Total Synthesis of (+)-9,10-*syn*- and (+)-9,10-*anti*-Copalol via Epoxy Trienylsilane Cyclizations[1]

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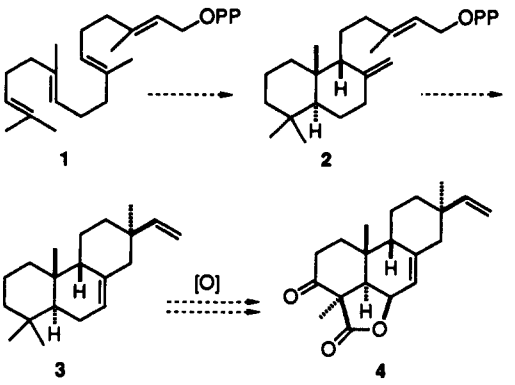
Total syntheses of (+)-9,10-*syn*-copalol (**5**), the pyrophosphate ester of which is a likely intermediate in the biosynthesis of 9,10-syn diterpenes, and its 9,10-anti isomer **39** are reported. Lithiation of (−)-(6*R*)-6,7-epoxygeranyl *p*-tolylsulfone (−)-**19** or (±)-**19** followed by alkylation with (*E*,*Z*)- and (*E*,*E*)-8-bromo-9-(trimethylsilyl)geranyl benzyl ethers (**15a** and **15b**) and selective reductive cleavage of the toluenesulfonyl and benzyl groups afforded (2*E*,6*E*,10*E*,14*R*)- and (2*E*,6*Z*,10*E*,14*R*)-14,15-epoxy-19-(trimethylsilyl)geranylgeraniols ((−)-**24a** and (±)-**26a**). Lewis acid treatment of the benzoate and/or acetates of (−)-**24a** and (±)-**26a** effected efficient but almost stereorandom bicyclizations to 9,10-*syn*- and 9,10-*anti*-labda-8(17),13(*E*)-diene-3β,15-diol esters (**27a,b** and **28a,b**) which were converted to (+)-9,10-*syn*- and (+)-9,10-*anti*-copalol.

The momilactones (e.g., momilactone A, **4**),[2] phytoalexins of the rice plant,[3] belong to a small group of tri- and tetracyclic diterpenes characterized by a syn stereochemical relationship between the C-9 H and C-10 CH_3 substituents.[4] It is reasonable to suppose that these 9,10-syn diterpenes are biosynthesized as shown in Scheme I by chair/boat cyclization of geranylgeranyl pyrophosphate (**1**) to 9,10-*syn*-copalyl pyrophosphate (**2**) followed by S_N' cyclization to (9β)-primara-7,15-diene (**3**) (Scheme I),[4b,5] in analogy with the usual biosynthetic pathway to the corresponding 9,10-anti diterpenes.[6] The 8,10-syn diterpenes such as aphidicolin presumably arise from **2** by C-9 → C-8 hydride shift following S_N' cyclization.[7,8]

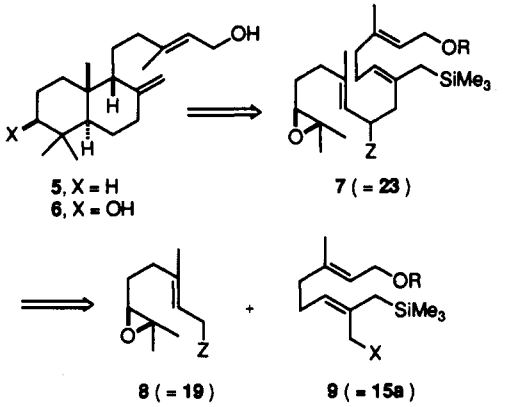
Wickham and West have identified (9β)-pimaradiene **3** as one component of a mixture of five diterpene hydrocarbons produced by enzymatic cyclization of **1** in a crude cell-free enzyme extract from UV-elicited rice leaves.[9] On the basis of bioassays using rice cell suspension cultures, Ren and West propose that soluble chitin fragments released from fungal hyphae walls serve as biotic elicitors of the diterpene synthases for phytoalexin biosynthesis.[10] The purpose of this research was to synthesize the previously unknown 9,10-*syn*-copalol (**5**) in enantiomerically pure form so that its pyrophosphate **2** could be prepared for evaluation as an intermediate in the biosynthesis of 9,10-syn diterpenes such as **3**.

The synthetic plan is illustrated in Scheme II. The decalin nucleus would be formed by Lewis acid-catalyzed

Scheme I



Scheme II



cyclization[11] of (14*S*)-*trans*,*cis*,*trans*-epoxy triene **7** (Z = H) with a terminating silyl transfer to establish the exocyclic double bond.[12-14] Although trans,cis dienes[11] usually cyclize stereospecifically to 9,10-syn bicyclic products, the

(1) (a) Portions of this work were presented at the following meetings of the American Chemical Society: National Convention, Atlanta, GA, April 1991; Great Lakes Regional Meeting, Dekalb, IL, June 1990. (b) Based in part on the PhD thesis of N. K. N. Yee, University of Illinois, Urbana-Champaign, 1991.

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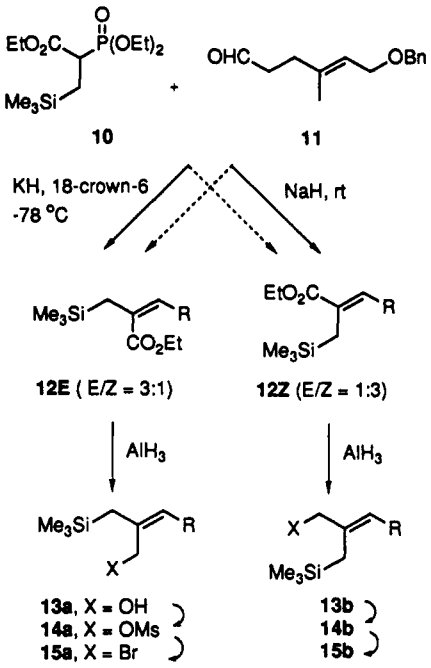
Scheme III



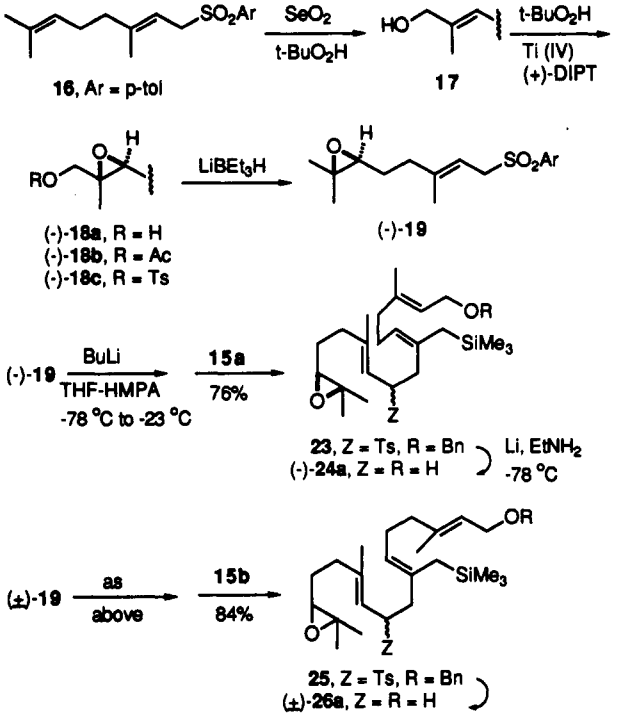
stereochemical outcome was uncertain since related silyl-terminated cyclizations occurred with minimal stereoselectivity at C-9/C-10.[13c] The compatibility of the epoxide with the reductive cleavage of the activating Z group and with the proposed Biellmann coupling[15] of **8** and **9** was also uncertain at the outset.[16]

In this paper we report the synthesis and cyclization of a *trans,cis,trans*-epoxy trienylsilane represented by **7** (Z = H) as well as its trans,trans,trans isomer. Total syntheses of 9,10-*syn*- and 9,10-*anti*-copalol ((+)-**5** and (+)-**39**) were completed by this approach. Preliminary evidence provided by our collaborators is mentioned indicating conversion of [^{3}H]-9,10-*syn*-copalyl pyrophosphate (**2**) to [^{3}H]-(9β)-pimeradiene (**3**) in chitin-elicited rice cell suspension cultures.[10,17]

Synthesis of Epoxy Trienylsilanes

Cis-selective Horner–Emmons condensation[18] of α-phosphono-β-silylpropionate **10**[14a,19] with aldehyde **11** (KH, 18-crown-6, THF, −78 °C) afforded a 3:1 mixture (87%) of **12*E*** and **12*Z*** (Scheme III). Complementary selectivity (**12*E*/12*Z*** = 1:3, 82%) was observed when the reaction was carried out by the usual procedure (NaH, THF, rt).[20] The isomers were separated by chromatography and identified by the characteristic ^{1}H NMR chemical shifts of the cis and trans α,β-enoate vinyl protons (δ_H **12*E***, 5.64; **12*Z***, 6.58).[21] Aluminum hydride reduction ($AlCl_3$, $LiAlH_4$, ether, 0 °C)[22] of the esters followed by mesylation (MsCl, Et_3N, CH_2Cl_2, 0 °C)[23] and bromide displacement (LiBr, DMF, 0 °C) afforded the isomeric allylic bromides **15a** (87%) and **15b** (80%).

Scheme IV



The scalemic epoxy sulfone component (−)-**19** (= **8**) was prepared from geranyl sulfone **16**[24] in four steps via asymmetric epoxidation (Scheme IV).[25,26] Hydroxylation of the trans terminal methyl group by catalytic oxidation with selenium dioxide (*tert*-BuOOH, CH_2Cl_2, rt; $NaBH_4$, EtOH, 0 °C)[27] afforded **17** in 71% yield following chromatography to remove ~1–2% of the allylic isomer. Conversion of **16** to **17** was also carried out in three steps[22c] via ozonolysis (O_3, CH_2Cl_2, −78 °C; Me_2S; 61%),[28] Wittig reaction [$CH_3C(PPh_3)CO_2Et$, CH_2Cl_2, reflux; 93%], and aluminum hydride reduction ($AlCl_3$, $LiAlH_4$, ether, 0 °C; 87%).

Asymmetric epoxidation of **17** was best accomplished by the catalytic procedure [Ti(O-*i*-Pr)$_4$, *t*-BuOOH, (+)-diisopropyl tartrate, CH_2Cl_2, −23 °C; 89%]. The enantiomeric purity of (−)-**18a** was ≥92% ee based on ^{1}H NMR analyses of both the acetate derivative **18b**[25] in the presence of Eu(hfc)$_3$ and the Mosher ester[29] of **18a**. Super-

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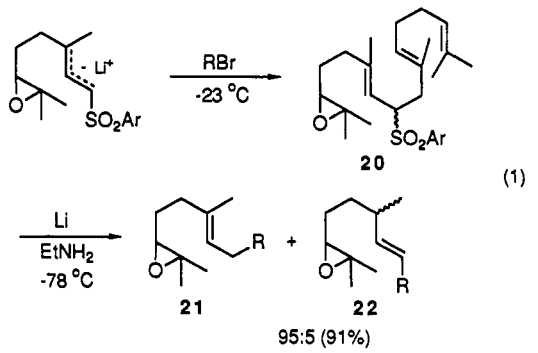
hydride reduction[30] of epoxy tosylate **18c** ($LiBEt_3H$, THF, rt) afforded (−)-**19** (65%), previously known in racemic form.[24b]

The feasibility of the Biellmann coupling[15] with epoxy sulfone **19** was initially demonstrated in model experiments (eq 1). Although lithiation of the related epoxygeranyl



(1)

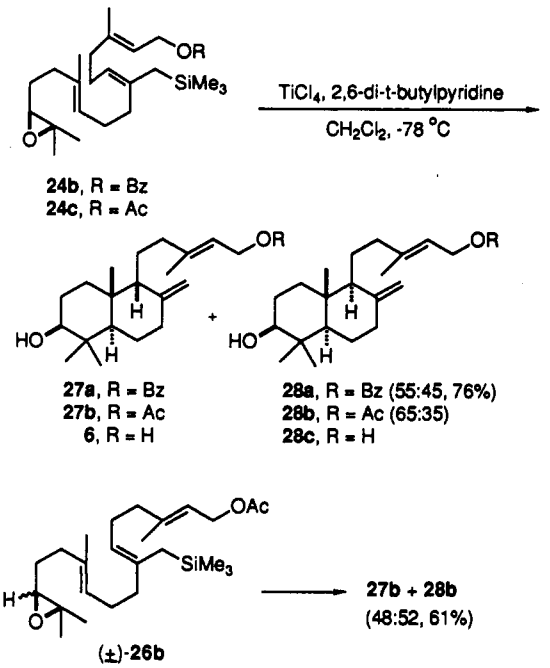
tert-butyl sulfide (**19** with *t*-BuS in place of $ArSO_2$) led to cyclization (3 h at 5 °C),[31] the carbanion generated from (±)-**19**[24b] with *n*-butyllithium (3:1 THF/HMPA, −78 °C)[15,32] was stable for 3 h at −23 °C, judging by its clean deuteration with methanol-*O*-*d* (**19**-d_1, 92%). Similarly, alkylation with geranyl bromide (−78 °C, 2 h and −23 °C, 1 h) afforded **20** in 85% yield.

A suitable procedure for selective reduction of the allylic sulfone in the presence of the epoxide was developed using **20** as model substrate. Although epoxides are known to undergo reductive ring opening with lithium in alkylamines,[33] moderately chemoselective reductions of benzyl ethers in the presence of epoxides have been accomplished with sodium[34] and calcium[35] in liquid ammonia. Selective reduction of **20** was first achieved with magnesium in methanol (50 °C, 4 h),[36,37] but the product proved to be a 70:30 mixture of double bond isomers **21** and **22** (61%).

Efficient and regioselective reductive desulfonylation of **20** to **21** (91%, **21**/**22** ratio 95:5) was realized by heterogenous reaction with lithium metal suspended in liquid ethyl amine/ether[15b,33b,36] at −78 °C in the presence or absence of methanol as proton donor. Completion of the sulfone reduction was indicated by the blue color associated with dissolved lithium which was then discharged quickly by adding 1-hexyne. Further model experiments showed that methanol should be omitted in order to accomplish simultaneous regioselective cleavage of the benzyl group from geranyl benzyl ether.[38]

The Biellmann couplings of (−)-**19** with allylic bromide **15a** and of (±)-**19** with **15b** were conducted as described

Scheme V

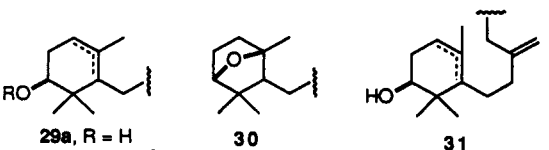


above for the model reaction and provided epoxy trienyl sulfones **23** and **25** as mixtures of diastereomers in high yield (Scheme IV). Simultaneous cleavage of the allylic sulfones and benzyl ethers was effected by the optimized lithium–ethylamine reduction procedure to give epoxy trienyl silanes (−)-**24a** (84%) and (±)-**26a** (74%). GC analyses and ^1H NMR spectra of the products revealed the presence of ca. 10% of the double bond isomer arising from conjugate reduction.[15b] These impurities were removed by chromatography of (−)-**24a** or the acetate (±)-**26b** on silver nitrate-impregnated silica gel or more readily by chromatography of benzoate (−)-**24b** on normal silica gel.

Epoxide Cyclizations

Cyclizations of the isomeric epoxy trienylsilanes as benzoate (**24b**) and acetate (**24c** and (±)-**26b**) derivatives were conducted by reaction with $TiCl_4$ (1.1 equiv) in dichloromethane containing 2,6-di-*tert*-butylpyridine (1.5 equiv)[14b,c] at −78 °C (Scheme V). After 5 min, 7 equiv each of triethylamine and methanol were added to neutralize the Lewis acid and to avoid release of HCl which might cause isomerization of the exocyclic methylene groups or proto desilylation of the allylsilane groups in the monocyclic byproducts.

Although the yields of bicyclic products were satisfactory (76% and 61%), they proved to be mixtures of 9,10-syn and 9,10-anti isomers **27** and **28** in 55:45 (from **24b**), 65:35 (from **24c**), and 48:52 (from **26b**) proportions. Changes of the Lewis acid ($SnCl_4$ and $BF_3{\cdot}OEt_2$), concentration (4-fold dilution) or temperature (−95 and −23 °C) did not alter appreciably the syn/anti and bicyclic/monocyclic ratios generated by cyclization of **24b** and **24c**. Small amounts of partially purified monocyclic byproducts were tentatively identified as **29a**, **29b**, **30**, and **31** (2–3% each, total ~10%) based on their ^1H NMR spectra. Similar cyclohexenols and bridged ethers have been reported as products of polyene epoxide cyclizations.[39]



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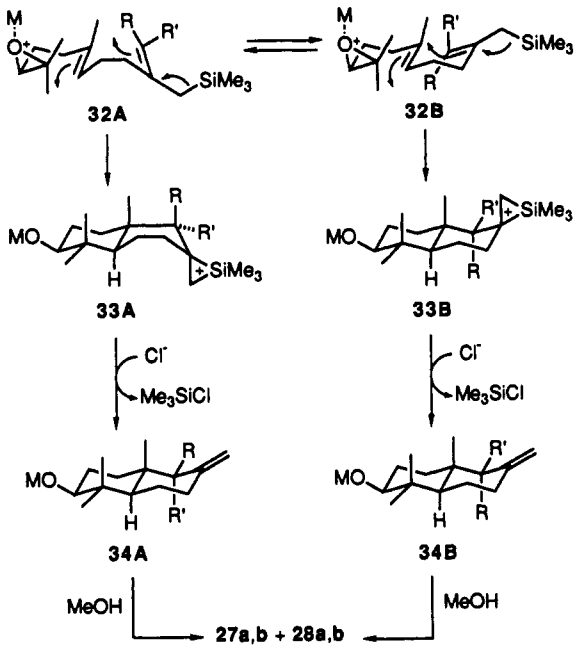
(38) In the presence of methanol, cleavage of the allylic C–O bond occurred, probably as a consequence of Birch reduction of the benzene ring of the benzyl ether. The alcohol proton donor is normally required for benzene ring reduction; see: Krapcho, A. P.; Bothner-By, A. A. *J. Am. Chem. Soc.* **1959**, *81*, 3658.

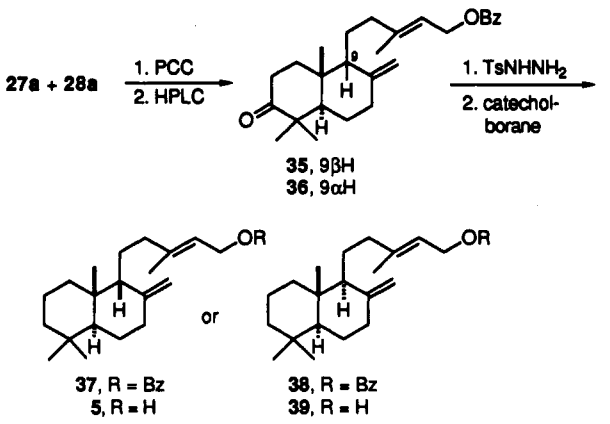
Scheme VI



Small amounts of 9,10-syn and 9,10-anti benzoates **27a** and **28a** were isolated in pure form by preparative HPLC and were saponified to syn and anti labdadienol isomers (+)-**6** and (+)-**28c**. The latter appears to be the enantiomer of the (−)-labdadienol isolated from the fruits of *Osteophloeum platyspermum* (*Myristicaceae*)[40,41] based on the reasonably good agreement between their ^1H and ^{13}C NMR spectral data.[42] The assignment of the syn and anti stereochemistry to diols **6** and **28c** is based upon comparisons of their ^1H and ^{13}C NMR spectral data with those of syn and anti copalol (Table I). For example, the chemical shift difference between the exocyclic methylene protons (syn $\Delta\delta_H = 0.18$, anti $\Delta\delta_H = 0.32$) and the ^{13}C NMR shifts for exocyclic methylene carbon (syn $\delta_C = 109.6 \pm 0.2$, anti $\delta_C = 106.5 \pm 0.2$) appear to be reliable indicators of the sidechain stereochemistry.

The mechanistic subtleties and variations of carbocation/polyene cyclizations have been discussed extensively in the literature.[11,43] While the limited results from the present investigation do not warrant a detailed analysis of the mechanism, some comments about the efficiency and stereochemistry of these epoxide cyclizations seem appropriate. The increased yields of bicyclic products in the cyclizations of epoxy trienylsilanes **24b,c** and **26b** and related compounds,[13] compared to those obtained from similar epoxy polyenes lacking the silyl terminator,[11b,16c,39] can be attributed to the enhanced nucleophilicity of the allylsilane double bond[44] and the greater stability of the

Scheme VII



β-silyl carbocation[45a–c] resulting from the bicyclization. Thus, the presence of the trimethylsilyl group increases the bicyclic/monocyclic product ratio from approximately 0.5[39b,46] to 7 and 3 for **24** and **26**, respectively. The less efficient bicyclization of the trans,trans,trans isomer **26** can be explained by a steric interaction between the cis-related carbon chain and the CH_2SiMe_3 group (R′ = $CH_2CH_2 \leftrightarrow CH_2SiMe_3$). It seems reasonable that this steric interaction which is not present in **24** might impede optimal alignment of the CH_2–Si bond with the incipient carbocation at C8 in the cyclization of **26**, thus decreasing the rate of the allylsilane cyclization.

The formation of comparable amounts of syn and anti bicyclic products from **24** and **26** indicates that the transition states for the chair/boat and chair/chair cyclizations have similar energies (Scheme VI, **32A** vs **32B**). This contrasts sharply with the consistent bias favoring the chair/chair orientation in cyclizations of polyene epoxides lacking the silyl substituent.[11] A possible explanation for the "equalization" of chair/boat and chair/chair transition states in the allylsilane cyclizations is partial or complete silicon bridging.[45b,c] The steric interactions in the transition states leading to siliconium ions **33A** and **33B** should be quite different from those producing classical carbocations owing to the sp^3 hybridization at C-8 and the proximity of the three methyl groups on silicon in the former.[45d] For example, the chair/chair siliconium ion **33B** might be destabilized by a 1,3-diaxial interaction between C10-CH_3 and C8-CH_2. However, similar steric interactions are present in the boat form also, and a more quantitative analysis and summation of steric interactions is unwarranted.

syn- and *anti*-Copalols

The 55:45 mixture of bicyclic benzoates (**27a** + **28a**) was oxidized (PCC, NaOAc, 4-Å molecular sieves, CH_2Cl_2, rt, 96%) to keto benzoates **35** and **36** which were more readily separated by preparative HPLC (Scheme VII). Catecholborane reduction (THF, 0 °C and rt) of the respective tosylhydrazones followed by boro sulfinate elimination

(39) (a) van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. A. *Bioorg. Chem.* **1982**, *11*, 133. (b) van Tamelen, E. E.; Coates, R. M. *Bioorg. Chem.* **1982**, *11*, 171.

(40) Braz Fo, R.; de Carvalho, M. G.; Gottlieb, O. R. *Planta Medica* **1984**, 53.

(41) For a total synthesis of the corresponding carboxylic acid, see ref 13c.

(42) The chemical shifts for the 14 upfield resonances in the ^{13}C NMR spectrum of **28c** agree with the reported values within ±0.1 ppm. However, significant difference are apparent in the data for the four olefinic carbons ($|\Delta\delta| = 0.3, 0.8, 7.5$, and 2.2 ppm).

(43) (a) Harding, K. E. *Bioorg. Chem.* **1973**, *2*, 248. (b) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522. (c) Snowden, R. L.; Eichenberger, J.-C.; Linder, S. M.; Sonnay, P.; Vial, C.; Schulte-Elte, K. H. *J. Org. Chem.* **1992**, *57*, 955–960.

(44) (a) Mayr, H.; Schneider, R.; Schade, C.; Bartl, J.; Bederke, R. *J. Am. Chem. Soc.* **1990**, *112*, 4446. (b) Mayr, H.; Schneider, R.; Irrgang, B.; Schade, C. *J. Am. Chem. Soc.* **1990**, *112*, 4454. (c) Mayr, H.; Schneider, R.; Grabis, U. *J. Am. Chem. Soc.* **1990**, *112*, 4460.

(45) The stabilizing effect of the β-silyl substituent on a tertiary carbocation has been estimated at 16–18 kcal/mol in the gas phase; see: (a) Li, X.; Stone, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 5586. (b) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677. (c) Ibrahim, M. R.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 819. (d) For a review on the steric influence of the trimethylsilyl group, see: Hwu, J. R.; Wang, N. *Chem. Rev.* **1989**, *89*, 1599–1615.

(46) Exact comparisons with the earlier results are not warranted because of the significantly different conditions (solvent, temperature, catalyst, and presence or absence of proton scavenger) and the different allylic substituents (CH_2R vs OAr).

(47) For an example of a chair/boat cyclization, see: van Tamelen, E. E.; Murphy, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 7204.

Table I. ^1H and ^{13}C NMR Spectral Data[a] for 9,10-*syn*- and 9,10-*anti*-Copalol ((+)-5 and (+)-39)

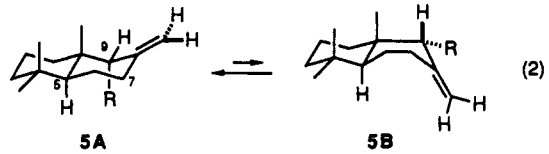
	$\delta_H^{CDCl_3}$		$\delta_C^{CDCl_3}$	
position	syn	anti	syn	anti
1	1.05,[b] 1.57	0.99,[c] 1.72	36.76	39.19
2	1.45, 1.61	1.39, 1.57	19.15	21.89
3	1.17,[d] 1.38	1.16,[e] 1.37	42.68	42.27
4			33.21	33.71
5	1.26	1.07[f]	45.78	55.63
6	1.30, 1.59	1.30,[g] 1.70	23.64	24.56
7	2.06, 2.17[h]	1.96,[i] 2.38[j]	31.56	38.47
8			149.20	148.74
9	1.50	1.54	57.90	56.40
10			38.00	39.77
11	1.47, 1.62	1.45, 1.60	24.46	19.52
12	1.74, 1.90	1.79, 2.15	38.15	38.55
13			140.58	140.78
14	5.41[k]	5.38[l]	122.94	123.05
15	4.15[m]	4.15[n]	59.44	59.54
16	1.67	1.65	16.52	16.49
17	4.51,[o] 4.69[p]	4.50,[q] 4.82[r]	109.44	106.38
18	0.87	0.86	33.49	33.75
19	0.80	0.79	22.15	21.86
20	0.91[s]	0.67	22.35	14.62

[a] 500 MHz and 125 MHz, respectively. Assignments are based upon APT, ^1H–^1H COSY, and ^1H–^{13}C HETCOR spectra. For complicated and overlapping multiplets in the ^1H NMR spectra, the midpoint is designated as δ_H. The multiplicity and coupling constants (Hz) for the first order multiplets are given in the following footnotes. [b] br d, J = 13. [c] td, J = 13, 4.0. [d] td, J = 13, 3.0. [e] td, J = 13, 4.0. [f] dd, J = 13, 2.7. [g] qd, J = 13, 4.3. [h] br d, J = 13. [i] td, J = 13, 5.2. [j] ddd, J = 13, 4.3, 2.4. [k] tq, J = 7.0, 1.5. [l] tq, J = 7.0, 1.3. [m] d, J = 7.0. [n] d, J = 6.9. [o] dd, J = 2.5, 1.5. [p] app t, J = 2.5. [q] br d, J = 1.3. [r] app q, J = 1.5. [s] d, J = 1.0.

(Bu_4NOAc, rt, 6 h) afforded benzoates **37** (78%) and **38** (72%) which were saponified to 9,10-*syn*- and 9,10-*anti*-copalols ((+)-**5** and (+)-**39**). The ^1H NMR, ^{13}C NMR, and MS of synthetic (+)-**39** are identical to those of *ent*-copalol obtained from natural copalic acid from Brazilian copal resin.[48,49]

The ^1H and ^{13}C NMR spectral data and assignments for *syn*- and *anti*-copalol presented in Table I were obtained from APT, ^1H–^1H COSY, and ^1H–^{13}C HETCOR spectra. The logic sequence by which the NMR assignments for *syn*-copalol were deduced is given in the supplementary material. The ^{13}C NMR assignments generally agree with those in the literature[50] for similar bicyclic and tricyclic diterpenes, except for the reversal of assignments for C-2 and C-11.

A few differences in the NMR spectra of the copalol isomers are noteworthy. The vinyl protons of the exocyclic methylene group appear as two doublets of doublets (δ_H 4.51 and 4.69, J = 1.5 and 2.5 Hz) in the ^1H NMR spectrum of *syn*-copalol, but the same protons in the anti isomer are a doublet and a quartet (δ_H 4.50 and 4.82, J = 1.3–1.5 Hz). The ^1H and ^{13}C signals for the C10-CH_3 of *syn*-copalol (δ_H 0.91 and δ_C 22.35) are both downfield from those of *anti*-copalol (δ_H 0.67 and δ_C 14.62). The upfield shifts of the ^{13}C NMR peaks for the C-5 and C-7 carbons ($\Delta\delta_C$ = −9.8 and −6.9 ppm) of *syn*-copalol are attributable to γ-shifts arising from 1,3-diaxial interactions of those carbons with the axial side chain at C-9.[50] The implication that 9,10-*syn*-copalol exists predominantly in a chair/chair conformation with the C-9 sidechain axial (eq 2) is supported by MM2 calculations which indicate a 6.6 kcal/mol enthalpy difference between the lowest energy chair/chair and chair/boat conformers.[51]



(2)

5A **5B**

In recent collaborative experiments West and Ren have obtained preliminary evidence concerning the role of 9,10-*syn*-copalyl pyrophosphate (**2**) in diterpene biosynthesis.[17] Incubation of [^3H]-**2** prepared in this laboratory with a cell-free enzyme extract from chitin-elicited rice suspension cells[10] resulted in a 74-fold increase in the net incorporation of tritium radioactivity into the pimaradiene region of silver nitrate-impregnated silica gel TLC plates in comparison to that from nonelicited cells. Radio GC analysis[52] of a similar pimaradiene fraction isolated by column chromatography on silver nitrate-impregnated silicic acid showed a major radioactivity peak (47% of total eluted counts) coincident with the mass peak of nonradioactive (9β)-pimaradiene (**3**) carrier.[4b] These and other experiments indicate that rice cells exposed to polymeric chitin generate (9β)-diterpene synthase activity and that 9,10-*syn*-copalyl pyrophosphate is an intermediate in the biosynthesis of 9β-pimaradiene and presumably the momilactone phytoalexins. The preparation of [^3H]-*syn*-copalyl PP and the biochemical results will be reported elsewhere.[53]

Experimental Section

General Aspects. Melting points were determined in open-ended capillary tubes and are uncorrected. All boiling points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, unless otherwise specified. Some ^1H NMR multiplets are characterized by the term app (apparent). This refers only to their appearance and may be an oversim-

(48) (a) Nakano, T.; Djerassi, C. *J. Org. Chem.* **1961**, *26*, 167. (b) Cavender, P. L. Ph.D. Thesis, University of Illinois, Urbana, 1977.

(49) For total syntheses of copalic acid via manool, see: (a) Ohloff, G. *Liebigs Ann. Chem.* **1958**, *617*, 134. (b) Fourrey, J.-L.; Polonsky, J.; Wenkert, E. *Chem. Commun.* **1969**, 714. (c) Manh, D. D. K.; Fetizon, M.; Kone, M. *Tetrahedron* **1975**, *31*, 1903.

(50) Breitmaier, E.; Voelter, W. *Carbon NMR Spectroscopy*; VCH: Weinheim, 1987; (a) pp 330–333; (b) pp 187–189.

(51) We are grateful to Mr. Raj Srinivasan for carrying out the MM2 computations using MACROMODEL Version 3.0 (C. W. Still, Columbia University, New York) running on a VAX station 3600.

(52) Croteau, R. B.; Satterwhite, D. M. *J. Chromatogr.* **1990**, *500*, 349. We thank Professor Croteau and Mr. A. Koepp (Washington State University, Pullman, WA) for carrying out the radio GC analyses.

(53) [^3H]-*syn*-Copalol was prepared by MnO_2 oxidation (hexane, 0 °C, 4 h; ~90%) and subsequent reduction with [^3H]$NaBH_4$ (absolute EtOH, rt, 1 h; 12.5 mCi, 113 mCi/mol). It was converted to [^3H]-*syn*-copalyl PP via the allylic chloride (*N*-chlorosuccinimide, dimethyl sulfide, CH_2Cl_2, −23 °C, 15 min; 0 °C, 1 h) and displacement with $(nBu_4N)_3OPP$ (CH_3CN, rt, 24 h) by adaption of literature procedures: Davisson, V. J.; Woodside, A. B.; Neal, T. R.; Stremler, K. E.; Muehlbacher, M.; Poulter, C. D. *J. Org. Chem.* **1986**, *51*, 4768. Davisson, V. J.; Zabriskie, T. M.; Poulter, C. D. *Bioorg. Chem.* **1986**, *14*, 46. The enzyme assays carried out by West and Ren[10,17] were typically performed by adding 50 μL (5000 pmol, 5×10^{-9} mol) of tritium-labeled substrates to a mixture of 100 μL of H_2O, 150 μL of enzyme extracts, and 150 μL of incubation buffer containing 5 mM $MgCl_2$ and 10 mM KH_2PO_4, pH = 7.0. The mixtures were incubated in a 30 °C water bath for 40 min. The reactions were quenched by addition of 1 mL of 1:3 (v/v) mixture of ethanol and hexane. The diterpene alcohols and hydrocarbons were isolated by extraction with hexane followed by chromatography on silicic acid, using hexane as eluant. The radioactivity associated with the hydrocarbon fraction was measured by liquid scintillation counting. TLC on silver nitrate-impregnated silica gel plate was also used to determine the composition of hydrocarbon fraction. The combined extracts from the enzyme reaction mixture were applied to the origin of the TLC plate and developed with a 13:7 (v/v) mixture of hexane and benzene. Polar materials remained at the origin and the hydrocarbon products migrated as a broad band to approximately 4–8 cm from origin, which has been referenced to sandararopimaradiene standard. Horizontal 1-cm-wide regions of silica gel were scraped from the TLC plate and placed into scintillation vials for counting. For further details concerning the pyrophosphate preparation and the results of the biochemical experiments, see: Yee, N. K. N. PhD thesis, University of Illinois, Urbana–Champaign, 1991.

plification. Preparative HPLC was carried out using an Ultrasil Si 10-μm (10.0-mm × 25-cm) column (Beckman Instruments, Inc.) and UV detection at 254 nm. GC analyses were carried out using a 30-m DB-J and 30-m RTX-5 fused silica capillary columns. Flash chromatography[54] was performed on Woelm 32–64-mm silica gel. The weights of the separated components are given in order of elution. Analytical TLC was conducted on Merck glass plates precoated with 0.25-mm silica gel 60 F-254. TLC plates were visualized with 5% phosphomolybdic acid reagent in 95% ethanol, iodine vapor, or UV light. $AgNO_3$-impregnated silica gel (15%, w/w) was prepared by adding silica gel (85 g) to a solution of $AgNO_3$ (15 g) in acetonitrile (400 mL), mixing well with a glass rod, and removing the solvent by rotary evaporation until the weight was close to ~100 g.

All reactions, except those performed in aqueous solvents, were carried out under N_2. Glassware used was dried at 120 °C for 10 h or flame dried. Technical-grade hexane, pentane, and ethyl acetate used for column chromatography were distilled prior to use. Diethyl ether, THF, and DME were distilled from the sodium ketyl of benzophenone prior to use. Acetonitrile, CH_2Cl_2, benzene, triethylamine, and HMPA were dried over CaH_2 and distilled prior to use. Molecular sieves were activated by heating at 160 °C for at least 10 h under vacuum (0.05 mm), and DMSO, DMF, and pyridine were dried with activated 4A molecular sieves. All other reagents and solvents were reagent grade and were used without further purification unless otherwise specified.

Ethyl 3-(Trimethylsilyl)-2-(diethylphosphono)propanoate (10). NaH (5.60 g of a 60% oil dispersion, 0.14 mol) was washed with hexane (2 × 50 mL). A suspension of the oil-free NaH in 600 mL of dry DME was mechanically stirred and cooled at 0 °C as a solution of 28.8 g (0.123 mol based on 96% purity) of triethyl phosphonoacetate in 20 mL of DME was added dropwise over 5 min. After 1.5 h at 0 °C, the solution was heated to 65–70 °C, and (iodomethyl)trimethylsilane (Petrarch Systems, 28.7 g, 0.134 mol) in 10 mL of DME was added. The solution was stirred and heated at 65–70 °C for 1.5 h, after which 5 mL of saturated NH_4Cl solution was added to destroy the remaining hydride. The mixture was cooled to rt, and the solvent was evaporated. The residue was swirled with 150 mL of benzene, the suspended salts were filtered, and the filtrate was evaporated. The benzene-soluble material from three such benzene treatments was suspended in water (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give 25.6 g of the crude product. GC analysis (165 °C) indicated two peaks in a 10:90 ratio. The residue was subjected to fractional distillation using a 0.6-cm × 6.0-cm Vigreux column, and four fractions were collected. The first two fractions (3.14 g, bp 75–85 °C (0.5 mm)) were enriched in the minor component (50:50 and 37:63 ratios) which was identified as unreacted triethyl phosphonoacetate. The third and fourth fractions (85–90 °C (0.5 mm)) amounted to 22.0 g (58%) of the known[19] phosphonate **10** of 98–99% purity by GC analysis. ^{13}C NMR spectral data were previously reported.[19a] Data: IR (neat) 2982, 1734, 1250, 1055, 1026, 850 cm^{-1}; ^1H NMR δ −0.03 (s, 9 H, $SiCH_3$), 1.00 (app dt, 1 H, J = 18, 2.4 Hz, CH_AH_BSi), 1.25 (t + m, 4 H, J = 7.2 Hz, CH_3 and CH_AH_BSi), 1.29 (t, 6 H, J = 7.1, 2 CH_3), 2.91 (ddd, 1 H, J = 22.5, 12.9, 2.4 Hz, CHP), 4.10 (q, 2 H, J = 7.2, OCH_2), 4.15 (q, 4 H, J = 6.9 Hz, 2 OCH_2); MS (70 eV) m/e (relative intensity) 295 ($M^+ - CH_3$, 22), 267 (9), 237 (25), 221 (18), 210 (30), 193 (32), 183 (17), 173 (20), 165 (100), 73 (64), 55 (53), 45 (23).

Anal. Calcd for $C_{12}H_{27}O_5PSi$: C, 46.43; H, 8.77; P, 9.98. Found: C, 46.41; H, 8.58; P, 9.86.

A dialkylated byproduct was formed in reactions run for longer times and/or higher temperature. It was isolated in pure form by preparative GC and was tentatively identified as **ethyl 2-[(trimethylsilyl)methyl]-2-(diethylphosphono)butanoate** on the basis of spectral data reported in the supplementary material.

(*E*)-6-(Benzyloxy)-4-methyl-4-hexenal (11).[22c] Purification by flash chromatography on silica gel using 20% ethyl acetate in hexane as eluant gave 9.0 g (40%) as a colorless liquid.

Ethyl (2*E*,6*E*)- and (2*Z*,6*E*)-8-(Benzyloxy)-6-methyl-2-[(trimethylsilyl)methyl]-2,6-octadienoate (12*E* and 12*Z*). Method A.[18] KH (7.81 g of a 35% oil dispersion, 68.2 mmol) was washed with dry THF (2 × 50 mL) under N_2. To a mechanically stirred suspension of the oil-free KH in 600 mL of THF at 0 °C was added a solution of 20.0 g (95%, 61.2 mmol) of phosphono ester **10** in 20 mL of THF dropwise over 10 min. After 1.5 h, the ice–water bath was removed and 65.0 g (246 mmol) of 18-crown-6 was added. The solution was stirred and cooled at −78 °C as 14.7 g (67.3 mmol) of aldehyde **11** in 10 mL of THF was added dropwise. After 6 h at −78 °C, the cooling bath was removed, and the flask was allowed to warm to rt over 30 min. A few drops of saturated NH_4Cl solution were added to destroy any remaining KH. Most of the THF was evaporated under reduced pressure, water (200 mL) was added, and the product was isolated by extraction with ether (3 × 200 mL). The combined ethereal extracts were washed with saturated NaCl (200 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography, using 5% ethyl acetate in hexane as eluant, afforded 20.0 g (87%) of a 75:25 mixture of **12*E*** and **12*Z*** according to capillary GC analysis (200 °C). The TLC R_f values (10% EtOAc/hexane) were 0.35 and 0.31, respectively. The isomers (3–4 g) were separated by careful flash chromatography on a 900-g silica column (6.5 × 78 cm) using 10% ethyl acetate in hexane as eluant. The purity of each isomer was ~99% by GC analysis: IR (neat, *E*/*Z* mixture) 2953, 1707, 1670, 1496, 1452, 1271, 852 cm^{-1}; ^1H NMR **12*E*** δ −0.03 (s, 9 H, $SiCH_3$), 1.29 (t, 3 H, J = 7.1 Hz, OCH_2CH_3), 1.64 (s, 3 H, CH_3), 1.72 (s, 2 H, $SiCH_2$), 2.13 (t, 2 H, J = 7.5 Hz, CH_2CH_2), 2.56 (q, 2 H, J = 7.4 Hz, CH_2CH_2), 4.02 (d, 2 H, J = 6.6 Hz, OCH_2CH=), 4.17 (q, 2 H, J = 7.1 Hz, OCH_2CH_3), 4.50 (s, 2 H, OCH_2Ph), 5.42 (t, 1 H, J = 6.3 Hz, =CH), 5.64 (t, 1 H, J = 7.4 Hz, CH=), 7.26–7.35 (m, 5 H, aryl H); **12Z** δ 0.00 (s, 9 H, $SiCH_3$), 1.27 (t, 3 H, J = 7.2 Hz, OCH_2CH_3), 1.66 (s, 3 H, CH_3), 1.81 (s, 2 H, CH_2Si), 2.16–2.26 (m, 4 H, CH_2CH_2), 4.04 (d, 2 H, J = 6.6 Hz, =$CHCH_2O$), 4.15 (q, 2 H, J = 7.1 Hz, OCH_2CH_3), 4.51 (s, 2 H, OCH_2Ph), 5.43 (t, 1 H, J = 6.3 Hz, =CH), 6.58 (t, 1 H, J = 6.8 Hz, =CH), 7.26–7.35 (m, 5 H, aryl H).

Anal. Calcd for $C_{22}H_{34}O_3Si$ (2*E*/2*Z*-mixture): C, 70.54; H, 9.15. Found: C, 70.79; H, 9.05.

Method B. A suspension of NaH (1.94 g of 50% oil dispersion, 40.5 mmol) in 280 mL of THF at 0 °C was stirred as 12.0 g (95%, 36.8 mmol) of phosphono ester **10** in 5 mL of THF was added over 5 min. After 1.5 h, the ice–water bath was removed, and the solution was warmed to rt. Aldehyde **11** (8.43 g, 38.7 mmol) in 5 mL of THF was added dropwise during 5 min. The solution was stirred at rt for 1 h. A few drops of saturated NH_4Cl was added to destroy any remaining NaH. The product was isolated and purified as described above. The yield was 11.2 g (82%) of a 25:75 mixture of **12*E*** and **12*Z***.

(2*E*,6*E*)-8-(Benzyloxy)-6-methyl-2-[(trimethylsilyl)methyl]-2,6-octadien-1-ol (13a). A literature procedure was followed.[22] A solution of 2.25 g (16.8 mmol) of $AlCl_3$ in 400 mL of dry diethyl ether was stirred and cooled at 0 °C as 2.02 g (95%, 50.5 mmol) of $LiAlH_4$ was added. After 30 min at 0 °C, a solution of 4.20 g (11.2 mmol) of **12*E*** in 5 mL of ether was added dropwise. The suspension was stirred at 0 °C for 5 h, after which water was added dropwise until the white solids were completely precipitated. The salts were removed by filtration, and the filtrate was poured into water (100 mL). The aqueous solution was extracted with ether (3 × 100 mL). The organic layers were combined and dried ($MgSO_4$). Evaporation of the solvent followed by Kuglerohr distillation at 200 °C (0.2 mm) afforded 3.39 g (91%) of **13a** as a colorless oil: IR (neat) 3441, 2951, 1454, 1246, 1068, 850 cm^{-1}; ^1H NMR δ 0.00 (s, 9 H, $SiCH_3$), 1.59 (s, 2 H, $SiCH_2$), 1.64 (s, 3 H, CH_3), 2.05 (t, 2 H, J = 7.2 Hz, CH_2CH_2), 2.20 (q, 2 H, J = 7.2 Hz, CH_2CH_2CH=), 3.98 (d, 2 H, J = 6.9 Hz, OCH_2CH=), 4.01 (s, 2 H, CH_2OH), 4.50 (s, 2 H, OCH_2Ph), 5.07 (t, 1 H, J = 7.4 Hz, CH=), 5.38 (t, 1 H, J = 6.5 Hz, CH=), 7.26–7.35 (m, 5 H, aryl H).

Anal. Calcd for $C_{20}H_{32}O_2Si$: C, 72.23; H, 9.70. Found: C, 72.30; H, 9.70.

(2*Z*,6*E*)-8-(Benzyloxy)-6-methyl-2-[(trimethylsilyl)methyl]-2,6-octadien-1-ol (13b). Reduction of **12*Z*** as described above gave 5.02 g (93%) of **13b**: IR (neat) 3416, 2951, 1454, 1363, 1248, 854 cm^{-1}; ^1H NMR δ 0.03 (s, 9 H, $SiCH_3$), 1.57 (s, 2 H, CH_2Si), 1.65 (s, 3 H, CH_3), 2.09 (br s, 4 H, CH_2CH_2), 3.93 (s, 2 H, CH_2OH), 4.02 (d, 2 H, J = 6.6 Hz, =$CHCH_2$), 4.51 (s, 2 H, OCH_2Ph), 5.26 (br s, 1 H, =CH), 5.40 (t, 1 H, J = 6.6 Hz, =CH), 7.26–7.36 (m, 5 H, aryl H).

(54) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, *43*, 2923.

Anal. Calcd for $C_{20}H_{32}O_2Si$: C, 72.23; H, 9.70. Found: C, 72.35; H, 9.78.

(2*E*,6*E*)-8-(Benzyloxy)-6-methyl-2-[(trimethylsilyl)methyl]-2,6-octadienyl Methanesulfonate (14a). A literature procedure was used.[23] A solution of 3.39 g (10.2 mmol) of alcohol **13a** and 2.56 mL (1.86 g, 18.4 mmol) of freshly distilled triethylamine in 50 mL of CH_2Cl_2 was stirred and cooled at 0 °C as a solution of 1.75 g (15.3 mmol) of freshly distilled methanesulfonyl chloride in 14 mL of CH_2Cl_2 was added. The resulting suspension was stirred at 0 °C for 1 h, diluted with 200 mL of CH_2Cl_2, and washed successively with 200 mL of water, 1% HCl, and saturated NaCl. Drying ($MgSO_4$) and evaporation gave 4.11 g (98%) of mesylate **14a** as a colorless liquid, which was converted to the bromide without further purification: IR (neat) 2953, 1454, 1358, 1248, 925, 856 cm^{-1}; ^1H NMR δ 0.02 (s, 9 H, $SiCH_3$), 1.58 (s, 2 H, CH_2Si), 1.65 (s, 3 H, CH_3CR=), 2.09 (t, 2 H, J = 7.5 Hz, CH_2CH_2), 2.26 (q, 2 H, J = 7.5 Hz, CH_2CH_2), 2.99 (s, 3 H, OSO_2CH_3), 4.02 (d, 2 H, J = 6.6 Hz, OCH_2CH=), 4.50 (s, 2 H, OCH_2Ph), 4.67 (s, 2 H, $CH_2OSO_2CH_3$), 5.33 (t, 1 H, J = 7.5 Hz, =C*H*), 5.41 (t, 1 H, J = 6.6 Hz, =C*H*), 7.27–7.35 (m, 5 H, aryl H).

Anal. Calcd for $C_{21}H_{34}O_4SSi$: C, 61.42; H, 8.35. Found: C, 61.26; H, 8.35.

(2*Z*,6*E*)-8-(Benzyloxy)-6-methyl-2-[(trimethylsilyl)methyl]-2,6-octadienyl Methanesulfonate (14b). Yield 5.02 g (90%). The purity was estimated to be greater than 95% by ^1H NMR spectroscopy: ^1H NMR (500 MHz) δ 0.06 (s, 9 H, $SiCH_3$), 1.62 (s, 2 H, CH_2Si), 1.65 (s, 3 H, CH_3), 2.09–2.14 (m, 4 H, CH_2CH_2), 2.96 (s, 3 H, OSO_2CH_3), 4.03 (d, 2 H, J = 7.0 Hz, =$CHCH_2$), 4.51 (s, 2 H, OCH_2Ph), 4.55 (s, 2 H, CH_2OMs), 5.41 (t, 1 H, J = 6.5 Hz, =C*H*), 5.46 (t, 1 H, J = 6.3 Hz, =C*H*), 7.26–7.35 (m, 5 H, aryl H).

(2*Z*,6*E*)-8-(Benzyloxy)-1-bromo-6-methyl-2-[(trimethylsilyl)methyl]-2,6-octadiene (15a). A solution of 4.11 g (10.0 mmol) of mesylate **14a** in 50 mL of dry DMF was stirred at 0 °C as 2.23 g (25.7 mmol) of LiBr was added. The suspension was stirred at 0 °C for 2 h, diluted with 500 mL of pentane, washed with water (3 × 500 mL), and dried ($MgSO_4$). Evaporation of the solvent afforded 3.90 g (98%) of bromide **15a** as a colorless oil. The purity was estimated to be greater than 95% by ^1H NMR spectroscopy: IR (neat) 2953, 2853, 1454, 1248, 1203, 1070, 848 cm^{-1}; ^1H NMR (200 MHz) δ 0.01 (s, 9 H, $SiCH_3$), 1.61 (s, 2 H, CH_2Si), 1.65 (s, 3 H, =$CRCH_3$), 2.05–2.30 (m, CH_2CH_2), 3.93 (s, 2 H, CH_2Br), 4.02 (d, 2 H, J = 6.6 Hz, OCH_2CH=), 4.50 (s, 2 H, OCH_2Ph), 5.19 (t, 1 H, J = 6.8 Hz, =C*H*), 5.42 (t, 1 H, J = 6.6 Hz, =C*H*), 7.26–7.35 (m, 5 H, aryl H); HRCIMS calcd for $C_{20}H_{31}OSiBr$ (M^+) 394.1327, found 394.1329.

(2*E*,6*E*)-8-(Benzyloxy)-1-bromo-6-methyl-2-[(trimethylsilyl)methyl]-2,6-octadiene (15b). Yield 4.61 g (96%). The purity was estimated to be greater than 95% by ^1H NMR spectroscopy: IR (neat) 2951, 1452, 1363, 1248, 1167, 852 cm^{-1}; ^1H NMR δ 0.04 (s, 9 H, $SiCH_3$), 1.64 (s, 3 H, CH_3), 1.71 (s, 2 H, CH_2Si), 2.08 (br s, 4 H, CH_2CH_2), 3.94 (s, 2 H, CH_2Br), 4.03 (d, 2 H, J = 6.9 Hz, =$CHCH_2$), 4.51 (s, 2 H, OCH_2Ph), 5.41 (t, 1 H, J = 6.6 Hz, =C*H*), 5.48 (br s, 1 H, =C*H*), 7.26–7.36 (m, 5 H, aryl H).

(*E*)-3,7-Dimethyl-1-(4-methylbenzenesulfonyl)-2,6-octadiene (16) was prepared by a literature procedure.[24a] Recrystallization with hexane gave 11.8 g (70%) of sulfone **16** as a crystalline solid, mp 44–45 °C. The spectral data for **16** agree with the literature values.[24b]

(2*E*,6*E*)-3,7-Dimethyl-1-(4-methylbenzenesulfonyl)-2,6-octadien-8-ol (17). Method A.[27] A suspension of 150 mg (1.35 mmol) of SeO_2 and 940 mg (6.81 mmol) of salicylic acid in 25 mL of dry CH_2Cl_2 was stirred at 0 °C as 27.3 mL (90%, 0.245 mmol) of *tert*-butyl hydroperoxide was added in one portion. After 10 min, a solution of 19.0 g (65.1 mmol) of sulfone **16** in 25 mL of CH_2Cl_2 was added at 0 °C over 30 min. The resulting mixture was stirred at rt for 24 h. TLC showed that a small amount of starting material remained. The reaction mixture was diluted with 35 mL of benzene and then concentrated under reduced pressure. The residue was dissolved in 100 mL of ether, and the organic layer was washed with 10% aqueous KOH (4 × 25 mL), dried ($MgSO_4$), and concentrated to give a yellow liquid. The residue was dissolved in 15 mL of acetic acid and stirred at 0 °C as 16 mL of dimethyl sulfide was added over 15 min. The cooling bath was removed and the resulting solution was stirred at rt for 5 h. The solution was then cooled to 0 °C, neutralized with 20% aqueous K_2CO_3, and poured into 150 mL of ether. The organic layer was washed with 150 mL of water and 150 mL of saturated NaCl solution, dried ($MgSO_4$) and evaporated. A solution of the remaining yellow liquid in 50 mL of absolute ethanol was stirred at 0 °C as 25 g (65 mmol) of $NaBH_4$ was added in three portions over 30 min. After an additional 15 min at 0 °C, 1 N HCl was carefully added to destroy the remaining $NaBH_4$. The solution was diluted with water (150 mL) and extracted with ether (3 × 150 mL). The combined organic layers were washed with saturated NaCl solution (200 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. Purification of the residue by flash chromatography, using 50% of ethyl acetate in hexane as eluant, gave 14.2 g (71%) of **17** as a colorless oil: IR (neat) 3514, 2920, 1597, 1302, 1147, 817 cm^{-1}; ^1H NMR δ 1.41 (s, 3 H, CH_3 (C-2)), 1.66 (s, 3 H, CH_3 (C-7)), 2.02–2.19 (m, 4 H, CH_2CH_2), 2.44 (s, 3 H, $ArCH_3$), 3.78 (d, 2 H, J = 8.1 Hz, CH_2SO_2), 3.99 (s, 2 H, CH_2OH), 5.19 (t, 1 H, J = 7.8 Hz, =C*H*), 5.34 (t, 1 H, J = 6.9 Hz, =C*H*), 7.33 (d, 2 H, J = 8.1 Hz, aryl H), 7.74 (d, 2 H, J = 8.1 Hz, aryl H).

Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84; S, 10.39. Found: C, 66.21; H, 7.80; S, 10.47.

Method B. Reduction of Ethyl (2*E*,6*E*)-2,6-Dimethyl-8-(4-methylbenzenesulfonyl)-2,6-octadienoate (See Supplementary Material). The procedure described above for **13a** gave 8.50 g (87%) of **17**.

(−)-(2*S*,3*S*,6*E*)-2,3-Epoxy-2,6-dimethyl-8-(4-methylbenzenesulfonyl)-6-octen-1-ol (18a). Method A. Catalytic Asymmetric Epoxidation.[25,26c] A suspension of 4 g of powdered, activated 4A molecular sieves in 80 mL of dry CH_2Cl_2 was stirred and cooled at −23 °C as 0.48 mL (535 mg, 2.28 mmol) of (+)-diisopropyl L-tartrate, 0.48 mL (458 mg, 1.61 mmol) of freshly distilled titanium(IV) isopropoxide, and 16.8 mL (3.0 M in 2,2,4-trimethylpentane, 50.4 mmol) of anhydrous *tert*-butyl hydroperoxide were added in order. After 15 min at −23 °C, 10.0 g (32.5 mmol) of sulfone **17** in 20 mL of CH_2Cl_2 was added over 30 min. The resulting mixture was stirred at −23 °C for 3.5 h and then treated with 3.3 mL (1.0 M in CH_2Cl_2, 0.33 mmol) of triethanolamine solution. The reaction mixture was stirred for 30 min and then filtered through a pad of silica gel covered with Celite. The filter cake was washed with 600 mL of ether. The combined filtrates were dried ($MgSO_4$) and concentrated by rotary evaporation. Purification of the viscous residue by flash chromatography, using 70% ethyl acetate in hexane as eluant, afforded 9.40 g (89%) of the epoxide **18a** as a colorless oil. The purity was estimated to be greater than 98% by ^1H NMR spectroscopy: $[\alpha]^{24}_D$ −3.56° (*c* 2.25, CH_2Cl_2); IR (neat) 3499, 2926, 1597, 1450, 1311, 816 cm^{-1}; ^1H NMR δ 1.28 (s, 3 H, CH_3 (C-2)), 1.43 (s, 3 H, CH_3 (C-6)), 1.64 (app q, J = 7.2 Hz, CH_2CH_2), 2.10–2.17 (symmetric 8 lines, app AB of ABX, 2 H, CH_2CH_2CHO), 2.44 (s, 3 H, $ArCH_3$), 3.00 (t, 1 H, J = 6.2 Hz, CH_2CHO), 3.59 and 3.64 (AB dd, 2 H, J_{AB} = 12.3 Hz, CH_2OH), 3.79 (d, 2 H, J = 7.8 Hz, CH_2SO_2), 5.24 (t, 1 H, J = 7.4 Hz, =C*H*), 7.33 (d, 2 H, J = 8.1 Hz, aryl H), 7.74 (d, 2 H, J = 8.1 Hz, aryl H); HRFABMS calcd for $C_{17}H_{25}O_4S$ (M + H) 325.1473, found 325.1477.

The enantiomeric purity of (−)-**18a** was determined by ^1H NMR spectroscopy with a chiral shift reagent.[25] The acetates of (−)- and (±)-**18a** (see below) were prepared by reaction with acetic anhydride in pyridine at rt. The ^1H NMR analysis involved sequential treatment of the acetate in C_6D_6 with a solution of Eu(hfc)$_3$ and observation of the acetate CH_3. Optimal resolution (δ 3.52 and 3.57) was achieved with a solution of racemic acetate (5 mg) in 0.7 mL of C_6D_6 containing 8 mol % of Eu(hfc)$_3$. The ee was estimated to be ≥92% by integration of these two peaks in the ^1H NMR spectrum.

Method B. Peracid Epoxidation.[24b] The literature procedure afforded 4.31 g (82%) of (±)-**18a** which had spectral properties identical to those of (−)-**18a**.

(−)-(2*S*,3*S*,6*E*)-2,3-Epoxy-2,6-dimethyl-8-(4-methylbenzenesulfonyl)-6-octen-1-yl 4-methylbenzenesulfonate (18c) was prepared by a literature procedure.[55] A solution of 9.00 g (27.8 mmol) of epoxy alcohol **18a** and 6.8 mL (6.65 g, 84.1

(55) Kabalka, G. W.; Varma, M.; Varma, R. S.; Srivastava, P. C.; Knapp, F. F., Jr. *J. Org. Chem.* **1986**, *51*, 2386.

mmol) of pyridine in 28 mL of $CHCl_3$ (spectrophotometric grade) was stirred at 0 °C as 10.6 g (55.6 mmol) of *p*-toluenesulfonyl chloride was added in one portion. The solution was stirred at 0 °C for 2.5 h after which time TLC indicated the reaction was completed. Water (100 mL) was added, and the product was extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated to a viscous oil. Purification of the residue by flash chromatography, using 40% ethyl acetate in hexane as eluant, gave 13.0 g (98%) of **18c** as a colorless oil. The purity was estimated to be greater than 98% by ^1H NMR spectroscopy: $[\alpha]^{24}_D$ −12.1° (*c* 2.27, $CHCl_3$); IR (neat) 2972, 1734, 1597, 1450, 1242, 816 cm^{-1}; ^1H NMR δ 1.28 (s, 3 H, CH_3 (C-2)), 1.38 (s, 3 H, CH_3 (C-6)), 1.52–1.61 (m, 2 H, CH_2CH_2), 2.03–2.23 (symmetric 8 lines, app AB of ABX, 2 H, CH_2CH_2CHO), 2.44 (s, 6 H, 2 $ArCH_3$), 2.76 (t, 1 H, *J* = 6.2 Hz, $OCHCH_{22}$), 3.78 (d, 2 H, *J* = 7.8 Hz, CH_2CH=), 3.92 (s, 2 H, CH_2OTs), 5.20 (t, 1 H, *J* = 7.7 Hz, C*H*=), 7.33 (t, 4 H, *J* = 7.7 Hz, aryl H), 7.72 (d, 2 H, *J* = 8.1 Hz, aryl H), 7.78 (d, 2 H, *J* = 8.1 Hz, aryl H); HRFABMS calcd for $C_{24}H_{31}O_6S_2$ (M + H) 479.1561, found 479.1567.

(−)-(6*S*,2*E*)-6,7-Epoxy-3,7-dimethyl-1-(4-methylbenzenesulfonyl)-2-octene (19) was prepared by a literature procedure[30a] with some modifications in the concentration, temperature, and time of reaction. A solution of 12.0 g (25.1 mmol) of tosylate **18c** in 40 mL of THF was stirred and cooled at 0 °C as 50 mL (1.0 M in THF, 50.0 mmol) of lithium triethylborohydride was added dropwise. After 15 min at 0 °C and 15 min at rt a few drops of water were added to destroy the remaining hydride. The organoborane intermediate was oxidized by adding 20 mL of 3 M NaOH and 20 mL of 30% H_2O_2. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. Purification of the residue by flash chromatography, using 30% ethyl acetate in hexane, gave 5.01 g (65%) of (−)-**19** as a viscous oil, which was crystallized from ether at −20 °C to give 4.43 g (57%) of (−)-**19** as a crystalline solid: mp 34–35 °C; $[\alpha]^{24}_D$ −4.05° (*c* 4.00, $CHCl_3$); IR (neat) 2963, 1699, 1450, 1244, 1086, 817 cm^{-1}; ^1H NMR δ 1.25, 1.30 (2s, 6 H, 2 CH_3), 1.38 (s, 3 H, =CCH_3), 1.50–1.61 (m, 2 H, CH_2CH_2), 2.05–2.25 (symmetric eight lines, app AB of ABX, 2 H, CH_2CH_2), 2.44 (s, 3 H, $ArCH_3$), 2.66 (t, 1 H, *J* = 6.2 Hz, C*H*O), 3.79 (d, 2 H, *J* = 8.1 Hz, CH_2SO_2Ar), 5.22 (t, 1 H, *J* = 8.1 Hz, =C*H*), 7.32 (d, 2 H, *J* = 8.1 Hz, aryl H), 7.73 (d, 2 H, *J* = 8.1 Hz, aryl H).

Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84; S, 10.39. Found: C, 66.26; H, 7.86; S, 10.43.

Racemic epoxy sulfone, (±)-**19**, was prepared by *m*-CPBA oxidation of **16** according to a literature procedure.[24b] Purification as described for (−)-**19** gave 4.31 g (82%) of (±)-**19** as a glass.

(6*E*,10*E*,14*E*)-2,3-Epoxy-2,6,10,15-tetramethyl-8-(4-methylbenzenesulfonyl)-6,10,14-hexadecatriene (20) was prepared according to a literature procedure.[15a] A solution of 1.43 g (4.64 mmol) of epoxy sulfone (±)-**19** in 28 mL of a 3:1 (v/v) mixture of THF and HMPA was stirred at −78 °C as 3.66 mL (1.28 M, 4.68 mmol) of *n*-BuLi in hexane was added. The mixture was kept at −78 °C for 15 min, warmed to −23 °C for 1 h, and then recooled to −78 °C. A solution of 1.01 g (4.67 mmol) of geranyl bromide[56] in 1 mL of THF was added. After 1 h at −78 °C and 1 h at −23 °C, the reaction was quenched at −23 °C by adding a few drops of methanol and warmed to rt. Water (20 mL) was added, and the aqueous solution was extracted with ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash chromatography, using 20% ethyl acetate in hexane as eluant, gave 1.75 g (85%) of the coupling product **20** as a colorless oil, which was a mixture of diastereomers: IR (neat) 2922, 1597, 1450, 1300, 1143, 1086 cm^{-1}; ^1H NMR δ 1.24, 1.25 (2s, 6 H, 2 CH_3), 1.29 (s, 6 H, 2 =CCH_3), 1.57, 1.64 (2s, 6 H, 2 =CCH_3), 2.42 (s, 3 H, $ArCH_3$), 1.45–1.60 (m, 2 H, CH_2CH_2), 1.87–2.20 (m, 5 H, CH_2CH_2), 2.25–2.40 (m, 1 H, CH_2CH_2), 2.61–2.88 (2m, 2 H, CH_2CHSO_2Ar), 3.71, 3.72 (1:1, 2td, superimposed, 1 H, $CHSO_2Ar$), 4.79–5.08 (m, 3 H, 3 C*H*=), 7.29 (d, 2 H, *J* = 7.8 Hz, aryl H), 7.69 (d, 2 H, *J* = 7.8 Hz, aryl H).

Anal. Calcd for $C_{27}H_{40}O_3S$: C, 72.93; H, 9.07. Found: C, 72.67; H, 9.10.

(56) Mori, K.; Funaki, Y. *Tetrahedron* **1985**, *41*, 2369.

(6*E*,10*E*,14*E*)-2,3-Epoxy-2,6,10,15-tetramethyl-6,10,14-hexadecatriene (21). A solution of 428 mg (0.961 mmol) of epoxy sulfone **20** in 12 mL of ethylamine and 9 mL of ether was stirred and cooled at −78 °C as 132 mg (19.0 mmol) of lithium wire, cut in small pieces (~0.2 cm), was added. The suspension of lithium pieces in the clear ethereal ethylamine was vigorously stirred at −78 °C. After stirring for ~45 min at −78 °C, a stable dark blue color persisted, and within seconds, the reaction was immediately stopped by adding 1-hexyne to discharge the blue color. The remaining lithium pieces were removed with a spatula at −78 °C, and the resulting yellow mixture was hydrolyzed by adding methanol until the yellow color disappeared. The mixture was allowed to warm to rt and concentrated by rotary evaporation. The gel-like residue was partitioned between ether (20 mL) and water (20 mL). The aqueous layer was extracted with ether (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography, using 10% ether in hexane as eluant, gave 253 mg (91%) of epoxide (±)-**21** as a colorless oil. ^1H NMR and GC analyses indicated the presence of 5% of a byproduct (**22**) resulting from the conjugate reduction of the sulfonyl group: IR (neat) 2920, 1448, 1377, 1321, 1248, 1120 cm^{-1}; ^1H NMR δ 1.26, 1.30 (2s, 6 H, 2 CH_3), 1.60 (s, 6 H, 2 =CCH_3), 1.62, 1.68 (2s, 6 H, 2 =CCH_3), 1.57–1.65 (m, 2 H, CH_2CH_2), 1.95–2.24 (m, 10 H, CH_2CH_2), 2.71 (t, 1 H, *J* = 6.3 Hz, OC*H*), 5.07–5.23 (m, 3 H, 3 C*H*=).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.70; H, 11.78.

(9*S*,14*S*,2*E*,6*E*,10*E*)- and (9*R*,14*S*,2*E*,6*E*,10*E*)-1-(Benzyloxy)-14,15-epoxy-3,11,15-trimethyl-9-(4-methylbenzenesulfonyl)-7-[(trimethylsilyl)methyl]-2,6,10-hexadecatrienes (23). The procedure was similar to that described above for **20**. A suspension of 7.01 g (22.8 mmol) of epoxy sulfone (−)-**19** in 160 mL of 3:1 (v/v) mixture of THF and HMPA was stirred at −78 °C as 15.5 mL (1.47 M, 22.8 mmol) of *n*-BuLi in hexane was added. The reaction mixture became dark brown immediately. Stirring was continued for 15 min at −78 °C and 1 h at −23 °C before recooling to −78 °C. A solution of 9.45 g (23.9 mmol) of bromide **15a** in 5 mL of THF was added at −78 °C. After 2 h at −78 °C, and another 2 h at −23 °C, a few drops of methanol were added, and the mixture was warmed to 25 °C. Water (200 mL) was added, and the aqueous layer was extracted with hexane (3 × 200 mL). The combined organic layers were washed with water (3 × 300 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography, using 20% ethyl acetate in hexane as eluant, afforded 10.7 g (76%) of the coupling product **23** as a colorless oil: IR (neat) 2955, 1597, 1452, 1143, 1086, 852 cm^{-1}; ^1H NMR δ −0.05 (s, 9 H, $SiCH_3$), 1.24, 1.25 (2s, 6 H, 2 CH_3), 1.30 (s, 5 H, CH_3 (C-11) and CH_2Si), 1.44–1.57 (m, 2 H, CH_2), 1.61 (s, 3 H, =CCH_3), 1.96–2.20 (m, 5 H, CH_2), 2.42 (s, 3 H, $ArCH_3$), 2.38–2.48 (m, 1 H, CH_2), 2.60–2.68 (m, 2 H, CH_2), 3.85, 3.86 (1:1, 2td, superimposed, 1 H, *J* = 10.5 and 3.0 Hz, $CHSO_2Ar$), 4.01 (d, 2 H, *J* = 6.9 Hz, =$CHCH_2O$), 4.50 (s, 2 H, OCH_2Ph), 4.96 (t, 1 H, *J* = 6.9 Hz, =C*H*), 5.01 (br d, 1 H, *J* = 12 Hz, =$CHCHSO_2Ar$), 5.37 (t, 1 H, *J* = 6.6 Hz, =C*H*), 7.26–7.36 (four peaks, 7 H, aryl H), 7.71 (d, 2 H, *J* = 8.1 Hz, aryl H).

Anal. Calcd for $C_{37}H_{54}O_4SSi$: C, 71.34; H, 8.74; S, 5.15. Found: 71.42; H, 8.76; S, 5.03.

(−)-(14*S*,2*E*,6*E*,10*E*)-14,15-Epoxy-3,11,15-trimethyl-7-[(trimethylsilyl)methyl]-2,6,10-hexadecatrien-1-ol (24a). The reduction of sulfone **23** (5.00 g, 8.04 mmol) was carried out as described above for **21**. Purification by flash chromatography, using 20% ethyl acetate in hexane as eluant, afforded 2.56 g (84%) of alcohol **24a**. The ^1H NMR spectrum indicated the presence of about 10% of a byproduct, resulting from the conjugate reduction of the allylic sulfonyl group. The product was further purified in three portions by flash chromatography on 15% silver nitrate-silica gel (200 g/g), using 20% ethyl acetate in hexane as eluant to give 2.16 g (71%) of pure (−)-**24a** as a colorless oil. The purity was estimated to be greater than 98% by ^1H NMR spectroscopy: $[\alpha]^{24}_D$ −2.23° (*c* 1.56, $CHCl_3$); IR (neat) 3427, 2955, 1456, 1379, 1246, 850 cm^{-1}; ^1H NMR δ −0.02 (s, 9 H, $SiCH_3$), 1.26, 1.30 (2s, 6 H, 2 CH_3), 1.44 (s, 2 H, CH_2Si), 1.62, 1.66 (2s, 6 H, 2 CH_3), 1.57–1.67 (m, 2 H, CH_2CH_2), 1.90–2.20 (m, 10 H, 3 CH_2CH_2), 2.71 (t, 1 H, *J* = 6.3 Hz, CH_2CHO), 4.13 (d, 2 H, *J* = 6.9 Hz, CH_2OH), 4.90 (t, 1 H, *J* = 6.8 Hz, =C*H*), 5.17 (t, 1 H, *J* = 6.3 Hz, =C*H*),

5.41 (t, 1 H, J = 6.6 Hz, =C*H*).

Anal. Calcd for $C_{23}H_{42}O_2Si$: C, 72.95; H, 11.18. Found: C, 73.01; H, 11.15.

The corresponding acetate of the byproduct resulting from the conjugate reduction of the sulfonyl group was obtained in pure form after flash chromatography on 15% $AgNO_3$-impregnated silica gel. The ^1H NMR spectral data are as follows: ^1H NMR δ −0.01 (s, 9 H, SiC*H*$_3$), 0.98 (d, 3 H, J = 6.6 Hz, CHC*H*$_3$), 1.25, 1.30 (2s, 6 H, 2 C*H*$_3$), 1.42 (s, 2 H, C*H*$_2$Si), 1.35–1.56 (m, 4 H, C*H*$_2$C*H*$_2$), 1.69 (s, 3 H, =CC*H*$_3$), 2.05 (s, 3 H, OCOC*H*$_3$), 2.00–2.18 (m, 5 H, C*H*$_2$C*H*$_2$ and C*H*CH$_3$), 2.63 (d, 2 H, J = 3.9 Hz, =CHC*H*$_2$C), 2.70 (t, 1 H, J = 6.0 Hz, CH$_2$C*H*O), 4.57 (d, 2 H, J = 6.6 Hz, C*H*$_2$OAc), 4.94 (t, 1 H, J = 6.6 Hz, =C*H*), 5.25–5.27 (unsymmetric 3 peaks, 2 H, C*H*=C*H*), 5.34 (t, 1 H, J = 6.8 Hz, =C*H*).

(−)-(14*S*,2*E*,6*E*,10*E*)-14,15-Epoxy-3,11,15-trimethyl-7-[(trimethylsilyl)methyl]-2,6,10-hexadecatrienyl Benzoate (24b). A solution of 2.24 g (5.91 mmol) of impure **24a** (containing ~10% of the 9,10-double bond isomer) and 50 mg of 4-(dimethylamino)pyridine in 8 mL of pyridine was stirred at rt as 2.01 g (8.87 mmol) of benzoic anhydride was added. After 4 h at rt, TLC analysis indicated the reaction was completed and methanol (1 mL) was added to consume the excess anhydride. After 1 h, the solution was concentrated by rotary evaporation. Purification of the residue by flash chromatography, using 20% ether in hexane gave 2.73 g (96%) of **24b**. If the 9,10-double bond isomer byproduct was not separated as described above for **24a**, its benzoate was separated from **24b** in this step by careful flash chromatography on silica gel. In this case, another flash chromatography on silica gel (200 g) was performed using 10% ether in hexane as eluant, afforded 1.78 g (62%) of **24b** as a colorless oil while some mixed fractions were discarded: $[\alpha]^{24}_D$ −1.67° (c 1.58, $CHCl_3$); IR (neat) 2957, 1718, 1450, 1377, 1269, 848 cm^{-1}; ^1H NMR δ −0.02 (s, 9 H, SiC*H*$_3$), 1.25, 1.30 (2s, 6 H, 2 C*H*$_3$), 1.44 (s, 2 H, C*H*$_2$Si), 1.58–1.70 (m, 2 H, C*H*$_2$CHO), 1.62, 1.76 (2s, 6 H, 2 =CC*H*$_3$), 1.95–2.20 (m, 10 H, C*H*$_2$C*H*$_2$), 2.70 (t, 1 H, J = 6.2 Hz, CH$_2$C*H*O), 4.83 (d, 2 H, J = 6.9 Hz, =CHC*H*$_2$O), 4.91 (t, 1 H, J = 6.6 Hz, =C*H*), 5.18 (t, 1 H, J = 6.5 Hz, =C*H*), 5.47 (t, 1 H, J = 7.1 Hz, =C*H*), 7.43 (t, 2 H, J = 7.7 Hz, aryl H), 7.55 (t, 1 H, J = 7.4 Hz, aryl H), 8.05 (d, 2 H, J = 7.5 Hz, aryl H).

Anal. Calcd for $C_{30}H_{46}O_3Si$: C, 74.64; H, 9.60. Found: C, 74.50; H, 9.62.

(−)-(14*S*,2*E*,6*E*,10*E*)-14,15-Epoxy-3,11,15-trimethyl-7-[(trimethylsilyl)methyl]-2,6,10-hexadecatrienyl Acetate (24c). A solution of 100 mg (0.265 mmol) of alcohol **24a** and 0.2 mL (216 mg, 2.12 mmol) of acetic anhydride in 2 mL of pyridine was allowed to stir at rt overnight (~10 h). The solution was evaporated under reduced pressure (0.5 mm), water (10 mL) was added, and the aqueous layer was extracted with ether (3 × 10 mL). The combined ethereal extracts were dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography, using 10% ether in hexane as eluant, afforded 110 mg (99%) of acetate **24c** as a colorless oil: IR (neat) 2953, 1741, 1448, 1365, 1246, 848 cm^{-1}; ^1H NMR δ −0.02 (s, 9 H, SiC*H*$_3$), 1.45 (s, 2 H, C*H*$_2$Si), 1.60 (s, 6 H, 2C*H*$_3$), 1.68, 1.69 (2s, 6 H, 2 C*H*$_3$), 2.05 (s, 3 H, OCOC*H*$_3$), 1.90–2.20 (m, 12 H, 3 C*H*$_2$C*H*$_2$), 4.58 (d, 2 H, J = 7.2 Hz, =CHC*H*$_2$O), 4.89 (t, 1 H, J = 6.6 Hz, =C*H*), 5.10 and 5.13 (2 overlapping t, 2 H, J = ~7.0 Hz, 2 C*H*=), 5.34 (t, 1 H, J = 7.1 Hz, =C*H*).

Anal. Calcd for $C_{25}H_{44}O_2Si$: C, 74.20; H, 10.96. Found: C, 74.27; H, 11.00.

Compounds **25**, **26a**, and **26b** were prepared and purified as described above for **23**, **24a**, and **24c**, respectively.

(2*E*,6*Z*,10*E*)-1-(Benzyloxy)-14,15-epoxy-3,11,15-trimethyl-9-(4-methylbenzenesulfonyl)-7-[(trimethylsilyl)methyl]-2,6,10-hexadecatriene (25) was prepared from epoxy sulfone (±)-**19** (2.14 g, 6.95 mmol) and bromide **15b** (2.5 g, 6.33 mmol) according to the procedure described above for **23**. The yield was 3.31 g (84%) of **25** as a colorless oil: IR (neat) 2955, 1653, 1597, 1452, 1248, 852 cm^{-1}; ^1H NMR δ −0.01 (s, 9 H, SiC*H*$_3$), 1.26, 1.27 (2s, 6 H, 2 C*H*$_3$), 1.30 (s, 5 H, C*H*$_3$ (C-11) and C*H*$_2$Si), 1.43–1.60 (m, 2 H, CH$_2$C*H*$_2$CHO), 1.60 (s, 3 H, =CC*H*$_3$), 1.90–2.22 (m, 7 H, =CC*H*$_2$), 2.43 (s, 3 H, ArC*H*$_3$), 2.65, 2.67 (1:1, two overlapping t, 1 H, J = 6.0 Hz, diastereomeric, OC*H*CH$_2$), 2.75 (br d, 1 H, J = 13.5 Hz, C*H*$_2$CHSO$_2$Ar), 3.86 (br t, 1 H, J = 10.7 Hz, C*H*SO$_2$Ar), 4.00 (d, 2 H, J = 6.6 Hz, OC*H*$_2$CH=), 4.49 (s, 2 H, OC*H*$_2$Ph), 4.94 (br s, 2 H, 2 C*H*=), 5.35 (t, 1 H, J = 6.3 Hz, =C*H*), 7.26–7.35 (m, 7 H, aryl H), 7.70 (d, 2 H, J = 8.1 Hz, aryl H).

Anal. Calcd for $C_{37}H_{54}O_4SSi$: C, 71.34; H, 8.74; S, 5.15. Found: C, 71.27; H, 8.76; S, 5.05.

(2*E*,6*Z*,10*E*)-14,15-Epoxy-3,11,15-trimethyl-7-[(trimethylsilyl)methyl]-2,6,10-hexadecatrien-1-ol (26a). The yield was 1.35 g (74%) of alcohol (±)-**26a** as a colorless oil after flash chromatography on 15% $AgNO_3$-impregnated silica gel: IR (neat) 3426, 2957, 1450, 1379, 1248, 856 cm^{-1}; ^1H NMR δ 0.02 (s, 9 H, SiC*H*$_3$), 1.26, 1.30 (2s, 6 H, 2 C*H*$_3$), 1.50 (s, 2 H, C*H*$_2$Si), 1.61, 1.68 (2s, 6 H, 2 =CC*H*$_3$), 1.59–1.66 (m, 2 H, C*H*$_2$CH$_2$), 1.90–1.95 (three peaks, 2 H, C*H*$_2$CH$_2$), 2.02–2.20 (m, 8 H, C*H*$_2$C*H*$_2$), 2.71 (t, 1 H, J = 6.2 Hz, OC*H*CH$_2$), 4.14 (d, 2 H, J = 6.9 Hz, =CHC*H*$_2$OH), 4.97 (br s, 1 H, =C*H*), 5.15 (t, 1 H, J = 6.9 Hz, =C*H*), 5.41 (t, 1 H, J = 6.9 Hz, =C*H*).

Anal. Calcd for $C_{23}H_{42}O_2Si$: C, 72.95; H, 11.18. Found: 72.66; H, 11.14.

(2*E*,6*Z*,10*E*)-14,15-Epoxy-3,11,15-trimethyl-7-[(trimethylsilyl)methyl]-2,6,10-hexadecatrienyl acetate (26b): yield 165 mg (99%); IR (neat) 2957, 1740, 1377, 1246, 1022, 854 cm^{-1}; ^1H NMR δ 0.02 (s, 9 H, SiC*H*$_3$), 1.26, 1.30 (2s, 6 H, 2 C*H*$_3$), 1.50 (s, 2 H, C*H*$_2$Si), 1.59–1.67 (m, 2 H, C*H*$_2$CH$_2$), 1.61, 1.70 (2s, 6 H, 2 =CC*H*$_3$), 2.05 (s, 3 H, OCOC*H*$_3$), 1.90–1.95, 2.03–2.20 (m, 10 H, C*H*$_2$C*H*$_2$), 2.70 (t, 1 H, J = 6.2 Hz, OC*H*CH$_2$), 4.59 (d, 2 H, J = 6.9 Hz, =CHC*H*$_2$O), 4.96 (br s, 1 H, =C*H*), 5.15 (t, 1 H, J = 6.6 Hz, =C*H*), 5.34 (t, 1 H, J = 7.1 Hz, =C*H*).

Anal. Calcd for $C_{25}H_{44}O_3Si$: C, 71.37; H, 10.54. Found: C, 71.43; H, 10.07.

(+)-3β-Hydroxy-(9βH)- and (+)-3β-Hydroxylabda-8-(17),13(*E*)-dien-15-yl Benzoates (27a and 28a). A solution of 500 mg (1.04 mmol) of epoxy benzoate **24b** and 297 mg (1.55 mmol) of 2,6-di-*tert*-butylpyridine in 20 mL of CH_2Cl_2 was stirred at −78 °C as 1.14 mL (1.14 mmol) of 1.0 M $TiCl_4$ in CH_2Cl_2 was added. After the solution was stirred at −78 °C for 5 min, the reaction was quenched at −78 °C by adding 1 mL of dry triethylamine followed by 1 mL of methanol. The resulting solution was allowed to warm to rt and diluted with 1% aqueous HCl (100 mL). The aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Isolation of the bicyclic products **27a**/**28a** by flash chromatography on silica gel (100 g), using 40% ether in hexane, led to the partial separation. The mixed fractions were combined and further purified by another flash chromatography on silica gel (100 g). The combined weight of the bicyclic products from these two chromatography separations was 324 mg (76%) (**27a**/**28a** = 55:45). The analytical samples were obtained by preparative HPLC using 5% ethyl acetate in hexane as eluant. The retention times were approximately 45 min for **27a** and 50 min for **28a**. The purity of each separated isomer was estimated to be greater than 98% by ^1H NMR spectroscopy: IR (neat, mixture) 3507, 2943, 1718, 1653, 1450, 1271, 887 cm^{-1}. **27a**: $[\alpha]^{24}_D$ +15.4° (c 0.805, $CHCl_3$); ^1H NMR (500 MHz) δ 0.78, 0.91, 1.00 (3s, 9 H, 3C*H*$_3$), 1.75 (s, 3 H, =CC*H*$_3$), 1.76–1.81 (m, 1 H), 1.92–1.98 (app td, 1 H), 2.00–2.08 (app td, 1 H), 2.15–2.20 (app, dd, 1 H), 3.20–3.27 (m, 1 H, C*H*OH), 4.54 (s, 1 H, =C*H*$_2$), 4.71 (t, 1 H, J = 2.0 Hz, =C*H*$_2$), 4.84 (d, 2 H, J = 7.0 Hz, =CHC*H*$_2$O), 5.45 (t, 1 H, J = 6.8 Hz, =C*H*), 7.44 (t, 2 H, J = 7.8 Hz, aryl H), 7.55 (t, 1 H, J = 7.0 Hz, aryl H), 8.05 (d, 2 H, J = 7.5 Hz, aryl H). **28a**: $[\alpha]^{24}_D$ +12.3° (c 0.92, $CHCl_3$); ^1H NMR (500 MHz) δ 0.68, 0.76, 0.96 (3s, 9 H, 3 C*H*$_3$), 1.76 (s, 3 H, =CC*H*$_3$), 1.84–1.98 (m, 2 H), 2.15–2.23 (app dt, 1 H), 2.37–2.42 (app br td, 1 H), 3.18–3.22 (m, 1 H, C*H*OH), 4.53 and 4.84 (2s, 2 H, =C*H*$_2$), 4.83 (d, 2 H, J = 7.5 Hz, =CHC*H*$_2$O), 5.43 (t, 1 H, J = 7.0 Hz, =C*H*), 7.44 (t, 2 H, J = 7.5 Hz, aryl H), 7.55 (t, 1 H, J = 7.5 Hz, aryl H), 8.05 (d, 2 H, J = 7.5 Hz, aryl H); HREIMS calcd for $C_{27}H_{38}O_3$ (M^+, **27a**/**28a** mixture) 410.2820, found 410.2816.

In a different experiment, the monocyclic products were isolated by flash chromatography. The column was first eluted with 5% ether in hexane, and two nonpolar products **29b** and **30** were obtained. Two polar components **31** and **29a** were obtained later with 40% ether in hexane as eluant. The yield of **29b** was 12 mg (~2%), and the ^1H NMR spectrum indicated a purity of ~80% owing to contamination by **30**. Two trimethylsilyl groups are apparent in the ^1H NMR spectrum. It was a 2:1 mixture of the

tetrasubstituted and trisubstituted cyclic olefins. **30**: yield 12 mg (~3%, ~95% purity); ^{1}H NMR δ −0.02 (s, 9 H, SiCH_3), 1.03, 1.05, 1.34 (3s, 9 H, 3 CH_3), 1.44 (s, 2 H, SiCH_2), 1.76 (s, 3 H, =CCH_3), 3.72 (d, 1 H, *J* = 5.1 Hz, *H*CO), 4.84 (d, 2 H, *J* = 6.9 Hz, =CHCH_2O), 4.89 (t, 1 H, *J* = 6.6 Hz, =C*H*), 5.47 (t, 1 H, *J* = 6.9 Hz, =C*H*), 7.43 (t, 2 H, *J* = 7.5 Hz, aryl H), 7.55 (t, 1 H, *J* = 7.4 Hz, aryl H), 8.05 (d, 2 H, *J* = 6.9 Hz, aryl H). **31**: yield 7 mg (~2%, a 1:4 mixture of Δ^3 and Δ^4 isomers). The ^{1}H NMR spectrum shows its purity was ~90% from contamination by a small amount of bicyclic products. The spectral properties of the Δ^4 isomer are as follows: ^{1}H NMR δ 1.01, 1.06, 1.61 (3s, 9 H, 3 CH_3), 1.76 (s, 3 H, =CCH_3), 3.49 (dd, 1 H, *J* = 9.0 and 3.0 Hz, C*H*OH), 4.73, 4.76 (2s, 2 H, =CH_2), 4.84 (d, 2 H, *J* = 7.5 Hz, CHCH_2O), 5.45 (t, 1 H, *J* = 7.5 Hz, =C*H*), 7.43 (t, 2 H, *J* = 7.5 Hz, aryl H), 7.55 (t, 1 H, *J* = 7.2 Hz, aryl H), 8.05 (d, 2 H, *J* = 7.5 Hz, aryl H). **29a**: yield 11 mg (~3%). The purity was estimated to be ~95% by ^{1}H NMR spectroscopy: ^{1}H NMR δ −0.02 (s, 9 H, SiCH_3), 0.81, 1.07 (2s, 6 H, 2 CH_3), 1.55 (s, 5 H, CH_3 and CH_2Si), 1.76 (s, 3 H, =CCH_3), 3.35 (dd, 1 H, *J* = 11.4 and 3.9 Hz, C*H*OH), 4.83 (d, 2 H, *J* = 7.2 Hz, =CHCH_2O), 4.91 (t, 1 H, *J* = 6.9 Hz, =C*H*), 5.47 (t, 1 H, *J* = 7.1 Hz, =C*H*), 7.43 (t, 2 H, *J* = 7.7 Hz, aryl H), 7.55 (t, 1 H, *J* = 7.4 Hz, aryl H), 8.05 (d, 2 H, *J* = 8.1 Hz, aryl H).

(±)-3β-Hydroxy-(9βH)- and (±)-3β-Hydroxylabda-8-(17),13(*E*)-dien-15-yl Acetates (27b and 28b). Cyclization of (2*E*,6*Z*,10*E*) Acetate 26b. Reaction of **26b** (140 mg, 0.333 mmol) as described above followed by flash chromatographic separation gave 71 mg (61%) of a 48:52 mixture bicyclic products **27b** and **28b** according to GC analysis. The yield of monocyclic products corresponding to **29a** and **31** (R = Ac) was 26.4 mg (19%).

(+)-(9βH)-Labda-8(17),13(*E*)-diene-3β,15-diol (6). A solution of 16 mg (0.039 mmol) of benzoate **27a** in 1 mL of 2% NaOH in methanol was stirred at rt for 1 h. Water (10 mL) was added, and the aqueous layer was extracted with ether (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. Purification of the residue by flash chromatography, using 20% ethyl acetate in hexane, gave 12 mg (100%) of diol **6** as a white solid. The purity was estimated to be greater than 95% by ^{1}H NMR spectroscopy: $[\alpha]^{24}_D$ +16.3° (*c* 0.60, $CHCl_3$); IR (neat) 3346, 2924, 1460, 1030, 1007, 885 cm^{-1}; ^{1}H NMR δ 0.77, 0.91, 1.00 (3s, 9 H, 3 CH_3), 1.66 (s, 3 H, =CCH_3), 1.84–2.10 (m, 2 H), 2.14–2.23 (2 br peaks, 1 H), 3.19–3.25 (br, s, 1 H, C*H*OH), 4.15 (d, 2 H, *J* = 6.9 Hz, CH_2OH), 4.53, 4.71 (2s, 2 H, =CH_2), 5.40 (t, 1 H, *J* = 6.8 Hz, =C*H*); ^{13}C NMR δ 15.56, 16.54, 22.40, 23.14, 24.37, 27.63, 28.31, 30.90, 34.26, 37.78, 38.01, 38.84, 45.00, 57.47, 59.29, 79.16, 109.88, 122.94, 140.38, 148.43; MS (70 eV) *m/e* (relative intensity) 306.3 (M^+, 3.50), 291.2 (20.09), 273.2 (32.65), 255.2 (15.03), 203.2 (10.65), 190.2 (32.83), 175.1 (43.74), 161.1 (14.80), 147.1 (29.38), 135.1 (100.00), 121.1 (46.06), 107.1 (74.59), 93.1 (64.74), 81.1 (71.70), 69.1 (46.09), 55.0 (55.57); HREIMS calcd for $C_{20}H_{34}O_2$ (M^+) 306.2558, found 306.2558.

(+)-Labda-8(17),13(*E*)-diene-3β,15-diol (28c). Hydrolysis of benzoate **28a** (18 mg, 0.044 mmol) as described above gave 12 mg (100%) as a white solid. The purity was estimated to be greater than 95% by ^{1}H NMR spectroscopy: $[\alpha]^{24}_D$ +23.4° (*c* 0.65, $CHCl_3$); [lit.[40] for *ent*-**28c** $[\alpha]^{24}_D$ −30° (*c* 2.0, $CHCl_3$)]; IR (neat) 3298, 2934, 1444, 1379, 1030, 889 cm^{-1}; ^{1}H NMR δ 0.68, 0.77, 0.99 (3s, 9 H, 3 CH_3), 1.67 (s, 3 H, =CCH_3), 1.96 (app td, 1 H, *J* = 12.9 and 4.8 Hz), 2.10–2.22 (m, 1 H), 2.40 (AB of ABXY, 1 H, *J* = 12.6, 3.9, and 2.7 Hz), 3.24 (dd, 1 H, *J* = 12.0 and 4.5 Hz, C*H*OH), 4.14 (d, 2 H, *J* = 6.9 Hz, CH_2OH), 4.53 and 4.85 (2s, 2 H, =CH_2), 5.38 (t, 1 H, *J* = 6.9 Hz, =C*H*); ^{13}C NMR δ 14.50, 15.39, 16.35, 21.89, 23.96, 27.84, 28.27, 37.04, 38.14, 38.32, 39.09, 39.33, 54.56, 55.98, 59.29, 78.71, 106.69, 123.01, 140.43, 147.91; MS (70 eV) *m/e* (relative intensity) 306.3 (M^+, 3.09), 291.2 (20.61), 273.2 (32.12), 255.2 (13.27), 203.2 (9.02), 187.1 (10.32), 175.1 (14.30), 159.1 (11.16), 147.1 (15.31), 135.1 (100.00), 121.1 (27.46), 107.1 (54.18), 93.1 (49.30), 81.1 (53.14), 67.0 (30.92), 55.0 (41.99); HREIMS calcd for $C_{20}H_{34}O_2$ (M^+) 306.2558, found 306.2549.

(−)-3-Oxo-(9βH)- and (+)-3-Oxolabda-8(17),13(*E*)-dien-15-yl Benzoates (35 and 36). A suspension of 207 mg (0.50 mmol) of epimeric alcohols **27a** and **28a**, 21 mg (0.25 mmol) of anhydrous NaOAc, and 400 mg of crushed and dried 4A molecular sieves in 12 mL of CH_2Cl_2 was stirred rapidly at rt as 163 mg (0.75 mmol) of pyridinium chlorochromate was added. After the suspension was stirred for 2 h at rt, it was diluted with 5 mL of ether and stirred for 10 min. The suspension was filtered through a 5-g silica gel column covered with a layer of Celite. Elution with ether (50 mL) followed by concentration afforded a pale green liquid. Purification of the residue by flash chromatography, using 10% ethyl acetate in hexane as eluant, gave 198 mg (96%) of epimeric ketones **35** and **36**. The isomers were separated by preparative HPLC eluting with 2.5% ethyl acetate in hexane (**35**, t_R = 50 min; **36**, t_R = 55 min). A total of 200 mg of ketone mixture in 3.5 mL of eluent was separated by ~60 50-μL injections: IR (neat, **35** and **36** mixture) 2943, 1714, 1450, 1271, 1109, 891 cm^{-1}. **35**: $[\alpha]^{24}_D$ −1.23° (*c* 2.82, $CHCl_3$); ^{1}H NMR δ 1.02, 1.09, 1.12 (3s, 9 H, 3 CH_3), 1.74 (s, 3 H, =CCH_3), 1.91–2.14 (app 2td, 2 H), 2.18–2.27 (2 br s, 1 H), 2.27–2.37 (app 2t, 1 H), 2.74 (td, 1 H, *J* = 14.7 and 5.7 Hz), 4.61 (s, 1 H, =CH_2), 4.78 (t, 1 H, *J* = 2.0 Hz, =CH_2), 4.83 (d, 2 H, *J* = 6.9 Hz, =CHCH_2O), 5.44 (t, 1 H, *J* = 6.9 Hz, =C*H*CH$_2$O), 7.43 (t, 2 H, *J* = 7.5 Hz, aryl H), 7.55 (t, 1 H, *J* = 7.4 Hz, aryl H), 8.05 (d, 2 H, *J* = 7.2 Hz, aryl H). **36**: $[\alpha]^{24}_D$ +9.5° (*c* 2.80, $CHCl_3$); ^{1}H NMR δ 0.85, 1.00, 1.05 (3s, 9 H, 3CH_3), 1.75 (s, 3 H, =CCH_3), 1.84–2.08 (m, 3 H), 2.13–2.26 (m, 1 H), 2.30–2.46 (m, 2 H), 2.54–2.67 (eight peaks, 1 H), 4.59 (s, 1 H, =CH_2), 4.82 (d, 2 H, *J* = 6.9 Hz, =CHCH_2O), 4.90 (s, 1 H, =CH_2), 5.43 (t, 1 H, *J* = 6.9 Hz, =C*H*CH$_2$), 7.42 (t, 2 H, *J* = 7.5 Hz, aryl H), 7.54 (t, 1 H, *J* = 7.4 Hz, aryl H), 8.03 (d, 2 H, *J* = 7.5 Hz, aryl H); HREIMS calcd for $C_{27}H_{36}O_3$ (M^+) 408.2664, found 408.2656.

(9βH)-Labda-8(17),13(*E*)-dien-15-yl Benzoate (37). The reactions were conducted as described below for the anti isomer (**36** → **38**). The yield was 81.2 mg (78%) of a colorless oil. The purity was estimated to be greater than 95% by ^{1}H NMR spectroscopy: IR (neat) 2939, 1718, 1645, 1450, 1269, 887 cm^{-1}; ^{1}H NMR δ 0.81, 0.87, 0.91 (3s, 9 H, 3CH_3), 1.76 (s, 3 H, =CCH_3), 4.52 (d, 1 H, *J* = 1.5 Hz, =CH_2), 4.69 (t, 1 H, *J* = 2.3 Hz, =CH_2), 4.84 (d, 2 H, *J* = 6.9 Hz, =CHCH_2O), 5.46 (t, 1 H, *J* = 7.5 Hz, =C*H*), 7.43 (t, 2 H, *J* = 7.7 Hz, aryl H), 7.55 (t, 1 H, *J* = 7.4 Hz, aryl H), 8.06 (d, 2 H, *J* = 7.2 Hz, aryl H).

Labda-8(17),13(*E*)-dien-15-yl Benzoate (38). The procedure was developed based on ones in the literature.[57] A solution of 112 mg (0.274 mmol) of ketone **36** in 2.8 mL of absolute ethanol in a 5-mL pear-shaped flask was stirred as 62 mg (0.333 mmol) of *p*-toluenesulfonylhydrazine was added at rt. The solution was heated at reflux for 5 h. TLC analysis indicated the reaction was completed. The solvent was removed with a stream of N_2 and evacuation at 0.5 mm for 20 min. The remaining crystalline solid was used immediately without purification.

To the above flask was added 0.6 mL of $CHCl_3$. The resulting solution was stirred at 0 °C as 0.55 mL (1.0 M, 0.55 mmol) of catecholborane in THF was added. After 1.5 h at 0 °C and 0.5 h at rt, methanol (200 μL) was added to decompose any remaining hydride. The solution was stirred for 10 min before 248 mg (0.823 mmol) of tetrabutylammonium acetate was added at rt. A few drops of $CHCl_3$ was added until all of the salt was dissolved. The solution was stirred at rt for 6 h. TLC analysis indicated the reaction was completed. The solution was diluted with water (10 mL), and the aqueous solution was extracted with ether (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash chromatography, using 5% ether in hexane as eluant, afforded 78.2 mg (72%) of benzoate **38** as a colorless oil. The purity was estimated to be greater than 95% by ^{1}H NMR spectroscopy: IR (neat) 2939, 1716, 1641, 1450, 1269, 887 cm^{-1}; ^{1}H NMR δ 0.67, 0.79, 0.85 (3s, 9 H, 3CH_3), 1.76 (s, 3 H, =CCH_3), 1.80–2.01 (m, 2 H), 2.13–2.25 (m, 1 H)), 2.33–2.42 (app 2q, 1 H), 4.51 and 4.82 (2s, 2 H, =CH_2), 4.84 (d, 2 H, *J* = 7.2 Hz, =CHCH_2O), 5.43 (t, 1 H, *J* = 7.5 Hz, =C*H*), 7.43 (t, 2 H, *J* = 7.5 Hz, aryl H), 7.55 (t, 1 H, *J* = 7.5 Hz, aryl H), 8.05 (d, 2 H, *J* = 7.2 Hz, aryl H).

The hydrolyses of benzoates **37** and **38** to **5** and **39**, respectively, were performed as described above for **27a** → **6**. The purities of **5** and **39** were estimated to be ≥95% from their ^{1}H and ^{13}C NMR spectra.

(+)-(9βH)-Labda-8(17),13(*E*)-dien-15-ol (9,10-*syn*-copalol, 5): yield 51.4 mg (86%) as a colorless oil; $[\alpha]^{24}_D$ +17.7° (*c* 2.39, $CHCl_3$); IR (neat) 3327, 2936, 1645, 1458, 1001, 887 cm^{-1}; ^{1}H and ^{13}C NMR date (see Table I); MS (70 eV) *m/e* (relative intensity)

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290 (M^+, 2.47), 275 (17.32), 257 (9.10), 205 (5.42), 192 (14.74), 177 (29.12), 163 (7.85), 149 (24.61), 137 (55.40), 123 (38.29), 109 (47.97), 95 (65.33), 81 (84.99), 69 (81.83), 55 (62.59), 41 (100.00); HREIMS calcd for $C_{20}H_{34}O$ (M^+) 290.2609, found 290.2613.

(+)-Labda-8(17),13(*E*)-dien-15-ol (copalol, 39): yield 27.2 mg (92%) as a colorless oil. The IR, ^1H NMR, ^{13}C NMR ($\Delta\delta \leq 0.07$ ppm), and mass spectra of (+)-**39** are identical to those of *ent*-copalol ((−)-**39**). Data for (+)-**39**: $[\alpha]^{24}_D$ +29.8° (*c* 1.36, $CHCl_3$) (lit.[58] $[\alpha]_D$ +30° (*c* 1.09, $CHCl_3$)); IR (neat) 3300, 2922, 1643, 1442, 1387. 997, 887 cm^{-1}; ^1H and ^{13}C NMR data (see Table I); MS (70 eV) *m/e* (relative intensity) 290 (M^+, 2.97), 275 (19.22), 257 (10.31), 205 (6.86), 191 (12.58), 177 (13.19), 161 (7.04), 149 (18.34), 137 (71.78), 123 (44.58), 109 (50.21), 95 (73.41), 81 (95.38), 69 (83.81), 55 (71.14), 41 (100.00); HREIMS calcd for $C_{20}H_{34}O$ (M^+) 290.2609, found 290.2613.

(−)-Labda-8(17),13(*E*)-dien-15-ol (*ent*-39). The reference sample of naturally derived *ent*-copalol was obtained by AlH_3 reduction of methyl copalate. The ester was prepared by CH_2N_2 esterification of copalic acid isolated from Brazilian copal resin.[48,59] They are identical with those for synthetic (+)-**39**.

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Supplementary Material Available: Spectral data for triethyl 2-[(trimethylsilyl)methyl]-2-phosphonobutanoate, procedures for preparation of the ester precursor to **17** (method B), logic used to assign NMR data for **5**, ^1H NMR spectra for **14b**, **18a**, **18c**, **27a**, **28a**, **28c**, **35–39**, **5**, and **6**, and ^{13}C NMR, COSY, and HETCOR spectra of **5** and **39** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Cavitands as Versatile Molecular Receptors

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X-ray crystal structure of **3**·2PhF and ^1H NMR complexation studies in solution reveal the strong tendency of cavitand **3** to selectively bind aromatic guests in organic solution. The association constants (K_a) for eight 1:1 caviplexes formed in acetone-d_6 were determined. The solvation effect is largely responsible for the relatively low K_a values observed. The orientation assumed by the guests inside the cavity is determined by dipole–dipole interactions between the host and the guest; additional CH_3–π interactions are present in the case of **3**·3$(CH_3)_2CO$. The modification of the structure of **3** by introducing a suitable and furtherly modifiable substituent allowed the synsesis of optically pure chiral cavitand **5**. ^1H NMR complexation studies of **5** in acetone-d_6 reveal that the CH_2OH group perching on top of the cavity rim affects the selectivity but not the orientation of the included aromatic guests for the 1:1 caviplexes formed.

The design of new molecular receptors, combining binding and orientation of neutral guests, requires the comprehension and modulation of the weak attractive forces responsible for molecular recognition phenomena.[1] Chirality and the presence of convergent functional groups are two further desirable features.

Among others, cavitands, synthetic organic compounds with enforced concave surfaces of molecular dimensions,[2] are extremely interesting and versatile synthetic receptors. Some attractive features of cavitands have been previously reported: the presence of a tunable solvation-temperature-driven equilibrium between a closed vaselike and an open kitelike form[3] and their strong tendency to complex organic molecules in the solid state,[4] in solution,[5] and in the gas phase,[6] with preference for aromatic guests.

In this paper we report the X-ray crystal structure of **3**·2PhF, the synthesis of chiral cavitands **4** and **5** (Scheme I), and the complexation studies in organic solution of **3** and **5** with aromatic guests.

Results and Discussion

Crystal Structure of 3·2PhF. The crystal and molecular structure of **3**·2PhF was determined by single-crystal X-ray diffraction methods. As shown in Figure 1, the conformation of the host molecule resembles that observed in the previously reported **3**·3$(CH_3)_2CO$[5] and in the analogue **6**·2CH_2Cl_2[3] (Scheme I). A deep intramolecular

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