the slope of the line obtained for 1α,25-$(OH)_2$-D_3; multiplication of this value by 100 gives the RCI value. By definition, the RCI for 1α,25-$(OH)_2$-D_3 is 100.

Acknowledgment. This study was supported by grants from the National Institutes of Health (Grant Nos. NIH-CA-43277, DK-09012, and DK-16595). We also acknowledge technical assistance from Ms. June Bishop and access to starting material from Solvay Duphar B. V. (Weesp, the Netherlands).

Supplementary Material Available: Spectral and analytical data (21 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.

An Intramolecular Diels–Alder Approach to the Cis Ring Fused Isomer of the 25-Hydroxy Vitamin D_2 Grundmann Ketone

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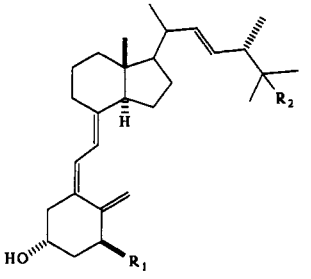
Stereospecific Claisen and intramolecular Diels–Alder reactions of chiral ester synthon **4** results in conversion of a single asymmetric center of commercially available ester **4** to a vitamin D synthon, the C/D cis Grundmann ketone **3**. The addition of propenyllithium to aldehyde **9** was dominated by a chelated anti-Cram transition state and yielded the threo isomer **12a** as the major product. The stereochemistry of **12a** was determined by X-ray crystallography. Conversion of benzyl-protected erythro isomer **11b** to its dimethylacryloyl ester followed by ester enolate Claisen rearrangement led to the C17 and C20 stereochemistry of vitamin D. Addition of a pentadienyl anion to aldehyde **15** gave a tetraene, **17**, which underwent an intramolecular Diels–Alder reaction to produce compound **18**. Removal of the C16 hydroxyl and hydrolysis gave only the cis-fused isomer of **3**.

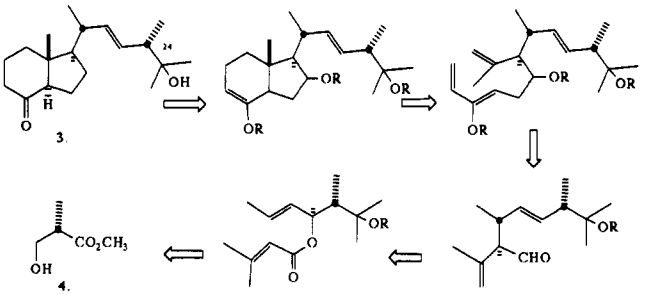
Recently there has been a resurgence of interest concerning vitamin D_2 and its hydroxylated metabolites **1** and **2**.[1] The tranditional activity of the vitamin D hormone in calcium homeostasis has been broadened by the discovery of its role in normal cell differentiation and the immune system. For example, recent work on the stim-



1. R_1 = H, R_2 = OH
2. R_1 = R_2 = OH

ulation of macrophages[2] has lead to the topical use of vitamin D analogs in the treatment of psoriasis.[3] New

Scheme I



analogs have been discovered with incredible immunosupresive activity[4] (one million times greater than cyclosporin A!). As part of a program of developing new synthetic methodology we have investigated a diastereoselective synthesis of the cis-fused isomer of 25-hydroxy Grundmann ketone **3**, using the intramolecular Diels–Alder reaction. The trans ketone **3** is a key building block used for the synthesis of vitamin D compounds by many groups.[5,6]

(1) (a) *Vitamin D: Chemical, Biochemical and Clinical Endocrinology of Calcium Metabolism*; Norman, A. W., Schaefer, K., Herrath, D. V., Grigoleit, H.-G., Eds.; Walter de Gruyter: New York, 1982. (b) Norman, A. W. *Vitamin D, The Calcium Homeostatic Steroid Hormone*; Academic: New York, 1980. (c) DeLuca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1–65. (d) DeLuca, H. F.; Schnoes, H. K. *Annu. Rev. Biochem.* **1983**, *52*, 411. (e) DeLuca, H. F.; Schnoes, H. K. *Annu. Rev. Med. Chem.* **1984**, *19*, 179. (f) Pardo, R.; Santelli, M. *Bull Soc. Chim. Fr.* **1985**, 98. (g) Smith, E. L.; Walworth, N. C.; Holick, M. F. *J. Invest. Dermatol.* **1986**, *86*, 709. (h) *Calcium Regulation and Bone Metabolism: Basic and Chemical Aspects*; Cohn, D. V., Ed.; Elsevier Science Publishers, B.V.: Amsterdam, 1987. (i) Ikekawa, N.; Eguchi, T. Hara, N.; Takatsuto, S.; Honda, A.; Mori, Y.; Otomon, S. *Chem. Pharm. Bull.* **1987**, *35*, 4362. (j) Kutner, A.; Perlman, K. L.; Lago, A.; Sicinski, R. R.; Schnoes, H, K.; DeLuca, H. F. *J. Org. Chem.* **1988**, *53*, 3450 and references cited therein. (k) de Costa, B. R.; Holick, S. A.; Holick, M. F. *J. Chem. Soc., Chem. Commun.* **1989**, 325. (l) *Proceedings of the Eighth Workshop on Vitamin D*; Norman, A. W., Ed.; Walter de Gruyter: Berlin, 1991.

(2) Ostrem, V. K.; Lau, W. F.; Lee, S. H.; Perlman, K.; Prahl, J.; Schnoes, H. K.; Deluca, H. F.; Ikekawa, N. *J. Biol. Chem.* **1987**, *282*, 14164.

(3) (a) Holick, M. F. In *Proceedings of the Sixth Workshop on Vitamin D*; Norman, A. W., Ed.; Walter de Gruyter: Berlin, 1985; pp 219–228. (b) Calverley, M. J. *Tetrahedron* **1987**, *43*, 4609. (c) Holick, M. F. In *Proceedings of the Eighth Workshop on Vitamin D*; Bouillon, R., Norman, A. W., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991; pp 940–948. (d) Calverley, M. J. Binderup, E.; Binderup, L. In *Proceedings of the Eighth Workshop on Vitamin D*; Bouillon, R., Norman, A. W., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991.

(4) For leading references to KH-1060, see: Latini, S.; Binderup, L. In *Proceedings of the Eighth Workshop on Vitamin D*; Bouillon, R., Norman, A. W., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991; pp 516 and 478.

(5) (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098–3108. (b) Sardina, F. J.; Mourino, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264–9. (c) Nemoto, N.; Kimura, T.; Kurobe, H.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1985**, 1131–2. (d) Nemoto, H.; Wu, X.-M.; Kurobe, H.; Masataka, I.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1984**, *26*, 3095–8. (e) Harrison, R. G.; Lythgoe, B.; Wright, P. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2654.

0022-3263/92/1957-4380$03.00/0

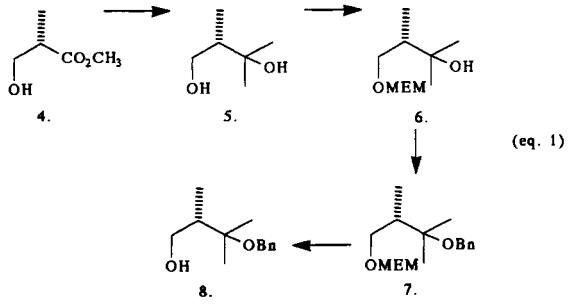
Table I. 1-Propenyllithium Addition to 9 and 10

starting aldehyde	temp, °C	ratio 11/12
9	-78	1:2
10	-78	5.2:1
10	-95	19:1

Our approach[7] uses the chirality at C24 of the side chain to control the stereochemistry of the fused ring system. The starting material is the commercially available homochiral ester 4. By employing stereospecific Claisen and intramolecular Diels–Alder reactions, 4 has been converted into compound *cis*-3 (Scheme I).

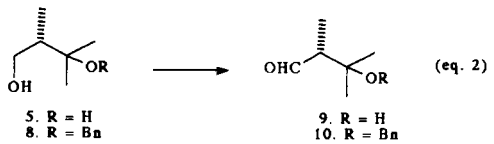
Discussion and Results

Vitamin D_2 metabolites have been synthesized by many routes but none in which a single asymmetric center is used to induce all the other chiral centers in the molecule. The commercially available ester 4 can be obtained as either enantiomer. When optically pure (*S*)-4 was reacted with methyllithium (eq 1), the diol 5 was obtained. Protection



of the primary alcohol of 5 as the (2-methoxyethoxy)-methoxy ether (MEM)[8] with MEMCl proceeded smoothly, and 6 was obtained in good yield. Protection of the tertiary alcohol used Sjoeberg's version[9a,b] of a Corey procedure.[9c] Sodium hydride was dissolved in dry dimethyl sulfoxide by sonication, and alcohol 6 was added to the solution of sodium methylsulfinyl carbanion. Benzylation proceeds in modest yields to form 7. The MEM ether was removed by the treatment of 7 with methanol containing several drops of concentrated hydrochloric acid.

Swern oxidation of 5 and 8 to their corresponding aldehydes was then carried out (eq 2).[10] The Swern oxidation of benzyl ether 8 was clean, with yields in excess of 90% whereas diol 5 gave only moderate (52%) yields. The use of pyridinium chromates resulted in dehydration and a lower yield.



The first reaction in which stereochemical control was important was the addition of *trans*-1-propenyllithium to

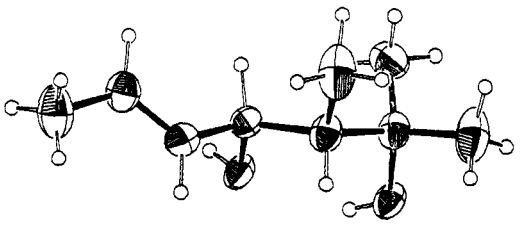
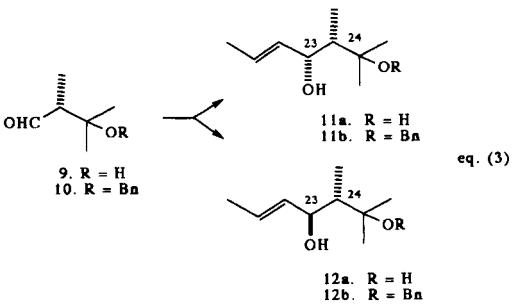


Figure 1. ORTEP drawing of compound **12a**.

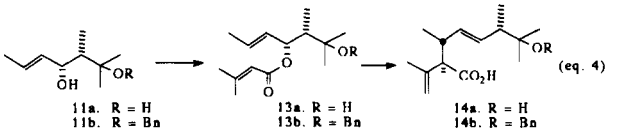
the chiral aldehydes 9 or 10 (eq 3). The addition of propenyllithium to 9 was dominated by a chelated anti-Cram transition state[11] and yielded the threo isomer **12a** as the major product. Our synthetic plan required, however, the erythro isomer. Fortunately, the more hindered benzyl-protected aldehyde 10 reacts to form the desired erythro isomer **11b** as the major product (Table I). When the addition was carried out at -95 °C, almost complete stereochemical control was achieved.

The stereochemistry of compounds **11a,b** and **12a,b** were determined by spectral and chemical correlation. Diol **12a** was a crystalline compound, and its structure was deduced by X-ay crystallography (Figure 1).[12] The ^{1}H-NMR spectrum of the threo isomer **12a** showed the proton on C23 (steroid numbering, see eq 3) as a triplet, not a doublet



of doublets. In contrast, the erythro isomer, **11a**, showed a doublet for the hydrogen on C23. Decoupling experiments and 2D (COSY) NMR spectra of **11a** indicated that there was little or no coupling between the proton on C22 and C23; therefore the dihedral angle between these protons must be close to 90°. Derivatives **11b** and **12b** showed similar couplings in their NMR spectra for the proton on C23 and were assigned the stereochemistry shown on this basis. In addition, the stereochemical relationship between **12a** and **12b** was verified by interconversion by standard procedures.[13,14]

With the asymmetric center destined to become C24 in place, we next addressed the issue of the Claisen rearrangement.[15] 3,3-Dimethylacryloyl chloride was reacted with the lithium salt of **11a** or **11b** to yield **13a** or **13b**, respectively (eq 4). The treatment of **13a** with lithium



diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide

(6) For a recent review of vitamin D methods, see: Wilson, S. R.; Yasmin, A. In *Studies in Natural Products Chemistry*; Ur-Raman, A., Ed.; Elsevier Science Publishers, B.V.: Amsterdam, 1992.

(7) (a) Wilson, S. R.; Haque, M. S. *Tetrahedron Lett.* **1984**, *25*, 3147–50. (b) Wilson, S. R.; Haque, M. S. *J. Org. Chem.* **1982**, *47*, 5411–3. (c) Wilson, S. R.; Venkatesan, A. M.; Yasmin, A. *Tetrahedron Lett.* **1991**, *32*, 2339–2342.

(8) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809–812.

(9) (a) Sjoeberg, K. *Tetrahedron Lett.* **1966**, 6383–4. (b) Sjoeberg, B.; Sjoeberg, K. *Acta Chim.* **1972**, *26*, 275–8. (c) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 866.

(10) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–60.

(11) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035–38.

(12) We would like to thank Dr. J. C. Huffman (Indiana University Molecular Structure Center report no. 85201, see supplementary material) for carrying out the single-crystal X-ray diffraction analysis.

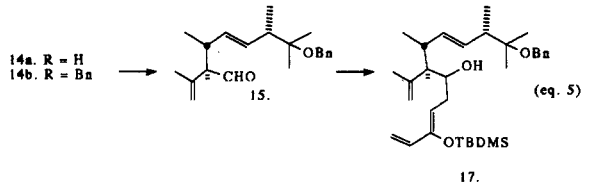
(13) Compound **12a** was converted to **12b** by reaction with TBDMSCl (DMF, imidazole, 87%) followed by benzylation (NaH, DMSO, PhCH2Br, 89%) and desilyation (AcOH, H_2O, 38%).[14]

(14) Jacob, L. Ph.D. Thesis, New York University, 1987.

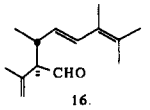
(15) Wilson, S. R.; Myers, R. S. *J. Org. Chem.* **1975**, *40*, 3309.

(LiTMP) and trimethylsilyl chloride (TMSCl) followed by slow warming to reflux lead to the formation of **14a** (9:1 *RR*). Similar isomerization of **13b** lead to a single stereoisomer (*RR*)-**14b**.

The acids **14a** and **14b** were easily converted into their corresponding alcohols with lithium aluminum hydride, which were oxidized using Swern's conditions[10] to produce an excellent yield of **15** from **14b** (eq 5). Unblocked al-

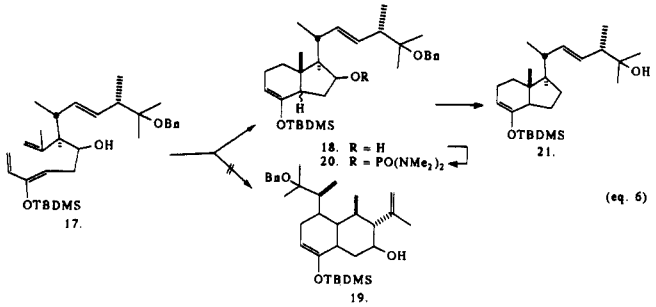


cohol **14a** (derived from **13a**) underwent dehydration under Swern conditions forming diene **16**. The diene portion



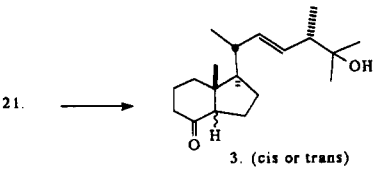
for the intramolecular Diels–Alder was introduced in the following way. 3-[(1,1-Dimethylethyl)dimethylsiloxy]-1,4-pentadiene was deprotonated using *sec*-butyllithium at −78 °C as described by Oppolzer and Snowden[16] and the anion reacted with aldehyde **15** to yield an epimeric mixture of alcohols **17** (1:2.5 ratio). Studies of the ^{1}H-NMR spectrum of the crude reaction mixture showed only the products resulting from the terminal addition of the dienyl anion to the aldehyde. These alcohols could be separated by preparative TLC, and the synthesis was completed using only the major epimer.

The tetraene, **17**, underwent an intramolecular Diels–Alder reaction (eq 6) to produce compound **18** on heating in dry toluene under nitrogen in a sealed tube overnight. No octalin product, **19**, corresponding to an alternative mode of intramolecular Diels–Alder reaction was seen.[16]

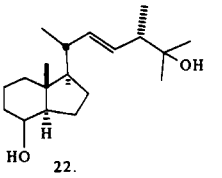


The C16 hydroxyl group (steroid numbering) was removed by the Ireland method.[15] The hydroxyl group was phosphorylated using *n*-butyllithium and bis(dimethylamino)phosphorochloridate[19] to yield **20**. Both the benzyl phosphorylamide groups were removed by reduction with lithium in refluxing methylamine at 0 °C (1 h) to yield **21**. Care must be exercised during the workup to prevent the loss of the TBDMS group.

The removal of the TBDMS group using potassium fluoride in methanol results in cis/trans epimerization. When **21** was deblocked using AcOH/THF/H_2O conditions only the cis ring fused compound *cis*-**3** was obtained.



The structure of *cis*-**3** was confirmed by the route shown in comparison to an authentic sample obtained from diol **22** obtained from Hoffmann-LaRoche[5a] (courtesy of the late Dr. Enrico Baggiolini) which was oxidized and epimerized to yield *cis*-**3**.[14,20] Epimerization during TBDMS ether hydrolysis means that it has not been possible to confirm the Diels–Alder cis/trans stereochemistry.



Considering our experience with the related D_3 series, which gives only trans Diels–Alder products,[7] it would be surprizing if only cis Diels–Alder product was formed. It could be that some subtle steric effect due to our side chain or electronic effect due to the OTBDMS ether caused us to obtain the cis compound in the Diels–Alder reaction. Alternatively, the conditions used to deblock **21** caused the loss of the trans compound through epimerization. In principle, the cis/trans isomers **3** could be equilibrated[20] and separated, although the equilibrium lies far on the side of the *cis*-**3**. *trans*-**3** has been converted into 1,25-dihydroxy vitamin D_2 (**2**) by the Hoffman-LaRoche group.[5a]

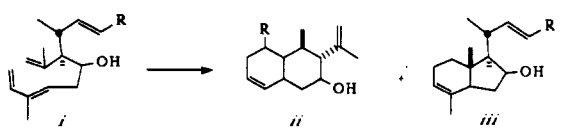
Experimental Section

General. ^{1}H- and ^{13}C-NMR spectra were taken on a General Electric QE-300 spectrometer. Melting points are uncorrected. Optical rotations were determined in anhydrous ethanol using a 1-dm cell and a sodium (589-nm) lamp. GC analyses were performed with a $^1/_8$-in. glass column packed with 2% OV-101 and 0.2% Carbowax on Chromabsorb of either 6 (6P) or 3-ft (3P) length or a 25-ft fused silica capillary column (CC).

2,3-Dimethyl-1,3-butanediol (5). A solution of CH_3Li (23 g, 1 mol) in ether (715 mL) under N_2 was stirred and cooled to −15 °C. A solution of (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (**4**) (33.0 g, 0.28 mol, Aldrich Chemical Co.) in ether (100 mL) was added from a dropping funnel and rapid stirring at such a rate that the internal temperature did not exceed −10 °C, and the addition was complete within $^1/_2$ h. Controlled rapid addition was necessary to minimize polymerization. The reaction mixture was kept at 0 °C for 1 h after the addition was complete and then quenched by the addition of saturated NH_4Cl solution (50 mL). The quenching was also done as rapidly and as safely possible. After the reaction mixture was filtered, the aqueous layer was drawn off. The ether was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was fractionally distilled

(16) Oppolzer, W.; Snowden, R. L. *Tetrahedron Lett.* **1976**, 4187–90.

(17) Related compounds i were shown to produce both 6,6- and 6,5-ring fused products ii and iii under identical cyclization conditions.[18] We anticipated, however, that steric strain induced in the transition state by the C24 methyl substituent in the vitamin D_2 series would preclude formation of the undesired 6,6-products in the vitamin D_2 series.



R = H, $CH_2CH_2CH(CH_3)_2$

(18) Tofigh, S. M. S. Thesis, New York Unveristy, 1982.

(19) (a) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145. (b) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098–9.

(20) Cis → trans isomerization of **3** is very easy and the equilibrium lies far on the side of the cis isomer: Peterson, P. E.; Leffew, R. L. B. *J. Org. Chem.* **1986**, *51*, 1948–1954.

to yield 24.0 g (73%) of **5** as a colorless oil: bp 76–80 °C (2 mm); R_f = 0.21 (50% CH_2Cl_2/hexane); GC (3P) 3.9 min; $[\alpha]_D$ = −9.36 (0.28, EtOH) [lit.[21a] $[\alpha]_D$ = −2.5 (0.18, $CHCl_3$)];[21b] ^1H NMR ($CDCl_3$) 0.83 (d, 3 H, J = 6.8 Hz), 1.16 (s, 3 H), 1.24 (s, 3 H), 1.78 (q, 1 H, J = 5 Hz, J = 7 Hz), 3.35 (s, 1 H), 3.68 (d, 2 H, J = 7 Hz), 3.70 (s, 1 H) [lit.[21a] 0.82 (d, 3 H, J = 7 Hz), 1.12 (s, 3 H), 1.19 (s, 3 H), 3.58 (d, 2 H, J = 7 Hz)]; MS m/e (% base) 103 (7) (m − 15), 85 (8), 59 (100), 43 (55). Anal. Calcd for $C_6H_{14}O_2$: C, 60.98; H, 11.94. Found: C, 60.75; H, 12.20.

2,3-Dimethyl-4-[(2-methoxyethoxy)methoxy]-2-butanol (6). NaH dispersion (60% in mineral oil) (8.0 g, 0.2 mol) was washed twice with ether (10 mL) under N_2. THF (120 mL) was added to the flask, the mixture was cooled to 0 °C, and compound **5** (11 g, 93 mmol) in THF (60 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and turned yellow in color. A solution of (2-methoxyethoxy)methyl chloride (MEMCl) in THF (30 mL) was added dropwise. The reaction mixture was stirred for an additional 15 min. The reaction was quenched by adding half saturated NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with ether (20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by fractional distillation to yield 16.6 g (86%) of compound **6** as a colorless oil: bp 115–120 °C (4 mm); R_f = 0.13 (50% ether/heptane); GC (3P) 5.2 min; ^1H NMR ($CDCl_3$) 0.83 (d, 3 H, J = 4 Hz), 1.07 (s, 3 H), 1.12 (s, 3 H), 1.78 (m, 1 H), 3.19 (s, 1 H), 3.37 (s, 3 H), 3.56 (t, 1 H, J = 6 Hz), 3.63 (d, 2 H, J = 6 Hz), 3.70 (t, 1 H, J = 6 Hz), 4.69 (s, 2 H); ^{13}C NMR 13.20, 24.84, 28.77, 42.65, 58.95, 67.05, 71.18, 71.63, 72.76, 95.54; MS m/e (% base) 188 (5), 115 (9), 89 (39), 84 (10), 83 (10), 77 (25), 59 (100), 57 (5).

2,3-Dimethyl-4-[(2-methoxyethoxy)methoxy]-2-(phenylmethoxy)butane (7). A solution of NaH in DMSO was prepared according to the procedure of Sjoeberg.[9] NaH (0.4 g, 60% dispersion in mineral oil) under N_2 was washed with ether, DMSO (10 mL) was added, and the mixture was sonicated for about 2 h until a cloudy gray solution was obtained. Compound **6** (1.0 g, 5 mmol) in dry DMSO (10 mL) under Ar was cooled to 0 °C. The NaH solution (5.5 mL, 5.5 mmol) was added, and the reaction stirred for $^1/_2$ h at rt. The reaction mixture turned a deep orange. Benzyl bromide (0.6 mL, 5 mmol) was then added, and the reaction mixture was stirred for an additional 1 h. The reaction was cooled to 0 °C and quenched cautiously with water (10 mL). Ether (100 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (50 mL) again. The combined organic layers were washed with half saturated NaCl. The ether was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography. Unreacted starting material (0.37 g) and the desired product **7** (0.60 g, 66%) were obtained: R_f = 0.48 (50% ethyl acetate/heptane); GC (3P) 8.4 min; ^1H NMR ($CDCl_3$) 1.05 (d, 3 H, J = 4 Hz), 1.22 (s, 3 H), 1.24 (s, 3 H), 2.05 (m, 1 H), 3.38 (s, 3 H), 3.55 (dd, 2 H, J = 6, 6 Hz), 3.60 (m, 1 H), 3.69 (dd, 2 H, J = 6, 6 Hz), 3.82 (dd, 1 H, J = 4, 10 Hz), 4.44 (apparent, AB pattern, 2 H), 4.73 (s, 3 H), 7.33 (m, 5 H); ^{13}C NMR 13.16, 22.74, 23.43, 41.60, 58.92, 63.06, 66.60, 69.19, 71.70, 89.62, 95.65, 127.51, 126.03, 127.06, 128.12, 128.27, 139.72; IR 2990, 1355, 1440, 1030, 830, 730; UV (MeOH) 221.5, 252, 258; MS m/e (% base) 149 (12), 113 (5), 107 (7), 92 (9), 91 (100), 89 (20), 84 (10), 59 (36), 45 (10), 43 (11).

2,3-Dimethyl-3-(phenylmethoxy)-1-butanol (8). Compound **7** (6.0 g, 20 mmol) was dissolved in methanol (150 mL), and concentrated hydrochloric acid (0.3 mL) was added. The solution was refluxed for 1 h. After the reaction mixture was cooled, saturated $NaHCO_3$ solution (1 mL) was added. The reaction mixture was concentrated to a residue, redissolved in ether, dried (Na_2SO_4), filtered, and reconcentrated to yield 4.1 g (97%) of **8** as a yellow oil. The crude product can be used for the next step: R_f = 0.28 (50% ether/heptane); GC (3P) 6.4 min; ^1H NMR ($CDCl_3$) 0.92 (d, 3 H, J = 7 Hz), 1.29 (s, 3 H), 1.34 (s, 3 H), 1.97 (m, 1 H), 3.53 (s, 1 H), 3.59 (dd, 1 H, J = 4, 6 Hz), 3.74 (dd, 1 H, J = 8, 11 Hz), 4.49 (d, 2 H, apparent d actually AB pattern), 7.32 (m, 5 H); ^{13}C NMR 13.00, 20.24, 24.46, 43.69, 63.64, 65.89, 80.18, 127.20, 127.39, 128.36, 128.50, 138.86; IR 3530; UV (MeOH) 220, 252, 258; MS m/e (% base) 149 (6), 108 (3), 107 (4), 92 (10), 91 (100), 84 (15), 65 (10). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.68. Found: C, 74.67; H, 9.88.

2,3-Dimethyl-3-hydroxybutanal (9). A solution of oxalyl chloride (1.47 mL, 17 mmol) in CH_2Cl_2 (40 mL) under N_2 was stirred and cooled to −78 °C. The addition of a solution of DMSO (1.6 mL, 23 mmol) in CH_2Cl_2 (4 mL) was done so that the internal temperature did not exceed −60 °C. After the addition was complete, the reaction mixture was stirred for another 5 min. A solution of **5** (1.3 g, 11 mmol) in CH_2Cl_2 (12 mL) was added dropwise, and the reaction mixture was stirred for 15 min. Triethylamine (8 mL, 57 mmol) was added fairly rapidly. The reaction mixture was stirred at −78 °C for 15 min and then warmed to 0 °C for 15–30 min. A mixture of benzene/ether (4:1) (100 mL) and water (20 mL) was added to the reaction. The layers were separated after vigorous shaking, and the organic phase was dried ($MgSO_4$). A small amount of activated charcoal was added before filtering the solution through Celite. The filtrate was concentrated under reduced pressure. The product **9** (0.67 g, 52%) was used immediately: R_f = 0.16 (50% ether/hexane); GC (3P) 3.4 min; ^1H NMR ($CDCl_3$) 1.14 (d, 3 H, J = 7 Hz), 1.24 (s, 3 H), 1.28 (s, 3 H), 2.45 (q, 1 H, J = 7 Hz), 9.82 (d, 1 H, J = 1 Hz).

2,3-Dimethyl-3-(phenylmethoxy)butanal (10). Compound **8** (100 mg, 0.48 mmol) was reacted with oxalyl chloride (109 mg, 0.86 mmol) and DMSO (99 mg, 1.2 mmol) in CH_2Cl_2 as described above. The yield was 98 mg (99%) of **10** as an oil: R_f = 0.57 (5% ether/heptane); GC (3P) 8.6 min; ^1H NMR ($CDCl_3$) 1.13 (d, 3 H, J = 7 Hz), 1.32 (s, 3 H), 1.34 (s, 3 H), 2.62 (m, 1 H), 4.51 (d, 2 H, J = 5 Hz), 7.32 (m, 5 H), 9.92 (d, 1 H, J = 2 Hz); IR 2900, 1720, 1540, 1470, 1150, 1040, 730.

***trans*-2,3-Dimethyl-5-heptene-2,4-diols (11a and 12a).** A solution of *trans*-1-propenyllithium was prepared from 30% lithium dispersion in mineral oil (4.0 g, 0.17 mol) and *trans*-1-chloropropene (3.6 g, 47 mmol) and cooled to −78 °C. Aldehyde **9** (0.67 g, 5.8 mmol) in ether (5 mL) was added dropwise, and the mixture was stirred for 1 h. The reaction mixture was warmed to −20 °C and slowly quenched with saturated NH_4Cl solution (4 mL). The aqueous layer was drawn off, and the solution was dried (Na_2SO_4). After filtration, the solution was concentrated and the residue purified by rotary TLC using ether/hexane (2:3). Compound **11a** was obtained as 100 mg of a colorless oil, and **12a** gave 200 mg of white crystals (mp 67–69 °C from ether). Another 60 mg of mixed fractions was isolated to give a total yield of 360 mg (39%). Compound **11a**: R_f = 0.18 (50% ether/hexane); GC (3P) 6.9 min; $[\alpha]_D$ = +2.6 (0.2, EtOH); ^1H NMR ($CDCl_3$) 0.99 (d, 3 H, J = 7 Hz), 1.23 (s, 3 H), 1.37 (s, 3 H), 1.44 (m, 1 H), 1.71 (d, J = 6 Hz), 2.61 (s, 2 H), 4.64 (d, 1 H, J = 5 Hz), 5.53 (dd, 1 H, J = 5, 16 Hz), 5.65 (m, 1 H); IR 3500. MS m/e (% base) 140 (4), 125 (13), 82 (42), 71 (48), 70 (100), 67 (53), 59 (24), 55 (43), 43 (63). Compound **12a**: R_f = 0.14 (50% ether/hexane); GC (3P) 7.0 min; $[\alpha]_D$ = −3.0 (0.17, EtOH);[22] ^1H NMR ($CDCl_3$) 0.72 (d, 3 H, J = 7 Hz), 1.21 (s, 3 H), 1.22 (s, 3 H), 1.61 (m, 1 H), 1.71 (d, 3 H, J = 7 Hz), 3.72 (s, 2 H), 4.01 (t, 1 H, J = 9 Hz), 5.45 (m, 1 H), 5.66 (m, 1 H); IR 3450, 2995, 2950, 1450, 1415, 1390, 1175, 1005, 965, 940, 920; MS m/e (% base) 140 (3), 125 (10), 82 (54), 71 (42), 70 (100), 67 (63), 59 (26), 55 (44), 43 (74). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.41; H, 11.59.

2,3-Dimethyl-3-(phenylmethoxy)-5-hepten-4-ol (11b + 12b). A solution of *trans*-1-propenyllithium in THF was prepared using lithium dispersion (2.0 g, 30% in mineral oil, 86 mmol) and *trans*-1-chloropropene (2.0 g, 26 mmol) under Ar and cooled to −95 °C (internally measured) using a methanol/liquid N_2 bath. A solution of **10** (2.0 g, 9.7 mmol) in THF (20 mL) was placed in a dropping funnel and cooled with a dry ice jacket. This solution was added dropwise to the alkyllithium at such a rate that the temperature of the reaction did not exceed −85 °C. The reaction mixture was stirred for 30 min and quenched with half saturated NH_4Cl (2 mL). The aqueous layer was drawn off, and

(21) (a) Yamada, S.; Shiraishi, M.; Ohmori, M.; Takayama, H. *Tetrahedron Lett.* **1984**, *25*, 3347–3350. (b) The rotation of diol **5** is concentration and solvent dependent. Characterization is best carried out on the monoacetate.[23] Our monoacetate gives $[\alpha]_D$ = −18.05 (0.56, $CHCl_3$) [lit.[23] $[\alpha]_D$ = −27.1 ($CHCl_3$)].

(22) Formation of the Mosher ester of **12a** showed >92% or greater optical purity based on NMR integration of the CH_3O signal.

(23) Matsumoto, T.; Takahasi, M.; Kashihara, Y. *Bull Chem. Soc. Jpn.* **1979**, *52*, 3329–3336.

the solution was dried ($MgSO_4$). After the solution was concentrated under reduced pressure, the crude compound was purified by flash column chromatography to yield 2.0 g (83%) of alcohols **11b** and **12b**. The ^1H-NMR spectrum showed that the crude mixture contained 95% erythro isomer **11b** and 5% threo isomer **12b**. (The product distribution was 84% of **11b** and 16% of **12b** if the addition of the aldehyde was conducted at −78 °C.) Compound **11b**: R_f = 0.43 (20% ether/hexane with 0.5% methanol); GC (3P) 7.3 min; ^1H NMR ($CDCl_3$) 1.03 (d, 3 H, J = 7 Hz), 1.33 (s, 3 H), 1.46 (s, 3 H), 1.52 (q, 1 H, J = 6 Hz), 1.71 (d, 3 H, J = 6 Hz), 3.68 (s, 1 H), 4.47 (d, 2 H, J = 3 Hz), 4.69 (d, 1 H, J = 5 Hz), 5.49 (dd, 1 H, J = 4, 15 Hz), 5.68 (m, 1 H), 7.31 (m, 5 H); ^{13}C NMR 7.54, 23.94, 24.79, 47.97, 64.06, 71.86, 78.17, 125.30, 127.12, 127.34, 127.48, 128.53, 133.40; UV (MeOH) 218; MS *m/e* (% base) 149 (14), 125 (8), 92 (47), 91 (100), 71 (16), 70 (47), 55 (12), 43 (24). Compound **12b**: R_f = 0.38 (20% ether/hexane with 0.5% methanol); GC (3P) 7.3 min; ^1H NMR ($CDCl_3$) 0.77 (d, 3 H, J = 7 Hz), 1.05 (m, 1 H), 1.12 (s, 3 H), 1.18 (s, 3 H), 1.82 (d, 3 H, J = 6 Hz), 3.72 (t, 1 H, J = 9 Hz), 4.31 (d, 1 H, J = 11 Hz), 4.61 (d, 1 H, J = 11 Hz), 5.01 (s, 1 H), 5.31 (dd, 1 H, J = 9, 16 Hz), 5.72 (m, 1 H), 7.33 (m, 5 H). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.31; H, 9.75. Found: C, 77.75; H, 9.39. Compound **12b** could also be prepared from **12a**.[13]

***trans*-2,3-Dimethyl-5-heptene-2,4-diol 4-Dimethylacryloyl Ester (13a).** Compound **11a** (237 mg, 1.5 mmol) was dissolved in THF (10 mL) under N_2 and cooled to −78 °C. *n*-Butyllithium (0.80 mL, 2.6 M in hexane, 2.1 mmol) was added dropwise, the mixture was stirred for 30 min, and then 3,3-dimethylacryloyl chloride (0.22 mL, 2.0 mmol) was added dropwise to the solution. After the reaction mixture was stirred at −78 °C for 30 min, water (0.5 mL) and ether (10 mL) were added, and the reaction mixture was allowed to warm to rt. The water was removed, and the organic layer dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (50% ether/heptane) to yield 210 mg (58%) of a colorless oil (**13a**): R_f = 0.30 (50% ether/heptane); GC (3P) 6.4 min; ^1H NMR ($CDCl_3$) 1.01 (d, 3 H, J = 7 Hz), 1.16 (s, 3 H), 1.22 (s, 3 H), 1.35 (m, 1 H), 1.68 (d, 3 H, J = 7 Hz), 1.89 (s, 3 H), 2.17 (s, 3 H), 5.47 (dd, 1 H, J = 7, 5 Hz), 5.65 (m, 2 H).

2,3-Dimethyl-2-(phenylmethoxy)-5-hepten-4-ol Dimethylacryloyl Ester (13b). A solution of **11b** (1.0 g, 4.0 mmol) in THF (20 mL) under N_2 was stirred and cooled to −78 °C. *n*-Butyllithium (2.3 mL, 1.85 M in hexane) was added dropwise with rapid stirring. The solution was stirred at this temperature for 10 min, warmed to −25 °C, and stirred for 1 h. 3,3-Dimethylacryloyl chloride (0.47 mL, 42 mmol) in THF (6 mL) was then added dropwise, and the reaction mixture was stirred an additional 30 min. After quenching with water (2 mL) the organic layer was dried ($MgSO_4$). After the solvent was removed under reduced pressure, the residue was purified by rotary chromatography. Some starting material was recovered (0.30 g). The product **13b** was obtained as 0.85 g (90%, corrected for recovered starting material) of a colorless oil: R_f = 0.58 (30% ether/hexane); GC (3P) 9.0 min; ^1H NMR ($CDCl_3$) 1.13 (d, 3 H, J = 7 Hz), 1.28 (s, 6 H), 1.74 (d, 3 H, J = 6 Hz), 1.92 (s, 3 H), 1.98 (q, 1 H, J = 7 Hz), 2.23 (s, 3 H), 4.48 (s, 2 H), 5.54 (dd, 1 H, J = 6, 6 Hz), 5.66 (q, 1 H, J = 6 Hz), 5.74 (s, 1 H), 5.84 (d, 1 H, J = 5 Hz), 7.36 (m, 5 H); ^{13}C NMR 8.83, 17.45, 19.98, 22.20, 23.61, 27.12, 45.56, 63.02, 72.06, 77.15, 116.36, 126.31, 126.88, 127.08, 127.88, 128.06, 130.32, 139.68, 155.94, 165.54; MS *m/e* (% base) 247 (4), 191 (3), 181 (3), 150 (3), 149 (29), 139 (4), 125 (3), 124 (17), 109 (10), 91 (100), 83 (81), 82 (21), 55 (15). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.23; H, 9.15.

***trans*-2-(1-Methylethenyl)-7-hydroxy-3,6,7-trimethyl-4-octenoic Acid (14a).** 2,2,5,5-Tetramethylpiperidine (74 mg, 52 mmol) was cooled to −78 °C under N_2. *n*-Butyllithium in hexane (0.22 mL, 2.6 M, 0.57 mmol) was added dropwise. The reaction mixture was stirred for 1 h, and then **13a** (60 mg, 0.25 mmol) in THF was added dropwise. After the mixture was stirred for an additional 15 min, chlorotrimethylsilane (54 mg, 0.50 mmol) was added and the reaction mixture heated slowly to reflux. When the reaction was complete (ca. 2 h), the reaction mixture was cooled to rt, a 15% KOH solution (2 mL) was added, and the reaction mixture was stirred overnight. Most of the THF was then removed under reduced pressure. The aqueous layer was washed with CH_2Cl_2, and the aqueous layer was acidified with dilute HCl and extracted twice with ether. The ether layers were dried with sodium sulfate, filtered, and concentrated. The 40 mg (66%) of white solid product **14a** obtained had a suitable ^1H-NMR spectrum and GC analysis. The solid was further purified by preparative TLC for elemental analysis: R_f = 0.18 (60% ether/heptane; GC (3P) 7.2 mL; ^1H NMR ($CDCl_3$) 0.94 (d, 3 H, J = 5 Hz). 0.96 (d, 3 H, J = 5 Hz), 1.11 (s, 3 H), 1.51 (s, 3 H), 1.79 (s, 3 H), 2.14 (m, 1 H), 2.63 (m, 1 H), 2.86 (d, 1 H, J = 11 Hz), 4.97 (s, 2 H), 5.47 (m, 2 H); ^{13}C NMR 15.14, 18.02, 19.80, 26.22, 27.12, 36.83, 47.68, 59.92, 72.68, 115.96, 132.35, 134.74, 140.65, 177.23. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.60; H, 10.27.

***trans*-2-(1-Methylethenyl)-7-(phenylmethoxy)-3,6,7-trimethyl-4-octenoic Acid (14b).** This compound was prepared by the same method as for **14a** using 2,2,5,5-tetramethylpiperidine (370 mg, 2.6 mmol), *n*-butyllithium (0.15 mL, 1.85 M in hexane), **13b** (0.84 g, 2.5 mmol), and chlorotrimethylsilane (29 mg, 2.7 mmol). The crude product was purified by flash chromatography to yield 510 mg (60%) of a yellowish oil: R_f = 0.40 (50% ether/heptane); GC (3P) 10.2 min; ^1H NMR ($CDCl_3$) 0.96 (d, 3 H, J = 7 Hz), 1.02 (d, 3 H, J = 7 Hz), 1.16 (s, 3 H), 1.21 (s, 3 H), 1.82 (s, 3 H), 2.43 (m, 1 H), 2.67 (m, 1 H), 2.88 (d, 1 H, J = 11 Hz), 4.45 (s, 2 H), 5.01 (s, 2 H), 5.36 (dd, 1 H, J = 8, 15 Hz), 5.63 (dd, 1 H, J = 8, 15 Hz), 7.36 (m, 5 H); ^{13}C NMR 15.00, 18.17, 19.84, 22.43, 23.76, 37.18, 45.33, 60.20, 63.35, 77.23, 116.20, 127.07, 127.23, 128.27, 133.03, 133.63, 140.15, 178.40; MS *m/e* (% base) 181 (6), 150 (5), 149 (36), 135 (14), 107 (5), 91 (100). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.69; H, 8.85.

***trans*-2-(1-Methylethenyl)-7-(phenylmethoxy)-3,6,7-trimethyl-4-octenal (15).** Acid **14b** (200 mg, 0.6 mmol) in ether (5 mL) was reduced in $LiAlH_4$ (75 mg, 2.0 mmol) to yield 145 mg of the alcohol as a colorless oil. A sample was purified by preparative TLC for analysis: R_f = 0.32 (40% ether/hexane); IR 3400; ^1H NMR ($CDCl_3$) 0.92 (d, 3 H, J = 6 Hz), 1.05 (d, 3 H, J = 7 Hz), 1.18 (s, 3 H), 1.21 (s, 3 H), 1.68 (s, 3 H), 2.07 (m, 1 H), 2.41 (m, 1 H), 3.40 (t, 1 H, J = 9 Hz), 3.63 (dd, 1 H, J = 4, 15 Hz), 4.44 (s, 2 H), 4.85 (s, 1 H), 4.98 (s, 1 H), 5.27 (dd, 1 H, J = 5, 14 Hz), 5.51 (dd, 1 H, J = 5, 14 Hz), 7.32 (m, 5 H); MS *m/e* (% base) 150 (3), 149 (30), 121 (3), 107 (6), 91 (100). Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.72; H, 10.21. This alcohol (130 mg, 41 mmol) was oxidized using oxalyl chloride (105 mg, 0.83 mmol), DMSO (96 mg, 1.2 mmol), and triethylamine (272 mg, 2.7 mmol). The crude product was suitable for use in the next step as judged by TLC and ^1H-NMR analysis. The yield was 120 mg (92%) of compound **15** as off-white oil: R_f = 0.70 (30% ether/hexane); IR 2950, 1730, 1640; ^1H NMR ($CDCl_3$) 0.99 (d, 3 H, J = 6 Hz), 1.02 (d, 3 H, J = 7 Hz), 1.16 (s, 3 H), 1.19 (s, 3 H), 1.74 (s, 3 H), 2.40 (m, 1 H), 2.73 (m, 2 H), 4.43 (s, 2 H), 4.90 (s, 1 H), 5.08 (s, 1 H), 5.31 (dd, 1 H, J = 7, 16 Hz), 5.58 (dd, 1 H, J = 8, 15 Hz), 7.32 (m, 5 H), 9.46 (d, 1 H, J = 3 Hz); ^{13}C NMR 15.25, 18.48, 21.75, 22.72, 23.63, 36.02, 45.62, 46.04, 63.38, 66.23, 115.94, 127.05, 127.20, 127.45, 128.28, 128.38, 133.22, 133.76, 139.59, 140.16, 200.82; MS *m/e* (% base) 165 (14), 149 (19), 147 (4), 137 (8), 95 (9), 91 (100), 43 (10).

3-[Dimethyl(1,1-dimethylethyl)siloxy]-7-(1-methylethenyl)-12-(phenylmethoxy)-8,11,12-trimethyltrideca-1,3,9-trien-6-ol (17). A solution of 3-[dimethyl(1,1-dimethylethyl)siloxy]-1,4-pentadiene (131 mg, 0.67 mmol) in THF (2 mL) under N_2 was stirred and cooled to −78 °C. A solution of *sec*-butyllithium (0.5 mL, 1.4 M) in cyclohexane was added dropwise, and the solution stirred for 30 min. Compound **15** dissolved in 2 mL of THF was then added dropwise to the pentadienyl anion solution. The reaction mixture was stirred for 15 min and then quenched with saturated NH_4Cl solution (0.5 mL). Ether extraction and preparative TLC gave 77 mg (67%) of a mixture of epimers of **17** in a ratio of 1:2.5 (GC and ^1H NMR). The isomers can be separated by TLC if desired. Compound **17** (less polar isomer): R_f = 0.27 (10% ether/hexane); GC (3P) 14.4 min; ^1H NMR ($CDCl_3$) 0.09 (s, 3 H), 0.10 (s, 3 H), 0.92 (d, 3 H, J = 6 Hz), 0.99 (s, 9 H), 1.06 (d, 3 H, J = 7 Hz), 1.17 (s, 3 H), 1.21 (s, 3 H), 1.77 (s, 3 H), 2.01 (m, 1 H), 2.40 (m, 2 H), 3.78 (m, 1 H), 4.43 (s, 2 H), 4.73 (s, 1 H), 4.88 (s, 1 H), 4.95 (s, 1 H), 4.98 (s, 1 H), 5.29 (d, 1 H, J = 18 Hz), 5.51 (m, 2 H), 6.17 (dd, 1 H, J = 11, 17 Hz), 7.32 (m, 5 H). Compound **17** (more polar isomer): R_f = 0.23 (10% ether/hexane); GC (3P) 14.6 min; ^1H NMR ($CDCl_3$) 0.08 (s, 3 H), 0.09 (s, 3 H). 0.93 3 (d, 6 H, J = Hz), 0.99 (s, 9 H), 1.05 (d, 3 H,

J = 7 Hz), 1.17 (s, 3 H), 1.21 (s, 3 H), 1.68 (s, 3 H), 2.01 (m, 1 H), 2.40 (m, 2 H), 3.68 (m, 1 H), 4.43 (s, 2 H), 4.73 (s, 1 H), 4.88 (s, 1 H), 4.94 (s, 1 H), 4.96 (s, 1 H), 5.27 (d, 1 H, J = 17 Hz), 5.50 (m, 2 H), 6.17 (dd, 1 H, J = 11, 7 Hz), 7.32 (m, 5 H). Calcd for $C_{32}H_{52}O_3$: C, 79.29; H, 10.81. Found (epimer mixture): C, 79.50; H, 10.54.

2-[Dimethyl(1,1-dimethylethyl)siloxy]-6-methyl-7-[5-(phenylmethoxy)-1,4,5-trimethyl-*trans*-2-hexenyl]bicyclo-[4.3.0]non-2-en-8-ol (18). Compound **17** (15 mg) was dissolved in freshly dried and distilled toluene and placed in a thick-walled pressure tube, which had been washed with NH_4OH and dried. The tube was flushed with N_2 while being cooled in an acetone/dry ice bath. After the tube was sealed, it was placed in an oil bath and slowly heated to 170 °C. This temperature was maintained for 16–20 h. The tube was cooled in ice and opened. The toluene was removed under reduced pressure, and the product was purified by preparative TLC. The yield was 13 mg (86%) of a mixture of isomers **18**: R_f = 0.49 (15% ether/heptane); ^{1}H NMR ($CDCl_3$) 0.10 (s, 6 H), 0.92 (s, 9 H), 1.20 (s, 3 H), 1.22 (s, 3 H), 4.11 (m, 1 H), 4.44 (s, 2 H), 5.31 (m, 1 H), 5.56 (m, 2 H), 7.73 (m, 5 H).

2-[Dimethyl(1,1-dimethylethyl)siloxy]-6-methyl-7-[5-(phenylmethoxy)-1,4,5-trimethyl-2-hexenyl]bicyclo[4.3.0]-non-2-en-8-ol Tetramethylphosphorodiamidate (20). Compound **18** (55 mg, 0.11 mmol) was dissolved in freshly distilled dry TMEDA (1.4 mL), and THF (5.5 mL) under N_2 was cooled to −23 °C. A solution of n-butyllithium in hexane (1.86 M, 0.25 mL, 0.46 mmol) was added dropwise with rapid stirring. The reaction was stirred for 3–5 min. Bis(dimethylamino)-phosphorochloridate (0.075 mL, 0.50 mmol) was added, and the reaction was slowly warmed to 70 °C. After 1 h, TLC showed no starting material. The reaction mixture was cooled and quenched with water (0.5 mL). The reaction mixture was extracted twice with ether, and the organic layers were washed with water. The solution was dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative TLC to yield 48 mg (69%) of a yellow oil, compound **20**: R_f = 0.48 (50% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$) 0.08 (d, 3 H, J = 7 Hz), 1.00 (s, 3 H), 0.90 (s, 3 H), 0.92 (s, 9 H), 1.57 (d, 2 H, J = 7 Hz), 1.59 (s, 3 H), 1.20 (s, 3 H), 2.63 (dd, 12 H, J = 10, 4 Hz), 4.43 (s, 2 H), 4.74 (m, 1 H), 5.39 (m, 3 H), 7.33 (m, 5 H).

***cis*-6-Methyl-7-(5-hydroxy-1,4,5-trimethyl-2-hexenyl)-2,3,3a,6,7,7a-hexahydroindan-4(5*H*)-one (3).** A variation of the general procedure of Ireland was used for the removal of the phosphoramide and benzyl functions.[19] Methylamine (10–15 mL) was condensed in a round-bottom flask in an ice bath under argon using a condenser filled with dry ice/acetone. Thin Li foil (3 mg) was added, and the reaction mixture was stirred rapidly. A deep blue color resulted. A solution of **20** (22 mg, 0.03 mmol) in THF (1 mL) was added dropwise. The reaction was stirred at 0 °C for 1 h. The ice bath and condenser were removed, and the CH_3NH_2 was allowed to evaporate. The residue was cooled in an ice bath and cautiously quenched with cold water (2 mL). The mixture was extracted several times with ether. The ether layers were dried with $MgSO_4$ and concentrated. The residue was purified by TLC to yield 5 mg (36%) of compound **21** (R_f of 0.59 in 1:3 ethyl acetate/heptane). The ^{1}H-NMR spectrum showed the absence of the phosphoramide and benzyl groups. Compound **21** (5 mg) was dissolved in a solution of acetic acid (3 mL), water (1 mL), and THF (1 mL). The solution was heated at 70 °C for 1 h. The solution was concentrated under reduced pressure, CCl_4 was added, and the solvent was removed again. The residue was dissolved in ether, washed with a small amount of saturated $NaHCO_3$, dried with Na_2SO_4, and concentrated. The crude product was purified by preparative TLC to yield 2 mg (56%) of compound *cis*-**3** as an oil: R_f = 0.42 (25% ethyl acetate in heptane); ^{1}H NMR ($CDCl_3$) 0.99 (d, 3 H, J = 7 Hz), 1.09 (d, 3 H, J = 6 Hz), 1.05 (s, 3 H), 1.13 (s, 3 H), 1.16 (s, 3 H), 5.34 (m, 2 H). The structure was confirmed by correlation with an authentic sample prepared as follows. Diol **22** was obtained from Hoffman-LaRoche courtesy of Dr. Enrico Baggiolini. This compound was oxidized according to their method[5a] to *trans*-**3**. Trans isomer **3** (~5 mg) was dissolved in benzene, several drops of trifluoroacetic acid were added, and the cis/trans epimerization was continued (TLC) until approximately 90% of *trans*-**3** was converted into *cis*-**3**.[20] This material was identical with the ketone obtained above from compound **21** by TLC and ^{1}H-NMR analysis.

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Supplementary Material Available: X-ray data for **12a** as well as 300-MHz ^{1}H-NMR spectra for compounds **3**, **5–7**, **10–15**, **17**, **18**, and **20** (26 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.