Stereoselective Synthesis and Thermal Rearrangement of the First Analogue of (7Z)-Vitamin D (I)

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · MAY 1991

Impact Factor: 4.72 · DOI: 10.1021/jo00011a024

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2*RS* Isomer **41**: ^{1}H NMR δ (discernible from mixture) 1.10 (d, 3, J = 7.2), 2.59 (m, 1), 3.27 (s, 3), 3.70 (t, 1, J = 8.4), 5.2-5.7 (m, 3).

Deprotonation in THF/23% HMPA. By use of the procedure outlined above, ester **39** was deprotonated in THF/23% HMPA, silylated, and rearranged to give 67% of a 25:75 mixture of acids **41** and **42**.[28,29]

2*SR* Isomer **42**: ^{1}H NMR δ (discernible from mixture) 1.18 (d, 3, J = 7.2), 2.67 (m, 1), 3.31 (s, 3), 3.84 (dd, 1, J = 7.2, 5.6), 5.2-5.8 (m, 3).

(2*RS*,3*SR*,4*SR*)-4-(Iodomethyl)-3-methoxy-2-methyl-γ-butyrolactone (43) and (2*RS*,3*SR*,4*RS*)-4-(Iodomethyl)-3-methoxy-2-methyl-γ-butyrolactone (44). By use of the procedure described for the preparation of iodo lactones **22** and **23**, a 87:13 mixture of acids **41** and **42** was cyclized to give a 56% yield of iodo lactones **43** and **44** that were separated by silica gel chromatography[53] (pentane/ether, 2:1). The major isomer, lactone **44**, was recrystallized from ether/pentane: mp 85 °C; IR 2980, 1750, 1200, 750, 650 cm^{-1}; R_f = 0.40 (pentane/ether, 3:1); ^{1}H NMR δ 1.31 (d, 3, J = 7.2), 2.74 (qd, 1, J = 7.2, 4.8), 3.41 (dd, 1, J = 8.7, 8.1), 3.43 (dd, 1, J = 8.7, 4.6), 3.56 (s, 3), 4.06 (dd, 1, J = 4.8, 3.3), 4.52 (ddd, 1, J = 8.1, 4.6, 3.3); ^{13}C NMR δ -1.1, 8.9, 42.8, 62.0, 80.1, 82.0, 177.7. Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.11. Found: C, 31.21; H, 4.18.

The minor isomer, lactone **43**: R_f = 0.35 (pentane/ether, 3:1); IR (neat) 2920, 2820, 1700, 1420, 1280, 1030 cm^{-1}; ^{1}H NMR δ 1.25 (d, 3, J = 7.2), 2.82 (qd, 1, J = 7.2, 6.3), 3.15 (dd, 1, J = 10.5, 8.1), 3.38 (dd, 1, J = 10.5, 3.9), 3.44 (s, 3), 3.94 (dd, 1, J = 6.3, 1.2), 4.49 (ddd, 1, J = 8.1, 3.0, 1.2); ^{13}C NMR δ 3.4, 8.8, 38.5, 58.0, 81.5, 81.7, 177.6. Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.11. Found: C, 31.23; H, 4.18.

(2*SR*,3*SR*,4*RS*)-4-(Iodomethyl)-3-methoxy-2-methyl-γ-butyrolactone (45). By use of the procedure described for the preparation of iodo lactones **22** and **23**, a 25:75 mixture of acids **41** and **42** was cyclized to give a 61% yield of an unseparable mixture of iodo lactones **43**, **44**, and **45**. The major isomer, lactone **45**: R_f = 0.45 (pentane/ether, 2:1); IR (neat) 2970, 2920, 2820, 1775, 1280, 1040 cm^{-1}; ^{1}H NMR δ 1.31 (d, 3, J = 7.5), 2.80 (qd, 1, J = 7.5, 1.2), 3.30-3.50 (m, 2), 3.39 (s, 3), 3.76 (dd, 1, J = 4.5, 1.2), 4.71 (ddd, 1, J = 7.2, 6.3, 1.2); ^{13}C NMR δ -0.7, 14.2, 41.6, 58.2, 81.1, 83.2, 177.9. Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.11. Found: C, 31.05; H, 4.20.

(2*S*)-[2-Methyl-5(*R*)-(2-propenyl)-2-cyclohexen-1(*R*)-yl]propionic Acid (67) and (2*R*)-[2-Methyl-5(*R*)-(2-propenyl)-2-cyclohexen-1(*R*)-yl]propionic Acid (68) by Deprotonation in THF. Carvyl propanoate (**62**) was enolized in THF as described above for propanoate **12**. Subsequent Claisen rearrangement led to a 25:75 mixture of acids **67** and **68** in 56% yield.

2*R* Isomer **68**: R_f = 0.20 (1:1 ether/*n*-hexane); bp 120 °C (0.1 mmHg); IR (neat) 3030, 2900, 1680, 1225, 875 cm^{-1}; ^{1}H NMR δ 0.96 (d, 3, J = 6.9), 1.65 (s, 3), 1.70 (s, 3), 2.92 (m, 2), 4.69 (bs, 2 H), 5.59 (t, 1, J = 2.1), 10.80 (bs, 1); ^{13}C NMR δ 9.6, 21.1, 21.3, 29.1, 31.5, 40.1, 41.6, 42.5, 109.2, 126.1, 133.7, 150.1, 183.0. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.90; H, 9.71.

Deprotonation in THF/45% DMPU. Carvyl propanoate (**62**) was enolized in THF/45% DMPU as described above for propanoate **12**. Subsequent Claisen rearrangement led to a >98:2 mixture of acids **67** and **68** in 60% yield.

2*S* Isomer **67**: ^{13}C NMR δ 13.2, 21.2, 21.9, 31.4, 32.2, 41.3, 42.1, 44.0, 109.1, 125.2, 134.7, 150.2, 182.4. For additional data, see ref 52.

Deprotonation in THF/23% HMPA. See ref 52.

(3*S*,3a*R*,5*R*,7*S*,7a*S*)-2,3,3a,4,5,6,7,7a-Octahydro-7-bromo-3,7a-dimethyl-5-(2-propenyl)-1-oxainden-2-one (69) and (3*R*,3a*R*,5*R*,7*S*,7a*S*)-2,3,3a,4,5,5,7,7a-Octahydro-7-bromo-3,7a-dimethyl-5-(2-propenyl)-1-oxainden-2-one (70). For the experimental procedure, see ref 52.

Isomer **70**: R_f = 0.25 (pentane/ether, 5:1); $[\alpha]^{25}_D$ +13.86° (*c* 0.94, $CHCl_3$); IR 2910, 1705, 1430, 1365, 1210, 1090, 1040 cm^{-1}; ^{1}H NMR δ 1.26 (d, 3, J = 7.2), 1.62 (s, 3), 1.77 (s, 3), 1.96 (m, 2), 2.15 (m, 2), 2.46 (m, 2), 2.66 (dq, 1, J = 11.1, 7.2), 4.38 (dd, 1, J = 12.5, 5.4), 4.82 (s, 1), 4.88 (s, 1); ^{13}C NMR δ 15.3, 22.0, 23.4, 26.9, 36.9, 39.8, 40.1, 50.6, 54.3, 84.9, 111.1, 146.6, 178.0. Anal. Calcd for $C_{13}H_{19}O_2Br$: C, 54.37; H, 6.67. Found: C, 54.12; H, 6.51.

Acknowledgment. We thank Dr. M. Sabat, University of Virginia, for the X-ray analysis of compound **44**.

Supplementary Material Available: Tables of coupling constants and MMX minimized geometries of halo lactones; X-ray data for lactone **44** (16 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis and Thermal Rearrangement of the First Analogue of (7*Z*)-Vitamin D[1,2]

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Received November 19, 1990

The first (7*Z*)-vitamin D analogue, **15**, was synthesized stereoselectively using, as the key step, Wittig-Horner coupling between an allylphosphine oxide anion and a α-benzoyloxy ketone. Compound **15** has the same triene system as the putative 7*Z* intermediate of the mechanism postulated by Okamura and co-workers for thermally induced [1,5]-sigmatropic hydrogen shifts in vinylallenes. Okamura's hypothesis is supported by the identity of the products of thermally induced [1,7]-sigmatropic hydrogen shifts in **15**.

Introduction

Vitamin D_3 (cholecalciferol, **1a**), the well-known calcium homeostatic prohormone,[3] is unique among the steroid hormones in lacking the steroid B ring, which is replaced by a conjugated $\Delta^{5,7,10(19)}$ triene. The presence of this structural feature gives rise to a plethora of thermal[4] and photochemical[5] rearrangements which have attracted a great deal of attention from physical organic chemists for more than two decades. Concurrently, the purely medi-

(1) Dedicated to the memory of Professor Francisco Gaviña.

(2) This paper was presented in part at the 7th Workshop on Vitamin D (Rancho Mirage, CA, April 1988).

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0022-3263/91/1956-3582$02.50/0

cinal and biochemical interest of the biological actions of cholecalciferol and its metabolites[3] (25-OH-D_3, **1b**; 1α,25-$(OH)_2$-D_3, **1c**) have motivated several synthetic approaches to **1a**, **1b**, **1c**, and their analogues.[6] From one of these approaches, the work of Okamura and co-workers on the thermal rearrangement of vinylallenes[7] has evolved a wealth of information about the thermal isomerization processes undergone by cholecalciferol and related trienes and, more specifically, about the nature of the thermal [1,7]-sigmatropic hydrogen shifts.[7]

The vinylallene rearrangement approach involves the thermolysis of compounds **2** to give the natural triene system (7*E*) of vitamin D (**1**) through a [1,5]-sigmatropic hydrogen shift, together with the isomeric trienes **5** and **6**, which arise from further rearrangements of the putative 7*Z* isomer of **1** (**4**, Scheme I). Abundant stereochemical[7d] and kinetic[7d,8] data have shed light on almost every step of this complex reaction, the postulated intermediate **4**,[7a,f] which should be derived from **2** through a competing [1,5]-H sigmatropic shift, has never been isolated or otherwise characterized.[7a,d] The only attempt at synthesizing **4** (from *iso*-tachysterol$_3$) did not succeed.[8]

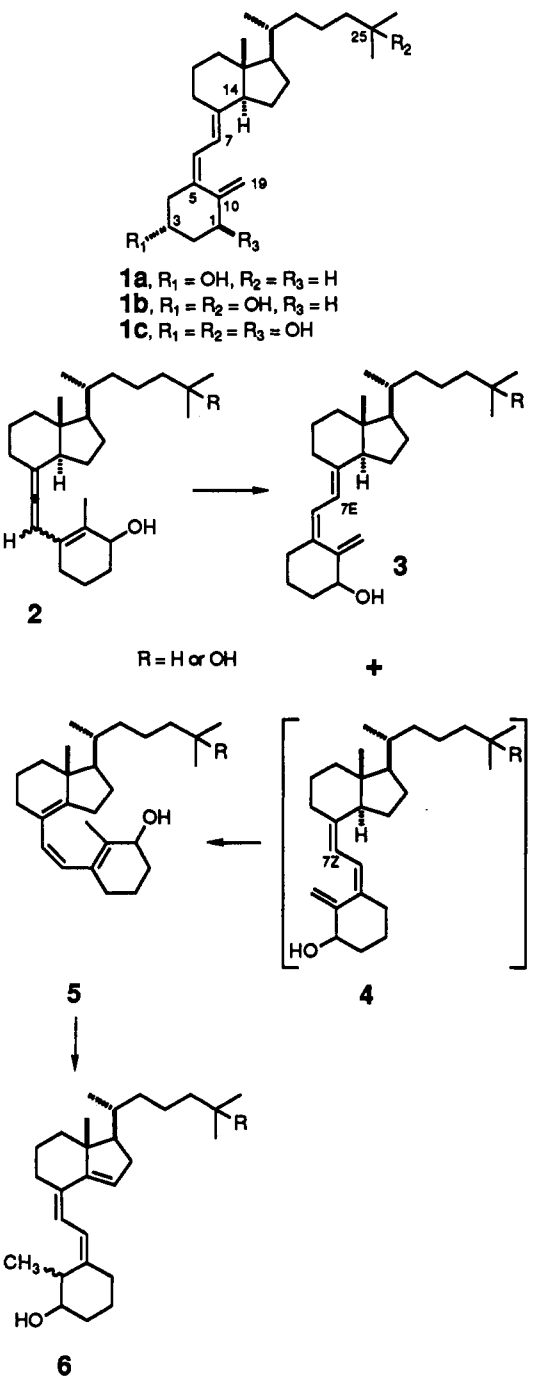
We report here that an analogue of **4** does indeed give rearrangement products corresponding to structures **5** and **6**, which supports the notion that **4** probably is the "missing triene link" in the vinylallene thermal sigmatropic shift reaction hypothesized by Okamura and co-workers.[7]

Results and Discussion

We have accidentally obtained the first example of the 7*Z* cholecalciferol triene moiety present in **4** (Scheme I). As part of an ongoing project for the purification of biological vitamin D receptors[3] by affinity chromatography, we planned a synthesis of 9α-hydroxycholecalciferol (**7**, Scheme II) involving the hydroxylation[9] of the kinetic enolate of Grundmann's ketone (**9**, readily available from vitamin D_3)[10] followed by protection of the resulting hydroxy ketone **10**. We reasoned that Wittig–Horner reaction of a protected form of **10** with the anion of the known phosphine oxide **16**[10] should provide the bis-protected form of triene **7**, but this proved not to be the case.

α-Hydroxylation of **9** proceeded with high regio- and stereoselectivity: the kinetic enolate of **9** (LDA, −80 °C)[6e] was treated with oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH)[9e] to give **10** in 75% yield, or alternatively, the enolate generated from **9** was trapped with TMSCl to afford **17**, which was treated with *m*-CPBA without further purification to give a mixture of **10** and **18**, which was deprotected with 5% aqueous NaOH (overall yield 51%). The axial orientation of the newly introduced hydroxyl group was deduced from the appearance of H9 in the ^{1}H NMR spectrum of **10** as a triplet with an apparent splitting of 3.5 Hz (δ 4.00), indicating the equatorial (β) orientation of this hydrogen atom. That the stereochemistry at C14 with trans hydrindane fusion was unchanged was deduced from the strong anisotropic downfield shift shown by H14 (δ 3.12), which is presumably due to the strong deshielding effect of the axial 9α-hydroxyl group. Benzoylation or silylation of the hydroxyl group of **10** was achieved using standard procedures.[11]

Scheme I



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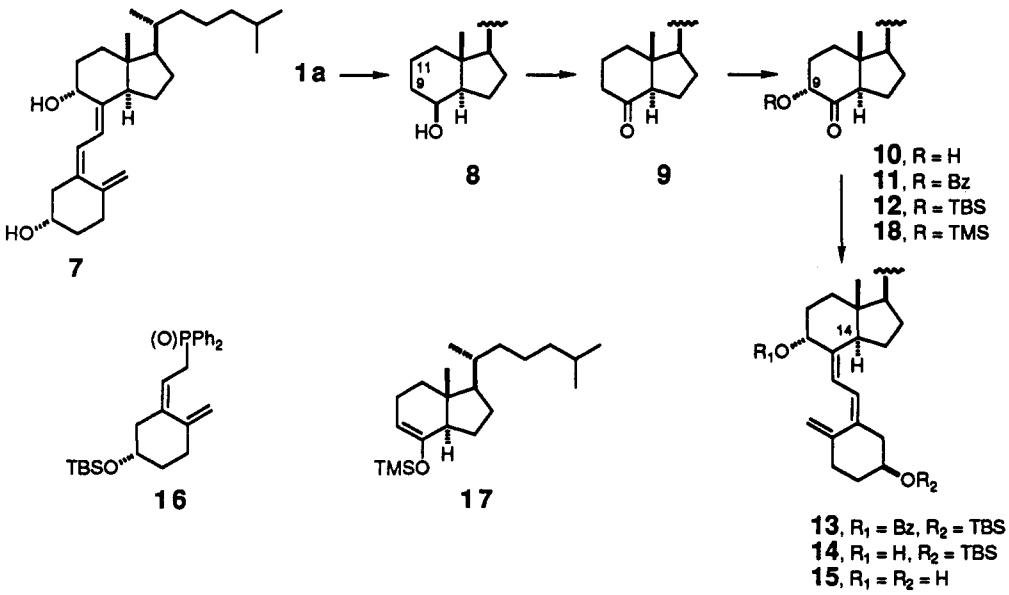
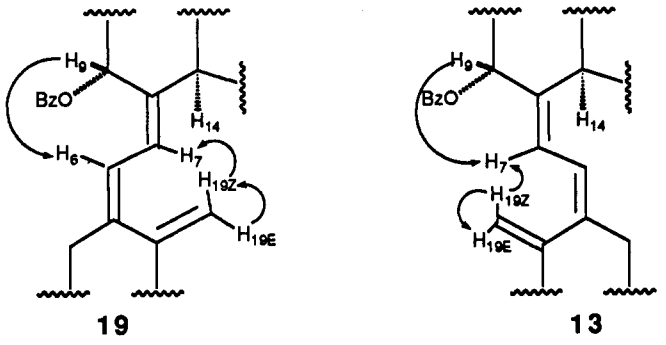
Scheme II



Scheme III



Wittig–Horner reaction[12] of the ketobenzoate 11 with the lithio anion derived from 16[10] (THF, −90 °C to room temperature) afforded 13 as the sole coupling product in 71% yield (vide infra). The triene nature of this product was apparent from its ^{1}H NMR spectrum, which featured an AB system at δ 6.59 and 6.28 (2 H, J = 11.4 Hz) and two broad singlets at δ 5.07 and 4.79 (1 H each). Definitive proof of the stereochemistry of the triene moiety was obtained from NOE difference experiments.[13]

Scheme III shows the expected NOE enhancements for the two possible geometries of the coupled product, the 7*E* isomer **13** and the 7*Z* isomer **19**. NOE experiments supported structure **13**: irradiation of H19*E* (δ 5.07) showed enhancement of H19*Z* (δ 4.79); irradiation of H19*Z* showed enhancement of H19*E* and H7 (δ 6.59); irradiation of H7 showed enhancement of H19Z and H9α (δ 5.48); irradiation of H9α showed enhancement of H7; and irradiation of H6 (δ 6.28) showed no detectable enhancement of any signal in the spectrum. It was thus concluded that the Wittig–Horner reaction had proceeded stereoselectively to afford only unstable (7*E*)-**13**, the analogue of (7*Z*)-vitamin D.[14]

The stereochemical outcome of the Wittig–Horner coupling is consistent with Lythgoe's proposal that the interactions of H6 in the transition state are responsible for the stereoselectivity in this kind of coupling.[15] In the transition state leading to **13** the largest steric interaction experienced by H6 must arise from the 9α-benzoyloxy substituent, which forces the newly formed double bond at C7 to be 7*E*.[14]

We next attempted the Wittig–Horner coupling with the silyloxy ketone **12**, but only starting materials were recovered from the reaction mixture after chromatography. When the unprotected hydroxy ketone **10** was subjected to our coupling conditions (−90 °C to room temperature) no reaction was observed. We reasoned that since nucleophile should approach from the more accesible α-face,[7b] the size of the group protecting the 9α-hydroxy group must influence the outcome of the coupling reaction. Molecular mechanics calculations on **11** and **12**[16] show that **12** adopts a minimal energy conformation with the substituents on the silicon atom effectively shielding the carbonyl group from nucleophilic attack. The less bulky, more planar benzoate group of **11** lies farther away from the C9–C11 bond, out of the path of the nucleophile attacking the C8 carbonyl group.

Deprotection of **13** was achieved by reaction with $LiAlH_4$ to afford in 85% yield the alcohol **14**, which was treated with $(Bu)_4NF$ to give the diol **15** in 60% yield. The synthesis of **15** from **9** was thus completed in five steps and 30% overall yield.

Thermal Rearrangement Studies

The thermal rearrangement behavior of **15** was studied in order to verify Okamura's hypothesis.[7a,d] The products expected from **15**, by analogy with the postulated behavior of its 9-deoxy analogues,[7] are shown in Scheme IV. Thermolysis of **15** should yield **20b** through a [1,7]-sigmatropic hydrogen shift (C14 → C19 H migration) while **21b** and **22b** would arise from **20b** through a second

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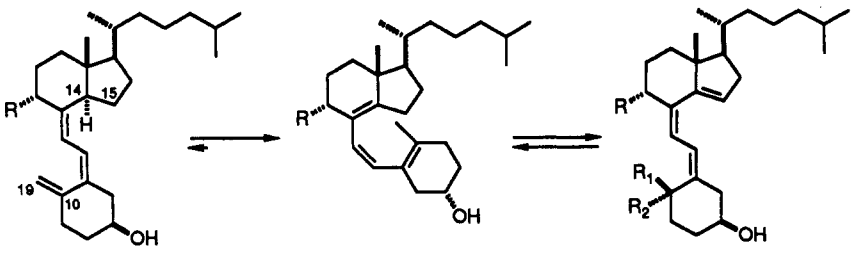
Scheme IV



15, R = OH

20a, R = H
20b, R = OH

21a, R = H, R_1 = CH_3, R_2 = H
21b, R = OH, R_1 = CH_3, R_2 = H
22a, R = H, R_1 = H, R_2 = CH_3
22b, R = OH, R_1 = H, R_2 = CH_3

[1,7]-sigmatropic hydrogen shift (C15 → C10 H migration).

A solution of **15** in toluene was refluxed (110 °C) under Ar in the dark. The progress of the reaction was followed by HPLC. After 3 h at 110 °C starting material **15** could not be detected in the reaction mixture, which was composed of two compounds whose concentrations reached a steady state after 18 h (ratio 2.0:1.0). The two products were isolated (total mass recovery 90%) and identified as 9α-hydroxy-*cis*-isotachysterol, **20b** (minor) and the triene **21b** (major), by comparison of their ^{1}H NMR spectral data with those of their known 9-deoxy analogues (H3 resonance results are unambiguous for determining C10 triene stereochemistry).[8] Triene **22b** was detected as a very minor component of the equilibrium mixture but could not be isolated at this stage. When previtamin **20b** was subjected to the above thermal conditions, the same 2.0:1.0 ratio was isolated, implying the attainment of true equilibrium with this ratio.

The almost neglible concentration of **22b** in the thermal equilibrium **15** → **20b** → **21b**, **22b** is surprising in view of the equlibrium ratio of 3.6:4.0:2.4 obtained for the 9-deoxy system **20a**:**21a**:**22a** by Schnoes.[8] At present we have no explanation for this difference. **22b** was isolated and identified from the thermolysis of **15** at a lower temperature (80 °C) and at shorter reaction times (<3 h), but under these conditions **22b** made up ≤10% of the thermolysis mixture.

Thermolysis of **15** at 80 °C allowed us to obtain data about the relative rates of formation of the trienes **20b**, **21b**, and **22b**. The primary rearrangement product is previtamin **20b**, whose concentration peaks after a 2-h reaction and then decays until the equilibrium concentration is reached. Of the two secondary rearrangement products, **22b** is formed faster than **21b**, but after peaking at 45 min the concentration decays to almost zero. This qualitative kinetic picture of the reaction is consistent with the data obtained for the 9-deoxy analogues **20a**, **21a**, and **22a**.[8]

Conclusion

Synthesis of the first analogue of (7Z)-vitamin D has been achieved through a highly stereoselective Wittig–Horner coupling of a protected α-hydroxy ketone and an allylphosphine oxide anion. Products from the thermolysis of this analogue lend support to the pathways proposed by Okamura for the thermal rearrangement of vinylallenes related to vitamin D.

Experimental Section

NMR spectra were recorded at 250.13 MHz for ^{1}H (δ, Me_4Si, $CDCl_3$) and 62.83 MHz for ^{13}C (δ, $CDCl_3$, carbon multiplicities assigned by DEPT techniques) except when otherwise stated. Low-resolution and high-resolution electron impact MS data (LREIMS and HREIMS) were obtained at 70 eV unless otherwise stated. Optical rotations were measured with Na 589-nm irradiation. Melting points are uncorrected. Kugelrohr distillation boiling points (bp) refer to the external air bath temperature. High-performance liquid chromatography (HPLC) was performed using a Phenomenex Zorbaxsil 10/250 column and a WATERS 490 programmable multiwavelength detector. Silica gel flash chromatography purifications were performed as described by Stille.[17] Ozone was generated in a Welsbach laboratory ozonator Model T-408. Thin-layer chromatography (TLC) was performed on plates of silica gel (2 × 5 cm, 0.2 mm thickness). Components were located by observation of the plates under UV light and/or by treating the plates with a phosphomolybdic acid reagent followed by heating. All reactions were performed under dry, deoxygenated argon except when otherwise stated. All glassware was dried at 150 °C overnight, assembled hot, and allowed to cool in a stream of dry argon. All transfers of liquid solutions and solvents were performed by syringe techniques or via a cannula. All solvents were freshly distilled from the appropiate drying agent before use. Et_2O, THF, toluene, and benzene were distilled from sodium benzophenone ketyl under argon. CH_2Cl_2 was distilled from P_2O_5 under argon. Pyridine was distilled from KOH and diisopropylamine was distilled twice from CaH_2 under nitrogen. MeOH was distilled from Mg. The solvents were removed under water-aspirator vacuum in a rotavapor.

De-*A*,*B*-9α-hydroxycholestan-8-one (10). A solution of lithium diisopropylamide (LDA) was prepared by adding *n*-BuLi (2.38 mL, 2.3 M in hexanes, 5.47 mmol) to a solution of diisopropylamine (0.77 mL, 5.47 mmol) in THF (10 mL) at −78 °C. After 20 min, a solution of the ketone **9**[18,19] (1.38 g, 5.21 mmol,

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(18) We have prepared Grundmann's ketone (**9**) by a two-step method that has better yield and easier workup than previously reported methods,[7d,19] avoiding the problem associated with distillation of the ketone, the epimerization of C14. **De-*A*,*B*-cholestan-8β-ol (8).** A solution of vitamin D_3 (**1a**, 8 g, 20.83 mmol) in methanol (700 mL) and pyridine (8 mL) was placed in a dry ozonation vessel with a magnetic stirring bar. The solution was cooled to −78 °C while purging with N_2. The N_2 flow was stopped and a stream of ozone was passed until a gray-blue color appeared (2 h). The ozone flow was discontinued, and the reaction mixture was purged with N_2 (−78 °C) until no ozone remained in solution (KI test). $NaBH_4$ (1 g) was added in one portion, and the resulting solution was stirred at −78 °C for 20 min while a gentle flow of N_2 was maintained. This operation was repeated twice before the reaction was allowed to reach room temperature overnight. An additional quantity of $NaBH_4$ (5 g, in portions) was added at room temperature, the resulting solution was stirred for 1 h and concentrated to a small volume, and the residue was poured into brine and extracted with Et_2O (3 × 50 mL). The combined organic layer was washed with HCl (10%, 100 mL) and water (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue obtained was flash chromatographed (3 × 30 cm, 8% EtOAc/hexanes) to yield 4.57 g of **8**[19] (89%, colorless oil): ^{1}H NMR δ 4.07 (1 H, br s, H8), 0.91 (3 H, d, *J* = 5.9 Hz, CH_3-C_{21}), 0.88 (3 H, s, CH_3-C_{18}), 0.86 (6 H, d, *J* = 6.5 Hz, CH_3-C_{27} and CH_3-C_{26}). **De-*A*,*B*-cholestan-8-one (9).** Pyridinium dichromate (12.8 g, 34.03 mmol) was added to a solution of **8** (2.09 g, 8.51 mmol, dried at 70 °C (0.3 mmHg) for 2 h) and pyridinium *p*-toluensulfonate (25 mg) in CH_2Cl_2 (150 mL). The resulting orange suspension was stirred for 15 h at room temperature. Et_2O was added, and the resulting suspension was filtered through a short column of Celite. Removal of solvents under reduced presure afforded a residue that was purified by silica gel column chromatography (3 × 30 cm, 4% EtOAc/hexanes) to yield 1.74 g of Grundmann's ketone (**9**[7d,19] 84%, colorless liquid): ^{1}H NMR δ 0.91 (3 H, d, *J* = 6.1 Hz, CH_3-C_{21}), 0.83 (6 H, dd, *J* = 6.5, 1.1 Hz, CH_3-C_{27} and CH_3-C_{26}), 0.60 (3 H, s, CH_3-C_{18}).

dried under vacuum over P_2O_5 overnight) in THF (20 mL plus 2 mL for rinsing) was added via a cannula. After stirring for 30 min at −78 °C, MoOPH[9a] (3.39 g, 7.81 mmol) was added. The reaction mixture was stirred at −60 °C for 4 h and then quenched by addition of a solution of Na_2SO_3 (15 mL). The mixture was stirred overnight at room temperature and diluted with Et_2O. The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with HCl (5%, 20 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL), and water (20 mL), dried ($MgSO_4$), and filtered. Removal of the solvent afforded a residue which was purified by flash chromatography (3 × 20 cm, 25% EtOAc/hexanes) to afford 1.1 g of **10** [75%; R_f = 0.5 (20% EtOAc/hexanes), bp 145 °C (6 mmHg), colorless oil]: ^{1}H NMR δ 4.00 (1 H, t, J = 3.5 Hz, H9), 3.12 (1 H, dd, J = 11.6, 7.4 Hz, H14), 0.94 (3 H, d, J = 6.4 Hz, CH_3-C_{21}), 0.87 (3 H, d, J = 1.1 Hz, CH_3-C_{26} or CH_3-C_{27}), 0.86 (3 H, d, J = 1.1 Hz, CH_3-C_{27} or CH_3-C_{26}), 0.64 (3 H, s, CH_3-C_{18}); ^{13}C NMR δ 212.8, 74.3, 56.7, 50.2, 35.9, 35.4, 34.0, 31.3, 27.9, 27.5, 23.7, 22.7, 22.4, 18.5, 12.7; IR (film) 3430 (OH, br), 2950 (=CH, s), 2920 (=CH, s), 2860 (CH, s), 1715 (C=O, s), 1460 (m), 1380 (m), 1260 (w), 1010 (m), 965 (w), 920 (w), 865 (w) cm^{-1}; LREIMS m/e (relative intensity) 280 (M^+, 16), 262 ($M^+ - H_2O$, 7), 223 (21), 221 (44), 193 (10), 168 (31), 149 (34), 123 (31), 109 (50), 95 (65), 86 (51), 81 (62), 69 (59), 55 (99), 43 (100). Anal. Calcd for $C_{18}H_{32}O_2$: C, 70.07; H, 11.41. Found: C, 70.41; H, 11.44.

De-*A*,*B*-9α-(benzoyloxy)cholestan-8-one (11). A solution of the alcohol **10** (1.04 g, 3.71 mmol) and a catalytic amount of DMAP in pyridine (10 mL) was cooled to 0 °C and then benzoyl chloride (0.86 mL, 7.42 mmol) was added dropwise via a syringe. The reaction was stirred at 0 °C for 3 h and at room temperature overnight. Addition of a saturated aqueous solution of $NaHCO_3$ (15 mL) resulted in a suspension that was stirred for 2 h. The mixture was extracted with EtOAc/hexanes. The organic extracts were washed with aqueous $CuSO_4$ (10%, 5 × 15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (2 × 20 cm, 5% EtOAc/hexanes) to afford 1.30 g of **11** [91%, 1.30 g; R_f = 0.85 (20% EtOAc/hexanes), thick colorless oil]: ^{1}H NMR δ 8.04–7.45 (5 H, m, Ph), 5.10 (1 H, t, J = 3.0 Hz, H9), 3.02 (1 H, dd, J = 11.6, 7.2 Hz, H14), 0.96 (3 H, d, J = 6.3 Hz, CH_3-C_{21}), 0.88 (3 H, d, J = 1.1 Hz, CH_3-C_{26} or CH_3-C_{27}), 0.86 (3 H, d, J = 1.3 Hz, CH_3-C_{27} or CH_3-C_{26}), 0.69 (3 H, s, CH_3-C_{18}); ^{13}C NMR δ 206.3, 165.3, 133.3, 129.8, 128.5, 77.3, 58.3, 57.0, 51.3, 39.4, 35.9, 35.5, 34.8, 29.8, 27.9, 27.5, 23.7, 22.7, 22.4, 18.6, 18.5, 12.2; IR (film) 3075 (=CH, w), 3040 (=CH, w), 2960 (CH, s), 2920 (CH, s), 2865 (CH, s), 1730 (C=O, s), 1600 (m), 1465 (s), 1450 (s), 1385 (m), 1265 (s), 1100 (s), 1070 (s), 990 (s), 710 (s) cm^{-1}; UV (95% EtOH) λ_{max} 202 (ε 15000), 231 (ε 12300), λ_{min} 212 nm (ε 4000); LREIMS m/e (relative intensity) 384 (M^+, 1), 262 ($M^+ - PhCO_2H$, 5), 221 (36), 150 (10), 149 (10), 105 (100), 77 (40), 55 (19), 43 (44); HREIMS calcd for $C_{25}H_{36}O_3$ 384.2664, found 384.2661.

9α-(Benzoyloxy)-(7*E*)-vitamin D_3 *tert*-Butyldimethylsilyl Ether (13). A solution of the phosphine oxide **16** (0.26 g, 0.57 mmol) in THF (10 mL) was cooled to −90 °C. After 10 min, MeLi·LiBr (0.43 mL, 1.33 M in hexanes, 0.57 mmol) was slowly added via a syringe. The red solution was stirred at −90 °C for 30 min. A solution of **10** (0.20 g, 0.52 mmol) in THF (4 mL) was added dropwise via a syringe. The reaction was stirred at −90 °C for 3 h and then allowed slowly to reach room temperature. The pale yellow reaction mixture was quenched by the addition of few drops of water and diluted with Et_2O. The solvents were evaporated under vacuum without heating. The residue was dissolved in EtOAc/hexanes and washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and water (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (1.5 × 20 cm, 1.5% EtOAc/hexanes) to afford 0.23 g of **13** [71%, mp 45–47 °C, R_f = 0.8 (10% EtOAc/hexanes), white foam]: ^{1}H NMR δ 8.04–7.40 (5 H, m, Ph), 6.59 and 6.28 (2 H, AB system, J = 11.4 Hz, H7 and H6), 5.48 (1 H, s, 3076 5.07 (1 H, s H19*E*), 4.79 (1 H, s, H19*Z*), 3.75 (1 H, m, H3α), 0.96 (3 H, d, J = 6.1 Hz, CH_3-C_{21}), 0.89 (3 H, d, J = 1.3 Hz, CH_3-C_{26} or CH_3-C_{27}), 0.87 (9 H, s, t-BuSi), 0.87 (3 H, d, J = 1.1 Hz, CH_3-C_{27} or CH_3-C_{26}), 0.70 (3 H, s, CH_3-C_{18}), 0.04 (6 H, s, Me_2Si); ^{13}C NMR δ 167.2, 144.6, 141.2, 132.6, 129.7, 128.3, 127.7, 121.7, 113.5, 79.0, 70.6, 55.0, 51.7, 47.0, 46.1, 39.4, 36.2, 36.1, 35.7, 32.5, 29.6, 28.6, 28.4, 27.9, 26.0, 25.8, 23.9, 22.8, 22.5, 19.0, 18.0, 11.8, −4.7; IR (KBr) 3076 (=CH, w), 2950 (CH, s), 2860 (CH, s), 1720 (C=O, s), 1600 (m), 1470 (m), 1320 (m), 1270 (s), 1095 (m), 870 (m), 840 (m), 775 (m), 710 (m) cm^{-1}; UV (EtOH, 95%) λ_{max} 263 (ε 18400), 222 (ε 18400), λ_{min} 244 (ε 14400), 207 nm (ε 15000); LREIMS m/e (relative intensity) 618 (M^+, 0.9), 496 ($M^+ - PhCO_2H$, 24), 364 ($M^+ - (PhCO_2H$ + t-Bu$(Me)_2SiOH$), 25), 251 (40), 209 (21), 197 (20), 181 (18), 169 (17), 157 (17), 155 (23), 143 (24), 141 (21), 131 (24), 129 (23), 105 (75), 91 (29), 81 (23), 75 (100), 73 (99); HREIMS calcd for $C_{33}H_{56}OSi$ ($M^+ - PhCO_2H$) 496.4100, found 496.4082.

9α-Hydroxy-(7*E*)-vitamin D_3 *tert*-Butyldimethylsilyl Ether (14). A solution of **13** (0.26 g, 0.42 mmol) in Et_2O (10 mL) was cooled to 0 °C and then $LiAlH_4$ (0.02 g, 0.5 mmol) was added in two portions. The reaction mixture was stirred for 3 h at 0 °C and then quenched with a few small pieces of ice. The resulting mixture was dissolved in EtOAc/hexanes (20 mL) and washed with brine. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. Concentration in vacuo afforded a residue that was purified by flash chromatography (1.5 × 15 cm, 3% EtOAc/hexanes) to afford 0.18 g of **14** [85%, mp 39–41 °C, R_f = 0.8 (20% EtOAc/hexanes), white foam]: ^{1}H NMR δ 6.42 and 6.27 (AB system, J = 12 Hz, 2 H, H7 and H6), 5.05 (s, 1 H, H19*E*), 4.78 (s, 1 H, H19*Z*), 4.12 (s, 1 H, H9), 3.76 (m, 1 H, H3α), 0.94 (d, J = 5.8 Hz, CH_3-21), 0.89 (d, J = 1.5 Hz, 3 H, CH_3-C_{26} or CH_3-C_{27}), 0.88 (s, 9 H, t-BuSi), 0.86 (d, J = 1.0 Hz, 3 H, CH_3-C_{27} or CH_3-C_{26}), 0.62 (s, 3 H, CH_3-C_{18}), 0.06 (s, 6 H, Me_2Si); ^{13}C NMR δ 146.4, 141.8, 140.7, 125.8, 123.3, 113.9, 76.7, 71.7, 56.2, 51.2, 48.0, 47.4, 40.6, 37.3, 36.0, 33.4, 31.3, 29.0, 27.1, 26.4, 25.0, 23.2, 23.0, 19.7, 12.3, −4.4; IR (KBr) 3375 (OH, br), 3080 (=CH, w), 2950 (CH, s), 2860 (CH, s), 1635 (w), 1470 (m), 1250 (m), 1090 (s), 1010 (m), 900 (m), 870 (m), 840 (m), 770 (m) cm^{-1}; UV (EtOH, 95%) λ_{max} 262 (ε 17200), 214 (ε 15300), λ_{min} 229 nm (ε 8800); LREIMS m/e (relative intensity) 514 (M^+, 1), 496 ($M^+ - H_2O$, 11), 364 ($M^+ - (H_2O$ + t-Bu$(Me)_2SiOH$), 17), 349 (18), 251 (34), 209 (18), 181 (16), 155 (21), 143 (22), 131 (23), 129 (22), 115 (17), 105 (31), 91 (29), 81 (24), 75 (100), 73 (95).

9α-Hydroxy-(7*E*)-vitamin D_3 (15). A solution of **14** (0.10 g, 0.19 mmol) in THF (10 mL) was treated with n-Bu_4NF. The reaction mixture was stirred for 2 h at room temperature while monitored by TLC. Additional amounts of n-Bu_4NF were added until the disappearance of the starting material. Solvents were removed in vacuo without heating. The residue was dissolved in EtOAc (20 mL) and washed with HCl (5%, 3 × 10 mL) and brine (2 × 15 mL). The combined aqueous layer was extracted with EtOAc (5 × 5 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give a residue that was purified by flash chromatography (1.5 × 10 cm, 25% EtOAc/hexanes) to afford starting material **14** (7 mg, 7%) and **15**, which was crystallized (Et_2O/hexane) [0.04 g, 60%, mp 120 °C, R_f = 0.55 (20% EtOAc/hexanes), $[\alpha]_D$ = 165° (c = 3, CH_2Cl_2)]: ^{1}H NMR (CD_3COCD_3) δ 6.33 (2 H, s, H6 and H7), 5.06 (1 H, s, H19*E*), 4.75 (1 H, s, H19*Z*), 4.00 (1 H, s, H9), 3.81 (1 H, d, J = 4.6 Hz, OH), 3.69 (1 H, m, H3α), 3.48 (1 H, d, J = 2.4 Hz, OH), 0.96 (3 H, d, J = 6.3 Hz, CH_3-C_{21}), 0.86 (6 H, d, J = 6.6 Hz, CH_3-C_{26} and CH_3-C_{27}), 0.64 (3 H, s, CH_3-C_{18}); ^{13}C NMR (CD_3OD) δ 146.2, 142.4, 140.6, 126.0, 123.5, 113.8, 76.8, 70.8, 56.4, 51.3, 47.5, 47.2, 40.7, 37.4, 36.7, 36.1, 33.7, 31.3, 29.5, 29.1, 27.1, 25.0, 23.1, 22.9, 19.6, 12.2; IR (KBr) 3340 (OH, br), 3076 (=CH, w), 2950 (CH, s), 2870 (CH, s), 1625 (w), 1510 (m), 1460 (m), 1220 (w) 1060 (m), 900 (m), 685 (w) cm^{-1}; UV (95% EtOH) λ_{max} 214 (ε 17000), 260 (ε 19500), λ_{min} 227 nm (ε 12000); LREIMS m/e (relative intensity) 400 (M^+, 53), 382 ($M^+ - H_2O$, 43), 367 ($M^+ - (H_2O + CH_3)$, 57), 364 ($M^+ - 2H_2O$, 52), 349 (50), 269 (51), 251 (77), 209 (46), 197 (50), 195 (50), 157 (42), 155 (52), 142 (54), 131 (50), 129 (47), 105 (100), 91 (55), 81 (54). Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.92; H, 11.09. Found: C, 80.67; H, 11.43.

Determination of the Thermodynamic Equilibrium in the Thermolysis of 9α-Hydroxy-(7*E*)-vitamin D_3 (15). A solution of **15** (0.015 g 0.037 mmol) in dry toluene (15 mL) was heated at 110 °C under argon in the dark. Samples were collected each 3 h and analyzed by HPLC (30% to 40% EtOAc/hexanes in 10

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min). After 30 h equilibrium was reached, the solvent was removed, and the reaction mixture was purified by HPLC (30% to 40% EtOAc/hexanes in 10 min) to afford 9α-hydroxy-*cis*-isotachysterol$_3$ (**20b**, 30%), (3*S*,9*S*,10*R*)-(*Z*,*Z*)-9,10-secocholesta-5,7,14-triene-3,9-diol (**21b**, 60%) and (3*S*,9*S*,10*S*)-(*Z*,*Z*)-9,10-secocholesta-5,7,14-triene-3,9-diol (**22b**, traces).

9α-Hydroxy-*cis*-isotachysterol$_3$ (20b): ^{1}H NMR δ 5.98 (2 H, AB system, J = 13 Hz, H6 and H7), 4.15 (1 H, s, H9), 3.91 (1 H, m, H3α), 1.57 (3 H, s, CH_3-C_{19}), 0.96 (3 H, d, J = 6.6 Hz, CH_3-C_{21}), 0.87 (3 H, s, CH_3-C_{18}), 0.87 (6 H, d, J = 6.6 Hz, CH_3-C_{26} and CH_3-C_{27}); ^{13}C NMR δ 151.6, 130.4, 130.3, 127.8, 127.4, 126.6, 67.0, 65.2, 55.7, 44.0, 39.5, 37.5, 35.8, 34.6, 31.7, 30.8, 29.6, 28.1, 28.0, 27.0, 26.4, 23.6, 22.7, 22.5, 19.8, 18.8, 16.8; IR (KBr) 3340 (OH, br), 2930 (CH, s), 2860 (CH, s), 1655 (w), 1465 (m), 1365 (m), 1040 (m), 1010 (m), 885 (w) cm^{-1}; UV (95% Et_2O) λ_{max} 215 (7400), 260 (8000); λ_{min} 227 nm (4900); LREIMS m/e (relative intensity) 400 (M^+, 10), 382 ($M^+ - H_2O$, 26), 367 ($M^+ - H_2O$–CH_3, 59), 364 ($M^+ - 2H_2O$, 12), 349 ($M^+ - 2H_2O - CH_3$, 34), 269 (M^+ - side chain - CH_3, 48), 251 (38), 209 (29), 197 (28), 195 (24), 183 (25), 169 (28), 157 (31), 155 (35), 143 (39), 131 (44), 129 (39), 119 (34), 105 (56), 91 (100), 81 (41), 79 (43); HREIMS calcd for $C_{27}H_{44}O_2$ 400.3341, found 400.3323.

(3*S*,9*S*,10*R*)-(*Z*,*Z*)-9,10-Secocholesta-5,7,14-triene-3,9-diol (21b): ^{1}H NMR δ 6.34 and 6.06 (AB, J = 11.5 Hz, 2 H, H6 and H7), 5.66 (dd, J = 3.1 and 1.8 Hz, 1 H, H15), 4.19 (s, 1 H, H9), 3.55 (m, 1 H, H3α), 3.05 (m, 1 H), 1.09 (d, J = 7.2 Hz, 3 H, CH_3-C_{19}), 0.95 (d, J = 6.2 Hz, 3 H, CH_3-C_{21}), 0.88 (d, J = 5.6 Hz, 6 H, CH_3-C_{26} and CH_3-C_{27}), 0.87 (s, 3 H, CH_3-C_{18}); UV (Et_2O) λ_{max} 273 nm; LREIMS m/e (relative intensity) 400 (M^+, 8), 382, ($M^+ - H_2O$, 57), 367 ($M^+ - H_2O - CH_3$, 34), 364 ($M^+ - 2H_2O$, 64), 349 ($M^+ - 2H_2O - CH_3$, 38), 269 (M^+ - side chain - CH_3, 40), 251 (50), 209 (29), 197 (29), 195 (23), 183 (22), 169 (24), 157 (31), 155 (29), 143 (36), 131 (37), 129 (38), 119 (27), 117 (23), 115 (21), 107 (26), 105 (44), 95 (40), 91 (43), 83 (43), 81 (57), 71 (53), 69 (100); HREIMS calcd for $C_{27}H_{44}O_2$ 400.3341, found 400.3342.

Thermolysis of 9α-Hydroxy-(7*E*)-vitamin D$_3$ (15) in Benzene. A solution of **15** (0.03 g, 0.078 mmol) in benzene (10 mL) was heated at 80 °C and monitored by HPLC analysis. After 3 h no starting material was observed. Concentration of the reaction mixture gave a residue that was purified by HPLC (30–40% EtOAc/hexanes in 10 min) to afford two products: 9α-hydroxy-*cis*-isotachysterol$_3$ (**20b**, 16 mg, 50%) and (3*S*,9*S*,10*S*)-(*Z*,*Z*)-9,10-secocholesta-5,7,14-treine-3,9-diol (**22b**, 3 mg, 10%).

(3*S*,9*S*,10*S*)-(*Z*,*Z*)-9,10-Secocholesta-5,7,14-triene-3,9-diol (22b): ^{1}H NMR δ 6.41 and 6.14 (2 H, AB system, J = 11.1 Hz, H6 and H7), 5.66 (1 H, dd, J = 3.1, 2.0 Hz, H15), 4.21 (1 H, s, H9), 4.07 (1 H, m, H3α), 3.05 (1 H, m, H10), 1.12 (3 H, d, J = 7.1 Hz, CH_3-C_{19}), 0.95 (3 H, d, J = 6.1 Hz, CH_3-C_{21}), 0.89 (3 H, s, CH_3-C_{18}), 0.87 (6 H, d, J = 6.5 Hz, CH_3-C_{26} and CH_3-C_{27}); UV (Et_2O) λ_{max} 273 nm; LREIMS m/e (relative intensity) 400 (M^+, 3), 382 ($M^+ - H_2O$, 10), 367 ($M^+ - H_2O - CH_3$, 10), 364 ($M^+ - 2H_2O$, 8), 349 ($M^+ - 2H_2O - CH_3$, 6), 269 (M^+ - side chain - CH_3, 10), 259 (11), 251 (9), 209 (6), 197 (7), 195 (5), 185 (9), 161 (25), 157 (10), 155 (9), 148 (25), 143 (11), 137 (12), 133 (14), 129 (23), 111 (26), 109 (18), 105 (17), 97 (40), 95 (30), 85 (36), 81 (40), 79 (14), 73 (40), 71 (59), 69 (100); HREIMS calcd for $C_{27}H_{44}O_2$ 400.3341, found 400.3336.

Acknowledgment. Support for this research under Grant PB87-0478 from the DGICYT (M.E.C., Spain) is gratefully acknowledged. M.A.M thanks the Ministerio de Educación y Ciencia (Spain) for an F.P.I. fellowship. We thank Hoffmann-La Roche (Basel, Switzerland) for the generous gift of vitamin D$_3$.

Partial Synthesis of Sesquiterpene Lactones: A Route to 7,11-Ene-13-hydroxyeudesmanolides

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Received June 25, 1990

An efficient partial synthesis of several sesquiterpene lactones has been carried out from costunolide by treatment with trimethyl(phenyl)ammonium perbromide. A selective bromination at the C-11=C-13 bond provides a new route to 7,11-ene-13-hydroxyeudesmanolides. A synthesis of arbusculin D has been achieved.

In recent years, several cytotoxic and phytotoxic brominated sesquiterpenes have been reported.[1-3] As part of our research program on the synthesis of biologically active compounds, we have focused attention on the preparation of brominated sesquiterpene lactones.

We have recently reported that trimethyl(phenyl)ammonium perbromide (TMPAP) is an efficient reagent for bromocyclization of germacranolides.[4] This reaction, which can be extended to other cyclodecadiene systems,[5] can lead to the formation of specifically functionalized cyclized compounds that are valuable intermediates in the synthesis of sesquiterpenoids. We have also shown that TMPAP can be used effectively in bromine addition to conjugated double bonds, as in the case of α,β-unsaturated γ-lactones, thus providing a method for obtaining sesquiterpene lactones functionalized at the lactone ring.

This paper deals with the application of TMPAP to the partial synthesis of several sesquiterpene lactones.

Results and Discussion

Our approach was based on the cyclization of costunolide (1), a natural germacranolide readily available from natural sources.[5a] The cyclization of medium-ring 1,5-dienes has been widely investigated.[6-13] It has been demonstrated

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