residue was purified by MPLC on silica gel to give 21 mg (72%) of **24** and 3 mg (12%) of unreacted lactone. For **24**: IR (neat, cm^{-1}) 1734, 1726; ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 3 H), 2.33–2.25 (m, 2 H), 2.20–2.08 (m, 2 H), 1.97–1.81 (m, 2 H), 1.76–1.53 (m, 4 H), 1.01 (s, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 0.80 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.69, 173.81, 54.47, 51.51, 47.68, 34.43, 30.22, 28.91, 27.62, 22.01, 21.04, 20.75, 18.61; MS m/z (M^+) calcd 226.1569, obsd 226.1554.

***tert*-Butyl[3-[(1*S*,3*S*)-3-isopropyl-1-methyl-2-oxocyclopentyl]propoxy]dimethylsilane (25).** A solution of lactone **7** (150 mg, 0.765 mmol) in anhydrous tetrahydrofuran (5 mL) was treated with lithium aluminum hydride (116 mg, 3.06 mmol), stirred at room temperature for 20 min, and quenched with water. Sodium hydroxide solution (5 mL of 30%) was added, and the diol was isolated by ether extraction. Without purification, the diol was dissolved in dichloromethane (10 mL) and treated in turn with *tert*-butyldimethylsilyl chloride (118 mg, 0.87 mmol), 4-(dimethylamino)pyridine (8.7 mg, 0.071 mmol), and triethylamine (359 mg, 3.55 mmol). After the solution was stirred overnight, the usual workup was applied and the selectively protected product was dissolved in dichloromethane (4 mL). Pyridinium dichromate (401 mg, 1.07 mmol) and powdered 3-Å molecular sieves (355 mg) were introduced, the mixture was stirred for 2 h, and ether was added. The reaction mixture was filtered through Celite, and the filtrate was evaporated to leave a residue that was purified by MPLC on silica gel. There was obtained 195 mg (82% overall) of **25** as a colorless oil; IR (neat, cm^{-1}) 1732; ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (t, J = 6.3 Hz, 2 H), 2.21–2.03 (m, 2 H), 1.95–1.87 (m, 1 H), 1.79–1.29 (m, 7 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.91 (s, 3 H), 0.88 (s, 9 H), 0.80 (d, J = 6.8 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) δ 221.04, 63.72, 55.70, 48.35, 34.45, 33.49, 28.35, 27.60, 26.18, 21.65, 21.10, 20.97, 18.70, 18.52, −5.13; MS m/z ($M^+ - CH_3$) calcd 297.2250, obsd 297.2299. Anal. Calcd for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61. Found: C, 69.34; H, 11.60.

***tert*-Butyl[3-[(1*S*,3*S*)-3-isopropyl-1-methyl-2-methylenecyclopentyl]propoxy]dimethylsilane (26).** A solution of **25** (33 mg, 0.106 mmol) in benzene (1 mL) was treated with tetrahydrofuran (0.3 mL) and pyridine (4 μL). The resulting mixture was cooled to −40 °C and treated with the Tebbe reagent[11,22] (0.32 mL of 0.5 M in benzene, 0.14 mmol). After 30 min at −40 °C, the solution was warmed to room temperature during an additional 30 min and stirred overnight before being quenched with 15% sodium hydroxide solution (0.3 mL) and dilution with ether. The organic phase was dried, filtered through a Celite pad, and evaporated. MPLC purification of the residue gave 5 mg (15%) of **26** and 18 mg (55%) of an epimeric mixture of starting ketone. For **26**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, J = 2.8 Hz, 1 H), 4.75 (d, J = 2.3 Hz, 1 H), 3.60–3.56 (m, 2 H), 2.45–2.35 (m, 1 H), 2.03–1.92 (m, 1 H), 1.64–1.24 (series of m, 8 H), 0.97 (d, J = 7.7 Hz, 3 H), 0.96 (s, 3 H), 0.90 (s, 9 H), 0.78 (d, J = 6.7 Hz, 3 H), 0.05 (s, 6 H).

(−)-(2*S*,5*S*)-2-(2-Hydroxyethyl)-2-methyl-5-isopropylmethylenecyclopentane (28). The vinyl ether derived from the reduction product of **10** (2.02 g, 11.2 mmol) was heated at 200 °C in a sealed tube for 11 h. ^1H NMR analysis showed aldehyde **27** to be present as a 32:1 mixture of isomers. Without purification, the thermolysate was dissolved in tetrahydrofuran (25 mL) and ethanol (8 mL). Sodium borohydride (508 mg, 13.4 mmol) was added with ice cooling to maintain the temperature below 30 °C. After 20 min, the reaction mixture was concentrated on a rotary evaporator, quenched with 5% hydrochloric acid, and diluted with ether. The usual workup followed by MPLC on silica gel furnished 1.59 g (78% overall) of isomerically pure **28** as a colorless oil alongside 5 mg of its epimer.

For **28**: IR (neat, cm^{-1}) 3350, 2965, 2880, 1645, 1470, 1390, 1370, 885; ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (d, J = 2.7 Hz, 1 H), 4.81 (d, J = 2.7 Hz, 1 H), 3.73–3.67 (m, 2 H), 2.45 (m, 1 H), 2.04–1.94 (m, 1 H), 1.85–1.34 (m, 7 H), 1.00 (s, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.77 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.74, 103.73, 60.27, 50.81, 44.63, 44.08, 37.34, 28.83, 27.51, 23.04, 21.86, 16.48; MS m/z ($M^+ - CH_3$) calcd 167.1436, obsd 167.1424; $[\alpha]^{20}_D$ −99.0° (c 6.35, $CHCl_3$). Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.83; H, 12.17.

For the epimer: IR (neat, cm^{-1}) 3340, 2960, 2870, 1640, 1460, 1050, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (d, J = 2.5 Hz, 1 H), 4.84 (d, J = 2.5 Hz, 1 H), 3.83–3.59 (m, 2 H), 2.44 (m, 1 H), 1.89 (m, 1 H), 1.73–1.32 (m, 6 H), 1.22 (br s, 1 H), 1.09 (s, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.80 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.81, 104.63, 60.26, 50.67, 44.53, 43.04, 38.23, 29.72, 27.77, 23.88, 21.85, 17.51; MS m/z (M^+) calcd 182.1671, obsd 182.1716.

(−)-(5*S*,6*S*,9*S*)-9-Isopropyl-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonane-6-ethanol (29). To a solution of **28** (270 mg, 1.48 mmol) in 6 mL of 50% aqueous acetone was added osmium tetroxide (3.76 mL of 0.0197 M in *tert*-butyl alcohol, 0.074 mmol) and *N*-methylmorpholine oxide (260 mg, 2.22 mmol). After the solution was stirred for 3 days, 5% sodium bisulfite solution (3 mL) was introduced. After 30 min, the reaction mixture was concentrated under reduced pressure, diluted with ether, and processed as usual.

The triol so obtained (14:1 mixture of epimers) was dissolved in acetone (5 mL), treated with 2,2-dimethoxypropane (308 mg, 2.96 mmol) and *p*-toluenesulfonic acid (5 mg), and stirred for 15 min. Following the addition of 10% sodium bicarbonate solution (1 mL), the total mixture was concentrated under reduced pressure. The usual workup and MPLC purification (silica gel) gave 227 mg (80% overall) of **29** as a white solid, mp 87.0–88.2 °C; IR (KBr, cm^{-1}) 3268, 2958, 1460, 1382, 1370; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (d, J = 9.2 Hz, 1 H), 3.75 (d, J = 9.2 Hz, 1 H), 3.81–3.65 (m, 2 H), 2.18–2.10 (m, 2 H), 2.01–1.26 (series of m, 7 H), 1.41 (s, 3 H), 1.38 (s, 3 H), 1.02 (d, J = 6.7 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.60, 93.69, 65.66, 59.93, 54.97, 45.18, 39.91, 35.92, 27.51, 27.37, 26.67, 24.11, 23.16, 20.92, 19.77; MS m/z (M^+) calcd 256.2038, obsd 256.2010. Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.23; H, 10.91.

(5*S*,6*R*,9*S*)-6-(3-Butenyl)-9-isopropyl-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonane (30). A solution of **29** (224 mg, 0.875 mmol) in dichloromethane (2 mL) was treated with pyridinium dichromate (395 mg, 1.05 mmol) and powdered 3-Å molecular sieves (438 mg). This mixture was stirred for 40 min, diluted with ether (60 mL), and filtered quickly through a Celite–silica gel pad. Evaporation of the filtrate gave the aldehyde, which was used without further purification.

A solution of methyltriphenylphosphonium iodide (477 mg, 1.18 mmol) in dry tetrahydrofuran (3 mL) was treated with *n*-butyllithium (0.74 mL of 1.5 M in hexanes, 1.10 mmol) at −20 °C, and the solution was allowed to warm to 0 °C. The aldehyde in 2 mL of anhydrous tetrahydrofuran was introduced dropwise, and the mixture was stirred at 0 °C for 20 min and at room temperature for 30 min before being quenched with 10% ammonium chloride solution (3 mL) and worked up in the usual way. MPLC purification (silica gel) gave 144 mg (65% overall) of **30** as a colorless liquid: IR (neat, cm^{-1}) 2960, 2880, 1640, 1380, 1370, 1240, 1055; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91–5.77 (m, 1 H), 5.08–5.01 (m, 2 H), 3.95 (d, J = 9.2 Hz, 1 H), 3.75 (d, J = 9.2 Hz, 1 H), 2.37 (dd, J = 7.1, 13.6 Hz, 1 H), 2.16–1.90 (m, 3 H),

1.75–1.55 (m, 2 H), 1.47–1.27 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.02 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.77 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.34, 116.66, 108.40, 93.82, 65.64, 56.07, 45.90, 41.20, 35.67, 27.72, 27.49, 26.72, 24.11, 23.22, 20.08, 19.71; MS m/z (M^+) calcd 252.2089, obsd 252.2109. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.19; H, 11.16.

(5*S*,6*S*,9*S*)-9-Isopropyl-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonane-6-propanol (31). A cold (0 °C), magnetically stirred solution of **30** (3.22 g, 12.76 mmol) in dry tetrahydrofuran (20 mL) was treated with 9-BBN (60 mL of 0.5 M in THF), and the reaction mixture was allowed to warm to room temperature, where stirring was maintained for 3 h. Sodium hydroxide solution (15 mL of 50%) and hydrogen peroxide (15 mL of 30%) were added to 0 °C, and the reaction mixture was allowed to warm to room temperature. After the solution was stirred overnight, the solvent was removed under reduced pressure and the residual aqueous solution was extracted with ether. The combined organic phases were washed with water, dried, and evaporated. Purification of the residue by silica gel chromatography afforded 3.21 g (93%) of **31** as a colorless oil: IR (neat, cm^{-1}) 3400, 2945, 2870, 1460, 1380, 1370, 1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (d, J = 9.2 Hz, 1 H), 3.81 (m, 2 H), 3.73 (d, J = 9.2 Hz, 1 H), 2.11 (m, 1 H), 1.97 (m, 1 H), 1.81–1.24 (series of m, 9 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 1.02 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.35, 94.02, 65.59, 63.88, 56.14, 45.69, 35.64, 32.17, 28.27, 27.72, 27.46, 26.67, 24.10, 23.35, 19.94, 19.72; MS m/z (M^+) calcd 270.2195, obsd 270.2195.

(4a*S*,7*S*,7a*S*)-Hexahydro-7a-(hydroxymethyl)-7-isopropyl-4a-methylcyclopenta[*b*]pyran-2(3*H*)-one (32a). A solution of **31** (180 mg, 0.664 mmol) in dimethylformamide (3 mL) was treated with pyridinium dichromate (1.25 g, 3.32 mmol), stirred overnight at room temperature, and poured into water. The product was extracted into ether, and the combined organic layers were dried and evaporated. The residual carboxylic acid was dissolved in tetrahydrofuran (2 mL), 10% hydrochloric acid (4 mL) was introduced, and the mixture was stirred overnight prior to neutralization and extraction with ether. The usual workup gave a 15:1 mixture of **32a** and an isomer (120 mg, 80%). MPLC on silica gel delivered pure **32a**: IR (neat, cm^{-1}) 3440, 2950, 2880, 1715, 1470; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (d, J = 12.0 Hz, 1 H), 3.75 (d, J = 11.9 Hz, 1 H), 2.50 (m, 2 H), 2.05–1.58 (series of m, 8 H), 1.39 (m, 1 H), 1.24 (s, 3 H), 1.05 (d, J = 6.4 Hz, 3 H), 0.88 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.77, 94.68, 62.56, 56.54, 40.61, 36.42, 32.73, 28.22, 26.76, 24.66, 22.55, 22.46, 22.09; MS m/z ($M^+ - H_2O$) calcd 208.1464, obsd 208.1477; $[\alpha]^{19}_D$ +20.9° (c 3.03, $CHCl_3$). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.79; H, 9.85.

(4a*S*,7*S*,7a*S*)-Hexahydro-7a-[(*tert*-butyldimethylsiloxy)methyl]-7-isopropyl-4a-methylcyclopenta[*b*]pyran-2(3*H*)-one (32b). To a solution of **32a** (418 mg, 1.847 mmol) in dimethylformamide (5 mL) was added *tert*-butyldimethylchlorosilane (1.39 g, 9.24 mmol) and imidazole (1.89 g, 27.7 mmol), and stirring was maintained for 2 days. Silica gel (1 g) was introduced, and the mixture was stirred overnight prior to being poured into water, extracted with ether, and dried. The residue obtained by solvent evaporation was purified by MPLC on silica gel. There was obtained 496 mg (79%) of **32b** and 64 mg (15%) of unreacted alcohol. For **32b**: white solid; IR (KBr, cm^{-1}) 2950, 1735, 1470, 1260, 1185, 1105; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (d, J = 10.4 Hz, 1 H), 3.73 (d, J = 10.4 Hz, 1 H), 2.46 (m, 2 H), 2.06–1.47 (series of m, 8 H), 1.19 (s, 3 H), 1.06 (d, J = 6.4 Hz, 3 H), 0.98 (s, 9 H), 0.89 (d, J = 7.0 Hz, 3 H), 0.084 (s, 3 H), 0.078 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.88, 94.11, 63.59, 55.96, 40.47, 37.03, 33.30, 28.50, 26.76, 25.76, 25.33, 22.52, 22.27, 21.11, 18.04, –5.85, –5.94; MS m/z ($M^+ - C_3H_7$) calcd 297.1886, obsd 297.1848.

(4a*S*,7*S*,7a*S*)-7a-[(*tert*-Butyldimethylsiloxy)methyl]-4a,5,6,7-tetrahydro-7-isopropyl-4a-methylcyclopenta[*b*]pyran-2(3*H*)-one (33). A solution of **32b** (495 mg, 1.45 mmol) and benzeneselenenic anhydride (786 mg, 2.18 mmol) in chlorobenzene (10 mL) was heated at 135 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with ether, washed with 2 N hydrochloric acid and water, and dried. Solvent evaporation left a residue, purification of which by MPLC on silica gel delivered 459 mg (92%) of **33** as a colorless solid: IR (KBr, cm^{-1}) 2960, 1720, 1520, 1365, 1105; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (d, J = 9.8 Hz, 1 H), 5.83 (d, J = 9.7 Hz, 1 H), 3.94 (d, J = 10.4 Hz, 1 H), 3.83 (d, J = 10.4 Hz, 1 H), 2.15–1.70 (m, 5 H), 1.54 (m, 1 H), 1.18 (s, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.90 (s, 9 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.30, 158.18, 117.53, 91.41, 62.80, 52.79, 44.30, 36.32, 28.94, 25.74, 25.49, 22.42, 22.10, 20.95, 17.98, –5.90; MS m/z ($M^+ - CH_3$) calcd 323.2043, obsd 323.2079; $[\alpha]^{18.5}_D$ –28.7° (c 2.18, $CHCl_3$).

(4a*S*,7*S*,7a*S*)-7a-(Hydroxymethyl)-4a,5,6,7-tetrahydro-7-isopropyl-4a-methylcyclopenta[*b*]pyran-2(3*H*)-one (37). A solution of **33** (103 mg, 0.304 mmol) and tetra-*n*-butylammonium fluoride (1 mL of 1.0 M in tetrahydrofuran) in dimethylformamide (3 mL) was stirred at room temperature for 2 h, poured into water, and processed in the usual manner. MPLC of the residue (silica gel) furnished 67.8 mg (99.8%) of **37** as a colorless solid: mp 80–81 °C; IR (KBr, cm^{-1}) 3490, 2960, 1700, 1385, 1285, 1120, 1080, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (d, J = 9.8 Hz, 1 H), 5.86 (d, J = 9.9 Hz, 1 H), 4.00 (d, J = 11.9 Hz, 1 H), 3.87 (dd, J = 6.8, 12.0 Hz, 1 H), 2.16 (m, 1 H), 1.95–1.30 (series of m, 6 H), 1.24 (s, 3 H), 1.06 (d, J = 6.5 Hz, 3 H), 0.85 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.56, 157.89, 117.52, 91.46, 61.87, 52.69, 44.41, 35.72, 29.02, 24.80, 22.44, 22.15, 22.11; MS m/z (M^+) calcd 224.1412, obsd 224.1443; $[\alpha]^{27}_D$ –50.7° (c 2.54, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.21; H, 8.99. Found: C, 69.58; H, 9.03.

(4a*S*,7*S*,7a*S*)-4a,5,6,7-Tetrahydro-7-isopropyl-4a-methyl-2-oxocyclopenta[*b*]pyran-7a(2*H*)-carboxaldehyde (38). A magnetically stirred solution of **37** (68 mg, 0.302 mmol) in dichloromethane (2 mL) was treated with pyridinium dichromate (227 mg, 0.605 mmol) and powdered 3-Å molecular sieves (151 mg). After 5 h, the reaction mixture was diluted with ether (40 mL), filtered quickly through a pad of Celite and anhydrous magnesium sulfate, and evaporated. This oily aldehyde was used without further purification: IR (neat, cm^{-1}) 2960, 2870, 1725, 1460, 1370, 1255, 1115; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (d, J = 1.8 Hz, 1 H), 6.53 (d, J = 9.8 Hz, 1 H), 5.95 (d, J = 9.8 Hz, 1 H), 2.22–1.86 (m, 4 H), 1.68–1.50 (m, 2 H), 1.10 (s, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.14, 161.16, 155.47, 118.42, 96.04, 55.63, 45.66, 35.38, 29.91, 25.90, 22.08, 22.02, 20.55; MS m/z ($M^+ - CHO$) calcd 193.1229, obsd 193.1229.

(4a*S*,7*S*,7a*S*)-5,6,7,7a-Tetrahydro-7-isopropyl-4a-methyl-7a-propenylcyclopenta[*b*]pyran-2(4a*H*)-one (39). A tetrahydrofuran solution (3 mL) containing ethyltriphenylphosphonium bromide (146 mg, 0.393 mmol) was treated with *n*-butyllithium (0.25 mL of 1.5 M in hexanes, 0.373 mmol) at –20 °C, and the resulting mixture was warmed to 0 °C during 20 min. The previous unpurified aldehyde as a solution in dry tetrahydrofuran (3 mL) was added dropwise at 0 °C. After the mixture had stirred for 30 min, it was allowed to come to room temperature where it was quenched with 10% ammonium chloride solution (3 mL). The customary workup followed by MPLC on silica gel afforded 55 mg (77%) of **39** as a colorless solid: mp 77.5–78.5 °C (from ether); IR (KBr, cm^{-1}) 2950, 2870, 1710, 1470, 1450, 1385, 1370, 1260, 1120; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (d, J = 9.8 Hz, 1 H), 5.87 (d, J = 9.8 Hz, 1 H), 5.74 (m, 1 H), 5.08 (m, 1 H), 2.13–1.25 (series of m, 6 H), 1.94 (dd, J = 1.8, 7.2 Hz, 3 H), 1.08 (s, 3 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.81 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.61, 157.16, 128.58, 123.25, 118.52, 95.11, 54.03, 45.62, 35.09, 30.70, 25.40, 22.24, 22.11, 21.41, 14.79; MS m/z (M^+) calcd 234.1619, obsd 234.1622; $[\alpha]^{20}_D$ –232° (c 4.9, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.76; H, 9.42.

The three-dimensional structure of **39**, determined crystallographically, is illustrated in Figure 1. When this reaction was performed starting with 700 mg of the hydroxy lactone, there was isolated 560 mg (77%) of **39**, as well as 32 mg (5%) of **40** as a single isomer (unknown configuration about the double bond): IR (neat, cm^{-1}) 3025, 2950, 2870, 1655, 1620, 1470, 1450, 1340, 1125, 1050, 800; ^{1}H NMR (300 MHz, C_6D_6) δ 5.78 (d, J = 9.8 Hz, 1 H), 5.62 (m, 1 H), 5.26 (d, J = 9.7 Hz, 1 H), 5.03 (m, 1 H), 4.54 (q, J = 9.0 Hz, 1 H), 2.11 (dd, J = 1.8, 7.1 Hz, 3 H), 2.1–1.2 (series of m, 6 H), 1.81 (d, J = 7.0 Hz, 3 H), 1.17 (d, J = 6.5 Hz, 3 H), 1.05 (s, 3 H), 0.80 (d, J = 6.6 Hz, 3 H): ^{13}C NMR (75 MHz, C_6D_6) δ 146.44, 134.96, 126.84, 126.40, 122.68, 104.64, 91.75, 50.26, 45.25, 35.30, 31.76, 25.91, 22.88, 22.72, 21.49, 15.23, 11.01; MS m/z (M^+) calcd 246.1983, obsd 246.1992.

(1*S*,3a*S*,8*S*)-1,2,3,3a,7,8-Hexahydro-1-isopropyl-3a,8-dimethyl-6*H*-cyclopentacycloocten-6-one (42). To a solution of **39** (442 mg, 1.89 mmol) in anhydrous benzene (7 mL) were added dry tetrahydrofuran (2 mL) and pyridine (6 drops). Following cooling of this solution to 0 °C, Tebbe reagent[11,22] (5 mL of 0.55 M in benzene) was introduced dropwise. The reaction mixture was warmed to room temperature, stirred for 2 h, and recooled to 0 °C. Aqueous 15% sodium hydroxide was added dropwise until gas evolution ceased. The product was extracted into ether, and the combined organic layers were dried and evaporated. The residue was passed down a short column of basic alumina (activity III, elution with petroleum ether) to provide 398 mg (91%) of **41**, which was thermolyzed without delay. A solution of **41** (39 mg, 0.168 mmol) in toluene (2 mL) was sealed under vacuum in a sodium hydroxide washed Carius tube and heated at 180 °C for 24 h. The yellowish solution was evaporated, and the residue was purified by MPLC on silica gel to give 14 mg (36%) of **42** as a colorless solid: mp 57–58 °C; IR (film, cm^{-1}) 2950, 2865, 1675, 1460, 1385, 1365, 1125; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, J = 12.8 Hz, 1 H), 5.86 (dd, J = 1.9, 12.7 Hz, 1 H), 5.41 (br t, J = 3.0 Hz, 1 H), 3.13 (dd, J = 11.7, 15.0 Hz, 1 H), 2.77 (m, 1 H), 2.48 (m, 1 H), 2.39 (dm, J = 15.0 Hz, 1 H), 2.0–1.3 (series of m, 5 H), 1.34 (s, 3 H), 1.14 (d, J = 7.1 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.80 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.56, 149.84,

145.90, 129.52, 129.14, 53.26, 50.12, 46.74, 45.49, 29.77, 29.60, 28.00, 24.22, 21.76, 21.65, 16.17; MS m/z (M^+) calcd 232.1828, obsd 232.1813; $[\alpha]^{19}_D$ −2.7° (c 2.3, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.73; H, 10.43.

In addition, 1 mg of the β-methyl epimer was isolated: ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (d, J = 13.2 Hz, 1 H), 5.51 (d, J = 13.2 Hz, 1 H), 5.07 (dd, J = 2.6, 9.8 Hz, 1 H), 3.32 (m, 1 H), 2.60 (dd, J = 4.4, 14.6 Hz, 1 H), 2.41 (m, 1 H), 2.21 (dd, J = 12.0, 14.6 Hz, 1 H), 1.93 (m, 1 H), 1.7–1.3 (series of m, 4 H), 1.22 (s, 3 H), 1.07 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.76 (d, J = 6.7 Hz, 3 H); MS m/z (M^+) calcd 232.1827, obsd 232.1824.

The yields of this reaction were found to vary widely (34–60%) with fluctuation in the relative percentages of the two epimers (on occasion up to 50:50). These variations have been attributed to the presence of metal salts that are not necessarily removed by chromatography following the Tebbe reaction.

(1*S*,3a*S*,4*S*,8*S*)-1,2,3,3a,7,8-Hexahydro-1-isopropyl-3a,8-dimethyl-4-(3-oxobutyl)-6*H*-cyclopentacycloocten-6-one (48). The Grignard reagent prepared from 4-bromo-2-butanone ethylene ketal (120 mg, 0.615 mmol) and magnesium turnings (120 mg, excess) in anhydrous tetrahydrofuran (1.5 mL) as described previously was added dropwise to a cold (−78 °C) magnetically stirred solution of cuprous bromide–dimethyl sulfide complex (6.0 mg, 0.029 mmol) and HMPA (120 mg, 0.66 mmol) in anhydrous tetrahydrofuran (2 mL). After the solution was stirred for 30 min, a solution of **42** (21 mg, 0.090 mmol) and trimethylsilyl chloride (60 mg, 0.55 mmol) in dry tetrahydrofuran (2 mL) was introduced dropwise and agitation was maintained for 2 h at −78 °C. Following the addition of a solution of triethylamine (1 mL) in petroleum ether (3 mL), the reaction mixture was allowed to warm to room temperature and worked up as detailed previously. Purification of the residue by MPLC on silica gel gave 36.4 mg (96%) of **47** that was used directly.

A dry tetrahydrofuran solution (2 mL) of **47** (60 mg, 0.143 mmol) was treated with phenylselenyl chloride (41 mg, 0.214 mmol) in the same solvent (2 mL) at 0 °C. After 20 min, the reaction mixture was quenched with triethylamine/petroleum ether/saturated ammonium chloride solution (1 mL/2 mL/2 mL). The usual workup and purification gave the selenide, which was dissolved in tetrahydrofuran (2.5 mL), treated with 30% hydrogen peroxide (1 mL), and stirred for 30 min. Following dilution with ether and washing with water (2×), the organic phase was dried and evaporated. The product was purified by rapid silica gel chromatography. There was isolated 44.3 mg (90% overall) of dienone ketal as a colorless liquid: IR (neat, cm^{-1}) 2955, 2870, 1675, 1455, 1375, 1220, 1055; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (s, 1 H), 5.37 (t, J = 2.9 Hz, 1 H), 3.94 (m, 4 H), 3.05–2.85 (m, 1 H), 2.79 (ddd, J = 1.0, 10.9, 18.1 Hz, 1 H), 2.53–2.16 (series of m, 4 H), 2.10–1.88 (m, 2 H), 1.87–1.73 (m, 2 H), 1.65–1.53 (m, 2 H), 1.48–1.35 (m, 1 H), 1.33 (s, 3 H), 1.23 (s, 3 H), 1.11 (d, J = 7.3 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H), 0.79 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.53, 153.26, 147.94, 129.50, 126.84, 109.51, 64.71 (2 C), 52.46, 51.88, 50.25, 39.04, 38.45, 30.81, 30.04, 29.49, 27.61, 24.29, 23.90, 21.83, 21.59, 15.86; MS m/z (M^+) calcd 346.2508, obsd 346.2514.

A mixture of dienone ketal (39 mg, 0.113 mmol) and 5% hydrochloric acid (1.5 mL) was stirred for 4 h and worked up in the usual manner. MPLC purification (silica gel) delivered 33 mg (97%) of **48** as a colorless liquid: IR (neat, cm^{-1}) 2950, 2870, 1715, 1675, 1455, 1365, 1160; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (s, 1 H), 5.39 (br s, 1 H), 3.05–2.80 (m, 1 H), 2.79 (dd, J = 10.9, 17.6 Hz, 1 H), 2.7–2.3 (series of m, 6 H), 2.16 (s, 3 H), 2.05–1.85 (m, 2 H), 1.70–1.45 (m, 2 H), 1.50–1.30 (m, 1 H), 1.24 (s, 3 H), 1.12 (d, J = 7.2 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.78 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.21, 206.98, 152.04, 147.86, 129.46, 126.99, 52.21, 52.01, 50.31, 42.79, 38.69, 30.04, 29.73, 29.64, 29.47, 27.76, 24.12, 21.83, 21.60, 15.86; MS m/z (M^+) calcd 302.2246, obsd 302.2252; $[\alpha]^{21}_D$ +124.5° (c 1.65, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.54; H, 10.02.

(6*S*,8*S*,10a*S*,10b*R*)-2,5,6,8,9,10,10a,10b-Octahydro-8-isopropyl-3,6,10a-trimethyldicyclopenta[*a*,*c*]cycloocten-4(1*H*)-one (4). A solution of **48** (33 mg, 0.109 mmol) in ethanol (2 mL) was mixed with 1 mg of platinum oxide and stirred under an atmosphere of hydrogen (balloon) for 1.5 h. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated. MPLC purification (silica gel) gave 13.7 mg (42%) of **49** and 16.0 mg (48%) of a 9:1 mixture of **50** and its epimer.

For pure **50**: colorless oil; IR (neat, cm^{-1}) 2955, 2870, 1705, 1465, 1365, 1315, 1280, 1165; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (dd, J = 2.5, 7.3 Hz, 1 H), 2.83 (dd, J = 8.9, 11.3 Hz, 1 H), 2.76–2.62 (m, 2 H), 2.49–2.33 (m, 5 H), 2.16 (s, 3 H), 2.08–2.00 (m, 1 H), 1.97–1.87 (m, 2 H), 1.63–1.47 (m, 2 H), 1.40–1.13 (series of m, 3 H), 1.23 (s, 3 H), 1.19 (d, J = 7.2 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.74 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 211.35, 206.37, 147.83, 124.38, 54.17, 49.07, 46.81, 44.10, 43.31, 41.62, 37.60, 31.63, 29.59, 29.01, 27.12, 24.55, 23.84, 21.79, 21.60, 15.38; MS m/z (M^+) calcd 304.2402, obsd 304.2457.

A methanolic solution (7 mL) containing **50** (102 mg, 0.336 mmol) was treated with potassium carbonate (46 mg, 0.336 mmol), stirred overnight at room temperature, and diluted with ether. The usual workup gave a residue, purification of which by MPLC (silica gel) furnished 87 mg (85%) of **49**.

To a solution of **49** (83 mg, 0.273 mmol) and pyridine (0.5 mL) in dichloromethane (2 mL) was added thionyl chloride (0.10 mL, 1.37 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was diluted with ether and processed as usual. MPLC on silica gel gave enone **4** (18 mg) and a pair of regioisomers of **51** (43 mg, 78% total).

A methanolic solution (5 mL) of these regioisomers (43 mg, 0.150 mmol) was treated with potassium carbonate (207 mg, 1.50 mmol), stirred at room temperature for 7 days, diluted with ether, and worked up as usual. MPLC (silica gel) furnished 30 mg (70%) of **4** and recovered starting material (3.2 mg, 7%).

For **4**: colorless solid; mp 115–118 °C; IR (KBr, cm^{-1}) 2980, 2920, 1670, 1615, 1460, 1368, 1310; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (dd, J = 2.4, 9.7 Hz, 1 H), 3.51 (br d, J = 9.2 Hz, 1 H), 2.97–2.82 (m, 1 H), 2.75 (dd, J = 6.8, 11.7 Hz, 1 H), 2.38–2.21 (m, 4 H), 2.13–1.80 (m, 3 H), 2.03 (d, J = 0.9 Hz, 3 H), 1.47–1.21 (m, 4 H), 1.27 (d, J = 7.4 Hz, 3 H), 1.11 (s, 3 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.73 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 199.67, 151.42, 151.02, 138.09, 122.68, 53.74, 52.95, 50.99, 47.21, 39.99, 33.91, 30.06, 29.27, 27.01, 26.27, 23.72, 21.57, 21.37, 16.09, 16.03; MS m/z (M^+) calcd 286.2297, obsd 286.2299; $[\alpha]^{20}_D$ −85.8° (c 1.28, $CHCl_3$).

(4*S*,6*S*,8*S*,10a*S*,10b*R*)-2,5,6,8,9,10,10a,10b-Octahydro-8-isopropyl-3,6,10a-trimethyldicyclopenta[*a*,*c*]cycloocten-4-ol (52). Lithium aluminum hydride (18.1 mg, 0.477 mmol) was added to a cold (0 °C), magnetically stirred solution of **4** (68 mg, 0.238 mmol) in dry tetrahydrofuran (3 mL). After 30 min, the reaction mixture was quenched with 30% sodium hydroxide solution (1 mL) and processed in the usual fashion. Purification by MPLC on silica gel gave **52** as a colorless oil (66 mg, 95%): IR (neat, cm^{-1}) 3550, 3450, 2950, 1650, 1455, 1385, 1090, 975; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (dd, J = 2.1, 10.1 Hz, 1 H), 4.55 (dd, J = 6.1, 11.3 Hz, 1 H), 3.09 (br d, J = 8.9 Hz, 1 H), 2.78–2.67 (m, 1 H), 2.52–2.26 (m, 4 H), 2.10–1.75 (m, 4 H), 1.78 (s, 3 H), 1.58–1.35 (m, 5 H), 1.23 (d, J = 7.5 Hz, 3 H), 1.08 (s, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.78 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 154.03, 141.42, 140.23, 124.20, 67.20, 55.02, 53.36, 50.90, 40.55, 38.18, 33.35, 30.43, 28.45, 28.37, 25.91, 23.94, 21.62, 21.59, 16.47, 14.67; MS m/z ($M^+ - CH_4$) calcd 272.2140, obsd 272.2164.

(3*S*,3a*S*,4*S*,6*S*,8*S*,10a*S*,10b*R*)-3,3a-Epoxy-1,2,3,3a,4,5,6,8,9,10,-10a,10b-dodecahydro-8-isopropyl-3,6,10a-trimethyldicyclopenta[*a*,*c*]-cycloocten-4-ol (53). A cold (0 °C), magnetically stirred solution of **52** (24.6 mg, 0.0853 mmol) in dichloromethane (1.5 mL) was treated with *m*-chloroperbenzoic acid (17.7 mg, 0.102 mmol) and stirred for 1 h. Methyl sulfide (0.2 mL) was added, and the resulting solution was stirred for 30 min at room temperature, diluted with ether, and worked up by the usual method. MPLC purification (silica gel) of the residue afforded **53** (22.4 mg, 86%) as a colorless oil: IR (neat, cm^{-1}) 3510, 2950, 2870, 1460, 1385, 1200, 1060; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (m, 1 H), 4.49 (m, 1 H), 2.75 (d, J = 1.9 Hz, 1 H), 2.63–2.47 (m, 1 H), 2.41 (m, 1 H), 2.34–2.12 (m, 2 H), 1.93–1.55 (m, 8 H), 1.58 (s, 3 H), 1.48–1.41 (m, 2 H), 1.28 (s, 3 H), 1.13 (d, J = 7.2 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 148.16, 129.33, 74.68, 72.39, 67.98, 56.02, 54.60, 46.20, 42.03, 40.43, 33.55, 31.90, 30.72, 30.01, 27.11, 25.94, 24.16, 21.98, 18.43, 17.62; MS m/z ($M^+ - H_2O$) calcd 286.2297, obsd 286.2285; $[\alpha]^{20}_D$ −43.8° (c 1.20, $CHCl_3$).

(3*S*,3a*R*,6*S*,8*S*,10a*S*,10b*R*)-3,3a-Epoxy-2,3,3a,5,6,8,9,10,10a,10b-decahydro-8-isopropyl-3,6,10a-trimethyldicyclopenta[*a*,*c*]cycloocten-4-(1*H*)-one (3). A cold (−70 °C), magnetically stirred solution of oxalyl chloride (23 μL, 0.26 mmol) in dichloromethane (3 mL) was treated with dimethyl sulfoxide (0.1 mL) and stirred for 20 min. A solution of **53** (40 mg, 0.132 mmol) in dichloromethane (2 mL) was next introduced, followed 20 min later by triethylamine (0.5 mL). The reaction mixture was stirred at −70 °C for 10 min and allowed to warm to room temperature. The usual workup left a residue that was purified by silica gel chromatography. There was obtained 39 mg (98%) of **3** as a colorless crystalline solid: mp 135–137 °C (from ether); IR (KBr, cm^{-1}) 2950, 2930, 2870, 1705, 1465, 1370, 1245, 1135; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (m, 1 H), 2.77–2.45 (m, 4 H), 2.31 (d, J = 17.8 Hz, 1 H), 2.07–1.91 (m, 5 H), 1.58–1.39 (m, 3 H), 1.30 (s, 3 H), 1.28–1.20 (m, 1 H), 1.56 (d, J = 6.9 Hz, 3 H), 1.12 (s, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.78 (d, J = 6.7 Hz, 3 H): ^{13}C NMR (75 MHz, C_6D_6) δ 205.79, 149.06, 127.34, 77.78, 73.70, 55.93, 53.84, 50.42, 47.46, 40.82, 32.31, 30.82, 30.17, 28.02, 26.98, 25.50, 21.67, 21.38, 17.36, 16.15; MS m/z ($M^+ - H_2O$) calcd

284.2140, obsd 284.2087; $[\alpha]^{19}_D$ +137.51° (c 3.09, $CHCl_3$).

The three-dimensional structure of **3**, determined crystallographically, is shown in Figure 2.

Double-Bond Isomerization in 49. A heptane solution (2.5 mL) of **49** (40 mg, 0.132 mmol) was treated with thiophenol (1 mL) and AIBN (27 mg, 0.197 mmol) and irradiated with a sunlamp for 3 h while being vigorously stirred. The volatiles were removed under reduced pressure, and the residue was purified by MPLC (silica gel, elution with ethyl acetate/petroleum ether, 1:4.5). There were isolated 14 mg of the less polar alcohol and 10 mg of the more polar alcohol (total yield 60%) corresponding to **54**.

For the less polar stereoisomer: IR ($CHCl_3$, cm^{-1}) 3600, 2960, 2870, 1680, 1455, 1385, 1300, 1110; ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (dt, J = 9.0, 12.2 Hz, 1 H), 2.71 (t, J = 11.4 Hz, 1 H), 2.55 (quin, J = 6.8 Hz, 1 H), 2.26-1.95 (m, 7 H), 1.82-1.69 (m, 3 H), 1.63-1.36 (m, 4 H), 1.31 (s, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 1.01 (s, 3 H), 0.92 (d, J = 6.2 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.14, 144.12, 137.41, 82.39, 65.01, 52.77, 48.93, 48.78, 41.85, 36.87, 32.89, 28.67, 27.43 (2 C), 27.33, 26.71, 24.66, 23.77, 21.08, 19.66; MS m/z (M^+) calcd 304.2402, obsd 304.2409.

For the more polar isomer: IR ($CHCl_3$, cm^{-1}) 3580, 2960, 2870, 1670, 1455, 1380, 1340, 1300, 1120; ^1H NMR (300 MHz, $CDCl_3$) δ 2.60-2.48 (m, 3 H), 2.37-1.97 (m, 6 H), 1.92-1.76 (m, 4 H), 1.63-1.39 (m, 4 H), 1.16 (s, 3 H), 1.06 (d, J = 6.5 Hz, 3 H), 1.02 (s, 3 H), 0.90 (d, J = 6.0 Hz, 3 H), 0.88 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.12, 145.05, 136.80, 80.33, 66.19, 53.36, 49.07, 47.37, 41.06, 37.07, 33.22, 28.78, 27.61, 27.44, 26.71, 24.51, 24.21, 23.20, 21.09, 16.69; MS m/z (M^+) calcd 304.2402, obsd 304.2418.

Double-Bond Isomerization in 3. A. Rhodium Catalysis. Epoxy ketone **3** (1.8 mg, 0.0060 mmol) dissolved in ethyl acetate (1 mL) was treated with 5% Rh/C, and the resulting mixture was stirred under 1500 psi of hydrogen at room temperature for 20 h. The reaction mixture was filtered through a Celite pad and evaporated. Purification of the residue by silica gel chromatography (elution with 2% ethyl acetate in petroleum ether) gave 1.3 mg (72%) of **55**: IR ($CHCl_3$, cm^{-1}) 2960, 1710, 1450, 1385, 1115, 990; ^1H NMR (300 MHz, $CDCl_3$) δ 2.73-2.51 (m, 3 H), 2.37-2.23 (m, 2 H), 2.16-2.05 (m, 3 H), 1.94-1.43 (m, 7 H), 1.50 (s, 3 H), 1.07 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.88 (s, 3 H), 0.87 (d, J = 5.9 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 205.87, 145.32, 137.61, 74.06; 73.39, 51.53, 48.76, 47.30, 36.50, 33.14, 32.97, 31.11, 27.89, 27.10, 23.97, 23.10, 22.39, 20.86, 19.79, 17.09; MS m/z (M^+) calcd 302.2246, obsd 302.2241.

B. Thiophenol Catalysis. A solution of **3** (10 mg, 0.033 mmol), thiophenol (1 ml), and AIBN (10 mg) in heptane (5 mL) was irradiated as described above for 3 h. The identical workup afforded 5.9 mg (59%) of **55**, identical in all respects with the material produced in part A.

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Registry No. 3, 126458-49-9; **4**, 126458-60-4; **6**, 126458-55-7; **7**, 131934-82-2; **10**, 62994-35-8; **11**, 131934-84-4; **11** (carbinol, isomer 1), 131934-81-1; **11** (carbinol, isomer 2), 131935-08-5; **12**, 131934-85-5; **13**, 131934-86-6; **14**, 131934-87-7; **15**, 131934-88-8; **16**, 131934-89-9; α-**17a**, 132072-20-9; β-**17a**, 131934-90-2; α-**17b**, 132072-21-0; β-**17b**, 131934-83-3; α-**17c**, 132072-23-2; β-**17c**, 131934-91-3; β-**17d**, 132072-24-3; **21**, 131934-92-4; **22**, 131973-37-0; **23**, 132072-22-1; **24**, 131934-93-5; **25**, 131934-94-6; **26**, 131973-38-1; **27**, 117152-55-3; *epi*-**27**, 132072-28-7; **28**, 131934-95-7; *epi*-**28**, 132072-25-4; **29**, 126458-50-2; **29** triol, 131935-09-6; (5*R*)-**29** triol, 132072-29-8; **29** aldehyde, 131935-07-4; **30**, 131934-96-8; **31**, 126458-51-3; **32a**, 126458-52-4; **32b**, 131935-00-7; **33**, 131934-97-9; **37**, 126458-53-5; **38**, 131934-98-0; **39**, 126458-54-6; **40**, 131934-99-1; **42**, 126458-56-8; **43**, 126576-00-9; **47**, 131935-01-8; **48**, 126458-57-9; **48** ketal, 131935-05-2; **49**, 126458-58-0; **50**, 126458-59-1; *epi*-**50**, 132072-26-5; Δ^8-**51**, 131935-06-3; $\Delta^{8(19)}$-**51**, 131935-02-9; **52**, 126458-63-7; **53**, 126458-64-8; **54** (isomer 1), 131935-03-0; **54** (isomer 2), 132072-27-6; **55**, 131935-04-1; (*E*)-$Me_3SiCH{=}CHBr$, 41309-43-7; $CH_2{=}C(CH_3)(CH_2)_2Br$, 20038-12-4; $Ph_3P^+CH_3$ I^-, 2065-66-9; 4-bromo-2-butanone ethylene ketal, 37865-96-6; 4-bromo-2-butanone neopentyl glycol ketal, 87842-52-2.

Supplementary Material Available: Figures illustrating the labeling schemes for **39** and **3**, experimental descriptions, and tables of the crystallographic details, final positional and thermal parameters, bond lengths, and bond angles for both compounds (19 pages). Ordering information is given on any current masthead page.

Structure Determination of Tolaasin, an Extracellular Lipodepsipeptide Produced by the Mushroom Pathogen *Pseudomonas tolaasii* Paine

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Abstract: The principal active component of tolaasin, the *Pseudomonas tolaasii* toxin, which is responsible for brown blotch disease of mushrooms, is shown to be a lipodepsipeptide of M_r 1985. The structure determined is β-hydroxyoctanoyl-ΔBut-D-Pro-D-Ser-D-Leu-D-Val-D-Ser-D-Leu-D-Val-L-Val-D-Gln-L-Leu-D-Val-ΔBut-D-*allo*-Thr-L-Ile-L-Hse-D-Dab-L-Lys (cyclized via lactone formation between D-*allo*-Thr and the C-terminus) by a combination of fast atom bombardment mass spectrometry (FABMS), ^1H NMR, automated sequencing, and chiral gas chromatography. A minor component of the toxin (M_r 1941) has a related structure in which the homoserine residue is substituted by glycine. In addition, the sequence of a modified form of the toxin, produced by a genetically engineered strain of *P. tolaasii*, is characterized.

Introduction

Pseudomonas tolaasii is the causal organism of the economically significant brown blotch disease of the cultivated mushroom *Agaricus bisporus* (Lange) Imbach.[1] Colonization of mushroom basidiocarps by the bacterium results in unsightly brown lesions that render affected mushrooms unmarketable.

P. tolaasii culture filtrates cause blotch symptoms identical with those caused by the whole organism.[2] Methods for isolation of

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(1) Tolaas, A. G. *Phytopathology* **1915**, *5*, 51-54.
(2) Nair, N. G.; Fahy, P. C. *Aust. J. Biol. Sci.* **1973**, *26*, 509-512.

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