Total Synthesis of the Cembranoid Diterpene Lactone (+)-Cleomeolide. Some Remarkable Conformational Features of Nine-Membered Belts Linked in 2,6-Fashion to a Methylenecyclohexane Core

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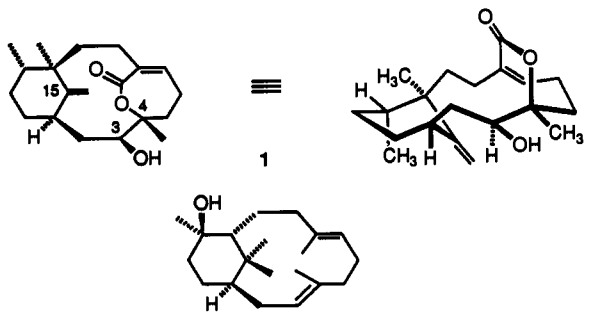
Abstract: The total synthesis of (+)-cleomeolide (**1**) has been accomplished. The key construction elements of this cembranoid lactone were (i) improved conversion of optically pure Wieland–Miescher ketone into dienol ether **12** and oxidative cleavage of the latter to aldehydo ester **13**; (ii) avoidance of complications arising from steric blockade of C-15 for introduction of the methylene group at that site; (iii) exploitation of an intramolecular Wadsworth–Emmons cyclization for macrocyclic ring construction; (iv) modulation of the conformation adopted by the medium ring by diastereofacial control of epoxidation of the C-3/C-4 double bond; and (v) intramolecular cyclization of the epoxy acid derived from **27** by nucleophilic capture at the more substituted oxiranyl carbon to deliver the target molecule. The deep-seated topographical change that accompanies the formation of **29** projects the macrocyclic ring quasi-axially from the methylenecyclohexane subunit in the manner known by X-ray crystallography to be adopted by the target compound. The intramolecular cyclization to set the bridgehead double bond was thereby facilitated.

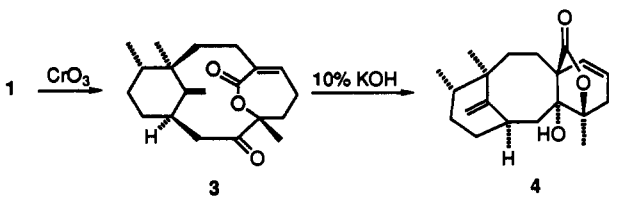
Cleomeolide (**1**), a macrocyclic diterpene lactone isolated independently in the late 1970s by research groups from the Indian Institute of Experimental Medicine,[1] the University of the West



1 **2**

Indies, and Hoffmann–LaRoche,[2] was shown by means of NMR, X-ray, and CD methods[3] to possess a framework somewhat akin to that present in verticillol (**2**).[4] The host plant is *Cleome viscosa* (syn. *Cleome icosandra*), a sticky, odoriferous herb widely distributed in India and renowned for its vesicant and anthelmintic properties.[5] From the biogenetic vantage point, cleomeolide is believed to arise either by the oxidative cyclization of geranyllinalool epoxide[1] or via head-to-tail cyclization of digeranyl pyrophosphate.[2]

The unusual structural features of **1** encompass a nine-membered carbon chain cis-fused to a methylenecylohexane subunit, as well as a seven-membered α,β-unsaturated lactone whose double bond resides at a bridgehead site. Our interest in cleomeolide arose not only because of its inherently novel topography and biological activity[6] but also as a consequence of its possible serviceability as a precursor to analogues of taxol. In a series of serendipitous experiments, **1** was oxidized to keto lactone **3**, which cyclized to **4** in the presence of base.[2] The possible



3 **4**

biosynthetic significance of these interconversions remains unclear, although the structural relationship of **4** to the taxane diterpenes is unmistakable.[7]

Herein, the complete details of an enantiospecific total synthesis of (+)-cleomeolide are described.[8] To the best of our knowledge, there has been no other report concerning construction of this natural substance.

Results and Discussion

Retrosynthetic Considerations. From the outset, it was envisioned that **1** could be elaborated in its final stages by epoxidation and lactonization[2] of the carboxylic acid **5** (Scheme 1). Accordingly, we were led to consider attempts to achieve formation of the macrocyclic ring by installation of the conjugated double bond in **5** via an intramolecular Wadsworth–Emmons reaction. The success of this scenario could rest on development of the proper electron-withdrawing substituent selected from options such as carbomethoxy, carbo-*tert*-butoxy, cyano, etc. Conciseness would be well served if **7** could be transformed

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(1) Mahato, S. B.; Pal, B. C.; Kawasaki, T.; Miyahara, K.; Tanaka, O.; Yamasaki, K. *J. Am. Chem. Soc.* **1979**, *101*, 4720.

(2) Burke, B. A.; Chan, W. R.; Honkan, V. A.; Blount, J. F.; Manchand, P. S. *Tetrahedron* **1980**, *36*, 3489.

(3) In transcribing the ORTEP representation of **1** into a two-dimensional formula, Burke et al. erred in depicting the configurations at C-3 and C-4. The corrected version is illustrated here.

(4) Karlsson, B.; Pilotti, A.-M.; Söderholm, A.-C.; Norin, T.; Sundin, S.; Sumimoto, M. *Tetrahedron* **1978**, *34*, 2349.

(5) *The Wealth of India, Raw Materials*; CSIR: New Delhi, India, 1950; Vol. II, p. 231.

(6) Manchand, P. S. Private communication (June 4, 1992).

(7) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat Prod.* **1993**, *61*, 156. Note that a second double bond is lacking in all of the cleomeolide-derived structures.

(8) Paquette, L. A.; Wang, T.-Z.; Wang, S.; Philippo, C. M. G. *Tetrahedron Lett.* **1993**, *34*, 3523.

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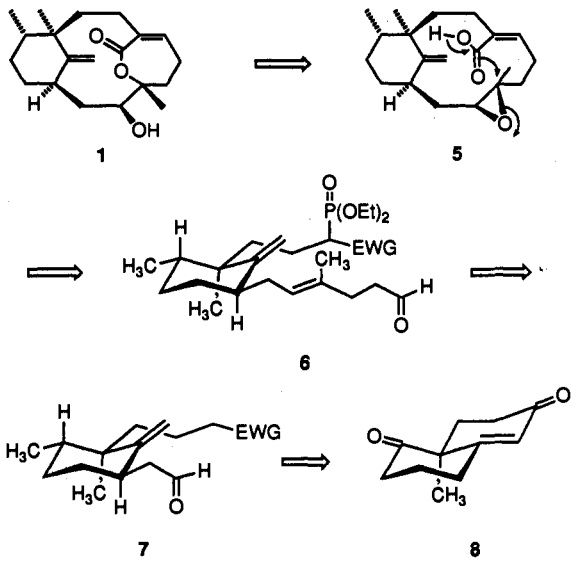
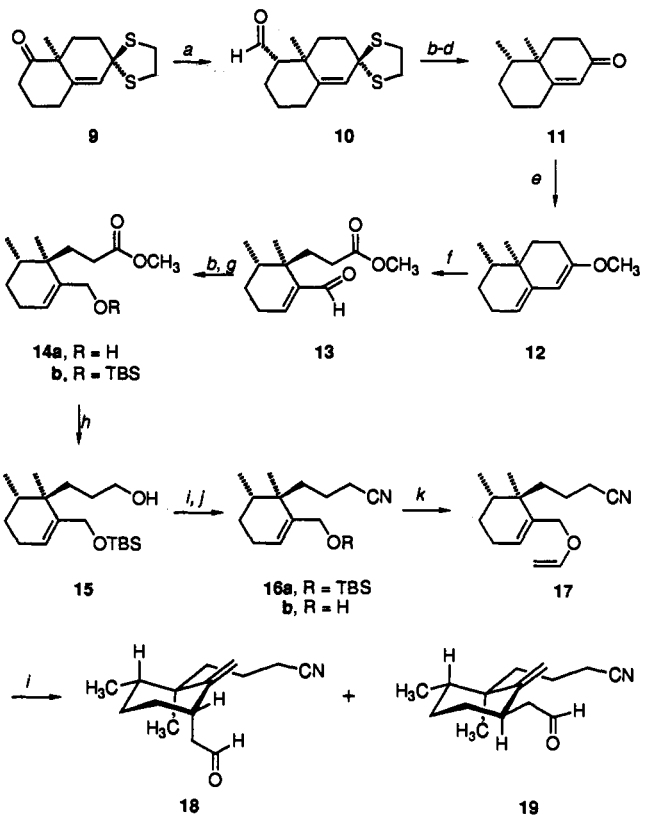
Scheme 1



Scheme 2



[a] $Ph_3P^+CH_2OCH_3\ Cl^-$, $KN(SiMe_3)_2$, THF, 0 °C → rt; 4 N HCl. [b] $NaBH_4$, MeOH. [c] CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; $LiBHEt_3$, THF, rt. [d] $Tl(NO_3)_3 \cdot 3H_2O$, MeOH–THF. [e] $HC(OCH_3)_3$, (TsOH), MeOH, DMF. [f] MCPBA, benzene–hexanes, 0 °C → rt; silica gel. [g] TBSCl, imid, DMF. [h] $LiAlH_4$, THF, 0 °C. [i] CH_3SO_2Cl, Et_3N, CH_2Cl_2; KCN, 18-crown-6, DMF. [j] Py-HF, CH_3CN, H_2O. [k] $CH_2{=}CHOC_2H_5$, $Hg(OCOCF_3)_2$, Et_3N. [l] Xylene, 200 °C, sealed tube.

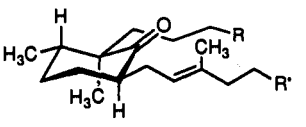
efficiently into **6**. Another attractive feature of intermediate **7** was discerned. The collection of diverse functional groups incorporated therein might be assembled from optically pure Wieland–Miescher ketone (**8**) if certain potentially troublesome tactics proved amenable to satisfactory resolution.

For the **8** → **7** conversion to be exploitable, it was necessary to set the cis, vic stereochemistry of the pair of methyl groups. Beyond that, the means would need to be found for properly installing the equatorially disposed acetaldehyde fragment, while simultaneously providing for introduction of the exocyclic methylene group into a highly congested sector of the six-membered ring.

In addition, there was need for concern about the anticipated dynamic conformational behavior of the macrocyclization product. Arrival at **5** demands that one surface of the original electron-rich trisubstituted π-bond be made available for attack by the epoxidizing agent. As will be discussed, the solution to this problem rests on precise knowledge of which chairlike arrangement of the methylenecyclohexane part of the structure is being adopted and effective liaison of this information with the mechanistic characteristics of the electrophilic oxidant ultimately deployed.

Construction of the Fully Functionalized Methylenecyclohexane. To meet the above retrosynthetic goals, optically pure Wieland–Miescher ketone (**8**)[9] was selectively dithioketalized[10] in order to differentiate between its two carbonyl groups. Exposure of **9** to (methoxymethylene)triphenylphosphorane[11] and ensuing acid hydrolysis resulted in smooth homologation to **10** in 82% overall yield (Scheme 2). The crystalline product was constituted of a 7:1 mixture of cis and trans isomers, which were not separated, since later purification efficiently removed the unwanted β epimer. When attempts to reduce **10** by the Wolff–Kischner method[12] gave only polar materials, recourse was made instead to a two-step procedure involving sodium cyanoborohydride reduction of the derived tosylhydrazone.[13] However, only moderate yields were realized and the purification problem was not thereby resolved. Consequently, this option was abandoned in favor of initial sodium borohydride reduction. The major carbinol was readily separated from the minor diastereomer and could be reduced in turn to the methyl derivative in 76% yield by treatment of its mesylate with lithium triethylborohydride. As anticipated, hydrolysis of this dithiane with thallium trinitrate trihydrate[14] delivered **11** efficiently and without detectable loss of optical activity throughout the sequence, thereby providing a new and efficient means for obtaining this octalone.[15,16]

With the cis, vic dimethyl substituents in place, cleavage of the A-ring had next to be addressed. Since preliminary studies had indicated that reattachment of a carbon atom to C-15 in ketones such as **20** is inordinately difficult,[17,18] we were confronted with



the need to accomplish the bond disconnection α to the carbonyl. To this end, **11** was subjected to acid-catalyzed condensation with trimethyl orthoformate. The result was isolation of dienol ether **12** in 89% yield. That the oxygen-substituted double bond in **12** was the more susceptible to electrophilic attack in nonpolar

(9) (a) Buschacher, P.; Fürst, A. *Org. Synth.* **1985**, *63*, 37. (b) The improved procedure given by Harada et al. (Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53) is preferred.

(10) Bosch, P. M.; Camps, F.; Coll, J.; Guerrero, A.; Tatsuoka, T.; Meinwald, J. *J. Org. Chem.* **1986**, *51*, 773.

(11) (a) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373. (b) Wittig, G.; Böll, W.; Krück, K.-H. *Chem. Ber.* **1962**, *95*, 2514.

(12) Zalkow, L. H.; Girotra, N. N. *J. Org. Chem.* **1964**, *29*, 1299.

(13) (a) Caglioti, L. *Tetrahedron* **1966**, *22*, 487. (b) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662. (c) Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299.

(14) Smith, R. A. J.; Hannah, D. J. *Synth. Commun.* **1979**, *9*, 301.

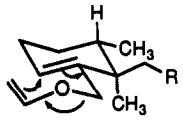
(15) Birnbaum, G. I.; Stoessl, A.; Grover, S. H.; Stothers, J. B. *Can. J. Chem.* **1974**, *52*, 993.

(16) For approaches to racemic **11**, consult: (a) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6867. (b) Zoretic, P. A.; Golen, J. A. *J. Org. Chem.* **1981**, *46*, 3554. (c) Huffman, J. W.; Potnis, S. M.; Satish, A. V. *J. Org. Chem.* **1985**, *50*, 4266. (d) Prasad, C. V. C.; Chan, T. H. *J. Org. Chem.* **1987**, *52*, 120.

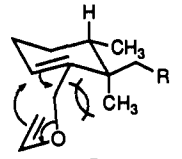
and aprotic solvents was confirmed by exposure to two equivalents of *m*-chloroperbenzoic acid in a benzene–hexane solvent system and subsequent chromatography on silica gel.[19] Direct chemoselective reduction of the resulting aldehydo ester **13** gave rise to **14a**. The overall efficiency of this sequence was 59%.

The allylic hydroxyl substituent in **14** was expected to serve as the point of departure for projected Claisen rearrangement. Prior to that, it was considered necessary to modify the propionic ester side chain so as to introduce the requisite additional carbon atom. This was accomplished without incident via initial protection of the hydroxyl as its *tert*-butyldimethylsilyl ether in advance of hydride reduction and displacement of the mesylate with cyanide ion.

With **16b** in hand, transetherification with ethyl vinyl ether was next undertaken. This step proved to be problematic until recourse was made to catalysis by mercuric trifluoroacetate in the presence of triethylamine.[20] Under these conditions, **17** was obtained in 73% yield. The thermal isomerization of **17** required heating at 200 °C in xylene solution (sealed tube) to proceed efficiently (95%). As a consequence of the substitution plan on the cyclohexane ring, our preliminary expectation was that transition state **A** would be adopted preferentially to **B** in order



A



B

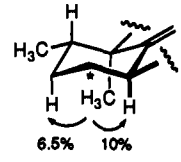
to circumvent the development of a 1,3-diaxial interaction. If this kinetic ordering were adopted, the new C–C bond would be installed cis to the butyronitrile side chain in the desired manner. In actuality, **17** (and several of its analogues[17,21]) isomerizes preferentially via **B** to set an axial bond and deliver **18** and **19** in a 2.7:1 ratio. The diastereomer distribution is more highly skewed toward **18** when the sigmatropic event is alternatively catalyzed by Et_2AlCl/PPh_3[22] or the bulky Yamamoto aluminum reagents.[23] Palladium(II) catalysts[24] proved ineffective in promoting the rearrangement.

The chromatographic separation of **18** from **19** proved to be notably straightforward. The stereochemistry of the individual isomers was made clearly apparent through combined 2-D COSY studies and NOE measurements performed by independent irradiation of the protons attached to the exocyclic double bond.

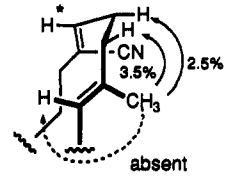
Elaboration of the Macrocyclic Ring. Having secured **19**, we quickly determined that the "lower" side chain could be appended with exceptionally good stereocontrol by implementation of a second Claisen rearrangement.[25] In the first series of experiments, the two allylic alcohols **21a** and **22a** resulting from the addition of 2-propenylmagnesium bromide to **19** were separated, transformed individually to **21b** and **22b**, and heated in benzene solution at 170 °C in sealed tubes. When both substrates were found to converge to **23** (Scheme 3), chromatography could be skirted and the three-step process streamlined so as to provide **23** in good yield.

Acetalization of **23** under Noyori conditions[26] provided **24** and set the stage for activation of the cyano-substituted carbon atom. This was efficiently accomplished by condensation of the derived carbanion with diethyl chlorophosphate.[27] Following unmasking of the aldehyde functionality, attention was turned to implementing suitable macrocyclization. After some experimentation, the use of potassium carbonate and 18-crown-6 in toluene at 20 °C[28] was found to be best suited to our purposes. Satisfyingly, **26** was obtained as a single isomer, the stereochemical and conformational features of which were established by NMR techniques.[29]

As a first step, the ^1H and ^{13}C NMR spectra of **26** were fully assigned on the basis of $^1H,^1H$- and $^1H,^{13}C$-COSY data. The broadness of the ^1H NMR spectrum recorded on C_6D_6 solutions at room temperature was taken to be an indication that the molecule was conformationally flexible. This dynamic character had necessarily to be confined to the large ring, since the data revealed the conformation of the cyclohexane subunit to be strictly defined as in **C**. The diequatorial disposition of the bonds to the



C



D

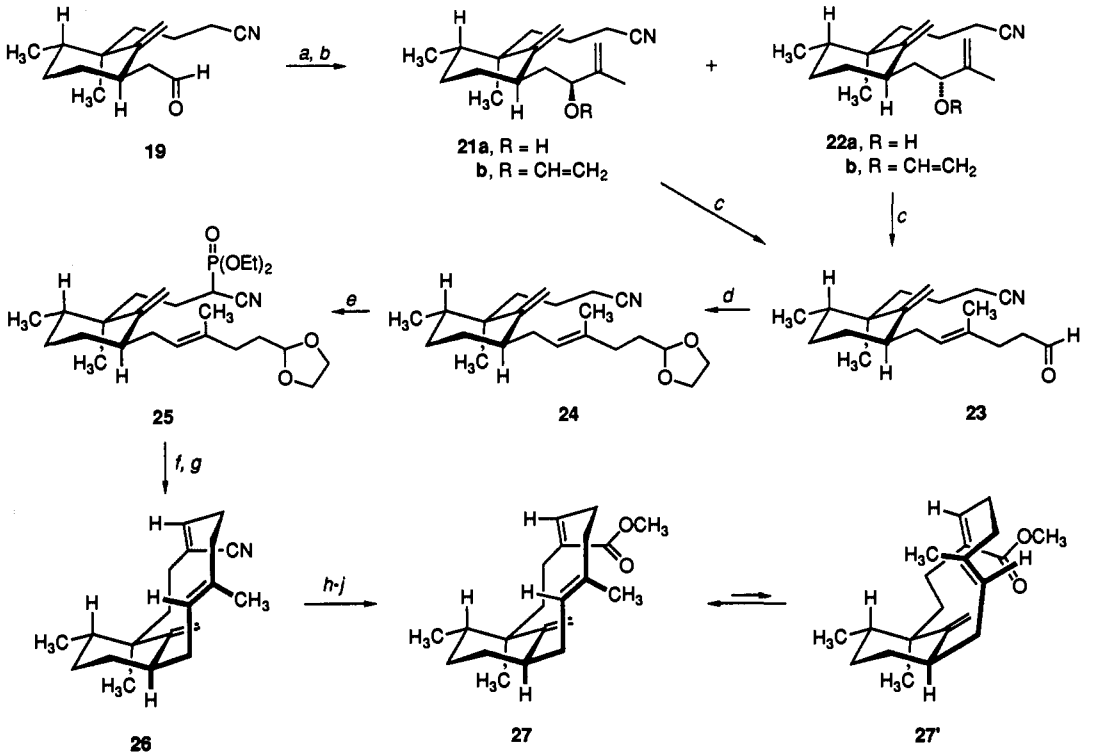
large ring was specifically recognized on the strength of the appearance of the axial proton residing on the asterisked carbon as a quite broad multiplet because of two large (ax/ax) couplings to vicinal axial neighbors. Beyond that, NOE data (see **C**) clearly established the syn/axial relationship of the angular methyl group to the two protons shown.

The important question of double-bond geometry was also elucidated by NOE. The absence of an interaction between the sp^2-bound methyl and the adjacent vinyl proton proved confirmatory of our earlier *E* assignment to the "front" olefin. The stereochemistry about the vinyl cyanide was established by selective decoupling studies, indicating $^3J_{H^*/CN}$ to be approximately 14 Hz, consistent uniquely with *Z* geometry. Informatively, more extensive NOE information obtained on this product was not compatible with a single distinct conformation for the large ring.

The issue of conformational dynamics was specifically addressed following conversion to the methyl ester **27**, since this chemical modification was easily recognized not to be accompanied by a meaningful topographical change. When attempts to hydrolyze **26** directly proved unsuccessful, a milder three-step process was utilized in order to suppress decomposition. Dibal-H reduction led to the imine, hydrolysis of which on silica gel furnished the labile aldehyde in excellent yield. Immediate oxidation of the aldehyde with buffered sodium chlorite[30] delivered the carboxylic acid, esterification of which with diazomethane provided **27**.

(17) Philippo, C. M. G. Ph.D. Dissertation, The Ohio State University, 1991.
(18) Steric hindrance is sufficiently elevated to prohibit attack by such nucleophiles as methylenetriphenylphosphorane and methylcerium dichloride, as well as the Lombardo [Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293; *Org. Synth.* **1987**, *65*, 81] and Tebbe reagents [Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270].
(19) Kirk, D. N.; Wiles, J. M. *Chem. Commun.* **1970**, 1015.
(20) Tulshian, D. B.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 2347.
(21) Wang, S. Unpublished results.
(22) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 3985.
(23) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316.
(24) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879.
(25) Faulkner, D. J.; Petersen, M. R. *Tetrahedron Lett.* **1969**, 3243.
(26) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
(27) Comins, D. L.; Jacobine, A. F.; Marshall, J. L.; Turnbull, M. M. *Synthesis* **1978**, 309.
(28) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(29) The authors are indebted to Dr. Dirk Friedrich for the NMR measurements.
(30) (a) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091. (b) Wright, J.; Dritina, G. J.; Roberts, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1988**, *110*, 5806.

Scheme 3



[a] CH_2=C(MgBr)CH_3, THF, -78 °C; H_2O. [b] CH_2=$CHOC_2H_5$, $(CH_3CH_2)_3N$, $Hg(OCOCF_3)_2$. [c] Benzene, 170 °C, sealed tube. [d] $(Me_3SiOCH_2)_2$, TMSOTf, CH_2Cl_2, -78 °C. [e] LDA, THF, -78 °C; $ClP(O)(OC_2H_5)_2$. [f] TsOH, H_2O, acetone. [g] K_2CO_3, 18-crown-6, toluene, 20 °C. [h] Dibal-H, toluene, ether, -78 °C → 0 °C; silica gel. [i] $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O, *t*-BuOH. [j] CH_2N_2, ether.

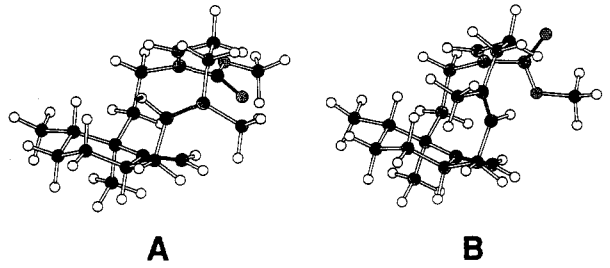


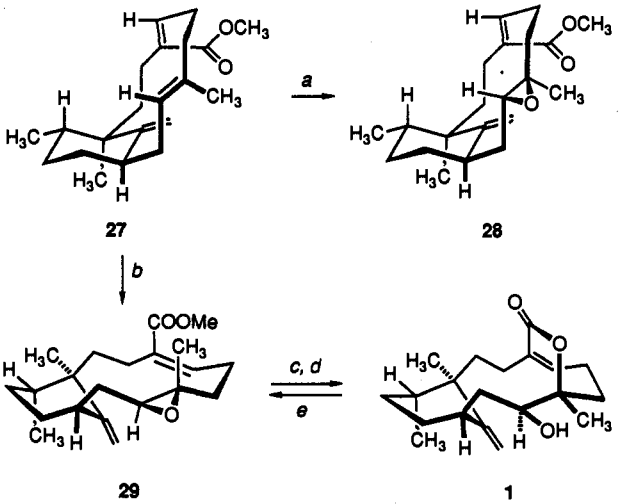
Figure 1. Lowest energy conformations of **27** (left) and **27'** (right) as computed by MM2. The conformation shown for **27** is the global minimum for this triene ester. The output graphics utilized the Chem 3-D software package.

Like the case of **26**, variable-temperature NMR studies performed on **27** suggested that this intermediate was prone to exist as an equilibrium mixture of conformers **27** and **27'** (see Scheme 3), with **27** being favored. MM2 calculations[31] performed on this ester likewise indicated that **27** was the global minimum-energy conformer (ΔE_{strain} = 31.1 kcal/mol, ΔE_{total} = 40.32 kcal/mol). Further, the indications were that **27'** was thermodynamically disadvantaged to the extent of approximately 1.5 kcal/mol (ΔE_{strain} = 32.6 kcal/mol, ΔE_{total} = 41.8 kcal/mol) (see Figure 1).

To the extent that MM2 can be relied upon to provide a reasonably accurate profile of relative stabilities, direct electrophilic addition to the most electron-rich trialkyl-substituted double bond in **27** should occur in the improper diastereofacial sense. This premise was tested by MCPBA oxidation. In the event, **28** was obtained as the sole identifiable product (Scheme 4).

The crystallographic analyses performed on natural cleomeolide convincingly demonstrate that the associated macrocyclic ring is projected quasi-axially from the methylenecyclohexane subunit.[1,2]

Scheme 4



[a] MCPBA, $NaHCO_3$, CH_2Cl_2. [b] I_2, Ag_2O, H_2O, dioxane. [c] 3.5% KOH in MeOH, reflux. [d] 5% HCl, THF. [e] 3.5% KOH in MeOH, Δ; H_3O^+; CH_2N_2.

As a consequence, a substantive topographical modification of the diequatorial conformation adopted by **27** had to be implemented if our target was to be reached. On the basis of detailed study of molecular models, we hypothesized that the requisite conformation might well be adopted should it be possible to reposition the oxirane ring on the substantially more hindered internal face of the trisubstituted double bond in **27**. After many unsuccessful experiences gained in connection with attempts to produce **29**, it was found that the combination of iodine and silver(I) oxide in aqueous dioxane[32] is conducive to providing the desired diastereofacial outcome, although in modest yield. In

(31) The illustrated conformations represent the global energy minima generated with MODEL (version KS 2.96) as subsequently optimized by means of MMX.

(32) (a) Parrilli, M.; Barone, G.; Adinolfi, M.; Mangoni, L. *Tetrahedron Lett.* **1976**, 207. (b) Polniaszek, R. P.; Stevens, R. V. *J. Org. Chem.* **1986**, *51*, 3023.

addition, three-dimensional realignment accompanies this oxidation as attested to by NOE measurements and the identity of synthetic **29**, $[\alpha]^{20}_D$ –67.4° (*c* 0.27, $CHCl_3$), with an authentic sample of this epoxide generated independently by saponification, acidification, and esterification of (+)-cleomeolide according to Burke et al.[2]

Once the two newly introduced stereogenic centers had been properly established as in **29**, the acquisition of **1** was no longer considered problematic. As shown in Scheme 4, saponification of this epoxy ester made available the carboxylic acid, acid-catalyzed cyclization of which resulted in transannular lactonization as desired. The high-field ^1H NMR spectrum of fully synthetic cleomeolide was identical with that of the natural material. Furthermore, TLC behavior in several solvent systems decisively revealed the absence of contamination.

Consequently, a succesful enantioselective route to (+)-cleomeolide has been realized. The ultimately successful stratagem was dependent on effective use of a diagnosable interpendence of functional group deployment and adoption of serviceable global energy conformational minima. The feasibility of these tactics encourages the adoption of related possibilities for stereocontrolled macrocyclic ring assembly in future synthetic ventures.

Experimental Section

(4'a*S*)-4',4'a,7',8'-Tetrahydro-4'a-methylspiro[1,3-dithiolane-2,2'(3'*H*)-naphthalen]-5'(6'*H*)-one (9). To a solution of Wieland–Miescher ketone **8** (5.87 g, 33.0 mmol, $[\alpha]^{25}_D$ +100° (*c* 1.00, toluene) in glacial acetic acid (14 mL) was added 1,2-ethanedithiol (3.41 g, 36.3 mmol), *p*-toluenesulfonic acid (2.94 g), and glacial acetic acid (34 mL). The mixture was stirred at room temperature for 5 h, poured into water, and stirred for 15 min. The white solid was filtered off, washed successively with water, dilute $NaHCO_3$ solution, and water, and then dried to yield 8.31 g (99%) of thioketal **9** as a white solid: mp 138 °C; IR (KBr, cm^{-1}) 2910, 1705, 1640: ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (s, 1 H), 3.39–3.32 (m, 3 H), 3.31–3.22 (m, 1 H), 2.68–1.96 (series of m, 6 H), 1.78–1.30 (series of m, 4 H), 1.29 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.8, 141.2, 128.1, 64.9, 49.5, 40.1, 39.7, 38.0, 37.7, 30.9, 30.8, 24.8, 24.6; MS *m/z* (M^+) calcd 254.0799, obsd 254.0799; $[\alpha]^{25}_D$ +112° (*c* 1.15, $CHCl_3$).

(4'a*R*,5'*S*)- and (4'a*R*,5'*R*)-4',4'a,5',6',7',8'-Hexahydro-4'a-methylspiro[1,3-dithiolane-2,2'(3'*H*)-naphthalene]-5'-carboxaldehyde (10). To a cold (–30 °C) solution of (methoxymethyl)triphenylphosphonium chloride (4.05 g, 11.8 mmol) in THF (40 mL) was added KHMDS (0.5 M in toluene, 19.7 mL, 9.85 mmol). The resulting red solution was stirred at 0 °C for 15 min before being treated with a solution of thioketal **9** (1.00 g, 3.94 mmol) in THF (10 mL). The mixture was stirred at room temperature for 24 h. A solution of methanol in THF (1:1, 10 mL) and 4 N HCl (10 mL) was added to the mixture at 0 °C. The resulting solution was allowed to stir at room temperature for 36 h and was then poured into water (40 mL) and extracted with ether (4 × 30 mL). The combined organic layers were washed with brine, dried, and concentrated. Purification of the residue by flash chromatography on silica gel (elution with 2.5% ethyl acetate in petroleum ether) gave 0.977 g (93%) of a 7:1 (β/α) mixture of aldehydes. The major isomer was obtained as a white solid: mp 98 °C; IR (KBr, cm^{-1}) 2985, 2940, 2860, 1715, 1440, 1195; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (d, J = 2.0 Hz, 1 H), 5.57 (s, 1 H), 3.45–3.32 (m, 3 H), 3.32–3.17 (m, 1 H), 2.26–2.10 (m, 4 H), 2.10–1.95 (m, 3 H), 1.95–1.82 (m, 1 H), 1.82–1.69 (m, 2 H), 1.42–1.22 (m, 1 H), 1.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.9, 143.1, 125.8, 65.0, 60.4, 39.9, 39.3, 37.1, 37.0, 36.6, 31.6, 25.8, 22.0, 19.4; MS *m/z* (M^+) calcd 268.0956, obsd 268.0965.

(4a*R*,5*S*)-4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3*H*)-naphthalenone (11). To a cold (0 °C) solution of the 7:1 aldehyde mixture (7.2 g, 27 mmol) in 150 mL of methanol and 30 mL of THF was added sodium borohydride (2.0 g, 54 mmol) in small portions. After being stirred for 20 min, the reaction mixture was quenched with saturated NH_4Cl solution, evaporated in vacuo, and taken up in ethyl acetate. The solution was washed with water, dried, and concentrated to leave a viscous oil, preparative HLPC purification of which (silica gel, elution with 15% ethyl acetate in petroleum ether) afforded 6.1 g (95% based on the major isomer) of the pure β alcohol as a white solid: mp 76 °C; IR (KBr, cm^{-1}) 3500, 2920, 2840, 1640, 1435, 1005; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 3.74 (d, J = 7.8 Hz, 2 H), 3.33–3.26 (m, 3 H), 3.19–3.15 (m, 1 H), 2.12–1.96 (m, 4 H), 1.81–1.61 (m, 4 H), 1.26 (m, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 145.5, 124.9, 65.6, 63.7, 51.5, 40.0, 39.6, 37.8, 37.3, 36.5, 32.6, 26.9, 25.6, 18.7; MS *m/z* (M^+) calcd 270.1112, obsd 270.1113; $[\alpha]^{25}_D$ +179° (*c* 1.19, $CHCl_3$).

To a cold (0 °C) solution of the above alcohol (30.8 g, 115 mmol) in CH_2Cl_2 (550 mL) and triethylamine (33 mL, 235 mmol) was added methanesulfonyl chloride (25.2 g, 220 mmol). The mixture was warmed to room temperature for 20 min and washed with water and brine prior to drying. Evaporation of the solvent afforded the crude mesylate (40 g) as a light yellow solid: mp 85 °C; IR (KBr, cm^{-1}) 2940, 2860, 1640, 1460, 1005; ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (s, 1 H), 4.33 (dd, J = 3.8, 9.6 Hz, 1 H), 3.99 (t, J = 9.7 Hz, 1 H), 3.37 (m, 3 H), 3.23 (m, 1 H), 3.00 (s, 3 H), 2.17 (m, 4 H), 1.83 (m, 4 H), 1.60 (m, 1 H), 1.37 (m, 3 H), 1.01 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.8, 125.4, 70.5, 65.0, 47.7, 39.8, 39.3, 37.3, 37.1, 36.8, 36.1, 31.9, 26.2, 25.2, 18.5; MS *m/z* (M^+) calcd 348.0887, obsd 348.0876.

To a cold (0 °C) solution of the above mesylate in THF (500 mL) was added Superhydride (250 mL of 1 M in THF, 250 mmol) via cannula. The mixture was stirred at room temperature for 20 h and quenched with water. After the usual extractive workup with ether and purification by silica gel chromatography (elution with 1% ethyl acetate in petroleum ether), 22.0 g (76% overall) of the dithioketal was obtained; colorless solid: mp 86 °C; IR ($CHCl_3$, cm^{-1}) 2970, 2930, 2860, 1465, 1440, 1210, 730; ^1H NMR (300 MHz, $CDCl_3$) δ 5.49 (s, 1 H), 3.36 (m, 3 H), 3.22 (m, 1 H), 2.14 (m, 2 H), 1.98 (m, 2 H), 1.75 (m, 2 H), 1.59 (m, 1 H), 1.32 (m, 4 H), 0.93 (s, 9 H), 0.82 (d, J = 5.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.4, 124.5, 66.0, 43.4, 39.9, 39.5, 38.0, 37.1, 33.2, 32.5, 30.9, 27.4, 17.2, 15.4; MS *m/z* (M^+) calcd 254.1163, obsd 254.1163; $[\alpha]^{25}_D$ +162.5° (*c* 1.09, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}S_2$: C, 66.06; H, 8.72. Found: C, 66.18; H, 8.87.

A solution of thallium(III) nitrate trihydrate (17.0 g, 43.5 mmol) in methanol (450 mL) was rapidly added to a solution of the preceding dithioketal (9.0 g, 35.4 mmol) in THF (80 mL) and water (1.5 mL). The turbid mixture was stirred for 10 min, and the white precipitate was filtered. The filtrate was diluted with ether and washed with water, saturated $NaHCO_3$ solution, and brine prior to drying and concentration. Purification of the residue by flash chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) gave 5.7 g (90%) of **11** as a yellow oil: IR (neat, cm^{-1}) 2930, 2850, 1675, 1615, 1465, 1445, 1435, 1235; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (s, 1 H), 2.34 (m, 2 H), 2.03 (m, 2 H), 1.85 (m, 2 H), 1.69 (m, 2 H), 1.45 (m, 3 H), 1.08 (s, 3 H), 0.89 (d, J = 5.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.5, 171.2, 124.0, 43.1, 39.0, 35.5, 34.0, 33.3, 30.5, 26.5, 16.0, 15.2; MS *m/z* (M^+) calcd 178.1358, obsd 178.1357; $[\alpha]^{25}_D$ +185.6° (*c* 1.63, $CHCl_3$).

(1*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-6-methoxy-1,8a-dimethylnaphthalene (12). A solution of **11** (8.4 g, 47.2 mmol) in a mixture of DMF (90 mL), trimethyl orthoformate (90 mL), and methanol (16 mL) was stirred with *p*-toluenesulfonic acid (160 mg, 0.84 mmol) in the dark for 24 h. Triethylamine (5 mL) was introduced, and the mixture was diluted with ether (500 mL), washed three times with saturated $NaHCO_3$ solution, and dried. Following solvent removal, the residue was passed down a column of basic alumina. There was obtained 8.0 g (89%) of **12** as a colorless oil: IR (neat, cm^{-1}) 2920, 1650, 1630, 1450; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (t, J = 2.7 Hz, 1 H), 5.12 (d, J = 1.2 Hz, 1 H), 3.54 (s, 3 H), 2.40–1.25 (series of m, 9 H), 0.86 (d, J = 6.7 Hz, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 155.2, 140.6, 119.0, 98.5, 54.0, 38.3, 35.1, 33.7, 27.0, 25.6, 25.3, 17.0, 15.7; MS *m/z* (M^+) calcd 192.1514, obsd 192.1495; $[\alpha]^{25}_D$ –31.5° (*c* 1.1, $CHCl_3$).

Methyl (1*R*,6*S*)-2-[(*tert*-butyldimethylsiloxy)methyl]-1,6-dimethyl-2-cyclohexene-1-propionate (14b). To a solution of *m*-chloroperoxybenzoic acid (18.0 g, 104 mmol) in benzene (500 mL) and hexane (800 mL) at 0 °C was added a solution of **12** (8.0 g, 41.7 mmol) in hexanes (100 mL) during 12 min. The white suspension was allowed to warm to room temperature during 30 min, silica gel (60 g of 240–400 mesh) was introduced, and stirring was continued for 40 min. This mixture was placed atop a column of silica gel and eluted with ether until the presence of aldehydo ester was no longer detected. The combined eluates were washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Solvent removal gave 9.0 g of **13**, a small aliquot of which was purified by silica gel chromatography (elution with 15% ethyl acetate in petroleum ether) for spectral analysis: IR (neat, cm^{-1}) 2940, 2720, 1750, 1695; ^1H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1 H), 6.81 (t, J = 3.4 Hz, 1 H), 3.62 (s, 3 H), 2.52–1.41 (series of m, 9 H), 1.05 (s, 3 H), 0.89 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 194.4, 174.1, 155.5, 146.5, 51.4, 38.7, 33.5, 29.6, 29.4, 26.7, 25.7, 20.1, 14.8; MS *m/z* (M^+) calcd 224.1413, obsd 224.1403.

The bulk of the above product was dissolved in cold (0 °C) methanol (150 mL), treated in small portions with sodium borohydride (4.5 g, 118 mmol), stirred for 20 min, and quenched with saturated NH_4Cl solution. The hydroxy ester was extracted into ethyl acetate, washed with brine, and dried. The concentrate was purified by chromatograpy on silica gel (elution with 25% ethyl acetate in petroleum ether) to give 5.5 g (59%) of **14a** as a colorless oil: IR (neat, cm^{-1}) 3415, 2940, 1740, 1440; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (t, J = 2.9 Hz, 1 H), 4.04 (s, 2 H), 3.63 (s, 3 H), 2.25–1.20 (series of m, 10 H), 0.93 (s, 3 H), 0.84 (d, J = 7.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.6, 142.1, 125.8, 62.8, 51.5, 39.4, 33.3, 31.2, 29.3, 26.3, 24.8, 21.2, 15.1; MS m/z (M^+) calcd 226.1569, obsd 226.1570; $[\alpha]^{22}_D$ –8.2° (c 2.4, CH_2Cl_2).

To a solution of **14a** (5.4 g, 23.9 mmol) in DMF (140 mL) was added *tert*-butyldimethylsilyl chloride (4.4 g, 29.2 mmol) and imidazole (3.1 g, 45.6 mmol). The reaction mixture was stirred for 2 h, diluted with ether, and washed sequentially with 5% HCl, saturated $NaHCO_3$ solution, and brine prior to drying and evaporation. Purification of the residue by silica gel chromatography (elution with 2% ethyl acetate in petroleum ether) afforded 7.4 g (91%) of **14b** as a colorless oil: IR (neat, cm^{-1}) 1750, 1480; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (t, J = 3.6 Hz, 1 H), 4.09 (m, 2 H), 3.64 (s, 3 H), 2.30–1.40 (series of m, 9 H), 0.94 (s, 3 H), 0.90 (s, 9 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.6, 141.1, 124.4, 63.4, 51.5, 39.3, 33.6, 31.3, 29.5, 26.6, 26.0, 25.0, 21.4, 18.4, 15.3, –5.4; MS m/z (M^+) calcd 340.2434, obsd 340.2440; $[\alpha]^{23}_D$ –12.2° (c 1.5, $CHCl_3$). Anal. Calcd for $C_{19}H_{36}O_3Si$: C, 67.01; H, 10.66. Found: C, 67.05; H, 10.70.

(1*R*,6*S*)-2-[(*tert*-Butyldimethylsiloxy)methyl]-1,6-dimethyl-2-cyclohexene-1-butyronitrile (16a). To a solution of **14b** (7.7 g, 22.6 mmol) in cold (0 °C) THF (200 mL) was carefully added lithium aluminum hydride (1.0 g, 26.3 mmol) and the reaction mixture was stirred at this temperature for 1 h before the reaction mixture was quenched by the addition of saturated $(NH_4)_2SO_4$ solution (10 mL). The solids were filtered off and rinsed with ethyl acetate. The combined filtrates were dried and concentrated to give 6.9 g (98%) of **15**: IR (neat, cm^{-1}) 3340, 2950, 1470; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (t, J = 3.7 Hz, 1 H), 4.08 (qd, J = 13.5, 2.0 Hz, 2 H), 3.57 (td, J = 6.3, 1.9 Hz, 2 H), 2.06–1.30 (series of m, 10 H), 0.92 (s, 3 H), 0.90 (s, 9 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.08 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 141.6, 123.2, 63.4, 63.3, 39.2, 33.4, 32.4, 27.4, 26.5, 25.9, 24.8, 21.5, 18.3, 15.1, –5.4; MS m/z (M^+) calcd 312.2485, obsd 312.2478; $[\alpha]^{23}_D$ –17.2° (c 0.32, CH_2Cl_2).

A cold (0 °C), magnetically stirred solution of **15** (6.9 g, 22.3 mmol) and triethylamine (6.5 mL, 46.5 mmol) in CH_2Cl_2 (150 mL) was treated dropwise with methanesulfonyl chloride (4.7 g, 41.5 mmol). After 30 min, the mixture was warmed to room temperature and washed with water and brine. The aqueous phases were reextracted with CH_2Cl_2 and the combined organic solutions were dried and concentrated. Silica gel chromatography of the residue (elution with 10% ethyl acetate in petroleum ether) furnished 7.0 g (81%) of the mesylate: IR (neat, cm^{-1}) 3030, 2950, 1465, 1180; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (br t, 1 H), 4.18 (t, J = 6.0 Hz, 2 H), 4.07 (qd, J = 3.5, 1.8 Hz, 2 H), 2.99 (s, 3 H), 2.04–1.39 (series of m, 9 H), 0.94 (s, 3 H), 0.91 (s, 9 H), 0.85 (d, J = 6.8 Hz, 3 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 141.1, 124.0, 70.5, 63.4, 39.2, 37.2, 33.5, 32.3, 26.4, 25.9, 24.7, 24.1, 21.5, 18.3, 15.1, –5.4; MS m/z (M^+) calcd 389.2182, obsd 389.2191.

A solution of the mesylate (6.6 g, 16.9 mmol) in DMF (150 mL) was treated with potassium cyanide (3.1 g, 47.7 mmol) and 18-crown-6 (0.5 g, 1.9 mmol), heated at 45 °C for 6 h, cooled, diluted with water, and extracted with ether. After drying and solvent evaporation, the residue was chromatographed on silica gel (gradient elution 5 → 40% ethyl acetate in petroleum ether) to give 4.6 g (85%) of **16a** and 140 mg (4%) of **16b**.

For **16a**: IR (neat, cm^{-1}) 2940, 2250; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (t, J = 3.4 Hz, 1 H), 4.06 (qq, J = 13.3, 1.8 Hz, 2 H), 2.27 (t, J = 6.7 Hz, 2 H), 2.00 (m, 2 H), 1.70–1.35 (m, 7 H), 0.93 (s, 3 H), 0.90 (s, 9 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 141.1, 124.3, 119.5, 63.5, 39.4, 35.9, 33.5, 26.4, 25.9, 24.7, 21.4, 20.4, 18.3, 17.6, 15.1, –5.4; MS m/z (M^+) calcd 321.2488, obsd 321.2461; $[\alpha]^{23}_D$ –20.5° (c 1.27, $CHCl_3$). Anal. Calcd for $C_{19}H_{35}NOSi$: C, 70.97; H, 10.98. Found: C, 70.95; H, 10.98.

(1*R*,6*S*)-2-(Hydroxymethyl)-1,6-dimethyl-2-cyclohexene-1-butyronitrile (16b). To a solution of **16a** (4.7 g, 14.6 mmol) in acetonitrile (100 mL) was added a solution of pyridinium fluoride in aqueous acetonitrile [prepared by addition of 5 mL of 48% HF (120 mmol) to pyridine (12 mL, 148 mmol) in 10 mL of acetonitrile]. The mixture was stirred at room temperature for 8 h, diluted with water, and extracted with ether. The combined organic phases were washed with 5% HCl and brine prior to drying and solvent evaporation. Chromatography of the residue on silica gel (elution with 30% ethyl acetate in petroleum ether) gave 3.0 g (98%) of **16b** as a colorless oil: IR (neat, cm^{-1}) 3410, 2940, 2255; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (t, J = 3.7 Hz, 1 H), 4.05 (m, 2 H), 2.29 (m, 2 H), 2.04 (m, 2 H), 1.72–1.35 (m, 8 H), 0.94 (s, 3 H), 0.86 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.6, 126.6, 119.8, 63.6, 39.7, 36.1, 33.5, 26.4, 24.9, 21.6, 20.6, 17.6, 15.3; MS m/z (M^+) calcd 207.1623, obsd 207.1623; $[\alpha]^{23}_D$ –31.6° (c 1.72, $CHCl_3$).

(1*R*,6*S*)-1,6-Dimethyl-2-(vinyloxy)-2-cyclohexene-1-butyronitrile (17) and Its Thermal Rearrangement. Alcohol **16b** (2.3 g, 11.1 mmol) was dissolved in freshly distilled ethyl vinyl ether (100 mL), treated with triethylamine (1 mL) and mercuric trifluoroacetate (1.6 g, 3.8 mmol), and stirred for 20 h at room temperature. Following solvent evaporation, the residue was taken up in petroleum ether, washed with 10% KOH and saturated $NaHCO_3$ solutions, and dried. Concentration afforded a yellow oil, chromatography of which on activity III basic alumina (elution with 7.5% ether in petroleum ether) afforded 1.8 g (70%) of **17** as a colorless oil: IR (neat, cm^{-1}) 2245, 1615; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (dd, J = 14.3, 6.7 Hz, 1 H), 5.84 (t, J = 3.7 Hz, 1 H), 4.21 (dd, J = 14.3, 2.0 Hz, 1 H), 4.14 (d, J = 1.7 Hz, 1 H), 4.05 (d, J = 1.7 Hz, 1 H), 4.00 (dd, J = 6.7, 2.0 Hz, 1 H), 2.27 (m, 2 H), 2.06 (m, 2 H), 1.68–1.44 (m, 7 H), 0.94 (s, 3 H), 0.87 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 151.4, 138.4, 130.3, 119.6, 86.9, 70.0, 39.8, 36.1, 33.4, 26.2, 25.0, 21.5, 20.6, 17.5, 15.2; MS m/z (M^+) calcd 233.1780, obsd 233.1776; $[\alpha]^{23}_D$ –27.2° (c 1.8, $CHCl_3$).

A solution of **17** (1.2 g, 5.1 mmol) in xylene (14 mL) was sealed in a thick-walled Pyrex tube under vacuum and heated at 210 °C for 14 h. The xylene was removed in vacuo, and the residue was subjected to MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether) to give 300 mg (25%) of syn isomer **19** and 850 mg (70%) of the anti isomer **18**.

For **19**: ^1H NMR (300 MHz, C_6D_6) δ 9.35 (t, J = 2.0 Hz, 1 H), 4.48 (d, J = 0.7 Hz, 1 H), 3.40 (d, J = 1.7 Hz, 1 H), 2.44 (m, 1 H), 2.17 (ddd, J = 16.5, 5.7, 2.0 Hz, 1 H), 1.83 (ddd, J = 16.5, 7.1, 2.0 Hz, 1 H), 1.51–0.72 (series of m, 11 H), 0.68 (s, 3 H), 0.56 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 200.5, 155.4, 119.3, 104.9, 47.7, 42.9, 38.1, 36.7, 34.2, 34.0, 30.5, 20.7, 19.7, 17.1, 15.8; $[\alpha]^{23}_D$ +61.5° (c 1.63, benzene).

For **18**: ^1H NMR (300 MHz, C_6D_6) δ 9.37 (t, J = 1.6 Hz, 1 H), 4.53 (s, 1 H), 4.50 (d, J = 1.6 Hz, 1 H), 2.36 (m, 1 H), 2.20 (ddd, J = 15.8, 7.7, 2.1 Hz, 1 H), 1.80 (m, 3 H), 1.48 (t, J = 6.7 Hz, 2 H), 1.30–0.81 (series of m, 7 H), 0.68 (s, 3 H), 0.67 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 200.3, 152.4, 119.5, 108.4, 47.5, 43.5, 39.1, 37.7, 33.7, 29.4, 28.7, 22.6, 20.4, 17.3, 15.4; $[\alpha]^{23}_D$ –75.8° (c 1.61, benzene).

As a consequence of the lability of **19**, the aldehyde was utilized directly without further characterization.

(1*R*,3*R*,6*S*)-3-[(*E*)-5-Formyl-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylenecyclohexanebutyronitrile (23). A solution of **19** (300 mg, 1.29 mmol) in dry THF (30 mL) was cooled to –78 °C and treated with 2-propenylmagnesium bromide (4 mL of 0.67 M in THF, 2.68 mmol). After being stirred for 1 h at –78 °C, the reaction mixture was quenched with saturated NH_4Cl solution, the product was extracted into ether, and the combined organic layers were dried and evaporated. MPLC of the residue (silica gel, elution with 15% ethyl acetate in petroleum ether) gave 56 mg of the less polar alcohol, 45 mg of the more polar alcohol, 144 mg of a mixed alcohol fraction, and 50 mg of unreacted **19** (combined yield of 83% based on recovered **19**).

For the less polar isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 4.93 (s, 1 H), 4.83 (d, J = 1.3 Hz, 1 H), 4.76 (d, J = 1.3 Hz, 1 H), 4.68 (s, 1 H), 4.18 (dd, J = 8.6, 4.8 Hz, 1 H), 2.33 (m, 3 H), 1.93 (m, 1 H), 1.82–1.38 (series of m, 11 H), 1.75 (s, 3 H), 0.93 (s, 3 H), 0.85 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 157.2, 148.3, 119.8, 110.7, 103.9, 73.3, 43.0, 38.9, 38.7, 37.0, 35.1, 33.4, 30.5, 20.5, 19.8, 17.7, 17.5, 16.0; $[\alpha]^{25}_D$ +42.6° (c 1.45, $CHCl_3$).

For the more polar isomer: IR (neat, cm^{-1}) 3450, 2940, 2260, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 4.93 (t, J = 0.8 Hz, 1 H), 4.83 (t, J = 1.5 Hz, 1 H), 4.73 (d, J = 1.4 Hz, 1 H), 4.69 (s, 1 H), 4.18 (dd, J = 7.5, 5.8 Hz, 1 H), 2.33 (m, 3 H), 1.85–1.40 (series of m, 12 H), 1.73 (s, 3 H), 0.93 (s, 3 H), 0.83 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 156.7, 147.8, 119.7, 111.4, 104.2, 74.3, 42.9, 39.0, 38.7, 37.1, 35.8, 34.2, 30.4, 20.5, 19.8, 17.7, 16.9, 15.9; MS m/z (M^+) calcd 275.2249, obsd 275.2235; $[\alpha]^{23}_D$ +9.5° (c 1.7, $CHCl_3$). Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61. Found: C, 78.42; H, 10.70.

The less polar alcohol (83 mg, 0.30 mmol) was dissolved in freshly distilled ethyl vinyl ether (8 mL), treated with triethylamine (50 μL) and mercuric trifluoroacetate (65 mg, 0.15 mmol), and stirred at room temperature for 24 h. Following dilution with petroleum ether, the reaction

mixture was washed with 10% KOH and saturated $NaHCO_3$ solutions and then dried and evaporated. Chromatography of the residue on activity III basic alumina (elution with 3% ethyl acetate in petroleum ether) afforded 75 mg (84%) of the vinyl ether: IR (neat, cm^{-1}) 3080, 2930, 2250, 1635; ^1H NMR (300 MHz, C_6D_6) δ 6.28 (dd, J = 14.1, 6.6 Hz, 1 H), 4.86 (d, J = 0.8 Hz, 1 H), 4.83 (t, J = 1.5 Hz, 1 H), 4.71 (d, J = 1.5 Hz, 1 H), 4.56 (s, 1 H), 4.47 (dd, J = 14.1, 1.3 Hz, 1 H), 4.23 (dd, J = 8.4, 5.3 Hz, 1 H), 4.01 (dd, J = 6.6, 1.3 Hz, 1 H), 2.33 (m, 1 H), 2.08 (m, 1 H), 1.76 (m, 1 H), 1.63 (s, 3 H), 1.48–0.73 (series of m, 11 H), 0.71 (s, 3 H), 0.62 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.8, 150.9, 145.4, 119.4, 113.1, 104.4, 89.0, 81.2, 43.0, 39.0, 37.7, 37.0, 35.1, 33.7, 30.8, 20.5, 19.9, 17.1, 16.9, 16.0; MS m/z (M^+) calcd 301.2406, obsd 301.2435; $[\alpha]^{23}_D$ +21.7° (c 1.63, $CHCl_3$).

Analogous processing of the more polar alcohol (78 mg) gave rise to 69 mg (81%) of the epimeric vinyl ether: ^1H NMR (300 MHz, C_6D_6) δ 6.26 (dd, J = 14.1, 6.5 Hz, 1 H), 4.87 (d, J = 0.7 Hz, 1 H), 4.82 (t, J = 1.5 Hz, 1 H), 4.69 (d, J = 1.3 Hz, 1 H), 4.61 (s, 1 H), 4.47 (dd, J = 14.1, 1.3 Hz, 1 H), 4.21 (dd, J = 8.2, 5.0 Hz, 1 H), 4.01 (dd, J = 6.6, 1.3 Hz, 1 H), 2.31 (m, 1 H), 1.85–1.65 (m, 3 H), 1.63 (s, 3 H), 1.48–0.76 (series of m, 10 H), 0.73 (s, 3 H), 0.62 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.5, 151.1, 145.2, 119.3, 113.1, 104.7, 88.9, 82.4, 43.0, 39.1, 37.8, 37.1, 36.0, 34.5, 30.7, 20.5, 20.0, 17.1, 16.8, 16.0; $[\alpha]^{23}_D$ +15.4° (c 1.43, $CHCl_3$).

A solution of either of the above vinyl ethers (or a mixture thereof, 157 mg, 0.52 mmol) in benzene (2 mL) was sealed into a thick-walled Pyrex tube under vacuum and heated at 170 °C for 20 h. After solvent evaporation, purification by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether) furnished 144 mg (92%) of **23** as a colorless oil: ^1H NMR (300 MHz, C_6D_6) δ 9.34 (t, J = 7.1 Hz, 1 H), 5.07 (m, 1 H), 4.73 (d, J = 1.4 Hz, 1 H), 4.63 (s, 1 H), 2.23–1.70 (series of m, 7 H), 1.52–0.78 (series of m, 11 H), 1.42 (s, 3 H), 0.76 (s, 3 H), 0.65 (d, J = 6.3 Hz, 3 H); ^{13}C (75 MHz, C_6D_6) ppm 200.5, 156.8, 134.0, 124.8, 119.4, 104.7, 42.9, 42.1, 39.7, 38.4, 36.9, 33.5, 32.3, 32.1, 30.8, 21.1, 19.9, 17.1, 16.2, 16.0; MS m/z (M^+) calcd 301.2406, obsd 301.2408; $[\alpha]^{23}_D$ +32.1° (c 1.59, benzene). Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.37. Found: C, 79.43; H, 10.34.

(1*R*,3*R*,6*S*)-3-[(*E*)-5-(1,3-Dioxolan-2-yl)-3-methyl-2-pentenyl]-1,6-dimethyl-2-methylenecyclohexanebutyronitrile (24). A cold (–78 °C), magnetically stirred solution of **23** (120 mg, 0.40 mmol) in CH_2Cl_2 (7 mL) was treated with 1,2-bis(trimethylsiloxy)ethane (0.45 mL, 1.83 mmol) and trimethylsilyl triflate (30 μL, 0.15 mmol). After 5 h at –78 °C, triethylamine (0.3 mL) was introduced and the mixture was warmed to room temperature, diluted with ether, and washed with saturated $NaHCO_3$ solution and brine prior to drying and solvent evaporation. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) provided 120 mg (87%) of **24** as a colorless oil: IR (neat, cm^{-1}) 2255, 1635; ^1H NMR (300 MHz, C_6D_6) δ 5.26 (m, 1 H), 4.86 (t, J = 4.8 Hz, 1 H), 4.76 (s, 1 H), 4.60 (s, 1 H), 3.55 (m, 2 H), 3.39 (m, 2 H), 2.31–1.74 (series of m, 8 H), 1.80–1.45 (series of m, 10 H), 1.57 (s, 3 H), 0.74 (s, 3 H), 0.64 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.8, 135.2, 124.1, 119.4, 104.6, 64.9, 42.8, 39.7, 38.4, 36.9, 34.6, 33.5, 33.2, 32.3, 30.9, 21.0, 19.9, 17.1, 16.3, 16.0; MS m/z (M^+) calcd 345.2668, obsd 345.2685; $[\alpha]^{23}_D$ +25.3° (c 1.5, $CHCl_3$). Anal. Calcd for $C_{22}H_{35}NO_2$: C, 76.48; H, 10.21. Found: C, 76.36; H, 10.27.

(1*R*,4*Z*,8*E*,11*R*,14*S*)-1,8,14-Trimethyl-15-methylenebicyclo[9.3.1]pentadeca-4,8-diene-4-carbonitrile (26). A solution of **24** (104 mg, 0.30 mmol) in anhydrous THF (3 mL) was cooled to –78 °C, treated with lithium diisopropylamide (1.7 mL of 0.4 M in THF, 0.68 mmol), stirred at –78 °C for 75 min, and admixed with a solution of diethyl chlorophosphate (60 mg, 0.35 mmol) in THF (1.5 mL). This mixture was stirred at –78 °C for 1 h, quenched with saturated NH_4Cl solution, and diluted with ethyl acetate. The organic solution was washed with brine, dried, and evaporated to leave a residue, purification of which by silica gel chromatography (elution with 50% ethyl acetate in petroleum ether) gave 125 mg (86%) of **25** as a colorless oily mixture of diastereomers: IR (neat, cm^{-1}) 2245, 1630, 1265; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (t, J = 6.4 Hz, 1 H), 4.84 (t, J = 4.8 Hz, 1 H), 4.73 (m, 2 H), 4.24 (m, 4 H), 3.96 (m, 2 H), 3.83 (m, 2 H), 2.87 (m, 1 H), 2.22–1.63 (series of m, 12 H), 1.61 (s, 3 H), 1.44 (m, 4 H), 1.38 (t, J = 7.1 Hz, 6 H), 0.94 (s, 3 H), 0.84 (t, J = 5.8 Hz, 3 H); MS m/z (M^+) calcd 481.2957, obsd 481.2968; $[\alpha]^{23}_D$ +14.5° (c 1.21, $CHCl_3$).

The above acetal (124 mg, 0.30 mmol) was dissolved in acetone–water (4:1, 10 mL), treated with p-toluenesulfonic acid (150 mg, 0.78 mmol), stirred at room temperature for 72 h, diluted with water, and extracted with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$ solution and brine prior to drying and solvent evaporation. Silica gel chromatography of the residue (elution with 50% ethyl acetate in petroleum ether) gave the aldehyde (106 mg, 94%) as a colorless oily mixture of diastereomers: IR (neat, cm^{-1}) 2250, 1730, 1635; ^1H NMR (300 MHz, C_6D_6) δ 9.34 (br s, 1 H), 5.05 (m, 1 H), 4.82 (m, 2 H), 3.94 (m, 4 H), 2.54 (m, 1 H), 2.28–1.44 (series of m, 12 H), 1.41 (s, 3 H), 1.38–1.04 (m, 4 H), 1.01 (td, J = 7.0, 2.9 Hz, 6 H), 0.83 (s, 3 H), 0.73 (d, J = 5.9 Hz, 1.5 H), 0.70 (d, J = 5.9 Hz, 1.5 H); MS m/z (M^+ + 1) calcd 438.2773, obsd 438.2762.

A suspension of potassium carbonate (155 mg, 1.12 mmol) and 18-crown-6 (300 mg, 1.13 mmol) in toluene (12 mL) was treated slowly with a solution of the above aldehyde (74 mg, 0.17 mmol) in toluene (6 mL) during 12 h. After an additional 12 h of stirring, the mixture was diluted with ether, washed with saturated NH_4Cl solution and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 3% ethyl acetate in petroleum ether) gave 18 mg (38%) of **26** as a colorless oil: ^1H NMR (300 MHz, C_6D_6) δ 5.73 (t, J = 7.4 Hz, 1 H), 5.12 (br s, 1 H), 4.84 (s, 1 H), 4.81 (s, 1 H), 2.41–2.05 (m, 6 H), 1.90 (t, J = 5.9 Hz, 2 H), 1.79 (m, 2 H), 1.53 (s, 3 H), 1.49–0.89 (series of m, 6 H), 0.86 (s, 3 H), 0.75 (d, J = 5.8 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 156.1, 146.0, 132.8, 125.1, 117.8, 116.1, 105.2, 43.0, 39.7, 38.4, 37.9, 36.6, 34.6, 32.4, 30.9, 29.2, 28.6, 21.4, 16.3, 16.0; MS m/z (M^+) calcd 283.2300, obsd 283.2317; $[\alpha]^{23}_D$ +26.5° (c 1.25, $CHCl_3$).

Methyl (1*R*,4*Z*,8*E*,11*R*,14*S*)-1,8,14-Trimethyl-15-methylenebicyclo[9.3.1]pentadeca-4,8-diene-4-carboxylate (27). A cold (–78 °C), magnetically stirred solution of **26** (9 mg, 0.032 mmol) in toluene (1.5 mL) and ether (0.15 mL) was treated with Dibal-H (0.06 mL of 1.0 M in toluene, 0.06 mmol) and allowed to warm to 0 °C after 30 min. After 20 min at 0 °C, the reaction mixture was quenched with methanol (4 drops) and triethylamine (3 drops). The intermediate imine was hydrolyzed with 0.6 g of silica gel. The mixture was filtered through a short column of silica gel (elution with 5% ethyl acetate in petroleum ether), and the eluate was concentrated in vacuo to provide 8 mg (88%) of the aldehyde as a colorless, air-sensitive oil that was directly oxidized: ^1H NMR (300 MHz, C_6D_6) δ 10.02 (s, 1 H), 6.22 (t, J = 7.9 Hz, 1 H), 5.20 (m, 1 H), 5.16 (s, 1 H), 4.90 (s, 1 H), 2.45 (m, 1 H), 2.23 (m, 6 H), 1.89 (m, 2 H), 1.77 (m, 2 H), 1.60–1.02 (series of m, 5 H), 1.45 (s, 3 H), 0.97 (s, 3 H), 0.95 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 190.1, 156.0, 147.4, 141.9, 132.1, 126.1, 105.6, 43.3, 39.7, 38.7, 38.2, 37.9, 34.8, 32.5, 31.1, 25.5, 23.4, 21.9, 16.3, 16.1.

A magnetically stirred solution of the aldehyde (8 mg, 0.028 mmol) and 2-methyl-2-butene (0.13 mL) in *tert*-butyl alcohol (1.3 mL) was treated with a solution of sodium chlorite (28 mg, 0.31 mmol) and sodium dihydrogen phosphate (30 mg, 0.25 mmol) in 0.5 mL of water. After 10 h of stirring, the resulting yellow mixture was taken up in water (2 mL), acidified to pH 3 with 5% HCl, and extracted with ethyl acetate. The combined organic extracts were washed with brine (3×), dried, and evaporated. Chromatography of the residue on silica gel (elution with 40% ethyl acetate in petroleum ether) gave 6.5 mg of acid, which was dissolved in ether (1 mL), treated with a slight excess of ethereal diazomethane, and again chromatographed (silica gel, elution with 5% ethyl acetate in petroleum ether). There was isolated 3.5 mg (40% overall) of **27** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1710, 905; ^1H NMR (300 MHz, C_6D_6) δ 5.95 (t, J = 7.0 Hz, 1 H), 5.32 (m, 1 H), 5.14 (s, 1 H), 4.99 (s, 1 H), 3.44 (s, 3 H), 2.76 (m, 2 H), 2.49 (m, 2 H), 2.25 (m, 3 H), 2.09 (t, J = 5.8 Hz, 2 H), 1.84 (m, 2 H), 1.57 (s, 3 H), 1.55–1.11 (m, 5 H), 0.97 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 168.2, 156.1, 142.1, 133.5, 133.3, 124.8, 105.5, 50.6, 43.3, 39.8, 39.0, 38.2, 34.6, 32.5, 31.2, 29.5, 26.9, 21.9, 16.3, 16.2; MS m/z (M^+) calcd 316.2402, obsd 316.2388; $[\alpha]^{23}_D$ +54.4° (c 1.8, $CHCl_3$).

Methyl (1*R*,4*Z*,8*R*,9*S*,11*R*,14*S*)-8,9-Epoxy-1,8,14-trimethyl-15-methylenebicyclo[9.3.1]pentadec-4-ene-4-carboxylate (28). To a solution of **27** (10 mg, 0.031 mmol) in CH_2Cl_2 (3 mL) was added m-chloroperbenzoic acid (7.1 mg, 0.041 mol) and $NaHCO_3$ (6 mg, 0.072 mmol). The mixture was stirred at room temperature for 1 h, diluted with ether, and washed with saturated $NaHCO_3$ solution and brine prior to drying and evaporation. The residue was purified by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether), affording 3.5 mg (33%) of **28** as a colorless gum: ^1H NMR (300 MHz, C_6D_6) δ 5.86 (m, 1 H), 5.06 (s, 1 H), 4.94 (s, 1 H), 3.42 (s, 3 H), 2.90 (dd, J = 7.6, 3.0 Hz, 1 H), 2.76–1.24 (series of m, 16 H), 1.22 (s, 3 H), 0.93 (s, 3 H), 0.83 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 168.1, 156.7, 141.0, 133.6, 105.1, 62.2, 59.2, 50.8, 43.4, 39.0, 38.4, 38.3, 38.0, 35.2, 33.1, 30.9, 29.3, 25.8, 21.0, 17.0, 16.1; MS m/z (M^+) calcd 332.2351, obsd 332.2352; $[\alpha]^{23}_D$ +32.2° (c 0.5, $CHCl_3$).

Methyl (1*R*,4*Z*,8*S*,11*R*,14*S*)-8,9-Epoxy-1,8,14-trimethyl-15-methylenebicyclo[9.3.1]pentadec-4-ene-4-carboxylate (29). A. By Epoxidation of 27. A solution of **27** (10 mg, 0.032 mmol) in aqueous dioxane (9:1, 2 mL) was treated with iodine (12 mg, 0.047 mmol) and silver(I) oxide (11 mg, 0.047 mmol), stirred at room temperature for 5 h (color turned from red to yellow), and diluted with ether. This mixture was washed twice with water, dried, and concentrated. Chromatographic purification of the residue (silica gel, elution with 10% ethyl acetate in petroleum ether) furnished 2.9 mg (28%) of **29** as a colorless gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (dd, J = 12.0, 3.0 Hz, 1 H), 5.10 (d, J = 1.6 Hz, 1 H), 4.95 (d, J = 1.8 Hz, 1 H), 3.74 (s, 3 H), 3.14 (br d, J = 12.2 Hz, 1 H), 2.79–1.14 (series of m, 16 H), 1.22 (s, 3 H), 0.90 (s, 3 H), 0.88 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.9, 150.6, 143.9, 132.6, 116.5, 60.0, 58.8, 50.6, 43.7, 42.2, 41.3, 39.4, 39.1, 34.1, 31.0, 28.4, 26.0, 25.4, 24.0, 17.1, 16.4; MS m/z (M^+) calcd 332.2351, obsd 332.2362; $[\alpha]^{23}_D$ –67.4° (c 0.27, $CHCl_3$).

B. By Saponification of (+)-Cleomeolide. (+)-Cleomeolide (15 mg) was gently refluxed with 2 mL of 3.5% KOH in methanol for 3 h. The methanol was evaporated under reduced pressure, and the residue was dissolved in water (2 mL), acidified carefully to pH 8 with 5% HCl, and returned to pH 6 with sodium acetate–acetic acid buffer. This mixture was extracted with ethyl acetate, and the carboxylic acid contained therein was esterified with diazomethane. Purification in the predescribed manner gave 9 mg (60%) of **29**, which proved spectroscopically identical to the material produced in part A. The optical rotation of this product was somewhat higher: $[\alpha]^{23}_D$ –71.6° (c 0.55, $CHCl_3$).

(+)-Cleomeolide (1). A solution of **29** (3 mg) in 1 mL of 3.5% KOH in methanol was gently refluxed for 3 h. The methanol was removed in vacuo, and the residue was taken up in water (2 mL) and acidified to pH 2 with 5% HCl. THF (1 mL) was added to dissolve the precipitate, stirring was maintained for 1 h, and the product was extracted into ether. Drying and evaporation of the combined organic phases furnished 1 mg of **1**, spectroscopically identical with the natural material provided by Dr. Manchand.

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Supplementary Material Available: Final calculated atomic coordinates for **27** and **27′** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.