Nickel-Mediated Conjugate Addition. Elaboration of Calcitriol from Ergocalciferol

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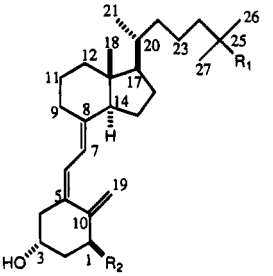
A convenient method for introducing the side chain of the hormone calcitriol (**3**) was achieved by coupling the nickel(0) complex derived from ethyl acrylate with the C-22 iodides **15**, **16**, **27**, and **30** to give the corresponding esters **18**, **21**, **28**, and **23** in yields of 73–82%. Iodide **15** was also coupled with the Ni(0) complex derived from methyl vinyl ketone. The C-22 iodides **15** and **27** were obtained from ergocalciferol (**6**) and the 1(*S*),3(*R*)-bis[(*tert*-butyldimethylsilyl)oxy]-(5*E*,7*E*)-ergocalciferol derivative **24**, respectively, by selective ozonolysis of their SO_2 adducts, followed by in situ reduction of the ozonides with $NaBH_4$ and iodination of the derived alcohols **14** and **26** with I_2/PPh_3/imidazole. The triene iodide **16** was prepared by extrusion of SO_2 from **15**, while **30** was obtained from the corresponding alcohol **29**. Extrusion of SO_2 from **21** and **28** gave the 5(*E*),7(*E*)-trienes **18** and **23**, respectively. The latter was also made from the former by C-1 hydroxylation with selenium dioxide followed by silylation with *tert*-butyldimethylsilyl chloride and chromatographic separation. Completion of the synthesis of **3** was accomplished by treating **23** with methylmagnesium bromide to give **31**, followed by desilylation with *n*-$Bu_4N^+F^-$ and triplet-sensitized photoisomerization. Alternatively, **31** was photoisomerized to **33**, desilylation of which gave **3**. Alcohol **33** was also prepared by the reaction of the 5*Z*,7*E*-triene ester **34**, which was obtained by the photoisomerization of **23**, with methylmagnesium bromide.

Vitamin D_3 (cholecalciferol, **1**) is the principal D vitamin responsible for the maintenance of calcium and phosphorus homeostasis.[1] A deficiency of **1** leads to rickets in children and osteomalacia in adults. It is now fairly well established that to become biologically active, **1** undergoes two hydroxylations: the first occurs in the liver to give 25-hydroxycholecalciferol (calcidiol, **2**), the major circulating form of the vitamin, and the second in the kidney to produce 1α,25-dihydroxycholecalciferol (calcitriol, **3**), the hormonally active form of the vitamin.[2] Calcitriol is currently used to treat osteodystrophy due to renal failure and (experimentally) primary osteoporosis.[3] In addition to its classical role in calcium homeostasis, calcitriol promotes normal cell differentiation and regulates the differentiation and proliferation of myeloid leukemia cells[4] and is therefore of some interest in the treatment of psoriasis[5] and certain types of cancer.[6] There is also evidence to implicate **3** in immune responses.[7] The receptors for **3**, which are present in a variety of tissues, belong to the steroid/thyroid/retinoid family of receptors.[8]



1: $R_1 = R_2 = H$
2: $R_1 = OH$, $R_2 = H$
3: $R_1 = R_2 = OH$

Because of the myriad of biological responses associated with it, it is not surprising that there have been considerable efforts to find efficient syntheses of calcitriol and of analogues that might possess better therapeutic indices.[9] Essentially, three principal approaches have been pursued for the synthesis of **3**.[10,11] The most common is the classic Windaus-type synthesis, adum-

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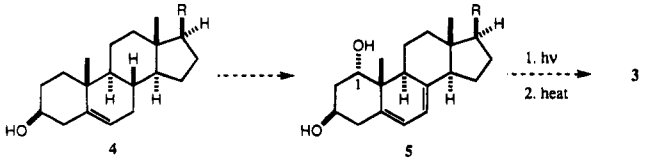
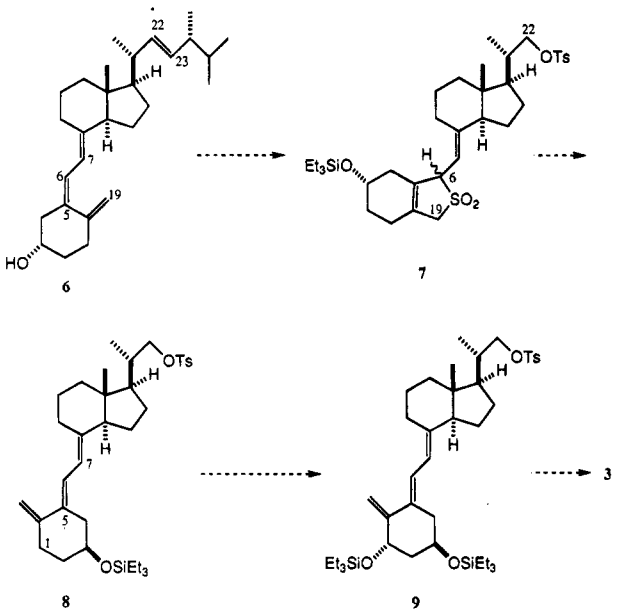
Scheme 1

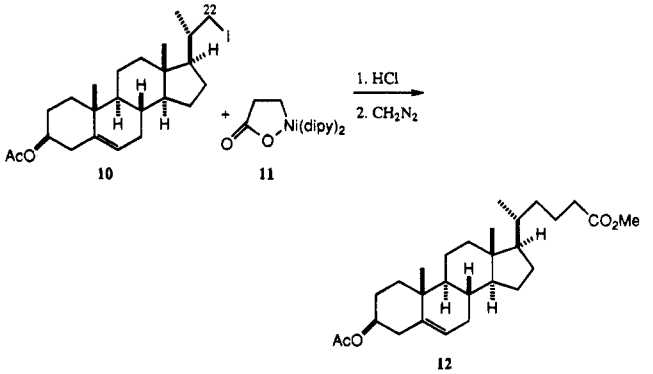


Scheme 2



brated in Scheme 1, which starts from cheap steroid precursors. However, problems associated with introduction of the 1α-hydroxy group, preparation of the 5,7-diene in ring B, and the photochemical electrocyclic opening of this ring, have made syntheses by this process inefficient. A second approach to **3** is through total and formally total syntheses, but for various reasons (primarily length and practicality) these are considered unsuitable for the large scale production of the bulk drug substance in a cost-effective manner. The third approach (Scheme 2), devised by Barton, Hesse, and their collaborators,[12] starts from readily available ergocalciferol (vitamin D_2, **6**) and

Scheme 3



entails three main chemical operations: selective ozonolysis of the C-22 double bond of an ergocalciferol derivative in which the sensitive triene unit is protected by reaction of the C-5 and C-19 double bonds with SO_2, C-1 hydroxylation of the 5(*E*),7(*E*)-triene derivative **8** with selenium dioxide, and attachment of the calcitriol side chain by a Schlosser coupling of the tosylate **9** with the triethylsilyl derivative of 3-hydroxy-3-methylbromobutane.

We describe herein syntheses of **3** from **6** based on the Barton–Hesse strategy, using, as the most salient feature, an under-utilized nickel-mediated conjugate addition of the C-22 iodides **15**, **16**, **27**, and **30** to an electron-deficient alkene (ethyl acrylate or methyl vinyl ketone) as a means of installing the calcitriol side chain. Our syntheses of calcitriol proceed in *ca.* 10% overall yield from **6** and are suitable for the large scale preparation of this important hormone.

It should be noted that Schonecker et al. have recently reported[13] a related method of introducing the steroid side chain that involves alkylation of the nickelacycle **11**, prepared from succinic anhydride, nickel acetylacetonate, and triethylaluminum, with the C-22 steroidal iodide **10** (Scheme 3).

Results and Discussion

As outlined in Scheme 4, the known[12] C-6 epimeric SO_2 adducts **13** derived from ergocalciferol **6** were ozonized at −10 °C in a mixture of CH_2Cl_2 and methanol followed by direct reduction of the ozonides with sodium borohydride to give the C-22 alcohols **14** in 87% yield. Conversion of **14** into the C-6 epimeric iodides **15** using I_2/PPh_3/imidazole,[14] followed by extrusion of SO_2 from **15** by heating in ethanol in the presence of $NaHCO_3$,[12] provided the 5(*E*),7(*E*)-triene iodide **16** in 92% yield. With the ready availability of **16**, our plan was to effect its conjugate addition to an appropriate electron-deficient alkene. However, various attempts to execute this with methyl vinyl ketone (MVK) using cuprate chemistry,[15] and the sonication conditions developed by Luche[16] using the reagents Zn/CuI and Zn/Ni(acac)$_2$, failed. In most cases iodide **16** was recovered, along with possibly traces of the desired product **17**, the tetraene **19**, resulting from

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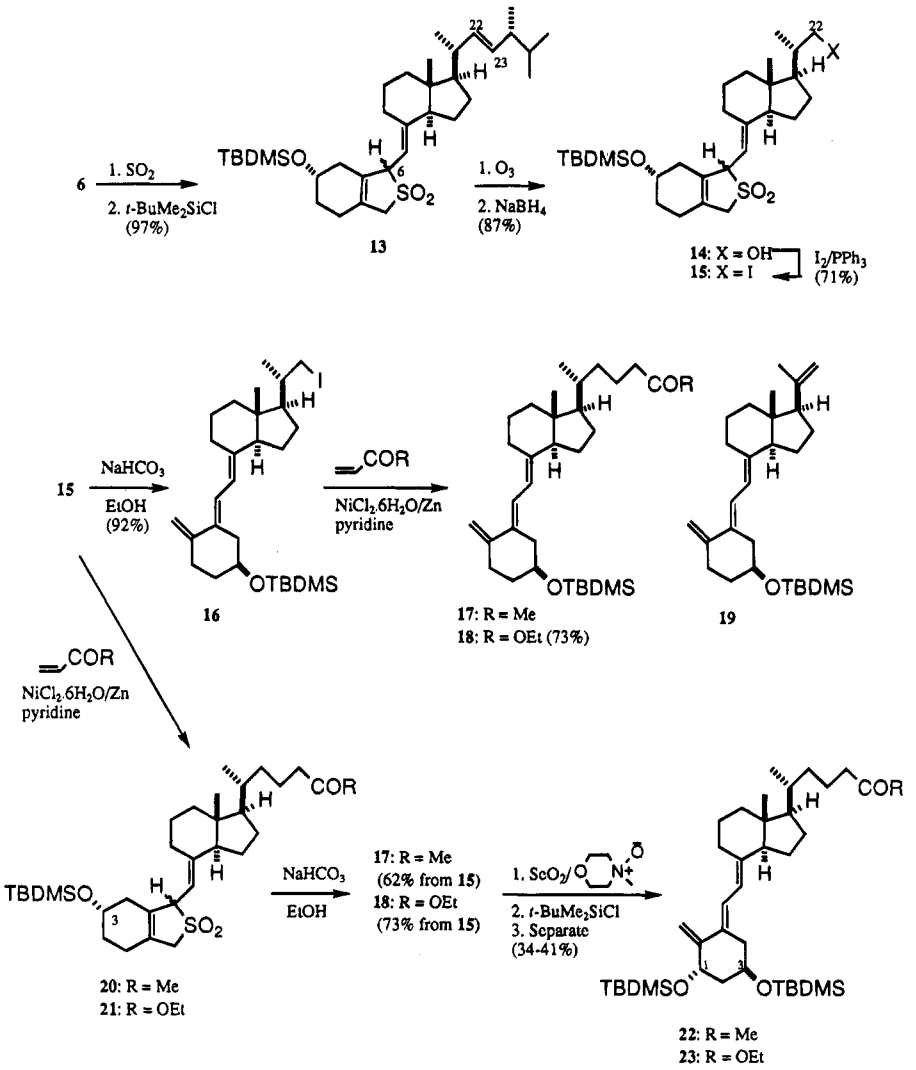
Scheme 4



elimination of iodide from **16**, and a substance tentatively identified by ^1H and ^{13}C NMR spectroscopy to be the Diels–Alder adduct between **16** and MVK. Similar disappointing results were obtained when the sulfone-protected iodides **15** and **27** were used in the Luche reaction. It should be noted that, for practical reasons, radical conjugate additions mediated by low valent cobalt[17] were not attempted, but an attempt to add **16** to MVK using AIBN/*n*-Bu_3SnH[18] gave a complex mixture.

Despite the discouraging results, the conjugate addition approach for introducing the calcitriol side chain was pursued. Pertinent to this approach are a few reports describing the alkylation of Ni(0) complexes of electron-deficient alkenes with simple alkyl and aryl halides to give products that, after protonolysis, are formally the result of conjugate addition of an alkyl group to the electron-deficient alkenes.[19]

In the present investigation, the Ni(0) complexes were conveniently prepared in situ by simply heating (to *ca.* 60 °C) 1 equiv of $NiCl_2 \cdot 6H_2O$ with *ca.* 5 equiv of zinc powder as the reducing agent in the presence of 5 equiv of the electron-deficient alkenes in pyridine. Generation of a brick-red color was found to be indicative of complex formation. It should be noted that in initial experiments, the complexes were prepared in a mixture of pyridine and THF,[19a] but this gave capricious results. Pyridine was subsequently found to be the solvent of choice. Although not always necessary, in one experiment addition of a catalytic amount of iodine appeared to facilitate complex formation. A cursory UV/vis spectroscopic examinaton of an aliquot from the reaction mixture containing the complex derived from ethyl acrylate gave a UV absorption of 450 nm (pyridine), which decreased during 1 h to 310 nm on exposure to air. However, except for conducting experiments under an inert atmosphere, no attempt was made to scrupulously deaerate the reaction mixture. Stoichiometric alkylation of the complexes was then carried out during 2–3 h at 25–40 °C with water[19a,b] supplying the α-H needed to complete the reaction.[20]

Using the above conditions, the Ni(0) complex derived from ethyl acrylate was alkylated with **16** to give the ester **18** in 73% yield with virtually no elimination of iodide (Scheme 4). In a similar manner, alkylation of the

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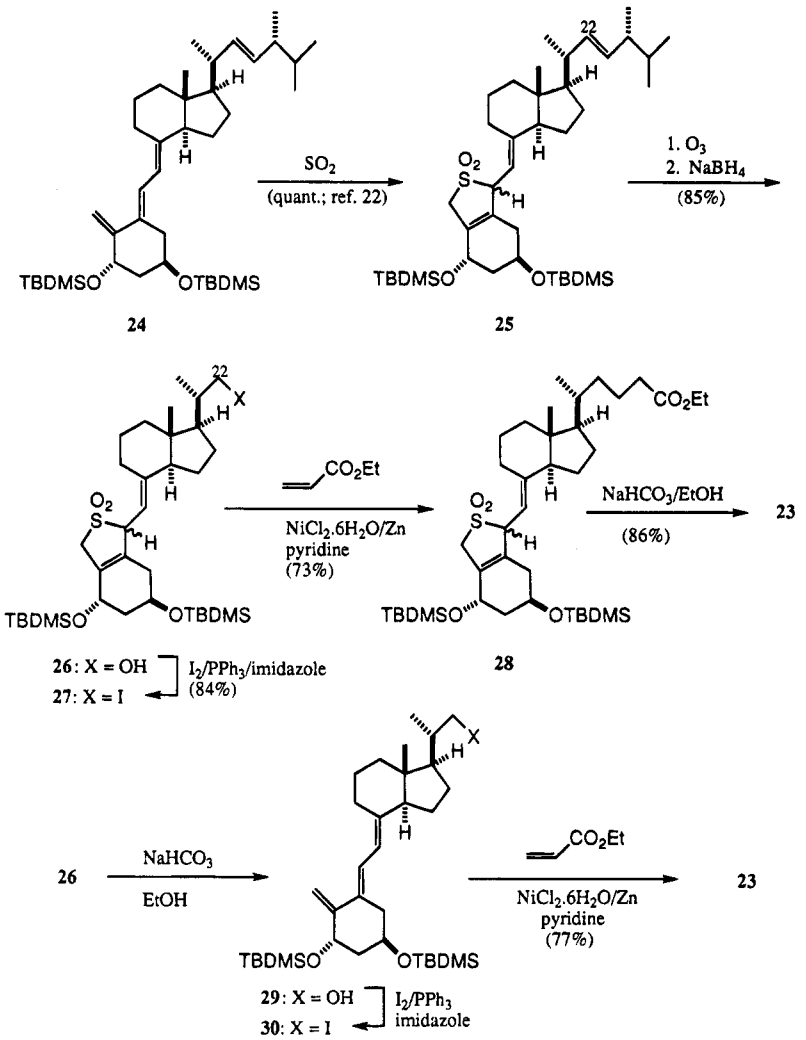
(20) Investigations on a catalytic process and other applications of low-valent nickel-mediated conjugate addition reactions will form the subject of a forthcoming publication from us.

Scheme 5



Ni(0) complexes derived from methyl vinyl ketone and ethyl acrylate with the sulfone iodides **15** gave ketones **20** and esters **21**, respectively, in 73–82% yield. Extrusion of SO_2 from **20** and **21** by heating in ethanol in the presence of $NaHCO_3$ gave the (5*E*)-trienes **17** and **18**, respectively. Applying conditions developed by Barton and Hesse,[12,21] C-1 hydroxylation of **18** was effected with selenium dioxide in hot CH_2Cl_2/MeOH accompanied by *N*-methylmorpholine *N*-oxide as a reoxidant to give a 7:1 mixture of (3*S*)- and (3*R*)-hydroxy compounds, which, after silylation with *tert*-butyldimethylsilyl chloride and chromatographic separation, afforded pure **23** in 41% yield. A similar sequence of reactions was used to prepare ketone **22** from the triene **17**.

Because of the low yields obtained in the selenium dioxide hydroxylation of **17** and of **18**, an alternative synthesis (Scheme 5) of the triene ester **23** was developed from the known, crystalline 1(*S*),3(*R*)-bis[(*tert*-butyldimethylsilyl)oxy]-(5*E*,7*E*)-ergocalciferol derivative **24**, which is readily available in five steps and 35% overall yield from ergocalciferol (**6**).[22] Protection of the triene unit in **24** with SO_2, followed by selective ozonolysis of the C-22 double bond, in situ reduction of the ozonides with $NaBH_4$, and iodination with PPh_3/I_2/imidazole as described for the preparation of **15** proceeded smoothly to give the C-22 iodides **27** in 64% overall yield from **24**. The nickel-mediated addition of **27** to ethyl acrylate gave a 73% yield of **28**, from which SO_2 was extruded to afford **23** in 86% yield. Ester **23** was also prepared in 77% yield by alkylation of the Ni(0) complex of ethyl acrylate with the triene iodide **30**.

The synthesis of calcitriol (**3**) was then completed in a straightforward manner (Scheme 6). A Grignard reaction between **23** and excess methyl magnesium bromide followed by deprotection of the silyl groups with *n*-$Bu_4N^+F^-$ gave the crystalline alcohol **32**, which on triplet-sensitized photoisomerization with a 450-W medium pressure lamp,[22b,23] afforded calcitriol in 81% yield after crystallization from methyl formate. Two variants of the aforementioned sequence were briefly examined. In one, photoisomerization of the silylated derivative **31** followed by desilylation of the 5(*Z*),7(*E*)-product **33** gave **3**. In the other, ester **23** was photoisomerized and the 5(*Z*),7(*E*) isomer **34** produced was reacted with excess methylmagnesium bromide to give **33**.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Optical rotations were determined at 25 °C. Unless otherwise indicated, infrared (IR) and ultraviolet (UV) spectra were determined in $CHCl_3$ and EtOH, respectively. ^1H NMR spectra

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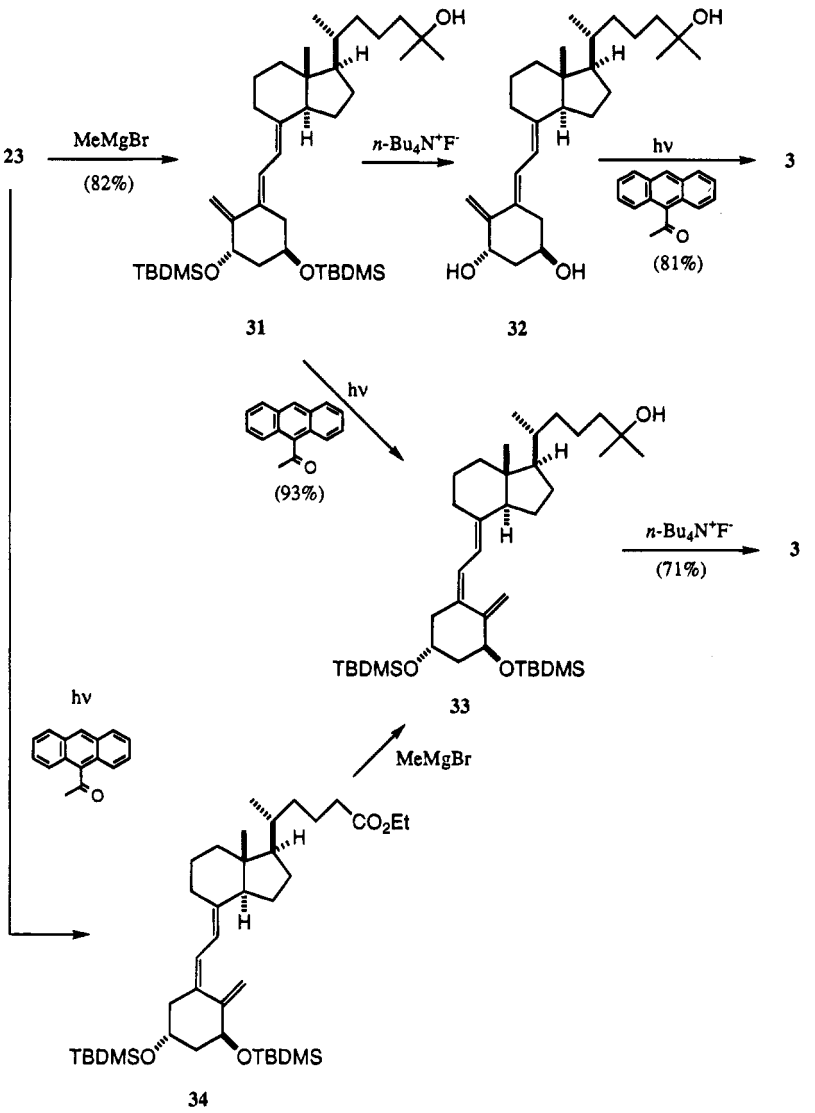
(23) We thank Drs. M. Okabe and M. R. Uskokovic (Roche) for suggesting the use of 9-acetylanthracene in the photoisomerization.

Scheme 6



were determined in $CDCl_3$, unless indicated to the contrary, with chemical shifts and coupling constants (J) reported in ppm (δ) and hertz, respectively. Mass spectra (MS, EI) were determined with an ionization energy of 70 eV; m/z values are given with relative intensities in parentheses. Thin-layer chromatography (TLC) was carried out on silica gel plates (Merck PF-254), with visualization of spots under short wavelength UV light or by spraying the plates with 10% phosphomolybdic acid in EtOH followed by heating. Flash chromatography[24] was carried out at 5 psi on silica gel (230–400 mesh, unless otherwise indicated).

SO_2 Adducts of 3(*S*)-[(*tert*-Butyldimethysilyl)oxy]-20-(*S*)-(hydroxymethyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (14). Ozonized oxygen, generated from a Welsbach ozone generator (8.0 psi of O_2, flow rate = 2 L/min), was passed through a stirred solution of 100 g (0.174 mol) of **13**[12] in 1.0 L of CH_2Cl_2 and 375 mL of MeOH at −10 °C until TLC (30% EtOAc in hexane) showed virtual disappearance of starting material (*ca.* 45 min). The solution was purged with argon and treated portionwise with $NaBH_4$ (24 g, 0.63 mol). The mixture was stirred at room temperature for 2.0 h, diluted with 1.0 L of 0.5 N HCl and 1.2 L of hexane, and the organic layer collected. It was washed with brine (2 × 2.0 L), dried ($MgSO_4$), and evaporated to give 139 g of an oil. Hexane (1.0 L) was added, the solution was stirred at 0 °C for 5.0 h and stored at 0 °C for 18 h, and the solid was collected by filtration. It was washed with 20 mL of cold (−10 °C) hexane and dried in vacuo to give 77.22 g (87%) of **14** as a colorless, amorphous solid: mp 83–92 °C; UV (EtOH) 205 (ϵ = 18 800), 273 (ϵ = 375) nm; ^1H NMR δ 0.05 (6 H, s), 0.59/0.65 (3 H, s), 0.88 (9 H, s), 1.05 (3 H, d, J = 6.5) 3.40/3.65 (4 H, m), 4.0 (1 H, m), 4.55/4.65 (1H, m), 4.70/4.75 (1 H, d, J = 2 and 9). Anal. Calcd for $C_{28}H_{48}O_4SSi$: C, 66.09; H, 9.51; S, 6.30. Found: C, 66.32; H, 9.38; S, 6.08.

SO_2 Adducts of 3(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-20-(*S*)-(iodomethyl)-9,10-secopregna-5(*Z*),7(*E*),10(19)-triene (15). Iodine (58 g, 0.228 mol) was added to a stirred, cooled (0 °C) solution of 41 g (0.60 mol) of imidazole and 60 g (0.228 mol) of triphenylphosphine in 500 mL of CH_2Cl_2. The mixture was stirred for 15 min and treated with a solution of 50.8 g (0.1 mol) of **14** in 250 mL of CH_2Cl_2 during 20 min, keeping the temperature below 10 °C. Stirring was continued at 5 °C for 0.5 h and at room temperature for 2.0 h, and the mixture was filtered. The filter cake was washed with 100 mL of CH_2Cl_2, and the combined filtrate and washing were washed with 400 mL of 2% sodium thiosulfate, 300 mL of 0.1 N HCl, and 300 mL of brine, dried ($MgSO_4$), and evaporated to give a pale yellow semisolid. This was stirred with 1.0 L of Et_2O and filtered (to remove most triphenylphosphine oxide) and the filtrate evaporated. Chromatography of the residue on 800 g of silica gel with 5% EtOAc in hexane (10 × 500 mL fractions) and 10% EtOAc in hexane (10 × 1.0 L fractions), combining fractions 4–20, and evaporation gave 50 g (71%) of **15** as a relatively unstable, pale yellow solid: ^1H NMR δ 0.05 (6 H) 0.60/0.69 (3 H), 0.90 (9 H), 1.02/1.06 (3 H, d, J = 7), 3.20–3.30 (2 H, m), 3.65 (2 H, br s), 4.00 (1 H, br s), 4.58 (1 H, d of d, J = 2 and 7), 4.72 (1 H, d of d, J = 2 and 7); MS m/z 554 (3, M − SO_2). Anal. Calcd for $C_{28}H_{47}IO_3SSi$: C, 54.35; H, 7.65; I, 20.50; S, 5.18. Found: C, 54.23; H, 7.75; I, 20.46; S, 5.12.

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

3(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-20(*S*)-(iodomethyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (16). A stirred mixture of 4.56 g (7.37 mmol) of **15** and 4.56 g (54.2 mmol) of $NaHCO_3$ in 100 mL of 95% EtOH was heated at reflux for 2.0 h and evaporated to almost dryness. Water (200 mL) and 100 mL of Et_2O were added, and the organic phase was separated. The aqueous phase was reextracted with 100 mL of Et_2O, and the combined extracts were dried ($MgSO_4$) and evaporated to give a gum. Flash chromatography on 100 g of silica gel with 2% EtOAc in hexane as eluent gave 3.78 g (92.5%) of **16**: mp 85–90 °C (from MeOH–Et_2O); $[\alpha]_D$ +106.26° ($CHCl_3$, *c* 1.069); UV 270 (ϵ = 19 920), 208 (ϵ = 12 700) nm; ^1H NMR δ 0.05 (6 H, s), 0.59 (3 H, s), 0.85 (9 H), 1.04 (3 H, d, J = 6.5), 3.19 (1 H, dd, J = 7 and 3), 3.35 (1 H, dd, J = 7 and 3), 3.85 (1 H, br s), 4.65 (1 H, s), 4.92 (1 H, s), 5.82 (1 H, d, J = 11.5), 6.45 (1 H, s, d, J = 11.5); MS *m/z* 554 (2, M^+). Anal. Calcd for $C_{28}H_{47}IOSi$: C, 60.63; H, 8.54; I, 22.88; Si, 5.05. Found: C, 60.85; H, 8.46; Si, 4.71. A satisfactory elemental analysis was not obtained for iodine.

SO_2 Adducts of Ethyl 3(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-9,10-seco-26,27-bisnorcholesta-5(*E*),7(*E*),10(19)-trien-25-oate (21). To a vigorously stirred mixture of 26.5 g (0.4 mol) of zinc dust and 25.7 mL (36.0 g 0.36 mol) of ethyl acrylate in 60 mL of pyridine was added 19.0 g (0.08 mol) of $NiCl_2{\cdot}6H_2O$. The mixture was heated to 50 °C, whereupon an exotherm ensued, and stirring was continued at 65 °C for 30 min. The resulting reddish-brown mixture was cooled to 25 °C and treated during 0.5 h with a solution of 50 g (0.08 mol) of **15** in 50 mL of pyridine at a rate so as to maintain the temperature below 25 °C. The mixture was stirred at 25 °C for 2.5 h, poured into 150 mL of EtOAc, and filtered through a pad of Celite. The pad was washed with EtOAc (2 × 100 mL), and the filtrate and washings were washed with 1.0 N HCl (4 × 150 mL), 200 mL of a solution of EDTA (80.0 g EDTA + 80 g $NaHCO_3$ in 1.0 L of H_2O), and brine (2 × 100 mL), dried ($MgSO_4$), and evaporated to give 39 g (83%) of crude **21**, which was used directly in the next step: IR 1725 cm^{-1}; ^1H NMR 0.057 (6 H, s), 0.55/0.63 (3 H, s), 0.87 (9 H, d), 0.93 (3 H, d, J = 6.6), 1.25 (3 H, t, J = 7), 3.65 (2 H, m), 3.90 (1 H, m), 4.10 (2 H, q, J = 7), 4.6–4.8 (2 H, m).

Ethyl (3*S*)-[(*tert*-Butyldimethylsilyl)oxy]-9,10-seco-26,-27-bisnorcholesta-5(*E*),7-(*E*),10(19)-trien-25-oate (18). (A) From 21. A stirred solution of 39 g of crude **21** from the preceding experiment in 500 mL of 95% EtOH was heated at reflux under Ar with 35 g (0.41 mol) of $NaHCO_3$ for 2 h, cooled, and filtered and the filter pad washed with EtOAc (2 × 150 mL). The filtrate and washings were evaporated, and the residue was dissolved in 1.0 L of EtOAc. The solution was washed with brine (3 × 300 mL), dried (Na_2SO_4), and evaporated to give 43 g of crude product. Flash chromatography on 800 g of silica gel, with 5% EtOAc in hexane (10 × 500 mL fractions) as eluent, combining fractions 4–7, and evaporation gave 31 g (73% from **15**) of **18** as a colorless oil: $[\alpha]_D$ +94.64° (EtOH, *c* 0.8980); IR 1725 cm^{-1}; ^1H NMR δ 0.05 (6 H), 0.55 (3 H, s), 0.93 (9 H, s), 0.95 (3 H, d, J = 6.5), 1.26 (3 H, t, J = 7), 3.82 (1 H, m), 4.12 (2 H, q, J = 7), 4.64 (1 H, s), 4.92 (1 H, s), 5.84 (1 H, d, J = 11.5), 6.45 (1 H, d, J = 11.5); MS *m/z* 528 (8, M^+). Anal. Calcd for $C_{33}H_{56}O_3Si$: C, 74.94; H, 10.67. Found: C, 74.72; H, 10.72.

The tetraene **19** (480 mg) was obtained in the nonpolar fractions from the above chromatography as a gum: $[\alpha]_D$ +37.73° ($CHCl_3$, *c* 1.158); UV 265 (ϵ = 17 000); IR 1645 cm^{-1}; ^1H NMR δ 0.05 (6 H, s), 0.45 (3 H, s), 0.95 (9 H, s), 1.78 (3 H, d, J = 7), 3.85 (1 H, m), 4.65 (1 H, s), 4.74 (1 H, s), 4.85 (1 H, s), 4.95 (1 H, s), 5.87 (1 H, d, J = 11.5), 6.48 (1 H, d, J = 11.5); MS *m/z* 426 (20, M^+). A satisfactory combustion analysis was not obtained.

(B) From 16. A stirred mixture of 2.37 g (10 mmol) of $NiCl_2{\cdot}6H_2O$ in 22 mL of pyridine was treated under Ar with 3.27 g (50 mmol) of Zn powder and 5.3 mL (5.0 g, 50.0 mmol) of ethyl acrylate and then heated at 60 °C for 30 min. The resulting brick-red mixture was cooled to 20 °C, treated with 5.54 g (10 mmol) of iodide **15** in 20 mL of pyridine, and stirred for a further 2.0 h. The mixture was worked up as described for the preparation of **21** to give, after flash chromatography on 100 g of silica gel with 5% EtOAc in hexane as eluent, 3.9 g (73%) of **18**, identical with the sample prepared above.

SO_2 Adducts of 3(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-25-keto-9,10-seco-27-norcholesta-5(*E*),7(*E*),10(19)-triene (20). A stirred suspension of 2.24 g (34 mmol) of Zn dust, 4.10 g (17.2 mmol) of $NiCl_2{\cdot}6H_2O$, and 3.0 mL (2.58 g, 36.8 mmol) of methyl vinyl ketone in 16 mL of pyridine was slowly heated under Ar to 65 °C. After 30 min of heating at 65 °C, the mixture was cooled to 35 °C and a solution of 10.6 g (18.7 mmol) of **15** in 12 mL of mixture of pyridine:THF (1:2) was added during 10 min. After being stirred at room temperature for 2 h, the mixture was worked up as described for the preparation of **21** to give 11 g of crude **20**, which was used directly in the next step: IR 1710 cm^{-1}; ^1H NMR δ 0.05 (6 H, s), 0.55/0.65 (3 H), 0.87 (9 H), 0.88/0.92 (3 H, d, J = 6.5), 2.12 (3 H, s), 3.65 (2 H, m), 4.0 (1 H, m), 4.5–4.8 (2H, m).

3(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-25-keto-9,10-seco-27-norcholesta-5(*E*),7(*E*),10(19)-triene (17). A stirred mixture of 11.0 g of crude **20** from the preceding experiment, 4.1 g (48.8 mmol) of $NaHCO_3$, and 55 mL of 95% EtOH was heated at reflux under Ar for 2 h and worked up as described for the preparation of **16**. Chromatograpy on silica gel with 2% EtOAc in hexane as eluent afforded 5.35 g (62% yield from **15**) of **17** as a gum: $[\alpha]_D$ +57.86° (EtOH, *c* 0.99); IR 1710 cm^{-1}; ^1H NMR δ 0.065 (3 H, s), 0.073 (3 H, s), 0.55 (1H, s), 0.80 (9 H, s), 0.95 (3 H, d, J = 6.5), 2.15 (3 H, s), 3.85 (1 H, m), 4.65 (1 H, s), 4.95 (1 H, s), 5.85 (1 H, d, J = 12), 6.48 (1 H, d, J = 12); MS *m/z* 498 (3, M^+).

1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-25-keto-9,-10-seco-27-norcholesta-5(*E*),7(*E*),10(19)-triene (22). A stirred mixture of 2.35 g (4.72 mmol) of **17**, 10 g (9.3 mmol) of *N*-methylmorpholine *N*-oxide, and 0.26 g (2.34 mmol) of selenium dioxide in 30 mL of MeOH:CH_2Cl_2 (1:1) was heated at reflux under Ar for 2 h and concentrated to one third of its volume. It was diluted with 150 mL of EtOAc, washed with brine (3 × 100 mL), dried (Na_2SO_4), and evaporated to give 2.4 g of a crude mixture of 1α- and 1β-hydroxy compounds. This was dissolved in 50 mL of CH_2Cl_2 and treated with 0.5 g (7.34 mmol) of imidazole and 0.9 g (5.97 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred at room temperature overnight, filtered, and evaporated to dryness. The residue was dissolved in 125 mL of EtOAc, washed with brine (3 × 50 mL), dried (Na_2SO_4), and evaporated in vacuo to afford 2.9 g of crude product. Flash chromatography on 100 g of silica gel with 1:1 hexane–CH_2Cl_2 (30 × 100 mL fractions), combining fractions 18–29, and evaporation gave 1.03 g (34.8%) of **22** as a gum as the less polar of the two isomers: $[\alpha]_D$ +69.89° (EtOH, *c* 0.966); IR 1710 cm^{-1}; ^1H NMR δ 0.005 (6H), 0.55 (3 H, s), 0.85 (18 H), 0.95 (3 H, d, J = 6.5), 2.12 (3 H, s), 4.25 (1 H, br s), 4.53 (1 H, br s), 4.94 (1 H, s), 4.98 (1 H, s), 5.85 (1 H, d, J = 11.5), 6.48 (1 H, d, J = 11.5); MS *m/z* 628 (0.1, M^+). Anal. Calcd for $C_{38}H_{68}O_3Si$: C, 71.50; H, 10.74. Found: C, 71.02; H, 10.93. This was converted into **32** with methyl magnesium bromide as described for the preparation of **32** from **23**.

SO_2 Adducts of 1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)-oxy]-20(*S*)-(hydroxymethyl)-9,10-secopregna-5(*E*),7(*E*),-10(19)-triene (26). A mixture of 63.0 g (0.0893 mol) of **25**[22] in 450 mL of CH_2Cl_2 and 150 mL of MeOH was cooled to −10 °C and ozonized for 45 min. The mixture was purged with argon, treated with 10.25 g (0.271 mol) of powdered $NaBH_4$, and then allowed to warm to room temperature. Stirring was continued at room temperature for 2.0 h, the mixture was concentrated in vacuo to dryness and the residue was treated cautiously with a mixture of 350 mL of 0.5 *N* HCl and 250 mL of EtOAc. The organic phase was separated, and the aqueous phase was reextracted with 250 mL of EtOAc. The combined extracts were washed with 150 mL of brine, dried ($MgSO_4$), filtered, and evaporated to give 65.4 g of a pale yellow glass. Flash chromatography of this over 500 g of silica gel 60, collecting 200 mL fractions, with 3.6 L of 10% EtOAc in hexane, 3.6 L of 15% EtOAc in hexane, 5.4 L of 20% EtOAc in hexane, and 2 L of 25% EtOAc in hexane gave 42.64 g (85.5%) of **26**. A pure sample of the major isomer was obtained as a glass: mp 100–103 °C; $[\alpha]_D$ +2.54° ($CHCl_3$, *c* 1.026); UV 203 (ϵ = 20 880) nm; IR 3625 cm^{-1}; ^1H NMR δ 0.05 (12 H, s), 0.65 (3 H, s), 0.85 (18 H), 1.05 (3 H, d, J = 7), 3.40 (1 H, d of d, J = 2 and 7), 3.60 (1 H, d, J = 14), 3.65 (1 H, d of d, J = 2 and 7), 3.95 (1 H, d, J = 14), 4.20 (1 H, br s), 4.37 (1 H, br s), 4.65

and 4.71 (2 H, q, $J = 6$); MS m/z 574 (M − SO_2). Anal. Calcd for $C_{34}H_{62}O_5SSi_2$: C, 63.90; H, 9.78; S, 5.02. Found: C, 64.29; H, 9.93; S, 4.75.

SO_2 Adducts of 1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-20(*S*)-(iodomethyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (27). A stirred solution of 19.5 g (0.286 mol) of imidazole and 36.61 g (0.143 mol) of triphenylphosphine in 300 mL of CH_2Cl_2 was treated with 33.1 g (0.130 mol) of iodine. The mixture was stirred at 10 °C for 15 min and treated with a solution of 41.64 g (0.065 mol) of the epimeric alcohols **26** in 200 mL of CH_2Cl_2. The mixture was stirred at room temperature for 2.5 h and worked up as described for the preparation of **15** to give 53.7 g of crude 6(*S*) and 6(*R*) epimeric iodides. Flash chromatography on 475 g of silica gel with 1.0 L of hexane, 3.6 L of 5% EtOAc in hexane, and 3.6 L of 10% EtOAc in hexane, collecting 200 mL fractions, gave 40.79 g (83.6%) of the (6*R*)- and (6*S*)-iodides **27**. Pure samples of each of the iodides (isomers A and B) were isolated from the above chromatography and characterized as follows. **Isomer A**: amorphous solid: mp 78−82 °C; $[\alpha]_D$ +31.94° ($CHCl_3$, *c* 1.00); UV 201 (ϵ = 23 100) and 253 (ϵ = 725) cm^{-1}; ^1H NMR δ 0.05 (6 H), 0.70 (3 H, s), 0.90 (18 H), 1.03 (3 H, d, $J = 6$), 3.21 (1 H, d of d, $J = 8$ and 4), 3.32 (1 H, d of d, $J = 8$ and 4), 3.61 (1 H, d, $J = 12$), 3.92 (1 H, d, $J = 12$), 4.20 (1 H), 4.36 (1 H, br s), 4.65 and 4.70 (2 H, q, $J = 6$); MS m/z 552 (M − SO_2 − 132). Anal. Calcd for $C_{34}H_{61}IO_4SSi_2$: C, 54.52; H, 8.21; I, 16.94; S, 4.28. Found: C, 54.40; H, 8.41; I, 17.19; S, 4.50. **Isomer B**: foam: $[\alpha]_D$ −12.35° ($CHCl_3$, *c* 0.8904). Anal. Calcd for $C_{34}H_{61}IO_4SSi_2$: C, 54.52; H, 8.21; I, 16.94; S, 4.28. Found: C, 54.48; H, 8.46; I, 17.23; S, 4.38.

SO_2 Adducts of Ethyl 1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-seco-26,27-bisnorcholesta-5(*E*),7(*E*),10(19)-trien-25-oate (28). A mixture of 2.38 g (10 mmol) of pulverized $NiCl_2{\cdot}6H_2O$, 3.27 g (50 mmol) of Zn powder and 4.88 mL (45 mmol) of ethyl acrylate in 20 mL of pyridine was stirred at 60 °C under Ar for 30 min. The resulting dark red, heterogeneous mixture was cooled to 23 °C and treated with a solution of 7.49 g (10 mmol) of iodides **27** in 10 mL of pyridine, producing a slight exotherm (23−28 °C). After being stirred at room temperature for 2.5 h, the mixture was worked up as described for the preparation of **21** to give 7.22 g of a pale yellow foam, which was purified by flash chromatography on 95 g of silica gel (40 μm), eluting with 3% EtOAc in hexane and then 5% EtOAc in hexane, collecting 30 mL fractions, and monitoring the progress of the chromatography by TLC (20% EtOAc in hexane) to give, after evaporation of the solvents, 5.28 g (73%) of **28**. Repeat chromatography gave 2.72 g of isomer A, 730 mg of isomer B, and 1.83 g of a mixture of A and B. **Isomer A.** This was obtained as an amorphous solid: mp 68−70 °C; $[\alpha]_D$ +19.09° ($CHCl_3$, *c* 0.958); UV 202 (ϵ = 22 210), 266 (ϵ = 230) nm; IR 1722 cm^{-1}; ^1H NMR δ 0.05 (12 H), 0.64 (3 H, s), 0.85 (18 H), 0.95 (3 H, d, $J = 6.6$), 1.10 (1 H, m), 1.25 (3 H, t, $J = 7.0$), 3.61 (1 H, d, $J = 12$), 3.95 (1 H, d, $J = 12$), 4.12 (2 H, q, $J = 7$), 4.18 (1 H, br s), 4.36 (1 H, br s), 4.65 and 4.72 (2 H, q, $J = 6$); MS m/z 658 (M − SO_2). Anal. Calcd for $C_{39}H_{70}O_6SSi_2$: C, 64.77; H, 9.76; S, 4.43. Found: C, 64.55; H, 9.87; S, 4.13. **Isomer B.** This was obtained as a gum: $[\alpha]_D$ −19.76° ($CHCl_3$, *c* 0.6830); IR 1725 cm^{-1}; ^1H NMR δ 0.05 (12 H, s), 0.55 (3 H, s), 0.90 (18 H, s), 0.95 (3 H, d, J = 6.5), 1.1 (1 H, m), 1.25 (3 H, t, $J = 7.0$), 3.65 (1 H, d, $J = 12$), 3.92 (1 H, d, $J = 12$), 4.15 (2 H, q, $J = 7$), 4.18 (1 H, br s), 4.38 (1 H, s), 4.63 and 4.82 (2 H, q, $J = 6$).

1(*S*),3(*R*)-Bis-[(*tert*-Butyldimethylsilyl)oxy]-20(*S*)-(hydroxymethyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (29). A mixture of 5.5 g (8.6 mmol) of alcohol **26** and 5.5 g (65 mmol) of $NaHCO_3$ in 56 mL of 95% EtOH was stirred at reflux under argon for 5 h and then evaporated at 50 °C under vacuum and worked up as described for the preparation of **16** to give 4.53 g (91%) of a thick yellow oil. Flash chromatography on 86 g of silica gel (40 μm) with 2%, 3%, and 5% EtOAc in hexane as eluent and evaporation of the solvents gave 2.35 g (47%) of **29** as a white solid: mp 116−117 °C; $[\alpha]_D$ +48.20° ($CHCl_3$, *c* 1.114); UV 269 (ϵ = 23 600), 208 (12 150) nm; IR 3625 cm^{-1}; ^1H NMR δ 0.60 (12 H), 0.57 (3 H, s), 0.86 (9 H, s), 0.90 (9 H, s), 1.06 (3 H, d, $J = 6.5$), 1.20 (1 H, s), 3.40 (1 H, d of d, $J = 11$ and 3), 3.66 (1 H, d of d, $J = 11$ and 3), 4.21 (1 H, br s), 4.53 (1 H, br s), 4.94 (1 H, s), 4.99 (1 H, s), 5.83 (1 H, d, $J = 11.4$), 6.45 (1 H, d, $J = 11.4$); MS m/z 574 (M^+, 5). Anal. Calcd for $C_{34}H_{62}O_3Si_2$: C, 71.02; H, 10.87. Found: C, 71.04; H, 10.99.

1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-20(*S*)-(iodomethyl)-9,10-secopregna-5(*E*),7(*E*),10(19)-triene (30). A solution of 0.861 g (12.6 mmol) of imidazole, 1.66 g (6.3 mmol) of triphenylphosphine, and 1.50 g (6 mmol) of iodine in 20 mL of CH_2Cl_2 was stirred at room temperature for 15 min, cooled to 10 °C, and treated with a solution of 1.65 g (2.87 mmol) of the alcohol **29** in 10 mL of CH_2Cl_2. Stirring was continued at room temperature for 1.5 h, and the mixture was worked up as described for the preparation of **15** to give 2.74 g of a gum. Flash chromatography over 45 g of silica (40 μm), with 1% EtOAc in hexane, collection of the appropriate fractions as determined by TLC (10% EtOAc in hexane), and evaporation gave a gum, which was dried at 0.2 Torr to give 1.72 g (87%) of **30** as a foam: $[\alpha]_D$ +24.99° ($CHCl_3$, *c* 1.0682); UV 267 (ϵ = 21 600) nm; ^1H NMR δ 0.05 (12 H), 0.58 (3 H, s), 0.90 (18 H), 1.05 (3 H, d, $J = 6.5$), 3.20 (1 H, d of d, $J = 7$ and 3), 3.33 (1 H, d, $J = 7$ and 3), 4.22 (1 H, br s), 4.55 (1 H, br s), 4.94 (1 H, s), 4.99 (1 H, s), 5.82 (1 H, d, $J = 11.5$), 6.47 (1 H, d, $J = 11.5$); MS m/z 684 (0.1, M^+). Anal. Calcd for $C_{34}H_{60}IOSi$: C, 59.71; H, 8.84; I, 18.56. Si, 8.51. Found: C, 59.45; H, 8.66; Si, 8.3. A satisfactory elemental analysis was not obtained for iodine.

Ethyl 1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-seco-26,27-bisnorcholesta-5(*E*),7(*E*),10(19)-trien-25-oate (23). (A) From 28. A mixture of 39.2 g (54.2 mmol) of esters **28** and 20.4 g (242 mmol) of $NaHCO_3$ in 300 mL of 95% EtOH under Ar was mechanically stirred and heated at reflux for 2.25 h, cooled to *ca.* 45 °C, and concentrated in vacuo. EtOAc (100 mL) and 250 mL of hexane were added, and the mixture was stirred for 30 min. It was filtered, and the filter cake was washed with 2 × 50 mL of hexane. The combined filtrate and washings were evaporated to give 36.8 g of a yellow semisolid. Chromatography on 380 g of silica gel, eluting with 1%, 3%, 5%, and 10% CH_2Cl_2 in hexane, removed some less polar impurities as revealed by TLC (1:1 CH_2Cl_2 in hexane) and finally with 10% EtOAc in hexane gave, after collection of the appropriate fractions and evaporation (water aspirator then high vacuum), 30.73 g (86.5%) of **23** as a colorless, waxy solid: mp 69−71 °C; $[\alpha]_D$ +51.35° ($CHCl_3$, *c* 0.9192). UV 268 (ϵ = 24 220) nm; IR 1725, 835 cm^{-1}; ^1H NMR δ 0.05 (12 H, s), 0.55 (3 H, s), 0.85 (9 H, s), 0.88 (9 H), 0.95 (3 H, d, $J = 6.5$), 1.10 (1 H, m), 1.26 (3 H, t, $J = 7$), 4.12 (2 H, q, $J = 7.0$), 4.21 (1 H, br s), 4.52 (1, br s), 4.93 (1 H, s), 4.98 (1 H, s), 5.82 (1 H, d, J = 11.2), 6.45 (1 H, d, $J = 11.2$); MS m/z 658 (M^+, 12). Anal. Calcd for $C_{39}H_{70}O_4Si_2$: C, 71.06; H, 10.70. Found: C, 71.19; H, 10.95.

(B) From 30. A mixture of 550 mg (2.3 mmol) of $NiCl_2{\cdot}6H_2O$, 10 mL of pyridine, 760 mg (11.6 mmol) of Zn powder, and 1.16 mL (10.7 mmol) of ethyl acrylate was stirred at 55−60 °C for 10 min, *ca.* 5 mg of iodine was added, and stirring was continued at 55−60 °C for 20 min. The resulting dark red heterogeneous mixture was cooled to 40 °C and treated with a solution of 1.59 g (2.32 mmol) of the iodide **29** in 5 mL of pyridine. After being stirred at room temperature for 45 min, the mixture was worked up as described for the preparation of **18** to give a gum, flash chromatography of which over 25 g of silica with 1% EtOAc in hexane as eluent gave, after collection of the appropriate fractions and evaporation, 1.18 g (77%) of **23** as an amorphous solid, identical with the sample from above.

(C) From 18. A stirred solution of 31 g (58.6 mmol) of **18** in 280 mL of 1:1 MeOH−CH_2Cl_2, 13.8 g (0.129 mol) of *N*-methylmorpholine *N*-oxide, and 2.30 g (20 mmol) of selenium dioxide was heated at reflux under Ar for 5 h. The mixture was cooled, concentrated in vacuo to one third of its volume, diluted with 1.0 L of EtOAc, washed with 1:1 brine−water (3 × 500 mL) and 500 mL of brine, dried (Na_2SO_4), and evaporated to afford 33 g of a gum. This was dissolved in 500 mL CH_2Cl_2 and treated with 6.1 g (0.089 mol) of imidazole followed by 9.8 g (0.065 mol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred at room temperature under Ar for 16 h filtered, and the filter cake was washed with CH_2Cl_2 (2 × 150 mL). The combined filtrate and washings were evaporated to dryness. The residue was dissolved in 1.0 L of EtOAc, washed with brine (3 × 500 mL), dried (Na_2SO_4), and evaporated in vacuo to afford 38.6 g of crude product. By TLC (silica,

2:1 hexane:CH_2Cl_2) the desired α-isomer is less polar than the β-isomer. Flash chromatography on 400 g of silica gel, eluting with 30% CH_2Cl_2 in hexane (20 × 250 mL fractions), combining fractions 7–20, and evaporation in vacuo, gave 15.85 g (41% yield) of **23** as a colorless amorphous solid, identical with the samples prepared above.

1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-seco-cholesta-5(*E*),7(*E*),10(19)-trien-25-ol (31). To a stirred, cooled (icebath) solution of 15.85 g (24.0 mmol) of ester **23** in 75 mL of dry THF (distilled from Na–benzophenone ketyl) under Ar was added 20 mL (0.060 mol) of methylmagnesium bromide (3.0 M in ether) during 5 min. The mixture was stirred at icebath temperature for 15 min and at room temperature for 3 h, cooled to 0 °C, and carefully quenched with 8 mL of saturated NH_4Cl. It was diluted with 800 mL of EtOAc, washed with brine (3 × 250 mL), dried (Na_2SO_4), and evaporated in vacuo to give 15.8 g of crude product, virtually homogeneous by TLC. Flash chromatography on 350 g of silica gel (200–400 mesh, 125 mL fractions) with 80% EtOAc in hexane as eluent, combining fractions 5–13, and evaporation of the solvents gave 12.7 g (82%) of **31** as a colorless foam: $[\alpha]_D$ +35.14° ($CHCl_3$, *c* 1.36); UV 269 (ε = 22 520) nm; IR 3605 and 1730 cm^{-1}; ^1H NMR δ 0.05 (12 H), 0.55 (3 H, s), 0.85 (9 H, s), 0.90 (9 H, s), 0.95 (3 H, d, *J* = 7), 1.05 (1 H, m), 1.20 (6 H, s), 4.22 (1 H, br s), 4.55 (1 H, br s), 4.93 (1 H, s), 4.99 (1 H, s), 5.82 (1 H, d, *J* = 11), 6.46 (1 H, d, *J* = 11); MS *m/z* 644 (1, M^+). Anal. Calcd for $C_{39}H_{72}O_2Si$: C, 72.26; H, 11.20. Found: C, 72.64; H, 11.05.

1(*S*),3(*R*)-9,10-Secocholesta-5(*E*),7(*E*),10(19)-triene-1,3,-25-triol (32). A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and argon inlet was charged with a solution of 19.01 g (29.5 mmol) of **31** in 50 mL of anhyd THF and 337 mL of a 1.0 M solution of *n*-$Bu_4N^+F^-$. The solution was stirred at room temperature for 5.5 h and concentrated in vacuo at 45 °C to give a thick, amber-colored oil. This was partitioned between a mixture of 500 mL of EtOAc and 500 mL of a 1:1 water–brine solution. The organic phase was separated, and the aqueous phase was extracted with 2 × 250 mL of EtOAc. The combined organic extracts were washed with brine (3 × 250 mL), dried ($MgSO_4$), and carefully evaporated at 50 °C to give 16.06 g of an off-white solid. This was slurried with 100 mL of 30% EtOAc in hexane and left at 0 °C overnight, and the product was collected by filtration. It was washed with 3 × 20 mL of 50% EtOAc in hexane and dried in vacuo to give 9.94 g (81%) of **32**: mp 170–173 °C; $[\alpha]_D$ +164.39° ($CHCl_3$, *c* 0.925); UV 273 (ε = 23 180) and 206 (ε = 12 260) nm; IR 3370, 1638, 1618 cm^{-1}; ^1H NMR δ 0.56 (3 H, s), 0.95 (3 H, d, *J* = 6.4), 1.22 (6 H, s), 2.85 (2 H, m), 4.23 (1 H, br s), 4.50 (1 H, br s), 4.95 (1 H, s), 5.12 (1 H, s), 5.88 (1 H, d, *J* = 11.5), 6.60 (1 H, d, *J* = 11.5); MS *m/z* 416 (8, M^+). Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.84; H, 10.65. Found: C, 77.76; H, 10.52.

1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-seco-cholesta-5(*Z*),7(*E*),10(19)-trien-25-ol (33). A solution of 12.5 g (19.4 mmol) of alcohol **31** and 600 mg (2.72 mmol) of 9-acetylanthracene in 800 mL of MeOH contained in a 1-L photochemical reactor was cooled to 5 °C and irradiated for 2.0 h through a uranium filter using a 450-W Hanovia lamp. The reactor was emptied and rinsed with MeOH (2 × 100 mL), and the combined MeOH was evaporated. Flash chromatography of the residue on 500 g of silica gel (125 mL fractions) with 20% EtOAc in hexane gave, after combination of fractions 7–15 and evaporation, 11.7 g (93% yield) of **33** as a colorless amorphous solid: ^1H NMR δ 0.05 (12 H), 0.55 (3 H, s), 0.85 (18 H), 0.92 (6 H, s), 4.20 (1 H, br s), 4.38 (1 H, br s), 4.84, (1 H, s), 5.18 (1 H, s), 6.04 (1 H, d, *J* = 11), 6.24 (1 H, d, *J* = 11); MS *m/z* 416 (4, M^+).

1α,25-Dihydroxycholecalciferol (Calcitriol, 3). (A) From 32. A solution of 9.79 g (23.5 mmol) of **32** and 0.43 g (1.95 mmol) of 9-acetylanthracene in 1.0 L of MeOH, contained in a 1.0-L photochemical reactor, was cooled (0 °C) and, with Ar passed through it, irradiated through a uranium filter with a medium-pressure 450 W Hanovia lamp for 2.0 h. The solution was transferred to a 3-L, round-bottomed flask and was concentrated at 45 °C to give a foam. This was dissolved in 30 mL of 70% EtOAc in hexane and chromatographed on 180 g of silica gel (40 μm, 100 mL fractions) with 1.0 L of 70% EtOAc in hexane (to remove a small amount of nonpolar material), 1.0 L of 80% EtOAc in hexane, and finally 1.0 L of 90% EtOAc in hexane. Collection of the appropriate fractions (ascertained by TLC using 30% EtOAc in hexane) and evaporation gave 10.17 g of a foam, which was crystallized from 220 mL of anhyd methyl formate to give 6.5 g (66%) of **3**: mp 115–116 °C (lit.[25] mp 118–119 °C); $[\alpha]_D$ +45.5° (EtOH, *c* 1.059) [lit.[25] $[\alpha]_D$ +47.9° (EtOH, *c* 0.5)] ; UV 263 (ε = 18 500), 211(ε = 17 750); IR (KBr) 3330, 1648, 1625 cm^{-1}; ^1H NMR [$(CD_3)_2CO$] δ 0.58 (3 H, s), 0.97 (3 H, d, *J* = 6.5), 1.05 (1 H, m), 1.15 (6 H, s), 1.22–2.1 (19 H, m), 2.27 (1 H, dd, *J* = 7, 13), 2.50 (1 H, d, *J* = 13), 2.85 (1 H, m), 3.1 (1 H, s), 3.63 (1 H, d, *J* = 3), 3.90 (1 H, d, *J* = 3), 4.16 (1 H, br s), 4.40 (1 H, br s), 4.86 (1 H, s), 5.32 (1 H, s), 6.09 (1 H, d, *J* = 11), 6.29 (1 H, d, *J* = 11); MS *m/z* 416 (3, M^+), 398 (25, $M^+ - H_2O$), 380 (90, $M^+ - 2 \times H_2O$), 362 (30, $M^+ - 3 \times H_2O$), 347 (10, $M^+ - 3 \times H_2O - CH_3$). Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.84; H, 10.65. Found: C, 77.87; H, 10.95. An additional 15% of calcitriol was obtained from the mother liquor. Calcitriol prepared above was identical (UV, IR, NMR, MS, mixed mp, HPLC, and TLC) with a sample provided by Dr. M. R. Uskokovic (Roche).

(B) From 33. A solution of 41 mL of *n*-$Bu_4N^+F^-$ (1.0 M in THF) and 11.5 g (17.8 mmol) of alcohol **33** was stirred under argon at 45 °C for 4 h and evaporated in vacuo to dryness. The residue was dissolved in 500 mL of EtOAc, washed with brine (3 × 200 mL), dried (Na_2SO_4), and evaporated in vacuo to give 12.0 g of crude product. Flash chromatography on 200 g of silica gel with 3:7 hexane–EtOAc as eluent gave, after evaporation of the appropriate fractions, 6.87 g of **3**. Crystallization from 30 mL of anhyd methyl formate gave 5.30 g (71%) of **3**: mp 110–113 °C, $[\alpha]_D$ +49.13° (EtOH, *c* 1.0).

Ethyl 1(*S*),3(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-9,10-seco-26,27-bisnorcholesta-5(*Z*),7(*E*),10(19)-trien-25-oate (34). A 1-L photochemical reactor was charged with a solution of 913 mg (1.38 mmol) of ester **23** and 16.0 mg of 9-acetylanthracene in 1.0 L hexane. With argon bubbled through it, the solution was cooled to 0–5 °C and was irradiated through a uranium filter with a 450-W medium pressure lamp for 45 min. The solution was concentrated to give 915 mg of **34**: ^1H NMR δ 0.05 (12 H), 0.55 (3 H, s), 0.85 (18 H), 0.95 (3 H, d, *J* = 6), 1.21 (3 H, t, *J* = 7), 4.10 (2 H, q, *J* = 7), 4.16 (1 H, br s), 4.39 (1 H, br s), 4.88 (1 H, s), 5.18 (1 H, s), 6.0 (1 H, d, *J* = 11), 6.24 (1 H, d, *J* = 11). This material was reacted with methyl magnesium bromide using conditions described for the preparation of **31**, and the product **33** was desilylated with *n*-$Bu_4N^+F^-$ to give calcitriol (**3**).

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