Functionalization and Utility of Bridging Ethers in the Transformations of Bicyclo[5.4.0]undecanes

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Received August 2, 1994®

Studies detail the formation and utility of bridged ethers of bicyclo[5.4.0]undecanes as a means for stereocontrolled functionalization as described in a survey of conjugate additions, reductions, and oxidative cyclizations. The intramolecular dipolar cycloaddition of 3-oxidopyrylium ylides affords a facile preparation of the starting *trans*-fused bicyclo[5.4.0]undecenone **1**. Efficient methods toward highly oxygenated bicycloundecanes are described via the highly selective reductive cleavage of 12-oxatricyclo[6.3.1.0^{1,6}]dodecanes such as **20** and **21**. Reclosure of the oxa-bridge was examined. Vanadium-catalyzed oxidative reclosure of **24** led exclusively to the novel 2-oxatricyclo[5.4.1.0^{3,8}]-dodecane system **31**.

The occurrence of the bicyclo[5.4.0]undecane framework is found in an interesting assortment of diterpenes, which include the cyathins and striatins,[1] the dolastanes and clavularanes,[2] grayanotoxins,[3] and phorbol and related structures.[4] This general family exhibits powerful biological effects as antibiotics, antitumor agents, hypotensives, and cocarcinogens. In fact, the regio and stereochemical arrangement of hydroxylations is paramount for tubulin disassembly in dolastanes related to taxol, for receptor binding and for the powerful biochemical responses to ester derivatives of phorbol.[5] Herein, we describe our exploratory investigations for regio- and stereocontrolled oxidations of bicyclo[5.4.0]undecanes.

Bridging ethers of this system confer structural rigidity to the carbon skeleton to provide for highly stereoselective transformations within the seven-membered carbocycle, which include processes of conjugate addition, epoxidation, and hydride reduction. Of course, the pivotal role of the oxygen bridge in the determination of these stereocontrolled processes is only expedient in the event that this element can be deleted or cleaved to form the desired bicyclo[5.4.0]undecane nucleus. Therefore, we have examined the structural requirements for the reductive cleavage of 12-oxatricyclo[6.3.1.0^{1,6}]undecanes as a general route to these 6−7 bicyclic systems. Moreover, the oxa-bridge serves as a latent hydroxyl substituent of defined stereochemistry upon reductive cleavage to a targeted family of polyhydroxylated bicyclo[5.4.0]-undecanes.[6]

Results and Discussion

Our studies were facilitated by the efficient preparation of the *trans*-fused bicyclo[5.4.0]undecenone **1** via the intramolecular dipolar cycloaddition of 3-oxidopyrylium ylide **2**.[7,8] This species was directly available from the precursor dihydropyranone **3**. Acetylation of **3** at 0 °C was followed by *in situ* elimination of acetic acid in methylene chloride with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) upon warming to room temperature, generating the intermediate carbonyl ylide. The ensuing stereoselective cyclization afforded 83−93% isolated yields of a single unsaturated ketone **1**. The observed preference for the trans-fused product was rationalized from consideration of favorable π overlap of the chairlike transition state with a minimization of steric interactions as shown in **2**.

In similar fashion, dihydropyranone **4** afforded a diastereoselective cycloaddition through **5** to yield bicyclic ether **6**, establishing relative stereochemistry at four asymmetric centers. The products were characterized by the distinctive ^{1}H NMR data exhibited for the enone system with δ 6.02 (d, J = 9.8 Hz, H_A); δ 7.49 (dd, J = 9.8, 4.7 Hz, H_B) and the adjacent bridgehead methine at δ 4.76 (ddd, J = 7.8, 4.7, 2.3 Hz, H_C). The methoxymethyl ether at C-2 of **6** was assigned as an equatorial substituent as a result of proton coupling data for the C-2 methine hydrogen at δ 4.76 (dd, J = 11.7 and 5.5 Hz). However, unambiguous confirmation of the *trans*-ring fusion of **1** and **6** was only assured upon subsequent X-ray crystallography of epoxide **11**.[9]

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® Abstract published in *Advance ACS Abstracts,* January 15, 1995.

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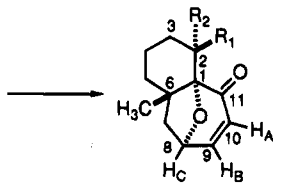
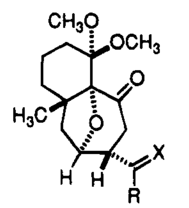
0022-3263/95/1960-0833$09.00/0

3 $R_1 = R_2 = OCH_3$
4 $R_1 = H$; $R_2 = OCH_2OCH_3$

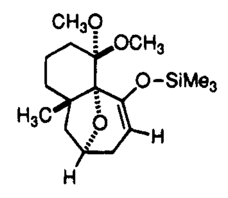
2 $R_1 = R_2 = OCH_3$
5 $R_1 = H$; $R_2 = OCH_2OCH_3$



1 $R_1 = R_2 = OCH_3$
6 $R_1 = H$; $R_2 = OCH_2OCH_3$



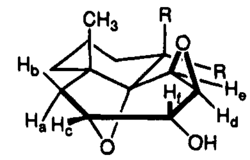
7 $X = CH_2$; $R = H$
8 $X = CH_2$; $R = CH_3$
9 $X = H_2$; $R = OH$



10

Exploratory studies ascertained that the enone system of **1** was an excellent Michael acceptor. A series of conjugate addition reactions were undertaken to evaluate the stereochemical bias imposed by the bridging ether element. For example, the facile conjugate addition of alcohols, or the addition of thiophenol to **1** in the presence of a borate buffer (pH = 9.2),[10] gave quantitative conversion to a single phenylsulfide diastereomer (α-C_9-phenyl sulfide). Facile additions of mixed Gilman reagents, prepared from vinylmagnesium bromide or 2-propenylmagnesium bromide and cuprous iodide, were totally stereoselective in providing ketones **7** (89%) and **8** (74%). Subsequent ozonolysis of **7** (O_3; CH_2Cl_2 at −78 °C; then $NaBH_4$) chemoselectively afforded the keto alcohol **9** (98%). Conjugate reductions of **1** also readily occurred with the Stryker copper hydride reagent in the presence of trimethylsilyl chloride[11] leading to the expected silyl enol ether **10** ($[Ph_3PCuH]_6$; PhH; TMSCl; 78% yield), and many of the usual hydride reagents also showed a strong tendency for 1,4-addition. In fact, reduction of **1** with L-Selectride (Aldrich) at −78 °C in THF provided 86% yield of the corresponding saturated ketone of **1** without effecting carbonyl reduction.[7]

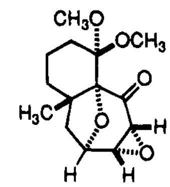
Transposition of the enone system of **1** was undertaken to investigate opportunities for nucleophilic conjugate additions at C-11. A stereoselective epoxidation of **1** with basic hydrogen peroxide (30% H_2O_2; 6 M NaOH in MeOH) afforded the crystalline epoxyketone **11** (mp 117–118 °C) in 93% yield. The X-ray diffraction study of **11** revealed that epoxidation had occurred *syn* with respect to the oxa-bridge.[9] Standard application of the Wharton reaction failed, and borohydride reduction of **11** gave exclusively the Payne rearrangement product **12**.



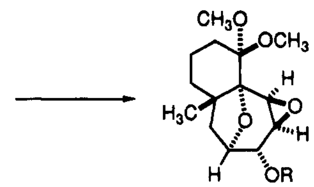
12 $R = OCH_3$

Chemical Shift (δ)		Coupling (J)
H_a	1.62	J_{ab} = 12.0 Hz
H_b	1.78	J_{ac} = 9.2 Hz
H_c	4.16	J_{cf} = 1.7 Hz
H_d	3.18	J_{cd} = 1.7 Hz
H_e	3.90	J_{bc} = 3.4 Hz
H_f	3.70	J_{de} = 4.0 Hz
		J_{df} = 1.1 Hz

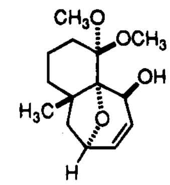
Figure 1.



11



12 $R = H$
14 $R = SO_2NMe_2$



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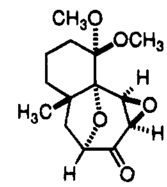

13

Proton magnetic resonance studies revealed important structural information necessary to identify **12**. The chemical shift of H_b was shifted further downfield from H_a by deshielding effects of the oxirane ring. This provided an opportunity for extensive decoupling studies summarized in Figure 1. The bridgehead proton H_c was observed as an apparent doublet of quintets. However, further studies demonstrated four coupling constants for H_c with equivalent vicinal (J_{cf}) and long range *W* coupling (J_{cd}).

Verification that **12** was indeed the Payne product was obtained by oxidation to epoxy ketone **13**, which was different from **11** in all aspects. Additionally, the formation and reductive cleavage of the *N,N*-dimethylsulfamate **14** with sodium in liquid ammonia–THF at −78 °C gave allylic alcohol **15** in 85% yield, which upon oxidation to **1** confirmed the double transposition.

A successful preparation of the alternative enone system was accomplished by careful reduction of **11** using sodium in liquid ammonia–tetrahydrofuran solution at −78 °C in the presence of 2 equiv of 2-methyl-2-propanol to give β-hydroxy ketone **16a** for further hydride addition to yield diol **16b**. Bis-silylation of **16b** with *tert*-butyldimethylsilyl triflate (3 equiv) and excess collidine also produced the facile elimination of methanol to give a cyclohexenyl methyl ether which was smoothly deprotected at C_9 for Swern oxidation and subsequent KH-induced elimination to **17** (mp 76–78 °C). No conditions of C_{11} hydroxyl silylation were uncovered to allow isolation of the C_2 dimethyl ketal, suggesting that the elimination of methanol was driven by the relief of nonbonded steric interactions. The transposed enone **17** could be reduced under dissolving metal conditions (6% Na/Hg in aqueous THF) without cleavage of the ether

(9) Structure assignment of the oxirane **11** was unambiguously confirmed by single crystal X-ray diffraction of a colorless cubic crystal at −155 °C. All atoms were located and refined to final residuals of $R_{(F)} = 0.030$ and $R_{w(F)} = 0.034$. Complete crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 88131. The author has also deposited atomic coordinates for **11** 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, UK.

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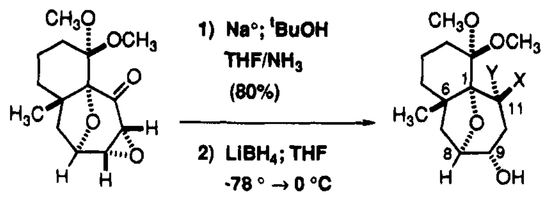
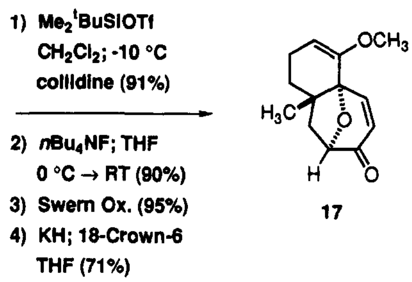
(11) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

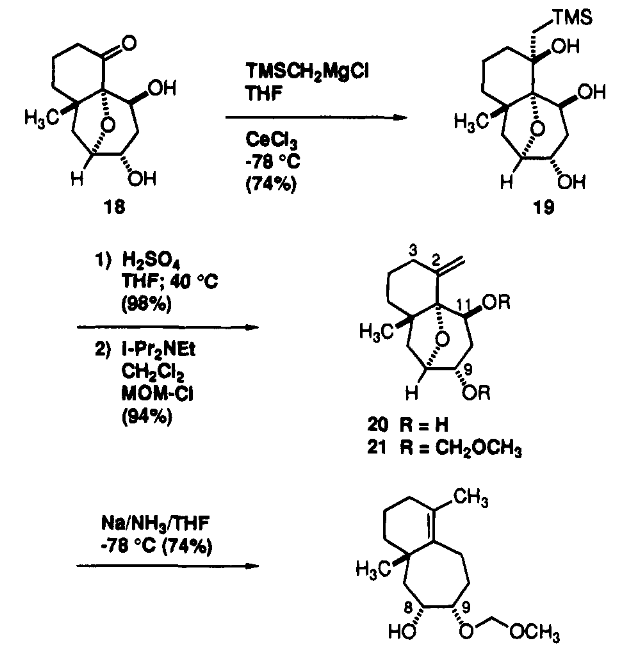


11

16a X, Y = O
16b X = OH; Y = H



17



18

19

20 R = H
21 R = CH₂OCH₃

22

bridge. However, we were disappointed to find that enone **17** exhibited very sluggish reactivity for conjugate additions and failed to react under our standard cuprate conditions.

Studies for the reductive cleavage of the ether bridge of the bicyclic[3.2.1] system were undertaken as a strategy for stereocontrolled introduction of hydroxylation of the bicyclo[5.4.0]undecanone. However, the reductive opening of the tetrahydrofuranyl ring for numerous C_9 or C_{11} ketones derived from **1** and **17** failed in all cases. Most of these attempts provided simple reduction of the ketone to its corresponding alcohol diastereomers without effecting elimination of the α-alkoxy bridge. This was surprising in light of examples of reductive eliminations in α-oxygenated ketones using mild dissolving metal conditions, such as calcium in liquid ammonia,[12a] zinc in acetic acid,[12b] aluminum–amalgum,[12c] and samarium diiodide.[12d] We presumed that this was a result of the fixed geometry of the α-alkoxy C–O bond relative to the plane of the neighboring carbonyl. This stereoelectronic misalignment could be evaluated, as a first approximation, based upon the dihedral angle of the carbonyl and the C–O ether. Our crystallographic study revealed a dihedral angle of 171° in the case of **11**. However, it is important and more difficult to consider a stereoelectronic requirement for the ketyl intermediate, particularly since the sp^3 carbon radical would presumably undergo facile pyramidal inversions.

In contrast, the placement of an *exo* methylene adjacent to the oxa-bridge gave an allylic ether moiety which proved to be useful for reductive elimination. For example, the keto diol **18** was available from **16b** via acid hydrolysis in aqueous methanol in 85% yield. Addition of an excess of organocerium reagent prepared from [(trimethylsilyl)methyl]magnesium bromide[13] afforded the stable triol **19** without competing unproductive α-deprotonation of the cyclohexanone **18**.

Nucleophilic attack of the cerium reagent occurred with high stereoselectivity, as compared with reactions of methylmagnesium chloride itself, which gave a 55% conversion to a 3:1 mixture of tertiary alcohols. Furthermore, this technique allowed for the regiocontrolled Peterson olefination to the exocyclic alkene **20**, avoiding competing generation of the trisubstituted $\Delta^{2,3}$ endocyclic cyclohexene.[14] The prior protection of diol **20** as the bis-β-methoxymethyl ether **21** afforded a route for the facile reductive elimination to alcohol **22**. The reductive removal of the C_{11} substituent occurred as a further transformation of the initial C–O cleavage product. However, this secondary reduction of the intermediate allylic MOM ether exclusively retained the $\Delta^{1,2}$ tetrasubstituted olefin in **22**. This general approach for reductive cleavage of the bridging ether succeeded as a result of the high reactivity of the initial anion radical from these exocyclic alkenes compared to the relatively more stable ketyls previously discussed, which led to their respective alcohols.[15]

In another case, reduction of the homoallylic alcohol **23** gave a high yield of diol **24** in which the β-hydroxyl substituent at C_{11} of **24** was not lost. This product was sensitive to mild protic conditions and readily afforded E_1 elimination to diene **25a** upon silylation with *tert*-butyldimethylsilyl chloride or the corresponding silyl triflate. Treatment of **24** with pyridinium tosylate (PPTs) in CH_2Cl_2 also produced moderate yields of the unstable diene alcohol **25b**. However, the diacetate was conveniently generated in excellent yield under basic conditions in which excess calcium hydride was introduced. Diacetate **26** was utilized for hydroxylations within the six-membered ring via a noteworthy, one-step allylic oxidation with *N*-bromosuccinimide to yield the desired cyclohexenone **27**. Exclusive endocyclic oxidation at C-11 of the tetrasubstituted alkene **26** was observed without evidence of bromohydrin intermediates, although small

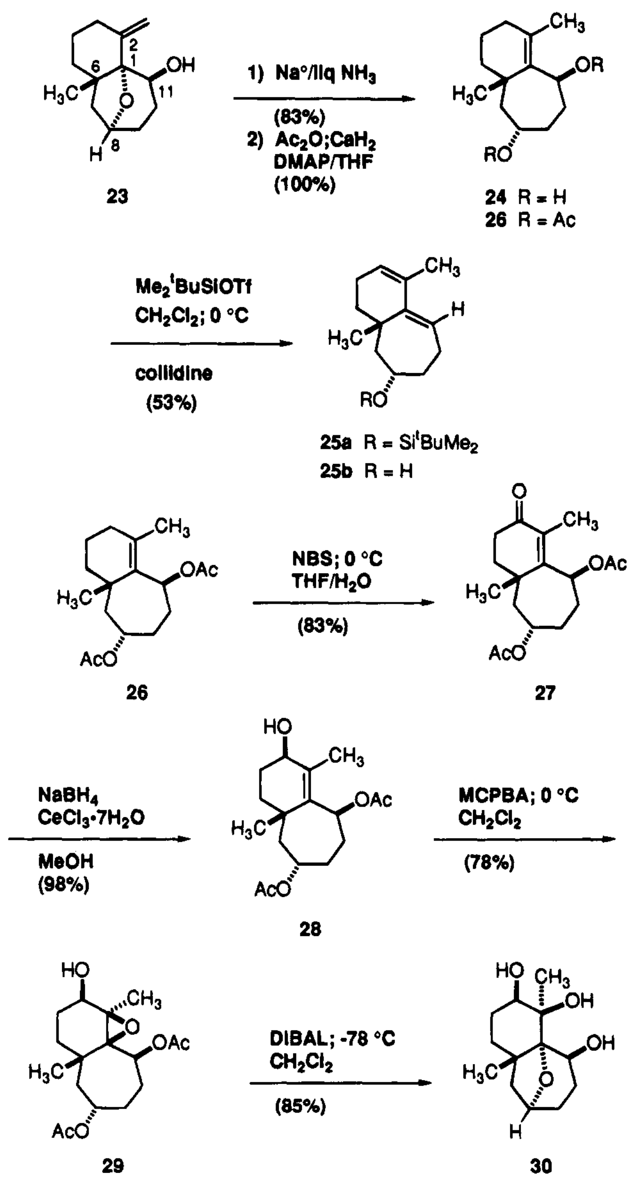
(12) (a) Chapman, J. H.; Elks, J.; Phillips, G. H.; Wyman, L. J. *J. Chem. Soc.* **1956**, 4344. (b) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223. (c) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537. (d) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945.

(13) Hauser, C. R.; Hance, C. R. *J. Am. Chem. Soc.* **1952**, *74*, 5091.

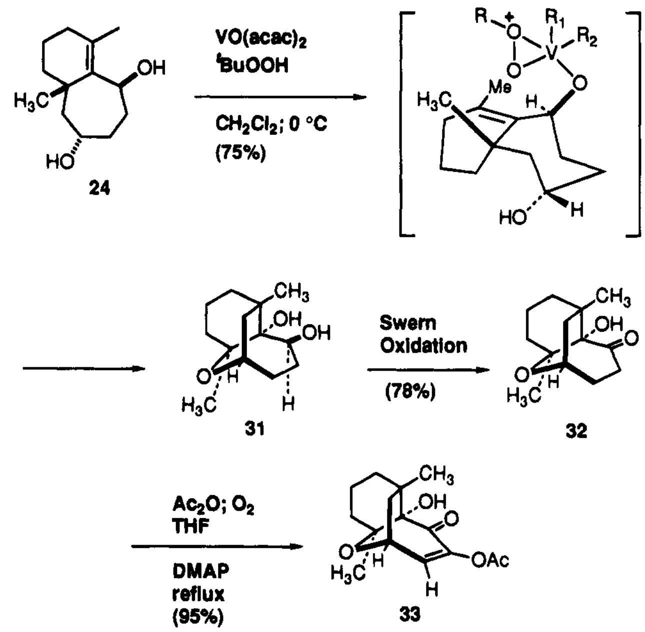
(14) Studies of elimination of the analogous C-2 tertiary alcohol obtained from addition of methyl magnesium chloride to **18** followed by MOM protection of the C_9,C_{11}-diol led to a 3:1 ratio of exocyclic **21** to endocyclic olefin ($SOCl_2$; pyridine; CH_2Cl_2 at −10 °C). Sodium reduction of the isomeric, endocyclic $\Delta^{2,3}$ alkene of **21** proceeded slowly and gave mixtures of products and recovery of starting material.

(15) Calculations available via PCModel suggest a 139° dihedral angle for the exo C=C and bridging C–O ether in the energy-minimized conformer of **20**.

(5%) quantities of allylic alcohols corresponding to α/β-**28** were obtained as byproducts in the oxidation process. Luche reduction[16] of **27** favored axial hydride delivery (5:1 ratio of β/α-alcohols) giving predominantly **28**. This stereoselectivity was reversed with the use of L-Selectride for reduction of **27** (1:3 ratio of β/α-alcohols). Finally, the epoxidation of **28** led to the expected β-oxirane **29**, which resulted in spontaneous reclosure to the oxabicyclo[3.2.1] triol **30** upon basic saponification or reductive removal of the acetate units. The oxidation of **28** with *tert*-butylhydroperoxide and VO(acac)$_2$ also rapidly proceeded to **29** in excellent yield. However, the diastereomeric axial α-alcohol of **28** proved to be completely unreactive to these epoxidation conditions.



Peracid oxidations of C-8 alcohols, such as **24**, directly re-formed the oxabicyclic system corresponding to **23** without observation of an intermediate epoxide. This is in striking contrast to vanadium-promoted oxidations of **24**, which exclusively afforded construction of the oxabicyclo[3.2.2] system **31**. The internally-directed peroxyvanadyl ligand (simplified for illustration purposes) was responsible for altering the regiochemical course of ring closure. Vicinal diol **31** was isolated in 75% yield as the sole product, and smoothly underwent Swern oxidation[17] at −78 °C to yield the α-hydroxyketone **32**.



An attempted acetylation of the tertiary bridgehead hydroxyl group led to the novel enone **33** via an air oxidation of the readily formed enol of **32** followed by *in situ* acetylation of the intermediate α-diketone. The transformation to α,β-unsaturated ketone **33** was quantitative upon passing a stream of oxygen over the reaction mixture. The assignment of the oxabicyclo[3.2.2] skeleton was unambiguously confirmed via an X-ray crystallographic study of **33**,[18] suggesting a concerted oxidative cyclization pathway for the VO(acac)$_2$ reaction of **24** without evidence of a discreet oxirane intermediate as produced in the stepwise conversion of **28** → **30**.

In conclusion, a bridging ethereal oxygen is an important structural element in the framework of bicyclo[5.4.0]-undecanes. It provides a highly effective means for stereocontrolled 1,4-conjugate and 1,2-nucleophilic addition processes. Pathways for the reductive cleavage of the oxygen bridge are efficient as a strategy for regio- and stereocontrolled hydroxylation of the bicyclo[5.4.0] skeleton. Reclosure of the oxa-bridge is highly reagent-dependent and has provided a scheme for synthesis of novel bicyclo[3.2.2] ethers. Efforts to utilize this approach for natural product synthesis are underway.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Samples were prepared as films on NaCl plates unless otherwise noted. Proton NMR spectra were recorded on either a Varian XL-300, a Nicolet NT-360, or a Bruker AM-500 spectrometer. Carbon NMR spectra were recorded on either a Varian XL-300 or a Bruker AM-500 spectrometer. Proton chemical shifts are given in

(16) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(17) Mancuso, A. J.; Huang, S.-L.; Swern, D. J. *J. Org. Chem.* **1978**, *43*, 2480.

(18) The structure of **33** was established via single crystal X-ray diffraction at −157 °C. Crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 89179. The author has also deposited atomic coordinates for **33** 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, UK.

parts per million downfield relative to a tetramethylsilane standard, and samples were prepared in deuteriochloroform unless otherwise stated. Mass spectra were recorded on a Kratos MS-80 spectrometer. Diethyl ether and tetrahydrofuran were distilled under argon from sodium benzophenone ketyl. Methylene chloride, triethylamine, pyridine, diisopropylethylamine, 2,4,6-trimethylpyridine, dimethylformamide, *N,N,N',N'*-tetramethylethylenediamine, hexamethylphosphoramide, 2,2,6,6-tetramethylpiperdine, *tert*-butanol, and dimethylsulfoxide were distilled from calcium hydride. Oxalyl chloride, (L)-diethyl tartrate, 1,8-diazabicyclo[5.4.0]undec-7-ene, titanium(IV) tetraisopropoxide, acetyl chloride, acetic anhydride, and *tert*-butyldimethylsilyl triflate were distilled prior to use. Ethyl acetate and hexanes for chromatography were distilled before use. Silica gel 60-H (E. Merck) was used for medium pressure flash chromatography. Precoated glass plates 60f-254 (E. Merck, 0.25 mm thickness) were used for analytical TLC. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Preparation of the Dihydropyranone 3. To a solution of 20.3 g (0.160 mol) of oxalyl chloride in 800 mL of THF at −78 °C was added 13.7 g (0.176 mol) of dry DMSO. The reaction mixture was maintained under a slow stream of N_2, and adequate ventilation through a drying tube was necessary to permit the escape of the large quantity of gases generated in this step. The mixture was allowed to stir at −78 °C for 30 min prior to the cannulation of a solution of 15.0 g (0.079 mol) of 2,2-dimethoxy-6-methyl-6-hepten-1-ol in 30 mL of THF. This mixture was stirred for 1 h to ensure formation of the Swern adduct, and 40.4 g (0.40 mol) of Et_3N was added followed by stirring at −78 °C for 15 min and then gradual warming to 0 °C over 45 min.

While the Swern oxidation was warming, 2-lithiofuran was prepared. A solution of 32.6 g (0.48 mol) of distilled furan and 51.0 g (0.44 mol) of *N,N,N',N'*-tetramethylethylenediamine in 800 mL of Et_2O was cooled to 0 °C, and 160.0 mL (0.40 mol) of a 2.5 M solution of *n*-BuLi in hexanes was added dropwise . This mixture was stirred at room temperature for 30 min to provide a light yellow solution which was cooled to −78 °C. The Swern oxidation mixture was recooled to −78 °C and the cold 2-lithiofuran was added *via* cannulation. This mixture was stirred for 8 h as it gradually warmed to room temperature and was quenched by the addition of saturated aqueous NH_4Cl solution (500 mL). The biphasic mixture was partitioned between Et_2O/H_2O (1 L each), and the organic phase washed with brine (1 L). The combined aqueous layers were extracted with Et_2O (2 × 500 mL), and the organic extracts dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (200 g of SiO_2; EtOAc/hexanes gradient) to provide 15.8 g (78%) of the expected furfuryl alcohol derivative as a light yellow liquid.

2,2-Dimethoxy-1-(2-furanyl)-6-methyl-6-hepten-1-ol was characterized as follows: R_f = 0.30 in 20% EtOAc/hexanes; IR (neat) 3460, 3120, 3070, 2940, 1650 cm^{-1}; ^{1}H NMR δ 7.40 (m, 1H), 6.40−6.35 (m, 2H), 4.89 (d, J = 3.5 Hz, 1H), 4.67 (m, 1H), 4.63 (m, 1H), 3.37 (s, 3H), 3.32 (s, 3H), 2.79 (m, 1H), 1.93 (t, J = 6.6 Hz, 2H), 1.67 (s, 3H), 1.65−1.54 (m, 2H), 1.40−1.25 (m, 2H); HRMS (EI) m/e calcd for $C_{13}H_{16}O_2$ (M^+ − CH_3OH and H_2O) 204.1151, found 204.1142.

A solution of 11.3 g (44.4 mmol) of the furfuryl alcohol prepared above and Rose Bengal (215 mg) in 400 mL CH_2Cl_2/MeOH (2:1) at −78 °C were irradiated with a 40 W tungsten-filament lamp for 6 h with O_2 bubbling through the solution using a standard photolysis immersion well. The solution was transferred to an Erlenmeyer flask wrapped with aluminum foil, and dimethyl sulfide (20 mL) was added. The mixture was allowed to stir for several hours at 22 °C. Starch iodide paper was used to test for the presence of peroxides. Solvent was removed *in vacuo*, and the crude material was purified by flash chromatography (45% EtOAc/hexanes) to give 9.28 g of dihydropyranone **3** (77%) as a mixture of epimers: R_f = 0.24 in 50% EtOAc/hexanes; IR ($CHCl_3$) 3580, 3400 (br), 2950, 1695, 1650, 1060 (br) cm^{-1}; ^{1}H NMR (mixture of anomers) δ 6.93−6.85 and 6.89 (m, and dd, J = 10.9 Hz, J = 3.5 Hz, 1H), 6.21−6.16 and 6.13 (m, and d, J = 10.9 Hz, 1H), 5.75 and 5.52 (d, J = 3.9 Hz, and br s, 1H), 5.03 and 4.32 (2 br s, 1H), 4.79 and 4.35 (2 s, 1H), 4.72 and 4.69 and 4.64 (3 m, 2H), 3.31 and 3.30 and 3.29 and 3.27 (4 s, 6H), 2.08−1.70 (m, 2H), 1.96 (m, 2H), 1.72 and 1.68 (2 s, 3H), 1.60−1.33 (m, 2H).

The acetate of **3** was prepared from **3** (AcCl, Pyr, DMAP, CH_2Cl_2, 0−22 °C, 90 m, 93%) and was isolated as a mixture of epimers: R_f = 0.51 in 50% EtOAc/hexanes; IR (neat) 3080, 2950, 1755, 1695, 1220 (br), 1180 (br) cm^{-1}; ^{1}H NMR (mixture of acetates) δ 6.91 and 6.84 (a pair of dd, J = 9.8 Hz, J = 3.5 Hz, J = 10.9 Hz, J = 2.0 Hz, 1H), 6.58 and 6.49 (d and m, J = 3.5 Hz, 1H), 6.29 and 6.24 (2 d, J = 1.6 Hz, J = 10.5 Hz, 1H), 4.69 (m, 1H), 4.64 (m, 1H), 4.62 and 4.34 (s and d, J = 2.0 Hz, 1H), 3.31 and 3.28 and 3.26 (3 s, 6H), 2.17 and 2.12 (2 s, 3H), 2.02−1.92 (m, 2H), 1.87−1.74 (m, 2H), 1.67 (s, 3H), 1.53−1.35 (m, 2H).

Preparation of Dihydropyranone 4. A solution of 0.140 g (0.551 mmol) of 1-(2-furanyl)-2-(methoxymethoxy)-6-methyl-6-hepten-1-ol and Rose Bengal (6 mg) in a 2:1 mixture of CH_2Cl_2/CH_3OH (11.0 mL) was cooled to −78 °C. A steady stream of oxygen was bubbled through the solution as it was irradiated with a 40 W tungsten-filament lamp. After 2.5 h, the lamp was turned off, the apparatus wrapped in foil, and 0.137 g (2.20 mmol) of dimethyl sulfide added to decompose the hydroperoxides. After 1 h, the solution was decanted, the solvents were removed *in vacuo*, and the residue was purified by flash chromatography (15 g of SiO_2; 40% EtOAc/hexanes) to provide 0.110 g (74%) of the pyranone **4** as a mixture of diastereomers: R_f = 0.42 in 60% EtOAc/hexanes; IR (neat) 3400 (br), 3088, 2940, 1697, 1030 cm^{-1}; ^{1}H NMR (major diastereomer) δ 6.92 (dd, J = 10.5, 3.5 Hz, 1H), 6.11 (d, J = 10.5 Hz, 1H), 5.73 (br d, J = 3.5 Hz, 1H), 4.89 (d, J = 2.4 Hz, 1H), 4.80−4.60 (m, 4H), 4.29−4.20 (m, 1H), 3.41 (s 3H), 2.10−2.00 (m, 3H), 1.80−1.29 (m, 4H), 1.69 (s, 3H); MS (CI, NH_3) m/e (relative intensity) 239 (3), 158 (40), 128 (43), 125 (35), 107 (43), 97 (100), 95 (90); HRMS (CI, NH_3) m/e calcd for $C_{13}H_{19}O_4$ (M^+ − OCH_3) 239.1289, found 239.1299.

(±)-(1*S,6*S**,8*R**)-2,2-Dimethoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodec-9-en-11-one (1).** A solution of 2.58 g (9.55 mmol) of **3** and a catalytic amount of 4-(*N,N*-dimethylamino)pyridine in CH_2Cl_2 (95 mL) was cooled to 0 °C. Anhydrous pyridine (1.0 mL, 12.41 mmol) was added, followed by addition of 1.08 mL (11.47 mmol) of acetic anhydride. After 1 h, the corresponding acetates of **3** had formed, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) 3.14 mL (21.0 mmol) was added. The ice bath was removed, and the deep red solution was stirred at 22 °C for 16 h. The mixture was diluted with EtOAc (60 mL) and washed with saturated aqueous NH_4Cl (60 mL) and brine (2 × 60 mL). The combined aqueous phases were washed with EtOAc (5 × 30 mL), and the organic extracts were dried (Na_2SO_4), filtered, and concentrated. The oily residue was purified by flash chromatography (170 g of SiO_2; 35% EtOAc/hexanes) to provide 2.08 g (86%) of **1** as a white crystalline solid with consistent yields ranging from 85 to 95%: mp 99−100 °C; R_f = 0.23 in 50% EtOAc/hexanes; IR ($CDCl_3$) 2960, 1690, 1615, 1450, 1140, 1050 cm^{-1}; ^{1}H NMR (C_6D_6) δ 6.44−6.36 (m, 1H), 5.82 (d, J = 9.0 Hz, 1H), 4.18−4.11 (m, 1H), 3.23 (s, 3H), 3.14 (s, 3H), 2.18−2.05 (m, 1H), 2.00−1.89 (m, 1H), 1.86−1.74 (m, 1H), 1.61−1.52 (m, 1H), 1.49−1.27 (m, 3H), 1.11 (m, 1H), 0.99 (s, 3H); ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 1H), 6.05 (d, J = 10.4 Hz, 1H), 4.82 (m, 1H), 3.29 (s, 3H), 3.19 (s, 3H), 2.11−1.88 (m, 4H), 1.68−1.52 (m, 4H), 1.08 (s, 3H); ^{13}C NMR (75.4 MHz, C_6D_6) δ 193.3 (s), 151.4 (d), 128.9 (d), 102.4 (s), 92.1 (s), 71.5 (d), 49.3 (q), 49.2 (q), 44.2 (t), 43.1 (s), 35.5 (t), 25.8 (t), 25.2 (q), 17.5 (t); HRMS (EI) m/e calcd for $C_{14}H_{20}O_4$ (M^+) 252.1362, found 252.1365. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.46; H, 7.78.

(±)-(1*R,2*S**,6*S**,8*R**)-2,2-Dimethoxy-2-(methoxymethoxy)-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodec-9-en-11-one (6).** To a solution of 100 mg (0.370 mmol) of hydroxypyranone **4** containing 4-(dimethylamino)pyridine (5 mg) and pyridine (44 mg; 0.555 mmol) in 3.7 mL of CH_2Cl_2 at 0 °C was added 49 mg (0.482 mmol) of acetic anhydride. This mixture was stirred for 1 h to form the anomeric acetates of **4** (R_f = 0.58 in 60% EtOAc/hexanes). Then the reaction mixture was directly treated with 0.124 g (0.814 mmol) of DBU and the ice bath removed. After being stirred at room temperature for

16 h, the mixture was diluted with Et_2O (30 mL) and washed with saturated aqueous NH_4Cl (30 mL) and brine (30 mL). The aqueous washes were extracted with Et_2O (15 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (15 g of SiO_2; 40% EtOAc/hexanes) to provide 47.4 mg (51%) of enone **6** as a single diastereomer: $R_f = 0.40$ in 60% EtOAc/hexanes; IR (neat) 3060, 1690, 1468, 1155, 1112, 1050 cm^{-1}; ^1H NMR δ 7.49 (dd, $J = 9.8$, 4.7 Hz, 1H), 6.02 (d, $J = 9.8$ Hz, 1H), 4.76 (ddd, $J = 7.8$, 4.7, 2.3 Hz, 1H), 4.68 (AB, $J_{AB} = 6.8$ Hz, $\Delta\upsilon = 10.7$ Hz, 2H), 4.45 (dd, $J = 11.7$, 5.5 Hz, 1H), 3.35 (s, 3H), 2.17 (dd, $J = 12.1$, 7.8 Hz, 1H), 2.04−1.99 (m, 1H), 1.69 (dd, $J = 12.1$, 2.3 Hz, 1H), 1.67−1.52 (m, 4H), 1.48−1.33 (m, 1H), 1.01 (s, 3H); MS (CI, NH_3) *m/e* (relative intensity) 221 (13), 191 (15), 140 (100), 110 (30); HRMS (CI, NH_3) *m/e* calcd for $C_{13}H_{17}O_3$ ($M^+ - OCH_3$) 221.1177, found 221.1160.

(±)-(1S*,6S*,8R*,9R*)-2,2-Dimethoxy-6-methyl-9-vinyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-11-one (7). A solution (0.5 M) of vinyl magnesium bromide was prepared by treating 0.171 g (7.14 mmol) of magnesium in 5.0 mL of THF with 0.38 mL of a 9.3 M solution of vinyl bromide in THF. The resulting Grignard reagent was diluted with 2.14 mL of THF and cannulated into a stirred suspension of 0.226 g (1.19 mmol) of CuI and 0.300 g (1.19 mmol) of enone **1** in 11.9 mL of THF at 0 °C. In 5 min, the reaction was quenched by the addition of CH_3OH (4 mL) and saturated aqueous NH_4Cl (5 mL). The resulting biphasic mixture was diluted with Et_2O (50 mL) and washed with saturated aqueous NH_4Cl (30 mL) and brine (30 mL) and the organic layer dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (35 g of SiO_2; 5% EtOAc/hexanes) to provide 0.298 g (89%) of the conjugate addition product **7** as a clear oil: $R_f = 0.58$ in 20% EtOAc/hexanes; IR (neat) 3090, 2950, 1730, 1645, 1465, 1084, 997 cm^{-1}; ^1H NMR δ 6.17−6.02 (m, 2H), 5.10−5.00 (m, 1H), 4.33 (dd, $J = 8.2$, 3.9 Hz, 1H), 3.24 (s, 6H), 2.58 (AB of ABX, $J_{AB} = 15.6$ Hz, $J_{AX} = 7.6$ Hz, $J_{BX} = 6.8$ Hz, $\Delta\upsilon = 119.0$ Hz, 2H), 2.32 (br q, $J = 8.2$ Hz, 1H), 2.11 (dd, $J = 12.9$, 8.2 Hz, 1H), 1.94−1.85 (m, 1H), 1.83−1.71 (m, 1H), 1.68−1.42 (m, 3H), 1.38−1.33 (m, 1H), 1.30 (dd, $J = 12.9$, 3.9 Hz, 1H), 1.17 (s, 3H); MS (CI, NH_3) *m/e* (relative intensity) 281 (3), 249 (36), 127 (53), 101 (100); HRMS (CI, NH_3) *m/e* calcd for $C_{16}H_{25}O_4$ ($M^+ + 1$) 281.1752, found 281.1733.

(±)-(1S*,6S*,8R*,9R*)-9-Isopropenyl-2,2-dimethoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-11-one (8). The same procedure was followed as for **7** with the following changes. The reaction was run in Et_2O with only 1.2 equiv of a 1.0 M solution of 2-propenylmagnesium bromide. The crude product was chromatographed in 10% EtOAc/hexanes to provide 0.259 g (74%) of the propenyl adduct **8** (based on 300 mg of starting enone **1**): $R_f = 0.65$ in 40% EtOAc/hexanes; IR (neat) 3059, 2950, 1722, 1640, 1460, 1073 (br) cm^{-1}; ^1H NMR δ 4.84 (br s, 1H), 4.80 (t, $J = 1.8$ Hz, 1H), 4.39 (dd, $J = 9.0$, 3.5 Hz, 1H), 3.29 (s, 3H), 3.24 (s, 3H), 2.82 (dd, $J = 14.5$, 7.4 Hz, 1H), 2.44−2.26 (m, 2H), 2.12 (dd, $J = 12.9$, 9.0 Hz, 1H), 1.95−1.80 (m, 2H), 1.84 (s, 3H), 1.69−1.43 (m, 4H), 1.29 (dd, $J = 12.9$, 3.5 Hz, 1H), 1.17 (s, 3H); MS (CI, NH_3) *m/e* (relative intensity) 294 (4), 105 (100), 101 (35); HRMS (CI, NH_3) *m/e* calcd for $C_{17}H_{26}O_4$ (M^+) 294.1831, found 294.1826.

(±)-(1S*,6S*,8R*,9R*)-9-(Hydroxymethyl)-2,2-dimethoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-11-one (9). A stirred solution of 0.150 g (0.536 mmol) of olefin **7** in a 3:1 mixture of CH_2Cl_2/CH_3OH (5.0 mL) at −78 °C was saturated with ozone until the blue color persisted. The system was purged with argon, and 0.036 g (1.07 mmol) of $NaBH_4$ was added with warming to room temperature. After being stirred for 8 h, the excess hydride was quenched with addition of aqueous NH_4Cl. The solids were dissolved in H_2O and the mixture partitioned with Et_2O and H_2O (30 mL each). The organic layer was washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (15 g of SiO_2, 60% EtOAc/hexanes) provided 0.150 g (98%) of alcohol **9** as a clear liquid: $R_f = 0.16$ in 60% EtOAc/hexanes; IR (neat) 3503, 2945, 1725, 1468, 1089, 1050 cm^{-1}; ^1H NMR δ 4.53 (dd, 8.2, 3.9 Hz, 1H), 3.75 (br d, $J = 6.3$ Hz, 2H), 3.24 (s, 3H), 3.21 (s, 3H), 2.47 (AB of ABX, $J_{AB} =$ 16.4 Hz, $J_{AX} = 19.9$ Hz, $J_{BX} = -18.7$ Hz, $\Delta\upsilon = 44.6$ Hz, 2H), 2.12 (dd, $J = 13.3$, 8.2 Hz, 1H), 1.99−1.83 (m, 3H), 1.80−1.69 (m, 1H), 1.59−1.42 (m, 4H), 1.30 (dd, $J = 13.3$, 3.9 Hz, 1H), 1.16 (s, 3H); MS (CI, NH_3), *m/e* (relative intensity) 285 (1), 284 (3), 254 (45), 101 (100); HRMS (CI, NH_3) *m/e* calcd for $C_{15}H_{25}O$ ($M^+ + 1$) 285.1702, found 285.1696.

(±)-(1S*,6S*,8R*,9R*,10R*)-2,2-Dimethoxy-9,10-epoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-11-one (11). To a solution of 2.33 g of enone **1** (9.22 mmol) in 40 mL methanol was added 6.2 mL of 6 N aqueous NaOH (37 mmol) followed by 3.2 mL of 30% H_2O_2 (28 mmol). After 5 min, $NaHSO_3$ solution was added until no peroxide could be detected by starch/iodide test paper. The mixture was saturated with NaCl and extracted five times with ethyl ether, and the combined organic material was concentrated *in vacuo*. An ether solution of the residue was washed twice with brine, dried over $MgSO_4$, and concentrated *in vacuo*, and the residue was crystallized from hexanes/acetone to give 2.29 g of epoxide **11** as needles (93%): $R_f = 0.31$ in 50% EtOAc/hexanes; mp 117−118 °C, IR (neat) 2960, 1740, 1155, 1140, 1120, 1080, 1020 cm^{-1}; ^1H NMR (C_6D_6) δ 4.16 (m, 1H), 3.16 (s, 3H), 3.09 (d, $J = 4.6$ Hz, 1H), 3.05 (s, 3H), 2.05 (m, 1H), 1.90−1.69 (m, 2H), 1.56−1.44 (m, 1H), 1.38−1.08 (m, 2H), 1.18−0.60 (m, 1H), 0.94 (s, 3H); ^{13}C NMR (C_6D_6) δ 200.1 (s), 102.6 (s), 91.6 (s), 69.3 (d, $J = 157$ Hz), 55.8 (d, $J = 187$ Hz), 55.3 (d, $J = 182$ Hz), 50.3 (q, $J = 140$ Hz), 47.8 (q, $J = 142$ Hz), 46.1 (s), 44.1 (t, $J = 134$ Hz), 37.5 (t, $J = 130$ Hz), 27.3 (t, $J = 130$ Hz), 22.1 (q, $J = 128$ Hz), 18.3 (t, $J = 133$ Hz); HRMS (EI) *m/e* calcd for $C_{14}H_{20}O_5$ (M^+) 268.1311, found 268.1317. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.65; H, 7.47.

(±)-(1S*,6S*,8R*,9R*,10S*,11S*)-2,2-Dimethoxy-10,11-epoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-9-ol (12). To a solution of 1.84 g of $LiBH_4$ (84.6 mmol) in 40 mL THF was added 2.27 g of epoxy ketone **11** in THF (10 mL). Initially, a small amount of a new substance appeared on TLC ($R_f =$ 0.43 in 50% EtOAc/hexanes), slightly less polar than starting material. This initial product quickly disappeared as a new product grew in intensity ($R_f = 0.21$ in 50% EtOAc/hexanes) corresponding to the alcohol **12**. After 4 h, the mixture was carefully poured into saturated NH_4Cl solution and extracted five times with ether. The combined organic material was dried over $MgSO_4$, concentrated *in vacuo*, and then crystallized from hexane. Three crops of crystals were taken, and the mother liquor was concentrated *in vacuo* for flash chromatography in 55% EtOAc/hexanes to result in a combined yield of 2.02 g of **12** (88%): mp 105−106 °C; IR ($CHCl_3$) 3570, 3470, 2940, 1460, 1095, 1050 cm^{-1}; ^1H NMR δ 4.20−4.13 (m, 1H), 3.90 (d, $J = 3.9$ Hz, 1H), 3.70 (d, $J = 10.9$ Hz, 1H), 3.44 (s, 3H), 3.30 (s, 3H), 3.18 (m, 1H), 2.23 (d, $J = 11.3$ Hz, 1H), 1.96 (m, 1H), 1.82−1.20 (m, 7H), 1.27 (s, 3H); ^1H NMR (C_6D_6) δ 4.03 (m, 1H), 4.03 (d, $J = 3.9$ Hz, 1H), 3.57 (s, 1H), 3.26 (s, 3H), 3.13 (m, 1H), 3.01 (s, 3H), 1.83−1.60 (m, 3H), 1.44 (s, 3H), 1.42−1.20 (m, 4H), 1.07−1.03 (m, 1H); ^{13}C NMR (C_6D_6) δ 102.1 (s), 85.8 (s), 76.5 (d, $J = 154$ Hz), 67.9 (d, $J = 148$ Hz), 57.0 (d, $J = 182$ Hz), 52.5 (q, $J = 140$ Hz), 52.1 (d, $J = 180$ Hz), 47.7 (q, $J = 142$ Hz), 47.2 (s), 42.5 (t, $J = 132$ Hz), 40.0 (t, $J = 125$ Hz), 25.2 (t, $J = 128$ Hz), 19.1 (t, $J = 127$ Hz), 18.8 (q, $J = 128$ Hz); HRMS (EI) *m/e* calcd for $C_{13}H_{19}O_4$ ($M^+ - CH_3O$) 239.1284, found 239.1288. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.29; H, 8.14.

(±)-(1S*,6S*,8R*,10R*,11S*)-2,2-Dimethoxy-10,11-epoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-9-one (13). To a solution of oxalyl chloride (12 μL; 17.6 mg; 0.139 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C was added 13 μL (14.4 mg; 0.185 mmol) of dry DMSO. After the mixture was stirred for 15 min, a solution of 25 mg (0.926 mmol) of epoxy alcohol **12** in CH_2Cl_2 (1.0 mL) was added dropwise. Upon stirring for 1 h, Et_3N (28 μL; 21 mg; 0.204 mmol) was added, and the reaction was allowed to warm to room temperature. After being stirred for 30 min, the mixture was concentrated *in vacuo* and directly purified by flash chromatography (4 g of SiO_2; 20% EtOAc in hexanes) to yield 24 mg (98%) of epoxy ketone **13**: $R_f = 0.65$ in 35% hexanes in EtOAc; IR (neat) 2950, 1740, 1460, 1095, 1080 cm^{-1}; ^1H NMR (500 MHz) δ 4.31 (d, $J = 3.8$ Hz, 1H), 4.22 (ddd, $J = 9.4$, 3.1, 1.3 Hz, 1H), 3.44 (s, 3H), 3.31 (s, 3H), 3.25 (dd, $J = 3.7$, 1.3 Hz, 1H), 2.08 (dd, $J = 12.5$, 3.2 Hz, 1H), 1.99−1.94 (m, 1H), 1.90 (dd, J = 12.5, 9.4 Hz, 1H), 1.81 (td, J = 13.3, 4.2 Hz, 1H), 1.60−1.48 (m, 2H), 1.47−1.37 (m, 2H), 1.35 (s, 3H); HRMS (EI) m/e calcd for $C_{14}H_{20}O_4$ (M^+) 252.1362, found 252.1364.

Preparation of *N,N*-Dimethylsulfamate 14. To a suspension of 570 mg of 57% NaH oil dispersion (24 mmol) in 30 mL of THF was added 1.99 g of **12** (7.38 mmol) in 10 mL of THF. After 5 min, *N,N*-dimethylsulfamoyl chloride (2.14 g; 14.9 mmol) was added and stirring continued at room temperature for 1 h. The reaction was quenched with water and extracted with ether (3×). The combined organic material was dried and filtered ($MgSO_4$) and concentrated *in vacuo*, and the residue was crystallized from hexanes/acetone to give 2.71 g of **14** as white needles (97%): R_f = 0.50 in 50% EtOAc/hexanes; mp 116−118 °C; IR ($CHCl_3$) 2950, 1460, 1360, 1170, 1100, 945 cm^{-1}; ^{1}H NMR (C_6D_6) δ 4.49 (s, 1H), 4.42−4.31 (m, 1H), 4.06 (d, J = 4.3 Hz, 1H), 3.30 (s, 3H), 3.28 (m, 1H), 3.03 (s, 3H), 2.41 (s, 5H), 1.86−1.72 (m, 1H), 1.65−1.54 (m, 2H), 1.50−1.16 (m, 4H), 1.35 (s, 3H), 1.11−1.01 (m, 1H); ^{13}C NMR (C_6D_6) δ 102.0 (s), 85.6 (s), 75.6 (d, J = 146 Hz), 73.7 (d, J = 155 Hz), 57.4 (d, J = 186 Hz), 52.7 (q, J = 142 Hz), 49.7 (d, J = 186 Hz), 47.5 (q, J = 142 Hz), 47.1 (s), 42.3 (t, J = 133 Hz), 39.9 (t, J = 128 Hz), 38.1 (q, J = 138 Hz), 24.8 (t, J = 130 Hz), 19.6 (t, J = 127 Hz), 18.6 (q, J = 123 Hz); HRMS (EI) m/e calcd for $C_{16}H_{27}NO_7S$ (M^+) 377.1509, found 377.1509. Anal. Calcd for $C_{16}H_{27}NO_7S$: C, 50.89; H, 7.21. Found: C, 50.96; H, 7.39.

(±)-(1*S,6*S**,8*R**,11*S**)-2,2-Dimethoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodec-9-en-11-ol (15).** To a solution of sodium (827 mg; 35.9 mmol) in 40 mL of liquid NH_3 and 10 mL of anhydrous THF at −78 °C was added 679 mg (1.80 mmol) of **14** in 20 mL of THF. After 20 min, methanol (10 mL) was added. The cold bath was removed, and NH_3 was allowed to evaporate over 2.5 h. The mixture was diluted with water and extracted three times with ether. The combined organic material was dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was purified by flash chromatography with 20% EtOAc/hexanes to give 333 mg of **15** (83%): R_f = 0.50 in hexanes/EtOAc/CH_2Cl_2 (2:1:1); IR ($CHCl_3$) 3530 (br), 2950, 1465, 1225 (br), 1060 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.66 (dd, J = 9.7, 2.3 Hz, 1H), 5.33 (s, 1H), 4.36 (dd, J = 7.0, 4.1 Hz, 1H), 3.46 (s, 3H), 3.40 (s, 1H), 3.33 (s, 3H), 2.01−1.93 (m, 2H), 1.93−1.86 (m, 1H), 1.78 (d, J = 11.5 Hz, 1H), 1.71−1.61 (m, 1H), 1.61−1.48 (m, 2H), 1.45 (s, 3H), 1.47−1.39 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 132.1 (d, J = 161 Hz), 128.1 (d, J = 162 Hz), 105.3 (s), 86.6 (s), 72.6 (d, J = 150 Hz), 69.7 (d, J = 145 Hz), 52.5 (q, J = 142 Hz), 49.5 (t, J = 119 Hz), 48.6 (q, J = 143 Hz), 47.4 (s), 39.5 (t, J = 126 Hz), 26.7 (q, J = 126 Hz), 21.7 (t, J = 125 Hz), 17.0 (t, J = 126 Hz); HRMS (CI, NH_3) m/e calcd for $C_{13}H_{19}O_3$ ($M^+ - CH_3O$) 223.1335, found 223.1337.

(±)-(1*S,6*S**,8*R**,9*S**)-2,2-Dimethoxy-9-hydroxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-11-one (16a).** A dry two-necked flask, fitted with a dry ice condenser, was cooled to −78 °C and charged with 112 mL of NH_3. Further addition of 1.98 g (26.8 mmol) of anhydrous 2-methyl-2-propanol and a solution of 3.60 g (13.4 mmol) of epoxy ketone **11** in THF (22.3 mL) was completed with continued cooling to −78 °C. With vigorous stirring, 0.647 g (28.1 mmol) of sodium (washed with hexanes) was added, in small pieces, and the mixture was stirred until the blue color had dissipated, leaving a white suspension. The reaction was quenched by the addition of solid NH_4Cl, the ammonia evaporated, and the solids dissolved in H_2O. The resulting biphasic mixture was partitioned with EtOAc and H_2O (100 mL each), and the organic layer was washed with brine (70 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (600 g of SiO_2; 80% EtOAc/hexanes) to provide 2.86 g (79%) of the β-hydroxy ketone **16a** as a white solid and 0.421 g (12%) of recovered starting material. Characterization of β-hydroxy ketone **16a** is as follows: mp 110−112 °C; R_f = 0.27 in 75% EtOAc/hexanes; IR (neat) 3500, 2950, 1725, 1468, 1057 cm^{-1}; ^{1}H NMR δ 4.44 (dd, J = 9.4, 4.3 Hz, 1H), 3.81 (m, 1H), 3.25 (s, 3H), 3.22 (s, 3H), 2.79 (AB of ABX, J_{AB} = 18.0 Hz, J_{AX} = 10.6 Hz, J_{BX} = 0.3 Hz, Δv = 47.8 Hz, 2H), 2.45 (d, J = 9.8 Hz, 1H), 2.02 (dd, J = 13.3, 9.4 Hz, 1H), 1.96−1.85 (m, 1H), 1.81−1.68 (m, 1H), 1.61−1.44 (m, 3H), 1.41−1.33 (m, 1H), 1.19 (dd, J = 13.3, 4.3 Hz, 1H), 1.13 (s, 3H); ^{1}H−^{1}H decoupling information: irradiation of the signal at δ 4.44 ppm caused the following changes; the signal at 2.02 ppm collapsed (d, J = 13.3 Hz) and that at δ 1.19 ppm became a doublet (J = 13.3 Hz); irradiation at δ 3.81 ppm caused the following changes: the signal at 2.79 ppm collapsed to an AB pattern (J_{AB} = 18.0 Hz, Δv = 30.1 Hz) while the signal at 2.45 ppm became a singlet; MS (CI, NH_3) m/e (relative intensity) 270 (5), 112 (27), 101 (100), 88 (43), 84 (51); HRMS (CI, NH_3) m/e calcd for $C_{14}H_{22}O_5$ (M^+) 270.1467, found 270.1461. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.52; H, 8.30.

(±)-(1*S,6*S**,8*R**,9*S**,11*S**)-2,2-Dimethoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecane-9,11-diol (16b).** To a suspension of 0.133 g (6.06 mmol) of $LiBH_4$ in 15.0 mL of THF at 0 °C was added a solution of 0.818 g (3.03 mmol) of β-hydroxy ketone from reduction of **11** in 18 mL of THF. After being stirred for 15 h, the reaction was diluted with Et_2O (20 mL) and cooled to 0 °C. Excess hydride was quenched by the careful addition of saturated NH_4Cl solution, the solids were dissolved in H_2O, and the resulting biphasic mixture was partitioned with EtOAc and saturated aqueous NH_4Cl (30 mL each). The organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (180 g of SiO_2, 85% EtOAc/hexanes) to provide 0.618 g (75%) of the diol **16b** as a white solid and 0.180 g (23%) of an over-reduction product described below. Characterization of **16b** is as follows: mp 108−110 °C; R_f = 0.18 in 85% EtOAc/hexanes; IR (neat) 3510, 2950, 1468, 1090−1040 (br) cm^{-1}; ^{1}H NMR δ 4.69 (dd, J = 11.9, 6.9 Hz, 1H), 4.35 (s, 1H), 4.19 (dq, J = 8.4, 2.0 Hz, 1H), 3.58 (m, 1H), 3.49 (s, 3H), 3.28 (s, 3H), 2.40 (d, J = 10.2 Hz, 1H), 2.07 (ddt, J = 14.2, 6.9, 1.7 Hz, 1H), 1.94−1.83 (m, 3H), 1.79 (dd, J = 12.8, 8.4 Hz, 1H), 1.61−1.47 (m, 4H), 1.40−1.37 (m, 1H), 1.39 (s, 3H); ^{1}H−^{1}H decoupling information: irradiation of the signal at δ 4.69 ppm caused the resonance at 2.07 ppm to collapse to a broad dd (J = 14.2, 1.7 Hz) while irradiation at δ 3.58 ppm produced the following signals; that at 4.19 ppm was a dt (J = 8.3, 2.1 Hz) while that at 2.07 ppm was observed as a ddd (J = 14.2, 6.9, 1.7 Hz). Irradiation at 2.07 ppm collapsed the signal at 4.69 ppm into a br d (J = 11.9 Hz), that at 4.19 ppm was a dt (J = 8.3, 2.4 Hz) (complete irradiation of this signal was not achieved). Irradiation at δ 4.19 ppm converted the signal at 3.58 ppm into a br d (J = 4.3 Hz), that at 2.07 ppm into a ddd (J = 14.2, 6.9, 1.7 Hz), that at 1.79 ppm into a d (J = 12.8 Hz), and enhanced a signal in the 1.61−1.47 region which now appeared at 1.54 ppm as a d (J = 12.8 Hz); ^{13}C NMR δ 105.3 (s), 86.3 (s), 77.4 (d), 70.0 (d), 65.9 (d), 53.2 (q), 47.5 (q), 45.1 (s), 44.4 (t), 42.2 (t), 33.2 (t), 24.4 (t), 20.0 (q), 19.5 (t); MS (CI, NH_3) m/e (relative intensity) 272 (1), 255 (1), 241 (23), 240 (73), 141 (64), 101 (100); HRMS (CI, NH_3) m/e calcd for $C_{14}H_{23}O_4$ ($M^+ - OH$) 255.1596, found 255.1592.

The alcohol byproduct of over-reduction proved to be (±)-(1*S**,6*S**,8*S**,11*S**)-2,2-dimethoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-11-ol as characterized by the following data: R_f = 0.31 in 35% EtOAc/hexanes; IR ($CHCl_3$) 3480, 2940, 1140, 1070 cm^{-1}; ^{1}H NMR (C_6H_6) δ 4.71 (m, 1H), 4.48 (br, 1, OH), 4.14 (m, 1H), 3.32 (s, 3H), 2.83 (s, 3H), 2.11−1.97 (m, 1H), 1.97−1.61 (m, 3H), 1.59−1.28 (m, 5H), 1.52 (s, 3H), 1.27−1.14 (m, 2H), 1.14−1.02 (m, 1H); ^{13}C NMR (C_6H_6) δ 105.7 (s), 86.2 (s), 73.7 (d, J = 150 Hz), 69.7 (d, J = 145 Hz), 52.9 (q, J = 142 Hz), 47.3 (s), 46.8 (q, J = 143 Hz), 45.8 (t, J = 126 Hz), 42.8 (t, J = 133 Hz), 30.9 (t, J = 125 Hz), 26.1 (t, J = 131 Hz), 24.3 (t, J = 131 Hz), 20.0 (t, J = 126 Hz), 19.3 (q, J = 127 Hz); HRMS (EI) m/e calcd for $C_{13}H_{21}O_3$ ($M^+ - OCH_3$) 225.1493, found 225.1489.

(±)-(1*R,6*S**,8*S**)-2-Methoxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodeca-2,10-dien-9-one (17).** To a solution of 0.635 g (2.33 mmol) of diol **16b** and 1.13 g (9.32 mmol) of dry collidine in 23.0 mL of CH_2Cl_2 at −10 °C was added 1.85 g (6.99 mmol) of *tert*-butyldimethylsilyl triflate. After 45 min, the mixture was diluted with Et_2O (75 mL) and washed with H_2O (50 mL), 50% aqueous $CuSO_4$ solution (2 × 50 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (110 g of SiO_2; 15% EtOAc/hexanes) to provide 1.00 g (91%) of the bis-silyl ether of **16b** as a clear liquid: R_f = 0.88 in 50% EtOAc/hexanes; IR (neat) 3000, 2978, 1668, 1467, 1388, 1362, 1208, 1104 (br) cm^{-1}; ^1H NMR δ 4.80 (dd, J = 6.6, 1.9 Hz, 1H), 4.70 (dd, J = 12.0, 6.2 Hz 1H), 4.06 (dq, J = 9.0, 2.3, 1.9 Hz, 1H), 3.66−3.60 (m, 1H), 3.48 (s, 3H), 2.18 (dddd, J = 16.7, 12.3, 4.1, 1.9 Hz, 1H), 2.10−1.89 (m, 2H), 1.87−1.71 (m, 2H), 1.80 (dd, J = 12.5, 9.0 Hz, 1H), 1.50 (dd, J = 12.5, 2.3 Hz, 1H), 1.29−1.22 (m, 1H), 1.25 (s, 3H), 0.90 (s, 9H), 0.81 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), −0.03 (s, 3H); MS (CI, NH_3) m/e (relative intensity) 412 (27), 411 (77), 301 (37), 197 (34), 171 (33), 139 (81), 135 (55), 73 (100); HRMS (CI, NH_3) m/e calcd for $C_{21}H_{39}O_4Si_2$ ($M^+ - C_4H_9$) 411.2387, found 411.2381.

To a solution of 1.00 g (2.13 mmol) of the bis-silyl ether **16b** in 21.0 mL of THF at 0 °C was added 2.78 mL (2.78 mmol) of a 1.0 M solution of tetra-n-butylammonium fluoride in THF. After the mixture was warmed to room temperature over 12 h, the solvent was removed *in vacuo* and the residue purified by flash chromatography (85 g of SiO_2; 40% EtOAc/hexanes) to provide 0.678 g (90%) of the C-11 monosilyl ether of **16b** as an oil which solidified upon standing: mp 90.5−92.0 °C; R_f = 0.30 in 50% EtOAc/hexanes; IR (neat) 3530, 3000, 2940, 1668, 1468, 1214, 1175, 1100 (br), 1050 cm^{-1}; ^1H NMR δ 4.88 (dd, J = 6.3, 2.3 Hz, 1H), 4.67 (dd, J = 10.2, 7.4 Hz, 1H), 4.18 (br d, J = 8.2 Hz, 1H), 3.68−3.57 (m, 1H), 3.51 (s, 3H), 2.57 (d, J = 10.5 Hz, 1H), 2.21 (dddd, J = 17.3, 12.8, 5.1, 2.0 Hz, 1H), 2.06−1.94 (m, 3H), 1.89 (dd, J = 13.3, 8.2 Hz, 1H), 1.76 (td, J = 12.9, 4.3 Hz, 1H), 1.61 (dd, J = 13.3, 2.0 Hz, 1H), 1.33−1.25 (m, 1H), 1.28 (s, 3H), 0.81 (s, 9H), 0.04 (s, 3H), −0.02 (s, 3H); MS (CI, NH_3) m/e (relative intensity) 355 (1), 297 (64), 187 (21), 140 (100); HRMS (CI, NH_3) m/e calcd for $C_{19}H_{35}O_4Si$ (M^+ + 1) 355.2338, found 355.2321.

To a solution of 0.267 g (2.10 mmol) of oxalyl chloride in 6.0 mL of CH_2Cl_2 at −78 °C was added 0.204 g (2.62 mmol) of dry DMSO. After the mixture was stirred for 15 min, a solution of 0.372 (1.05 mmol) of the C-9 alcohol (prepared via monodesilylation) in 4.5 mL of CH_2Cl_2 was added dropwise. This mixture was stirred for 1 h at −78 °C prior to the addition of 0.424 g (4.2 mmol) of anhydrous Et_3N. The bath was removed, and after being stirred at room temperature for 30 min, the mixture was partitioned with EtOAc and saturated aqueous NH_4Cl (40 mL each). The organic layer was washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (80 g of SiO_2; 10% EtOAc/hexanes) to provide 0.362 g (98%) of the C-9 ketone as an oil which crystallized on standing: mp 103−105 °C; R_f = 0.73 in 50% EtOAc/hexanes; IR (neat) 3000, 2960, 1730, 1660, 1362, 1249, 1210, 1097 (br), 1013, cm^{-1}; ^1H NMR δ 4.99 (dd, J = 6.5, 1.9 Hz, 1H), 4.89 (dd, J = 10.0, 8.1 Hz, 1H), 4.22 (dt, J = 8.8, 1.5 Hz, 1H), 3.54 (s, 3H), 2.73 (AB of an ABX with one proton coupled to resonance at 4.22 (J = 1.5 Hz), J_{AB} = 16.4 Hz, J_{AX} = 10.6 Hz, J_{BX} = −1.2 Hz, $\Delta\upsilon$ = 27.6 Hz, 2H), 2.25 (dddd, J = 17.3, 12.7, 4.3, 1.9 Hz, 1H), 2.15 (dd, J = 13.6, 8.9 Hz, 1H), 2.04 (dddd, J = 17.3, 6.5, 4.7, 2.1 Hz, 1H), 1.83 (dd, J = 13.6, 1.9 Hz, 1H), 1.75 (td, J = 12.7, 4.7 Hz, 1H), 1.45−1.35 (m, 1H), 1.39 (s, 3H), 0.82 (s, 9H), 0.04 (s, 3H), −0.02 (s, 3H); $^1H-^1H$ decoupling information: the signal at 4.22 ppm was irradiated which caused the signals at 2.15 and 1.83 ppm to collapse into an AB pattern (J_{AB} = 13.6 Hz, $\Delta\upsilon$ = 96.9 Hz); the signal at 2.73 collapsed, but not cleanly, into an AB pattern; irradiation of the signal at 4.99 ppm caused simplification of the patterns at 2.25 and 2.04 ppm; that at 2.25 ppm simplified into a ddd (J = 17.2, 12.5, 4.3 Hz) while that at 2.04 ppm collapsed into a ddd (J = 17.2, 5.0, 2.0 Hz); ^{13}C NMR δ 204.8 (s), 151.9 (s), 100.1 (d), 83.8 (s), 79.9 (d), 70.6 (d), 54.4 (q), 44.8 (t), 43.6 (t), 43.5 (s), 38.8 (t), 25.5 (q), 21.7 (t), 20.7 (d), 17.7 (s), 2.0 (q), 1.1 (q); MS (CI, NH_3) m/e (relative intensity) 353 (15), 295 (73), 221 (43), 166 (100), 140 (56), 135 (51), 73 (35); HRMS (CI, NH_3) m/e calcd for $C_{19}H_{33}O_4Si$ (M^+ + 1) 353.2148, found 353.2139.

To a solution of 84 mg (0.239 mmol) of C-11 silyloxy C-9 ketone described above, in 3.0 mL of THF was added 29 mg (0.716 mmol) of potassium hydride (previously washed with pentane). The mixture was vigorously stirred while 95 mg (0.358 mmol) of 18-crown-6 was added. Stirring was continued for 5 min at 22 °C, followed by the addition of H_2O (2 mL). The biphasic mixture was partitioned with EtOAc and H_2O (20 mL each), and the organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (10 g of SiO_2; 20% EtOAc/hexanes) to afford 38 mg (71%) of the enone **17** as an oil which crystallized upon standing: mp 76−78 °C; R_f = 0.51 in 50% EtOAc/hexanes; IR (neat) 3052, 3000, 2945, 1707, 1685, 1667, 1450, 1378, 1362, 1210, 1102 cm^{-1}; ^1H NMR δ 7.14 (d, J = 10.5 Hz, 1H), 6.15 (dd, J = 10.5, 2.3 Hz, 1H), 4.99 (dd, J = 5.9, 2.3 Hz, 1H), 4.51 (br d, J = 8.2 Hz, 1H), 3.61 (s, 3H), 2.28 (dd, J = 13.3, 8.2 Hz, 1H), 2.31−2.09 (m, 2H), 1.81 (td, J = 12.5, 5.8 Hz, 1H), 1.69 (dd, J = 13.3, 1.2 Hz, 1H), 1.57 (br dd, J = 13.0, 2.9 Hz, 1H), 1.07 (s, 3H); $^1H-^1H$ decoupling information: irradiation of the signal at 4.51 ppm caused the signal at 6.15 ppm to collapse to a doublet (J = 10.5 Hz) while the signals at 2.28 and 1.69 ppm became an AB pattern (J_{AB} = 13.3 Hz, $\Delta\upsilon$ = 178.5 Hz); ^{13}C NMR δ 196.8 (s), 154.3 (d), 152.3 (s), 126.9 (d), 98.6 (d), 82.6 (s), 80.2 (d), 54.8 (q), 44.6 (s), 42.1 (t), 34.8 (t), 21.7 (t), 20.5 (q); MS (CI, NH_3) m/e (relative intensity) 221 (37), 192 (39), 177 (79), 161 (64), 149 (40), 145 (66), 137 (40), 133 (32), 117 (69), 105 (48) ; HRMS (CI, NH_3) m/e calcd for $C_{13}H_{17}O_3$ (M^+ + 1) 221.1178, found 221.1173. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.87; H, 7.33. Found: C, 70.45; H, 7.28.

(±)-(1*S,6*S**,8*R**,9*S**)-9,11-Dihydroxy-6-methyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-2-one (18).** A small volume of 10% aqueous H_2SO_4 (0.5 mL) was added to a solution of 1.49 g (5.48 mmol) of diol **16b** in a 4:1 mixture of CH_3OH/H_2O (22.0 mL). The reaction was stirred for 10 h, and the acid was then quenched by the addition of solid $NaHCO_3$. The solution was saturated with solid NaCl, and the resulting suspension was extracted with EtOAc (3 × 35 mL). Organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (100 g of SiO_2; 80% EtOAc/hexanes) to provide 1.01 g (81%) of the keto diol **18** as a white crystalline solid: mp 113−115 °C; R_f = 0.17 in 75% EtOAc/hexanes; IR ($CHCl_3$) 3360 (v br), 2980, 1710, 1462, 1345, 1070, 1019 cm^{-1}; ^1H NMR δ 4.45−4.35 (m, 2H), 3.68 (br s, 1H), 3.29 (d, J = 3.1 Hz, 1H), 2.78 (ddd, J = 13.3, 11.7, 6.2 Hz, 1H), 2.45 (br d, J = 9.0 Hz, 1H), 2.27 (dtd, J = 13.3, 4.3, 2.0 Hz, 1H), 2.13−1.87 (m, 4H), 2.04 (dd, J = 12.9, 9.0 Hz, 1H), 1.82−1.68 (m, 1H), 1.66 (dd, J = 12.9, 3.1 Hz, 1H), 1.54−1.42 (m, 1H), 1.35 (s, 3H); MS (CI, NH_3), m/e (relative intensity) 227 (7), 209 (19), 127 (100); HRMS (CI, NH_3) m/e calcd for $C_{12}H_{19}O_4$ (M^+ + 1) 227.1283, found 227.1274. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.68; H, 8.02. Found: C, 63.56; H, 7.91.

(±)-(1*S,2*R**,6*S**,8*R**,9*S**,11*S*)-6-Methyl-2-[(trimethylsilyl)methyl]-12-oxatricyclo[6.3.1.0^{1,6}]dodecane-2,9,11-triol (19).** Cerium trichloride heptahydrate (4.22 g, 11.33 mmol) was dried at 170 °C, under full vacuum (10.5 mm Hg), for 2 h to provide a white solid which was cooled to 22 °C and suspended in 30 mL of THF for 2.5 h. To the suspension, a −78 °C bath was applied and, after cooling, [(trimethylsilyl)methyl]magnesium chloride (17.03 mmol) in a 1 M ethereal solution was added via cannula. The resulting yellow suspension stirred for 1 h prior to the addition of a solution of 640 mg (2.83 mmol) of keto diol **18** in 5 mL of THF. The mixture was stirred for 75 min and then warmed to room temperature over 45 min. After being stirred overnight (18 h), the reaction was quenched by the addition of saturated aqueous NH_4Cl solution followed by the addition of H_2O to dissolve the solids. Dilution with EtOAc (5 mL) was followed by extraction of the organic phase with NH_4Cl solution (5 mL) and once with brine (5 mL). Combined aqueous layers were extracted with EtOAc (2 × 10 mL), the organic extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (70 g of SiO_2, 80% EtOAc/hexanes) to provide 659 mg (74%) of white solid: R_f = 0.54 in 80% EtOAc/hexanes; IR (nujol) 3460, 1245, 1142, 1015 cm^{-1}; ^1H NMR δ 4.76−4.67 (m, 1H), 4.18−4.11 (m, 1H), 3.86 (d, J = 2.34 Hz, 1H), 3.66−3.59 (m, 1H), 2.48 (s, 1H), 2.34 (d, J = 9.77 Hz, 1H), 2.09−2.02 (m, 2H), 1.89−1.81 (m, 2H), 1.79−1.60 (m, 4H), 1.55 (s, 3H), 1.46 (s, 2H), 1.28−1.19 (m, 2H), 0.15 (s, 9H); MS (EI, 30 eV) m/e (relative intensity) 296 (47), 124 (43), 115 (36), 91 (23), 75 (54), 73 (100); HRMS (EI) *m/e* calcd for $C_{16}H_{28}O_3Si$ ($M^+ - H_2O$) 296.1808, found 296.1790.

(±)-(1*R,6*S**,8*R**,9*S**,11*S**)-6-Methyl-2-methylene-12-oxatricyclo[6.3.1.0^{1,6}]dodecane-9,11-diol (20).** To a suspension of 20 mg (0.063 mmol) of triol **19** in 1.5 mL of THF at 22 °C was added 1 drop of concentrated H_2SO_4. The mixture was subsequently warmed to 40 °C. After 7 h, the reaction was quenched with several drops of saturated aqueous $NaHCO_3$ solution and diluted with 5 mL of EtOAc. The organic portion was washed with $NaHCO_3$ solution (3 mL) and brine (5 mL). The organic extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (2 g of SiO_2, 80% EtOAc/hexanes) to afford 14 mg (98%) of white solid: R_f = 0.21 in 70% EtOAc/hexanes; IR ($CHCl_3$) 3690, 3601, 3462, 3009, 2942, 1069, 1030, 995 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.27 (s, 1H), 5.19 (br s, 1H), 4.29 (ddd, *J* = 11.8, 6.4, 3.2 Hz, 1H), 4.20 (dq, *J* = 8.0, 2.0 Hz, 1H), 3.71–3.65 (m, 1H), 2.51 (d, *J* = 10 Hz, 1H), 2.32 (t, *J* = 7.2 Hz, 1H), 2.12 (ddt, *J* = 14.0, 6.4, 2.0 Hz, 1H), 2.02 (ddd, *J* = 14.0, 11.6, 4.0 Hz, 1H), 1.94 (dd, *J* = 12.8, 8.4 Hz, 1H), 1.73 (d, *J* = 4.0 Hz, 1H), 1.72–1.51 (m, 4H), 1.38 (t, *J* = 3.2 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 113.7, 85.4, 77.6, 71.7, 70.7, 44.3, 43.6, 40.0, 34.1, 31.4, 21.7, 20.8; HRMS (EI) *m/e* calcd for $C_{13}H_{20}O_3$ (M^+) 224.1413, found 224.1432.

(±)-(1*R,6*S**,8*R**,9*S**,11*S**)-9,11-Bis(methoxymethoxy)-6-methyl-2-methylene-12-oxatricyclo[6.3.1.0^{1,6}]dodecane (21).** To a suspension of diol **20** (25 mg, 0.11 mmol) in CH_2Cl_2/THF (1.1/0.5 mL) was added diisopropylethylamine (0.12 mL, 0.66 mmol) at 0 °C followed by 0.042 mL (0.55 mmol) of methoxymethyl chloride (MOM-Cl). The ice bath was removed, and the mixture was allowed to stir at 22 °C. After 42 h, the reaction was quenched by the addition of H_2O (5 mL) and diluted with EtOAc (10 mL). The organic portion was washed with H_2O (5 mL), 50% aqueous $CuSO_4$ solution (2 × 5 mL), and 10 mL of brine. The combined aqueous extracts were extracted once with EtOAc (10 mL). The organic extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (3 g of SiO_2, 30% EtOAc/hexanes) affording 35 mg of **21** (97%) as a yellow oil: R_f = 0.57 in 60% EtOAc/hexanes; IR (neat) 2943, 2890, 1468, 1150, 1107, 1050–1020 (br) cm^{-1}; ^{1}H NMR δ 5.23 (t, *J* = 1.9 Hz, 1H), 5.02 (br s, 1H), 4.72 (s, 2H), 4.58 (s, 2H), 4.27 (br dd, *J* = 8.6, 2.3 Hz, 1H), 4.02 (dd, *J* = 11.3, 6.2 Hz, 1H), 3.61–3.57 (m, 1H), 3.40 (s, 3H), 3.32 (s, 3H), 2.41–2.25 (m, 3H), 2.10–1.97 (m, 1H), 1.92 (dd, *J* = 12.9, 8.6 Hz, 1H), 1.90–1.80 (m, 1H), 1.75–1.45 (m, 2H), 1.51 (dd, *J* = 12.9, 2.3 Hz, 1H), 1.39 (s, 3H), 1.35–1.20 (m, 1H); MS (CI, NH_3) *m/e* (relative intensity) 313 (3), 267 (100), 205 (40), 107 (67); HRMS (CI, NH_3) *m/e* calcd for $C_{17}H_{29}O_5$ (M^+ + 1) 313.2015, found 313.1996.

(±)-(4*S,5*R**,7*S**)-7,11-Dimethyl-5-hydroxy-4-(methoxymethoxy)-1(11)-bicyclo[5.4.0]undecene (22).** A two-necked flask, equipped with a dry ice condensor, was cooled to −78 °C and charged with 5.0 mL of NH_3. Sodium pieces (60 mg; 2.61 mmol), washed with dry THF, were added with stirring to produce a blue solution. The exocyclic olefin **21** (136 mg, 0.436 mmol) was added as a solution in 1.5 mL of THF, and after being stirred for 20 min, the reaction was quenched by the addition of CH_3OH (3.0 mL). Ammonia was evaporated, and the remaining solids were dissolved in H_2O. This mixture was extracted with EtOAc (2 × 20 mL), and the organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (12 g of SiO_2; 20% EtOAc/hexanes) to provide 83 mg (74%) of the cleavage product **22** as an oil: R_f = 0.45 in 50% EtOAc/hexanes; IR (neat) 3500, 2930, 1450, 1150, 1105, 1040 cm^{-1}; ^{1}H NMR δ 4.67 (s, 2H), 4.14–4.04 (m, 1H), 3.54 (ddd, *J* = 10.2, 5.9, 2.3 Hz, 1H), 3.37 (s, 3H), 2.41 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.10–1.68 (m, 7H), 1.64 (s, 3H), 1.64–1.52 (m, 4H), 1.47–1.38 (m, 1H), 1.00 (s, 3H); MS (CI, NH_3) *m/e* (relative intensity) 255 (2), 254 (25), 191 (23), 177 (41), 148 (75), 135 (63), 122 (100); HRMS (CI, NH_3) *m/e* calcd for $C_{15}H_{27}O_3$ (M^+ + 1) 255.1960, found 255.1974.

(±)-(1*R,6*S**,8*S**,11*S**)-6-Methyl-2-methylene-12-oxatricyclo[6.3.1.0^{1,6}]dodecan-11-ol (23).** The alcohol **23** was prepared from the saturated ketone from **1** via the same reaction sequence as reported for synthesis of diol **20**. The reaction conditions and yields were analogous to those detailed for conversion of **16b** to olefin **20**. Alcohol **23** was fully characterized as follows: R_f = 0.30 in 20% EtOAc/hexanes; IR (neat) 3465, 3100, 2955, 1460, 1080, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (s, 1H), 5.14 (br s, 1H), 4.31 (d, *J* = 7.4 Hz, 1H), 4.06–3.98 (m, 1H), 2.32 (t, *J* = 6.6 Hz, 2H), 2.05–1.85 (m, 4H), 1.73–1.45 (m, 6H), 1.37 (s, 3H), 1.36–1.06 (m, 1H); ^{13}C NMR (126 MHz) δ 148.7, 113.1, 84.8, 75.2, 73.6, 46.1, 45.0, 39.8, 31.2, 26.2, 21.5, 19.6; HRMS (EI) *m/e* calcd for $C_{13}H_{20}O_2$ (M^+) 208.1464, found 208.1465.

(±)-(2*S,5*S**,7*S**)-7,11-Dimethylbicyclo[5.4.0]undec-1(11)-ene-2,5-diol (24).** Ammonia (6.7 mL), passed over BaO, was condensed into a dry three-necked flask, cooled to −78 °C and charged with anhydrous THF (1.35 mL). Freshly cut pieces of sodium (0.065 g; 2.81 mol) were added. After the mixture was stirred for 20 min, a solution of olefin **23** (167 mg; 0.803 mmol) in THF (3 mL) was added dropwise to the deep blue mixture. Starting alkene was consumed in 20 min, and the reaction was quenched by addition of CH_3OH (1.5 mL). The cold bath was removed, and ammonia was allowed to evaporate. Remaining material was partitioned with Et_2O and H_2O (30 mL each). The organic phase was washed with brine, and combined aqueous components were extracted with Et_2O (10 mL). The organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (20 g of SiO_2; 80% EtOAc/hexanes) to provide 132 mg (78%) of diol **24** as a white foam. Yields ranged from 78% to 89% of diol **24**: R_f = 0.28 in 20% hexanes in EtOAc; IR (neat) 3380, 3065, 2950, 1270, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (dd, *J* = 9.4, 7.8 Hz, 1H), 3.97 (m, 1H), 2.16 (m, 1H), 2.04 (m, 1H), 1.77 (s, 3H), 1.25 (s, 3H), 1.95–1.20 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 134.9, 71.7, 70.8, 51.5, 43.1, 35.1, 33.7, 32.8, 30.5, 27.3, 20.0, 18.5; MS (EI) *m/e* (relative intensity) 210 ((M^+), 35), 195 (59), 177 (49), 159 (62), 137 (46), 117 (43), 109 (69), 91 (100), 81 (79); HRMS (EI) *m/e* calcd for $C_{13}H_{22}O_2$ (M^+) 210.1620, found 210.1617.

(±)-(5*S,7*S**)-7,11-Dimethyl-5-hydroxybicyclo[5.4.0]-undeca-1,10-diene (25b).** A solution of diol **24** (29 mg; 0.138 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was treated with dry collidine (34 mg; 0.286 mmol) followed by addition of *tert*-butyldimethylsilyl triflate (56 mg; 50 μL; 0.214 mmol), and the mixture was slowly allowed to warm to 22 °C over 2 h. The reaction was diluted with aqueous $NaHCO_3$ and Et_2O. The organic phase was washed with aqueous $CuSO_4$, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (5 g of SiO_2; 10% EtOAc in hexanes) led to the isolation of 23.5 mg (53%) of the diene **25a**. No attempts to optimize the elimination reaction were pursued. Diene **25** was characterized as follows: R_f = 0.75 in 20% EtOAc/hexanes; IR (neat) 3025, 2940, 1260, 1070, cm^{-1}; ^{1}H NMR δ 5.75 (t, *J* = 6.5 Hz, 1H), 5.57 (br d, *J* = 5.5 Hz, 1H), 4.10–4.00 (m, 1H), 2.47–2.35 (m, 1H), 2.30–1.90 (m, 5H), 1.77 (s, 3H), 1.75–1.20 (m, 4H), 1.02 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 133.2, 124.8, 124.6, 70.6, 51.4, 39.9, 36.8, 35.6, 25.9 (3C), 23.2, 22.6, 21.6, 21.3, 18.3, 1.0 (2C); HRMS (EI) *m/e* calcd for $C_{19}H_{34}OSi$ (M^+) 306.2379, found 306.2369.

The corresponding alcohol **25b** was produced directly by treatment of diol **24** with a catalytic amount of pyridinium *p*-toluenesulfonate (PPTs) in CH_2Cl_2 at 22 °C for 1 h. However, this diene–alcohol readily decomposed upon standing at room temperature: ^{1}H NMR δ 5.76 (t, *J* = 6.5 Hz, 1H), 5.59 (br d, *J* = 5.5 Hz, 1H), 4.15–4.05 (m, 1H), 2.47–2.35 (m, 1H), 2.30–1.92 (m, 5H), 1.78 (s, 3H), 1.75–1.20 (m, 4H), 1.04 (s, 3H).

(±)-(2*S,5*S**,7*S*)-2,5-Diacetoxy-7,11-dimethylbicyclo-[5.4.0]undec-1(11)-ene (26).** To a solution of enediol **24** (44 mg; 0.209 mmol) in dry THF (2.5 mL) was added 76 mg (0.627 mmol) of 4-(dimethylamino)pyridine and 44 mg (1.04 mmol) of CaH_2. Acetic anhydride (64 mg; 59 μL; 0.627 mmol) was added, and the mixture was stirred at 22 °C overnight. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl (1 mL) and partitioned with Et_2O and H_2O (15 mL each). The organic layer was washed with brine, and combined aqueous phases were extracted with Et_2O (10 mL). Organic extracts were dried (Na_2SO_4), filtered, and concentrated to an oily residue, which was purified by flash chromatography (10 g of SiO_2; 5% EtOAc in hexanes) to yield 61 mg (100%) of the diacetate **26**: $R_f = 0.72$ in 60% EtOAc in hexanes; IR (neat) 3010, 2940, 1745, 1735, 1370, 1240 cm^{-1}; ^1H NMR δ 5.98 (t, $J = 7.8$ Hz, 1H), 5.07 (m, 1H), 2.22 (m, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.68 (s, 3H), 1.21 (s, 3H), 1.90–1.35 (m, 11H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 136.0, 133.7, 73.9, 73.0, 46.5, 41.8, 35.3, 33.4, 29.0, 27.7, 27.4, 21.4, 20.1, 18.5; MS (CI, NH_3) m/e (relative intensity) 234 ((M^+ – HOAc), 5), 175 (57), 174 (100), 159 (95), 91 (40); HRMS (CI, NH_3) m/e calcd for $C_{15}H_{22}O_2$ (M^+ -HOAc) 234.1620, found 234.1623.

(±)-(2*S,5*S**,7*S**)-2,5-Diacetoxy-7,11-dimethylbicyclo[5.4.0]undec-1(11)-en-10-one (27).** A solution of diacetate **26** (30.7 mg; 0.1 mmol) in 2 mL of THF/H_2O (4:1 by volume) was cooled to 0 °C and maintained in darkness. Recrystallized NBS (46 mg; 0.26 mmol) was added with stirring, and the mixture was allowed to warm to room temperature. After 1 h, starting **26** was consumed, and the reaction was quenched with saturated $NaHCO_3$ and diluted with Et_2O (10 mL). The ethereal layer was washed with brine (10 mL), and the combined aqueous phases were extracted with Et_2O (10 mL). Organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (4 g of SiO_2; 20% EtOAc/hexanes) to provide 27 mg (83%) of **27** as a colorless oil: $R_f = 0.30$ in 30% EtOAc/hexanes; IR (neat) 3065, 2950, 1740, 1670, 1370, 1240, cm^{-1}; ^1H NMR δ 6.14 (t, $J = 5.9$ Hz, 1H), 5.22 (m, 1H), 2.59 (ddd, $J = 5.3$, 12.2, 17.6 Hz, 1H), 2.47 (dt, $J = 5.1$, 17.7 Hz, 1H), 2.31 (dt, $J = 5.0$, 12.6 Hz, 1H), 2.22 (dd, $J = 3.0$, 14.7, 1H), 2.10 (s, 3H), 1.99 (s, 3H), 1.87 (s, 3H), 2.02–1.81 (m, 3H), 1.68–1.60 (m, 3H), 1.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 170.2, 169.8, 157.7, 132.6, 72.7, 72.2, 43.4, 38.6, 37.7, 34.1, 28.0, 27.3, 26.9, 21.3, 21.2, 11.3; MS (CI, NH_3) m/e (relative intensity) 309 (M +1, 11), 266 (38), 206 (54), 188 (100), 173 (37), 163 (63), 145 (34); HRMS (CI, NH_3) m/e calcd for $C_{17}H_{25}O_5$ (M^+ + 1) 309.1702, found 309.1702.

(±)-(2*S,5*S**,7*S**,10*R**)-2,5-Diacetoxy-7,11-dimethylbicyclo[5.4.0]undec-1(11)-en-10-ol (28).** To a solution of enone **27** (27 mg; 0.087 mmol) in 2.0 mL of methanol was added 32 mg (0.087 mmol) $CeCl_3$ heptahydrate. The mixture was stirred until homogeneous, and $NaBH_4$ (33 mg; 0.087 mmol) was added causing vigorous gas evolution. Consumption of **27** was complete in 30 min, and the reaction was quenched by addition of saturated aqueous NH_4Cl. The mixture was stirred for 30 min and then partitioned with Et_2O and saturated aqueous NH_4Cl (10 mL each). The organic phase was washed with brine (10 mL), and the combined aqueous layers were extracted with Et_2O (10 mL). Organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified via flash chromatography (4.0 g of SiO_2; 30% EtOAc/hexanes) to yield 27 mg (100%) of the expected allylic alcohols as a 5:1 ratio of β/α-isomers: $R_f = 0.17$ in 40% EtOAc/hexanes; IR (neat) 3460, 3070, 2950, 1735, 1375, 1250 cm^{-1}; major isomer **28** ^1H NMR δ 5.93 (t, $J = 9$ Hz, 1H), 5.08 (m, 1H), 3.95 (m, 1H), 2.24 (m, 1H), 2.04 (s, 3H), 2.00 (s, 3H), 1.82 (s, 3H), 2.00–1.29 (m, 10H), 1.26 (s, 3H); minor isomer (α-alcohol) ^1H NMR δ 5.97 (dd, $J = 10.0$, 6.0 Hz, 1H), 5.15 (m, 1H), 3.96 (br m, 1H), 2.06 (s, 3H), 2.07 (s, 3H), 1.83 (s, 3H), 1.17 (s, 3H), 2.10–1.12 (m, 11H); MS (EI) m/e (relative intensity) 310 (M^+, 1), 250 (20), 190 (100), 175 (32), 169 (72), 131 (62); HRMS (EI) m/e calcd for $C_{17}H_{26}O_5$ (M^+) 310.1780, found 310.1779.

(±)-(1*R,2*S**,5*S**,7*S**,10*R**,11*R**)-2,5-Diacetoxy-7,11-dimethyl-1,11-epoxybicyclo[5.4.0]undecan-10-ol (29).** A solution of the allylic alcohol **28** (27 mg; 0.087 mmol) in CH_2Cl_2 (4.0 mL) was treated with 20 mg (0.11 mmol) of *meta*-chloroperbenzoic acid at 0 °C. After being stirred for 2 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified directly via flash chromatography (8 g of SiO_2; 40% EtOAc/hexanes) to afford 21.8 mg (78%) of the epoxide **29**: $R_f = 0.24$ in 40% hexanes in EtOAc; IR (neat) 3500, 3070, 2955, 1735, 1370, 1240 cm^{-1}; ^1H NMR δ 5.24 (br m, 1H), 4.99 (t, $J = 4.9$ Hz, 1H), 3.71 (dd, $J = 9.8$, 5.5 Hz, 1H), 2.24 (dd, $J = 15.2$, 3.1 Hz, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 1.85–1.60 (m, 7H), 1.55 (s, 3H), 1.52–1.20 (m, 2H), 1.16 (s, 3H), 1.06 (ddd, $J = 13.7$, 5.4, 2.3 Hz, 1H); ^{13}C NMR (126 MHz) δ 170.1, 169.8, 77.9, 72.7, 72.2, 70.8, 66.1, 41.5, 35.7, 35.1, 27.7, 26.7, 25.7, 25.3, 21.4, 21.2, 15.7; MS (EI) m/e (relative intensity) 206 (M^+ –(2 × HOAc), 3), 183 (20), 123 (100), 100 (38); HRMS (EI) m/e calcd for $C_{13}H_{18}O_2$ (M^+ – ($C_4H_8O_4$)) 206.1307, found 206.1300.

(±)-(1*S,2*R**,3*R**,6*S**,8*S**,11*S**)-2,6-Dimethyl-12-oxatricyclo[6.3.1.0^{1,6}]dodecane-2,3,11-triol (30).** A solution of the diacetate **29** (22 mg; 0.067 mmol) in 2.0 mL of CH_2Cl_2 was cooled to 0 °C, and freshly distilled collidine (27 μL; 0.201 mmol) and *tert*-butyldimethylsilyl triflate (31 μL; 0.134 mmol) were added sequentially. After being stirred for 45 min, the mixture was diluted with Et_2O (15 mL) and washed with H_2O (10 mL), aqueous $CuSO_4$ (10 mL), and brine (5 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 25 mg (85%) of the corresponding C-3 silyl ether of **29**: $R_f = 0.63$ in 40% hexanes in EtOAc; ^1H NMR δ 5.90 (s, 1, OH), 4.25 (m, 2H), 3.60 (dd, $J = 9.7$, 5.5 Hz, 1H), 2.90 (s, 1, OH), 1.95 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H), 1.85–1.20 (m, 9H), 0.90 (s, 9H), 0.09 (s, 6H).

To a solution of the silyl ether of **29** (5.6 mg; 0.013 mmol) in 1.0 mL of CH_2Cl_2 at –78 °C was added 26 μL (0.026 mmol) of a 1 M solution of DIBAL-H in CH_2Cl_2. After 10 min at –78 °C, the reaction was quenched via addition of CH_3OH (2 drops) followed by aqueous CsF (2 mL). The mix was stirred for 30 min and extracted with Et_2O (3 × 2 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by flash chromatography (800 mg of SiO_2; 30% EtOAc in hexanes) to provide 3.0 mg of triol **30**: IR (neat) 3290, 2920, 1460, 1380, 1025 cm^{-1}; ^1H NMR δ 4.08 (m, 2H), 3.73 (dd, $J = 10.1$, 5.5 Hz, 1H), 3.47 (s, 1, OH), 2.75 (s, 1, OH), 2.03 (m, 1H), 1.90 (m, 1H), 1.80–1.40 (m, 8H), 1.39 (s, 3H), 1.20 (s, 3H), 1.05 (m, 1H); MS (CI, CH_4) m/e (relative intensity) 225 (59), 224 (100), 125 (70); HRMS (CI, CH_4) m/e calcd for $C_{13}H_{21}O_3$ (M^+ – OH) 225.1492, found 225.1482.

(±)-(1*S,3*S**,7*S**,8*R**,9*S**)-3,7-Dimethyl-2-oxatricyclo[5.4.1.0^{3,8}]dodecane-8,9-diol (31).** To a solution of diol **24** (88 mg; 0.419 mmol) in CH_2Cl_2 (4.2 mL) at 0 °C was added $VO(acac)_2$ (111 mg; 0.419 mmol), and the mixture was stirred for 20 min. Dropwise addition of 28 mL of a 3 M solution of ^tBuOOH in isooctane produced a rust-red solution, which was allowed to warm to room temperature with stirring. Consumption of **24** was complete after 1 h, and the reaction was quenched by addition of aqueous saturated $NaHCO_3$. After stirring for 30 min, the mixture was partitioned with Et_2O and H_2O (10 mL each). The organic phase was washed with brine, and the combined aqueous phases were extracted once with Et_2O (10 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated to an oily residue, which was purified via flash chromatography (10 g of SiO_2; 30% EtOAc in hexanes) to provide 73 mg (78%) of **31**: $R_f = 0.55$ in 20% hexanes in EtOAc; IR (neat) 3385, 3055, 2930, 1470, 1460, 1375, 1010 cm^{-1}; ^1H NMR δ 4.23 (m, 2H), 3.24 (s, 1H), 2.10 (m, 3H), 1.82 (m, 6H), 1.57–1.28 (m, 3H), 1.20 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (126 MHz) δ 75.5, 74.6, 73.7, 69.3, 38.7, 37.3, 36.4, 35,6, 33.0, 28.5, 26.0, 25.7, 17.7; MS (CI, NH_3) m/e (relative intensity) 209 (33), 208 (100), 127 (37), 126 (37), 125 (94), 109 (41), 98 (92); HRMS (CI, NH_3) m/e calcd for $C_{13}H_{22}O_3$ (M^+ + 1) 227.1647, found 227.1641.

(±)-(1*S,3*S**,7*S**,8*S**)-3,7-Dimethyl-8-hydroxy-2-oxatricyclo[5.4.1.0^{3,8}]dodecan-9-one (32).** To a solution of 118 mg (0.929 mmol) of oxalyl chloride in CH_2Cl_2 (0.6 mL) at –78 °C was added dry DMSO (97 mg; 1.24 mmol). The mixture was stirred for 15 min prior to the addition of a solution of diol **31** (70 mg; 0.31 mmol) in CH_2Cl_2 (2.5 mL). After the mixture was stirred for 45 min at –78 °C, Et_3N (131 mg; 1.30 mmol) was added and the cold bath removed. After 30 min, the reaction mixture was partitioned with Et_2O and saturated aqueous NH_4Cl (10 mL each). The organic phase was washed with brine (15 mL), and combined aqueous layers were extracted once with Et_2O (15 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated to a residue, which was purified by flash chromatography (10 g of SiO_2; 15% EtOAc in hexanes) to yield 54 mg (78%) of ketone **32**: $R_f =$ 0.54 in 30% EtOAc in hexanes; IR (neat) 3445, 2940, 1695, 1195, 1095, 1080 cm^{-1}; ^1H NMR δ 4.42 (m, 1H), 4.34 (s, 1H), 2.83 (m, 1H), 2.58 (m, 1H), 2.36 (dd, $J = 14.5$, 8.2 Hz, 1H), 2.05–1.65 (m, 6H), 1.50–1.05 (m, 4H), 0.95 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz) δ 214.0, 83.2, 74.6, 68.4, 37.8, 36.5, 35.9, 34.7, 34.3, 31.5, 25.5, 24.7, 17.4; MS (CI, NH_3) *m/e* (relative intensity) 225 (25), 224 (68), 139 (47), 126 (40), 109 (41), 108 (73), 98 (100); HRMS (CI, NH_3) *m/e* calcd for $C_{13}H_{21}O_3$ (M^+ + 1) 225.1491, found 225.1487.

(±)-(1*R,3*S**,7*S**,8*S**)-10-Acetoxy-8-hydroxy-3,7-dimethyl-2-oxatricyclo[5.4.1.0^{3,8}]dodec-10-en-9-one (33).** To a solution of α-hydroxy ketone **32** (18.3 mg; 0.082 mmol) in THF (1.0 mL) at 0 °C was added 50% NaH dispersion (5 mg; 0.106 mmol), and the ice bath was removed. After the solution was stirred at 22 °C for 30 min, oxygen gas blanketed the stirring solution and freshly distilled acetic anhydride (17 mg; 15 μL) was added with two crystals of 4-(dimethylamino)pyridine. The yellow color of the solution substantially faded, and after 30 min, the reaction was quenched by addition of saturated aqueous NH_4Cl. Upon extraction with Et_2O (2 × 5 mL), the organic layers were dried (Na_2SO_4), filtered, and concentrated to a yellow oil, which was purified by flash chromatography (4 g of SiO_2; 10% EtOAc in hexanes) to yield 22 mg (95%) of the enone **33** as a white crystalline solid: mp 91–93 °C; R_f = 0.28 in 20% EtOAc in hexanes; IR (neat) 3430, 2970, 2950, 1767, 1670, 1375, 1205, 1121 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.16 (d, J = 8.3 Hz, 1H), 4.66 (t, J = 8.1 Hz, 1H), 4.53 (s, 1H), 2.43 (dd, J = 14.4, 7.9 Hz, 1H), 2.27 (s, 3H), 1.85 (m, 3H), 1.70 (d, J = 14.2 Hz, 1H), 1.53–1.38 (m, 2H), 1.15 (m, 1H), 0.98 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (101 MHz) δ 196.3, 168.7, 148.3, 144.3, 84.4, 77.2, 75.4, 64.6, 39.6, 35.0, 33.7, 32.4, 26.1, 24.0, 20.4, 17.3; MS (CI, NH_3) *m/e* (relative intensity) 238 (17), 220 (64), 153 (100), 112 (23); HRMS (CI, NH_3) *m/e* calcd for $C_{15}H_{20}O_5$ (M^+ + 1) 281.1389, found 281.1379.

Acknowledgment. We thank the National Institutes of Health (GM 42897) for generous financial support. The authors also thank Ms. Kim Werner for technical assistance.

Supplementary Material Available: Proton NMR spectra for compounds **1**, **3**, **4**, **7–9**, **11–18**, and **20–33** (34 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO941322M