0.39 mmol) and lithium borohydride (0.2 mL of a 2 M solution in tetrahydrofuran, 0.4 mmol) in 1.8 mL of tetrahydrofuran was stirred for 1.5 h at −78 °C. The reaction was quenched with acetic acid and methanol; the mixture was then allowed to warm to room temperature. The volatiles were removed in vacuo, and the residue was separated by two successive stages of TLC: the first plate was developed with acetone/chloroform (3:2) to remove unreacted **5**; the second plate was developed with chloroform/methanol (9:1) to yield 40 mg (40%) of **11d** and 21 mg (21%) of **10d**, which exhibited spectrometric properties indistinguishable from those previously reported.[18]

(b) 10d by Desilylation of 10a. To a cooled (ice bath) solution of **10a** (114 mg, 0.28 mmol) in 25 mL of tetrahydrofuran was added 0.28 mL of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran. The reaction was complete (TLC) in 30 min. The volatiles were removed, and the resulting residue was purified by preparative TLC using acetone/chloroform (3:2) (R_f 0.26) for development to yield 67 mg (94%) of **10d**.

(c) 11d by Desilylation of 11a. Desilylation of **11a** (125 mg, 0.30 mmol) was accomplished according to the procedure described above for desilylation of **10a** to afford 66 mg (86%) of **11d**: R_f 0.49 (9:1 chloroform/methanol); MS, m/z (relative intensity) 257 (6, M + H^+).

Anal. Calcd for $C_{11}H_{16}N_2O_5 \cdot 0.5H_2O$: C, 49.8; H, 6.49; N, 10.6. Found: C, 49.5; H, 6.62; N, 10.3.

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Registry No. 1, 65904-27-0; **2a**, 86436-80-8; **2b**, 86436-81-9; **2c**, 96760-97-3; **2d**, 96760-96-2; **2e**, 96761-01-2; **2f**, 103003-61-8; **2g**, 96760-93-9; **2h**, 96760-95-1; **3a**, 86455-85-8; **3b**, 86436-84-2; **3c**, 98839-18-0; **3d**, 103003-62-9; **3e**, 103003-63-0; **3f**, 103003-50-5; **4**, 96761-00-1; **5**, 103003-52-7; **6**, 103003-47-0; **7**, 103003-46-9; **8a**, 103003-48-1; **8b**, 103003-49-2; **8c**, 103003-51-6; **9**, 103003-53-8; **10a**, 103003-55-0; **10b**, 103003-56-1; **10c**, 103003-59-4; **10d**, 65358-16-9; **11a**, 103003-54-9; **11b**, 103003-57-2; **11c**, 103003-58-3; **11d**, 103003-60-7.

Stereocontrolled Total Synthesis of 1α,25-Dihydroxycholecalciferol[1] and 1α,25-Dihydroxyergocalciferol

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1α,25-Dihydroxycholecalciferol (**4**) and 1α,25-dihydroxyergocalciferol (**7**), the hormonally active forms of vitamin D_3 (**1**) and vitamin D_2 (**5**), were synthesized by a Horner–Wittig reaction of the phosphine oxide **11** with the ketones **10** and **12**, respectively. The synthon **11** was obtained by a sequence that involves the stereospecific opening of epoxide **15**, with sodium acetate in acetic acid, followed by oxidative degradation of the isopropenyl side chain and dehydration of the intermediate **22**. Photoisomerization of the resulting **23** gave **24**, which was finally converted to **11**. The hydroxylated ketone **10** was obtained from the known intermediate **28**. The introduction of the 25-hydroxy side chain was achieved by reaction of the lithium derivative of **30** with the tosylate **29** to give **31**, which was catalytically hydrogenated to **32** and then converted to **10**. The ketone **12** was prepared by a stereocontrolled route that involves as the key step, the [3 + 2] dipolar cycloaddition of nitrone **35** with methyl 3,3-dimethylacrylate (**36**) to give a 1:1 mixture of isoxazolidines **37** and **38**. Stereochemical control was achieved by taking advantage of the thermal reversibility of the cycloaddition, which allows the reequilibration of undesired **37**. Isoxazolidine **38** was readily transformed to **43** by reduction, followed by elimination of the nitrogen function, and finally oxidation to **12**.

In the past two decades, extensive investigations of the vitamin D_3 (cholecalciferol, **1**) metabolism have led to the discovery of a number of transformations which this essential vitamin undergoes in biological systems.[2] The most fundamental of these transformations is the sequence of hydroxylations of **1**, which starts in the liver to give 25-hydroxycholecalciferol (**2**) and then continues in the kidney to give 24(*R*),25-dihydroxycholecalciferol (**3**) and 1α,25-dihydroxycholecalciferol (**4**). The latter is believed to be the hormonally active form of the vitamin and plays a central role in the maintenance of the calcium and phosphorus homeostasis in the blood plasma and in the induction of mineralization and calcium mobilization of the bones. In addition, the widespread distribution of receptors for **4** in many tissues not regarded to participate directly in mineral metabolism[3] seems to indicate that this hormone plays a much wider biological role than initially suspected. More recently, 1α,25-dihydroxycholecalciferol has also been found to induce differentiation of certain myeloid and leukemic cells,[4] thus suggesting a possible link between the vitamin D system and cancers.

(1) Published in part as preliminary communication: Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovič, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945.

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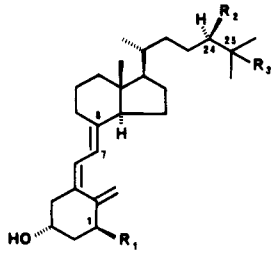
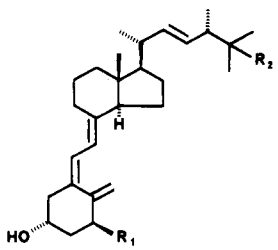
Vitamin D_2 (ergocalciferol **5**), in contrast to vitamin D_3, is not produced endogenously in animals and humans. It enters the body through the diet and has been shown to undergo metabolic transformations similar to those of cholecalciferol,[5] leading to the formation of 25-hydroxyergocalciferol (**6**) and 1α,25-dihydroxyergocalciferol (**7**). The biological activity of the latter has been proven to be comparable to that of **4** in humans and mammals but to be substantially lower in avian species.[6]

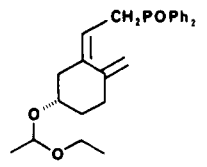




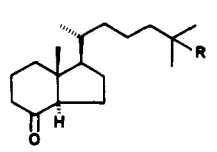
1 $R_1 = R_2 = R_3 = H$
2 $R_1 = R_2 = H, R_3 = OH$
3 $R_1 = H, R_2 = R_3 = OH$
4 $R_1 = R_3 = OH, R_2 = H$

5 $R_1 = R_2 = H$
6 $R_1 = H, R_2 = OH$
7 $R_1 = R_2 = OH$

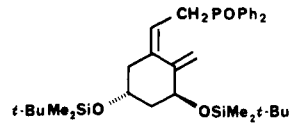
Originally, 1α,25-dihydroxycholecalciferol (**4**) was prepared from suitably hydroxylated 7-dehydrocholesterol precursors, via the classical photolysis and thermal isomerization sequence.[7] The chemical synthesis of 1α,25-dihydroxyergocalciferol (**7**) on the other hand had not yet been reported. We describe here a convergent total synthesis of both **4**[1] and **7**,[8] which has been applied also in the preparation of other 1α-hydroxylated vitamin D metabolites.[9,21] Our approach is based on a previous finding of Lythgoe and co-workers, who have shown[10] that the lithium anion of **8** (Figure 1) undergoes a Horner–Wittig reaction with the Windaus and Grundmann ketone **9**[11] at low temperature to give, after deprotection, cholecalciferol (**1**) in good yield. Under the conditions in which the olefination reaction is carried out, no geometric isomerization of the *Z* allylic phosphine oxide **8** occurs, and the geometry of the newly created 7,8-double bond is exclusively the desired *E*. In reexamining these results, we found that the intermediary lithium derivative of the β-hydroxy phosphine oxide, which is formed by reaction of the metalated **8** with **9**, does not require warming but undergoes elimination of lithium diphenylphosphinate completely within 1–2 h at −78 °C. Under these conditions, the yields of the resulting vitamin **1** are reproducibly in the 80–90% range, making this method particularly suitable for the synthesis of vitamin D metabolites. As an extension of the Lythgoe findings, we anticipated that the lithium carbanion of the 1α-hydroxylated allylic phosphine oxide **11**[12] would react with the ketone **10** or **12** to give after deprotection 1α,25-dihydroxycholealciferol (**4**) or 1α,25-dihydroxyergocalciferol (**7**), respectively. In order to verify these predictions, we turned our attention to the preparation of these intermediates.



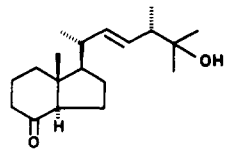
8



9 R = H
10 R = OH



11



12

Figure 1.

For the synthesis of **11** (Scheme I), the epoxide **14**, easily obtained by known regio- and stereospecific epoxidation of (*S*)-(+)-carvone (**13**),[13] was subjected to a Horner–Emmons reaction with the sodium carbanion of ethyl (diethoxyphosphinyl)acetate[14] to give an approximately 9:1 mixture of the 5*E* unsaturated ester **15** and the corresponding 5*Z* isomer, which were separated by chromatography. Our synthetic strategy at this point was to oxidatively degrade the isopropenyl side chain of **15** at C-3 with retention of configuration and then to convert the epoxide moiety into the desired allylic alcohol with an exocyclic double bond. Since we were unable to find suitable conditions to carry out the latter conversion efficiently, the epoxide **15** was cleaved in a highly regio- and stereoselective manner[15] to **16** on heating with sodium acetate in acetic acid. Under the same conditions, the corresponding 5*Z* isomer undergoes epoxide cleavage with good stereoselectivity but poor regioselectivity possibly because of the steric crowding by the carbethoxy group, which in this case hinders the approach of the nucleophile to C-6. Acetylation gave the crystalline diacetate **17**, which was converted to the corresponding methyl ketone **18** and subsequently by Baeyer–Villiger oxidation with trifluoroperacetic acid to the triacetate **19**. Since the hydrolysis of the acetoxy groups under basic conditions was always accompanied by partial elimination of the acetoxy group

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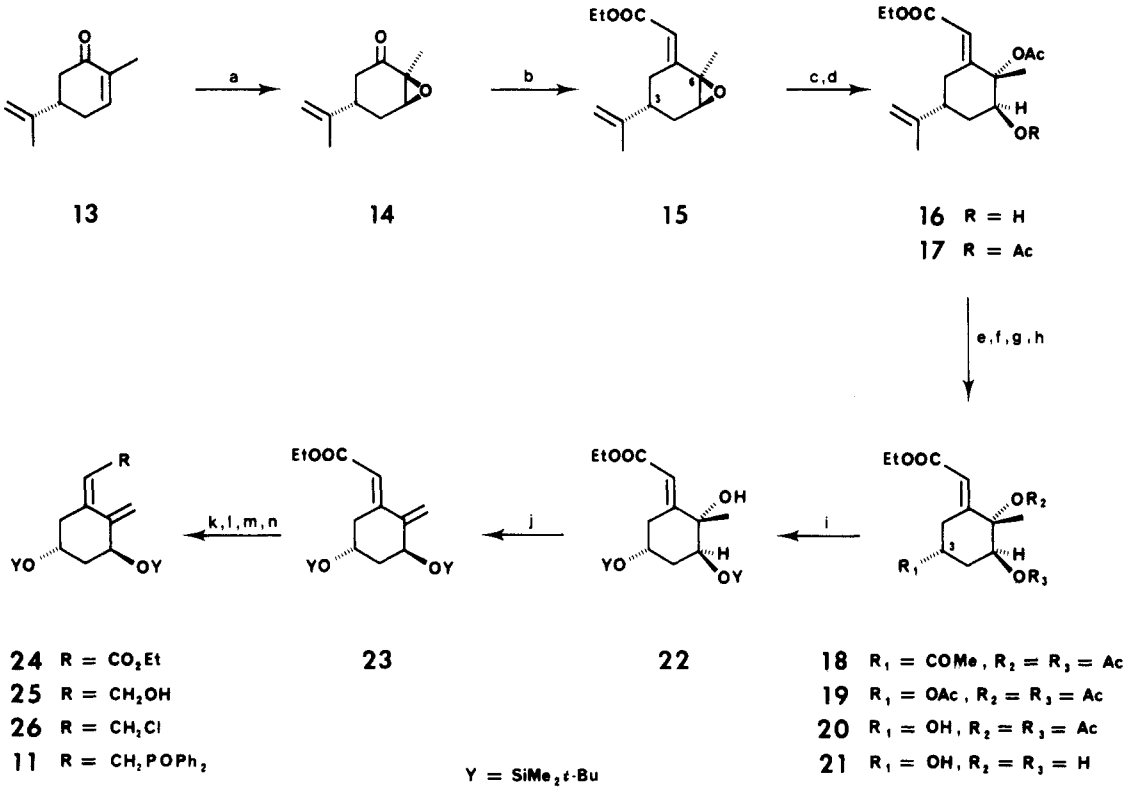
Scheme I[a]



[a] (a) H_2O_2/NaOH, MeOH, 88%; (b) $(EtO)_2POCH_2CO_2Et$/NaH, THF, 87%; (c) NaOAc, AcOH, 50 °C, 84%; (d) Ac_2O, py, 92%; (e) KIO_4/OsO_4, THF/H_2O, 97%; (f) CF_3CO_3H, NaH_2PO_4, CH_2Cl_2, 0 °C, 85%; (g) AG 50W-X4, EtOH, 50 °C; (h) EtONa, EtOH, 86% from **19**; (i) *t*-$BuMe_2SiCl$/imidazole, DMF, 95%; (j) $(Ph_2)S[OC(CF_3)_2Ph]_2$, CCl_4, 81%; (k) 9-Fluorenone/hν, *t*-BuOMe, 88%; (l) DIBAL-H, $PhCH_3$, −78 °C, 92%; (m) NCS/DMS, CH_2Cl_2, 0 °C, 91%; (n) Ph_2PLi, THF, −78 °C and then 5% H_2O_2, CH_2Cl_2, 90%.

at C-3, a sequence of mild acid treatment (H^+ cation exchange resin in ethanol) to give **20**, followed by base hydrolysis, was performed instead. The structure of the resulting **21** was confirmed by single-crystal X-ray analysis. Treatment of **21** with *tert*-butyldimethylsilyl chloride under standard conditions[16] selectively gave the bissilylated derivative **22**.

It was anticipated at this point that, under the conditions of an E_2 elimination, the tertiary hydroxyl group of **22** would preferentially give the desired exocyclic double bond. However, the usual dehydrating agents (e.g., thionyl chloride or phosphorus oxychloride in pyridine) gave complex mixtures of products. Ultimately, we found that bis[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethoxy]diphenylsulfurane[17] was the reagent of choice for this transformation and gave the desired **23** in high yield. Triplet-sensitized photoisomerization using 9-fluorenone (E_T = 53 kcal/mol) as sensitizer, efficiently converted **23** to the corresponding 5*Z* isomer **24**. The latter was reduced to the allylic alcohol **25** with diisobutylaluminum hydride, which was then converted to the corresponding allylic chloride **26** by reaction with the complex made from *N*-chlorosuccinimide and methyl sulfide[18] and finally transformed to the desired phosphine oxide **11** on treatment with lithium diphenylphosphide followed by oxidation with hydrogen peroxide.[19]

Attention was next turned to the construction of the synthons **10** and **12**, required for the synthesis of 1α,25-dihydroxycholecalciferol and 1α,25-dihydroxyergocalciferol. For the preparation of **10** (Scheme II), the monosilylated Inhoffen–Lythgoe diol **28**,[20] derived[21] from the asymmetrically synthesized keto acid **27**,[22] was chosen as starting material. Previously we reported a preparation of **10**[1] using intermediates with the α-configuration of the C-8 hydroxyl group.[12] It was later found preferable to use the corresponding β-isomer, since the axial hydroxyl group is quite hindered and can, without protection, withstand a variety of reaction conditions (vide infra). Tosylation to **29** and reaction with the lithium derivative of 3-methyl-1-butyn-3-yl tetrahydropyranyl ether (**30**) in refluxing dioxane[23] gave **31**. Catalytic hydrogenation of the acetylenic moiety over rhodium on charcoal to **32**, removal of the alcohol protective groups[24] to give **33**, and oxidation with pyri-

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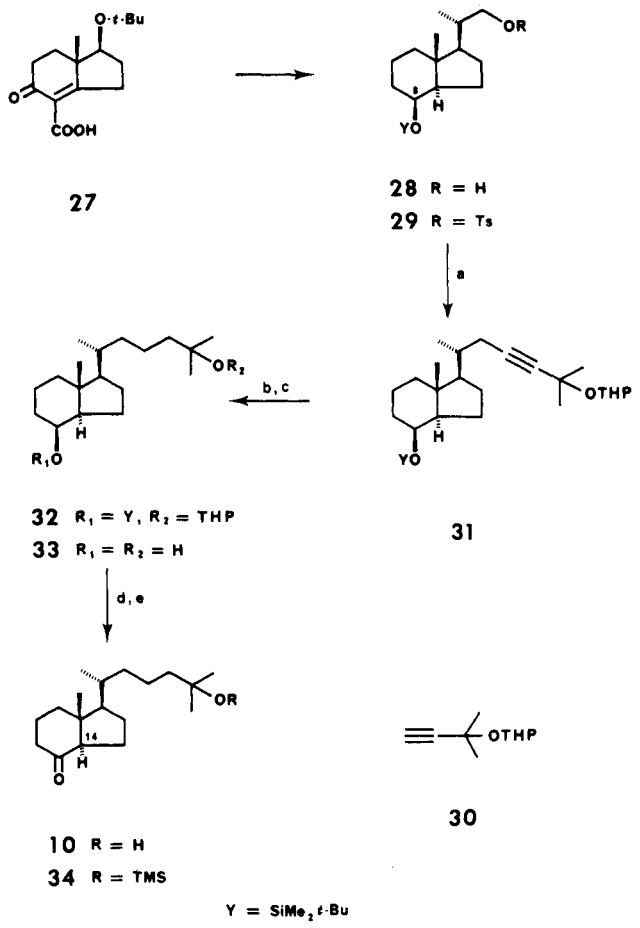
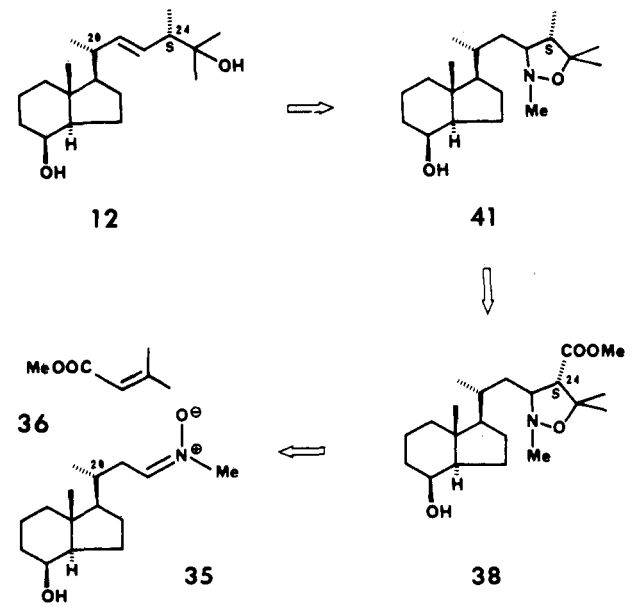
Scheme II[a]



[a] (a) 30/BuLi, Dioxane, reflux, 86%; (b) 5% Rh/C, H_2, EtOAc, 1 atm, 99%; (c) AG 50W-X4, MeOH and then aqueous HF, CH_3CN, 87%; (d) PCC, Me_2Cl_2, 93%; (f) TSIM, THF, 98%.

Scheme III



dinium chlorochromate[25] gave the desired hydroxylated Windaus and Grundman ketone **10**,[26] the precursor of **4**.

Next, the preparation of the intermediate **12**, required for the synthesis of 1α,25-dihydroxyergocalciferol (**7**), was undertaken.[8] In this case, the strategy (Scheme III) for

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(26) Cohen, Z.; Berman, E.; Mazur, Y. *J. Org. Chem.* **1979**, *44*, 3077.

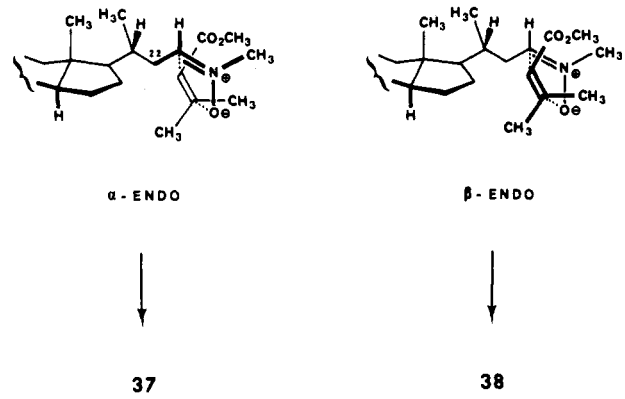
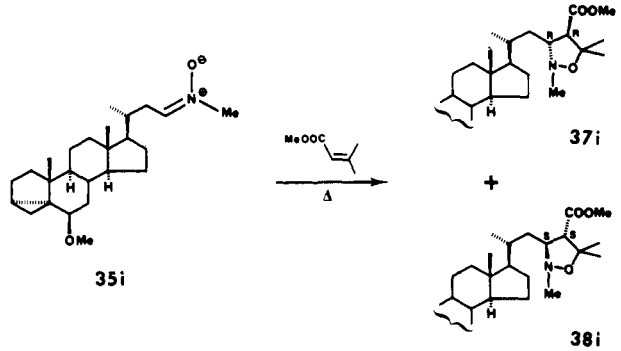


Figure 2.

the introduction of the side chain, which bears five contiguously functionalized carbon atoms, evolved from our previous experience in the use of a thermodynamically controlled dipolar cycloaddition as a convenient route to 1α,25,26-trihydroxycholecalciferol.[21] Thus, our objective was the isoxazolidine ester **38**, with the required *S* configuration at the critical C-24 center, which could then easily be converted to **12** via **41**. The configuration at C-23 appears to be of no consequence since C-23 is destined to become part of the olefinic bond; however, it may exert an influence on the regiochemistry of the subsequent nitrogen elimination.

Cyclization of the previously described *Z* nitrone **35**[21] with methyl 3,3-dimethylacrylate (**36**) in refluxing xylenes gave a readily separable 1:1 mixture of isoxazolidine esters **37** and **38** (Scheme IV). The structure of the desired crystalline isomer **38** was established by X-ray. The structure of the noncrystalline isomer was inferred from the similarity of the NMR spectrum to the corresponding steroidal products obtained from a model reaction.[27] The regiochemistry of the cycloaddition was, as expected, consistent with previous observations.[29] The high degree of stereoselection to form only two of the four possible diastereomers, the result of virtually exclusive endo addition to the *Z* nitrone (Figure 2), can be attributed to the steric hindrance which occurs in the exo transition states between the C-22 methylene group of the nitrone and the

(27) The i-steroid nitrone **35i**[28] afforded a 1:1 mixture of two crystalline products **37i** and **38i**, whose structures were established by X-ray. The ^1H NMR spectra correlated very well with their CD counterparts **37** and **38**. **37i**: mp 128–129 °C (from CH_3CN); ^1H NMR (200 MHz) δ 0.67

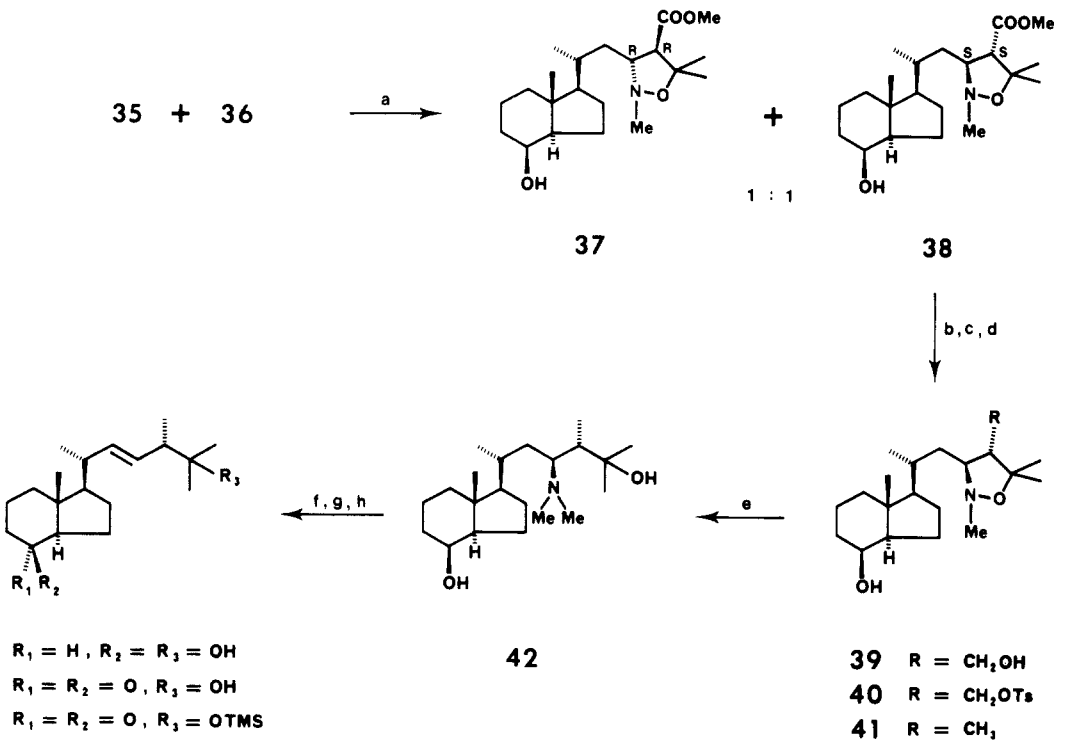


(s, 3 H), 0.93 (d, *J* = 6 Hz, 3 H), 1.02 (s, 3 H), 1.18 (s, 3 H), 1.44 (s, 3 H), 2.67 (s, 3 H), 2.77 (d, *J* = 8.5 Hz, 2 H), 2.80 (br s, 1 H), 3.08 (br t, 1 H), 3.34 (s, 3 H), 3.72 (s, 3 H). **38i**: mp 136–137 °C (from CH_3CN); ^1H NMR (200 MHz) δ 0.72 (s, 3 H), 0.97 (d, *J* = 6 Hz, 3 H), 1.04 (s, 3 H), 1.18 (s, 3 H), 1.46 (s, 3 H), 2.72 (s, 3 H), 2.78 (br s, 1 H), 2.90 (d, *J* = 9 Hz, 1 H), 3.33 (s, 3 H), 3.73 (s, 3 H).

(28) Batcho, A. D.; Sereno, J.; Chadha, N. K.; Partridge, J. J.; Baggiolini, E. G.; Uskokovič, M. R. *Current Trends in Organic Synthesis*: Pergamon: New York, 1983; p 193.

(29) (a) Huisgen, R.; Hauk, H.; Grashey, R.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2568. (b) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287.

Scheme IV[a]



[a] (a) Xylene, 140 °C, 40% of **37** and 41% of **38**; (b) LAH, THF, 90%; (c) *p*-TsCl, py, 91%; (d) LAH, THF, reflux, 80%; (e) MeI, toluene, 60 °C, and then Zn dust, AcOH, 89%; (f) MeI, toluene, 70 °C, and then *t*-BuOH, *t*-BuOK, reflux, 78%; (g) PCC, CH_2Cl_2, 91%; (h) TSIM, THF, 88%.

carbomethoxy group of the approaching dipolarophile. Although no diastereofacial selection was observed, the product distribution could be controlled by chromatographic separation and reequilibration of the undesired isomer (**37**) by heating with an excess of the dipolarophile in xylene. It was gratifying that the axial hydroxyl function at C-8 required no protection throughout the entire sequence.

Conversion of the ester function to a methyl group (**38** → **41**) was accomplished by lithium aluminum hydride reduction, followed by selective monotosylation of the resulting primary alcohol **39** (to give **40**) and hydrogenolysis with lithium aluminum hydride. After N-methylation of the latter product (**41**), the isoxazolidine ring was cleaved with zinc in aqueous acetic acid. Hofmann degradation of the resulting amino diol **42** was carried out by N-methylation with methyl iodide followed by treatment with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol. Elimination proceeded regiospecifically as desired to give only the *trans*-Δ^{22}-olefin **43** (80% yield) accompanied by a minor byproduct (20% yield) **45** (see Figure 3), the result of a Grob fragmentation. The structure of **43** was fully confirmed by X-ray analysis.

The regioselectivity of the elimination process can be understood from a comparison of the transition states necessary for β-elimination. Formation of a Δ^{23}-olefin would have to proceed via transition state TS-1 (Figure 3) which is severely strained and highly disfavored. Transition state TS-2 (leading to Δ^{22}-*trans*-olefin) is less strained than TS-3 (progenitor of Δ^{22}-*cis*-olefin).

Fragmentation, on the other hand, requires the somewhat strained transition-state TS-4 which gives rise to acetone and the olefin **45** as a minor byproduct.

With the required synthons on hand, the final convergent formation of 1α,25-dihydroxycholecalciferol (**4**) and 1α,25-dihydroxyergocalciferol (**7**) were now within reach. Wittig–Horner reaction of the lithium phosphinoxy carbanion prepared from **11** and *n*-butyllithium at −78 °C tetrahydrofuran with **10** proceeded extremely slowly. At higher temperature, epimerization at C-14[12] began to occur. On the other hand, reaction of the metalated **11** with the trimethylsilyl ether derivative of **10** (**34**) proceeded very

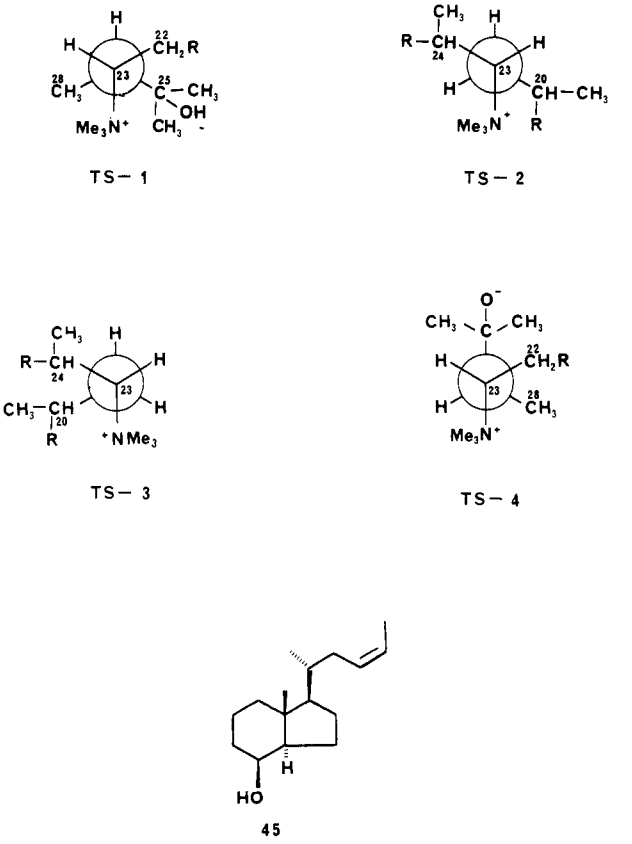


Figure 3.

smoothly to give, after 1.5 h at −78 °C, the desired metabolite (with silyl-protected hydroxy functions) as the solely discernible product. Deprotection gave the crystalline 1α,25-dihydroxycholecalciferol **4** (mp 118–119 °C) in 90% yield from **34**.

In completely analogous fashion, reaction of the lithium derivative of **11** with the trimethylsilyl ether **44** which was obtained by oxidation of **43** with PCC followed by silylation with trimethylsilimidazole gave, after removal of the protecting groups, the corresponding 1α,25-dihydroxyergocalciferol **7** (mp 169–170 °C) in 91% yield (from **44**).

In summary, the generality of the Lythgoe convergent total synthesis of vitamin D_3 has been extended to the efficient preparation of the important metabolites 1α,25-dihydroxycholecalciferol and 1α,25-dihydroxyergocalciferol, thus demonstrating further the versatility of this approach.

Experimental Section

Materials and Methods. Melting points were measured on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Infrared spectra were obtained on a Digilab Model FTS-15E spectrometer. The proton NMR spectra were recorded on a Varian XL-400 (400 MHz), Varian XL 200 (200 MHz), or Varian XL 100 (100 MHz) spectrometer in $CDCl_3$ (unless otherwise stated). Chemical shifts are reported in ppm downfield from internal Me_4Si. Mass spectral data were obtained on a Varian MAT CH-5 instrument. The ultraviolet absorption spectra were measured with a Cary Model 14 spectrophotometer and the optical rotations with a Perkin-Elmer 241 polarimeter. Chromatographic purifications were carried out with EM Merck silica gel (60, particle size 0.040–0.063 mm).

[1*R*-(1α,2*E*,4α,6α)]-[1-Methyl-4-(1-methylethenyl)-7-oxabicyclo[4.1.0]hept-2-ylidene]acetic Acid Ethyl Ester (15). To a suspension of sodium hydride (57% oil dispersion, washed with hexane, 6.65 g, 0.158 mol) in 200 mL of anhydrous THF was slowly added, under argon and external ice cooling, 35.42 g (0.158 mmol) of ethyl (diethoxyphosphinyl)acetate. After the initial hydrogen evolution subsided, the mixture was stirred at room temperature for 1.5 h, and then 25.00 g (0.150 mol) of carvone oxide[13] (**14**) in 100 mL of anhydrous tetrahydrofuran was slowly added and the stirring continued for 20 h. The solvent was evaporated in vacuo and the residue partitioned between ethyl acetate and 2 N sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate, and the combined extracts were washed with brine and dried (Na_2SO_4). Following evaporation of the solvent in vacuo, the residual material was applied to a silica column (1.2 kg) and eluted with hexane–ethyl acetate (5:1) to give 30.84 g of pure **15** (87% yield) as a colorless liquid: $[\alpha]^{25}_D$ +37.3° (*c* 0.5, EtOH); ^1H NMR (100 MHz) δ 1.28 (t, *J* = 8.0 Hz, 3 H), 1.47 (s, 3 H), 1.71 (br s, 3 H), 3.27 (t, *J* = 2.4 Hz, 1 H), 3.33 (br d, *J* = 14.5 Hz, 1 H), 4.25 (q, *J* = 8.0 Hz, 2 H), 4.82 (br s, 2 H), 6.11 (br s, 1 H); IR ($CHCl_3$) 1713, 1646, 1200, 1170 cm^{-1}; mass spectrum, *m/e* (relative intensity) 236 (M^+, 5), 203 (50), 165 (20), 163 (32), 147 (52), 119 (100); UV (EtOH) λ_{max} 226 nm (ε 14 870).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.93; H, 8.45.

Also, 3.43 g (9.6%) of the corresponding geometric isomer, [1*R*-(1α,2*Z*,4α,6α)]-[1-methyl-4-(1-methylethenyl)-7-oxabicyclo-[4.1.0]hept-2-ylidene]acetic acid ethyl ester was isolated as a colorless liquid: $[\alpha]^{25}_D$ +139.4° (*c* 0.5, EtOH); ^1H NMR (100 MHz) δ 1.32 (t, *J* = 8.0 Hz, 3 H), 1.59 (s, 3 H), 1.70 (br s, 3 H), 3.05 (br s, 1 H), 4.24 (q, *J* = 8.0 Hz, 2 H), 4.70 (br s, 2 H), 5.88 (br s, 1 H); IR ($CHCl_3$) 1720, 1650, 1185 cm^{-1}; mass spectrum, *m/e* (relative intensity) 193 (36), 163 (16), 142 (23), 119 (46), 43 (100); UV (EtOH) λ_{max} 218 nm (ε 11 600).

Anal. Calcd or $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.24; H, 8.54.

[2*S*-(1*E*,2α,3β,5α)]-[2-(Acetyloxy)-3-hydroxy-2-methyl-5-(1-methylethenyl)cyclohexylidene]acetic Acid Ethyl Ester (16). A solution of 22.20 g (93.94 mmol) of [1*R*-[1α,2*E*,4α,6α)]-[1-methyl-4-(1-methylethenyl)-7-oxabicyclo-[4.1.0]hept-2-ylidene]acetic acid ethyl ester (**15**) in 250 mL of a 1 M solution of anhydrous sodium acetate in acetic acid was stirred under argon at 50 °C for 16 h. After the mixture was cooled, most of the acetic acid was evaporated in vacuo. The residue was diluted with 300 mL of water, neutralized under ice cooling with 1 N aqueous ammonia solution, and extracted with ethyl acetate. The combined organic extracts were washed with water and then with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by fast filtration through silica (0.8 kg), using hexane–ethyl acetate (3:1) as the eluent, to give 23.42 g (84% yield) of pure **16** as a thick, colorless liquid: $[\alpha]^{25}_D$ −77.3° (*c* 0.5, EtOH); ^1H NMR (100 MHz) δ 1.28 (t, *J* = 7.5 Hz, 3 H), 1.68 (s, 3 H), 1.76 (br s, 3 H), 2.03 (s, 3 H), 3.80 (br d, *J* = 12.0 Hz), 4.17 (q, *J* = 7.5 Hz, 2 H), 4.78 (br s, 2 H), 5.89 (br s, 1 H); IR ($CHCl_3$) 3625, 1740, 1715, 1650, 1450, 1380, 1240, 1180, 897 cm^{-1}; mass spectrum, *m/e* (relative intensity) 254 (4), 236 (6), 208 (9), 190 (13), 33 (100); UV (EtOH) λ_{max} 225 nm (ε 12 590).

Anal. Calcd for $C_{16}H_{28}O_5$: C, 64.84; H, 8.16. Found: C, 65.09; H, 8.02.

[2*S*-(1*E*,2α,3β,5α)]-[2,3-Bis(acetyloxy)-2-methyl-5-(1-methylethenyl)cyclohexylidene]acetic Acid Ethyl Ester (17). A solution of 20.00 g (67.48 mmol) of [2*S*-(1*E*,2α,3β,5α)]-2-(acetyloxy)-3-hydroxy-2-methyl-5-(1-methylethenyl)cyclohexylidene]acetic acid ethyl ester (**16**) in 100 mL of anhydrous pyridine and 50 mL (0.53 mol) of acetic anhydride was stirred at room temperature for 15 h. The reaction mixture was then evaporated to dryness in vacuo. The residue, dissolved in ethyl acetate, was successively washed with 1 N hydrochloric acid, water, 2 N potassium bicarbonate, and finally with brine. After the mixture was dried (Na_2SO_4) and the solvent was evaporated, the residue was crystallized from heptane to give 21.08 g (92% yield) of pure **17** as white crystals; mp 85–85.5 C; $[\alpha]^{25}_D$ −69.1° (*c* 0.5, EtOH); ^1H NMR (100 MHz) δ 1.29 (t, *J* = 7.0 Hz, 3 H), 1.57 (s, 3 H), 1.75 (s, 3 H), 2.02 (s, 3 H), 2.04 (s, 3 H), 3.96 (br d, *J* = 13.0 Hz, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 4.76 (br s, 1 H), 5.20 (t, *J* = 4.0 Hz, 1 H), 5.87 (br s, 1 H); IR ($CHCl_3$) 1740, 1710, 1650, 1370, 1230, 1175 cm^{-1}; mass spectrum, *m/e* (relative intensity) 278 (5), 251 (7), 236 (20), 218 (16), 190 (24), 145 (18), 43 (100); UV (EtOH) λ_{max} 222 nm (ε 12 050).

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.84; H, 7.67.

[2*S*-(1*E*,2α,3β,5α)]-[5-Acetyl-2,3-bis(acetyloxy)-2-methylcyclohexylidene]acetic Acid Ethyl Ester (18). A solution of 20.0 g (59.10 mmol) of [2*S*-(1*E*,2α,3β,5α)]-[2,3-bis(acetyloxy)-2-methyl-5-(1-methylethenyl)cyclohexylidene]acetic acid ethyl ester (**17**) in 800 mL of a 1:1 mixture of tetrahydrofuran–water was combined with 10 mL of a 1% aqueous solution of osmium tetraoxide and 33.0 g (143.48 mmol) of finely pulverized potassium periodate and stirred vigorously for 16 h at room temperature. Most of the tetrahydrofuran was then evaporated in vacuo and the aqueous residue diluted with 1.5 L of water and extracted with ethyl acetate. The combined organic extracts were washed with 1 N aqueous sodium bisulfite, followed by water, 2 N aqueous sodium bicarbonate, and brine. After the mixture was dried (Na_2SO_4) and the solvents were evaporated, 19.6 g (97% yield) of **18** was obtained as colorless, thick liquid, which was used without further purification in the next step: $[\alpha]^{25}_D$ −24.5° (*c* 0.5, EtOH); ^1H NMR (100 MHz) δ 1.30 (t, *J* = 8.0 Hz, 3 H), 1.57 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 2.20 (s, 3 H), 4.14 (br d, *J* = 13.0 Hz, 1 H), 4.20 (q, *J* = 8.0 Hz, 2 H), 5.23 (t, *J* = 4.0 Hz, 1 H), 5.90 (br s, 1 H); IR ($CHCl_3$) 1745, 1714, 1658, 1380, 1235, 1190, 1050 cm^{-1}; mass spectrum, *m/e* (relative intensity) 280 (3), 253 (6), 238 (12), 192 (26), 123 (19), 149 (36), 43 (100); UV (EtOH) λ_{max} 220 nm (ε 12 900).

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.76; H, 7.07.

[2*S*-(1*E*,2α,3β,5α)]-[2,3,5-Tris(acetyloxy)-2-methylcyclohexylidene]acetic Acid Ethyl Ester (19). To a mixture of 6.4 mL (0.235 mol) of 90% hydrogen peroxide and 200 mL of dichloromethane, cooled to 0 °C, a solution of 33.1 mL (0.234 mol) of trifluoroacetic anhydride in 100 mL of dichloromethane was added dropwise with vigorous stirring over a 2-h period. When the addition was completed, 70 g of finely pulverized, anhydrous potassium dihydrogen phosphate was added and the resulting suspension stirred for 30 min at 0 °C and then treated dropwise at 0 °C with a solution of 20.0 g (0.059 mol) of [2*S*-(1*E*,2α,3β,5α)]-[5-acetyl-2,3-bis(acetyloxy)-2-methylcyclohexylidene]acetic acid ethyl ester (**18**) dissolved in 200 mL of dichloromethane. The addition was carried out over a 30-min

period. The resulting mixture was stirred overnight at 0 °C, and then 200 mL of a 10% aqueous sodium sulfite solution was slowly added and stirring continued for 15 min after the addition was completed. The organic phase was separated and the aqueous phase extracted with dichloromethane. The combined organic extracts were washed subsequently with water, 2 N potassium bicarbonate solution, and brine and finally dried over Na_2SO_4. Evaporation of the solvent in vacuo and chromatography of the oily residue over silica gel, using hexane–dichloromethane (7:3) as eluent, gave 17.8 g (85%) of pure **19**: mp 71.5–72 °C (after recrystallization from hexane); $[\alpha]^{25}_D$ −55.4° (*c* 1.0, EtOH); ^{1}H NMR (100 MHz) δ 1.29 (t, *J* = 8.0 Hz, 3 H), 1.58 (s, 3 H), 2.03 (s, 3 H), 2.06 (s, 6 H), 3.86 (dd, *J* = 5.0, 14.0 Hz, 1 H), 4.19 (q, *J* = 8.0 Hz, 2 H), 4.90 (br m, 1 H), 5.32 (br t, *J* = 4.0 Hz, 1 H), 5.91 (br s, 1 H); IR ($CHCl_3$) 1745, 1720, 1660, 1375, 1240, 1180, 1100, 1050 cm^{-1}; mass spectrum, *m/e* (relative intensity) 256 (M^+, 1), 314 (3), 269 (6), 254 (2), 212 (10), 194 (19), 176 (16), 148 (22), 121 (32), 33 (100); UV (EtOH) λ_{max} 217 nm (*e* 13 400).

Anal. Calcd for $C_{17}H_{24}O_8$: C, 57.30; H, 6.79. Found: C, 57.48; H, 7.10.

[2*S*-(1*E*,2α,3β,5α)]-(2,3,5-Trihydroxy-2-methylcyclohexylidene)acetic Acid Ethyl Ester (21). To a solution of 5.00 g (14.03 mmol) of [2*S*-(1*E*,2α,3β,5α)]-[2,3,5-tris(acetyloxy)-2-methylcyclohexylidene]acetic acid ethyl ester (**19**) in 75 mL of ethanol, 35.0 g of cation exchange resin AG 50W-X4 (200–400 mesh)[30] washed with ethanol was added and the suspension stirred at 50 °C under argon overnight. After cooling, the resin was filtered and washed with 3 × 10 mL of ethanol and the filtrate treated with 2 mL of 1% sodium ethoxide in ethanol. After being stirred at room temperature for 2 h, the reaction mixture was neutralized by addition of 1.6 g of AG 50W-X4 (200–400 mesh),[30] filtered, and evaporated to dryness in vacuo. Chromatographic purification on silica (ethyl acetate as the eluent) gave 2.79 g (86%) of **21**: mp 95–96 °C (after recrystallization from hexane–dichloromethane); $[\alpha]^{25}_D$ +76.5° (*c* 0.5, EtOH); ^{1}H NMR (100 MHz) δ 1.29 (t, *J* = 7.2 Hz, 3 H), 1.32 (s, 3 H), 3.84 (br m, 1 H), 3.98 (br m, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 6.30 (br s, 1 H); IR ($CHCl_3$) 3600, 3400, 1700, 1650, 1250, 1180 cm^{-1}; mass spectrum, *m/e* (relative intensity) 212 (10), 184 (4), 166 (14), 112 (21), 111 (22), 43 (100); UV (EtOH) λ_{max} 222 nm (ε 12 300).

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.36; H, 8.14.

[2*S*-(1*E*,2α,3β,5α)]-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-hydroxy-2-methylcyclohexylidene]acetic Acid Ethyl Ester (22). To a solution of 10.8 g (46.90 mmol) of [2*S*-(1*E*,2α,3β,5α)]-(2,3,5-trihydroxy-2-methylcyclohexylidene)-acetic acid ethyl ester (**21**) in 250 mL of *N*,*N*-dimethylformamide were added 28.0 g (0.186 mol) of *tert*-butyldimethylsilyl chloride and 25.0 g (0.212 mol) of imidazole, and the resulting mixture was stirred at room temperature under argon overnight. Crushed ice was then added, and, after being stirred for 30 min, the reaction mixture was diluted with water and extracted with 5 × 100 mL of ether. The combined ether extracts were washed with 5 × 100 mL of water and dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was purified by chromatography over silica, using hexane–ethyl acetate as the eluent (10:1), to give 20.5 g (95% yield) of a colorless thick oil: $[\alpha]^{25}_D$ +54.0° (*c* 0.3, EtOH); ^{1}H NMR (100 MHz) δ 0.03 (s, 6 H), 0.07 (s, 3 H), 0.09 (s, 3 H), 0.82 (s, 9 H), 0.89 (s, 9 H), 1.27 (t, *J* = 7.6 Hz, 3 H), 1.28 (s, 3 H), 3.86 (br m, 1 H), 4.06 (br m, 1 H), 4.14 (q, *J* = 7.6 Hz, 2 H), 6.28 (s, 1 H); IR ($CHCl_3$) 1710, 1660, 1470, 1260, 1180, 1110 cm^{-1}; mass spectrum, *m/e* (relative intensity) 458 (M^+, 1), 401 (43), 355 (16), 326 (6), 269 (44), 223 (30), 195 (28), 149 (38), 75 (85), 73 (100); UV (EtOH) λ_{max} 223 nm (ε 11 660).

Anal. Calcd for $C_{23}H_{46}O_5Si_2$: C, 60.21; H, 10.11. Found: C, 59.91; H, 10.23.

[3*S*-(1*E*,3α,5β)]-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetic Acid Ethyl Ester (23). A solution of 15.0 g (32.69 mmol) of [2*S*-(1*E*,2α,3β,5α)]-[3,5-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-hydroxy-2-methylcyclohexylidene]acetic acid ethyl ester (**22**) in 50 mL of anhydrous carbon tetrachloride was rapidly added to a magnetically stirred solution of 25.0 g (37.17 mmol) of bis-[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethoxy]diphenylsulfurane[17] in 150 mL of anhydrous carbon tetrachloride at 0 °C under argon. After the addition, the cooling bath was removed and the mixture stirred for 15 min. It was then transferred to a separatory funnel, washed with ice water and then brine, and dried (Na_2SO_4). After evaporation of the solvent, the oily residue was purified by a sequence of two rapid chromatographies on silica, the first with hexane–ethyl acetate (10:1) as the eluent and the second with dichloromethane, to give 11.7 g (81% yield) of pure **23** as a thick, colorless oil: $[\alpha]^{25}_D$ −4.7° (*c* 0.5, EtOH); ^{1}H NMR (100 MHz) δ 0.06 (s, 12 H), 0.86 (s, 9 H), 0.90 (s, 9 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 2.66 (br d, *J* = 10.6 Hz, 1 H), 3.36 (br dd, *J* = 5.4, 10.6 Hz, 1 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.25 (br m, 1 H), 4.58 (br m, 1 H), 5.07 (br s, 2 H), 5.89 (br s, 1 H); IR ($CHCl_3$) 1710, 1640, 1475, 1380, 1260, 1180, 1090, 900, 840 cm^{-1}; mass spectrum, *m/e* (relative intensity) 425 (2), 383 (97), 355 (3), 337 (5), 263 (12), 251 (17), 75 (66), 73 (100); UV (EtOH) λ_{max} 240 nm (ε 10 750).

Anal. Calcd for $C_{23}H_{44}O_4Si_2$: C, 62.67; H, 10.06. Found: C, 62.70; H, 10.19.

[3*S*-(1*Z*,3α,5β)]-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetic Acid Ethyl Ester (24). A solution of 5.00 g (11.34 mmol) of [3*S*-(1*E*,3α,5β]-[3,5-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetic acid ethyl ester (**23**) and 0.2 g of fluorenone in 400 mL of *tert*-butyl methyl ether was irradiated for 30 min with a Hanovia 450-W mercury lamp using a uranium glass filter. During the photolysis, a gentle stream of argon was passed through the solution. The solvent was removed in vacuo and the residue first purified by rapid filtration through silica, using hexane–ethyl acetate (10:1) as eluent, and then by preparative high-performance liquid chromatography (eluent, 50:1 hexane–ethyl acetate) to give 4.44 g (88% yield) of pure **24** as a thick, colorless oil: $[\alpha]^{25}_D$ −36.9° (*c* 0.3, EtOH); ^{1}H NMR (100 MHz) δ 0.05 (s, 6 H), 0.09 (s, 6 H), 0.86 (s, 9 H), 0.89 (s, 9 H), 1.24 (t, *J* = 7.6 Hz, 3 H), 4.10 (q, *J* = 7.6 Hz, 2 H), 4.22 (br m, 1 H), 4.51 (br m, 1 H), 5.02 (br s, 1 H), 5.18 (br s, 1 H), 5.62 (br s, 1 H); IR ($CHCl_3$) 1730, 1720, 1640, 1460, 1250, 1170, 1060, 1090, 900, 830 cm^{-1}; mass spectrum, *m/e* (relative intensity) 440 (M^+, 12), 425 (4), 383 (79), 75 (68), 73 (100); UV (EtOH) λ_{max} 222 nm (ε 8100).

Anal. Calcd for $C_{23}H_{44}O_4Si_2$: C, 62.67; H, 10.06. Found: C, 62.97; H, 9.86.

[3*S*-(1*Z*,3α,5β)]-2-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]ethanol (25). A solution of 5.40 g (12.25 mmol) of [3*S*-(1*Z*,3α,5β)-2-[3,5-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]-acetic acid ethyl ester (**24**) in 60 mL of toluene was treated at −78 °C under argon and over a period of 20 min with 20 mL (35.20 mmol) of a 1.76 M solution of diisobutylaluminum hydride in toluene. After the addition, stirring was continued or 30 min at −78 °C. The reaction mixture was then quenched by adding it to rapidly stirred 800 mL of 2 N potassium sodium tartrate, the organic phase separated, and the aqueous phase extracted with ethyl acetate. The combined organic extracts were washed with water and brine and dried (Na_2SO_4) and the solvents evaporated in vacuo. The residue was purified by rapid filtration through silica, using hexane–ethyl acetate (10:1) as eluent, to give 4.50 g (92% yield) of pure **25** as a crystalline white solid: mp 69–71 °C, $[\alpha]^{25}_D$ +7.9° (*c* 0.4, EtOH); ^{1}H NMR (100 MHz) δ 0.04 (s, 6 H), 0.09 (s, 6 H), 0.89 (s, 18 H), 1.83 (br t, *J* = 6.0 Hz, 2 H), 2.20 (br dd, *J* = 6.4, 12.0 Hz, 1 H), 2.41 (br dd, *J* = 4.0, 12.0 Hz, 1 H), 4.80 (m, 1 H), 4.20 (br d, *J* = 6.3 Hz, 2 H), 4.41 (br t, *J* = 6.0 Hz, 1 H), 4.77 (br s, 1 H), 5.17 (br s, 1 H), 5.54 (br t, *J* = 6.3 Hz, 1 H); IR ($CHCl_3$) 1475, 1465, 1250, 1090, 1070, 835 cm^{-1}; mass spectrum, *m/e* (relative intensity) 383 (1), 341 (8), 249 (15), 223 (7), 209 (44), 191 (18), 183 (21), 117 (18), 75 (87), 73 (100); UV (EtOH) λ_{max} 216 nm (ε 6300).

Anal. Calcd for $C_{21}H_{42}O_3Si_2$: C, 63.26; H, 10.62. Found: C, 63.16; H, 10.70.

[3*S*-(1*Z*,3α,5β)]-2-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]-1-chloroethane (26). A solution of 4.20 g (31.5 mmol) of *N*-chlorosuccinimide in 100 mL of dichloromethane was treated dropwise at 0 °C and under argon with 2.40 mL (32.7 mmol) of dimethyl sulfide over 15 min. A white, voluminous precipitate formed. After the addition, the mixture was stirred for an additional 15 min at 0 °C, then cooled

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at −20 °C, and treated dropwise with a solution of 6.12 g (15.35 mmol) of [3*S*-(1*Z*,3α,5β)]-2-[3,5-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]ethanol (**25**) in 50 mL of dichloromethane. After an additional 30 min of being stirred at −20 °C, the reaction mixture was allowed to come to room temperature, washed with water and then brine, and dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was purified by rapid filtration over silica, eluting with hexane–ethyl acetate (10:1), to give 5.89 g (91% yield) of pure **26** as a thick, colorless oil: ^{1}H NMR (100 MHz) δ 0.06 (s, 12 H), 0.88 (s, 18 H), 1.80 (m, 2 H), 2.17 (dd, *J* = 6.0, 13.8 Hz, 1 H), 2.41 (br dd, *J* = 3.2, 13.8 Hz, 1 H), 4.16 (d, *J* = 7.0 Hz, 2 H), 4.41 (br t, *J* = 6.0 Hz, 1 H), 4.96 (br s, 1 H), 5.22 (br s, 1 H), 5.52 (br t, *J* = 7.0 Hz, 1 H); IR ($CHCl_3$) 1475, 1465, 1260, 1090, 830 cm^{-1}; mass spectrum, *m/e* (relative intensity) 359 (6), 249 (25), 227 (31), 117 (21), 73 (100); UV (EtOH) λ_{max} 219 nm (ε 7190).

[3*S*-(1*Z*,3α,5β)]-[2-[3,5-Bis[[(1,1-dimethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]ethyl]diphenylphosphine Oxide (11). To a solution of 5.80 g (13.90 mmol) of [3*S*-(1*Z*,3α,5β)]-2-[3,5-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]-1-chloroethane (**26**) in 40 mL of anhydrous tetrahydrofuran at −70 °C, under argon, was added very slowly an approximately 0.3 M solution of lithium diphenylphosphide[19c] in tetrahydrofuran until the deep orange color of the reagent persisted. After the addition of a few drops of water, the reaction mixture was allowed to reach room temperature and the solvent evaporated in vacuo. The gummy residue was dissolved in 50 mL of dichloromethane and stirred vigorously with 120 mL of a 5% hydrogen peroxide solution for 1 h. The dichloromethane layer was separated and the aqueous phase extracted with dichloromethane, and the combined organic extracts were washed with aqueous sodium sulfite (2 N), water, and brine and then dried (Na_2SO_4). Evaporation of the solvent and chromatographic purification of the residue (1:1 hexane–ethyl acetate) gave 7.31 g (90% yield) of pure **11** as a thick, colorless oil. Crystallization from cyclohexane–hexane (4:1) at low temperature, gave white crystals containing 0.5 mol of cyclohexane: mp 54–55 °C; $[\alpha]^{25}_D$ −2.3° (*c* 0.5, EtOH); ^{1}H NMR (100 MHz) δ 0.04 (4 s, 12 H), 0.84 (s, 9 H), 0.90 (s, 9 H), 2.20 (br d, *J* = 6.4 Hz, 1 H), 2.40 (br d, *J* = 6.4 Hz, 1 H), 3.19 (dt, *J* = 9.0, 16.0 Hz, 1 H), 3.41 (dt, *J* = 9.0, 16.0 Hz, 1 H), 4.15 (br s, 1 H), 4.39 (m, 1 H), 4.77 (br s, 1 H), 5.15 (br s, 1 H), 5.34 (q, *J* = 9.0 Hz, 1 H); IR ($CHCl_3$) 1475, 1465, 1250, 1120, 1080, 830 cm^{-1}; mass spectrum, *m/e* (relative intensity) 582 (M^+, 2), 567 (2), 525 (64), 393 (40), 73 (100); UV (EtOH) λ_{max} 220 (ε 14 220), 258 (970), 265 (945), 272 nm (708).

Anal. Calcd for $C_{33}H_{51}O_3PSi_2$: C, 68.00; H, 8.82; P, 5.31. Found: C, 68.36; H, 9.08; P, 5.08.

[1*R*-[1α(*S),3aβ,4α,7aα]-Octahydro-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-β,7a-dimethyl-1*H*-indene-1-ethanol 4-Toluenesulfonate (29).** To a solution of 2.00 g (6.12 mmol) of [1*R*-[1α(*S**),3aβ,4α,7aα]-octahydro-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-β,7a-dimethyl-1*H*-indene-1-ethanol (**28**) in 50 mL of anhydrous pyridine kept at 0 °C was rapidly added 2.90 g (15.21 mmol) of *p*-toluenesulfonyl chloride and the resulting mixture stirred at 0 °C under argon for 19 h and then at room temperature for 3 h. Ice chips (150 mL) were then added, and after being stirred for 1 h, the mixture was partitioned between 500 mL of dichloromethane and 500 mL of ice cold 1 N sulfuric acid solution, and the aqueous phase was brought to pH 2 by addition of 2 N sulfuric acid and then extracted with 2 × 400 mL of dichloromethane. The combined organic extracts were washed with water, 2 N aqueous potassium bicarbonate, and brine, then dried (Na_2SO_4), and evaporated to dryness. The residue was purified by fast filtration through silica, using hexane–ethyl acetate (8:1) as the eluent, to give 2.81 g (95% yield) of pure **29** as a crystalline mass: mp 47–48 °C; $[\alpha]^{25}_D$ +34.1° (*c* 0.3, $CHCl_3$); ^{1}H NMR (200 MHz) δ 0.89 (s, 9 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 2.46 (s, 3 H), 3.82 (m, 1 H), 3.98 (m, 1 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.82 (d, *J* = 8.0 Hz, 2 H); IR ($CHCl_3$) 1360, 1140 cm^{-1}; mass spectrum, *m/e* (relative intensity) 423 (1), 229 (72), 177 (100).

Anal. Calcd for $C_{26}H_{44}O_4SiS$: C, 64.95; H, 9.23; S, 6.67. Found: C, 64.82; H, 9.11; S, 6.67.

[1*R*-[1α(*R),3aβ,4α,7aα]]-Octahydro-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1,5-dimethyl-3-hexynyl]-7a-methyl-1*H*-indene (31).** To a solution of 1.40 g (8.32 mmol) of 3-methyl-1-butyn-3-yl tetrahydropyranyl ether (**30**)[23] in 25 mL of anhydrous dioxane at 5 °C was added slowly under argon 5.2 mL (8.32 mmol) of a 1.6 M solution of *n*-butyllithium in hexane and the resulting mixture stirred for 0.5 h at 5 °C and 1 h at 25 °C. It was then treated dropwise with a solution of 1.00 g (2.08 mmol) of [1*R*-[1α(*S**),3aβ,4α,7aα]-octahydro-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-β,7a-dimethyl-1*H*-indene-1-ethanol 4-toluenesulfonate (**29**) in 5 mL of dioxane and the resulting mixture heated at reflux for 40 h. The cooled resulting brown suspension was poured into a mixture of ice and 2 N potassium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were washed with brine and dried (Na_2SO_4) and the solvent evaporated. The residue was purified by rapid chromatography on silica, eluted with hexane–ethyl acetate (50:1), to give 0.85 g (86% yield) of pure **31** as a colorless thick oil: ^{1}H NMR (400 MHz) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.91 (s, 9 H), 0.94 (s, 3 H), 1.04 (d, *J* = 6.4 Hz, 3 H), 1.48 (s, 3 H), 1.51 (s, 3 H), 3.49 (m, 1 H), 3.96 (m, 2 H), 5.07 (br s, 1 H); IR ($CHCl_3$) 2240, 1250, 1060, 1025 cm^{-1}; mass spectrum, *m/e* (relative intensity) 419 (1), 475 (2), 243 (36), 159 (100).

Anal. Calcd for $C_{29}H_{52}O_3Si$: C, 73.05; H, 10.99. Found: C, 72.91; H, 10.94.

[1*R*-[1α(*R),3aβ,4α,7aα]]-Octahydro-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1,5-dimethylhexyl]-7a-methyl-1*H*-indene (32).** A mixture of 1.50 g (3.15 mmol) of [1*R*-[1α(*R**),3aβ,4α,7aα]]-octahydro-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1,5-dimethyl-3-hexynyl]-7a-methyl-1*H*-indene (**31**), 50 mL of ethyl acetate, 0.30 g of anhydrous, powdered sodium hydrogen carbonate, and 0.10 g of 5% rhodium on carbon was stirred under 1 atm of hydrogen until gas uptake ceased (18 h). The resulting mixture was filtered through Celite and the catalyst washed repeatedly with ethyl acetate. The combined filtrates were evaporated to dryness to give 1.50 g (99% yield) of pure **32** as a colorless, thick oil: ^{1}H NMR (400 MHz) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.90 (s, 9 H), 0.91 (s, 3 H), 2.20 (s, 3 H), 2.21 (s, 3 H), 3.44 (m, 1 H), 3.95 (m, 2 H), 4.72 (br s, 1 H); IR ($CHCl_3$) 1475, 1375, 1255, 1075, 1030 cm^{-1}; mass spectrum, *m/e* (relative intensity) 321 (5), 245 (5), 159 (10), 135 (18), 75 (100).

Anal. Calcd for $C_{29}H_{56}O_3Si$: C, 72.44; H, 11.74. Found: C, 72.69; H, 11.42.

[1*R*-[1α(*R),3aβ,4α,7aα]]-Octahydro-4-hydroxy-α,α,ε,7a-tetramethyl-1*H*-indene-1-pentanol (33).** A solution of 860 mg (1.79 mmol) of [1*R*-[1α(*R**),3aβ,4α,7aα]]-octahydro-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy-1-[5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1,5-dimethylhexyl]-7a-methyl-1*H*-indene (**32**) in a mixture of 4 mL of dichloromethane and 25 mL of methanol was treated with 7.5 g of cation exchange resin AG 50W-X4 (200–400 mesh)[30] and stirred at room temperature for 1 h. After filtration and washing of the resin with methanol, the combined filtrates were evaporated to dryness in vacuo. The residue, dissolved in a mixture of 15 mL of acetonitrile and 12 mL of tetrahydrofuran, was treated with 8.5 mL of a 48% aqueous hydrofluoric acid and the resulting cloudy solution stirred at room temperature for 3 h. Water (30 mL) was then added and, after being stirred for 15 min, the resulting mixture extracted with 3 × 150 mL of dichloromethane. The combined extracts were then washed with 2 N potassium bicarbonate solution, brine, dried (Na_2SO_4), andd evaporated to dryness. The residue was purified by rapid chromatography through silica (using 2:1 hexane–ethyl acetate as the eluent) to give 440 mg (87% yield) of **33** as a crystalline white solid: mp 90–91 °C (after recrystallization from hexane–dichloromethane); $[\alpha]^{25}_D$ +51.4° (*c* 0.2, EtOH) [lit.[20b] mp 91–92 °C; $[\alpha]^{21}_D$ +44.7°]; ^{1}H NMR (200 MHz) δ 0.91 (d, *J* = 7.2 Hz, 3 H), 0.93 (s, 3 H), 1.22 (s, 6 H), 4.09 (br s, 1 H); IR (KBr) 3400, 1480, 1460, 1380, 1250, 1150 cm^{-1}; mass spectrum, *m/e* (relative intensity) 264 (11), 249 (9) 246 (10) 203 (4), 111 (100).

Anal. Calcd for $C_{10}H_{34}O_2$: C, 76.54; H, 12.13. Found: C, 76.17; H, 11.76.

[1*R*-[1α(*R),3aβ,7aα]]-Octahydro-1-(5-hydroxy-1,5-dimethylhexyl)-7a-methyl-4*H*-inden-4-one (10).** A solution of 170 mg (0.60 mmol) of [1*R*-[1β(*R**),3aβ,4α,7aα]-octahydro-4-hydroxy-α,α,ε,7a-tetramethyl-1*H*-indene-1-pentanol (**33**) in 2 mL of dichloromethane was added to a suspension of 350 mg (1.63 mmol) of pyridinium chlorochromate in 10 mL of dichloromethane and the resulting mixture stirred at room temperature for 3 h.

It was then diluted with ether and filtered through Celite. After evaporation of the solvents, the residue was triturated several times with ether and filtered, and the combined fitrates were evaporated to dryness. Chromatography on silica of the crude product obtained (eluent, 3:1 hexane–ethyl acetate) gave 157 mg (93% yield) of **10** as a colorless oil: $[\alpha]^{25}_D$ +17.9° (*c* 0.3, EtOH) [lit.[25] $[\alpha]_D$ +5.3° ($CHCl_3$)]; ^1H NMR (200 MHz) δ 0.64 (s, 3 H), 0.97 (d, *J* = 5.2 Hz, 3 H), 1.22 (s, 6 H); IR ($CHCl_3$) 3610, 1710, 1470, 1380, 1220 cm^{-1}; mass spectrum, *m/e* (relative intensity) 280 (M^+, 1), 262 (24), 247 (16), 178 (21), 159 (100).

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 76.69; H, 11.64.

[1*R*-[1α(*R),3aβ,7aα]]-Octahydro-1-[5-[(trimethylsilyl)oxy]-1,5-dimethylhexyl]-7a-methyl-4*H*-inden-4-one (34).** A solution of 150 mg (0.53 mmol) of [1*R*-[1α(*R**),3aβ,7aα]]-octahydro-1-(5-hydroxy-1,5-dimethylhexyl)-7a-methyl-4*H*-inden-4-one (**10**) in 100 mL of anhydrous dichloromethane was treated with 300 mg (2.54 mmol) of *N*-(trimethylsilyl)imidazole and stirred at room temperature under argon for 18 h. Water (1 mL) was then added, and, after being stirred for 30 min, the mixture was treated with additional water (50 mL) and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by rapid chromatography on silica, eluted with hexane–ethyl acetate (5:1), to give 185 mg (98%) of **34** as a colorless oil.

1α,25-Dihydroxycholecalciferol (4). A solution of 450 mg (0.77 mmol) of [3*S*-(1Z,3α,5β)]-[2[3,5-bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-2-methylenecyclohexylidene]ethyl]diphenylphosphine oxide (**11**) in 12 mL of anhydrous THF was cooled at −78 °C and treated dropwise under argon with 0.50 mL (0.77 mmol) of 1.55 M *n*-butyllithium in hexane. The resulting deep red solution was stirred for 5 min and then treated dropwise at −78 °C with a solution of 185 mg (0.52 mmol) of [1*R*-[1α-(*R**),3aβ,7aα]]-octahydro-1-[5-[(trimethylsilyl)oxy]-1,5-dimethylhexyl]-7a-methyl-4*H*-indene-4-one (**34**) in 3 mL of anhydrous THF over 10 min, and the stirring was continued under argon at −78 °C for 2 h. After the addition of 4 mL of a 1:1 mixture of 2 N sodium potassium tartrate and 2 N potassium bicarbonate, the reaction mixture was allowed to come to room temperature and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by fast filtration through silica (eluent, 20:1 hexane–ethyl acetate), then dissolved in 10 mL of anhydrous THF, treated with 2.5 mL (2.50 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF, and stirred at room temperature under argon for 24 h. After partial evaporation of the solvent in vacuo, the residue was diluted with water (50 mL) and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried (Na_2SO_4), and evaporated to dryness. The crude product obtained was purified by fast filtration through silica (eluent, ethyl acetate) to give 195 mg (90% yield from **34**) of 1α,25-dihydroxycholecalciferol (**4**) as a white solid: mp 118–119 °C (after recrystallization from methyl formate): $[\alpha]^{25}_D$ +47.9° (*c* 0.5, EtOH), ^1H NMR (100 MHz, CD_3OD) δ 0.57 (s, 3 H), 0.96 (d, *J* = 6.0 Hz, 3 H), 1.16 (s, 6 Hz), 4.10 (br m, 1 H), 4.33 (br m, 1 H), 4.87 (br s, 1 H), 5.28 (br s, 1 H), 6.08 (d, *J* = 11.6 Hz, 1 H), 6.32 (d, *J* = 11.6 Hz, 1 H); IR (KBr) 3325, 1650, 1620, 1470, 1430, 1380, 1140, 1070, 1050, 900 cm^{-1}; mass spectrum, *m/e* (relative intensity) 416 (M^+, 5), 398 (10), 380 (5), 285 (8), 134 (100); UV (EtOH) λ_{max} 264 nm (ε 18783).

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.84; H, 10.65. Found: C, 77.80; H, 10.72.

Reaction of Nitrone 35 with Methyl 3,3-Dimethylacrylate (36). A solution of 7.50 g (29.6 mmol) of [1*R*-[1α(*R**,*Z*)-3aβ,4α,7aα]]-octahydro-7a-methyl-1-[1-methyl-3-(methylimino)propyl]-1*H*-inden-4-ol *N*-oxide (**35**)[21] and 10.13 g (89 mmol) of methyl 3,3-dimethylacrylate (**36**) in 75 mL of xylenes (purified by percolation through a silica gel column followed by distillation) was heated under a nitrogen atmosphere in an oil bath at 140 °C for 15 h. Evaporation under reduced pressure on a rotary evaporator gave 11.6 g of crude product. Chromatography on 40–60 mesh silica gel (0.5 m × 45 mm column) at 60 psi with 3:1 dichloromethane–ethyl acetate as the eluent gave, on combining fractions according to TLC (R_f 0.54, 2:1 dichloromethane–ethyl acetate), and subsequent rechromatography using 5:1 dichloromethane–ethyl acetate, afforded 4.5 g (41% yield) of pure [3*S*-[3β,4α,3[(2*R**),1*R**(1α,3aβ,4α,7aβ)]]]-3-[2-(octahydro-4-hydroxy-7a-methyl-1*H*-inden-1-yl)propyl]-2,5,5-trimethyl-4-isoxazolidinecarboxylic acid methyl ester (**38**). An analytical sample had mp 80–81 °C (from hexanes) and $[\alpha]^{25}_D$ +102.6° (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz) δ 0.89 (s, 3 H), 0.92 (d, *J* = 6 Hz, 3 H), 1.17 (s, 3 H), 1.44 (s, 3 H), 2.67 (s, 3 H), 2.78 (d, *J* = 8.5 Hz, 1 H), 3.07 (br t, *J* = 10 Hz, 1 H), 3.71 (s, 3 H), 4.08 (br s, 1 H); IR ($CHCl_3$) 3625, 1737 cm^{-1}; mass spectrum, m/*e* (relative intensity) 367 (6), 172 (100), 140 (5).

Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.90; H, 10.25; N, 3.77.

The more polar (R_f 0.3) fraction amounted to 4.4 g (40% yield) of [3*R*-[3α,4β,3-[(2*R**),1*R**(1α,3aβ,4α,7aα)]]]-3-[2-(octahydro-4-hydroxy-7a-methyl-1*H*-inden-1-yl)propy]-2,5,5-trimethyl-4-isoxazolidinecarboxylic acid methyl ester (**37**) as a colorless oil. An analytical sample had $[\alpha]^{25}_D$ −10.8° (*c* 0.6, $CHCl_3$): ^1H NMR (200 MHz) δ 0.84 (s, 3 H), 0.96 (d, *J* = 7 Hz, 3 H), 1.18 (s, 3 H), 1.45 (s, 3 H), 2.73 (s, 3 H), 2.90 (d, *J* = 9 Hz, 1 H), 3.17 (br m, 1 H), 3.74 (s, 3 H), 4.09 (br s, 1 H); IR ($CHCl_3$) 3620, 1735, 2780 cm^{-1}; mass spectrum, *m/e* (relative intensity) 367 (7), 336 (0.5), 254 (1), 172 (100), 140 (7), 28 (74).

Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.66; H, 9.92; N, 3.93.

Reequilibration of 37. A solution of 557 mg of **37**, 1 mL of methyl 3,3-dimethylacrylate (**36**), and 5.0 mL of xylenes (distilled from CaH_2) was heated at reflux for 5 days. The equilibration was monitored by 200-MHz NMR (a few drops were removed and evaporated to dryness with a vacuum pump) at δ 3.696 vs. 3.693 (OMe) and at δ 2.702 vs. 2.656 (NMe). After 2 days the ratio of **37** to **38** was 2:1; after 5 days it was 45:55.

The reaction mixture was chromatographed directly on three, 0.5 m × 25 mm silica gel columns in series at 200 psi with 2:1 CH_2Cl_2–EtOAc as the eluent. The fractions were combined according to TLC and afforded 208 mg (37%) of **38** and 180 mg (32%) of **37**.

[3*S*-[3β,4α,3-[(2*R),1*R**(1α,3aβ,4α,7aα)]]]-3-[2-(Octahydro-4-hydroxy-7a-methyl-1*H*-inden-1-yl)propyl]-2,5,5-trimethyl-4-isoxazolidinemethanol (39).** To a solution of 3.0 g (8.2 mmol) of [3*S*-[3β,4α,3-[(2*R**),1*R**(1α,3aβ,4α,7aα)]]]-3-[2-(octahydro-4-hydroxy-7a-methyl-1*H*-inden-1-yl)propy]-2,5,5-trimethyl-4-isoxazolidinecarboxylic acid methyl ester (**38**) in 100 mL of dry tetrahydrofuran under an argon atmosphere was added portionwise 930 mg (24.5 mmol) of lithium aluminum hydride over 10 min. After being stirred for 3.5 h at room temperature, the suspension was cooled in an ice bath and 1.0 mL of water was added dropwise followed by 1.5 mL of 1 N sodium hydroxide. After 15 min, the granular suspension was filtered (glass fiber paper) and the filter cake washed with 2 × 100 mL of ether. The combined filtrates were evaporated under reduced pressure to give 2.85 g of residue. Chromatography on silica gel (0.3 m × 25 mm column) with ethyl acetate as the eluent afforded 2.49 g (90% yield) of [3*S*-[3β,4α,3-[(2*R**),1*R**(1α,3aβ,4α,7aα)]]]-3-[2-(octahydro-4-hydroxy-7a-methyl-1*H*-inden-1-yl)-propyl-2,5,5-trimethyl-4-isoxazolidinemethanol (**39**). An analytical sample had mp 153 °C (acetonitrile): $[\alpha]^{25}_D$ +106.4° (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz) δ 0.95 (d, *J* = 6 Hz, 3 H), 0.95 (s, 3 H), 1.29 (s, 3 H), 1.36 (s, 3 H), 2.36 (m, 1 H), 2.64 (s, 3 H), 3.72 (d, *J* = 6 Hz, 2 H), 4.08 (br s, 1 H); IR ($CHCl_3$) 3630, 1230, cm^{-1}; mass spectrum, *m/e* (relative intensity) 339 (8), 324 (0.5), 144 (100), 126 (4).

Anal. Calcd for $C_{20}H_{37}NO_3$: C, 70.75; H, 10.98; N, 4.13. Found: C, 70.86; H, 10.88; N, 4.02.

[1*R*-[1α(*R),3aβ,4α,7aα,(3*S**,4*S**)]]-Octahydro-7a-methyl-1-[1-methyl-2-[4-[[[(4-methylphenyl)sulfonyl]oxy]-methyl]-2,5,5-trimethyl-3-isoxazolidinyl]ethyl]inden-4-ol (40).** To a stirred solution of 2.49 g (7.33 mmol) of [3*S*-[3β,4α,3-[(2*R**),1*R**(1α,3aβ,4α,7aα)]]]-3-[2-octahydro-4-hydroxy-7a-methyl-1*H*-inden-1-yl)propyl]-2,5,5-trimethyl-4-isoxazlidinemethanol (**39**) in 75 mL of dry pyridine under argon atmosphere cooled in an ice bath to 5 °C was added portionwise 2.10 g (11.0 mmol) of recrystallized *p*-toluenesulfonyl chloride over 10 min. The bath was removed and the reaction mixture allowed to stir at room temperature for 48 h, then it was cooled to 5 °C, and 5.0 mL of water was added. After 30 min, the reaction mixture was poured into 2 L of cold 2 N sulfuric acid and then extracted with 3 × 150 mL of dichloromethane which was back-washed with 50

mL of 10% sodium bicarbonate. The combined dichloromethane phases were dried (sodium sulfate), filtered, and evaporated to give 3.28 g (91%) of [1*R*-[1α(*R**),3aβ,4α,7aα(3*S**,4*S**)]]-octahydro-7a-methyl-1-[1-methyl-2-[4-[[[(4-methylphenyl)sulfonyl]oxy]methyl]2,5,5-trimethyl-3-isoxazolidinyl]ethyl]-1*H*-inden-4-ol (**40**). An analytical sample of the hydrate had mp 114–115 °C (from hexanes): $[\alpha]^{25}_D$ +53.3° (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz) δ 0.84 (d, *J* = 6 Hz, 3 H), 0.86 (s, 3 H), 1.16 (s, 3 H), 1.32 (s, 3 H), 2.47 (s, 3 H), 2.59 (s, 3 H), 3.96 (dd, *J* = 4.5, 9.5 Hz, 1 H), 4.09 (m, 2 H), 7.36 (d, *J* = 8 Hz, 2 H), 7.79 (d, *J* = 8 Hz, 2 H); IR ($CHCl_3$) 3630, 1230 cm^{-1}; mass spectrum, *m/e* (relative intensity) 493 (10), 475 (0.5), 478 (0.5), 298 (100), 126 (52).

Anal. Calcd for $C_{27}H_{43}NO_5S{\cdot}H_2O$: C, 63.37; H, 8.86; N, 2.74; S, 6.26. Found: C, 63.45; H, 8.84; N, 2.97; S, 6.52.

[1*R*-[1α(*R),3aβ,4α,7aα,(3*S**,4*S**)]]-Octahydro-7a-methyl-1-[1-methyl-2-(2,4,5,5-tetramethyl-3-isoxazolidinyl)ethyl]-1*H*-inden-4-ol (41).** To a stirred suspension of 3.28 g (6.65 mmol) of [1*R*-[1α(*R**),3aβ,4α,7aα(3*S**,4*S**)]]-octahydro-7a-methyl-1-[1-methyl-2-[4-[[[(4-methylphenyl)sulfonyl]oxy]-methyl]-2,5,5-trimethyl-3-isoxazolidinyl]ethyl-1*H*-inden-4-ol (**40**) in 100 mL of dry tetrahydrofuran under an argon atmosphere was added portionwise 756 mg (19.9 mmol) of lithium aluminum hydride over 10 min. The suspension was heated at reflux for 1 h, left standing at room temperature overnight, and then cooled in an ice bath. After the addition of 10 mL of water followed by 1.5 mL of 1 N sodium hydroxide, the suspension was stirred for 30 min and then filtered (glass fiber paper). The filter cake was washed with 2 × 100 mL of ether, and the combined filtrates were evaporated to give 2.48 g of residue. Chromatography on silica gel (0.5 m × 25 mm column) at 60 psi using 1:1 hexanes–ethyl acetate as the eluent afforded 1.90 g (80% yield) of [1*R*-[1α-(*R**),3aβ,4α,7aα,(3*S**,4*S**)]]-octahydro-7a-methyl-1-[1-methyl-2-(2,4,5,5-tetramethyl-3-isoxazolidinyl)ethyl-1*H*-inden-4-ol (**41**) as a colorless oil: ^1H NMR (200 MHz) δ 0.95 (s, 3 H), 0.96 (d, *J* = 6 Hz, 3 H), 1.02 (d, *J* = 7 Hz, 3 H), 1.11 (s, 3 H), 1.27 (s, 3 H), 2.26 (br t, *J* = 9 Hz, 1 H), 2.64 (s, 3 H), 4.09 (br s, 1 H); IR ($CHCl_3$) 3625, 2950 cm^{-1}; mass spectrum, *m/e* (relative intensity) 323 (4), 308 (0.5), 128 (100).

[1*R*-[1α(*R,*S**,*S**),3aβ,4α,7aα]]-Octahydro-γ-(dimethylamino)-4-hydroxy-α,α,β,ε,7a-pentamethyl-1*H*-indene-1-pentanol (42).** A solution of 1.556 g (4.8 mmol) of [1*R*-[1α-(*R**),3aβ,4α,7aα,(3*S**,4*S**)]]-octahydro-7a-methyl-1-[1-methyl-2-(2,4,5,5-tetramethyl-3-isoxazolidinyl)ethyl]-1-inden-4-ol (**41**) and 0.5 mL (1.0 g, 7.2 mmol) of freshly distilled methyl iodide in 75 mL of dry toluene was heated in a 60 °C oil bath under argon atmosphere for 17 h. The suspension was evaporated under reduced pressure, and the methiodide residue was treated at room temperature with 100 mL of aqueous acetic acid (1:1, v/v) and 1.72 g (26.3 mmol) of zinc dust for 2.5 h. After evaporation under reduced pressure, the residue was partitioned between 100 mL of ethyl acetate and 25 mL of 1.5 N ammonium hydroxide followed by 25 mL of brine wash. The aqueous phase was extracted with 3 × 50 mL of ethyl acetate in a countercurrent manner. The ethyl acetate phases were combined, dried (sodium sulfate), filtered, and evaporated to give 1.554 g of crude product. Chromatography on silica gel (0.5 m × 25 mm column) afforded, on elution with ethyl acetate–triethylamine (95:5), 1.46 g (89% yield) of pure [1*R*-[1α(*R**,*S**,*S**),3aβ,4α,7aα]]-octahydro-γ-(dimethylamino)-4-hydroxy-α,α,β,ε,7a-pentamethyl-1*H*-indene-1-pentanol (**42**). An analytical sample had mp 180–181 °C (from EtOAc): $[\alpha]^{25}_D$ +4.79° (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz) δ 0.83 (d, *J* = 7 Hz, 3 H), 0.94 (s, 3 H), 0.95 (d, *J* = 6 Hz, 3 H), 1.12 (s, 3 H), 1.18 (s, 3 H), 2.18 (s, 6 H), 2.60 (dd, *J* = 8, 10 Hz, 1 H), 4.09 (br s, 1 H); IR ($CHCl_3$) 3625, 2795 cm^{-1}; mass spectrum, *m/e* (relative intensity) 324 (1), 252 (100), 163 (2), 144 (4), 86 (11).

Anal. Calcd for $C_{21}H_{41}NO_2$: C, 74.28; H, 12.17; N, 4.12. Found: C, 74.52; H, 12.23; N, 4.10.

[1*R*-[(1α-(*R),2*E*,4*S**,3aβ,4α,7aα]]-Octahydro-1-(5-hydroxy-1,4,5-trimethyl-2-hexenyl)-7a-methyl-1*H*-inden-4-ol (43).** A solution of 679 mg (2.0 mmol) of [1*R*-[1α-(*R**,*S**,-*S**),3aβ,4α,7aα]]-octahydro-γ-(dimethylamino)-4-hydroxy-α,α,-β,ε,7a-pentamethyl-1*H*-indene-1-pentanol (**42**) and 0.35 mL (850 mg, 6.0 mmol) of freshly distilled methyl iodide in 10 mL of toluene (dried over 4A molecular sieves) was heated at 70 °C under an argon atmosphere for 20 h. After evaporation under reduced pressure, and residue was dissolved in 25 mL of distilled *tert*-butyl alcohol under an argon atmosphere, and 450 mg (4.0 mmol) of potassium *tert*-butoxide was added. The suspension was heated at reflux for 5 h, cooled to room temperature, and, after the addition of 0.5 mL of water, evaporated to dryness. The residue was triturated with 2 × 25 mL of dichloromethane to give 0.71 g of crude product. Chromatography on 40–60 mesh silica gel (0.3 m × 25 mm column) at 42 psi, with 3:1 hexanes–ethyl acetate as the eluent and a combination of fractions according to TLC (same eluent, R_f 0.21) afforded 460 mg (78% yield) of [1*R*-[(1α-(*R**),2*E*,4*S**,3aβ,4α,7aα]]-octahydro-1-(5-hydroxy-1,4,5-trimethyl-2-hexenyl)-7a-methyl-1*H*-inden-4-ol (**43**). An analytical sample had mp 103–104 °C (from hexanes): $[\alpha]^{25}_D$ +2.01° (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz) δ 0.95 (s, 3 H), 0.99 (d, *J* = 7 Hz, 3 H), 1.01 (d, *J* = 7 Hz, 3 H), 1.13 (s, 3 H), 1.17 (s, 3 H), 4.09 (br s, 1 H), 5.32 (m, 2 H); IR ($CHCl_3$) 3615 cm^{-1}; mass spectrum, *m/e* (relative intensity) 279 (1), 261 (3), 243 (2), 236 (10), 218 (10), 203 (4), 181 (17), 163 (48), 135 (91), 81 (95), 59 (100).

Anal. Calcd for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.32; H, 11.57.

A less polar fraction (TLC, R_f 0.4) amounted to 133 mg of [1*R*-[1α(1*R**,*Z*),3aβ,4α,7aα]]-octahydro-7a-methyl-1-(1-methyl-3-pentenyl)-1*H*-inden-4-ol (**45**). An analytical sample, obtained by Kugelrohr distillation, 128 °C (0.1 mm), as an oil had $[\alpha]^{25}_D$ +29.6° (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz) δ 0.89 (d, *J* = 7 Hz, 3 H), 0.94 (s, 3 H), 1.60 (d, *J* = 6 Hz, 3 H), 4.09 (br s, 1 H), 5.3–5.6 (m, J_{cis} = 12 Hz, 2 H); IR ($CHCl_3$) 3630, 1660 cm^{-1}; mass spectrum, *m/e* (relative intensity) 236 (1), 221 (1), 218 (4), 203 (3), 181 (25), 163 (100), 81 (45), 55 (42).

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.07; H, 12.01.

[1*R*-[1α(1*R,2*E*,4*S**),3aβ,7aα]-Octahydro-1-(5-hydroxy-1,4,5-trimethyl-2-hexenyl)-7a-methyl-4*H*-inden-4-one (12).** With using the procedure described for the preparation of **10**, 265 mg (0.90 mmol) of [1*R*-[1α(1*R**,2*E*,4*S**),3aβ,4α,7aα]-octahydro-1-(5-hydroxy-1,4,5-trimethyl-2-hexenyl)-7a-methyl-1*H*-inden-4-ol (**43**) was converted to 239 mg (91% yield) of **12** as white crystals, mp 101–102 °C (after recrystallization from hexane–dichloromethane): $[\alpha]^{25}_D$ –6.9° (*c* 0.5, EtOH); ^1H NMR (200 MHz) δ 0.64 (s, 3 H), 100 (d, *J* = 6.8 Hz, 3 H), 1.08 (d, *J* = 6.4 Hz, 3 H), 1.13 (s, 3 H), 1.16 (s, 3 H), 5.33 (br s, 2 H); IR (KBr) 3475, 1680, 1450, 1380, 1360, 1110, 965 cm^{-1}; mass spectrum, *m/e* (relative intensity) 277 (2), 234 (18), 82 (98), 59 (100).

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.86; H, 10.95.

[1*R*-[1α(1*R,2*E*,4*S**),3aβ,7aα]-Octahydro-1-[5-[(trimethylsilyl)oxy]-1,4,5-trimethyl-2-hexenyl]-7a-methyl-4*H*-inden-4-one (44).** Following the procedure described for the preparation of **34**, 135 mg (0.46 mmol) of [1*R*-[1α-(1*R**,2*E*,4*S**),3aβ,7aα]-octahydro-1-(5-hydroxy-1,4,5-trimethyl-2-hexenyl)-7a-methyl-4*H*-inden-4-one (**12**) was converted to 214 mg (88% yield) of pure **44** as a colorless oil.

1α,25-Dihydroxyergocalciferol (7). Following the procedure described for the preparation of **4** and with 610 mg (1.05 mmol) of the phosphine oxide **11** and 214 mg (0.59 mmol) of [1*R*-[1α-(1*R**,2*E*,4*S**),3aβ,7aα]-octahydro-1-[5-[(trimethylsilyl)oxy]-1,4,5-trimethyl-2-hexenyl)-7a-methyl-4*H*-inden-4-one (**44**), 230 mg (91% yield based on **44**) of pure 1α,25-dihydroxyergocalciferol (**7**) was obtained as white crystals, mp 169–170 °C (from methyl formate): $[\alpha]^{25}_D$ +47.2° (*c* 0.2, EtOH); ^1H NMR (200 MHz) δ 0.55 (s, 3 H), 0.98 (d, *J* = 7.6 Hz, 3 H), 1.03 (d, *J* = 7.5 Hz, 3 H), 1.12 (s, 3 H), 1.16 (s, 3 H), 4.25 (br s, 1 H), 4.44 (br s, 1 H), 4.98 (s, 1 H), 5.32 (s, 1 H), 5.32 (AB q, *J* = 14.8 Hz, Δγ = 28 Hz, 2 H), 6.01 (d, *J* = 11.2 Hz), 6.38 (d, *J* = 11.2 Hz); IR (KBr), 3400, 1640, 1450, 1440, 1375, 1060 cm^{-1}; mass spectrum, *m/e* (relative intensity) 428 (M^+, 6), 410 (14), 392 (6), 352 (8), 152 (39), 134 (100); UV (EtOH) λ_{max} 264 nm (ε 18 560).

Anal. Calcd for $C_{28}H_{44}O_3$: C, 78.46; H, 10.35. Found: C, 78.07; H, 10.64.

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81522-68-1; **12**, 95716-68-0; **14**, 39903-97-4; **15** (isomer 1), 81570-18-5; **15** (isomer 2), 81570-19-6; **16**, 81506-17-4; **17**, 81506-18-5; **18**, 81506-19-6; **19**, 81506-20-9; **21**, 81506-21-0; **22**, 81506-22-1; **23**, 81506-23-2; **24**, 81570-20-9; **25**, 81506-24-3; **26**, 81506-25-4; **28**, 100928-03-8; **29**, 100928-04-9; **30**, 27943-46-0; **31**, 103095-15-4; **32**, 103095-16-5; **33**, 66774-84-3; **34**, 81506-41-4; **35**, 103189-00-0; **35i**, 83872-38-2; **36**, 924-50-5; **37**, 103189-01-1; **37i**, 103189-73-7; **38**, 95716-62-4; **38i**, 103095-18-7; **39**, 95716-63-5; **40**, 95716-64-6; **41**, 95716-65-7; **42**, 95716-66-8; **43**, 95716-67-9; **44**, 95716-69-1; **45**, 103095-17-6; $(EtO)_2POCH_2CO_2Et$, 867-13-0; Ph_2PLi, 4541-02-0; *tert*-butyldimethylsilyl chloride, 18162-48-6; *N*-(trimethylsilyl)-imidazole, 18156-74-6.

An Asymmetric Synthesis and Absolute Configuration of (*S*)-(−)-Deplancheine

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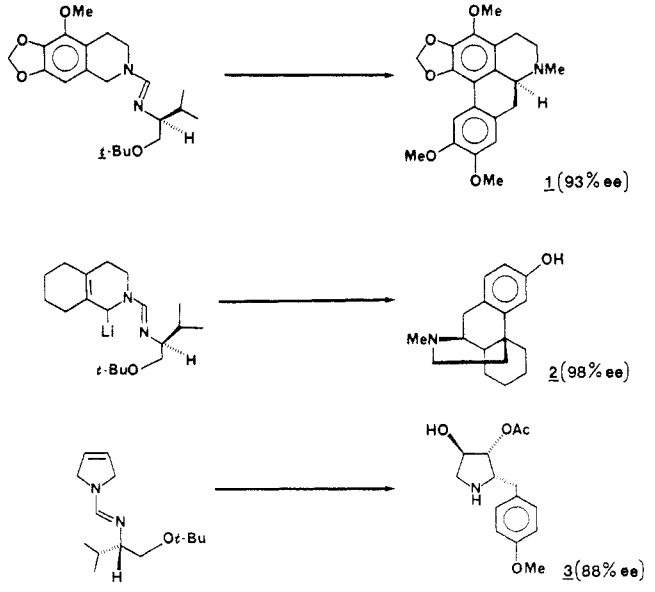
An asymmetric synthesis of (*S*)-(−)-deplancheine has been achieved in 96.5% ee via the chiral valine-based formamidine **8** of β-carboline. Alkylation of the latter, via its lithio salt, with the appropriate alkyl bromide **19c** gave the highly enantioenriched intermediate **20**, which was carried forward to the title product. On the basis of the stereochemical properties of deplancheine, the original assignment of absolute configuration (*S*) has now been reassigned as *R*-(+).

In our continuing study to evaluate the synthetic utility of α-amino carbanions derived from achiral and chiral formamidines,[1] we have been fortunate to reach a number of naturally occurring compounds in high enantiomeric purity. Additional achievements, since the review report, focused on the asymmetric total synthesis of the aporphine alkaloid (+)-ocoteine (**1**),[2] the morphinan dextrorphan (**2**),[3] and the antibiotic anisomycin **3**, as its unnatural antipode.[4] These processes occur with high asymmetric induction and involve relatively few synthetic steps, making this route to alkaloids one of considerable efficiency.



We now report that indole alkaloids are also accessible via the chiral formamidines, and to demonstrate this we have prepared the alkaloid (−)-deplancheine in greater than 95% ee and established the correct absolute configuration as *R*-(+).

(+)-Deplancheine (**4**) was recently isolated[5] from the New Caledonian plant *Alstonia deplanchei* van Heurck et Mueller Arg. (Apocyanaceae) and assigned the *S* configuration on the basis of an analogy with the majority of indole alkaloids. After its structure elucidation, a number

(S)-4 (R)-4

of total syntheses were reported,[6] while one synthesis was described before it was known as a natural product.[7] However, all of the synthetic approaches led to racemic material, thus no question regarding its absolute configuration became an issue. During the course of the asymmetric synthesis of **4**, we were forced to the conclusion that the original assignment was incorrectly made and that natural deplancheine possesses the *R* configuration. The synthesis of (*S*)-(−)-deplancheine has been performed by using two slightly different routes which differ markedly in their overall yield and these will be described herein.

In our anticipated scheme to reach deplancheine, we felt that β-carboline (**5**) would serve as an appropriate starting point.[8] Thermal exchange with the *N*,*N*-dimethylformamidine of (*S*)-*tert*-butylvalinol[3b] afforded the chiral carboline derivative **7** in 80% yield. The indole nitrogen was protected as its methoxymethyl ether by using potassium

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