A Unified Strategy for the Stereocontrolled Construction of Structurally Unusual Sesquiterpene Lactones. Asymmetric Synthesis of Vulgarolide and Deoxocrispolide

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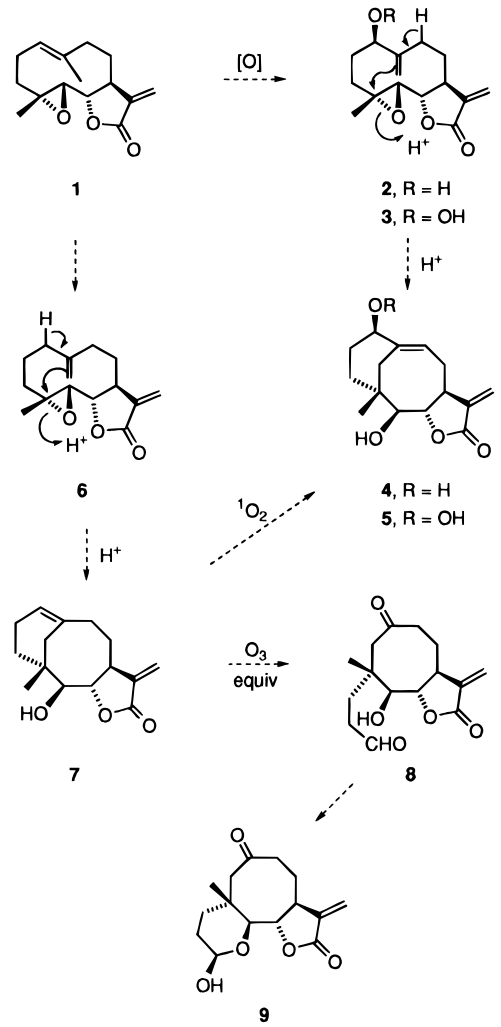
Abstract: The bicyclic ketone (+)-**17b** reacts with vinylmagnesium bromide from its exo face, thus enabling exploitation of the anionic oxy-Cope rearrangement and direct alkylation of the enolate so formed with ethyl iodoacetate to provide **24** in an efficient, stereocontrolled manner. Tricyclic lactone **26b**, readily produced from **24**, proved to be a common precursor to both synthetic targets. The construction of vulgarolide (**9**) proceeded by transforming the SEM group in **26b** into a mesylate for the purpose of conversion to epoxy acid **39** in advance of oxidative cleavage of the double bond. This transformation resulted in direct conversion to **9** and its epimer **42**. Central to the companion synthesis of deoxocrispolide (**4**) was the ability of **37** to undergo the Michael addition of methoxide ion and of **54** to experience regiocontrolled dehydration to bridgehead olefin **55** in a protocol that involves the smooth translocation of bridgehead unsaturation with concomitant functionalization as an allylic alcohol.

Detailed chemosystematic investigation by Appendino of *Tanacetum vulgare*[1−3] and by Bohlmann of several *Eriocephalus* species[4] during the past two decades has resulted in the isolation and characterization of several structurally unique and distinctive sesquiterpene lactones. As a direct result of their efforts, crispolide (**5**)[1,2] and deoxocrispolide (**4**)[4] are now recognized to possess an unprecedented 4,14-cyclogermacrane framework. Although the biosynthetic origins of these substances remain to be elucidated, **4** and **5** are believed to arise from parthenolide (**1**)[5] and the 4,5-epoxide of artemorin (**2**),[6] respectively (Scheme 1).[3,4] The plausibility of forming allylic hydroperoxide **3** has been identified, although some concern has been raised that this labile functionality may not survive the subsequent acid-catalyzed transannular cyclization. Alternatively, **1** could experience double bond isomerization to **6** in advance of singlet oxygenation (or alternative ene reaction) with migration of the bridgehead double bond. The involvement of **7** holds significance in that a biooxidative step formally related to ozonolysis[7,8] would eventuate in the formation of **8**, the logical precursor to vulgarolide (**9**).[3] Thus, the novel highly rearranged isoprenoid nature of **9**, constituted of a cyclooctanone core to which a tetrahydropyran and a γ-lactone ring are serially fused in trans−anti−trans fashion, may be intimately linked to the cyclogermacranes **4** and **5**.

Scheme 1



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[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1996.

(1) Appendino, G.; Gariboldi, P.; Nano, G. M. *Phytochemistry* **1982**, *21*, 1099.

(2) Chiari, G.; Appendino, G.; Nano, G. M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 263.

(3) Appendino, G.; Gariboldi, P.; Valle, M. G. *Gazz. Chim. Ital.* **1988**, *118*, 55.

(4) Zdero, C.; Bohlmann, F.; Müller, M. *Phytochemistry* **1987**, *26*, 2763.

(5) Bawdekar, A. S.; Kelkar, G. R.; Bhattacharyya, S. C. *Tetrahedron Lett.* **1966**, 1225.

(6) Geismann, T. *Phytochemistry* **1970**, *9*, 2377.

(7) (a) Bohlmann, F.; Misra, L. N.; Jakupovic, J.; King, R. M.; Robinson, H. *Phytochemistry* **1985**, *24*, 1315. (b) Kobayashi, M.; Son, B. W.; Kyogotu, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1984**, *32*, 1667. (c) Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H. *Liebigs Ann. Chem.* **1984**, 503.

(8) Appendino, G.; Gariboldi, P.; Calleri, M.; Chiari, G.; Viterbo, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2705.

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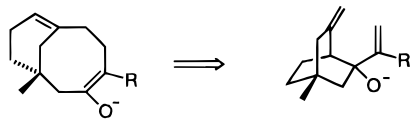
The synthesis of cyclooctanoid natural products continues to be the focal point of a great deal of research.[9] The unprecedented structural features of **4**, **5**, and **9**, when coupled to the likelihood that their elaboration might be accomplished via a common intermediate, provided the stimulus for advancing on these targets. Cognizance was taken of assimilating certain of the biogenetic hypotheses outlined in Scheme 1 into an otherwise concise tactical approach.[10]

Discussion of Results

Charge-Accelerated Sigmatropy as the Introductory Maneuver. β,γ-Unsaturated ketone **10**, readily available from the known diketone[11a,b] by reaction with 1 equiv of methylenetriphenylphosphorane,[11c] was chosen as a probe substrate for evaluating convergent application of the anionic oxy-Cope rearrangement.[12] Retrosynthetic considerations had targeted the potential benefits of generating enolate anion **A** directly from alkoxide **B**. A provocative feature of ketone **10** relates to the

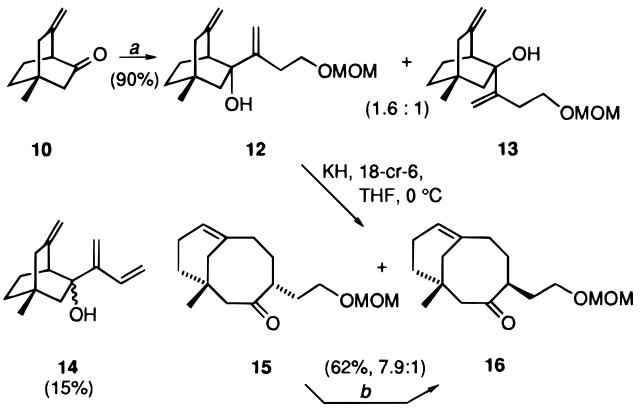


A **B**

directionality and degree of π-facial selectivity attainable during 1,2-addition to its carbonyl group. The presence of an exocyclic double bond proximate to the exo surface serves to remove a methylene proton found below-plane. The resultant dissymmetry was anticipated to favor approach of a vinyl anion syn to the preexisting unsaturation, thereby positioning the two π bonds within bonding distance as required for a subsequent sigmatropic event.

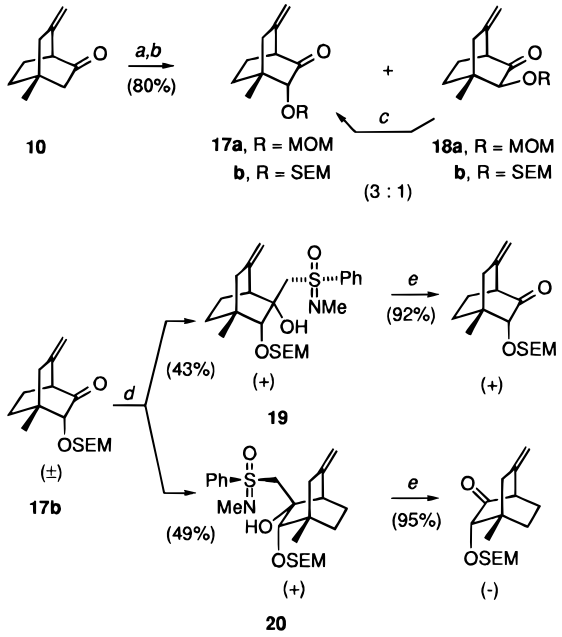
A nucleophile adequately substituted to encompass most of the lactonic substructure was first considered. Selected from among several options, bromide **11**[13] was transformed into the cerium reagent[14] by halogen−lithium exchange and exposure to anhydrous $CeCl_3$ (Scheme 2). Optimal reaction conditions involving its coupling to **10** provided a 1.6:1 mixture of the diasteromeric adducts **12** and **13** in 90% yield. Direct exposure of unpurified **12** to the action of KH and 18-crown-6 in THF at 0 °C followed by an ammonium chloride quench afforded ketones **15** and **16** (ratio 7.9:1; 62%) as well as diene **14** (15%). The latter byproduct presumably arises via intramolecular elimination of the OMOM group, thereby signaling that a change in the structural nature of the nucleophilic reagent would be desirable.

Scheme 2



[a] BrC(=CH_2)CH_2CH_2OMOM (**11**), *t*-BuLi, THF, −78 °C; $CeCl_3$, THF. [b] K_2CO_3, MeOH.

Scheme 3



[a] LDA, MoOPD, THF, −23 °C or LDA, Me_3SiCl, THF, −78 °C; dimethyldioxirane, acetone, CH_2Cl_2, −78 °C → rt; citric acid, CH_3OH. [b] MOMCl or SEMCl, $(i\text{-Pr})_2$NEt. [c] K_2CO_3, MeOH. [d] (*S*)-(+)-PhS(O)$(NCH_3)CH_3$, *n*-BuLi, THF, −78 °C. [e] Toluene, reflux.

It was of further interest to ascertain the relative stereochemistry of **15** and **16**. Although 2D NMR techniques failed to provide unequivocal assignments, the epimerization of **15** to **16** under basic conditions was considered tacit proof that the minor product was the more thermodynamically stable β (pseudoequatorial) isomer. In light of these facts, two corrective measures had to be implemented: (a) addition to **10** or a derivative thereof must be made highly exo stereoselective, and (b) the side chain that is to serve as the lactone ring should be introduced *after* the oxy-Cope rearrangement in order to capitalize on the kinetic advantage enjoyed by enolate anion **A** for electrophile capture from the β direction.

On this basis, we came to favor a more direct route wherein the bicyclic ketone would be oxygenated as in **17** (Scheme 3). The rationale behind the choice of **17** was to direct by steric means exclusive exo attack by the vinyl anion, to reduce the acidity of the α-carbonyl proton sufficiently that Grignard or lithium reagents could be used directly,[15] and to have an oxygen

(9) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

(10) A preliminary communication describing a portion of this work has appeared: Paquette, L. A.; Koh, D.; Wang, X.; Prodger, J. C. *Tetrahedron Lett.* **1995**, *36*, 673.

(11) (a) Paquette, L. A.; Poupart, M.-A. *J. Org. Chem.* **1993**, *58*, 4245. (b) Poupart, M.-A.; Lassalle, G.; Paquette, L. A. *Org. Synth.* **1990**, *69*, 173. (c) Paquette, L. A.; Maleczka, R. E., Jr., Qiu, F. *J. Org. Chem.* **1991**, *56*, 2455.

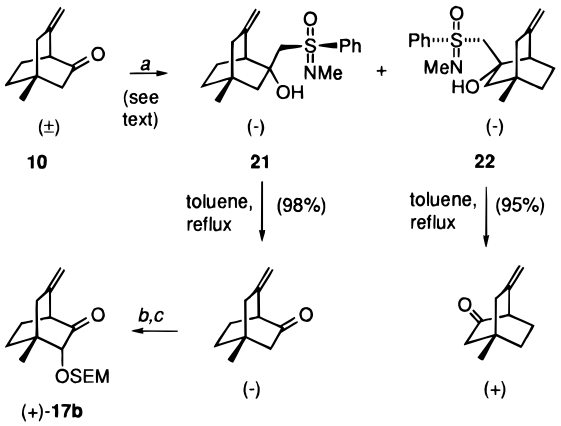
(12) (a) Paquette, L. A. *Synlett* **1990**, 67. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609.

(13) Bromide **11** was prepared by hydrobromination of 3-buyyn-1-ol [Cousseau, J. *Synthesis* **1980**, 805] followed by MOM protection of the hydroxyl substituent.

(14) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *285*, C21. (c) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763. (d) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (e) Denmark, S. E; Edwards, J. P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 569. (f) Doyon, J.; He, W.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 2033 and earlier references cited therein.

(15) Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 889.

Scheme 4



[a] (*R*)-(−)-PhS(O)(NCH$_3$)CH$_3$, *n*-BuLi, THF, −78 °C. [b] LDA, Me$_3$SiCl, THF, −78 °C; dimethyldioxirane, acetone, CH$_2$Cl$_2$, −78 °C → rt. [c] SEMCl, (*i*-Pr)$_2$NEt, CH$_2$Cl$_2$.

atom strategically disposed early in the scheme with a configuration suitably conducive to implementation of the end game (see below).

The α-hydroxylation of **10** could be realized efficiently either by direct exposure of the enolate anion to MoOPD[16,17] or by chemoselective oxidation of the reactive silyl enol ether with dimethyldioxirane.[18] The resulting products were protected as their MOM[19] or SEM ethers,[20] thereby allowing as well for facile chromatographic separation of the epimers. While the predominance of endo isomers **17a** and **17b** occasioned no surprise,[15,18,21] the relative ease with which **18a**/**18b** could be transformed into their endo counterparts via equilibration with potassium carbonate in methanol was a welcome bonus.

The resolution of **17b** was accomplished by condensation with the anion of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine.[22] These conditions delivered a readily separable mixture of diastereoisomers **19** (43%) and **20** (49%). The very heavy predominance of exo bonding was a favorable case scenario. When **10** had earlier been subjected to identical treatment with the (−)-(*R*)-sulfoximine (Scheme 4), not only were **21** (16%) and **22** (35%) formed but 27% of an endo isomer mixture resulted also. Consequently, maximum conciseness was realized according to the events in Scheme 3. The absolute configuration of **22** was determined by X-ray crystallographic analysis (Figure 1). On this basis, the structural features of the two enantiomers of **10**, obtained by heating the respective sulfoximine adducts **21** and **22** in toluene at 130 °C, could be defined unambiguously. Furthermore, the information gained by transforming (−)-**10** into (+)-**17b** in the predescribed manner was adequate to permit definition of the SEM-substituted enantiomers in absolute stereochemical terms as well.

From this stage onward, racemic **17a** was used for pilot experiments. Once individual steps were determined to be workable, we turned to enantiopure (+)-**17b** in order to provide configurationally pure intermediates.

Exposure of **17** directly to vinylmagnesium bromide in THF at low temperature resulted in highly efficient formation of alcohol **23**. The necessary indication that exo attack had again

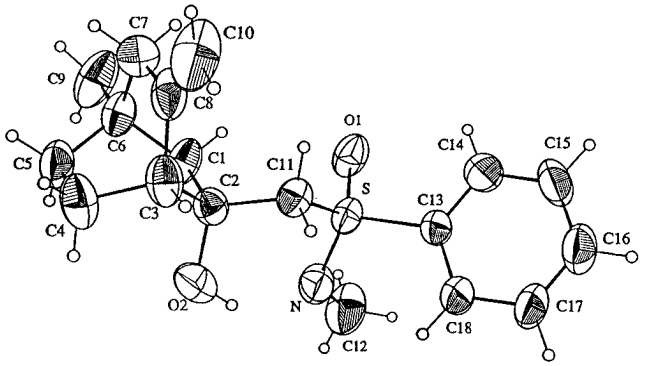
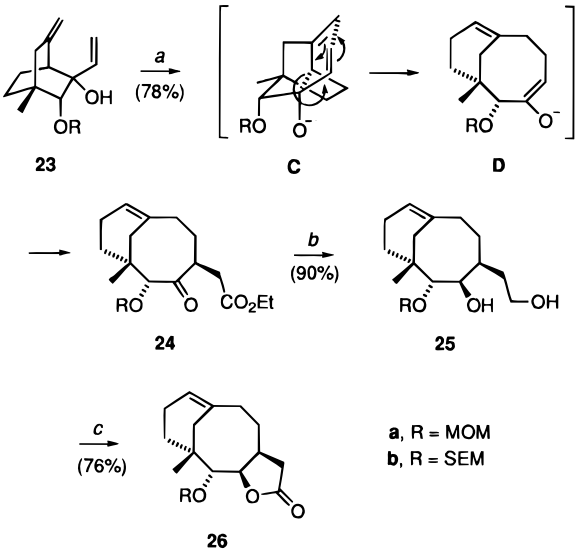


Figure 1. Computer-generated perspective drawing of **22** as determined by X-ray crystallography. The atom numbering is arbitrary.

Scheme 5



[a] KN(SiMe$_3$)$_2$, THF, Δ, 20 min; ICH$_2$CO$_2$Et, HMPA, THF, −78 °C → rt. [b] LiAlH$_4$, THF. [c] TPAP, NMO, 4 Å MS, CH$_2$Cl$_2$, rt.

prevailed arose from the subsequent observation that anionic oxy-Cope rearrangement of **23a** and **23b** proceeded with remarkable facility. Thus, treatment of either compound with a modest excess of potassium hydride or potassium hexamethyldisilazide in THF at the reflux temperature resulted in isomerization within a short time. An enhancement in the level of charge separation through addition of 18-crown-6 was not required. The conversion to enolate anion **D** is formulated as most plausibly arising by way of the six-centered chairlike transition state **C** (Scheme 5).[23] Introduction of the acetic acid unit was conveniently realized by the addition of ethyl iodoacetate to the enolate anion solution so formed. High diastereoselectivity was operational, resulting in the formation of keto ester **24**. The stereochemistry of **24** was made apparent by NOE studies. That the proton geminal to the OMOM or OSEM substituent is proximal to the one-carbon bridge was apparent from an observed 3% signal enhancement of its syn proton on double irradiation. In contrast, no observable effect was generated at the absorption associated with the proton positioned on the carbon also substituted by the acetic ester group. The relationship of this pair of protons must therefore be trans.

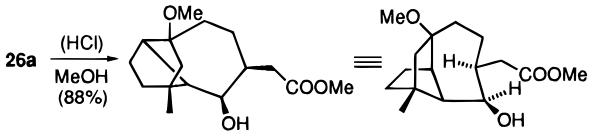
The conversion of **24** to lactone **26** was most conveniently initiated by reduction to diol **25** with lithium aluminum hydride. Perruthenate oxidation[24] of **25** resulted in smooth cyclization

(16) Anderson, J. C.; Smith, S. C. *Synlett* **1990**, 107.
(17) The explosive nature of MoOPD caused us to abandon the use of this reagent. Consult *Chem. Eng. News* **1992**, *70* (No. 37), p 2.
(18) Adam, W.; Prechtl, F. *Chem. Ber.* **1991**, *124*, 2369.
(19) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.
(20) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
(21) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
(22) (a) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021. (b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418.

(23) Strictly speaking, the structural features of **24** are insufficient to distinguish between the actual operation of a chair or boat transition state. The point is therefore a mute one. However, the normal energetic ordering of the two geometric options favors the chairlike option.

to give **26**. Consequently, a very direct six-step route from the previously described **10** to a tricyclic cyclooctanoid lactone related to **7** had been successfully implemented. Attention is called to the fact that both CH−O bonds in **26** possess configuration opposite that of the corresponding stereogenic centers in **7**. As will become apparent in the sequel, this preplanned structural modification is a logical outgrowth of our synthetic design.

Transannular Ring Closures and Other Distractions. A large number of methods have been reported for the removal of MOM protecting groups.[25] When these conditions were applied to **26a**, none resulted in isolation of the alcohol. Subsequent more detailed investigation revealed that these observations were due to a proclivity on the part of this lactone for transannular cyclization under acidic conditions. This property was best revealed by stirring **26a** in methanol containing a trace of hydrochloric acid, this acidic environment inducing near-quantitative conversion into **27**. That this ester had



27

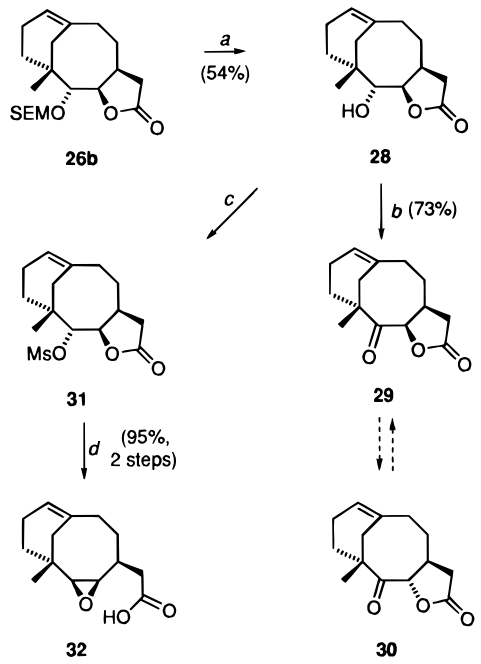
experienced internal ring formation was confirmed by the absence of the original double bond and the incorporation of a tertiary methoxyl group concurrent with loss of the MOM substituent. Further, the 300-MHz ^{1}H NMR spectrum displayed the α-carbinol proton as a doublet of doublets coupled to both the vicinal proton α to the ester and the adjacent bridging C*H*.

In contrast, the deprotection of **26b** with tetrabutylammonium fluoride in HMPA at 80 °C[20] proceeded without event to provide **28** (Scheme 6). Although keto lactone **29** did not figure directly into the synthetic pathway, our interest in its preparation arose from two independent, although related, considerations. Molecular mechanics calculations[27] suggested that the trans-fused ketone **30** (ΔE_{strain} = 17.9, ΔH_f = 119.6, and ΔE_{total} = 28.1 kcal/mol) was more stable than **29** (ΔE_{strain} = 20.9, ΔH_f = 116.6, and ΔE_{total} = 31.1 kcal/mol). The individual global minimum conformations are illustrated in Figure 2. Also, a chemically-related base-promoted epimerization was utilized by Still in the course of a successful synthesis of eucannabinolide.[27] In our hands, however, submission of **29** to various basic conditions provided no positive indication that **30** had formed.

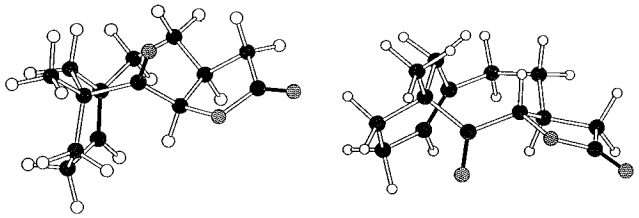
An initial probe of the reactivity of an epoxy acid of type **32** prompted its acquisition from **28**. Once mesylate **31** was produced, stereoalignment factors were satisfactorily exploited upon its dissolution into 10% methanolic KOH. Once lactone hydrolysis occurred, oxirane ring formation ensued and **32** was obtained in 95% overall yield.

The singular unreactivity of **32** under alkaline conditions is noteworthy. The precise factors that inhibit relactonization probably reside in a less than ideal reaction trajectory for backside attack at the oxiranyl carbon and the delocalized nature of the carboxylate anion. In contrast, **32** was completely

Scheme 6



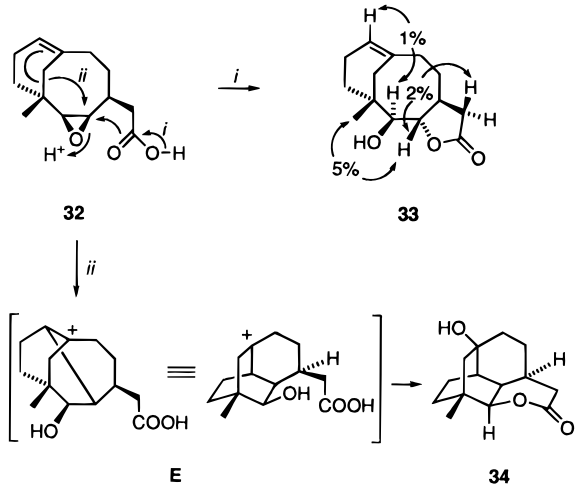
[a] TBAF/HMPA, 80 °C, 24 h. [b] TPAP, NMO, 4 Å MS, CH_2CL_2. [c] MsCl, Et_3N, DMAP, CH_2Cl_2. [d] 10% KOH, MeOH; H_3O^+.



29 **30**

Figure 2. Global minimum energy conformations of **29** and **30** (Chem 3-D output).

Scheme 7



destroyed in the presence of boron trifluoride etherate or trimethylsilyl triflate. When efforts were redirected to the use of camphorsulfonic acid in $CHCl_3$ at rt, conversion to a 1:1 mixture of **33** and **34** was realized in 60% yield. The trans lactone configuration was in complete agreement with the NOE enhancements given in Scheme 7. This stereochemistry is compatible with the notion of oxirane cleavage according to path *i*, involving backside neighboring group participation by the carboxyl group.

(24) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. (b) Griffith W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.

(25) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1990.

(26) We thank Professor W. C. Still (Columbia University) for making his program available for use and Prof. K. Steliou (Boston University) for providing us with updates of this software package.

(27) Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625.

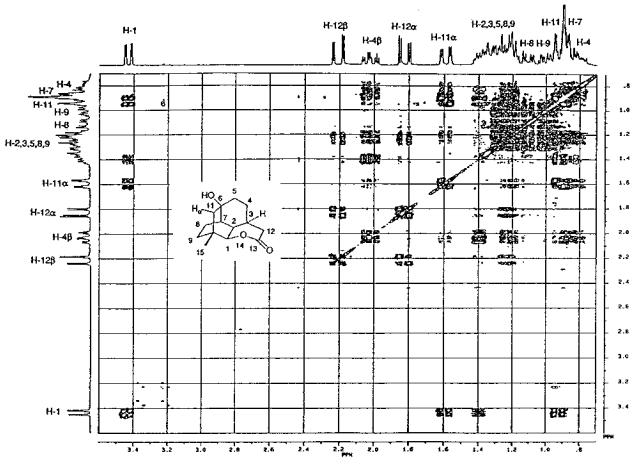
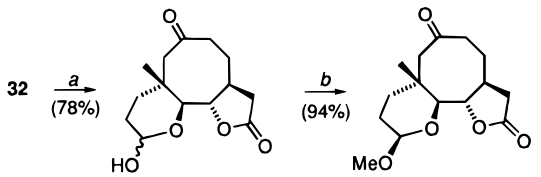


Figure 3. $^1H^1H$ COSY spectrum of **34** (C_6D_6 solution).

Scheme 8



[a] OsO_4 (cat.), $NaIO_4$, 1:1, Et_2O-H_2O. [b] Ag_2O, CH_3I, CH_2Cl_2.

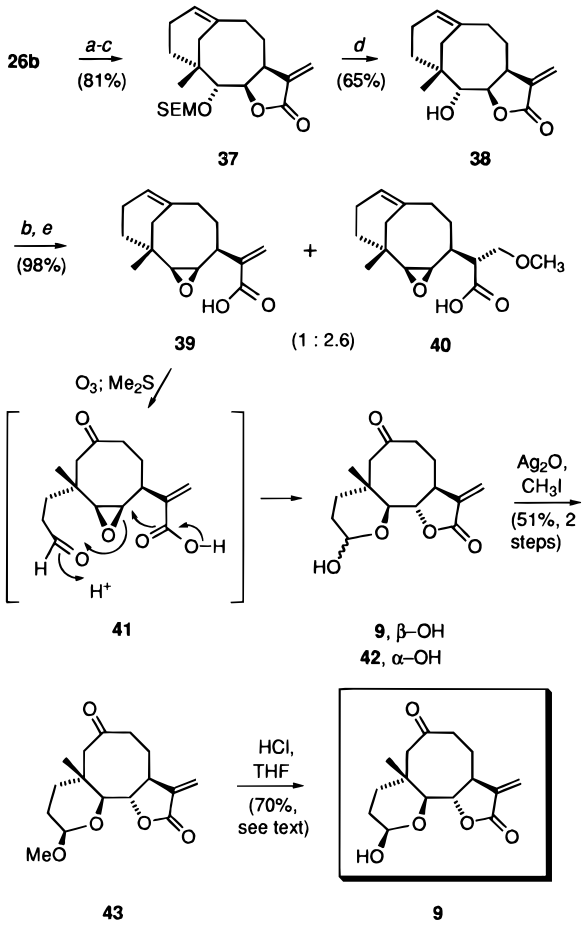
The gross structural features of **34** were deduced through a combination of DEPT, NOE, and COSY experiments (see Figure 3). Assignment of the doublet of doublets centered at δ 3.42 to the C*H*−OH proton was evident from its chemical shift. The coupling pattern was considered diagnostic of a W-plan arrangement to a methylene proton of the bicyclo[2.2.2]octane substructure. Similarly, the AB pair located at δ 2.22 and 1.83 could be attributed to the geminal protons α to the carbonyl. This conclusion was confirmed by a C−H correlation and DEPT measurement. Related probe experiments allowed the remaining assignments to be defined. These data are considered telltale for the operation of path *ii* in Scheme 7.

Introduction of the Exocyclic Methylene Group and Arrival at Vulgarolide. In the context of Scheme 7, ring closure of epoxy acid **32** to give **33** was recognized to constitute an exploitable means for establishing the key stereochemical features of **4**, **5**, and **9**. Although undesirable transannular bonding is a very significant problem in this parent system, substitution α to the carboxylic acid as required for acquisition of the targeted sesquiterpene lactones was expected to accelerate path *i* at the expense of path *ii* because of the release of nonbonded steric compression. The suitability of these structural modifications is presented in the next section.

For the moment, attention was given to the biomimetic conversion of **26b** to vulgarolide **9**. In light of the availability of **32**, the consequences of its double bond cleavage were examined first (Scheme 8). Dihydroxylation with concurrent periodate oxidation smoothly afforded lactol **35** as a 1:1 mixture of epimers. To our delight, treatment of this mixture with silver oxide and methyl iodide[4] afforded only the β-methoxy acetal **36** in 94% yield. Central to this configurational assignment is the appearance of the acetal proton as a doublet of doublets (J = 2.4, 9.5 Hz) at δ 4.06 (in $CDCl_3$).

In light of these very favorable results, lactone **26b** was transformed sequentially by classical means into the methylene lactones **37** and **38** (Scheme 9). Following the conversion of

Scheme 9



[a] LDA, CH_2O, THF, −78 → −25 °C. [b] MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C. [c] DBU, C_6H_6, rt. [d] 5% HF, CH_3CN. [e] LiOH, CH_3OH.

38 to its mesylate, saponification with lithium hydroxide in methanol gave rise efficiently to a mixture of **39** (27%) and **40** (71%). Although it is likely that **40** could be made to undergo E_2 elimination, this transformation was not undertaken because of our desire to utilize this intermediate as a precursor of the crispolides.

Cleavage of the bridgehead double bond in **39** was approached with greater caution than before because of the need for chemoselectivity. Recourse to controlled low-temperature ozonolysis proved quite serviceable in this context, delivering vulgarolide (**9**) and its anomer **42** in equal proportions. Rather than perform the difficult separation of these lactols, the mixture was converted into the stereochemically homogeneous *O*-methylvulgarolide (51%) as before. Appendino and co-workers[4] had previously methylated vulgarolide in order to obtain a more soluble material for purification purposes. The synthetic sample prepared as described here exhibited spectral properties and an optical rotation identical to those of naturally-derived **43**. Hydrolysis of **43** with 10% HCl in THF resulted in slow hydrolysis and the recovery of vulgarolide (**9**) together with **42** (ratio 2.1:1) in 70% combined yield.

Chemistry in the Vicinity of the Bridgehead Double Bond. Preparation of Deoxocrispolide. As a prelude to experiments involving substrates with properly defined stereochemistry, it was of interest to ascertain the response of **37** to the action of singlet oxygen. Conformational global energy minima, previously computed for stereoisomers **F** and **G** using the MODEL program (version KS 2.96), provided the basis for recognizing appreciably different allylic proton alignments in the two systems. Some indication of these geometric modifications can

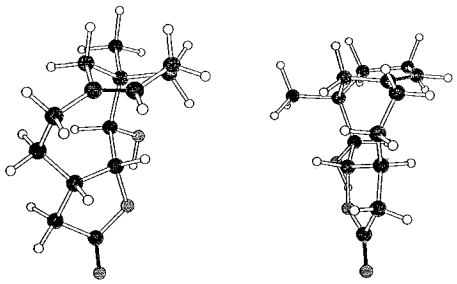
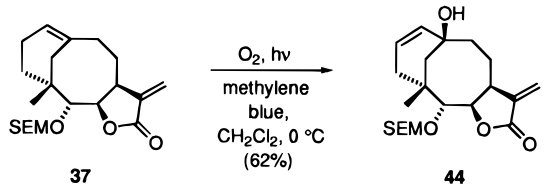


Figure 4. Global minimum energy conformations of **F** and **G** (Chem 3-D output). The double bond is depicted with a solid line.

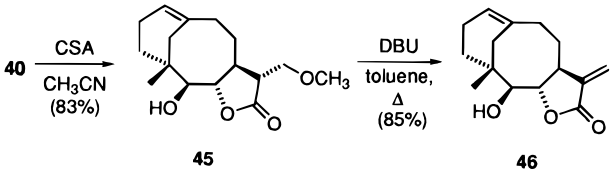
Table 1. Dihedral Angle Relationship in **F** and **G**

structure	identification of dihedral angle	angle, deg	structure	identification of dihedral angle	angle, deg
F	$C_{11}-C_{12}-H_{11}$	78.5	**G**	$C_{21}-C_{22}-H_{21}$	117.3
	$C_{12}-C_{11}-H_{12}$	122.1		$C_{22}-C_{21}-H_{22}$	119.1
	$C_{12}-C_{11}-H_{13}$	−67.5		$C_{22}-C_{21}-H_{23}$	−81.2

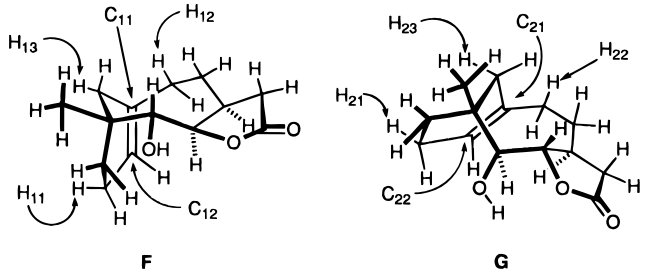
Scheme 10



Scheme 11



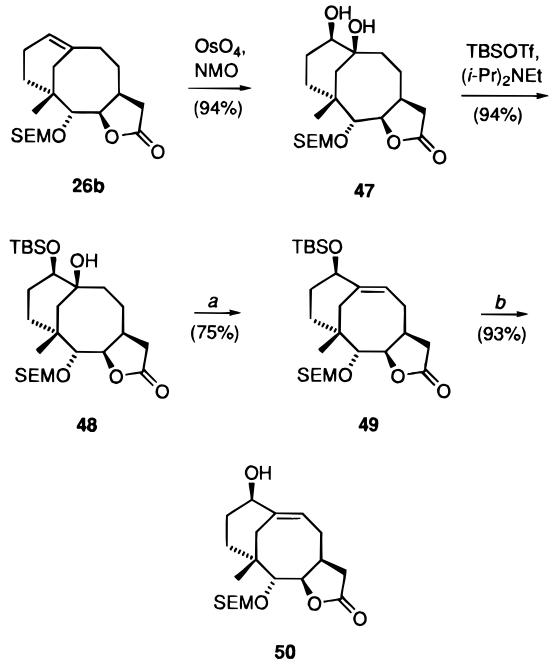
be gained by inspection of the Chem 3D drawings in Figure 4. The relevant dihedral angles of importance have been compiled in Table 1. In **F**, the objective indication was that the quite good orthogonal relationship of H_{11} to the flanking π bond and the less than ideal orientation of H_{12} should be conducive to ene reaction in the wrong direction. Reaction of **37** with singlet oxygen resulted in the exclusive production of **44** (Scheme 10), which was readily identified by its display of four vinylic protons in its ^{1}H NMR spectrum.



Stereochemical inversion of two trigonal centers as in **G** provides a framework in which H_{21} and H_{22} are aligned equally poorly with the unsaturated center. Predictably, **46** (Scheme 11) reacted with singlet oxygen not by an ene mechanism but via a [2+2] cycloaddition pathway to produce a dioxetane.[28]

(28) Wang, X. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 1994.

Scheme 12



[a] $CH_3O_2CN^-SO_2^+N(C_2H_5)_3$, C_6H_6, 25−50 °C. [b] TBAF, THF, rt, 2.5 h.

This observation dictated in a most decisive way that a different protocol had to be utilized to access the crispolides.

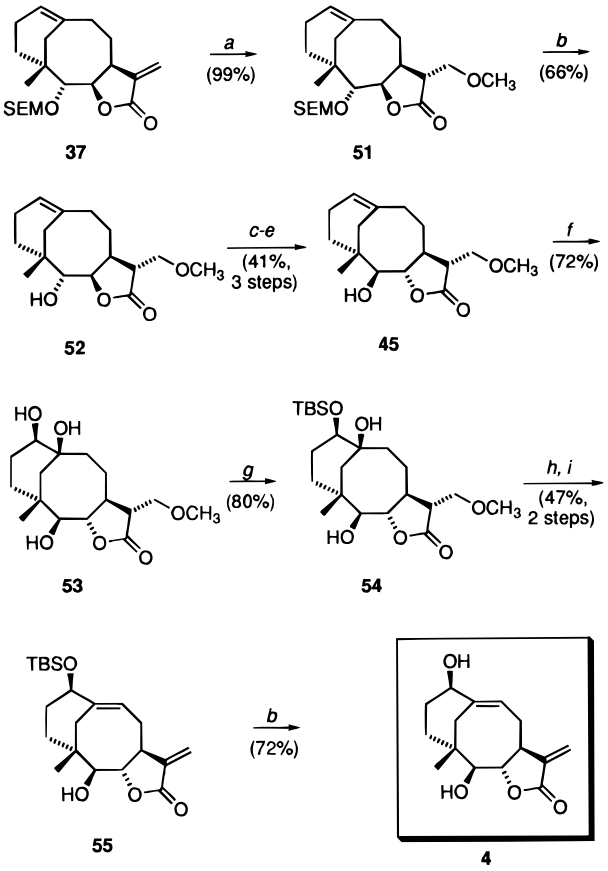
The stereochemical features present in these tricyclic lactones essentially guarantee that the bridgehead double bond will be attacked from the exo surface (see **F** and **G**). Since this π-facial selectivity aptly addresses the question of the allylic hydroxyl configuration in deoxocrispolide (**4**), a model study involving the conversion of **26b** to **50** as in Scheme 12 was next undertaken. Dihydroxylation with a catalytic quantity of osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide effected the smooth conversion of **26b** into **47**. Treatment of this diol with 1.5 equiv of *tert*-butyldimethylsilyl triflate resulted in chemoselective protection of the secondary hydroxyl group to deliver **48** efficiently. When Martin's sulfurane reagent[29] was examined for the purpose of effecting the regiocontrolled dehydration of **48**, purification of the product proved to be difficult because of its coelution with reagent-derived byproducts. In order to skirt these complications, elimination of the bridgehead hydroxyl group was brought about instead by warming with the Burgess reagent[30] in benzene solution. These conditions permitted the ready isolation of **49** in 75% yield. Confirmation that the OTBS group was indeed β as expected was derived from NOE studies. Deprotection of **49** with tetra-*n*-butylammonium fluoride in the conventional way gave rise to **50**. Thus, this series of experiments was taken to be an indication that alcohols such as **48** are indeed amenable to dehydration at a convenient rate. Consequently, this route was adopted for arrival at **4**.

Exploitation of **37** as the precursor of choice required that it not be channeled through **39** and **40** because of the unfavorable product distribution. Therefore, a simultaneous objective was to improve access and maximize throughput to more advanced intermediates. Important insight was gained when it was recognized that conjugate addition of methoxide ion to **37** could be implemented quantitatively without cleavage of the lactone

(29) (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327. (b) Arhart, R. J.; Martin J. C. *J. Am. Chem. Soc.* **1972**, *94*, 4997.

(30) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224; *J. Org. Chem.* **1973**, *38*, 26.

Scheme 13



[a] NaOMe, MeOH, rt. [b] HF−py CH_3CN. [c] MsCl, Et_3N, DMAP, CH_2Cl_2. [d] LiOH, H_2O, MeOH. [e] CSA, CH_3CN. [f] OsO_4, NMO, THF/H_2O (1:1); Na_2SO_3. [g] TBSOTf, $(i\text{-Pr})_2NEt$, CH_2Cl_2. [h] $[C_6H_5C(CF_3)_2O]_2S(C_6H_5)_2$, C_6H_6, rt. [i] DBU, toluene, Δ.

ring (Scheme 13). In addition, only the α-isomer **51** was formed, as established by NOE measurements (see the Experimental Section). Removal of the SEM group from **51** in order to liberate the secondary hydroxyl was accomplished as before with the hydrogen fluoride−pyridine complex. Submission of **52** to the double inversion protocol was found to be somewhat capricious, perhaps because the epoxy acid was a sensitive compound during attempted purification. Consequently, to avoid material losses, this intermediate was directly subjected to the identical acid-catalyzed ring closure previously observed for the conversion of **40** to **45**. When these controls were put into effect, lactone **45** could be obtained in an overall yield of 41% for the three steps.

As in the model study, **45** was easily dihydroxylated and monosilylated to reach **54**. At this stage, it was presumed that the ability of **54** to undergo dehydration would compare favorably with **48**, particularly since the secondary hydroxyl in the more highly functionalized lactone was recognized to be rather inaccessible due to the adjoining substitution. However, entirely comparable treatment of **54** with the Burgess inner salt gave **55** in only 26% yield. Although it is unclear why reaction efficiency dropped to this level, there exists a need for warming in this instance which does not apply to the Martin sulfurane reagent. In keeping with this reactivity difference, the latter dehydration agent emerged as the preferred means for effecting the loss of water in **54**. Subsequent heating of the resultant bridgehead olefin with DBU in toluene generated the unsaturated lactone **55**, whose desilylation served to provide deoxycrispolide (**4**), the spectral properties of which (at 300 MHz) matched those previously detailed by Bohlmann at 400 MHz.[4]

Summary. In conclusion, adaptation of the anionic oxy-Cope rearrangement leads very concisely to lactone **26b** of established absolute configuration. This central maneuver singlehandedly sets the entire carbocyclic framework, introduces a vital bridgehead olefinic center, and provides for setting the stereochemistry of two vicinal C−O bonds on the "southern" perimeter of the cyclooctane ring. Concurrent inversion of configuration at these two stereogenic centers proved feasible by way of a three-step sequence featuring extensive neighboring group participation. The excellent stereocontrol attainable in this conversion could then be parlayed in two directions. In the first, oxidative cleavage of the double bond and the ensuing lactol ring formation gave rise directly to vulgarolide. Alternative involvement of the same double bond in a dihydroxylation−dehydration process led to deoxocrispolide. Notably, this protocol involves the translocation of a bridgehead double bond from a six-membered ring to an adjoining cyclooctyl site, and concomitant functionalization with an allylic hydroxyl group. This ultimate solution argues well for the effective utilization of intrabridgehead olefin transformations in other synthetic contexts.

Experimental Section[31]

2-Bromo-4-(methoxymethoxy)-1-butene (11). 3-Butyne-1-ol was hydrobrominated as described in ref 13 with an efficiency of 70%. The resultant bromo alcohol (10.0 g, 60.2 mmol) and diisopropylamine (45 mL) were dissolved in CH_2Cl_2 (50 mL), cooled to 0 °C, and treated dropwise with chloromethyl methyl ether (12.6 mL). The mixture was stirred at rt for 1 h, poured into saturated $NaHCO_3$ solution (100 mL), and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried, and evaporated. Distillation of the residue gave 8.85 g (70%) of **11** as a colorless oil: bp 45 °C at 1.5−2.0 Torr; ^{1}H NMR (80 MHz, $CDCl_3$) δ 5.70 (d, J = 1.5 Hz, 1 H), 5.50 (d, J = 1.5 Hz, 1 H), 4.70 (s, 2 H), 3.75 (t, J = 6.4 Hz, 2 H), 3.40 (s, 3 H), and 2.70 (t, J = 6.4 Hz, 2 H). Anal. Calcd for $C_6H_{11}BrO_2$: C, 36.95; H, 5.68. Found: C, 36.56; H, 5.56.

Coupling of 11 to 10. A 50 mL flask fitted with a magnetic stirring bar was charged with cerium trichloride heptahydrate (1.91 g, 5.2 mmol) and heated under vacuum (0.1 Torr) at 140 °C overnight. After cooling, dry THF (10 mL) was introduced and the resultant slurry was stirred for 3 h at rt under N_2. In a separate flask, *tert*-butyllithium (3.05 mL of 1.7 M in hexanes, 5.2 mmol) was added to a solution of **11** (500 mg, 2.6 mmol) in THF (10 mL) at −78 °C under N_2. After 1 h of stirring at this temperature, the anion solution was transferred to the cold $CeCl_3$ slurry via cannula. This slurry was stirred at −78 °C for 8 h before **10**[11c] (195 mg, 1.3 mmol) dissolved in equally cold and dry THF (10 mL) was introduced slowly. The reaction mixture was stirred at −78 °C for 15 h, quenched with saturated NH_4Cl solution (10 mL), and allowed to return to rt. After dilution with brine (20 mL) and multiple extraction with ether, the combined organic extracts were washed with brine, dried, and evaporated. Flash chromatography of the residue on silica gel (elution with 20% ethyl acetate in petroleum ether) afforded 300 mg (90%) of a colorless oil consisting of a 1.6:1 mixture of **12** and **13**: IR (neat, cm^{-1}) 3450; ^{1}H NMR (300 MHz, $CDCl_3$) (for **12**) δ 5.15−5.00 (m, 1 H), 4.85 (m, 2 H), 4.65 (d, J = 6.5 Hz, 1 H), 4.60 (s, 2 H), 3.80−3.60 (m, 2 H), 3.34 (s, 3 H), 2.65 (s, 1 H), 2.60−1.75 (series of m, 6 H), 1.75−1.10 (series of m, 5 H), 0.90 (s, 3 H); (for **13**) δ 5.15−5.00 (m, 1 H), 4.85 (m, 2 H), 4.65 (d, J = 6.5 Hz, 1 H), 4.60 (s, 2 H), 3.80−3.60 (m, 2 H), 3.33 (s, 3 H), 3.05 (s, 1 H), 2.60−1.10 (series of m, 11 H), 0.88 (s, 3 H). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.91; H, 9.77.

Anionic Oxy-Cope Rearrangement of 12. To a slurry of potassium hydride (270 mg, 6.73 mmol) and 18-crown-6 (1.8 g, 6.73 mmol) in anhydrous THF (2.5 mL) cooled to 0 °C under N_2 was added a solution containing 360 mg (1.3 mmol) of **12** (not separated from **13**) dissolved in the same solvent (2.5 mL). The reaction mixture was stirred at rt

(31) The general experimental protocols followed in this study parallel those described in a recent report: Paquette, L. A.; Ezquerra, J.; He, W. *J. Org. Chem.* **1995**, *60*, 1435.

for 48 h, cooled to −78 °C, quenched with methanol (5 mL), poured into saturated NH_4Cl solution, and extracted with ether. The combined organic extracts were washed with brine, dried, and evaporated to leave an oil that was subjected to flash chromatography (silica gel, elution with 20% ethyl acetate in petroleum ether). First to elute was **14** (25 mg, 15%), followed by a 7.9:1 mixture of **15** and **16** (132 mg, 62%), which were separated by MPLC on silica gel.

Data for **14**: IR (neat, cm^{-1}) 3500, 1605, 1585; ^1H NMR (300 MHz, $CDCl_3$) δ 6.55 (dd, J = 11.3, 18.0 Hz, 1 H), 5.55 (dd, J = 1.9, 17.3 Hz, 1H), 5.36 (d, J = 0.5 Hz, 1 H), 5.12 (d, J = 1.9 Hz, 1 H), 5.09 (t, J = 1.9 Hz, 1 H), 5.02−4.85 (m, 2 H), 2.45−2.35 (m, 1 H), 2.30−1.90 (m, 4 H), 1.75−1.45 (m, 2 H); MS m/z (M^+) calcd 204.1514, obsd 204.1532.

Data for **15**: colorless oil; IR (neat, cm^{-1}) 1740; ^1H NMR (300 MHz, $CDCl_3$) δ 5.38 (m, 1 H), 4.54 (s, 2 H), 3.50−3.37 (m, 2 H), 3.31 (s, 3 H), 2.45−2.32 (m, 1 H), 2.20 (d, J = 10.9 Hz, 1 H), 2.15−1.93 (m, 5 H), 1.87−1.55 (series of m, 7 H), 1.50−1.38 (m, 1 H), 1.08 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 215.8, 138.0, 127.0, 96.4, 65.3, 55.2, 51.7, 50.9, 38.9, 38.6, 35.7, 33.7, 31.8, 31.0, 30.3, 22.3; MS m/z (M^+) calcd 266.1882, obsd 266.1859. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.11; H, 9.81.

Data for **16**: colorless oil; IR (neat, cm^{-1}) 1735; ^1H NMR (300 MHz, $CDCl_3$) δ 5.38 (t, J = 2.8 Hz, 1 H), 4.57 (s, 2 H), 3.60−3.40 (m, 2 H), 3.34 (s, 3 H), 2.69−2.63 (m, 1 H), 2.44 (d, J = 10.8 Hz, 1 H), 2.30−2.20 (m, 1 H), 2.18−1.87 (series of m, 9 H), 1.85−1.73 (m, 1 H), 1.60−1.38 (m, 2 H), 1.08 (s, 3 H); MS m/z (M^+) calcd 266.1882, obsd 266.1883. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.29; H, 9.76.

α-Oxygenation of 10. A. Via Direct Action of MoOPD to the Enolate Anion. A solution of **10** (300 mg, 2 mmol) in dry THF (7 mL) was cooled to −78 °C under N_2, treated with lithium diisopropylamide (4.45 mL of 0.5 M in THF, 2.2 mmol), stirred for 30 min at −78 °C, and transferred via cannula during 1 h to a slurry of MoOPD (1.915 g, 5 mmol) in THF (7 mL) at −23 °C. The reaction mixture was stirred at this temperature for 2 h, treated with saturated Na_2SO_3 solution, allowed to warm to rt, and extracted with ether. The combined organic phases were copiously washed with water, dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 1% triethylamine and 10% ethyl acetate in petroleum ether) furnished the endo and exo α-hydroxy ketones (240 mg, 70%) as an oily 3.5:1 mixtue of diastereomers (^1H NMR analysis).

B. Via Action of Dimethyldioxirane on the Silyl Enol Ether. A solution of lithium diisopropylamide [from *n*-butyllithium (9.1 mL of 1.6 M in hexanes, 14.6 mmol) and diisopropylamine (2.05 mL, 14.6 mmol)] in THF (20 mL) was stirred at 0 °C for 10 min, cooled to −78 °C, and treated with chlorotrimethylsilane (8.56 mL, 67.5 mmol). After 5 min, a solution of **10** (2.0 g, 13.3 mmol) in THF (2 mL) was introduced, and the mixture was stirred for 10 min at −78 °C, quenched sequentially with triethylamine (15 mL) and saturated $NaHCO_3$ solution (10 mL), allowed to warm to rt, and extracted with petroleum ether (3 × 20 mL). The combined organic phases were washed with water (10 mL) and 0.1 N citric acid (10 mL), dried, and concentrated. The residue was filtered through a plug of Florisil and reconcentrated to give 2.9 g (98%) of the silyl enol ether: ^1H NMR (300 MHz, $CDCl_3$) δ 4.92 (d, J = 2.0 Hz, 1 H), 4.86 (d, J = 1.9 Hz, 1 H), 4.65 (d, J = 1.8 Hz, 1 H), 2.94 (dd, J = 2.7, 5.1 Hz, 1 H), 1.97 (d, J = 1.9 Hz, 2 H), 1.67−1.61 (m, 2 H), 1.32−1.07 (m, 2 H), 1.07 (s, 3 H), 0.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 150.4, 110.0, 104.6, 48.0, 43.6, 36.2, 34.5, 28.3, 25.5, 0.2; MS m/z (M^+) calcd 150.1045, obsd 150.1043.

A 2.4 g (10.8 mmol) sample of the above material in CH_2Cl_2 (150 mL) was cooled to −78 °C and treated with a cold (−78 °C) solution of dimethyldioxirane in acetone (*ca.* 12.5 mmol). The reaction mixture was allowed to warm to rt overnight, evaporated, diluted with ether, and dried. After solvent removal, the residual siloxy ketones were separated by chromatography on Florisil, dissolved in methanol containing citric acid (0.1 mmol), and stirred at rt for 30 min. Workup as above gave the α-hydroxy ketones which were combined with the previous lot, dissolved in CH_2Cl_2 (20 mL) at 0 °C, and treated with diisopropylethylamine (3.0 mL, 17.1 mmol) and SEM chloride (2.24 mL, 12.7 mmol) dropwise. Workup in the manner described in part C, including chromatography on silica gel, gave 1.9 g (60%) of **17b** and 630 mg (20%) of a mixture of **17b** and **18b**. Flash chromatography gave pure **18b**.

Data for **17b**: colorless oil; IR (neat, cm^{-1}) 1740, 1655; ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, J = 6.9 Hz, 1 H), 4.91 (t, J = 2.0 Hz, 1 H), 4.81−4.76 (m, 2 H), 3.78−3.61 (m, 2 H), 3.59 (d, J = 1.6 Hz, 1 H), 2.89 (t, J = 2.9 Hz, 1 H), 2.43 (dt, J = 2.5, 17.4 Hz, 1 H), 2.30 (dq, J = 2.3, 17.4 Hz, 1 H), 2.04−1.79 (m, 3 H), 1.38−1.28 (m, 1 H), 1.03 (s, 3 H), 1.00−0.85 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 141.6, 110.6, 95.5, 80.9, 65.7, 53.7, 40.8, 37.8, 26.2, 26.0, 22.9, 18.0, −1.5; FAB MS m/z ($M^+ + 1$) calcd 297.18, obsd 297.23. Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52. Found: C, 64.91; H, 9.52.

Data for **18b**: colorless oil; IR (neat, cm^{-1}) 1745, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, J = 6.8 Hz, 1 H), 4.90−4.84 (m, 1 H), 4.76−4.73 (m, 1 H), 4.70 (d, J = 6.8 Hz, 1 H), 3.73−3.57 (m, 2 H), 3.53 (d, J = 1.7 Hz, 1 H), 2.84 (t, J = 2.8 Hz, 1 H), 2.53 (dq, J = 17.2, 2.4 Hz, 1 H), 2.07 (dq, J = 17.2, 2.1 Hz, 1 H), 1.86−1.77 (m, 2 H), 1.65−1.44 (m, 2 H), 0.99 (s, 3 H), 0.99−0.81 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.2, 143.4, 110.1, 95.1, 79.7, 65.5, 53.8, 36.8, 35.6, 30.7, 23.0, 22.8, 17.9, −1.5; FAB MS m/z (M^++1) calcd 297.18, obsd 297.23. Anal. Calcd for $C_{26}H_{28}O_3Si$: C, 64.82; H, 9.52. Found: C, 64.92; H, 9.52.

C. Via Preparation of the MOM Ethers. To a solution of the α-hydroxy ketones (810 mg, 4.9 mmol, prepared according to part A) and diisopropylethylamine (3.4 mL, 20 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added MOM chloride (0.93 mL, 12.3 mmol). The reaction mixture was stirred at rt for 48 h and treated with saturated $NaHCO_3$ solution. Following extraction of the aqueous phase with CH_2Cl_2, the combined CH_2Cl_2 solutions were washed with brine, dried, and evaporated. The residue was subjected to flash chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) to give 614 mg (65%) of a 3.5:1 mixture of **17a** and **17b**. These diastereomers were separated by MPLC under identical conditions to give the pure ethers as colorless oils.

Data for **17a**: IR (neat, cm^{-1}) 1735, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, J = 6.7 Hz, 1 H), 4.90 (m, 1 H), 4.80 (m, 1 H), 4.70 (d, J = 6.7 Hz, 1 H), 3.56 (d, J = 1.7 Hz, 1 H), 3.43 (s, 3 H), 2.90 (t, J = 2.9 Hz, 1 H), 2.43 (dt, J = 17.4, 2.5 Hz, 1 H), 2.30 (dq, J = 17.4, 2.3 Hz, 1 H), 2.05−1.78 (m, 3 H), 1.40−1.25 (m, 1 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 141.5, 110.6, 97.4, 81.0, 56.1, 53.7, 40.8, 37.8, 26.2, 26.0, 22.8; MS m/z (M^+) calcd 210.1256, obsd 210.1218. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.99; H, 8.69.

Data for **18a**: IR (neat, cm^{-1}) 1730, 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (d, J = 6.7 Hz, 1 H), 4.94 (m, 1 H), 4.85 (m, 1 H), 4.67 (d, J = 6.7 Hz, 1 H), 3.55 (d, J = 1.7 Hz, 1 H), 3.43 (s, 3 H), 2.90 (t, J = 2.8 Hz, 1 H), 2.58 (dq, J = 17.2, 2.5 Hz, 1 H), 2.13 (dq, J = 17.2, 2.3 Hz, 1 H), 1.93−1.82 (m, 2 H), 1.73−1.50 (m, 1 H), 1.33−1.20 (m, 1 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 143.3, 110.0, 96.9, 79.8, 55.9, 53.7, 36.7, 35.5, 30.6, 22.9, 22.8; MS m/z (M^+) calcd 210.1256, obsd 210.1231. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.77; H, 8.69.

Epimerization of 18b. A solution of **18b** (1.1 g, 3.7 mmol) in methanol (15 mL) was treated with K_2CO_3 (1.04 g, 7.5 mmol), and the suspension was stirred at rt overnight. The insoluble material was separated by filtration, and the filtrate was evaporated to leave a residue that was partitioned between water (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the organic phase was dried, filtered, and evaporated to leave a residue consisting of a 1:1 mixture of **17b** and **18b**. Flash chromatography on silica gel afforded 460 mg of **18b** and 430 mg of **17b**.

Resolution of 17b. To a cold (−30 °C) solution of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (1.37 g, 8.10 mmol) in THF (20 mL) was added *n*-butyllithium (5.06 mL of 1.6 M in hexanes, 8.01 mmol), and the resulting yellow reaction mixture was stirred at rt for 15 min before being cooled to −78 °C and treated via cannula with a solution of **17b** (1.20 g, 4.05 mmol) in 5 mL of THF. After 40 min at −78 °C, the contents were poured into a 2:1 mixture of ether and saturated NH_4Cl solution (20 mL). The aqueous phase was extracted with ether (4 × 20 mL), and the combined organic phases were dried to leave a residue that was purified by chromatography on silica gel (elution with

5% ethyl acetate in petroleum ether) to give 930 mg (43%) of **19** and 800 mg (49%) of **20**, both as colorless oils.

Data for **19**: IR (film, cm^{-1}) 3500, 1740, 1650, 1450; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, J = 1.3, 7.7 Hz, 2 H), 7.61−7.50 (m, 3 H), 4.91 (d, J = 6.7 Hz, 1 H), 4.74 (d, J = 6.7 Hz, 1 H), 4.64 (d, J = 1.8 Hz, 1 H), 4.54 (d, J = 1.7 Hz, 1 H), 3.69−3.54 (m, 2 H), 3.42 (dd, J = 14.5, 1.8 Hz, 2 H), 3.19 (d, J = 1.5 Hz, 1 H), 2.63 (s, 3 H), 2.58 (t, J = 2.9 Hz, 1 H), 2.23−2.08 (m, 2 H), 1.94 (dd, J = 2.3, 17.5 Hz, 1 H), 1.70 (m, 1 H), 1.41−0.72 (series of m, 5 H), 0.86 (s, 3 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 139.5, 132.8, 129.3, 129.2, 110.0, 97.0, 84.9, 72.7, 66.0, 63.3, 45.9, 40.4, 35.5, 28.9, 25.2, 24.0, 20.6, 18.0, −1.47; MS m/z (M^+) calcd 465.2369, obsd 465.2361; $[\alpha]_D^{20}$ +23.3° (c 0.8, $CHCl_3$). Anal. Calcd for $C_{24}H_{39}NO_4SSi$: C, 61.90; H, 8.44. Found: C, 61.44; H, 8.50.

Data for **20**: IR (film, cm^{-1}) 3500, 3250, 3080, 2950, 2820, 1745, 1655, 1450; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J = 1.1, 7.8 Hz, 2 H), 7.62−7.50 (m, 3 H), 6.07 (br, 1 H), 4.99 (d, J = 2.0 Hz, 1 H), 4.89 (d, J = 7.0 Hz, 1 H), 4.76 (d, J = 2.0 Hz, 1 H), 4.71 (d, J = 7.0 Hz, 1 H), 3.91−3.82 (m, 1 H), 3.66−3.55 (m, 2 H), 3.28 (d, J = 14.0 Hz, 1 H), 2.98 (d, J = 1.5 Hz, 1 H), 2.92 (br, 1 H), 2.60 (s, 3 H), 2.26 (m, 1 H), 2.16 (dt, J = 2.4, 17.4 Hz, 1 H), 1.95 (dd, J = 2.3, 17.4 Hz, 1 H), 1.75 (m, 1 H), 1.39 (m, 1 H), 1.34−0.87 (series of m, 3 H), 0.85 (s, 3 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 139.1, 130.0, 129.4, 128.9, 110.2, 96.6, 84.8, 73.8, 66.0, 62.4, 45.7, 40.7, 35.7, 29.0, 25.2, 24.0, 20.8, 18.3, −1.47; MS m/z (M^+) calcd 465.2369, obsd 465.2357; $[\alpha]_D^{20}$ +16.3° (c 0.76, $CHCl_3$).

Adducts **19** and **20** were individually refluxed in toluene overnight. The cooled solutions were placed atop a column of silica gel, and the ketones were eluted as before. From **19**, the dextrorotatory ketone was isolated in 92% yield, $[\alpha]_D^{20}$ +128° (c 2.7, $CHCl_3$). From **20**, the levorotatory ketone was isolated in 95% yield, $[\alpha]_D^{20}$ −156° (c 2.2, $CHCl_3$).

Resolution of 10. To a cold (−30 °C) solution of (−)-(*R*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (214 mg, 1.26 mmol) in THF (5 mL) was added *n*-butyllithium (1.26 mL of 1.3 M in hexanes, 1.64 mmol) followed ultimately by 189 mg (1.26 mmol) of **10** according to the predescribed procedure. Following chromatography, 57 mg (16%) of **21**, 124 mg (35%) of **22**, and 97 mg (27%) of the two endo diastereomers were isolated.

Data for **21**: colorless crystals, mp 87−88 °C; IR (KBr, cm^{-1}) 3210, 3080, 2960, 1650, 1455, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86−7.84 (m, 2 H), 7.63−7.52 (m, 3 H), 6.65 (br, 1 H), 4.99 (dd, J = 2.2, 4.5 Hz, 1 H), 4.75 (dd, J = 2.1, 4.1 Hz, 1 H), 3.25 (s, 2 H), 2.95 (t, J = 2.8 Hz, 1 H), 2.61 (s, 3 H), 2.31 (m, 1 H), 2.06 (ddd, J = 2.5, 5.6, 16.9 Hz, 1 H), 1.79 (dd, J = 2.3, 6.8 Hz, 1 H), 1.52−1.39 (m, 3 H), 1.26 (m, 1 H), 1.10 (dd, J = 2.9, 4.0 Hz, 1 H), 0.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 139.3, 133.0, 129.5, 129.0, 110.0, 73.6, 63.7, 51.4, 44.8, 40.9, 31.4, 31.2, 28.9, 27.2, 21.2; MS m/z (M^+) calcd 319.1606, obsd 319.1596; $[\alpha]_D^{20}$ −17.5° (c 1.04, $CHCl_3$).

Data for **22**: colorless crystals, mp 135−136 °C; IR (KBr, cm^{-1}) 3210, 3070, 2960, 1645, 1450, 1240; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2 H), 7.63−7.52 (m, 3 H), 7.16 (br, 1 H), 4.62 (dd, J = 2.0, 3.9 Hz, 1 H), 4.54 (dd, J = 2.2, 4.3 Hz, 1 H), 3.26 (d, J = 13.8 Hz, 1 H), 3.16 (d, J = 13.8 Hz, 1 H), 2.60 (s, 3 H), 2.27 (m, 1 H), 2.14 (dd, J = 2.7, 4.2 Hz, 1 H), 2.09−1.99 (m, 2 H), 1.90 (m, 1 H), 1.75 (dd, J = 3.1, 4.8 Hz, 1 H) 1.54 (m, 1 H), 1.37 (m, 1 H), 1.25 (m, 1 H), 0.87 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 139.1, 133.0, 129.5, 129.0, 109.1, 72.5, 65.3, 48.3, 47.6, 40.8, 31.10, 31.05, 28.8, 27.1, 20.7; MS m/z (M^+) calcd 319.1606, obsd 319.1586; $[\alpha]_D^{20}$ −63.2° (c 1.08, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.89. Found: C, 67.78; H, 7.92.

Adducts **21** and **22** were individually refluxed in toluene overnight. The cooled solutions were placed atop a column of silica gel, and the ketones were eluted as before. From **21**, the levorotatory ketone was isolated in 98% yield, $[\alpha]_D^{20}$ −44.3° (c 0.82, $CHCl_3$). From **22**, the dextrorotatory ketone was isolated in 95% yield, $[\alpha]_D^{20}$ +45.5° (c 0.88, $CHCl_3$).

(1*R,2*R**,3*S**,4*S**)-3-(Methoxymethoxy)-4-methyl-6-methylene-2-vinyl-bicyclo[2.2.2]octan-2-ol (23a).** A solution of **17a** (800 mg, 3.8 mmol) in THF (15 mL) was cooled to −78 °C, treated with a solution of vinylmagnesium bromide (6.72 mL of 1.1 M, 7.6 mmol), stirred at this temperature for 3 h, and poured into saturated NH_4Cl solution. The product was extracted into ether, and the combined organic phases were washed with brine, dried, and evaporated. The residue was subjected to flash chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) to furnish **23a** as a colorless oil (728 mg, 80%): IR (neat, cm^{-1}) 3530, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (dd, J = 17.0, 10.6 Hz, 1 H), 5.36 (dd, J = 16.1, 1.9 Hz, 1 H), 5.01 (dd, J = 10.6, 1.9 Hz, 1 H), 4.80 (q, J = 2.3 Hz, 1 H), 4.73−4.70 (m, 1 H), 4.71 (d, J = 6.4 Hz, 1 H), 4.60 (d, J = 6.4 Hz, 1 H), 3.40 (s, 3 H), 3.23 (d, J = 1.9 Hz, 1 H), 2.80−2.15 (series of m, 5 H), 1.77−1.65 (m, 1 H), 1.45−1.33 (m, 1 H), 1.17−1.05 (m, 1 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 144.4, 111.2, 108.8, 97.9, 83.7, 72.0, 56.4, 47.7, 40.9, 35.0, 25.2, 24.0, 21.4; FAB MS m/z (M^+ + 1) 239.16, obsd 239.21.

Analogous coupling of (+)-**17b** (930 mg 3.13 mmol) to vinylmagnesium bromide afforded 940 mg (92%) of **23b** as a colorless oil: IR (neat, cm^{-1}) 3510, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (dd, J = 10.6, 17.0 Hz, 1 H), 5.35 (dd, J = 1.9, 17.0 Hz, 1 H), 4.99 (dd, J = 1.7, 10.6 Hz, 1 H), 4.79−4.70 (m, 2 H), 4.73 (d, J = 6.6 Hz, 1 H), 4.64 (dd, J = 6.6 Hz, 1 H), 3.64 (t, J = 8.4 Hz, 2 H), 3.48 (s, 1 H), 3.23 (d, J = 1.7 Hz, 1 H), 2.25−2.02 (m, 4 H), 1.76−1.63 (m, 1 H), 1.42−1.31 (m, 1 H), 1.19−1.03 (m, 1 H), 0.97−0.84 (m, 2 H), 0.89 (s, 3 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 144.4, 111.1, 108.8, 96.2, 83.6, 72.0, 66.2, 47.7, 40.8, 35.0, 25.1, 23.9, 21.3, 18.0, −1.5; FAB MS m/z (M^+ + 1) calcd 325.21, obsd 325.22; $[\alpha]_D^{20}$ +50.7° (c 2.4, $CHCl_3$). Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.87; H, 9.93.

Ethyl (1*R,2*R**,4*S**)-2-(Methoxymethoxy)-1-methyl-3-oxobicyclo-[5.3.1.]undec-7-ene-4-acetate (24a). A. Use of 18-Crown-6.** A solution of **23a** (728 mg, 0.31 mmol) and 18-crown-6 (770 mg, 0.37 mmol) in dry THF (10 mL) at 0 °C was treated with potassium hexamethyldisilazide (7.34 mL of 0.5 M, 0.37 mmol), allowed to warm to rt during 1 h, cooled to −78 °C, and treated with ethyl bromoacetate (2.0 mL, 18 mmol). Once the reaction mixture had returned to rt, it was poured into saturated brine and extracted with ether. The combined organic extracts were dried and evaporated, and the residue was purified by flash chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) to give 650 mg (68%) of **24a** as a white solid: mp 45−47 °C; IR (KBr, cm^{-1}) 1730, 1690; ^1H NMR (300 MHz, $CDCl_3$) δ 5.37−5.35 (m, 1 H), 4.46 (d, J = 7.1 Hz, 1 H), 4.39 (d, J = 7.1 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.81 (s, 1 H), 3.27 (s, 3 H), 2.75−2.62 (m, 1 H), 2.35 (s, 1 H), 2.32 (d, J = 1.4 Hz, 1 H), 2.25−1.76 (series of m, 7 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 171.4, 137.0, 128.3, 95.7, 82.8, 60.7, 55.8, 51.4, 42.6, 37.7, 37.4, 35.5, 29.0, 27.5, 25.7, 22.0, 14.2; MS m/z (M^+) calcd 324.1937, obsd 324.1918. Anal. Calcd for $C_{18}H_{25}O_5$: C, 66.64; H, 8.70. Found: C, 66.49; H, 8.89.

B. Absence of 18-Crown-6. A mixture of (+)-**23b** (110 mg, 0.32 mmol) and potassium hexamethyldisilazide (0.94 mL of 0.5 M in toluene, 0.47 mmol) in anhydrous THF (5 mL) was refluxed for 20 min, cooled to −78 °C, and treated with ethyl iodoacetate (0.07 mL, 0.62 mmol) dissolved in HMPA (1.5 mL). The reaction mixture was stirred at −78 °C for 6 h, allowed to warm to rt overnight, and quenched with saturated NH_4Cl solution. Following extraction of the aqueous phase with ether, the combined organic layers were dried and evaporated. The residue was purified by chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) to give 101 mg (78%) of **24b** as a colorless, viscous oil: IR (film, cm^{-1}) 1735, 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 5.37−5.35 (m, 1 H), 4.53 (d, J = 7.4 Hz, 1 H), 4.39 (d, J = 7.4 Hz, 1 H), 4.20−4.07 (m, 3 H), 3.87 (s, 1 H), 3.66−3.45 (m, 2 H), 2.77−2.65 (m, 1 H), 2.35 (d, J = 7.4 Hz, 2 H), 2.36−1.67 (m, 8 H), 1.29−1.18 (m, 4 H), 1.13 (s, 3 H), 0.91−0.84 (m, 2 H), −0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 171.3, 137.0, 128.3, 93.4, 82.4, 65.5, 60.6, 51.3, 42.6, 37.6, 37.5, 35.5, 28.9, 27.4, 25.7, 22.0, 17.9, 14.2, −1.5; FAB MS m/z (M^+ + 1) calcd 411.25, obsd 411.24; $[\alpha]_D^{20}$ +101° (c 2.6, $CHCl_3$). Anal. Calcd for $C_{22}H_{38}O_5Si$: C, 64.35; H, 9.33. Found: C, 63.91; H, 9.21.

(1*R,2*R**,3*R**,4*S**)-3-Hydroxy-2-(methoxymethoxy)-1-methylbicyclo[5.3.1]undec-7-ene-4-ethanol (25a).** A solution of **24a** (53 mg, 0.16 mmol) in dry THF (1 mL) was transferred via cannula into a cold (−78 °C), magnetically stirred slurry of lithium aluminum hydride (6 mg, 0.16 mmol) in THF (1.5 mL). The reaction mixture

was allowed to warm to rt, stirred for 1 h, and treated dropwise in turn with water (1 drop), 15% NaOH solution (1 drop), and water (3 drops). The resultant white solid was amply rinsed with ether, and the combined filtrates were evaporated and subjected to flash chromatography on silica gel (elution with ethyl acetate) to give 36 mg (78%) of **25a** as a clear oil: IR (neat, cm^{-1}) 3450; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68−5.65 (m, 1 H), 4.72 (d, J = 6.3 Hz, 1 H), 4.66 (d, J = 6.3 Hz, 1 H), 4.30 (dd, J = 3.9, 7.3 Hz, 1 H), 3.76−3.65 (m, 1 H), 3.63−3.57 (m, 1 H), 3.43 (s, 3 H), 3.16 (d, J = 7.3 Hz, 1 H), 2.28−1.26 (series of m, 15 H), 1.17 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 124.7, 99.5, 87.1, 69.4, 62.2, 56.8, 40.8, 39.6, 36.5, 34.1, 33.1, 30.0, 29.9, 29.2, 23.5; FAB MS m/z ($M^+ + 1$) calcd 285.20, obsd 285.22. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 67.72; H, 10.28.

Analogous reduction of (+)-**24b** (600 mg, 1.46 mmol) furnished 490 mg (90%) of **25b** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3400; ^1H (300 MHz, $CDCl_3$) δ 5.60 (dd, J = 4.6, 5.4 Hz, 1 H), 4.77 (d, J = 6.5 Hz, 1 H), 4.68 (d, J = 6.5 Hz, 1 H), 4.27 (dd, J = 3.9, 7.3 Hz, 1 H), 3.76−3.46 (m, 4 H), 3.15 (d, J = 7.3 Hz, 1 H), 2.23−1.67 (series of m, 12 H), 1.51−1.20 (m, 3 H), 1.16 (s, 3 H), 0.98−0.91 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 124.7, 97.8, 87.4, 69.6, 66.8, 62.2, 40.7, 39.6, 36.6, 34.1, 33.1, 30.1, 30.0, 29.1, 23.4, 18.1, −1.5; FAB MS m/z ($M^+ + 1$) calcd 371.25, obsd 371.24; $[\alpha]_D^{20}$ +48.2° (c 3.0, C_2H_5OH). Anal. Calcd for $C_{20}H_{38}O_4Si$: C, 64.82; H, 10.34. Found: C, 64.91; H, 10.26.

(3a*R,10*S**,11*S**,11a*S**)-3a,4,5,8,9,10,11,11a-Octahydro-11-(methoxymethoxy)-10-methyl-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (26a).** A mixture of **25a** (25 mg, 0.088 mmol), 4-methylmorpholine N-oxide (31 mg, 0.26 mmol), crushed 4 Å molecular sieves (70 mg), and 1,2-dichloroethane (3 mL) was stirred for 10 min before the addition of TPAP (4.3 mg, 10 mol %) in one portion. After 30 min, the mixture was diluted with CH_2Cl_2 and washed sequentially with saturated Na_2SO_3 solution, brine, and saturated $CuSO_4$ solution. The organic phase was dried and evaporated, and the residue was purified by flash chromatography on silica gel (elution with ethyl acetate) to give **26a** (16 mg 65%) as a white crystalline solid: mp 58−62 °C; IR (KBr, cm^{-1}) 1775; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (m, 1 H), 4.74 (dd, J = 9.5, 7.5 Hz, 1 H), 4.62 (d, J = 7.0 Hz, 1 H), 4.47 (d, J = 7.0 Hz, 1 H), 3.41 (s, 3 H), 3.24 (d, J = 9.5 Hz, 1 H), 2.58−1.73 (series of m, 12 H), 1.43 (ddd, J = 1.4, 4.9, 10.1 Hz, 1 H), 1.21 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 139.7, 124.4, 99.6, 83.4, 82.4, 57.1, 40.0, 39.9, 36.7, 34.8, 34.7, 30.0, 28.0, 26.7, 22.7; MS m/z (M^+) calcd 280.1674, obsd 280.1674. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.80; H, 8.63.

A mixture of (+)-**25b** (490 mg, 1.31 mmol), NMO (460 mg, 3.93 mmol), 4 Å molecular sieves (200 mg), and 1,2-dichloroethane (15 mL) was comparably treated with TPAP (69 mg, 0.2 mmol), and the resulting black mixture was stirred at rt for 5 min before being diluted with ether. The mixture was filtered through a plug of silica gel, and the eluate was evaporated. The residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give pure **26b** (360 mg, 76%) as a colorless, crystalline solid: mp 73−75 °C; IR ($CHCl_3$, cm^{-1}) 1775; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (dd, J = 1.8, 3.7 Hz, 1 H), 4.75 (dd, J = 7.4, 9.7 Hz, 1 H), 4.70 (d, J = 7.4 Hz, 1 H), 4.46 (d, J = 7.4 Hz, 1 H), 3.71 (ddd, J = 5.8, 9.6, 11.3 Hz, 1 H), 3.63 (ddd, J = 6.2, 9.7, 11.2 Hz, 1 H), 3.27 (d, J = 9.7 Hz, 1 H), 2.57−1.77 (series of m, 12 H), 1.42 (ddd, J = 1.3, 8.2, 14.3 Hz, 1 H), 1.22 (s, 3 H), 1.00−0.81 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 139.8, 124.4, 97.5, 82.8, 82.7, 66.7, 39.8, 39.75, 36.8, 34.8, 34.7, 30.1, 28.0, 26.7, 22.7, 18.1, −1.5; MS m/z (M^+) calcd 366.2226, obsd 366.2264; $[\alpha]_D^{20}$ +70.9° (c 2.4, $CHCl_3$). Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.78; H, 9.37.

Methyl (1*R,3a*S**,4*S**,7*S**,8*R**,8a*S**)-Decahydro-8-hydroxy-4-methoxy-1-methyl-1,4-methanoazulene-7-acetate (27).** A solution of **26a** (28 mg, 0.1 mmol) in methanol (5 mL) was treated with 5 μL of concentrated HCl, refluxed for 10 h, cooled, and neutralized with solid $NaHCO_3$. The mixture was filtered and evaporated, and the residue was purified by flash chromatography on silica gel (elution with ethyl acetate) to furnish **27** (25 mg, 88%) as a colorless oil: IR (film, cm^{-1}) 3500, 1735; ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3 H), 3.17 (dd, J = 0.6, 2.9 Hz, 1 H), 3.15 (s, 3 H), 2.37 (dd, J = 9.1, 14.2 Hz, 1 H), 2.27 (dd, J = 6.2, 14.2 Hz, 1 H), 2.03−1.04 (series of m, 14 H), 0.89 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.7, 75.4, 73.1, 51.7, 48.7, 48.1, 44.0, 37.8, 37.4, 36.3, 33.9, 33.1, 26.9, 24.4, 24.3, 20.1; MS m/z (M^+) calcd 282.1831, obsd 282.1823. Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.38; H, 9.00.

(3a*S*,10*R*,11*R*,11a*R*)-3a,4,5,8,9,10,11,11a-Octahydro-11-hydroxy-10-methyl-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (28). A sample of (+)-**26b** (275 mg, 0.75 mmol) was treated with 4 mL of a 1.0 M solution of tetra-*n*-butylammonium fluoride in THF (4.0 mmol), and the solvent was removed in vacuo. The residue was diluted with dry HMPA (1.5 mL) and heated at 80 °C for 24 h. The cooled reaction mixture was diluted with ether (50 mL) and washed with brine (10 × 5 mL). The organic layer was dried and evaporated, and the residue was subjected to chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether) to provide 96 mg (54%) of pure **28** as white crystals: mp 104−105 °C; IR ($CHCl_3$, cm^{-1}) 3550, 1770; ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (m, 1 H), 4.18 (dd, J = 7.6, 9.9 Hz, 1 H), 3.42 (d, J = 9.9 Hz, 1 H), 2.69 (s, 1 H), 2.66−2.41 (m, 2 H), 2.42 (d, J = 7.8 Hz, 1 H), 2.40−1.76 (series of m, 9 H), 1.36 (ddd, J = 1.7, 8.4, 14.5 Hz, 1 H), 1.24 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 140.0, 124.2, 83.2, 75.4, 39.5, 39.2, 36.3, 34.6, 34.4, 29.7, 27.0, 26.9, 22.7; MS m/z (M^+) calcd 236.1412, obsd 236.1411; $[\alpha]_D^{20}$ +40.8° (c 1.2, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.07; H, 8.53.

(3a*S*,10*R*,11a*R*)-3a,5,8,9,10,11a-Hexahydro-10-methyl-6,10-methanocyclo-deca[*b*]furan-2,11(3*H*,4*H*)-dione (29). A solution of **28** (29 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was treated with 4 Å molecular sieves (61 mg), NMO (29 mg, 2 equiv), and TPAP (4.3 mg, 10 mol %). The mixture was stirred for 20 min at rt, diluted with a 15% solution of ethyl acetate in petroleum ether (3 mL), and filtered through a short column of silica gel (elution with the same solvent system). Evaporation of the eluate gave pure **29** as a viscous, colorless oil (21 mg, 73%): IR (neat, cm^{-1}) 1800, 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (m, 1 H), 5.51 (d, J = 8.3 Hz, 1 H), 2.61 (m, 1 H), 2.48−2.38 (m, 2 H), 2.38−2.28 (m, 2 H), 2.23−2.13 (m, 2 H), 2.06−1.90 (m, 3 H), 1.71−1.52 (m, 3 H), 1.23 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 175.6, 140.3, 126.2, 79.5, 48.7, 40.8, 36.4, 35.2, 33.1, 29.7, 28.9, 24.4, 22.4; MS m/z (M^+) calcd 234.1256, obsd 234.1265.

(1*R*,2*S*,3*R*,4*S*)-2,3-Epoxy-1-methylbicyclo[5.3.1]undec-7-ene-4-acetic Acid (32). A cold (0 °C), magnetically stirred solution of (+)-**28** (56 mg, 0.24 mmol), triethylamine (0.34 mL, 2.4 mmol), and 4-(dimethylamino)pyridine (33 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) was treated dropwise with methanesulfonyl chloride (0.093 mL, 1.2 mmol). The solution, which became cloudy after 5 min, was stirred for 1 h before being quenched with saturated NH_4Cl solution. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried and concentrated. The residue was purified by short column chromatography over silica gel to give mesylate **31** as a white solid.

The mesylate was dissolved in methanol (20 mL), treated with 2 mL of 5% KOH solution, stirred at rt for 2 h, and reduced in volume under vacuum. The residual aqueous mixture was extracted with ethyl acetate (3 × 10 mL) prior to adjusting the pH to 2 with 5% HCl. The acidic solution was again extracted with ethyl acetate (3 × 10 mL), and all of the extracts were combined, dried, and evaporated. The residue was purified by chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 53 mg (95%) of **32** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3600, 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (m, 1 H), 2.87 (d, J = 4.5 Hz, 1 H), 2.56 (d, J = 7.3 Hz, 2 H), 2.52 (dd, J = 4.5, 1.6 Hz, 1 H), 2.25 (dd, J = 7.6, 15.6 Hz, 1 H), 2.16−2.06 (m, 3 H), 1.94−1.80 (m, 3 H), 1.62−1.48 (m, 3 H), 1.31−1.22 (m, 1 H), 1.16 (s, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 136.7, 121.8, 67.5, 65.2, 42.4, 36.5, 35.5, 34.7, 33.8, 31.8, 28.0, 24.8, 23.0; MS m/z (M^+) calcd 236.1412, obsd 236.1416; $[\alpha]_D^{20}$ +88.8° (c 2.8, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.91; H,8.53.

(3a*S*,10*R*,11*S*,11a*S*)-3a,4,5,8,9,10,11,11a-Octahydro-11-hydroxy-10-methyl-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (33) and (3a*S*,6*S*,6a*R*,9*R*,9a*R*,9b*R*)-Decahydro-6-hydroxy-9-methyl-6,9-methanonaphtho[1,8-*bc*]pyran-2(3*H*)-one (34). A solution of **32** (71 mg, 0.30 mmol) in $CHCl_3$ (11 mL) containing camphorsulfonic acid (175 mg, 2.5 equiv) was stirred for 5 h at rt under N_2, diluted with $CHCl_3$ (30 mL), washed with brine, and dried. The residue remaining after solvent evaporation was subjected to flash chromatography on silica

gel (gradient elution with 20−50% ethyl acetate in petroleum ether) to give pure samples of **33** (21 mg, 30%) and **34** (22 mg, 30%).

Data for **33**: colorless oil; IR (neat, cm^{-1}) 3600, 1760; ^1H NMR (300 Mz, $CDCl_3$) δ 5.41 (m, 1 H), 4.06 (t, J = 9.0 Hz, 1 H), 3.75 (d, J = 9.2 Hz, 1 H), 2.64 (dd, J = 7.6, 17.3 Hz, 1 H), 2.41 (dd, J = 12.7, 17.3 Hz, 1 H), 2.30−2.22 (m, 3 H), 2.08−1.69 (series of m, 6 H), 1.38 (dt, J = 8.0, 13.7 Hz, 1 H), 1.31−1.11 (m, 2 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 133.6, 123.6, 86.1, 75.0, 41.8, 38.0, 36.7, 34.3, 34.1, 32.1, 28.8, 22.9, 22.5; MS m/z (M^+) calcd 236.1412, obsd 236.1405.

Data for **34**: colorless oil; IR (neat, cm^{-1}) 3410 (br), 1720, 1350, 1235, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (dd, J = 1.9, 10.3 Hz, 1 H), 2.53 (dd, J = 3.0, 16.6 Hz, 1 H), 2.43 (dd, J = 3.9, 16.6 Hz, 1 H), 2.30 (m, 1 H), 2.19−2.02 (m, 2 H), 1.86 (dd, J = 2.6, 14.8 Hz, 1 H), 1.81−1.68 (m, 2 H), 1.59−1.25 (m, 6 H), 1.19 (dd, J = 1.8, 14.8 Hz, 1 H), 0.99 (s, 3 H) (OH not oserved); ^1H NMR (300 MHz, C_6D_6) see Figure 3; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 82.3, 70.2, 41.4, 39.8, 39.3, 39.2, 37.8, 34.0, 31.1, 30.6, 27.7, 23.4, 19.8; MS m/z (M^+) calcd 236.1412, obsd 236.1425.

(3a*S*,7a*R*,10*R*,11a*S*,11b*S*)-Decahydro-10-methoxy-7a-methyl-2*H*-furo[3′,2′:7,8]cycloocta[1,2-*b*]pyran-2,6(7*H*)-dione (36). A solution of **32** (53 mg, 0.22 mmol) in 10 mL of a 1:1 mixture of ether and water was treated with osmium tetroxide (6 mg, 0.022 mmol), and the black mixture was stirred for 10 min before sodium periodate (105 mg, 0.49 mmol) was introduced. The reaction mixture was stirred for 6 h and filtered through a short plug of silica gel, which was rinsed with ethyl acetate (20 mL). The eluate was concentrated, and the residue was purified by chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether) to give 47 mg (78%) of a 1:1 mixture of **35a** and **35b** (^1H NMR analysis: integration of the signals at δ 5.36 and 4.23 in $CDCl_3$ solution).

The above mixture (43 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was treated with silver(I) oxide (200 mg) and excess methyl iodide (0.4 mL). The black suspension was stirred overnight, filtered through a cotton plug, and concentrated. The residue was chromatographed on silica gel (elution with 50% ethyl acetate in petroleum ether) to furnish 43 mg (94%) of **36** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1785, 1705, 1460; ^1H NMR (300 MHz, C_6D_6) δ 4.06 (dd, J = 2.4, 9.5 Hz, 1 H), 3.66 (t, J = 8.6 Hz, 1 H), 3.43 (s, 3 H), 2.89 (d, J = 8.6 Hz, 1 H), 2.06 (dd, J = 7.8, 16.5 Hz, 1 H), 1.96−1.85 (m, 2 H), 1.81−1.43 (series of m, 7 H), 1.10 (m, 1 H), 1.16−0.99 (m, 2 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 173.6, 104.0, 83.5, 83.0, 56.1, 49.1, 44.9, 41.5, 38.7, 37.6, 36.3, 28.3, 27.4, 18.8; MS m/z (M^+) calcd 282.1467, obsd 282.1448; $[\alpha]_D^{20}$ +13.0° (c 2.2, $CHCl_3$).

(3a*S*,10*R*,11*R*,11a*R*)-3a,4,5,8,9,10,11,11a-Octahydro-10-methyl-3-methylene-11-[[2-(trimethylsiloxy)ethoxy]methoxy]-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (37). To a cold (−78 °C) solution of lithium diisopropylamide (0.65 mL of 0.5 M in THF, 0.33 mmol) was added 60 mg (0.14 mmol) of (+)-**26b** dissolved in THF (1 mL) via cannula during 2 min. The reaction mixture was stirred at −78 °C for 1 h and warmed to −30 °C over 30 min. Gaseous formaldehyde, produced by heating 40 mg (1.3 mmol) of paraformaldehyde at 160−180 °C, was slowly bubbled into a mixture in a flow of N_2. After an additional 4 min of stirring, saturated NH_4Cl solution (1 mL) was added followed by dilution with ethyl acetate. The separated aqueous phase was extracted with ethyl acetate (5 × 4 mL), and the combined organic layers were dried and evaporated. Chromatography of the residue on silica gel (elution with 20% ethyl acetate in petroleum ether) gave 52 mg (81%) of a 5:1 mixture of the two hydroxymethyl products.

Data for the major isomer: colorless oil; IR ($CHCl_3$, cm^{-1}) 3480, 1770, 1470; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (dd, J = 1.8, 4.0 Hz, 1 H), 4.75 (dd, J = 7.5, 9.6 Hz, 1 H), 4.66 (d, J = 7.4 Hz, 1 H), 4.45 (d, J = 7.3 Hz, 1 H), 3.97 (dd, J = 3.3, 11.6 Hz, 1 H), 3.70−3.58 (m, 3 H), 3.26 (d, J = 9.7 Hz, 1 H), 2.47−1.79 (series of m, 12 H), 1.41 (ddd, J = 7.4, 8.9, 13.3 Hz, 1 H), 1.20 (s, 3 H), 0.97−0.79 (m, 2 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 139.8, 124.3, 97.5, 83.1, 81.1, 66.7, 59.3, 46.0, 40.7, 40.0, 36.7, 34.7, 30.0, 27.8, 25.5, 22.7, 18.1, −1.5; MS m/z ($M^+ - H_2O$) calcd 378.2226, obsd 378.2217; $[\alpha]_D^{20}$ +26° (c 2.8, $CHCl_3$).

Data for the minor isomer: colorless oil; IR ($CHCl_3$, cm^{-1}) 3480, 1775, 1470; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (dd, J = 2.0, 3.8 Hz, 1 H), 4.68 (dd, J = 7.9, 18.9 Hz, 2 H), 4.09 (dd, J = 2.0, 11.7 Hz, 1 H), 3.99 (ddd, J = 6.3, 9.7, 15.5 Hz, 1 H), 3.72 (d, J = 9.2 Hz, 1 H), 3.74−3.71 (m, 1 H), 3.53−3.43 (m, 2 H), 2.66 (dd, J = 1.4, 11.3 Hz, 1 H), 2.51 (dt, J = 3.0, 10.2 Hz, 1 H), 2.29−1.72 (series of m, 8 H), 1.38 (ddd, J = 4.2, 8.8, 14.7 Hz, 1 H), 1.12 (s, 3 H), 0.94−0.83 (m, 2 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 140.0, 123.9, 98.2, 86.5, 82.1, 67.4, 59.6, 47.0, 40.9, 39.7, 36.9, 35.5, 29.5, 27.8, 22.7, 22.6, 18.1, −1.5; MS m/z ($M^+ - H_2O$) calcd 378.2226, obsd 378.2177; $[\alpha]_D^{20}$ −21° (c 1.1, $CHCl_3$).

The diastereomeric mixture from above was added to cold (0 °C) CH_2Cl_2 (2 mL) containing triethylamine (0.23 mL, 1.64 mmol) and 4-(dimethylamino)pyridine (24 mg, 0.20 mmol), treated with methanesulfonyl chloride (63 mg, 0.82 mmol), stirred for 1 h, quenched with triethylamine (0.2 mL), and diluted with ether (2 mL). After removal of the solvent, the remaining yellow solid was suspended in benzene (3 mL) containing 5 drops of DBU, and the mixture was stirred for 30 min. Following solvent evaporation, the residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give **37** (50 mg, 81% from **26b**) as a white solid: mp 66−67 °C; IR ($CHCl_3$, cm^{-1}) 1770, 1660; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, J = 3.2 Hz, 1 H), 5.72−5.70 (m, 1 H), 5.47 (d, J = 3.2 Hz, 1 H), 4.81 (dd, J = 8.4, 9.2 Hz, 1 H), 4.70 (d, J = 7.1 Hz, 1 H), 4.35 (d, J = 7.1 Hz, 1 H), 3.81−3.72 (m, 1 H), 3.61−3.52 (m, 1 H), 3.07 (d, J = 9.6 Hz, 1 H), 3.01−2.91 (m, 1 H), 2.36−1.80 (series of m, 9 H), 1.43 (ddd, J = 2.4, 8.7, 14.7 Hz, 1 H), 1.20 (s, 3 H), 1.00−0.81 (m, 2 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 139.8, 138.5, 124.2, 120.2, 87.5, 84.3, 81.8, 66.6, 43.9, 39.8, 36.8, 34.5, 30.2, 28.1, 25.1, 22.7, 18.1, −1.5; MS m/z (M^+) calcd 378.2226, obsd 378.2225; $[\alpha]_D^{20}$ +50.3° (c 2.9, $CHCl_3$).

(3a*S*,10*R*,11*R*,11a*R*)-3a,4,5,8,9,10,11,11a-Octahydro-11-hydroxy-10-methyl-3-methylene-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (38). A solution of **37** (40 mg, 0.10 mmol) in acetonitrile (1 mL) was placed in a small plastic vessel, treated with 5% HF in acetonitrile (0.1 mL), and stirred for 5 h. Without removal of the solvent, the reaction mixture was loaded onto silica gel and quickly flashed (10% ethyl acetate in petroleum ether) to return 10 mg (25 mg) of unreacted **37** and give 16.3 mg (65%) of **38** as a white solid: mp 110−112 °C; IR ($CHCl_3$, cm^{-1}) 3500, 1765, 1660; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (d, J = 3.3 Hz, 1 H), 5.71−5.68 (m, 1 H), 5.54 (d, J = 3.3 Hz, 1 H), 4.73 (dd, J = 8.4, 9.6 Hz, 1 H), 3.24 (d, J = 9.8 Hz, 1 H), 3.05−2.94 (m, 1 H), 2.37−2.31 (m, 1 H), 2.20−1.76 (series of m, 8 H), 1.40 (ddd, J = 2.4, 8.6, 14.7 Hz, 1 H), 1.21 (s, 3 H) (OH not oserved); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 140.0, 137.9, 124.2, 121.5, 82.2, 77.1, 43.3, 39.6, 36.5, 34.6, 29.8, 27.1, 25.8, 22.7; MS m/z (M^+) calcd 248.1412, obsd 248.1413; $[\alpha]_D^{20}$ −1.0° (c 2.5, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.25; H, 8.11.

(1*R*,2*S*,3*R*,4*S*)-2,3-Epoxy-1-methyl-α-methylenebicyclo[5.3.1]undec-7-ene-4-acetic Acid (39) and (1*R*,2*S*,3*R*,4*S*)-2,3-Epoxy-α-(methoxymethyl)-1-methylbicyclo-[5.3.1]undec-7-ene-4-acetic Acid (40). A solution of **38** (33 mg, 0.12 mmol), triethylamine (0.17 mL, 1.22 mmol), and 4-(dimethylamino)pyridine (18 mg, 0.15 mmol) in cold (0 °C) CH_2Cl_2 (2 mL) was reacted with methanesulfonyl chloride (0.047 mL, 0.61 mmol) in the predescribed manner, and the unpurified mesylate was dissolved in methanol (2 mL), treated with 5% LiOH solution (0.7 mL), and stirred for 1 h. After removal of the methanol, the residue was diluted with water (1 mL) and extracted with ethyl acetate (5 × 2 mL). The aqueous solution was then brought to pH 1 with 5% HCl and again extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried and evaporated, and the residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 8 mg (27%) of **39** and 22 mg (71%) of **40**.

Data for **39**: colorless oil: IR ($CHCl_3$, cm^{-1}) 3200 (br), 1693, 1623; ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1 H), 5.97 (s, 1 H), 5.47 (d, J = 2.8 Hz, 1 H), 3.02 (d, J = 5.5 Hz, 1 H), 2.96 (d, J = 8.0 Hz, 1 H), 2.54 (dd, J = 1.4, 4.4 Hz, 1 H), 2.20−2.00 (m, 4 H), 1.95 (d, J = 7.3 Hz, 1 H), 1.87 (d, J = 15.1 Hz, 1 H), 1.62 (t, J = 7.6 Hz, 2 H), 1.55 (d, J = 15.0 Hz, 1 H), 1.39 (d, J = 8.1 Hz, 1 H), 1.19 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 145.9, 136.6, 127.3, 121.5, 67.0, 64.5, 38.6, 36.8, 35.5, 33.8, 31.9, 28.0, 25.9, 23.2; MS m/z (M^+) calcd 248.1412, obsd 248.1411; $[\alpha]_D^{20}$ +57.6° (c 0.95, $CHCl_3$).

Data for **40**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3300 (br), 1732, 1714, 1457; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (br s, 1 H), 3.74 (d, J = 7.4

Hz, 2 H), 3.40 (s, 3 H), 2.92 (d, J = 4.5 Hz, 1 H), 2.82 (ddd, J = 3.5, 6.4, 7.6 Hz, 1 H), 2.50 (dd, J = 1.1, 4.4 Hz, 1 H), 2.40 (dd, J = 2.9, 8.4 Hz, 1 H), 2.11−2.04 (m, 3 H), 1.85−1.64 (m, 3 H), 1.59 (t, J = 7.4 Hz, 2 H), 1.50 (d, J = 14.9 Hz, 1 H), 1.39 (dd, J = 2.0, 11.6 Hz, 1 H), 1.19 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 136.6, 121.9, 69.5, 66.5, 65.4, 59.1, 53.3, 37.4, 36.8, 35.8, 33.6, 31.8, 28.4, 23.0, 20.9; MS m/z (M^+) calcd 280.1674, obsd 280.1671; $[\alpha]_D^{20}$ +56.7° (c 0.8, $CHCl_3$).

Ozonolysis of 39. Arrival at (−)-Vulgarolide (9) and (−)-*O*-Methylvulgarolide (43). To a cold (−78 °C) solution of **39** (20 mg, 0.081 mmol) in 4 mL of a 1:1 mixture of CH_2Cl_2 and methanol was added a solution of ozone in CH_2Cl_2 at −78 °C until **39** was totally consumed (TLC analysis). Nitrogen was bubbled through the blue solution for 5 min, and 0.5 mL of dimethyl sulfide was introduced before the reaction mixture was allowed to warm to 25 °C overnight. After solvent evaporation, the residue was chromatographed on silica gel (elution with ethyl acetate) to give 14 mg (62%) of a 1:1 mixture of **9** and **42** (integration of their respective signals at δ 6.37 and 6.31 in pyridine-d_5).

To a suspension of the above mixture in CH_2Cl_2 were added excess silver(I) oxide (120 mg) and methyl iodide (0.1 mL), and the resulting mixture was stirred vigorously for 1 day, filtered through a short plug of anhydrous $MgSO_4$, and freed of solvent. The residue was chromatographed on silica gel (elution with 50% ethyl acetate in petroleum ether) to give 12 mg (80%) of **43** as a white solid: mp 160−161 °C; $[\alpha]_D^{20}$ −32° (c 0.3, $CHCl_3$). The spectral properties of **43** were identical to those reported earlier.[4]

Hydrolysis of *O*-Methylvulgarolide (43). To a solution of **43** (6 mg, 0.02 mmol) in 3 mL of THF was added 0.2 mL of 10% HCl, and the mixture was stirred for 2 days. The solution was diluted with ethyl acetate (5 mL) and dried. After solvent removal, the residue was purified by chromatography on silica gel (elution with ethyl acetate) to give 4 mg (70%) of a 2.1:1 mixture of **9** and **42** as a white solid (integration of the δ 6.37 and 6.31 absorption as described above).

(3a*S*,6*S*,10*R*,11*R*,11a*R*)-3a,4,5,6,9,10,11,11a-Octahydro-6-hydroxy-10-methyl-3-methylene-11-[[2-(trimethylsiloxy)ethoxy]methoxy]-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (44). A solution of **37** (20 mg, 0.053 mmol) in CH_2Cl_2 (12 mL) containing adequate methylene blue to provide an intense blue color was cooled to 0 °C and irradiated with a 600 W tungsten lamp while oxygen was bubbled in. After 5 min, the reaction mixture was passed through a short column of silica gel (elution with 50% ethyl acetate in petroleum ether) to give **44** (13 mg, 62%) as a colorless oil: IR (neat, cm^{-1}) 3750−3400, 1755, 1650; ^{1}H NMR (300 MHz, C_6D_6) δ 6.16 (d, J = 3.2 Hz, 1 H), 5.61−5.56 (m, 1 H), 5.09 (dd, J = 10.1, 3.1 Hz, 1 H), 4.88−4.80 (m, 2 H), 4.69 (d, J = 6.6 Hz, 1 H), 4.31−4.22 (m, 1 H), 3.98−3.81 (m, 1 H), 3.75−3.58 (m, 1 H), 3.00 (d, J = 9.9 Hz, 1 H), 2.52−2.14 (m, 2 H), 2.08 (d, J = 15.1 Hz, 1 H), 1.95−1.17 (series of m, 7 H), 1.16 (s, 3 H), 1.13−0.79 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 168.9, 141.3, 133.5, 129.9, 120.9, 98.2, 83.0, 82.5, 82.0, 66.9, 40.8, 39.1, 39.0, 37.0, 31.8, 31.4, 25.3, 18.3, −1.3; MS m/z (M^+) calcd 394.2175, obsd 394.2134.

(3a*S*,10*R*,11*S*,11a*S*)-3a,4,5,8,9,10,11,11a-Octahydro-11-hydroxy-3-(methoxymethyl)-10-methyl-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (45). A solution of **40** (35 mg, 0.125 mmol) and camphorsulfonic acid (58 mg, 0.25 mmol) in acetonitrile (2 mL) was stirred at rt for 16 h and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 29 mg (83%) of **45** as a white solid: mp 165−166 °C; IR ($CHCl_3$, cm^{-1}) 3600, 1780; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (br s, 1 H), 4.00 (t, J = 9.0 Hz, 1 H), 3.74 (dd, J = 2.2, 10.8 Hz, 1 H), 3.64 (ddd, J = 3.3, 4.0, 10.0 Hz, 2 H), 3.36 (s, 3 H), 2.46 (dt, J = 3.5, 11.9 Hz, 1 H), 2.37 (d, J = 1.5 Hz, 1 H), 2.37−2.13 (m, 3 H), 2.11−1.92 (m, 3 H), 1.98 (d, J = 1.9 Hz, 1 H), 1.77 (dq, J = 2.8, 15.4 Hz, 2 H), 1.46−1.25 (m, 1 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 133.6, 123.6, 84.0, 74.9, 68.2, 59.3, 48.6, 43.3, 36.7, 34.3. 34.2, 32.0, 27.9, 22.8, 22.4; MS m/z (M^+) calcd 280.1674, obsd 280.1660; $[\alpha]_D^{20}$ +75.1° (c 0.65, $CHCl_3$).

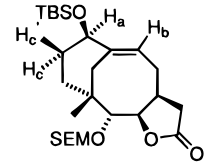
(3a*S*,10*R*,11*S*,11a*S*)-3a,4,5,8,9,10,11,11a-Octahydro-11-hydroxy-10-methyl-3-methylene-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (46). A solution of **45** (6 mg, 0.021 mmol) and DBU (4 drops) in toluene (4 mL) was refluxed for 4 h, cooled to rt, and freed of solvent under reduced pressure. The residue was purified by chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) to furnish 4.5 mg (85%) of **46** as a white solid: mp 85−87 °C; IR ($CHCl_3$, cm^{-1}); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (d, J = 3.7 Hz, 1 H), 5.58 (d, J = 3.3 Hz, 1 H), 5.44 (br s, 1 H), 4.00 (dd, J = 8.3, 9.2 Hz, 1 H), 3.79 (d, J = 9.4 Hz, 1 H), 2.54−2.48 (m, 1 H), 2.43−2.35 (m, 2 H), 2.29−2.22 (m, 2 H), 2.16−1.92 (series of m, 4 H), 1.80 (dq, J = 2.9, 12.5 Hz, 2 H), 1.41 (dt, J = 9.9, 13.7 Hz, 1 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 139.7, 134.0, 123.9, 121.0, 84.4, 75.3, 45.4, 36.9, 34.5, 34.4, 32.1, 28.0, 22.9, 22.5; MS m/z (M^+) calcd 248.1412, obsd 248.1420.

(3a*S*,6*S*,7*R*,10*R*,11*R*,11a*R*)-Decahydro-6,7-dihydroxy-10-methyl-11-[[2-(trimethylsilyl)ethoxy]methoxy]-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (47). A solution of **26b** (278.5 mg, 0.76 mmol) in 1:1 THF−H_2O (25 mL) containing *N*-methylmorpholine-*N*-oxide (178.4 mg, 1.52 mmol) was treated with osmium tetroxide (5 mg) and stirred for 1 h. An additional 10 mL of THF was introduced, and following another hour of agitation, the reaction mixture was poured into a separatory funnel containing ethyl acetate (50 mL) and saturated sodium sulfite solution (50 mL). The separated aqueous layer was extracted with ethyl acetate (4 × 50 mL), and the combined organic solutions were dried and concentrated. The residue was purified by flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether) to give **47** as a clear, colorless oil (287.2 mg, 94%): IR (neat, cm^{-1}) 3500, 1780; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72−4.66 (m, 3 H), 4.00 (d, J = 7.6 Hz, 1 H), 3.70−3.63 (m, 1 H), 3.58−3.51 (m, 2 H), 2.72−2.59 (m, 2 H), 2.35−2.17 (m, 5 H), 1.91−1.81 (m, 1 H), 1.74−1.64 (m, 3 H), 1.47−1.39 (m, 4 H), 1.11 (s, 3 H), 0.99−0.82 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 97.4, 84.4, 82.6, 74.6, 72.5, 66.1, 39.0, 38.4, 37.6, 36.3, 34.5, 31.0, 28.5, 24.6, 18.2, −1.5 (3 C); MS m/z (M^+ − CH_3) calcd 385.2037, obsd 385.3063; $[\alpha]_D^{20}$ −38.7° (c 2.49, $CHCl_3$). Anal. Calcd for $C_{20}H_{36}O_6Si$: C, 59.97; H, 9.06. Found: C, 60.26; H, 9.22.

(3a*S*,6*S*,7*R*,10*R*,11*R*,11a*R*)-7-(*tert*-Butyldimethylsiloxy)decahydro-6-hydroxy-10-methyl-11-[[2-(trimethylsilyl)ethoxy]methoxy]-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (48). A solution of **47** (193.9 mg, 0.64 mmol) and diisopropylethylamine (0.2 mL, 1.15 mmol) in freshly distilled CH_2Cl_2 (10 mL) was cooled to −78 °C, treated with *tert*-butyldimethylsilyl triflate (170 μL, 0.74 mmol), and allowed to stir at this temperature for 2 h prior to quenching with saturated $NaHCO_3$ solution (10 mL). After partitioning between water (50 mL) and ethyl acetate (50 mL), the aqueous phase was extracted with ethyl acetate (4 × 50 mL), and the combined organic solutions were dried and concentrated. The resulting oil was purified by flash chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether) to give **48** as a colorless oil (257.9 mg, 94%): IR (neat, cm^{-1}) 3600, 1790; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71−4.65 (m, 3 H), 3.98 (d, J = 7.6 Hz, 4 H), 3.70−3.66 (m, 1 H), 3.64−3.48 (m, 2 H), 2.72−2.57 (m, 2 H), 2.28−2.16 (m, 4 H), 1.96−1.91 (m, 1 H), 1.69−1.52 (m, 3 H), 1.48−1.23 (m, 4 H), 1.08 (s, 3 H), 0.98−0.81 (m, 2 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 97.3, 84.5, 82.6, 74.2, 73.7, 66.0, 39.1, 38.3, 37.6 (2 C), 34.6, 31.1, 29.6, 29.5, 25.8 (3 C), 24.8, 18.2, 18.0, −1.5 (3 C), −4.6, −5.0; MS m/z (M^+ − CH_3) calcd 499.2898, obsd 499.2926; $[\alpha]_D^{20}$ −56.9° (c 0.43, $CHCl_3$). Anal. Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.91; H, 9.88.

(3a*S*,5*E*,7*R*,10*R*,11*R*,11a*R*)-7-(*tert*-Butyldimethylsiloxy)decahydro-3a,4,7,8,9,10,11,11a-octahydro-10-methyl-11-[[2-(trimethylsilyl)-ethoxy]methoxy]-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (49). A solution of **48** (304 mg, 0.59 mmol) and the Burgess reagent (282 mg, 1.18 mmol) in dry benzene (40 mL) was stirred overnight at rt. At this point, an additional 280 mg of the inner salt was introduced, and the reaction mixture was heated at 50 °C for 36 h. The solvent was removed under reduced pressure, and the residue was taken up in ethyl acetate (20 mL), filtered, and concentrated. The product was purified by flash chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) to give **49** (219 mg, 75%) as a clear, colorless oil: IR (neat, cm^{-1}) 1724, 1601; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (dd, J = 8.9, 6.3 Hz, 1 H), 4.70 (d, J = 6.9 Hz, 1 H), 4.69−4.60 (m, 1 H), 4.55 (d, J = 6.8 Hz, 1 H), 4.24 (br s, 1 H), 3.70−3.61 (m, 2 H), 3.53 (d, J = 9.1 Hz, 1 H), 2.80−2.71 (m, 1 H), 2.53−2.41 (m, 2 H), 2.38−2.21 (m, 3 H), 2.11−2.01 (m, 1 H), 1.98−1.83 (m, 1 H), 1.79−1.70

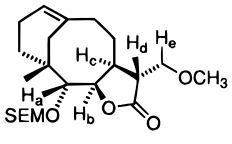
(m, 2 H), 1.65−1.51 (m, 1 H), 1.15 (s, 3 H), 0.95−0.81 (m, 2 H), 0.87 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 9 H), −0.02 (s 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 145.6, 117.8, 98.0, 85.2, 84.0, 72.9, 66.3, 44.7, 41.9, 36.3, 35.3, 32.4, 31.8, 29.4, 27.5, 25.8 (3 C), 18.2, 18.1, −1.4 (3 C), −4.7, −4.9; MS *m*/*z* (M^+) calcd 496.3027, obsd 496.3041; $[\alpha]_D^{20}$ −2.4° (*c* 3.8, $CHCl_3$). Anal. Calcd for $C_{26}H_{48}O_5Si_2$: C, 62.86; H, 9.74. Found: C, 63.05; H, 9.75.



Irridiate	Observe	% NOE
H_a	H_b	14.0
	H_c	4.4
	H_c'	1.9

(3a*S*,5*E*,7*R*,10*R*,11*R*,11a*R*)-3a,4,7,8,9,10,11,11a-Octahydro-7-hydroxy-10-methyl-11-[[2-(trimethylsilyl)ethoxy]methoxy]-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (50). A sample of **49** (66.3 mg, 0.133 mmol) was blanketed with N_2, dissolved in dry THF (5 mL), and treated with a solution of tetra-*n*-butylammonium fluoride (0.16 mL of 1.0 M in THF, 0.16 mmol). The reaction mixture was stirred at rt for 30 min, treated with an additional 0.2 mL of TBAF, and agitated for a further 2.5 h. The solvent was removed under reduced pressure, and the residue was subjected to flash chromatography on silica gel (elution with 40−60% ethyl acetate in petroleum ether) to furnish **50** as a clear, colorless oil (47.3 mg, 93%); IR (neat, cm^{-1}) 3460, 1770, 1461, 1423, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (dd, J = 8.4, 6.4 Hz, 1 H), 4.68 (br d, J = 6.8 Hz, 1 H), 4.63−4.58 (m, 2 H), 4.33−4.30 (m, 1 H), 3.64−3.57 (m, 3 H), 2.83−2.75 (m, 1 H), 2.57−2.48 (m, 1 H), 2.46−2.24 (m, 3 H), 2.18−2.05 (m, 3 H), 2.03−1.52 (series of m, 4 H), 1.18 (s, 3 H), 0.94−0.88 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 144.3, 120.4, 97.8, 85.2, 83.5, 72.5, 66.3, 44.7, 41.6, 36.0, 33.5, 31.8, 30.9, 29.9, 18.1, −1.5 (3 C); MS *m*/*z* (M^+) calcd 382.2166, obsd 382.2164; $[\alpha]_D^{20}$ −57.1° (*c* 1.36, $CHCl_3$).

(3a*R*,3a*S*,10*R*,11*R*,11a*R*)-3a,4,5,8,9,10,11,11a-Octahydro-3-(methoxymethyl)-10-methyl-11-[[2-(trimethylsilyl)ethoxy]methoxy]-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (51). Lactone **37** (197.6 mg, 0.52 mmol) was added to a solution of sodium methoxide (42.5 mg, 0.79 mmol) in methanol (10 mL) and stirred at rt for 7 h. The reaction mixture was concentrated, and the residue was passed through a short plug of silica gel with 500 mL of 30% ethyl acetate in petroleum ether. The filtrate was concentrated to provide **51** as a white solid (211.7 mg, 99%): mp 117−120 °C; IR ($CHCl_3$, cm^{-1}) 1766, 1455; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89−5.69 (m, 1 H), 4.75−4.67 (m, 2 H), 4.44−4.41 (m, 1 H), 3.76−3.56 (m, 4 H), 3.35 (s, 3 H), 3.24 (d, J = 9.6 Hz, 1 H), 2.54−2.47 (m, 1 H), 2.32−2.27 (m, 2 H), 2.26−2.11 (m, 2 H), 2.08−1.93 (m, 4 H), 1.91−1.79 (m, 2 H), 1.45−1.25 (m, 1 H), 1.21 (s, 3 H), 0.97−0.82 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 139.9, 124.1, 97.5, 83.1, 80.7, 68.6, 66.6, 59.3, 44.8, 41.3, 39.9, 36.7, 34.7, 30.1, 27.8, 25.6, 22.7, 18.1, −1.5; MS *m*/*z* ($M^+ - CH_2O$) calcd 380.2373, obsd 380.2385; $[\alpha]_D^{21}$ +47.5° (*c* 0.52, $CHCl_3$). Anal. Calcd for $C_{22}H_{38}O_5Si$: C, 64.35; H, 9.33. Found: C, 64.02; H, 9.19.



Irridiate	Observe	% NOE
H_b	H_c	10.0
H_c	H_b	11.3
H_d	H_e	4.6
H_d	H_a	2.3
H_e	H_c	3.4

(3a*R*,3a*S*,10*R*,11*R*,11a*R*)-3a,4,5,8,9,10,11,11a-Octahydro-11-hydroxy-3-(methoxymethyl)-10-methyl-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (52). A sample of **51** (237.6 mg, 0.58 mmol) contained in a dry 20 mL plastic vial was blanketed with N_2, dissolved in acetonitrile (10 mL), and treated with the HF−pyridine complex (0.5 mL of approximately 70% purity). After the mixture had been stirred for 4 h, an additional 0.2 mL of HF•py was introduced. After another 4 h had elapsed, triethylamine (5 mL) was added and the mixture was filtered through a small pad of silica gel (elution with 500 mL of 50% ethyl acetate in petroleum ether). The concentrated filtrate was further purified by flash chromatography on SiO_2 (elution with 40% ethyl acetate in petroleum ether) to furnish 107.1 mg (66%) of **52** as a white solid: mp 71−73 °C; IR ($CHCl_3$, cm^{-1}) 3566, 1772; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67−5.66 (m, 1 H), 5.62 (dd, J = 8.4, 9.1 Hz, 1 H), 3.72−3.54 (m, 2 H), 3.39−3.36 (m, 1 H), 3.34 (s, 3 H), 2.64−2.36 (m, 2 H), 2.34−2.29 (m, 2 H), 2.21−2.09 (m, 2 H), 2.06−1.75 (m, 6 H), 1.41−1.23 (m, 1 H), 1.21 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 140.1, 124.1, 81.5, 75.9, 68.3, 59.3, 45.1, 40.6, 39.7, 36.4, 34.7, 29.8, 26.9, 26.0, 22.7; MS *m*/*z* (M^+) calcd 280.1668, obsd 280.1671; $[\alpha]S_D^{21}$ +18.6° (*c* 12.9, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.46; H, 8.84.

Isomerization of 52 to 45. A cold (0 °C), magnetically stirred solution of **52** (24.3 mg, 0.09 mmol) in dry CH_2Cl_2 (2 mL) was treated with triethylamine (50 μL), 4-(dimethylamino)pyridine (2 mg), and methanesulfonyl chloride (10 μL) and stirred at rt for 1 h. At this time, an additional 10 μL of the sulfonyl chloride was introduced, and agitation was maintained for another hour. The reaction mixture was concentrated, and the resulting solid was leached with ample quantities of ether. The ether solutions were concentrated, and the residue was taken up in methanol (2 mL), treated with lithium hydroxide (0.2 mL of a 5% aqueous solution, 0.42 mmol), stirred at 20 °C for 2 h, and concentrated on a rotary evaporator. Water (2 mL) was added, and the product was extracted into ethyl acetate (6 × 10 mL). The aqueous phase was acidified to pH 1 with 10% HCl and extracted again with ethyl acetate (2 × 20 mL). The combined organic layers were dried and concentrated to leave the crude epoxy acid which was dissolved in acetonitrile (2 mL), treated with camphorsulfonic acid (36.1 mg), and stirred overnight at rt. The reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether) to give **45** as a white solid (10.1 mg, 41% overall), spectroscopically identical to the material described above.

(3a*R*,3a*S*,6*S*,7*R*,10*R*,11*S*,11a*S*)-Decahydro-6,7,11-trihydroxy-3-(methoxymethyl)-10-methyl-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (53). A nitrogen-blanketed solution of **45** (21.4 mg, 0.076 mmol) and N-methylmorpholine *N*-oxide (17.3 mg, 1.53 mmol) in 1:1 THF−water (2 mL) was treated with osmium tetroxide (2 mg) and stirred at rt for 1 h. Introduction of saturated Na_2SO_3 solution (5 mL) and extraction with ethyl acetate (6 × 30 mL) followed by the predescribed workup and chromatography (elution with 5% methanol in ethyl acetate) gave 17.2 mg (72%) of **53** as a white foam: IR ($CHCl_3$, cm^{-1}) 3443, 1778, 1468; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15−4.02 (m, 1 H), 3.92 (d, J = 3.8 Hz, 1 H), 3.76−3.62 (m, 2 H), 3.52 (br s, 1 H), 3.56 (s, 3 H), 2.48 (dt, J = 12.8, 3.4 Hz, 1 H), 2.28−2.14 (m, 5 H), 2.00−1.87 (m, 2 H), 1.85−1.79 (m, 2 H), 1.74−1.62 (m, 1 H), 1.58−1.50 (m, 2 H), 1.48−1.40 (m, 2 H), 0.96 (s, 3 H);^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 80.1, 73.1, 71.8, 71.7, 67.7, 59.4, 49.9, 48.2, 38.0, 37.9, 36.7, 27.5, 26.2, 23.7, 20.6; MS *m*/*z* (M^+) calcd 314.1722, obsd 314.1724; $[\alpha]_D^{20}$ +3.6° (*c* 1.12, $CHCl_3$).

(3*R*,3a*S*,6*S*,7*R*,10*R*,11*S*,11a*S*)-7-(*tert*-Butyldimethylsiloxy)decahydro-6,11-dihydroxy-3-(methoxymethyl)-10-methyl-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (54). Triol **53** (15.2 mg, 0.042 mmol) dissolved in CH_2Cl_2 (5 mL) was treated at −78 °C with diisopropylethylamine (15 μL) and *tert*-butyldimethylsilyl triflate (15 μL) and stirred at −78 °C for 1 h. After the predescribed workup and flash chromatography (silica gel, elution with 50% ethyl acetate in petroleum ether) 16.6 mg (80%) of **54** was obtained as a clear colorless oil: IR (neat, cm^{-1}) 3459, 1772, 1460; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09−3.99 (m, 1 H), 3.92−3.88 (m, 1 H), 3.77−3.62 (m, 1 H), 3.49−3.46 (m, 1 H), 3.37 (s, 3 H), 2.47 (dt, J = 12.7, 3.5 Hz, 1 H), 2.45 (br s, 1 H), 2.27−2.21 (m, 1 H), 1.99−1.90 (m, 2 H), 1.85−1.53 (series of m, 7 H), 1.50−1.31 (m, 4 H), 1.29−1.21 (m, 1 H), 0.93 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H) (one O*H* not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 80.1, 73.3, 72.4, 71.9, 67.5, 59.3, 49.8, 48.2, 39.2, 37.9, 35.4, 27.7, 26.8, 25.8, 23.9, 20.8, 18.1, −4.4, −5.0; MS *m*/*z* ($M + H)^+$ calcd 429.2661, obsd 429.2667; $[\alpha]_D^{20}$ −16.7° (*c* 0.77, $CHCl_3$).

(3a*S*,5*E*,7*R*,10*R*,11*S*,11a*S*)-7-(*tert*-Butyldimethylsiloxy)-3a,4,7,8,9,10,-11,11a-octahydro-11-hydroxy-10-methyl-3-methylene-6,10-methanocyclodeca[*b*]furan-2(3*H*)-one (55). Diol **53** (17.1 mg, 0.04 mmol) dissolved in dry benzene (5 mL) under N_2 was treated with Martin's sulfurane reagent (135.2 mg, 0.20 mmol) and allowed to stir ar rt for

2 h. At this time an additional 30.4 mg of the dehydrating agent was introduced. After a further 2 h, the solvent was evaporated and the majority of the sulfurane byproduct was removed by medium-pressure chromatography on silica gel (elution with 30% EtOAc in petroleum ether). The resulting oil was taken up in toluene (3 mL), treated with DBU (0.2 mL), heated at reflux for 4 h, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 25% ethyl acetate in petroleum ether) to provide 7.1 mg (47%, two steps) of **55** as a white foam: IR (neat, cm^{-1}) 1766; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (d, $J = 3.3$ Hz, 1 H), 5.51 (d, $J = 3.1$ Hz, 1 H), 5.47 (t, $J = 7.9$ Hz, 1 H), 4.21−4.11 (m, 2 H), 3.94−3.90 (m, 1 H), 2.63−2.62 (m, 1 H), 2.39−2.25 (m, 4 H), 2.24−2.11 (m, 1 H), 1.79−1.70 (m, 4 H), 0.98 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 144.6, 139.2, 119.5, 116.5, 81.5, 72.6, 72.3, 50.9, 40.9, 33.5, 32.4, 30.2, 25.8 (3 C), 24.3, 22.5, 18.1, −4.8, −5.0; MS *m*/*z* (M^+) calcd 378.2217, obsd 378.2220; $[\alpha]_D^{21}$ −15.7° (*c* 0.41, $CHCl_3$).

Deoxocrispolide (4). A solution of **55** (8.7 mg, 0.02 mmol) in dry CH_3CN (3 mL) under N_2 was treated wtih the HF−py reagent (0.2 mL, ca 70%), stirred at rt for 5 h, quenched with 2 mL of saturated $NaHCO_3$ solution, and poured into a separatory funnel containing 5 mL of H_2O and 10 mL of ethyl acetate. The separated aqueous layer was extracted with ethyl acetate (5 × 10 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2 × 2 mL) and brine (5 mL), dried, and concentrated. The resulting oil was purified by flash chromatography on silica gel (elution with 60% ethyl acetate in petroleum ether) to provide 4.4 mg (72%) of deoxocrispolide: IR (neat, cm^{-1}) 3596, 3461, 1764; ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, $J = 3.3$ Hz, 1 H), 5.61 (t, $J = 7.6$ Hz, 1 H), 5.53 (d, $J = 3.1$ Hz, 1 H), 4.31 (br s, 1 H), 4.19 (dd, $J = 8.3$, 8.2 Hz, 1 H), 3.90 (d, $J = 8.1$ Hz, 1 H), 2.67−2.60 (m, 1 H), 1.46−1.40 (m, 1 H), 2.39−2.27 (m, 2 H), 2.20−2.19 (m, 1 H), 2.15−1.78 (series of m, 5 H), 1.68−1.61 (m, 1 H), 1.01 (s, 3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 143.1, 139.0, 119.7, 118.7, 81.4, 72.3, 71.9, 50.7, 40.9, 32.2 (2 C), 30.0, 24.3, 22.4; $[\alpha]_D^{20}$ −3.4° (*c* 0.38, $CHCl_3$).

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Supporting Information Available: Crystallographic experimental and X-ray crystal data for **22**, including tables of bond lengths and angles, final fractional coordinates, and thermal parameters, and the final computed atomic coordinates for **29**, **30**, **F**, and **G** (10 pages). Ordering information is given on any current masthead page. Atomic coordinates for the structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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