3 mL/min 3:1 MeOH–H_2O; refractive index detection). 1 was purified by similar RPLC steps; 1 and 2 could be separated and detected by silica gel TLC (Merck DC-Plastikfolien Kieselgel 60 F_{254}), developed with 1:19 EtOH–EtOAc, and visualized by dipping in 0.1:1:100 anisaldehyde–H_2SO_4–AcOH and then heating at 120 °C for 3–5 min to give light brown spots at R_f 0.35 and 0.5, respectively. **Caution**! Mycalamide-rich samples cause adverse skin reactions.

Mycalamide B (2): an oil; $[\alpha]_D$ +39° (c 0.2, $CHCl_3$); HREIMS ($M^+ - CH_3O$) 486.26993 (–0.8 ppm), ($M^+ - CH_3OH$) 485.26422 (+3.5 ppm); DCIMS (NH_3) 535 (7, M + NH_4^+), 505 (28), 504 (38), 503 (100, M + NH_4^+ – CH_3OH), 488 (23), 487 (36), 486 (89); DCIMS (ND_3) 543 (5), 542 (14), 541 (10), 513 (17), 512 (19), 511 (34), 510 (100), 509 (82), 508 (29), 493 (8), 492 (9), 491 (15), 490 (36), 489 (37), 488 (16); DCIMS (CH_4) 488 (16), 487 (32), 486 (100, $MH^+ - CH_3OH$), 456 (16); IR 3600–3300, 2900, 1690, 1390, 1100, 1040 cm^{-1}; ^1H NMR in Table I; ^{13}C NMR ($CDCl_3$) 171.88 (C8), 145.10 (C4), 111.02 (4=CH_2), 99.95 (C6), 86.49 (OCH_2), 79.27 (C13), 78.84 (C17), 75.46 (C15), 74.44 (C12), 73.90 (C10), 71.73 (C7), 70.94 (C11, broad), 69.64 (C2), 63.48 (C18), 61.78 (13-O-CH_3), 56.64 (17-O-CH_3), 48.57 (6-O-CH_3), 41.47 (C14), 41.27 (C3), 33.64 (C5), 29.63 (C16), 23.13 (14-CH_3(eq)), 17.93 (2-CH_3), 13.32 (14-CH_3(ax), broad), 12.13 (3-CH_3); AV 2 ng/disk.

Mycalamide B Diacetate (3). Mycalamide B (2) (3.5 mg) was dissolved in pyridine (0.1 mL) and Ac_2O (0.1 mL). After 4 h at 21 °C, H_2O (0.2 mL) was added and the mixture extracted with $CHCl_3$ (3 × 0.2 mL). Silica CC on the organic extracts gave a fraction (3 mg, 1:1 hexane–EtOAc) which was pure 3: an oil; HRFABMS M + Na^+ 624.2973 (–3.7 ppm); HREIMS M^+ – CH_3OH 569.2848 (+2.1 ppm); DCIMS (NH_3) 619 (22, M + NH_4^+), 589 (16), 588 (32), 587 (100, M + NH_4^+ – CH_3OH), 570 (25, MH^+ – CH_3OH), 318 (19), 290 (25), 258 (62), 257 (26), 241 (45); IR 3400, 2950, 2900, 1750, 1710, 1380, 1100, 1030, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (NH9, d, J = 9.4), 5.75 (H10, t, J = 9.4), 5.45 (H7, s), 5.07 (10-O-CH_2, d, J = 7.0), 4.88 (4=CH_2, m), 4.85 (10-O-CH_2, d, J = 6.9), 4.75 (4=CH_2, m), 4.28 (H18, dd, J = 2.5, 12.3), 4.17 (H12, dd, J = 6.6, 10.2), 4.07 (H18, dd, J = 4.7, 12.5), 4.02 (H2, dq, J = 2.8, 6.7), 3.77 (H11, dd, J = 6.5, 9.4), 3.53 (13-O-CH_3, s), 3.39 (H13, d, J = 9.8), 3.38 (H15, m), 3.35 (H17, m), 3.25 (17-O-CH_3, s), 3.17 (6-O-CH_3, s), 2.4 ($H_2$5, m), 2.28 (H3, dq, J = 2.7, 7.3), 2.20 (7-O-CO-CH_3, s), 2.08 (18-O-CO-CH_3, s), 1.6–1.7 ($H_2$16, m), 1.22 (2-CH_3, d, J = 6.5), 1.04 (3-CH_3, d, J = 7.2), 0.97 (14-CH_3(eq), s), 0.86 (14-CH_3(ax), s); ^{13}C NMR 170.85 (C8), 169.68 and 166.67 (7-O-CO and 18-O-CO), 144.75 (C4), 111.26 (4=CH_2), 99.15 (C6), 86.53 (O-CH_2), 79.43 (C13), 76.25 (C17), 75.68 (C15), 74.18 (C12), 74.02 (C10), 71.48 (C7), 70.64 (C11, broad), 69.95 (C2), 63.47 (C18), 61.70 (13-O-CH_3), 56.88 (17-O-CH_3), 48.49 (6-O-CH_3), 41.24 (C14), 41.16 (C3), 34.39 (C5), 30.33 (C16), 23.38 (14-CH_3(eq)), 20.97 and 20.65 (7-O-CO-CH_3 and 18-O-CO-CH_3), 17.92 (2-CH_3), 13.8 (14-CH_3(ax), broad), 12.19 (3-CH_3).

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Synthesis of the Tumor Inhibitory Tobacco Constituents α- and β-2,7,11-Cembratriene-4,6-diol by Diastereoselective [2,3] Wittig Ring Contraction

James A. Marshall,* Edward D. Robinson, and Jacques Lebreton

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

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The synthesis of β-CBT (**25**) and α-CBT (**47**), cembranoid constituents of tobacco with plant growth inhibitory and antitumor properties, is described. The route employs [2,3] Wittig ring contraction of the 17-membered propargylic ethers **8a** or **8c** to construct the 14-membered carbocyclic cembrane nucleus with the requisite syn relationship at C-1 and C-6. The (*E*)-enone **16** was prepared by 1,4-addition of Me_2CuLi to the derived ynone **13**. Epoxidation of enone **16b** with H_2O_2, NaOH afforded the β-epoxide **18** stereoselectively (7:1). Reductive elimination of the epoxy mesylate **22** and hydrogenation of the isopropenyl double bond afforded racemic β-CBT (**25**). [2,3] Wittig ring contraction of the 6*R* enantiomer of ether **8c** afforded the nonracemic anti, syn alcohol **9c** as the major product. This intermediate was converted to natural α-CBT (**47**) by a sequence involving directed epoxidation of the allylic alcohol **43** and reductive elimination of the mesylate derivative **46**.

Recently we described a new approach to carbocyclic compounds by [2,3] Wittig rearrangement of cyclic allylic propargylic ethers.[1] Our initial application of this methodology employed readily available farnesyl derivatives as starting materials for the synthesis of 14-membered cembrane alcohols. Subsequently we were able to synthesize 6- and 10-membered terpene natural products along similar lines.[2] An interest in the tobacco cembranes α- and β-CBT (I and II)[3] and related 6-oxygenated cembra-

(1) Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 4316. Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1987**, *52*, 3860.

(2) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883. Marshall, J. A.; Lebreton, J. *Tetrahedron Lett.* **1987**, *28*, 3323. Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925. Marshall, J. A.; Lebreton, J. *J. Org. Chem.* **1988**, *53*, 4108.

(3) Saito, Y.; Takayawa, H.; Konishi, S.; Yoshida, D.; Mizusaki, S. *Carcinogenesis* **1985**, *6*, 1189. The trivial name "CBT" is an abbreviation of the systematic name "2,7,11-cembratriene-4,6-diol".

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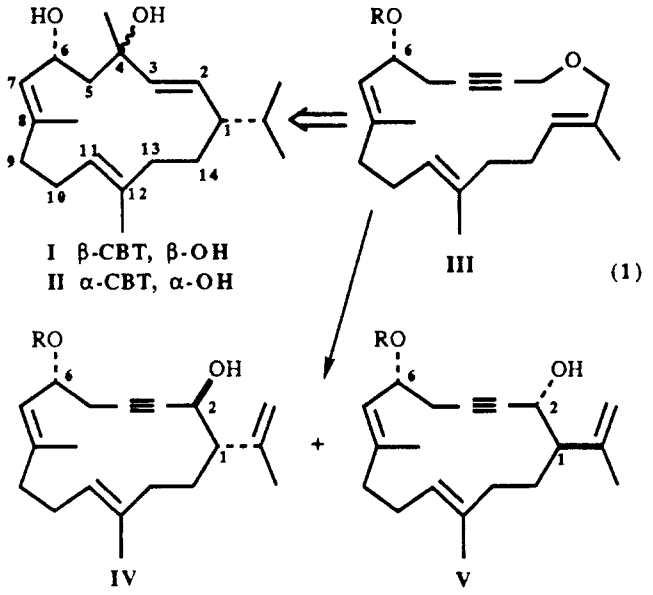
noids[4] prompted our consideration of this strategy as a route to such compounds through rearrangement of ether III. However, the presence of a stereo center in III posed a problem in that two trans diastereoisomers IV and V could be produced.[5]



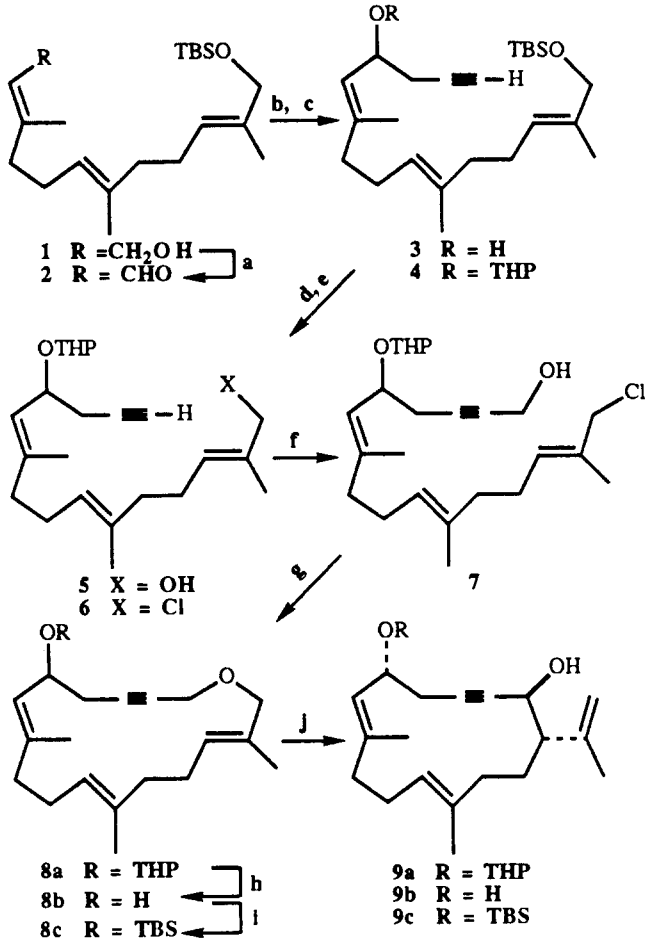
(1)

The effect of remote centers on the stereochemistry of the [2,3] Wittig rearrangement had not been examined when this project was initiated.[6] In the case of III we might expect the ratio of products IV and V to depend upon the relative energetics of diastereomeric transition states, which, in turn, would be sensitive to conformationally transmitted steric effects engendered by the substituent at C6. Owing to the size of the systems and uncertainties regarding the actual transition state of the rearrangement, we did not attempt to calculate which of the two possibilities would be preferred. Instead, we elected to pursue an experimental approach to the problem.

As the initial goal of these investigations, we selected the tobacco cembrane β-CBT (I). This constituent of aged burley tobacco was first isolated together with its C4 epimer, α-CBT (II), by Roberts and Rowland, who assigned to it the then unique 14-membered ring structure now known to typify cembrane diterpenes.[7] These workers recognized the diastereomeric relationship of I and II, but the assignment of relative stereochemistry awaited X-ray structure analysis of the β-isomer by Clardy and coworkers.[8] Both diols were found to inhibit the growth of lateral shoots in burly tobacco plants. Recently Saito et al. isolated these same diols from cigarette smoke condensate and showed that they strongly inhibit tumor promotion by 12-*O*-tetradecanoylphorbol 13-acetate in mice.[3]

The starting material for our projected synthesis, aldehyde **2** (Scheme I), was conveniently prepared by selective allylic oxidation of farnesyl acetate (SeO_2, *t*-BuOOH), along the lines reported for analogous oxidation

Scheme I[a,b]



[a] (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C (90%); (b) BrMgCH_2C≡CH, Et_2O, −20 °C (96%); (c) DHP, PPTS, CH_2Cl_2 (96%); (d) TBAF, THF, 0 °C (98%); (e) LiCl, DMF, MsCl, 2,6-lutidine, 0 °C (84%); (f) *n*-BuLi, THF, $(CH_2O)_n$, −78 to 15 °C (83%); (g) EtMgBr, THF–HMPA, 0.01 M, 0 °C to reflux (84%); (h) PPTS, MeOH (85%); (i) TBSCl, Et_3N, DMAP (80%); (j) *n*-BuLi, THF, pentane, −78 °C (see Table I). [b] All compounds are racemic.

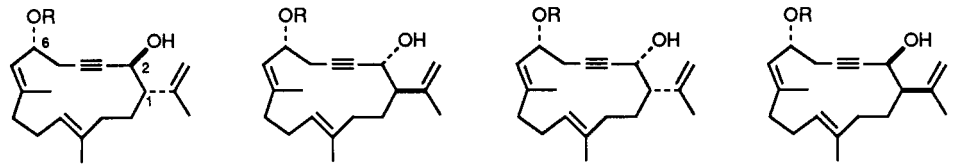
of geranyl acetate, followed by protection, acetate methanolysis, and Swern oxidation.[1] Addition of propargylmagnesium bromide afforded the alcohol **3**. Although eventually we planned to use nonracemic intermediates, we elected to conduct preliminary studies on racemates to establish the feasibility of the synthetic route.

The racemic alcohol **3** was protected as the THP ether **4**. Cleavage of the TBS ether with TBAF in THF afforded the alcohol **5**, which was converted to chloride **6** upon treatment with MsCl and LiCl in DMF–2,6-lutidine.[9] Addition of formaldehyde to the derived lithio acetylide led to the chloro alcohol **7**. Cyclization was readily effected by addition of EtMgBr to a dilute solution of **7** in THF–HMPA under conditions previously employed for related ethers.[1] The 17-membered ether **8a** was thus secured in 80–85% yield.

Rearrangement of the ether **8a** was achieved with *n*-BuLi in THF–TMEDA at −78 °C for 3 h (Table I). The resulting inseparable mixture of products **9a–12a** was hydrolyzed to a corresponding inseparable mixture of diols **9b–12b**. Acetylation of this mixture afforded the diacetates corresponding to **9–12**. These diacetates were readily analyzed by capillary GC. The major diacetate crystallized from the mixture and was shown to be the

(4) Marchand, P. S.; Blout, J. F. *J. Org. Chem.* **1977**, *42*, 3824.
(5) (*E*)-Allylic ethers generally afford anti or trans products. For a recent review of the [2,3] Wittig rearrangement, see: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.
(6) Preliminary reports: Marshall, J. A.; Robinson, E. D.; Adams, R. D. *Tetrahedron Lett.* **1988**, *29*, 4913. Marshall, J. A.; Robinson, E. D.; Lebreton, J. *Tetrahedron Lett.* **1988**, *29*, 3547.
(7) Roberts, D. L.; Rowland, R. L. *J. Org. Chem.* **1962**, *27*, 3989. The parent hydrocarbon, named "duvane" by Roberts and Rowland, is now commonly known as cembrane.
(8) Springer, J. P.; Clardy, J.; Cox, R. H.; Cutler, H. G.; Cole, P. J. *Tetrahedron Lett.* **1975**, 2737.
(9) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

Table I. [2,3] Wittig Rearrangement Products of Ether 8



9 trans,syn **10** trans,anti **11** cis,syn **12** cis,anti

a, series, R = THP; **b**, series, R = H; **c**, series, R = TBS

R	conditions[a]	yield, %	9	10[b]	11	12[b]	trans/cis	syn/anti
THP	A	93	65	14	15	6	79:21	80:20
THP	B	c	54	20	16	10	74:26	70:30
THP	C	90	81	7	6	6	88:12	87:13
THP	D	c	66	15	12	7	81:19	78:22
TBS	A	94	74	8	14	4	82:18	88:12
TBS	C	c	80	5	11	4	85:15	91:9
TBS	D	c	66	19	10	5	85:15	76:24
TBS	E	90	89	4	6	1	93:7	95:5
TBS	F	c	86	4	9	1	90:10	95:5
TBDPS	C	c	67	14	19	0	81:19	86:14
H	A	71	20	29	39	12	49:51	59:41
H	C	c	18	32	21	29	50:50	39:61
H	E	c	36	28	9	27	64:36	45:55
$Me_2C(OMe)$	C	69	48	35	12	5	83:17	60:40
EE	C	c	56	27	16	1	83:17	72:28
MOM	A	c	58	19	14	8	77:23	72:28

[a] A, *n*-BuLi added slowly to the propargyl ether in pentane–THF–TMEDA at −78 °C; B, *n*-BuLi added rapidly to the propargyl ether in pentane–THF–TMEDA at −78 °C; C, *n*-BuLi–TMEDA added to propargyl ether in pentane–THF–TMEDA at −78 °C; D, propargyl ether added to Li 2,2,6,6-tetramethylpiperidide in THF–pentane at −78 °C; E, *n*-BuLi added to the propargyl ether in THF–pentane at −78 °C; F, *s*-BuLi added to the propargyl ether in THF–pentane at −78 °C. [b] The assignments are tentative. [c] Small scale GC experiment. The yield was not determined.

trans, syn isomer **15**[10] through X-ray structure analysis.[6,11]

The TBS ether **8c** likewise afforded an inseparable mixture of rearranged products **9c–12c** upon treatment with *n*-BuLi in THF–TMEDA at −78 °C (Table I). The ratio of isomers, as measured by GC analysis of the derived diacetates, was similar to that produced from the THP ether **8a**. Product ratios from both **8a** and **8c** were dependent upon temperature, rate of addition, and the nature of the base–solvent system.

Oxidation of a 64:11:24:1 mixture of diastereoisomeric alcohols **9c–12c** yielded an 88:12 mixture of ketones **13c** and **14c**. Accordingly, the 24% component of the TBS ether mixture must be the cis, syn isomer **11c**.[10] We assume that the trans, anti isomer **10c** is the third most abundant product based on the previously observed preference for trans stereochemistry in rearrangements of the 6-desoxy analogue of **8c**.[1] Thus **12c**, the cis, anti isomer, is presumed to be the least favored product. These latter two assignments are tentative as trans products are not invariably formed in rearrangements of *E* allylic ethers.[5,12]

We have examined several methods for conversion of alkynols such as **9–12** into *E* γ-methylated allylic alcohols typical of cembranoids.[1,13] In the case at hand, methyl cuprate addition to ynone **13** under equilibrating conditions seemed most promising in terms of the overall synthetic strategy. Accordingly the mixture of diastereomeric alcohols **9a–12a** was oxidized by the Swern protocol[14] to an 80:20 mixture of syn and anti ynones **13a** and **14a** (Scheme II). Hydrolysis of the THP ether yielded a like mixture of hydroxy ynones **13b** and **14b**. Addition of Me_2CuLi in THF–ether proceeded readily at 0 °C, affording a 77:23 mixture of syn and anti *E* enones **16b** and **17b** in 86% yield. Nearly 10% of the corresponding *Z* enones were present according to ^1H NMR analysis of the characteristic C4 vinyl methyl signals (2.14 ppm for **16b**/**17b** vs 2.02 ppm for the *Z* enones).

For completion of the synthesis we envisioned epoxidation of enone **16b** to the β-epoxy ketone **18** and Wharton rearrangement of the hydrazone derivative leading directly to dehydro β-CBT **24**.[15] This strategy necessitated epoxidation of enone **16b** from the β-face. Although several epoxidation protocols are available the most straightforward involves addition of alkaline H_2O_2 to enones. In order to evaluate the likely stereochemical consequences of such an epoxidation we turned to molecular modeling. Figure 1 depicts the three lowest energy conformers of hydroxy enone **16b** according to MM2 calculations performed with Still's Macromodel program.[16] All three show an (*E*)-*s*-*cis* enone system with considerable steric bias for outside face (*re*) approach by an attacking nucleophile. A similar bias was seen for the next two lowest energy conformers (25.7, 26.8 kcal) as well. In each conformer the double bond assumes the same orientation relative to the C1 isopropenyl grouping. Addition of hydroperoxide to the accessible outside face of this double bond would expectedly afford the desired β-epoxide.

In fact, reaction of the hydroxy enone mixture of **16b** and **17b** (72:28) with alkaline H_2O_2 at room temperature yielded a 62:9:14:14 mixture of epoxy hydroxy ketones

(10) The terms "syn" and "anti" are used to designate relative stereochemistry at C1 and C6. "Cis" and "trans" refer to the relative stereochemistry at C1 and C2.

(11) We are greatful to Dr. Lukasz Lebioda for performing this analysis. For details of the structure, see ref 6.

(12) Marshall, J. A.; Nelson, D. J. *Tetrahedron Lett.* **1988**, *29*, 741.

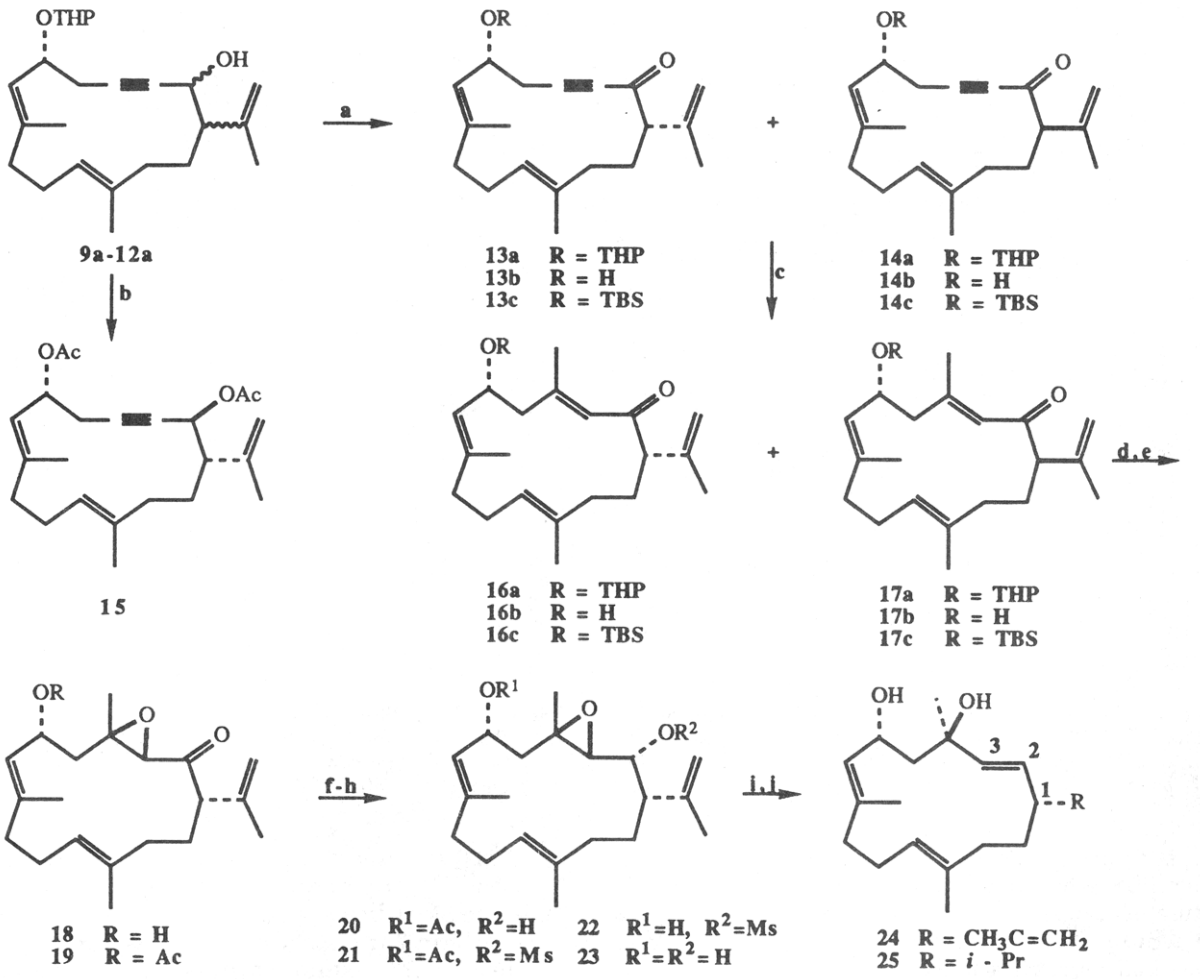
(13) Cf.: Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 3899. Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616.

(14) Omurka, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(15) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.

(16) The Multiconformer subroutine of MACROMODEL (Version 2.0) was employed. We are indebted to Professor Still for providing a copy of this program and for helpful advice. Structure analysis was performed by Walter Scrivens.

Scheme II[a,b]



[a] (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C (86%); (b) PPTS, EtOH; Ac_2O, C_5H_5N; (c) Me_2CuLi, THF 0 °C (86%); (d) 30% H_2O_2, NaOH, MeOH, THF (93%); (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (f) $NaBH_4$, MeOH, 0 °C (86%); (g) MsCl, Et_3N, CH_2Cl_2, 0 °C (75%); (h) K_2CO_3, MeOH, 0 °C (93%); (i) Na, NH_3, THF, −33 °C (77%); (j) $Rh(PPh_3)_3Cl$, H_2, C_6H_6, EtOH (92%). [b] All compounds are racemic.

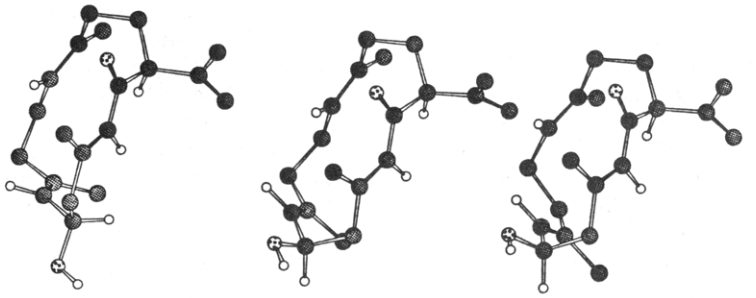


Figure 1. Chem3D display of the lowest energy conformers of enone **16b** as calculated by MACROMODEL. Only essential hydrogens are shown.

according to gc analysis of the TBS ether derivatives. Considering the composition of the starting enone, the 62 and 9% products must be related to the syn enone **16b** and the two 14% products to the anti enone **17b**. The analysis is only approximate as it fails to account for the 5–10% of *Z* enone present in **16b**/**17b**. The epoxidation mixture was converted to the acetates, which could be partially separated by column chromatography. The first eluted fraction (80% yield) consisted of at least two compounds in the ratio 66:34 according to GC analysis. The major component crystallized (52% isolated yield) and was identified as the β-epoxide isomer **19** through X-ray structure analysis.[17] The second fraction (16% yield) showed two GC peaks in the ratio 84:16. Thus epoxidation of the syn hydroxy enone **16b** proceeds as predicted by molecular modeling. Epoxidation of the anti hydroxy enone **17b** appears to be less selective, but the presence of inseparable products derived from the *Z* enone prevents accurate measurement of product ratios.

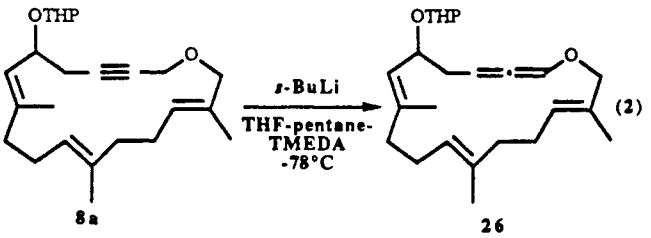
Attempts to form the hydrazone derivative of keto acetate **19** or keto alcohol **18** for Kischner elimination were uniformly unsuccessful.[15,18] We therefore examined a less

(17) We are grateful to Dr. Richard D. Adams for performing this analysis. For details of the structure, see ref 6.
(18) Benn, W. R.; Dodson, R. M. *J. Org. Chem.* **1964**, *29*, 1142.

direct route involving reductive elimination of epoxy mesylate **22**.[19] Reduction of keto acetate **19** with methanolic $NaBH_4$ afforded a single alcohol presumed to be the α-epimer **20**. This assignment is based on the expected addition of hydride to the less hindered face of epoxy ketone **19** as judged by examination of the X-ray structure.[6] Treatment of the acetoxy mesylate **21** with Na in NH_3 effected the desired reductive elimination but with considerable hydrogenolysis of the allylic acetate. Accordingly the acetate was removed with methanolic K_2CO_3, and the hydroxy mesylate **22** was reduced with Na in NH_3 to yield the allylic diol **24** in 77% yield along with 15% of the epoxy diol **23** arising from S–O cleavage. The ^1H NMR spectrum showed coupling of 15.8 Hz for the 2,3 vinylic protons indicative of an *E* double bond. None of the isomeric *Z* product could be detected. Selective hydrogenation of the isopropenyl double bond of diol tetraene **24** led to racemic β-CBT (**25**), identical with an authentic sample according to ^1H NMR and infrared spectral comparisons and TLC mobility.

With the viability of the synthetic route secured we turned our attention to the question of syn/anti diastereoselectivity in the [2,3] Wittig ring contraction of the macrocyclic ether **8** as a function of reaction conditions and alkoxy substituent. Rearrangements were effected by adding a solution of *n*-BuLi in hexanes to the THP and TBS ethers **8a** and **8c** in pentane–THF–TMEDA at −78 °C. Under these conditions higher syn:anti[10] ratios resulted when the *n*-BuLi was added slowly (Table I, condition A). Rapid addition gave lower ratios (Table I, condition B). Premixing the *n*-BuLi and TMEDA gave high selectivity independent of addition rates (Table I, condition C).[20]

The stronger, more bulky base system *s*-BuLi–TMEDA caused isomerization of propargylic ether **8a** to the allenic ether **26** (eq 2). No rearranged alcohols **9a–12a** were



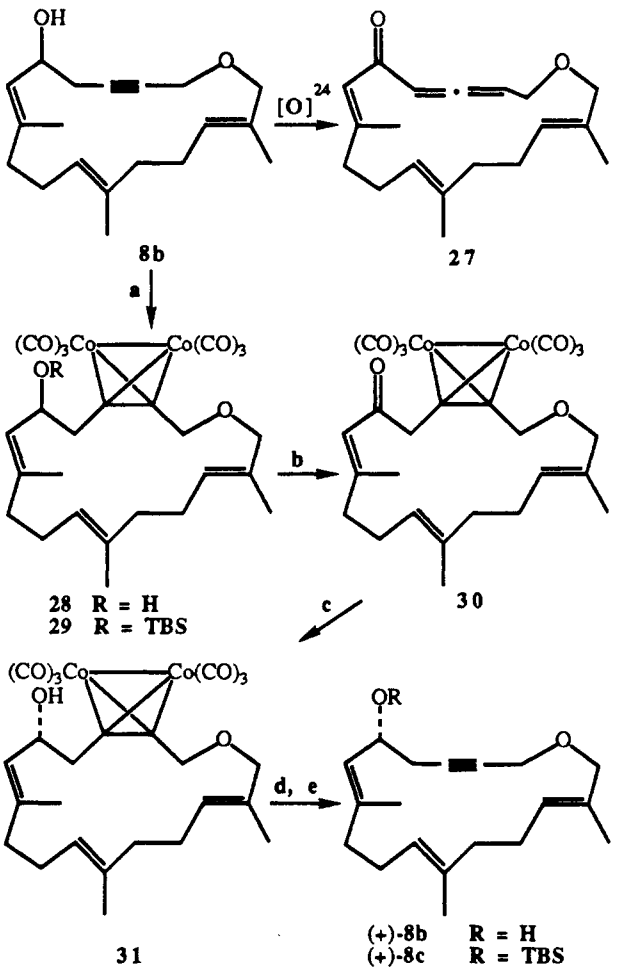
(2)

formed. In the absence of TMEDA, *s*-BuLi in pentane–THF effected smooth rearrangement of ethers **8a** and **8c** to the alchol products (Table I, condition F). In fact, *n*-BuLi gave virtually the same ratio of rearranged products with ether **8c** favoring the syn isomer **9c** and **11c** by 95:5 (Table I, condition E). Rearrangement of the free alcohol **8b** with this base was considerably less selective, giving a nearly 1:1 mixture of syn and anti products.[10]

We previously found that Li 2,2,6,6-tetramethylpiperidide was an effective base for ring contraction of 13-membered allylic propargylic ethers.[2] Ether **8a** rearranged more slowly and less selectively with this base than with *n*-BuLi–TMEDA (Table I, condition D). We also examined a number of other protected alcohols including 1-ethoxyethyl, 1-methoxy-1-methylethyl, and TBDPS (Table I). None gave higher syn:anti ratios than the TBS derivative **8c**.

Thus, syn:anti ratios in the [2,3] Wittig rearrangement of ether **8** are clearly influenced by the nature of the C-6

Scheme III[a,b]



[a] (a) $(Co)_2(CO)_8$, Et_2O (98%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (86%); (c) Chirald–$LiAlH_4$, Et_2O, −78 °C; (d) $(NH_4)_2Ce(NO_3)_6$, MeOH, Et_2O (90%, two steps); (e) TBSCl, Et_3N, DMAP, CH_2Cl_2 (89%). [b] Compounds **31**, (+)-**8b**, and (+)-**8c** are nonracemic.

substituent. However, a simple correlation between the steric bulk of that substituent and product ratios is not apparent. Moreover, the choice of reaction conditions can significantly influence product ratios. The use of premixed *n*-BuLi–TMEDA or *n*-BuLi alone gives the most reproducible and highest syn:anti ratios of the bases examined thus far.

Our next objective was to modify the foregoing synthetic route to permit the synthesis of nonracemic α- or β-CBT. This could be achieved through resolution or asymmetric synthesis of the macrocyclic hydroxy ether **8b**. Although the absolute stereochemistry of α- and β-CBT has not been determined, the 1*S*,6*R* configuration (I, II) seemed most likely in view of assignments to related tobacco cembranoids.[21] Accordingly the *R* ether **8c** (Scheme III) represented a logical starting point for these efforts. Preparation of the alcohol precursor of this ether was envisioned through reduction of the derived enone with an asymmetric reducing agent such as Chirald–$LiAlH_4$[22] or (*S*)-BINAL-

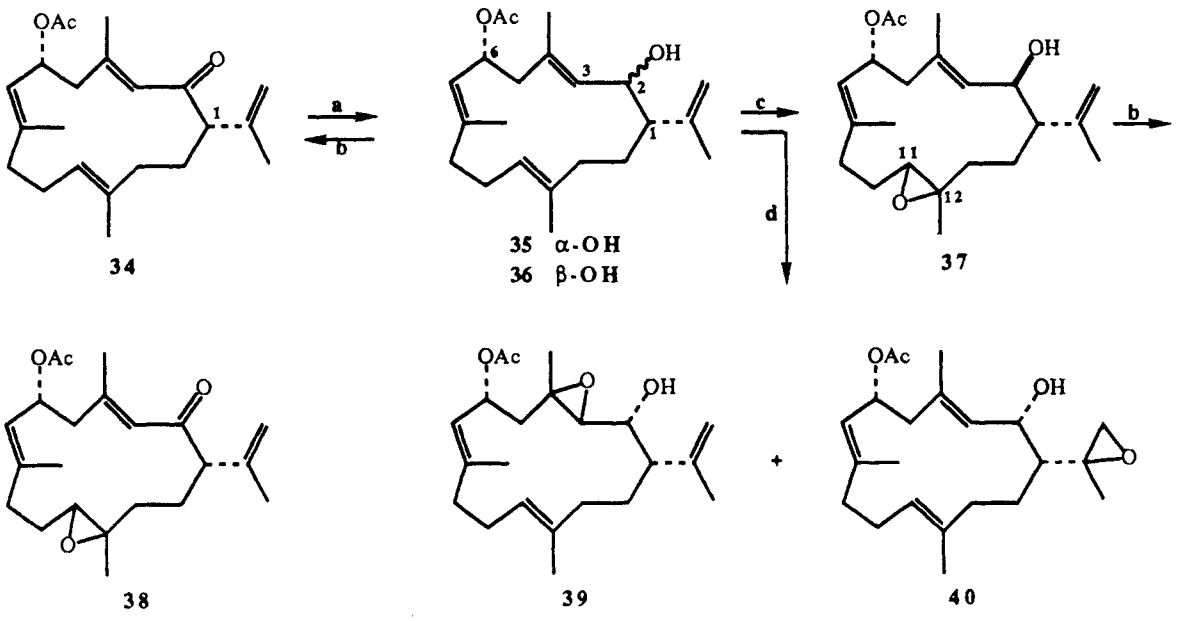
(19) Cf.: Marshall, J. A.; Ellison, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 4312. Kato, T.; Suzuki, M.; Takahashi, M.; Kitahara, Y. *Chemistry Lett.* **1977**, 465.

(20) We thank Dr. Timothy Brocksom for suggesting this experimental protocol.

(21) Clasin, A. J.; Junker, N.; Enzell, C. R.; Berg, J.; Pilotti, A. *Tetrahedron Lett.* **1976**, 2607. Wahlberg, I.; Forsblom, I.; Vogt, C.; Eklund, A. M.; Nishida, T.; Enzell, C. R.; Berg, J. E. *J. Org. Chem.* **1985**, *50*, 4527. For an excellent review of cembranoid natural products, see: Weinheimer, A. J.; Chang, C. W.; Matson, J. A. *Fortschr. Chem. Org. Naturst.* **1979**, *36*, 281. For a recent review of cembranoid total synthesis, see: Tius, M. A. *Chem. Rev.* **1988**, *88*, 719.

(22) Yamaguchi, S.; Mosher, H.; Phland, A. *J. Am. Chem. Soc.* **1972**, *94*, 9254. Chirald is available from the Aldrich Chemical Co., Milwaukee, WI.

Scheme IV[a,b]



[a] (a) $NaBH_4$, MeOH (67%); (b) PCC NaOAc, CH_2Cl_2; (c) *m*-CPBA, CH_2Cl_2 (55%); (d) $VO(acac)_2$, TBHP, $CH_3C_6H_5$ (82%). [b] All compounds are racemic.

H.[23] However, attempted oxidation of racemic alcohol **8b** with various reagents[24] led not to the desired enone but instead to the allenone **27** (Scheme III). Consequently, an alternative plan was formulated whereby the alkynyl moiety was protected as its dicobalt hexacarbonyl adduct **28**.[25] This adduct was prepared in near quantitative yield by addition of $Co_2(CO)_8$ to alkyne **8b**. Swern oxidation[14] led to ketone **30** in 86% yield. This ketone was reduced by the Chirald–$LiAlH_4$ reagent[22] at −78 °C to the *R* alcohol **31**. Removal of the bridging Co moieties was easily achieved through oxidation with ceric ammonium nitrate, affording alkynol (+)-**8b** in 90% yield.[25] This sequence offers a novel protecting strategy for sensitive β,γ-alkynones.

The absolute stereochemistry of alcohol (+)-**8b** could be assigned by analogy with related reductions.[22] Confirmation of this assignment was secured through ^1H NMR analysis of the *O*-methyl mandelate **32** (Figure 2) and comparison with authentic samples of **32** and the diastereoisomer **33** obtained by esterification of the racemic alcohol **8b** with (−)-(*R*)-*O*-methyl mandelic acid according to the method of Trost et al.[26] Esters **32** and **33** could be separated by chromatography on silica gel. The diastereoisomer with the shielded vinylic H-2 (5.3 vs 5.4 ppm) was assigned the 1*R* configuration **32**, and the diastereoisomer with the shielded propargylic CH_2 (2.5 vs 2.7 ppm) was assigned the 1*S* configuration **33** in accord with literature precedent.[26]

[2,3] Wittig ring contraction of the enantiomerically enriched TBS ether (+)-**8c** (70% ee) with *n*-BuLi–TMEDA in THF–hexanes at −78 °C followed by oxidation and

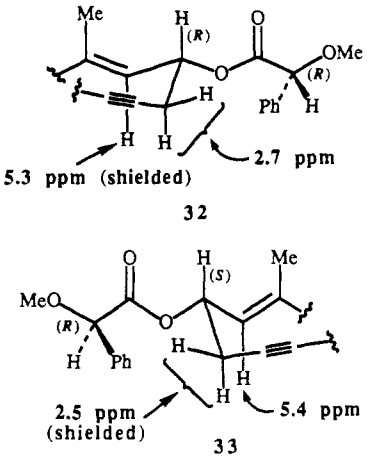


Figure 2. Configurational assignments of (*R*)-*O*-methyl mandelates **32** and **33** based on ^1H NMR chemical shifts.

methylcuprate addition proceeded as described in Scheme II for the racemic analogues to afford the nonracemic 6*R* syn and anti enones **16c** and **17c** as a 90:10 mixture.

With a view toward the synthesis of α-CBT we wished to effect epoxidation of enone **16c** on the α-face. As noted in Scheme II alkaline H_2O_2 affords mainly the β-epoxide with hydroxy enone **16b**. Therefore, we explored hydroxyl-assisted epoxidations as an alternative. Initial studies were conducted on the racemic keto acetate **34**, a 90:10 mixture of syn and anti diastereoisomers containing ca. 10% of the *Z* isomers (Scheme IV). Reduction of this mixture with methanolic $NaBH_4$ afforded a 2:1 separable mixture of epimeric alcohols, mainly **35** and **36**. The relationship of these alcohols was established by oxidation of each to the same 90:10 mixture of epimeric ketones **34**.

The ^1H NMR spectrum of alcohols **35** and **36** showed significant differences which, when considered in the light of molecular modeling, could be used to tentatively assign the stereochemistry. The spectrum of the major alcohol epimer contained a triplet at 4.10 ppm (J = 10.4 Hz) assignable to H2, the carbinyl proton. The spectrum of the minor alchol featured H2 as a broad doublet at 4.37 ppm ($J \sim 9$ Hz). Structures for **35** and **36** were generated by

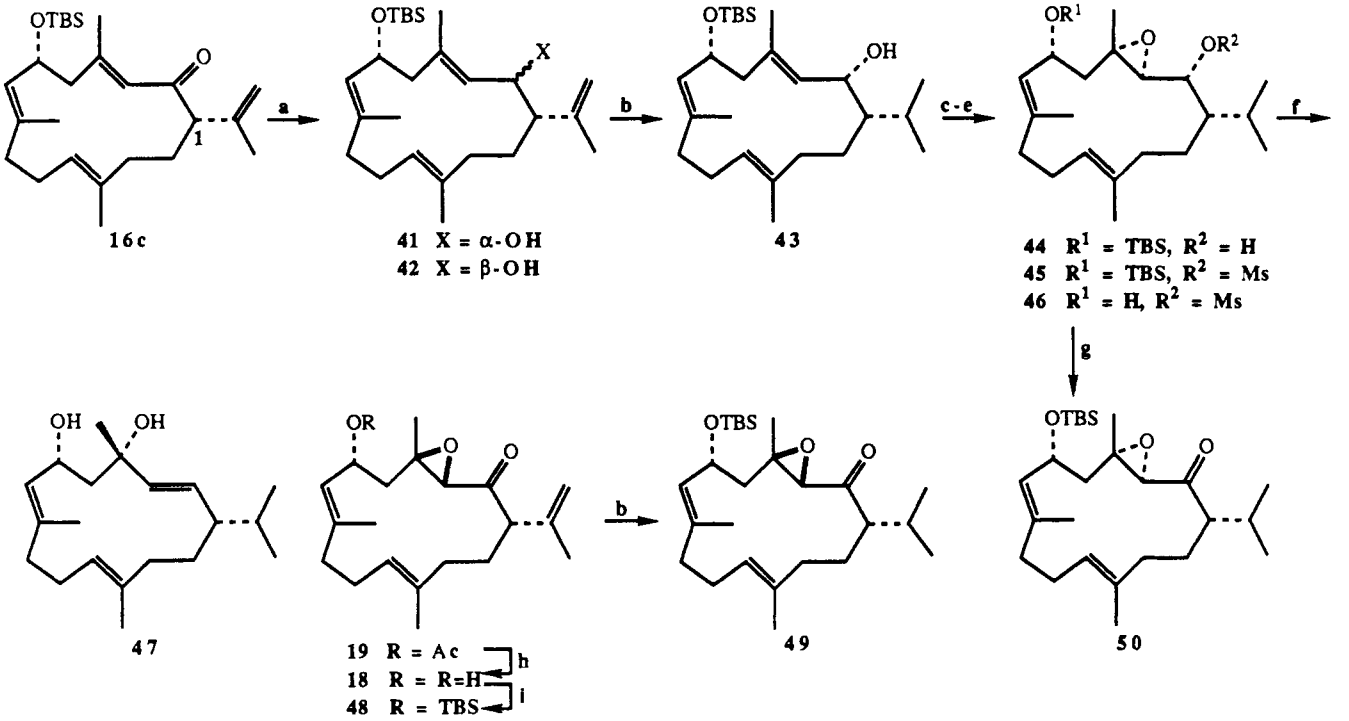
(23) Noyori, R.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

(24) Including: (a) Swern oxidation.[14] (b) Buffered PCC: Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647; (c) Bu_4NReO_4: Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(25) Cf.: Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207. Schreiber, S. L.; Klimas, M. T.; Sammakia, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.

(26) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. A.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Vargas, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. For a related application, see: Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925.

Scheme V[a,b]



[a] (a) DIBAH, THF, −78 °C (96%); (b) $(Ph_3P)_3RhCl$, H_2, EtOH, C_6H_6 (95%); (c) $VO(acac)_2$, TBHP, toluene (88%); (d) MsCl, C_5H_5N, 0 °C (92%); (e) Bu_4NF, THF, 0 °C (92%); (f) Na, NH_3, THF, −40 °C (75%); (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (h) K_2CO_3, MeOH (97%); (i) TBSCl, DMF, Im (68%). [b] All compounds except **18**, **19**, **48**, and **49** are nonracemic.

means of Still's MACROMODEL program.[16] Calculated coupling constants for H2/H3 and H2/H1 obtained through the Analyze/NMR subroutine were 6.6, 10.2; 10.4, 10.5; and 10.6, 10.2 Hz for the three lowest energy conformers of **36** in accord with the values of 10.4 and 10.4 observed for the major reduction product.[27,28] Values for **35** were calculated as 9.2, 0.5; 6.9, 1.6; and 10.3, 0.6 for the three lowest energy conformers concordant with the ca. 9 and 0.5 ppm coupling constants found for the minor epimer. Accordingly the major reduction product is most likely **36**.

Attempted OH-directed epoxidation of this major alcohol epimer with MCPBA afforded not the desired 3,4-epoxide, but led instead to the 11,12-epoxide **37**. The course of this reaction was clearly shown by the ^1H NMR spectrum of the derived ketone **38**. Epoxidation of the minor alcohol **35** with $VO(acac)_2$–TBHP led to a mixture of the 3,4-epoxide **39** and the isopropenyl epoxide **40**.

In view of the poor stereoselectivity of $NaBH_4$ in the reduction of enone **34**, it was desirable to examine other reducing agents. In order to preclude cleavage of the C-6 acetate we employed the TBS ether enone **16c** (90:10) for these studies (Scheme V). Reduction of the nonracemic enone mixture with DIBAH afforded an inseparable mixture of alcohols in 96% yield. The ^1H NMR spectrum of this mixture showed a doublet at 4.35 (major) and a triplet at 4.09 ppm (minor), which by analogy to the acetoxy alcohols **35** and **36** could be attributed to the α-alcohol **41** and β-alcohol **42**. Selective hydrogenation of the isopropenyl double bond with Wilkinson's catalyst[29] led to a mixture from which the major product, alcohol **43**, could be separated from the several minor components in 69% isolated yield by chromatography on silica gel.

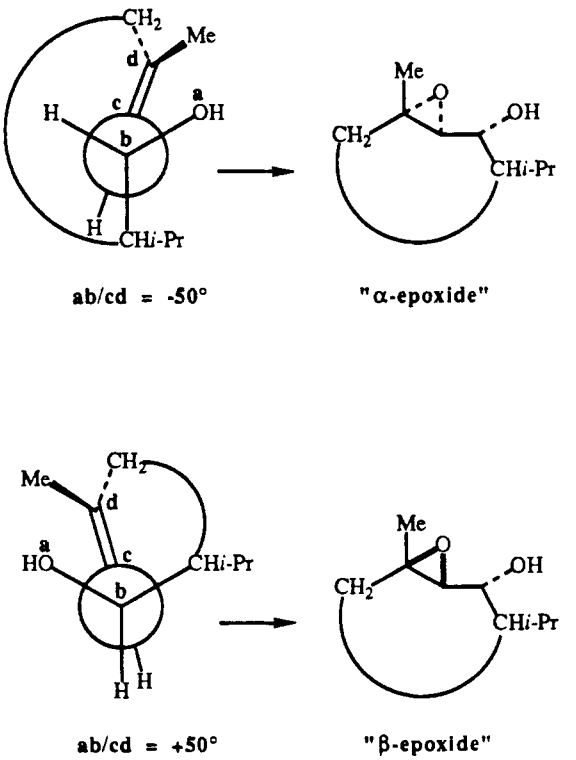


Figure 3. OH-directed epoxidation of alcohol **43**.

Epoxidation of the allylic alcohol **43** with $VO(acac)_2$–*t*-BuOOH afforded a single product shown to be the 3,4-epoxide by ^1H NMR analysis of the derived ketone **50**. Sharpless has proposed an optimum dihedral angle of ±50° for $VO(acac)_2$-promoted epoxidations of allylic alcohols.[30]

(27) The five lowest energy conformations of **36** were calculated as 85.8, 87.9, 88.9, 89.9, and 91.6 kJ and the five lowest energy conformations of **35** were calculated as 91.6, 93.3, 93.3, 93.5, and 94.8 kJ.

(28) Cf.: Garbisch, E. W. *J. Am. Chem. Soc.* **1964**, *86*, 5561.

(29) Cf.: Djerassi, C.; Gutzwiller, J. *J. Am. Chem. Soc.* **1986**, *88*, 4537.

(30) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733.

As shown in Figure 3 for alcohol **43**, a dihedral angle of −50° would lead to the desired "α-epoxide" and an angle of +50° would give the "β-epoxide". An ab/cd dihedral angle of −61° was found in the calculated low energy conformer of alcohol **43**.[16] Additionally, the five lowest energy conformers of **43** all showed negative ab/cd dihedral angles with values ranging from −120° to −166 °.[31] Accordingly, epoxidation would expectedly afford the α-epoxide **44**. This assignment was confirmed by comparison of ketone **50** with the β-epoxy ketone **49** prepared from the racemic acetoxy epoxy ketone **19** of established structure.

Preparatory to introduction of the (*E*)-2,3 double bond required for α-CBT, epoxy alcohol **44** was converted to the mesylate derivative **45**. In order to prevent hydrogenolysis of the C-6 oxygen the TBS ether was cleaved prior to treatment with Na in NH_3. Reduction–elimination then led to the allylic diol **47**, $[\alpha]_D$ +89°, identical with a sample provided by Dr. Y. Saito of Japan Tobacco Inc. according to infrared, ^1H NMR, and ^{13}C NMR comparison. The sign of rotation was the same for synthetic and natural α-CBT, although the magnitude was smaller for the synthetic sample owing to the presence of racemic material in the starting ether ^{19}F NMR analysis of the Mosher ester derivative indicated an ee of 70% for the synthetic material in accord with the ee of the starting alcohol. The configurational assignment of natural α-CBT is thus established as 1*S*,4*S*,6*R*.

Experimental Section

(2*E*,6*E*,10*E*)-12-[(*tert*-Butyldimethylsilyl)oxy]-3,7,11-trimethyl-2,6,10-dodecatrienal (2). The method of Swern was employed.[14] To a solution of 0.47 mL (5.4 mmol) of oxalyl chloride in 15 mL of CH_2Cl_2 at −78 °C was slowly added 0.77 mL (10.9 mmol) of dry DMSO. The resulting slurry was stirred for 5 min, and 1.74 g (4.9 mmol) of alcohol **1**[1] was added in 5 mL of CH_2Cl_2. This mixture was stirred for 20 min at −78 °C, and 3.5 mL (24.7 mmol) of triethylamine was added. The thick white mixture was warmed to 0 °C for 0.5 h and acidified with 10% HCl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of the solvent left an oil that was purified by column chromatography on silica gel providing 1.55 g (90%) of the aldehyde **2**: IR (CCl_4) ν 2960, 2930, 2900, 2860, 2780, a1680, 1635, 1615, 1480, 1370, 1250, 1190, 1115, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.98 (d, 1 H, *J* = 8.1 Hz, CHO), 5.88 (d, 1 H, *J* = 8.1 Hz, H-2), 5.33 (t, 1 H, *J* = 6.6 Hz, H-10), 5.07 (m, 1 H, H-6), 3.98 (s, 2 H, CH_2OTBS), 2.15 (s, 3 H, vinyl CH_3), 2.0–2.4 (m, 8 H, allylic CH_2), 1.59 (s, 3 H, vinyl CH_3), 1.54 (s, 3 H, vinyl CH_3), 0.89 (s, 9 H, Si-*t*-Bu), 0.04 (s, 6 H, $Si(CH_3)_2$) ppm; MS 281 (M − C_4H_5O).

Anal. Calcd for $C_{21}H_{38}O_2Si$: C, 71.94; H, 10.92. Found: C, 72.02; H, 10.95.

(5*E*,9*E*,13*E*)-15-[(*tert*-Butyldimethylsilyl)oxy]-6,10,14-trimethyl-5,9,13-pentadecatrien-1-yn-4-ol (3). A slurry of 1.1 g (46 mmol) of oven-dried magnesium powder, a catalytic amount of mercuric chloride, and 25 mL of anhydrous ether was stirred vigorously as 0.20 mL of 80% propargyl bromide in toluene was added by syringe. After 5 min, the reaction initiated, whereupon the slurry was cooled to −20 °C and a solution of 1.2 mL (10.8 mmol) of 80% propargyl bromide in toluene and 2.51 g (7.2 mmol) of aldehyde **2** in 30 mL of ether was added by syringe pump over 6 h. After an additional 6 h of vigorous stirring at −20 °C, the mixture was carefully quenched with saturated NH_4Cl and then diluted with ether. The resulting mixture was filtered, and the organic layer was washed with water and brine, dried over $MgSO_4$, and filtered. Removal of the solvent left an oil that was purified by distillation, providing 2.66 g (96%) of the acetylene **3**: IR (film) ν 3370, 3320, 2980, 2930, 2860, 1670, 1440, 1390, 1245, 1110, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.34 (t, 1 H, *J* = 5.9 Hz, vinyl H), 5.25 (d, 1 H, *J* = 8.4 Hz, H-5), 5.09 (m, 1 H, vinyl H), 4.54 (m, 1 H, carbinyl H), 3.98 (s, 2 H, CH_2OTBS), 2.2 (m, 2 H, $CH_2C{\equiv}C$), 1.95–2.1 (m, 10 H, allylic CH_2), 1.70 (s, 3 H, vinyl CH_3), 1.58 (s, 3 H, vinyl CH_3), 1.57 (s, 3 H, vinyl CH_3), 0.8 (s, 9 H, Si-*t*-Bu), 0.04 (s, 6 H, $Si(CH_3)_2$) ppm; MS 390 (M), 372 (M − H_2O), 357 (M − H_2O − CH_3), 351 (M − $CH_2C{\equiv}CH$).

Anal. Calcd for $C_{24}H_{42}O_2Si$: C, 73.85; H, 10.77. Found: C, 73.69; H, 10.89.

(5*E*,9*E*,13*E*)-15-[(*tert*-Butyldimethylsilyl)oxy]-6,10,14-trimethyl-5,9,13-pentadecatrien-1-yn-4-ol Tetrahydropyranyl Ether (4). A solution of 2.66 g (6.9 mmol) of alcohol **3**, 1.4 mL (15.3 mmol) of dihydropyran, a catalytic amount of pyridinium *p*-toluenesulfonate, and 70 mL of CH_2Cl_2 was stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 and saturated aqueous Na_2CO_3. The separated organic layer was washed with water and brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel, providing 3.12 g (96%) of the tetrahydropyranyl ether **4**: IR (film) ν 3520, 3420, 3360, 2240, 2120, 1670, 1460, 1330, 1390, 1370, 1260, 1205, 1110, 1070, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.35 (t, 1 H, *J* = 7.0 Hz, vinyl H), 5.25 (d, 1 H, *J* = 8.9 Hz, H-5), 5.1 (m, 1 H, vinyl H), 5.0 (d, 1 H, *J* = 9.9 Hz, CH_2O), 4.8 (t, 1 H, *J* = 3.7 Hz, acetal CH), 4.5 (m, 2 H, H-4 and CH_2O), 3.98 (s, 2 H, CH_2OTBS), 3.8 (m, 1 H, C≡CH), 3.45 (m, 2 H, $THPCH_2O$), 2.6–2.3 (m, 2 H, $CH_2C{\equiv}C$), 2.2–1.4 (m, 14 H), 1.69 (s, 3 H, vinyl CH_3), 1.58 (s, 3 H, vinyl CH_3), 1.57 (s, 3 H, vinyl CH_3), 0.88 (s, 9 H, Si-*t*-Bu), 0.034 (s, 6 H, $Si(CH_3)_2$) ppm; MS 474 (M), 389 (M − THP), 373 (M − OTHP).

Anal. Calcd for $C_{29}H_{50}O_3Si$: C, 73.42; H, 10.55. Found: C, 73.35; H, 10.64.

(2*E*,6*E*,10*E*)-12-[(Tetrahydropyranyl)oxy]-2,6,10-trimethyl-2,6,10-pentadecatrien-14-yn-1-ol (5). The *tert*-butyldimethylsilyl ether **4** (2.85 g, 6.0 mmol) was treated with 9 mL (9.9 mmol) of 1.1 M *n*-Bu_4NF in THF. The solution was stirred for 5 h at 0 °C, poured into water, and extracted with ether. The combined organic extracts were washed with water and brine and dried over $MgSO_4$. Removal of the solvent left an oil that was purified by column chromatography on silica gel, providing 2.14 g (98%) of alcohol **5**: IR (film) ν 3420, 3320, 2940, 2860, 2250, 2120, 1670, 1450, 1390, 1120, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.4 (t, 1 H, *J* = 7.0 Hz, vinyl H), 5.25 (d, 1 H, *J* = 8.9 Hz, H-11), 5.1 (m, 1 H, vinyl H), 5.0 (m, 1 H, CH_2O), 4.8 (t, 1 H, *J* = 3.3 Hz, acetal H), 4.6 (m, 1 H, CH_2O), 4.5 (m, 1 H, H-12), 4.0 (s, 2 H, CH_2OTBS), 3.85 (m, 1 H, C≡CH), 3.45 (m, 2 H, $THPCH_2O$), 2.6–2.4 (m, 2 H, $CH_2C{\equiv}C$), 2.2–1.6 (m, 13 H), 1.68 (s, 3 H, vinyl CH_3), 1.63 (s, 3 H, vinyl CH_3), 1.57 (s, 3 H, vinyl CH_3) ppm.

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.67; H, 10.00. Found: C, 76.54; H, 10.07.

(5*E*,9*E*,13*E*)-15-Chloro-6,10,14-trimethyl-5,9,13-pentadecatrien-1-yn-4-ol Tetrahydropyranyl Ether (6). The method of Collington and Meyers was employed.[9] A solution of anhydrous LiCl (0.03 g, 7 mmol) in 10 mL of dry DMF was cooled to 0 °C, and a solution of 1.30 g (3.62 mmol) of allylic alcohol **5** in 0.72 mL (5.9 mmol) of 2,6-lutidine was added. After 45 min 0.48 mL (5.8 mmol) of methanesulfonyl chloride was added, and the resulting slurry was stirred at 0 °C for 2.5 h. Water and ether were then added, the layers were separated, and the organic extracts were washed with water and brine and dried over $MgSO_4$. Filtration and removal of the solvent left an oil that was purified by column chromatography on silica gel, affording 1.14 g (84%) of the chloride **6**: IR (film) ν 3320, 2950, 2860, 2120, 1670, 1440, 1380, 1260, 1205, 140, 1120, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) 5.5 (t, 1 H, *J* = 7.0 Hz, vinyl H), 5.25 (d, 1 H, *J* = 7.6 Hz, H-5), 5.1 (m, 1 H, vinyl H), 5.05 (m, 1 H, CH_2O), 4.8 (t, 1 H, *J* = 3.3 Hz, acetal H), 4.6 (m, 2 H, H-4 and CH_2O), 3.99 (s, 2 H, CH_2Cl), 3.85 (m, 1 H, C=CH), 3.5 (m, 2 H, $THPCH_2O$), 2.6–1.4 (m, 14 H), 1.71 (s, 3 H, vinyl CH_3), 1.68 (s, 3 H, vinyl CH_3), 1.58 (s, 3 H, vinyl CH_3) ppm.

Anal. Calcd for $C_{23}H_{35}ClO_2$: C, 72.89; H, 9.31. Found: C, 72.82; H, 9.34.

(6*E*,10*E*,14*E*)-16-Chloro-5-[(tetrahydropyranyl)oxy]-7,11,15-trimethyl-6,10,14-hexadecatrien-2-yn-1-ol (7). To a

(31) The following values were found: (1) 35.2 kcal, −60.0°; (2) 35.3 kcal, −166.3°; (3) 35.5 kcal, −165.1°; (4) 35.6 kcal, −119.8°; (5) 35.7 kcal, −156.3°. The coupling constant for H2/H3 found for alcohol **29** (8.6 Hz) is in best agreement with the value calculated for conformer **5** (7.8 Hz). Calculations were performed on the *tert*-butyl ether analogue of **29**.

solution of 1.14 g (3.0 mmol) of alkyne **6** in 6 mL of THF and a small amount of 1,10-phenanthroline at −78 °C was added 1.25 mL (3.12 mmol) of 2.5 M *n*-BuLi. The resulting dark solution was stirred at −78 °C for 1 h, and 0.24 g (6.0 mmol) of paraformaldehyde was added. The mixture was slowly warmed to 0 °C and stirred for 0.5 h. The mixture was quenched with water and diluted with Et_2O. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography on silica gel gave 1.02 g (83%) of alcohol **7**: IR (film) ν 3330, 2940, 2860, 2800, 2220, 1670, 1440, 1380, 1260, 1200, 1140, 1380, 1260, 1200, 1140, 1120, 1080, 1020 cm^{-1}; ^1H NMR δ 5.5 (t, 1 H, J = 7.0 Hz, vinyl H), 5.3 (d, 1 H, J = 8.8 Hz, H-6), 5.1 (m, 1 H, vinyl H), 5.0 (m, 1 H, CH_2O), 4.8 (t, 1 H, J = 3.3 Hz, acetal H), 4.6 (m, 2 H, CH_2O and H-5), 4.2 (d, 2 H, J = 3.8 Hz, CH_2OH), 3.98 (s, 2 H, CH_2Cl), 3.85 (m, 1 H, C=CH), 3.5 (m, 2 H, $THPCH_2O$), 2.6–1.4 (m, 14 H), 1.71 (s, 3 H, vinyl CH_3), 1.69 (s, 3 H, vinyl CH_3), 1.58 (s, 3 H, vinyl CH_3) ppm.

Anal. Calcd for $C_{24}H_{37}ClO_3$: C, 70.55; H, 9.13. Found: C, 70.45; H, 9.18.

(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-13-oxa-2,6,10-cycloheptadecatrien-15-yn-1-ol Tetrahydropyranyl Ether (8a). To a stirred, cooled (0 °C) solution of 1.01 g (2.5 mmol) of the propargylic alcohol **7** and a small amount of 1,10-phenanthroline in 1.7 mL (10.3 mmol) of hexamethylphosphoramide and 250 mL of THF was added 1.2 mL (2.88 mmol) of 2.4 M ethylmagnesium bromide in THF, whereupon a persistent violet color appeared. After 5 min, the cold bath was removed, and the reaction solution was heated to reflux. After 4 h the mixture was cooled to room temperature, saturated aqueous NH_4Cl was added, the layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography on silica gel afforded 769 mg (84%) of the cyclic ether **8a** as a colorless oil: IR (film) ν 2930, 2830, 2740, 2280, 2220, 1670, 1440, 1390, 1370, 1350, 1200, 1135, 1115, 1080, 1060, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.5 (m, 1 H, vinyl H), 5.4 (d, 1 H, J = 7.0 Hz, H-6), 5.2 (m, 1 H, vinyl H), 5.15 (m, 2 H, CH_2O), 4.7 (m, 1 H, acetal H), 4.6 (m, 2 H, CH_2O and H-5), 4.2–3.8 (m, 4 H, CH_2OCH_2), 3.5 (m, 2 H, $THPCH_2O$), 2.7–1.4 (m, 14 H), 1.70 (s, 3 H, vinyl CH_3), 1.59 (s, 3 H, vinyl CH_3), 1.55 (s, 3 H, vinyl CH_3) ppm; MS 288 (M + 1 − THP).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.45; H, 9.77.

(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-13-oxa-2,6,10-cycloheptadecatrien-15-yn-1-ol (8b). A solution of 267 mg (0.72 mmol) of the tetrahydropyranyl ether **8a**, 60 mg (0.24 mmol) of pyridinium *p*-toluenesulfonate, and 5 mL of methanol was stirred at room temperature for 16 h. The solution was diluted with ether, and saturated Na_2CO_3 was added. The separated organic layer was washed with water and brine and dried over $MgSO_4$. Removal of the solvent left a residue that was purified by column chromatography on silica gel, affording 177 mg (85%) of racemic alcohol **8b** as a colorless oil: IR (film) ν 3310, 2990, 2930, 2860, 2280, 2220, 1670, 1440, 1390, 1370, 1350, 1250, 1220, 1140, 1060, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) 5.45 (m, 2 H, vinyl H), 5.15 (m, 1 H, vinyl H), 4.5 (m, 1 H, carbinyl H), 4.0 (m, 4 H, CH_2OCH_2), 2.7–2.4 (m, 2 H, C=CCH_2), 2.3–2.0 (m, 9 H), 1.73 (s, 3 H, vinyl CH_3), 1.59 (s, 3 H, vinyl CH_3), 1.55 (s, 3 H, vinyl CH_3) ppm; MS 273 (M − Me), 255 (M − Me − H_2O).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.85; H, 9.81.

(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-13-oxa-2,6,10-cycloheptadecatrien-15-yn-1-yl *tert*-Butyldimethylsilyl Ether (8c). The TBS ether was prepared from 103.7 mg (0.360 mmol) of the racemic alcohol **8b** as described for (+)-**8c** below. Column chromatography on silic gel afforded 115 mg (80%) of ether **8c** as a colorless oil: IR (film) ν 2960, 2940, 2860, 2280, 2220, 1670, 1450, 1440, 1380, 1360, 1340, 1250, 1070, 1030, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.42 (t, 1 H, J = 5.5 Hz, vinyl H), 5.29 (d, 1 H, J = 8.8 Hz, H-2), 5.17 (t, 1 H, J = 4.4 Hz, vinyl H), 4.5 (ddd, 1 H, J = 8.8, 7.4, 4.4 Hz, H-1), 4.2–3.8 (m, 4 H, CH_2OCH_2), 2.5–2.0 (m, 10 H), 1.65 (s, 3 H, vinyl CH_3), 1.58 (s, 3 H, vinyl CH_3), 1.55 (s, 3 H, vinyl CH_3), 0.85 (s, 9 H, Si-*t*-Bu), 0.01 (s, 6 H, $Si(CH_3)_2$) ppm.

Anal. Calcd for $C_{25}H_{42}O_2Si$: C, 74.57; H, 10.51. Found: C, 74.47; H, 10.55.

(7*E*,11*E*)-6-[(2-Tetrahydropyranyl)oxy]-1-isopropenyl-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-2-ol (9a–12a): Rearrangement with *n*-BuLi–TMEDA as the Base. Condition A. To a solution of 985.5 mg (2.645 mmol) of the cyclic ether **8a** and 4.8 mL (31.7 mmol of TMEDA in 38 mL of pentane–THF (9:1) at −78 °C was added 2.7 mL (5.30 mmol) of *n*-BuLi (2.5 M in hexanes) over 1.5 h. After 3 h at −78 °C, the solution was quenched with saturated aqueous NH_4Cl solution and the mixture was warmed to room temperature. The solution was acidified with 10% HCl, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic extracts were washed with $NaHCO_3$ and brine and dried over $MgSO_4$. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel, affording 910.4 mg (93%) of the rearranged products (**9a–12a**): IR (CCl_4) ν 3600–3300, 3000–2850, 2210, 1650, 1450, 1250, 1200, 1150, 1110, 1080, 1050, 1020 cm^{-1}; ^1H NMR δ 5.2 (m, 2 H, acetal CH and H-7), 5.0 (m, 1 H, H-11), 5.0 and 4.8 (s, 2 H), C=CH_2), 4.6 (m, 2 H, CH_2O), 4.05 (d, 1 H, J = 10.4 Hz, H-2), 3.8 (m, 1 H, H-6), 3.4 (m, 1 H, OH), 2.9–1.2 (m, 17 H), 1.69 (s, 3 H, vinyl CH_3), 1.61 (s, 3 H, vinyl CH_3), 1.57 (s, 3 H, vinyl CH_3) ppm; MS 354 (M − H_2O).

(7*E*,11*E*)-1-Isopropenyl-8,12-dimethyl-6-[(*tert*-butyldimethylsilyl)oxy]-7,11-cyclotetradecadien-3-yn-2-ol (9c–12c): Rearrangement with *n*-BuLi as the Base. Condition E. To a solution of 23.8 mg (0.059 mmol) of the TBS protected cyclic ether **8c** in 0.7 mL of pentane and 0.1 mL of THF at −78 °C was added 52 μL of *n*-BuLi (2.5 M in hexanes). The mixture was stirred for 3 h at −78 °C and quenched with saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give 21.5 mg (90%) of the rearranged alcohols: IR ν 3700–3200, 3000–2800, 2200, 1650, 1450, 1370, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.1 (m, 2 H, H-7, 11), 4.98 (s, 1 H, C=CH_2), 4.78 (s, 1 H, C=CH_2), 4.53 (m, 1 H, H-6), 4.05 (m, 1 H, H-2), 2.7–1.2 (m, 12 H), 1.65 (s, 3 H, vinyl CH_3), 1.61 (s, 3 H, vinyl CH_3), 1.57 (s, 3 H, vinyl CH_3) ppm.

To a solution of 21.5 mg (0.053 mmol) of the rearranged alcohols **9c–12c** in 0.2 mL of THF was added 0.16 mL of TBAF (1.0 M in THF). The mixture was stirred at room temperature for 3 h and diluted with brine. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was acetylated as described below for **15**. GC analysis showed a 89:4:6:1 mixture of diastereoisomers with the same retention times as the acetates derived from **9a–12a** as described below.

(7*E*,11*E*)-1-Isopropyl-8,12-dimethyl-7,11-cyclotetradecadien-3-yne-2,6-diol (9b–12b). To a solution of 7.4 mg (0.02 mmol) of the tetrahydropyranyl ethers (**9a–12a**) in 0.1 mL of EtOH was added 1 mg (0.004 mmol) of pyridinium *p*-toluenesulfonate. The mixture was stirred for 5 h at 55 °C, cooled to room temperature, and diluted with CH_2Cl_2 and brine. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressue, and the crude diols **9b–12b** were purified by column chromatography on silica gel: IR (film) ν 3600–3200, 3000–2800, 1650, 1440, 1380, 1250, 1230, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.4–5.3 (d, 1 H, J = 6.7 Hz, H-7), 5.25–5.1 (m, 1 H, H-11), 5.0 and 4.8 (m, 2 H, C=CH_2), 4.5 (m, 1 H, H-6), 4.06 (d, 1 H, J = 10.4 Hz, H-2), 2.7–0.8 (m, 13 H), 1.67 (s, 3 H, vinyl CH_3), 1.65 (s, 3 H, vinyl CH_3), 1.64 (s, 3 H, vinyl CH_3) ppm.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.88; H, 9.90.

***trans*,*syn*-(7*E*,11*E*)-1-Isopropenyl-8,12-dimethyl-7,11-cyclotetradecadien-3-yne-2,6-diyl Diacetate (15).** The above diols were dissolved in 0.1 mL of CH_2Cl_2, and then 22 μL (0.16 mmol) of triethylamine, 8 μL (0.08 mmol) of acetic anhydride, and a catalytic amount of 4-DMAP were added. The mixture was stirred at room temperature for 2 h and diluted with CH_2Cl_2 and brine, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

GC analysis showed a 65:14:15:6 mixture of diastereomers, corresponding to the trans,syn/trans,anti/cis,syn/cis,anti diacetates derived from **9b**, **10b**, **11b**, and **12b**, respectively. Treatment of the diacetate mixture with ether hexanes caused the major diastereomer (**15**) to crystallize in a form suitable for X-ray analysis, mp 122–124 °C: IR (film) ν 3000–2850, 2550, 2500, 1735, 1440, 1370, 1230, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.58 (ddd, 1 H, J = 13.3, 9.4, 3.9 Hz, H-6), 5.08 (m, 3 H, H-2,7,11), 4.83 and 4.70 (s, 2 H, C=CH_2), 2.7–1.2 (m, 11 H), 2.01 (s, 3 H, OAc), 2.00 (s, 3 H, OAc), 1.74 (s, 3 H, vinyl CH_3), 1.58 (s, 3 H, vinyl CH_3), 1.54 (s, 3 H, vinyl CH_3) ppm.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.01; H, 8.68.

(7*E*,11*E*)-6-[(2-Tetrahydropyranyl)oxy]-1-isopropenyl-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-2-one (13a/14a). The method of Swern[14] as detailed above for **2** was employed with 890.8 mg (2.391 mmol) of the alcohols (**9a–12a**) (65:14:15:6 according to GC analysis of the diacetates). Column chromatography of the residue afforded 759.6 mg (86%) of an 80:20 syn:anti mixture of ketones **13a/14a** as a yellow solid: IR (CCl_4) ν 3000–2800, 2280, 1670, 1435, 1375, 1200, 1180, 1150, 1100, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 and 5.05 (m, 1 H, anti and syn H-7), 5.05 (m, 1 H, acetal CH), 4.86 and 4.78 (s, 2 H, C=CH_2), 4.65 (m, 2 H, H-1, H-6), 3.85 (m, 1 H, CH_2O), 3.50 (m, 2 H, CH_2O), 3.35 (m, 1 H, H-1), 2.8–1.4 (m, 16 H), 1.70 (s, 3 H, vinyl CH_3), 1.67 (s, 3 H, vinyl CH_3), 1.55 (s, 3 H, vinyl CH_3) ppm; MS 371 (M + 1), 315 (M – C_4H_7), 286 (M – THP).

(7*E*,11*E*)-6-Hydroxy-1-isopropenyl-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-2-one (13b/14b). A solution of 249.8 mg (0.674 mmol) of the THP-protected ynones **13a/14a** and 17 mg (0.067 mmol) of PPTS in 3.3 mL of EtOH was stirred at 55 °C for 12 h. The EtOH was distilled under reduced pressure, and the residue was diluted with CH_2Cl_2 and brine. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel, affording 63.9 mg of the recovered THP-protected ynones **14a** and 130.1 mg (91%) of a syn/anti mixture of hydroxy ynones **13b/14b**: IR (CCl_4) ν 3650–3150, 3000–2820, 2210, 1665, 1430, 1375, 1180, 1140, 1015 cm^{-1}; ^1H NMR δ 5.3 and 5.23 (d, 1 H, J = 8.3 Hz, H-7), 5.0 (m, 1 H, H-1), 4.87 and 4.77 (s, 2 H, C=CH_2), 4.62 (m, 1 H, H-6), 3.30 (dd, 1 H, J = 10.9, 3.2 Hz, H-1), 2.6 (ABX, 2 H, J = 17.2, 10.4, 4.4 Hz, H-5), 2.4–1.4 (m, 9 H), 1.71 (s, 3 H, vinyl CH_3), 1.67 (s, 3 H, vinyl CH_3), 1.55 (s, 3 H, vinyl CH_3) ppm.

Anal. Calcd for $C_{19}H_{25}O_2$: C, 79.68; H, 9.15. Found: C, 79.58; H, 9.21.

(3*E*,7*E*,11*E*)-6-Hydroxy-1-isopropenyl-4,8,12-trimethyl-3,7,11-cyclotetradecatrien-2-one (16b/17b). To a solution of 574 mg (3.015 mmol) of CuI in 5 mL of THF at 0 °C was added 4.3 mL (6.03 mmol) of 1.4 M CH_3Li in ether. The solution was stirred at 0 °C for 15 min, and 215.9 mg (0.754 mmol) of the hydroxy ynones **13b/14b** (72:28 syn/anti) in 2.5 mL of THF was added. The mixture was stirred at 0 °C for 0.5 h and quenched with 20 mL of a 1:1 mixture of saturated NH_4Cl and 10% NH_4OH. The layers were separated, and the blue aquous layer was extracted with ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel, affording 197.1 mg (86%) of a syn/anti mixture of 1,4 addition products **16b** and **17b**: IR (CCl_4) ν 3600–3200, 3000–2850, 1680, 1620, 1440, 1385, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05 and 5.77 (s, 1 H, H-3 anti and syn), 5.2 (d, 1 H, J = 9.3 Hz, H-7), 4.8 (m, 3 H, H-11 and C=CH_2), 4.7 (m, 1 H, H-6), 3.1 and 3.0 (m, 1 H, H-1 anti and syn), 2.75 (1 H, OH), 2.2–1.2 (m, 10 H), 2.14 (s, 3 H, C-4 CH_3 of **16b/15b**), 2.02 (C-4 CH_3 of *Z* enones), 1.73 (s, 3 H, vinyl CH_3), 1.67 (s, 3 H, vinyl CH_3), 1.53 (s, 3 H, vinyl CH_3) ppm; MS 302 (M), 284 (M – H_2O).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.36; H, 10.00.

(3*E*,7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropenyl-4,8,12-trimethyl-3,7,11-cyclotetradecatrien-2-one (16c/17c). To a solution of 182.9 mg (0.605 mmol) of the hydroxy enones **16b/17b** in 1.2 mL of DMF was added 82.0 mg (1.21 mmol) of imidazole, 0.34 mL (2.42 mmol) of triethylamine, and 182.0 mg (1.21 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred at room temperature for 5 h and acidified with 3% HCl, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel to give 226.5 mg (90%) of the TBS protected enones **16c**, **17c**: IR (CCl_4) ν 3000–2800, 1680, 1610, 1430, 1370, 1360, 1245, 1090–1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95 and 5.75 (s, 1 H, H-3 syn and anti), 5.05 (m, 1 H, H-7), 4.85 (m, 1 H, H-11), 4.80 (m, 2 H, C=CH_2), 4.65 (m, 1 H, H-6), 3.08 (m, 1 H, H-1), 2.5–1.4 (m, 10 H), 2.18 (s, 3 H, C-4 CH_3), 1.75 (s, 3 H, vinyl CH_3), 1.65 (s, 3 H, vinyl CH_3), 1.50 (s, 3 H, vinyl CH_3), 0.80 (s, 9 H, Si-*t*-Bu), 0.02 (m, 6 H, $Si(CH_3)_2$) ppm; MS 416 (M), 359 (M – C_4H_9).

Anal. Calcd for $C_{26}H_{44}O_2Si$: C, 74.94; H, 10.64. Found: C, 74.76; H, 10.58.

***rel*-(1*S*,3*S*,4*R*,6*R*)-(7*E*,11*E*)-6-Hydroxy-1-isopropenyl-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-2-one (18).**

A. From Enone 16b. To a solution of 197.1 mg (0.652 mmol) of the hydroxy enones **16b/17b** in 1.3 mL of a 1:1 mixture of MeOH and THF was added 1.95 mL of 1 M aqueous NaOH and 0.80 mL (26.1 mmol) of 30% H_2O_2. The mixture was stirred at room temperature for 18 h and cooled to 0 °C, and 5 mL of saturated aqueous Na_2SO_3 was slowly added. The solution was diluted with CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel (deactivated with triethylamine), affording 37.0 mg of recovered hydroxy enones and 157.5 mg (93%) of the epoxides **18** (mixture of stereoisomers at C3, C4), MS 318 (M), 300 (M – H_2O).

B. From Acetate 19. To a solution of 19.4 mg (0.054 mmol) of the epoxy acetate **19** in 0.5 mL of CH_3OH was added 2 mg (0.013 mmol) of K_2CO_3. The mixture was stirred for 12 h at room temperature and diluted with CH_2Cl_2 and saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and concentration left a residue that was purified by column chromatography on silica gel to afford 16.7 mg (97%) of the hydroxy epoxy ketone **18**: IR 3600–3100, 2900, 1710, 1380, 1110, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.32 (d, 1 H, J = 9.3 Hz, H-7), 4.92 (s, 1 H, C=CH_2), 4.80 (s, 1 H, C=CH_2), 4.75 (d, 1 H, J = 10.0 Hz, H-11), 4.50 (dt, 1 H, J = 9.3, 4.9 Hz, H-6), 3.71 (s, 1 H, H-3), 3.07 (dd, 1 H, J = 10.7, 2.0 Hz, H-1), 1.55 (s, 3 H, vinyl CH_3) ppm; MS 319 (M + 1), 318 (M), 300 (M – H_2O); accurate mass calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2199.

***rel*-(1*S*,3*S*,4*R*,6*R*)-(7*E*,11*E*)-6-Acetoxy-3,4-epoxy-1-isopropenyl-4,8,12-trimethyl-7,11-cyclotetradecadien-2-one (19).** To a solution of 650.5 mg (2.043 mmol) of the foregoing epoxy keto alcohol mixture (mainly **18**) in 4.1 mL of CH_2Cl_2 was added 25.0 mg (0.204 mmol) of DMAP, 0.85 mL (6.13 mmol) of triethylamine, and 0.29 mL (3.06 mmol) of acetic anhydride. The mixture was stirred for 1 h at room temperature and acidified with 3% HCl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel deactivated with triethylamine. The first fraction contained 588 mg (79%) of a 66:34 mixture (GC analysis) of two epoxides. The major epoxide **19** was isolated by recrystallization from ether–hexanes to afford a white solid, mp 140–142 °C, suitable for X-ray analysis: IR (CCl_4) ν 3000–2820, 1750–1700, 1450, 1380, 1100, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.61 (ddd, 1 H, J = 14.8, 9.7, 5.1 Hz, H-6), 5.25 (d, 1 H, J = 9.7 Hz, H-7), 4.94 and 4.82 (s, 2 H, C=CH_2), 4.77 (m, 1 H, H-11), 3.75 (s, 1 H, H-3), 3.10 (dd, 1 H, J = 8.8, 1.4 Hz, H-1), 2.6–1.2 (m, 10 H), 2.00 (s, 3 H, $OCOCH_3$), 1.73 (s, 3 H, vinyl CH_3), 1.70 (s, 3 H, vinyl CH_3), 1.56 (s, 3 H, vinyl CH_3), 1.33 (s, 3 H, epoxide CH_3) ppm; MS 360 (M), 318 (M – CH_3CH=CH_2), 300 (M – CH_3CO_2H).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.16; H, 8.98.

***rel*-(1*S*,2*R*,3*R*,4*R*,6*R*)-(7*E*,11*E*)-6-Acetoxy-1-isopropenyl-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-2-ol (20).** To a solution of 17.0 mg (0.466 mmol)

of $NaBH_4$ in 0.3 mL of MeOH at 0 °C was added 112.0 mg (0.311 mmol) of the epoxy ketone **19** in 0.3 mL of CH_2Cl_2. The mixture was stirred for 2 h at 0 °C, and an additional 34.0 mg of $NaBH_4$ was added. After 4 h more at 0 °C, the mixture was diluted with CH_2Cl_2 and quenched by dropwise addition of H_2O, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the organic layers were combined. Removal of the solvent gave an oil that was purified by column chromatography on silica gel deactivated with triethylamine, affording 38.1 mg of the recovered epoxy ketone **19** and 63.9 mg (86%) of the epoxy alcohol **20**: IR (CCl_4) ν 3600–3150, 3000–2850, 1730, 1460, 1380, 1260, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.71 (dt, 1 H, J = 9.2, 3.3 Hz, H-6), 5.20 (d, 1 H, J = 9.2 Hz, H-7), 5.15 (m, 1 H, H-11), 4.86 and 4.82 (s, 2 H, C=CH_2), 3.82 (ddd, 1 H, J = 6.4, 4.8, 1.8 Hz, H-2), 2.87 (d, 1 H, J = 6.4 Hz, H-3), 2.2–1.6 (m, 12 H), 2.00 (s, 3 H, CH_3CO), 1.76 (s, 3 H, vinyl CH_3), 1.65 (s, 3 H, vinyl CH_3), 1.61 (s, 3 H, vinyl CH_3), 1.48 (s, 3 H, C-4, CH_3) ppm; MS 360 (M), 345 (M – CH_3), 318 (M – CH_2=CCH_3 – H), 300 (M – CH_3CO_2H).

***rel*-(1*S*,2*R*,3*R*,4*R*,6*R*)-(7*E*,11*E*)-6-Acetoxy-1-isopropenyl-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-2-yl Methanesulfonate (21).** To a solution of 91.6 mg (0.25 mmol) of the epoxy alcohol **20** in 0.75 mL of CH_2Cl_2 at −10 °C was added 0.28 mL (2.02 mmol) of triethylamine and 0.030 mL (0.38 mmol) of methanesulfonyl chloride. The mixture was stirred for 6 h at −10 °C and acidified with 3% HCl, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, and brine and dried over Na_2SO_4. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel deactivated with triethylamine affording 83.9 mg (75%) of the epoxy mesylate **21**: IR (CCl_4) ν 3000–2850, 1720, 1450, 1360, 1240, 1170, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.51 (dt, 1 H, J = 9.2, 2.9 Hz, H-6), 5.20 (d, 1 H, J = 9.2 Hz, H-7), 5.05 (m, 1 H, H-11), 4.93 and 4.83 (s, 2 H, C=CH_2), 4.72 (dd, 1 H, J = 6.6, 2.6 Hz, H-2), 3.07 (d, 1 H, J = 6.6 Hz, H-3), 3.01 (s, 3 H, SO_2CH_3), 2.4–1.4 (m, 11 H), 1.99 (s, 3 H, $COCH_3$), 1.77 (s, 3 H, vinyl CH_3), 1.68 (s, 3 H, vinyl CH_3), 1.59 (s, 3 H, vinyl CH_3), 1.50 (s, 3 H, carbinyl CH_3) ppm; MS 440 (M), 380 (M – CH_3CO_2H), 301 (M – CH_3CO_2H – SO_2CH_3).

***rel*-(1*S*,2*R*,3*R*,4*R*,6*R*)-(7*E*,11*E*)-1-Isopropenyl-2-[(methylsulfonyl)oxy]-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-6-ol (22).** To a solution of 80.0 mg (0.182 mmol) of the acetate **21** in 0.9 mL of MeOH at 0 °C was added 13.0 mg (0.091 mmol) of K_2CO_3. The mixture was stirred at 0 °C for 18 h, diluted with H_2O and CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel deactivated with triethylamine, affording 66.3 mg (93%) of the alcohol **21**: IR (CCl_4) ν 3600–3100, 3000–2800, 1550, 1340, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.29 (d, 1 H, J = 8.8 Hz, H-7), 5.01 (t, 1 H, J = 5.9 Hz, H-11), 4.98 and 4.82 (s, 2 H, C=CH_2), 4.72 (dd, 1 H, J = 6.5, 2.6 Hz, H-2), 4.4 (m, 1 H, H-6), 3.07 (d, 1 H, J = 6.5 Hz, H-3), 3.02 (s, 3 H, SO_2CH_3), 2.4–1.4 (m, 12 H), 1.76 (s, 3 H, vinyl CH_3), 1.66 (d, 3 H, J = 1.2 Hz, vinyl CH_3), 1.60 (s, 3 H, vinyl CH_3), 1.60 (s, 3 H, carbinyl CH_3) ppm; MS 398 (M), 319 (M – SO_2CH_3), 301 (M – SO_2CH_3 – H_2O).

***rel*-(1*R*,4*R*,6*R*)-(2*E*,7*E*,11*E*)-1-Isopropenyl-4,8,12-trimethyl-2,7,11-cyclotetradecatriene-4,6-diol (24).** To a solution of 29.7 mg (0.074 mmol) of the epoxy mesylate alcohol **22** in 0.75 mL of THF at −40 °C was added a small clean piece of Na. Ammonia was distilled into the solution until an intense blue color appeared. After 10 min, the excess Na was quenched by careful addition of solid NH_4Cl. The solution was warmed to 0 °C, allowing the NH_3 to evaporate, and the residue was diluted with ether and H_2O. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine and dried over Na_2SO_4. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel, affording 3.6 mg (15%) of the epoxy diol **23** and 17.4 mg (77%) of the diol **24**: IR (CCl_4) ν 3600–3100, 2980–2820, 1550, 1440, 1380, 1250, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.44 (d, 1 H, J = 15.8 Hz, H-3), 5.32 (dd, 1 H, J = 15.8, 8.8 Hz, H-2), 5.30 (d, 1 H, J = 3.0 Hz, H-7), 5.00 (m, 1 H, H-11), 4.77 (dt, 1 H, J = 8.5, 3.0 Hz, H-6), 4.64 (s, 2 H, C=CH_2), 2.2–1.2 (m, 17 H), 1.68 (s, 3 H, vinyl CH_3), 1.64 (s, 3 H, vinyl CH_3), 1.51 (s, 3 H, vinyl CH_3), 1.36 (s, 3 H, carbinyl CH_3) ppm; MS 304 (M), 286 (M – H_2O), 271 (M – H_2O – CH_3).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.10; H, 10.60.

***rel*-(1*S*,4*R*,6*R*)-2,7,11-Cembratriene-4,6-diol (β-CBT) (25).** A solution of 47.4 mg (0.051 mmol) of $(Ph_3P)_3RhCl$ in 0.5 mL of EtOH and 0.5 mL of C_6H_6 was stirred under a hydrogen atmosphere for 20 min, and then 15.6 mg (0.051 mmol) of the isopropenyl compound **24** in 0.5 mL of C_6H_6 was added. After 4 h the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel to afford 14.4 mg (92%) of the diol **25**: IR (CCl_4) ν 3600–3100, 3000–2800, 1440, 1360, 1110, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (d, 1 H, J = 15.6 Hz, H-3), 5.3–5.1 (m, 2 H, H-3 and H-7), 5.19 (dd, 1 H, J = 15.6, 8.9 Hz, H-2), 4.97 (m, 1 H, H-11), 4.80 (dt, 1 H, J = 9.6, 1.5 Hz, H-6), 2.2–1.1 (m, 14 H), 1.68 (d, 3 H, J = 1.1 Hz, C-8 CH_3), 1.49 (s, 3 H, C-12 CH_3), 1.38 (s, 3 H, C-4 CH_3), 0.81 (d, 3 H, J = 6.7 Hz, $(CH_3)_2CH$), 0.77 (d, 3 H, J = 6.7 Hz, $(CH_3)_2CH$) ppm; ^{13}C NMR ($CDCl_3$) δ 136.49, 136.14, 133.05, 131.43, 130.39, 124.43, 71.47, 64.47, 52.48, 46.26, 38.84, 36.49, 32.92, 28.75, 27.67, 23.06, 20.59, 19.36, 15.90, 14.99 ppm; MS 306 (M), 288 (M – H_2O), 277 (M – C_2H_5), 273 (M – H_2O – CH_3), 263 (M – C_3H_7), 245 (M – C_3H_7 – H_2O); exact mass calcd for $C_{20}H_{34}O_2$ 306.2559, found 306.2550; calcd for $C_{20}H_{32}O$ (M – H_2O) 288.2453, found 288.2458. This material was identical with an authentic sample of β-CBT as judged by comparison of the spectra and TLC behavior.

(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-13-oxa-2,6,10-cycloheptadecatrien-14-yn-1-ol Dicobalt Hexacarbonyl Complex (28). To a solution of 1.63 g (4.77 mmol) of $Co_2(CO)_8$ in 10 mL of ether was added dropwise 1.377 g (4.77 mmol) of the cyclic ether alcohol **8b** in 6 mL of ether.[25] The solution was stirred for 0.5 h until CO evolution was no longer visible. The solvent was removed, and the residue was purified by column chromatography on silica gel. Elution, first with hexanes to remove nonpolar cobalt impurities, followed by 3% ether–hexanes, afforded 2.68 g (98%) of the desired cobalt complex **28**: IR (CCl_4) ν 3600–3200, 3000–2850, 2100–1990, 1440, 1030 cm^{-1}. The ^1H NMR spectrum was broadened by paramagnetic Co impurities.

The TBS ether derivative **29** was prepared in 90% yield from 161 mg of alcohol **28**, 63 mg of TBSCl, 0.23 mL of Et_3N, and 6 mg of imidazole in 1 mL of DMF with stirring for 8 h: ^1H NMR ($CDCl_3$) δ 5.3 (m, 2 H, H-2,6), 5.1 (m, 1 H, H-6), 4.6 (m, 1 H, H-1), 4.35 (AB q, 2 H, J = 13.4 Hz, CH_2O), 3.98 (d, 2 H, J = 4.6 Hz, CH_2O), 3.2 (m, 2 H, CH_2), 2.3–1.9 (m, H), 1.65 (s, 3 H, vinyl CH_3), 1.61 (s, 3 H, vinyl CH_3), 1.59 (s, 3 H, vinyl CH_3), 0.87 (s, 9 H, Si-*t*-Bu), 0.05 and 0.03 (s, 6 H, $Si(CH_3)_2$) ppm.

(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-13-oxa-2,6,10-cycloheptadecatrien-14-ynone Dicobalt Hexacarbonyl Complex (30). Swern oxidation[14] of alcohol **28** (2.770 g, 4.823 mmol) was effected as described above for alcohol **1**. Column chromatography on silica gel gave 2.260 g (86%) of ketone **30**: IR (CCl_4) ν 3000–2830, 2100–1990, 1690, 1610, 1430, 1390, 1120–1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.17 (s, 1 H, H-2), 5.3 (m, 1 H, H-6), 4.9 (m, 1 H, H-10), 4.59 (s, 2 H, $COCH_2$), 3.93 (s, 2 H, CH_2O), 3.92 (s, 2 H, CH_2O), 2.4–1.2 (m, 8 H), 2.12 (s, 3 H, C-3, CH_3), 1.61 (s, 3 H, vinyl CH_3), 1.57 (s, 3 H, vinyl CH_3) ppm.

(+)-(1*R*)-(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-13-oxa-2,6,10-cycloheptadecatrien-14-yn-1-ol ((+)-8b). To a solution of 4.34 mL (4.34 mmol) of 1.0 M $LiAlH_4$ in THF in 100 mL of ether at 0 °C was added 2.830 g (9.987 mmol) of Chirald in 20 mL of ether.[22] The mixture was stirred for 2 min and then cooled to −78 °C, and 2.260 g (3.950 mmol) of the dicobalt hexacarbonyl complexed ketone **30** in 40 mL of ether was added dropwise over 45 min. The mixture was stirred at −78 °C for 5 h; then it was quenched at −78 °C by addition of wet ether. Aqueous 10% HCl was added, and the product was extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Filtration and removal of the solvent gave the alcohol **31** as a red oil. This oil was dissolved in 30 mL of ether and 30 mL of MeOH, and 3 g of ceric ammonium nitrate was added portionwise over 0.5 h.[25] The solvent was removed at reduced pressure, water was added, and the product was extracted with ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent and column chromatography of the residue on silica gel gave 1.020 g (90%) of the alcohol (+)-**8b**: $[\alpha]^{22}_D$ + 50.0° (*c*

2.250, $CHCl_3$); IR (CCl_4) ν 3600–3250, 3000–2280, 2280, 2220, 1670, 1440, 1350, 1230, 1050–1000 cm^{-1}; ^1H NMR δ ($CDCl_3$) 5.5 (m, 2 H, H-2, 11), 5.1 (m, 1 H, H-10), 4.5 (m, 1 H, H-1), 4.0 (m, 4 H, CH_2OCH_2), 2.7–2.3 (m, 2 H, C≡CCH_2), 2.2–2.0 (m, 6 H), 1.7–1.5 (m, 3 H), 1.73 (s, 3 H, vinyl CH_3), 1.60 (s, 3 H, vinyl CH_3), 1.55 (s, 3 H, vinyl CH_3) ppm.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.00; H, 9.80.

(+)-(1*R*)-(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-13-oxa-2,6,10-cycloheptadecatrien-14-yl *tert*-Butyldimethylsilyl Ether ((+)-8c). To a solution of 1.110 g (3.847 mmol) of the homopropargylic alcohol (+)-**8b** in 8 mL of CH_2Cl_2 were added 2.10 mL (15.39 mmol) of triethylamine, 0.12 g (0.096 mmol) of DMAP, and 0.87 g (5.77 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred at room temperature for 48 h and acidified with 3% HCl, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel, affording 1.377 g (89%) of the TBS protected cyclic ether (+)-**8c**, $[\alpha]^{22}_D$ + 31.3° (*c* 1.750, $CHCl_3$). The spectral properties were identical with those reported above for racemic **8c**.

(1*R*)- and (1*S*)-(2*E*,6*E*,10*E*)-3,7,11-Trimethyl-13-oxa-2,6,10-cycloheptadecatrien-15-ynyl (*R*)-1-Methoxy-1-phenylacetate (32 and 33). To a solution of 191.9 mg (0.665 mmol) of the racemic alcohol **8b** in 1.5 mL of CH_2Cl_2 were added 165 mg (0.80 mmol) of DCC, 93 mg (0.80 mmol) of (−)-(*R*)-α-methoxyphenylacetic acid, and 8 mg (0.07 mmol) of DMAP.[26] The mixture was stirred at room temperature for 24 h and chromatographed directly on silica gel. Elution with Et_2O–hexanes gave 95.3 mg of the *R,S* diastereomer **33**, 41.1 mg of a mixture, and 132.5 mg of the *R,R* diastereomer **32**.

32: IR ν 3000–2850, 1740, 1450, 1250, 1200, 1170, 1115, 1080, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4–7.2 (m, 5 H, arom), 5.6 (m, 1 H, H-1), 5.4 (t, 1 H, *J* = 6.1 Hz, H-10), 5.32 (d, 1 H, *J* = 8.6 Hz, H-2), 4.98 (t, 1 H, *J* = 6.1 Hz, H-6), 4.71 (s, 1 H, MeOC*H*), 4.2–3.9 (m, 4 H, CH_2OCH_2), 3.38 (s, 3 H, CH_3O), 2.8–2.4 (2 H, CH_2C≡C), 2.3–2.0 (m, 8 H), 1.61 (s, 3 H, vinyl CH_3), 1.52 (s, 3 H, vinyl CH_3), 1.41 (s, 3 H, vinyl CH_3) ppm; $[\alpha]^{21}_D$ −12.5° (*c* 1.48, $CHCl_3$).

Anal. Calcd for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.16; H, 8.37.

33: IR ν 3000–2850, 1740, 1450, 1250, 1200, 1170, 1115, 1080, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4–7.2 (m, 5 H, arom), 5.6 (m, 1 H, H-1), 5.5 (m, 1 H, H-10), 5.42 (d, 1 H, *J* = 9.0 Hz, H-2), 5.1 (m, 1 H, H-6), 4.72 (s, 1 H, MeOC*H*), 4.1–3.9 (m, 4 H, CH_2OCH_2), 3.39 (s, 3 H, CH_3O), 2.6–2.4 (m, 2 H, CH_2C≡C), 2.4–2.0 (m, 8 H), 1.66 (s, 3 H, vinyl CH_3), 1.61 (s, 3 H, vinyl CH_3), 1.56 (s, 3 H, vinyl CH_3) ppm; $[\alpha]^{21}_D$ −39.1° (*c* 1.89, $CHCl_3$).

(7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropenyl-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-1-ol (9c–11c). Procedure A described for racemic **8a** was followed with 1.333 g (3.310 mmol) of the TBS-protected cyclic ether (+)-**8c** and 1.5 mL (9.93 mmol) of TMEDA in 46 mL of pentane at −78 °C to which was added dropwise a solution comprised of 6.2 mL (9.93 mmol) of 1.6 M *n*-BuLi in hexanes and 1.5 mL (9.93 mmol) of TMEDA in 5 mL of THF premixed at −78 °C for 10 min. Column chromatography on silica gel afforded 1.134 g (85%) of a 73:11:16 mixture of rearranged products **9c–11c** according to GC analysis of the diacetate derivatives. The spectral properties were in close agreement to a sample prepared from racemic **8c** as described above.

Anal. Calcd for $C_{25}H_{42}O_2Si$: C, 74.57; H, 10.51. Found: C, 74.51; H, 10.55.

(6*R*)-(7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropenyl-8,12-dimethyl-7,11-cyclotetradecadien-3-yn-2-one (13c/14c). The procedure described for **13a/14a** was employed with 1.134 g (2.816 mmol) of the TBS-protected propargylic alcohols **9c–11c** (73:11:16). Column chromatography on silica gel afforded 1.088 g (96%) of the ynones **13c** and **14c** as a 90:10 mixture of diastereomers: IR (CCl_4) ν 3000–2800, 2100, 1665, 1440, 1380, 1250, 1190, 1160, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.14 (d, 1 H, *J* = 9.6 Hz, H-7), 5.04 (m, 1 H, H-11), 4.87 (s, 1 H, C=CH_2), 4.78 (s, 1 H, C=CH_2), 4.56 (dt, 1 H, *J* = 4.7, 9.6 Hz, H-6), 3.32 (dd, 1 H, *J* = 11.1, 3.0 Hz, H-1), 2.7–1.4 (m, 10 H), 1.70 (s, 3 H, vinyl CH_3), 1.67 (s, 3 H, vinyl CH_3), 1.55 (s, 3 H, vinyl CH_3), 0.83 (s, 9 H, Si-*t*-Bu), 0.02 (s, 6 H, $Si(CH_3)_2$) ppm.

Anal. Calcd for $C_{25}H_{40}O_2Si$: C, 74.94; H, 10.06. Found: C, 74.86; H, 10.14.

(6*R*)-(3*E*,7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropenyl-4,8,12-trimethyl-3,7,11-cyclotetradecatrien-2-one (16c/17c). The procedure described for **16b/17b** was employed with 1.045 g (2.82 mmol) of the TBS-protected ynones **13c** and **14c**, a 90:10 mixture of isomers. Column chromatography on silica gel afforded 942.8 mg (86%) of the 1,4-addition products **16c** and **17c**: IR (CCl_4) ν 3000–2800, 1680, 1610, 1430, 1370, 1360, 1245, 1090–1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95 and 5.75 (s, 1 H, H-3 syn and anti), 5.05 (m, 1 H, H-7), 4.85 (m, 1 H, H-11), 4.80 (m, 2 H, C=CH_2), 4.65 (m, 1 H, H-6), 3.08 (m, 1 H, H-1), 2.5–1.4 (m, 10 H), 2.18 (s, 3 H, (*E*)-C-4 vinyl CH_3), 1.80 (s, (*Z*)-C-4, vinyl CH_3, ca. 10% by peak height), 1.75 (s, 3 H, vinyl CH_3), 1.65 (s, 3 H, vinyl CH_3), 1.50 (s, 3 H, vinyl CH_3), 0.80 (s, 9 H, Si-*t*-Bu), 0.02 (m, 6 H, $Si(CH_3)_2$) ppm; MS 416 (M), 359 (M − C_4H_9).

Anal. Calcd for $C_{26}H_{44}O_2Si$: C, 74.94; H, 10.64. Found: C, 74.76; H, 10.58.

(6*R*)-(3*E*,7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropenyl-4,8,12-trimethyl-3,7,11-cyclotetradecatrien-2-one (41 and 42). To a solution of 7.1 mL (7.10 mmol) of 1.0 M DIBAH in hexanes at −78 °C was added 591.4 mg (1.42 mmol) of the above TBS-protected enones **16c** and **17c** in 4.3 mL of THF. The mixture was stirred at −78 °C for 1 h and quenched by dropwise addition of 10 mL of saturated aqueous Rochelle's salt. The solution was stirred for 0.5 h at 0 °C, the layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine and dried over Na_2SO_4. Filtration and removal of the solvent gave an oil that was purified by column chromatography on silica gel, affording 569.5 mg (96%) of the cis and trans allylic alcohols **41** and **42** (90:10 syn:anti): IR (CCl_4) ν 3600–3300, 3000–2810, 1640, 1430, 1370, 1250, 1100–1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (d, 1 H, *J* = 8.3 H-7 syn and anti), 5.2–4.9 (m, 3 H, H-11, H-3, C=CH_2), 4.8 (m, 1 H, C=CH_2), 4.7–4.5 (m, 1 H, H-6), 4.5–4.3 (b d, 1 H, *J* ~ 8 Hz, H-2 α-OH), 4.10 (b t, *J* ~ 10 Hz, H-2 β-OH), 2.5–1.5 (m, 12 H), 1.77 (s, 3 H, vinyl CH_3), 1.58 (s, 3 H, vinyl CH_3), 1.56 (s, 3 H, vinyl CH_3), 1.53 (s, 3 H, vinyl CH_3), 0.86 (m, 9 H, Si-*t*-Bu), 0.02 (m, 6 H, $Si(CH_3)_2$) ppm; MS 419 (M + 1), 418 (M), 400 (M − H_2O), 361 (M − C_4H_9).

Anal. Calcd for $C_{26}H_{46}O_2Si$: C, 74.58; H, 11.07. Found: C, 74.49; H, 11.11.

(1*S*,2*R*,6*R*)-(3*E*,7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-4,8,12-trimethyl-3,7,11-cyclotetradecatrien-2-ol (43). A solution of 813 mg (0.879 mmol) of $(Ph_3P)_3RhCl$ in 6 mL of EtOH and 6 mL of C_6H_6 was stirred under a hydrogen atmosphere for 20 min before 368.0 mg (0.879 mmol) of the foregoing alcohol mixture **41** and **42** in 6 mL of C_6H_6 was added.[29] After 4 h the reaction mixture was concentrated under reduced pressure, affording 775 mg (95%) of product, which was purified by column chromatography on silica gel to give 255.1 mg (69%) of the cis, syn isomer **43**:[10] $[\alpha]^{22}_D$ +59.3° (*c* 0.995, $CHCl_3$); IR (CCl_4) ν 3600–3100, 3000–2800, 1450–1430, 1380, 1245, 1080–1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.31 (d, 1 H, *J* = 10.6 Hz, H-7), 5.05 (d, 1 H, *J* = 8.6 Hz, H-3), 4.95 (m, 1 H, H-11), 4.55 (m, 2 H, H-6, H-2), 2.4–1.2 (m, 13 H), 1.58 (s, 3 H, vinyl CH_3), 1.53 (s, 3 H, vinyl CH_3), 1.51 (s, 3 H, vinyl CH_3), 0.95 (d, 3 H, *J* = 7.0 Hz, $(CH_3)_2CH$), 0.92 (d, 3 H, *J* = 7.0 Hz, $(CH_3)_2CH$), 0.86 (s, 9 H, Si-*t*-Bu), 0.03 and 0.15 (s, 6 H, $Si(CH_3)_2$) ppm; MS 420 (M), 402 (M − H_2O), 363 (M − C_4H_9).

Anal. Calcd for $C_{26}H_{48}O_2Si$: C, 74.22; H, 11.50. Found: C, 73.72; H, 11.52.

(1*S*,2*R*,3*S*,4*S*,6*R*)-(7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-2-ol (44). To a solution of 255.1 mg (0.598 mmol) of the allylic alcohol **43** in 2.0 mL of toluene was added 0.23 mL (0.90 mmol) of 3.9 M *t*-BuOOH in isooctane and 5.0 mg (0.018 mmol) of $VO(acac)_2$.[30] The red solution turned yellow after stirring for 1 h at room temperature. The mixture was quenched with saturated Na_2SO_3 at 0 °C, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine. Removal of the solvent gave an oil that was purified by column chromatography on silica gel (deactivated with triethylamine), affording 234.5 mg (88%) of the epoxy alcohol **44**: $[\alpha]^{22}_D$ +27.7° (*c* 1.515, $CHCl_3$); IR (CCl_4) ν 3600–3200, 3000–2800, 1440, 1370, 1240, 1070, 1040, 1020 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 5.01 (d, 1 H, J = 10.6 Hz, H-7), 4.96 (m, 1 H, H-11), 4.46 (m, 1 H, H-6), 3.49 (dd, 1 H, J = 6.3, 8.6 Hz, H-2), 2.68 (d, 1 H, J = 8.6 Hz, H-3), 2.5–1.2 (m, 13 H), 1.65 (s, 3 H, vinyl CH_3), 1.64 (s, 3 H, vinyl CH_3), 1.28 (s, 3 H, epoxy CH_3), 0.88 (d, 3 H, J = 6.9 Hz, $(CH_3)_2CH$), 0.84 (s, 9 H, Si-*t*-Bu), 0.83 (d, 3 H, J = 6.9 Hz, $(CH_3)_2CH$), 0.02 (s, 3 H, $SiCH_3$), −0.01 (s, 3 H, $SiCH_3$) ppm; MS 436 (M), 418 (M − H_2O), 379 (M − C_4H_9), 361 (M − C_4H_9 − H_2O).

Anal. Calcd for $C_{26}H_{48}O_3Si$: C, 71.50; H, 11.08. Found: C, 71.37; H, 11.12.

(1*S*,2*R*,3*S*,4*S*,6*R*)-(7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-2-yl Methanesulfonate (45). To a solution of 172.6 mg (0.395 mmol) of the epoxy alcohol **44** in 1.0 mL of CH_2Cl_2 and 0.64 mL of pyridine at −10 °C was added 0.062 mL (0.079 mmol) of methanesulfonyl chloride. The mixture was stirred for 18 h at 0 °C, diluted with CH_2Cl_2, and acidified with 10% HCl, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. Filtration and removal of solvent gave an oil that was purified by column chromatography on silica gel (deactivated with triethylamine), affording 187.5 mg (92%) of the mesylate **45**: $[\alpha]^{22}_D$ +7.8° (*c* 0.51, $CHCl_3$); IR (CCl_4) ν 3000–2850, 1460, 1370, 1240, 1170, 1070, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.05 (d, 1 H, J = 10.6 Hz, H-7), 4.95 (m, 1 H, H-11), 4.64 (d, 1 H, J = 9.6 Hz, H-2), 4.50 (m, 1 H, H-6), 3.15 (s, 3 H, SO_2CH_3), 2.83 (d, 1 H, J = 9.6 Hz, H-3), 2.5–1.1 (m, 12 H), 1.66 (s, 3 H, vinyl CH_3), 1.65 (s, 3 H, vinyl CH_3), 1.33 (s, 3 H, epoxy CH_3), 0.91 (d, 3 H, J = 7.0 Hz, $(CH_3)_2CH$), 0.86 (d, 3 H, J = 7.0 Hz, $(CH_3)_2CH$), 0.83 (s, 9 H, Si-*t*-Bu), 0.02 and −0.01 (s, 6 H, $Si(CH_3)_2$) ppm.

Anal. Calcd for $C_{27}H_{50}O_5SSi$: C, 62.99; H, 9.79. Found: C, 63.09; H, 9.83.

(1*S*,2*R*,3*S*,4*S*,6*R*)-(7*E*,11*E*)-1-Isopropyl-2-[(methylsulfonyl)oxy]-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-6-ol (46). To a solution of 157.1 mg (0.305 mmol) of the TBS-protected epoxy mesylate **45** in 0.9 mL of THF at 0 °C was added 0.46 mL (0.460 mmol) of 1.1 M Bu_4NF in THF. The solution was stirred for 2 h at 0 °C and diluted with brine, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic extracts were concentrated under reduced pressure and purified by column chromatography on silica gel (deactivated with triethylamine) to give 112.4 mg (92%) of the hydroxy epoxy mesylate **46**: $[\alpha]^{22}_D$ +10.0° (*c* 0.30, $CHCl_3$); IR (CCl_4) ν 3600–3100, 3000–2800, 1550, 1340, 1170, 970, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.10 (d, 1 H, J = 10.6 Hz, H-7), 4.90 (m, 1 H, H-11), 4.64 (d, 1 H, J = 9.6 Hz, H-2), 4.54 (m, 1 H, H-6), 3.15 (s, 3 H, SO_2CH_3), 2.85 (d, 1 H, J = 9.6 Hz, H-3), 2.5–1.2 (m, 13 H), 1.73 (s, 3 H, vinyl CH_3), 1.66 (s, 3 H, vinyl CH_3), 1.35 (s, 3 H, epoxy CH_3), 0.91 (d, 3 H, J = 7.0 Hz, $(CH_3)_2CH$), 0.86 (d, 3 H, J = 7.0 Hz, $(CH_3)_2CH$) ppm.

Anal. Calcd for $C_{21}H_{36}O_5S$: C, 62.97; H, 9.06. Found: C, 63.06; H, 9.09.

(1*S*,4*S*,6*R*)-2,7,11-Cembratriene-4,6-diol (α-CBT) (47). The procedure described for **24** was employed with 24.0 mg (0.060 mmol) of the epoxy mesylate alcohol **46**. Column chromatography on silica gel afforded 13.7 mg (75%) of the diol **47**: $[\alpha]^{22}_D$ +89.2° (*c* 0.325, $CHCl_3$); IR (CCl_4) ν 3600–3100, 3000–2800, 1650, 1440, 1370, 1250, 1150–950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.31 (m, 3 H, H-2,3,7), 5.01 (t, 1 H, J = 5.9 Hz, H-11), 4.47 (dt, 1 H, J = 8.5, 2.2 Hz, H-6), 2.3–1.2 (m, 14 H), 1.65 (d, 3 H, J = 1.2 Hz, vinyl CH_3), 1.50 (s, 3 H, vinyl CH_3), 1.33 (s, 3 H, carbinyl CH_3), 0.80 (d, 3 H, J = 6.7 Hz, $(CH_3)_2CH$), 0.77 (d, 3 H, J = 6.7 Hz, $(CH_3)_2CH$) ppm; ^{13}C NMR 137.6, 136.4, 133.3, 130.7, 127.7, 124.4, 72.4, 56.2, 52.3, 46.4, 38.9, 36.8, 33.0, 30.1, 27.9, 23.3, 20.7, 19.4, 16.1, 15.0 ppm; MS 306 (M), 288 (M − H_2O). An authentic sample of α-CBT showed $[\alpha]^{22}_D$ +200° (*c* 0.845, $CHCl_3$). The spectral properties of this sample were identical with those of the synthetic material.

***rel*-(1*S*,3*S*,4*R*,6*R*)-(7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropenyl-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-2-one (48).** To a solution of 16.7 mg (0.053 mmol) of the hydroxy epoxy ketone **18** in 0.16 mL of CH_2Cl_2 was added 0.044 mL (0.31 mmol) of triethylamine, 12 mg (0.079 mmol) of TBSCl, and 1 mg (0.005 mmol) of DMAP. The mixture was stirred at room temperature for 18 h and acidified with 3% HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ and brine and dried over $MgSO_4$. Filtration and concentration left a residue that was chromatographed on silica gel to afford 15.4 mg (68%) of the TBS protected epoxy ketone **48**: IR 3000–2850, 1720, 1450, 1390, 1260, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.25 (d, 1 H, J = 9.0 Hz, H-7), 4.93 (s, 1 H, C=CH_2), 4.81 (s, 1 H, C=CH_2), 4.85 (m, 1 H, H-11), 4.50 (dt, 1 H, J = 9.0, 4.9 Hz, H-6), 3.61 (s, 3 H, H-3), 3.18 (dd, 1 H, J = 10.4, 2.7 Hz, H-1), 2.5–1.2 (m, 8 H), 1.69 (s, 3 H, vinyl CH_3), 1.66 (s, 3 H, vinyl CH_3), 1.56 (s, 3 H, vinyl CH_3), 1.31 (s, 3 H, vinyl CH_3), 0.83 (s, 9 H, Si-*t*-Bu), 0.01 (s, 6 H, $SiMe_2$) ppm; MS 433 (M + 1), 432 (M), 417 (M − CH_3), 404 (M − CO), 375 (M − CH_3 − CH_2=$CHCH_3$).

***rel*-(1*S*,3*S*,4*R*,6*R*)-(7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-2-one (49).** A solution of 23 mg (0.025 mmol) of Wilkinson's catalyst in 0.25 mL of EtOH and 0.25 mL of benzene was stirred under a hydrogen atmosphere for 20 min, then 10.8 mg (0.025 mmol) of the isopropenyl compound **48** in 0.25 mL of benzene was added. After 4 h, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel to afford 9.7 mg (89%) of the isopropyl product **48**: ^{1}H NMR ($CDCl_3$) δ 5.24 (d, 1 H, J = 8.7 Hz, H-7), 4.86 (m, 1 H, H-11), 4.47 (dt, 1 H, J = 8.7, 4.7 Hz, H-6), 3.52 (s, 3 H, H-3), 2.5–1.2 (m, 8 H), 1.62 (d, 3 H, J = 1.2 Hz, vinyl CH_3), 1.54 (s, 3 H, vinyl CH_3), 1.33 (s, 3 H, CH_3), 1.00 (d, 3 H, J = 6.9 Hz, isopropyl CH_3), 0.84 (s, 9 H, Si-*t*-Bu), 0.81 (d, 3 H, J = 6.9 Hz isopropyl CH_3), 0.02 and 0.0 (s, 6 H, $SiMe_2$) ppm.

(1*S*,3*R*,4*S*,6*R*)-(7*E*,11*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-isopropyl-3,4-epoxy-4,8,12-trimethyl-7,11-cyclotetradecadien-2-one (50). To a solution of 10 mg (0.046 mmol) of PCC and 10 mg (0.125 mmol) of NaOAc in 0.5 mL of CH_2Cl_2 was added 5.5 mg (0.0125 mmol) of epoxy alcohol **44** in 0.7 mL of CH_2Cl_2. The mixture was stirred for 6 h at room temperature. Addition of ~50 mg of Florisil, filtration through Celite, and removal of the solvent at reduced pressure left an oil that was purified by column chromatography on silica gel to afford 4.5 mg (82%) of the ketone **50**: ^{1}H NMR ($CDCl_3$) δ 5.23 (d, 1 H, J = 7.6 Hz, H-7), 5.13 (m, 1 H, H-11), 4.40 (m, 1 H, H-6), 3.59 (s, 1 H, epoxide H), 2.46 (m, 1 H, H-1), 2.4–1.4 (m), 1.72 (s, 3 H, vinyl CH_3), 1.61 (s, 3 H, vinyl CH_3), 1.26 (s, 3 H, CH_3), 0.91 (d, 3 H, J = 6.8 Hz, isopropyl CH_3), 0.85 (s, 9 H, Si-*t*-Bu), 0.81 (d, 3 H, J = 6.8 Hz, isopropyl CH_3), 0.0 (s, 6 H, $Si(CH_3)_2$) ppm.

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Registry No. **1**, 104465-86-3; **2**, 121747-11-3; (±)-**3**, 121747-12-4; **4**, 121747-13-5; **5**, 121747-14-6; **6**, 121747-15-7; **7**, 121747-16-8; **8a**, 121747-17-9; (±)-**8b**, 121747-18-0; (+)-**8b**, 123406-64-4; (±)-**8c**, 121747-19-1; (+)-**8c**, 123406-65-5; (±)-**9a**, 121747-20-4; (±)-**9b**, 121747-22-6; (±)-**9c**, 121747-21-5; (6*R*)-**9c**, 123406-66-6; (±)-**10a**, 121841-54-1; (±)-**10b**, 121841-56-3; (±)-**10c**, 121841-55-2; (6*R*)-**10c**, 123406-67-7; (±)-**10** diacetate, 121841-63-2; (±)-**11a**, 121841-57-4; (±)-**11b**, 121841-59-6; (±)-**11c**, 121841-58-5; (6*R*)-**11c**, 123406-68-8; (±)-**11** diacetate, 121841-64-3; (±)-**12a**, 121841-60-9; (±)-**12b**, 121841-62-1; (±)-**12c**, 121841-61-0; (±)-**12** diacetate, 121841-65-4; (±)-**13a**, 122621-66-3; (±)-**13b**, 122552-55-0; (±)-**13c**, 121747-24-8; (6*R*)-**13c**, 123482-28-0; (±)-**14a**, 122552-63-0; (±)-**14b**, 122620-37-5; (±)-**14c**, 121841-66-5; (6*R*)-**14c**, 123406-69-9; (±)-**15**, 121747-23-7; (±)-**16b**, 122552-56-1; (±)-**16c**, 123311-98-8; (6*R*)-**16c**, 123406-70-2; (±)-**17b**, 122620-38-6; (±)-**17c**, 123406-63-3; (6*R*)-**17c**, 123406-71-3; (±)-**18**, 122552-57-2; (±)-**19**, 122552-58-3; (±)-**20**, 122552-59-4; (±)-**21**, 122552-60-7; (±)-**22**, 122552-61-8; (±)-**23**, 122552-64-1; (±)-**24**, 122552-62-9; (±)-**25**, 122620-36-4; **28**, 123311-99-9; **29**, 123312-00-5; **30**, 123312-01-6; **31**, 123406-72-4; **32**, 123311-84-2; **33**, 123311-85-3; (±)-**34**, 123311-86-4; (±)-**35**, 123311-87-5; (±)-**36**, 123406-61-1; (±)-**37**, 123311-88-6; (±)-**38**, 123311-89-7; **39**, 123538-32-9; **40**, 123311-90-0; **41**, 123311-91-1; **42**, 123408-81-1; **43**, 123311-92-2; **44**, 123311-93-3; **45**, 123311-94-4; **46**, 123311-95-5; **47**, 57605-80-8; (±)-**48**, 123311-96-6; (±)-**49**, 123311-97-7; **50**, 123406-62-2; CH≡CCH_2Br, 106-96-7; (*R*)-MeOCH(Ph)CO_2H, 3966-32-3.