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Synthesis of 1α-Hydroxyvitamin D_5 Using a Modified Two Wavelength Photolysis for Vitamin D Formation

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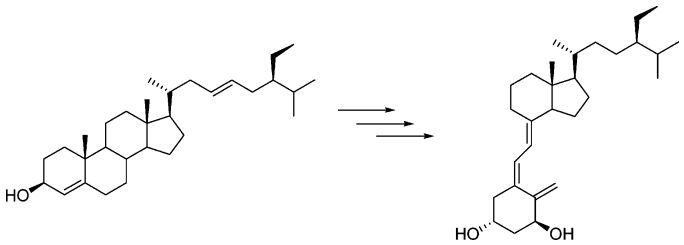
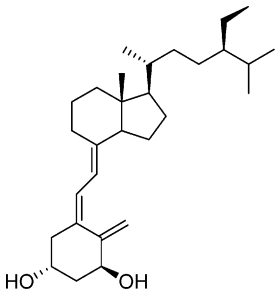


1α-Hydroxyvitamin D_5 (**1**) is a promising chemopreventive agent for breast cancer and is being developed as a drug. We report a synthesis for this vitamin D analogue which uses a photochemical method for the B-ring opening, leading to the conjugated triene system. The precursor 7-dehydrositosteryl acetate (**4**) obtained through a one-pot, five-step procedure, was completely free of the 4,6-diene isomer that usually forms in the 5,7-diene synthesis. The pre-vitamin isomer (**11**) was generated using a modified two-wavelength photolysis procedure that increases the yield for this step more than 3-fold compared to classically used photolysis. The 1α-hydroxylation step was performed on the 3-triethylsilyl-*trans*-vitamin D_5 (**17**) obtained via the sulfur dioxide adduct of c*is*-vitamin D_5, in an overall yield of 48%. Photoisomerization and deprotection completed the synthesis.

Introduction

1α-Hydroxyvitamin D_5 **1** was first synthesized in 1997[1a] in our group, and preliminary biological studies showed that this novel vitamin D analogue not only possessed lower calcemic activity than the metabolically activated form of vitamin D_3, calcitriol **2**, but also inhibited the development of preneoplastic lesions in mouse mammary glands in organ culture.[1b] Since then, several biological studies have shown the potential of this vitamin D analogue as a breast cancer chemopreventive agent.[1c−g] The original synthetic route used to synthesize 1α-hydroxyvitamin D_5 did not allow for the production of a sufficient amount of **1** for extensive biological activity investigations.

One drawback of the original synthesis was the low purity of the starting material, sitosterol.



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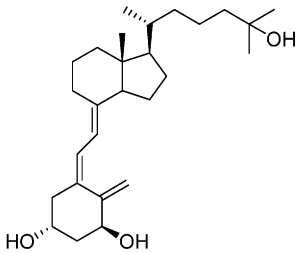

2

Difficulties in removal of the contaminants campesterol and dihydrobrassicasterol detracted from the efficiency of the entire synthesis. In the original synthesis (Scheme 1), sitosterol **3** was converted to the corresponding acetate and further to 7-dehydrositosteryl acetate **4**, using dibromantin for the allylic bromination step, followed by dehydrobromination, with Bu_4NF and *s*-collidine (50%, for two steps). Removal of the acetate group by reduction

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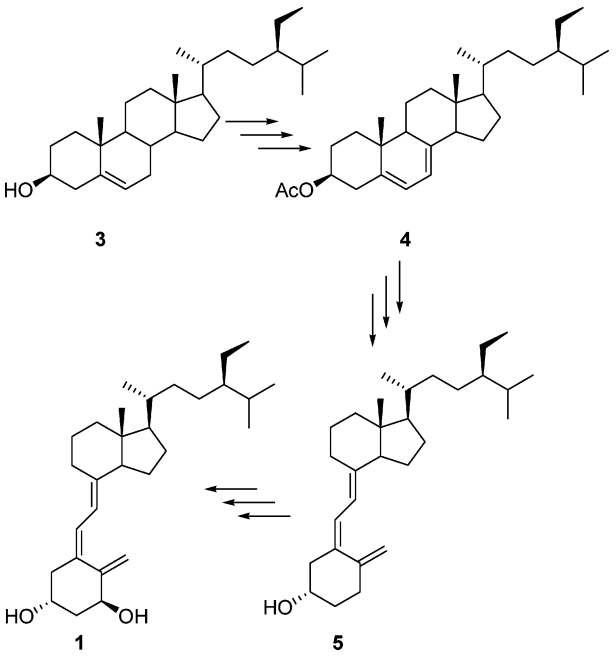
SCHEME 1



with lithium aluminum hydride was followed by classical photolysis and by thermal isomerization in refluxing ethanol to give **5** (15% from **4**). The resulting vitamin D_5 **5** underwent 1α-hydroxylation using the Paaren−DeLuca sequence[2] (27% for this sequence), leading to the title compound **1**. We sought to improve the synthesis in order to obtain amounts of 1α-hydroxyvitamin D_5 **1** sufficient for additional biological data.

In summary, the present synthetic route[1h] proceeds from *β*-stigmasterol **6** which was converted into 7-dehydrositosteryl acetate **4** (Scheme 2).

The next step in the synthesis is the photolysis.In the classical photolysis, simple exposure of 7-dehydroprecursor **8** to UV light using a high-pressure mercury lamp and solvents such as ether, ethanol, or benzene generates a mixture of photoisomers[3] **4**, **11**, **12**, and **13** (Scheme 3) out of which only the pre-isomer **11** can undergo thermal isomerization[4] to vitamin D **14** in an overall yield of about 15%. A more efficient photolytic method, leading to higher overall yields of **14** (about 55% versus 15% in classical photolysis), is known as "the two wavelength photolysis".[5]

In the two wavelength photolysis method, higher yields of preisomer **11** can be obtained by irradiating **4** with a narrow band of 250 nm UV light generated by a low-pressure mercury lamp or by a laser,[3] and then selective isomerization of the tachy-isomer **13** to **11** can be effected by irradiation with light at 350 nm or by use of a sensitizer.[6] In the present case, we used a modification[5] of the two wavelength photolysis method that employs one broad UV light spectrum generated by a 450 W medium-pressure mercury lamp. Formation of the lumi-isomer **12** is circumvented by filtering out the 300−315 nm light, using 20% ethyl 4-(dimethylamino)benzoate, with respect to the amount of **4** in the reaction mixture, which has a strong, relatively sharp absorption at 305 nm. This prevents ring closure of the pre-isomer **11** to the lumi-isomer. Tachy-isomer **13** is converted back to pre-isomer **11** by filtering out the light domain below 340 nm, using a uranium glass filter and 9-acetylanthracene as a sensitizer.[5]

1α-Hydroxylation of the *trans*-vitamin D_5 derivative **17** obtained via extrusion of the sulfur dioxide from its adduct with *cis*-vitamin D_5 **15** followed by photoisomerization of the *trans*-derivative **18** to the *cis*-configuration **19** completes the sequence, leading to the desired 1α-hydroxyvitamin D_5 **1** (Scheme 4).

Results and Discussion

The commercially available *β*-stigmasterol **6** was converted to *p*-toluenesulfonate **7** by treatment with *p*-toluenesulfonyl chloride in pyridine/methylene chloride, in the presence of 4-(dimethylamino)pyridine as catalyst (95%) (Scheme 2). The *p*-toluenesulfonate **7** underwent solvolysis[7] in refluxing methanol, in the presence of anhydrous potassium acetate, to afford the isostigmasteryl methyl ether **8** (80%). Catalytic hydrogenation[7] of **8** with 10% palladium on charcoal led to **9**. The ether **9** was refluxed in glacial acetic acid[7] in the presence of anhydrous zinc acetate to yield the acetate **10** (80%), which was converted into the corresponding 7-dehydroacetate **4** through a one-pot five-step process[8] as follows: **10** was refluxed with dibromantin in hexanes, and the resulting mixture of 7α- and 7*β*-bromo derivatives (1:1 ratio) was equilibrated with anhydrous lithium bromide in acetone/toluene at 0 °C to enrich the ratio of the α-bromo isomer to about 4α:1*β*. Subsequent treatment of the 7-bromo derivatives with benzenethiol and Et_3N afforded the corresponding phenyl sulfides (4*β*:1α), which were oxidized to the corresponding sulfoxides using *m*-CPBA at 0 °C. Only the *β*-sulfoxide isomer underwent *cis*-elimination of sulfenic acid at 70 °C, in the presence of triethylamine in toluene, leading to the desired 7-dehydroacetate **4**, free of 4,6-diene contaminant (40% for five steps). Irradiation of a solution of diene acetate **4** (Scheme 4) in *tert*-butyl methyl ether at −20 to 0 °C with a 450 W Hanovia medium-pressure mercury lamp in the presence of 20% ethyl 4-(dimethylamino)benzoate followed by irradiation through a uranium glass filter in the presence of 9-acetylanthracene as a photosensitizer is equivalent to using two wavelength light and practically eliminates the formation of **12** and **13**. The resulting crude pre-vitamin **11** underwent thermal isomerization in refluxing ethyl acetate to afford the vitamin D_5 acetate **14**. Hydrolysis of **14** with 10 M sodium hydroxide in methanol afforded vitamin D_5 **5** (50% from **4**).

Direct 1-hydroxylation of vitamins D is feasible, but because of difficulty in controlling the site, extent, and stereochemistry of the hydroxylation, it has not yet

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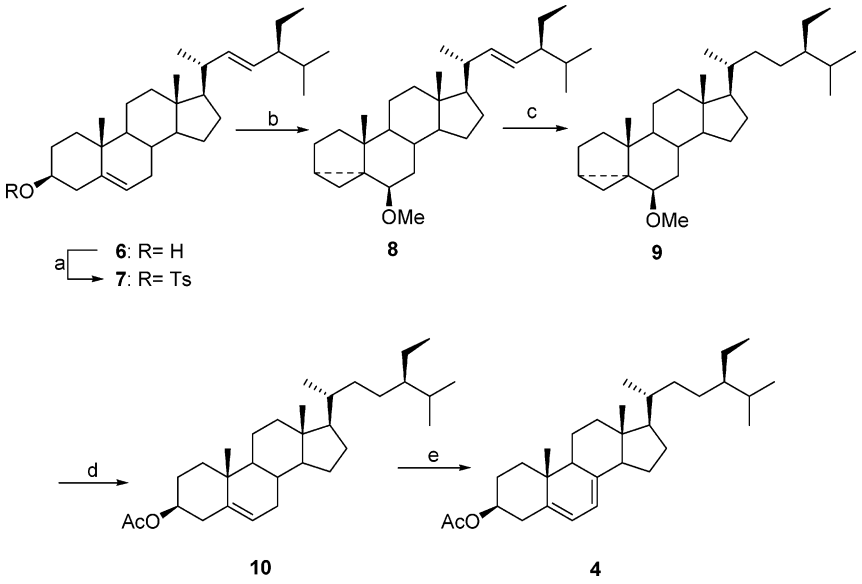
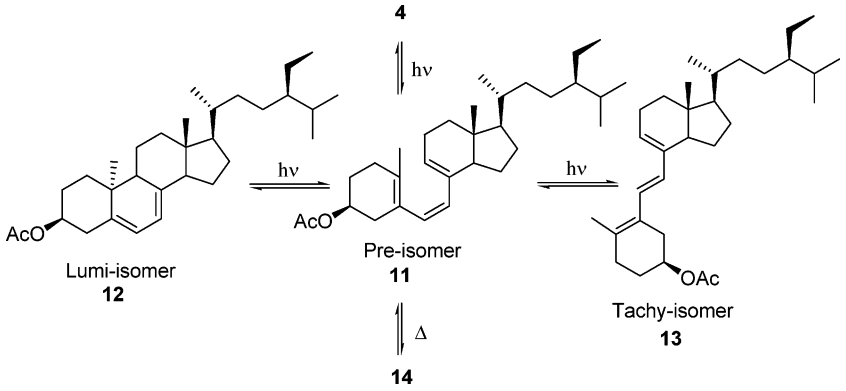
SCHEME 2[a]



[a] Reagents and conditions: (a) TsCl, DMAP, Py, CH_2Cl_2, room temperature, 95%; (b) AcOK, MeOH reflux, 80%; (c) H_2, 10% Pd/C, AcOEt, room temperature, 100%; (d) $(AcO)_2Zn$, AcOH, reflux, 80%; (e) (i) dibromantin, hexanes, $NaHCO_3$, reflux, (ii) LiBr, Me_2CO, PhMe, 0 °C, (iii) PhSH, Et_3N, room temperature; (iv) *m*-CPBA, AcOEt, 0 °C; (v) PhMe, Et_3N, 70 °C, 40%.

SCHEME 3



emerged as an efficient process. A much more efficient approach, leading to 1α-hydroxy vitamin D derivatives, is the direct 1α-hydroxylation of a 5,6-*trans*-geometric isomer of vitamin D, protected as a triethylsilyl or *tert*-butyldimethylsilyl derivative at C-3. The process involves the conversion of vitamin D into its sulfur dioxide adduct through addition of sulfur dioxide to the vitamin D. Thermal elimination of sulfur dioxide from its adduct leads to the 5,6-*trans*-vitamin D.[9,10] According to this procedure, vitamin D_5 **5** was converted into the sulfur dioxide adduct **15**, which underwent extrusion of sulfur dioxide, at 90 °C in dimethylformamide and sodium bicarbonate,[10] to yield the *trans*-vitamin D_5 **16** (80%). The hydroxyl group in **16** was protected as the triethylsilyl ether, and the resulting derivative **17** underwent 1α-hydroxylation with selenium dioxide and NMO (*N*-methylmorpholine *N*-oxide)[11] to yield the 1α-hydroxylated derivative **18** (60%). Photo-isomerization of **18**, back to the *cis*-configuration using phenazine as photosensitizer,[12] afforded derivative **19** (80%). Removal of the TES (triethylsilyl) group with Bu_4NF yielded the desired final product, 1α-hydroxyvitamin D_5 **1** (95%). The product was recrystallized three times from methyl formate in order to remove the C-1 epimer, 1β-hydroxyvitamin D_5, formed during the 1α-hydroxylation step, and other impurities. A total amount of 0.2 g of pure 1α-hydroxyvitamin D_5 was obtained. The overall yield for 18 steps and three recrystallizations of the final product **1** was 1.2%.

A convergent approach to the synthesis of 1α-hydroxyvitamin D_5 has been recently reported.[13] The convergent synthetic approach was described as an 11-step total synthesis of 1α-hydroxyvitamin D_5 in high overall yield (46%) from commercially available vitamin D_2. However, the 11-step and 46% yield refer exclusively to the

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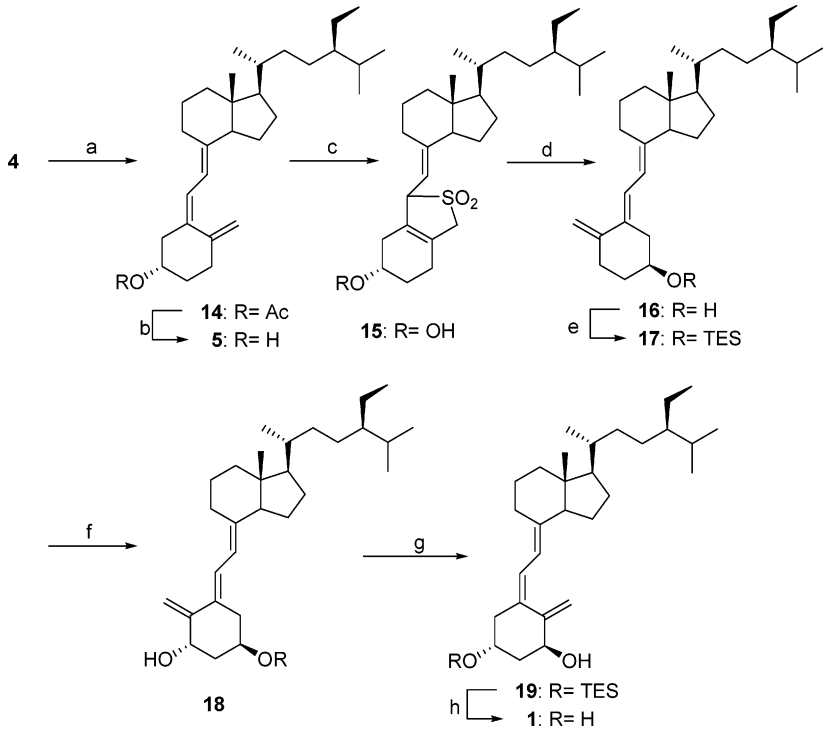
SCHEME 4[a]



[a] Reagents and conditions: (a) (i) *hν*, *t*-BuOMe, ethyl 4-(dimethylamino)benzoate, −20 °C to 0 °C, (ii) uranium glass filter, 9-acetylanthracene, −20 to 0 °C, (iii) AcOEt, reflux; (b) 10 M NaOH, MeOH, room temperature, 50% from **8**; (c) SO_2, −10 °C, 100%; (d) $NaHCO_3$, DMF, 90 °C, 80%; (e) Et_3SiCl, DMF, CH_2Cl_2, *i*-Pr_2EtN, 95%; (f) SeO_2, NMO, MeOH, CH_2Cl_2, reflux, 60%; (g) *hν*, uranium glass filter, phenazine, C_6H_6, room temperature, 80%; (h) Bu_4NF, THF, 95%.

synthesis of the side chain. Moreover, the total synthesis of 1α-hydroxyvitamin D_5 from commercially available vitamin D_2, as it is described in the paper, requires no less than 40 steps and the overall yield barely exceeds 3%. Therefore, we believe that the present 18-step synthesis in 1.2% yield compares favorably with the convergent method for the synthesis of 1α-hydroxyvitamin D_5.

Experimental Section

General Experimental Details. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ and are referenced to 77.23 (^{13}C) and 7.27 (^1H) chloroform peaks. The IR spectra were recorded on a FTIR spectrometer. Melting points were determined on a capillary melting point apparatus and are uncorrected. The reactions were performed under argon using anhydrous solvents.

3*β*-Acetoxystigmast-5-ene (10). A mixture of **9** (17.1 g, 0.040 mol) and zinc acetate (25 g, 0.136 mol) in glacial acidic acid (300 mL) was stirred under reflux for 3 h. The reaction mixture was cooled to room temperature, and water (200 mL) was added. The resulting precipitate was filtered, washed with water, and dissolved in diethyl ether (100 mL). The ethereal solution was washed with 5% sodium bicarbonate, water, and brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the solid was recrystallized from diethyl ether−methanol to afford the acetate **10** (15.25 g, 84%) as a white, crystalline solid: mp 121−122 °C (lit.[7] mp 121−122 °C).

3*β*-Acetoxystigmasta-5,7-diene (4). A mixture of **10** (15 g, 35 mmol), dibromantin (7 g, 24.5 mmol), and sodium bicarbonate (15.8 g, 189 mmol), in hexanes (310 mL), was heated under reflux for 0.5 h. The reaction mixture was cooled and filtered to remove 5,5-dimethylhydantoin and inorganic salts, and the filtrate was evaporated in vacuo to dryness. The residue was taken up in toluene (110 mL) and treated with anhydrous lithium bromide (6.05 g, 69.7 mmol) in dry acetone (80 mL). The mixture was stirred at 0 °C for 2 h, removed from the ice bath, and treated with triethylamine (6.5 mL, 46.9 mmol) and thiophenol (4.8 mL, 46.9 mmol). After being stirred for 1.25 h at room temperature, the reaction mixture was diluted with ethyl acetate (400 mL) and washed with 1 N hydrochloric acid (50 mL) and then with water (200 mL), twice. The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. The residue was dissolved in ethyl acetate (200 mL), cooled to 0 °C, and treated with *m*-chloroperoxybenzoic acid (11.59 g, 38.29 mmol) for 2 h. The reaction mixture was washed with 10% sodium bicarbonate and water. The organic phase was dried over anhydrous sodium sulfate and evaporated. The residue was dissolved in toluene (200 mL), treated with triethylamine (10.7 mL, 76.58 mmol), heated at 70 °C for 28 h, cooled, and washed twice with water (300 mL). The organic phase was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was chromatographed over silica gel using dichloromethane as the eluent. The fractions containing the desired product were concentrated, and the solid residue was recrystallized from diethyl ether/methanol to afford the desired diene (5.97 g, 40%) as a white, crystalline solid. Mp: 130−132 (lit.[14] 126 °C). IR (neat): 2941, 2823, 1729, 1468, 1373, 1235, 1030 cm^{-1}. ^1H NMR ($CDCl_3$), δ (ppm): 0.62 (1H, s, 18-H), 0.84 & 0.81 (2H each, d's, J = 6.5 Hz), 0.96 (3H, s), 2.02 (3H, s, MeCO), 4.72 (1H, m), 5.37 (1H, m), 5.57 (1H, m). ^{13}C NMR ($CDCl_3$), δ (ppm): 170.7, 141.7, 138.7, 120.4, 116.5, 73.0, 56.0, 54.6, 46.2, 46.0, 43.1, 39.3, 38.1, 37.3, 36.8, 36.7, 36.8, 34.1, 29.3, 28.3, 26.3, 23.25, 23.2, 21.6, 21.2, 20.0, 19.2, 19.1, 16.3, 12.5, 12.0. Anal. Calcd for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 81.92; H, 11.15.

9,10-*seco*-Stigmasta-5(*Z*),7(*E*),10(19)-trien-3*β*-ol (5). A solution of **4** (3 g, 6.6 mmol) and ethyl 4-(dimethylamino)-

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benzoate (0.3 g) in *tert*-butyl methyl ether (250 mL) at −20 °C was irradiated with a 450 W medium-pressure mercury lamp through a quartz immersion well. After 8 h of irradiation at −20 to 0 °C, a uranium glass filter was inserted in the arc housing and then 9-acetylanthracene (12 mg, 0.055 mmol) was added to the solution. After 1 h 45 min of irradiation through the filter at −20 to 0 °C, the lamp was turned off, and the solution was allowed to warm to room temperature , washed four times with a total of 50 mL of 3 N hydrochloric acid and then with saturated sodium bicarbonate, and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum. A second experiment involving 2.7 g of compound **4** gave a second crop of crude photolysis product. The two combined photolysis products were purified by column chromatography (hexanes/ethyl acetate 96:4) to yield pre-vitamin D_5 acetate **11** (3.7 g, 65%). Compound **11** (3.7 g, 8.2 mmol) was dissolved in ethyl acetate (100 mL) and refluxed overnight. The solvent was evaporated under low pressure, the residue was dissolved in methanol (100 mL), and the solution was treated with 10 M aqueous sodium hydroxide (4 mL, 40 mmol) for 3 h at room temperature. The excess sodium hydroxide was neutralized with acetic acid, and the solution was diluted with water (50 mL) and extracted three times with diethyl ether. The organic phase was dried over anhydrous sodium sulfate, the solvent was evaporated, and the crude product was chromatographed on silica gel using hexanes/ethyl acetate 9:1 as the eluent to afford vitamin D_5 **5** (2.6 g, 50%). Mp: 105−106 °C (lit.[15] mp 106 °C). $[\alpha]^{20}_D$: +45 (*c* 0.5, $CHCl_3$). IR (neat): 3361, 2940, 2865, 1590, 1456, 1378, 1291, 1045, 890 cm^{-1}. ^1H NMR ($CDCl_3$), δ (ppm): 0.56 (3H, s), 3.90 (1H, br m), 4.68 and 4.98 (2H, s), 5.88 (1H, d, J = 12 Hz), 6.54 (1H, d, J = 12 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 145.3, 142.6, 135.2, 122.7, 117.7, 112.6, 69.4, 56.7, 56.6, 46.1, 46.1, 46.0, 40.7, 36.7, 35.4, 34.1, 32.1, 29.3, 29.2, 27.9, 26.3, 23.8, 23.3, 22.5, 20.0, 19.2, 19.1, 12.2, 12.2. Anal. Calc. for $C_{29}H_{48}O_2$: C, 84.40; H, 11.72. Found: C, 84.20; H, 11.92.

SO_2 Adduct of 9,10-*seco*-Stigmasta-5(*Z*),7(*E*),10(19)-trien-3β-ol (15). The vitamin D_5 **5** (2.6 g, 6.3 mmol) was dissolved in liquid sulfur dioxide (about 10 mL) at −20 to −10 °C and maintained under stirring at −10 °C for 1 h. The excess sulfur dioxide was evaporated, and the adduct was chromatographed on silica gel using hexanes/ethyl acetate 4:6 as the eluent. Evaporation of the solvent gave the sulfur dioxide adduct (3 g, 100%) as a white foamy solid. The product was used in the next step without purification. IR (neat): 3427, 2930, 2867, 1453, 1303, 1103, 1090, 1025, 950 cm^{-1}. ^1H NMR ($CDCl_3$), δ (ppm): 0.56 (3H, s), 0.65 (3H, s), 3.37 (4H, s), 4.11 (2H, m), 4.59 (1H, d, J = 9 Hz), 4.68 (1H, d, J = 9 Hz), 4.75 (2H, d, J = 9 Hz).

9,10-*seco*-Stigmasta-5(*E*),7(*E*),10(19)-trien-3β-ol (16). A mixture of **15** (3 g, 6.3 mmol) and sodium bicarbonate (3 g, 35 mmol) in dimethylformamide (30 mL) was stirred at 90 °C for 1.5 h while argon was passed through the reaction mixture. The reaction mixture was cooled to 0 °C, and water (30 mL) was added. The aqueous layer was extracted three times with ethyl acetate, and the organic layer was washed with water and brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel using hexanes/ethyl acetate 8:2 as the eluent to yield the trans-derivative (2.24 g, 86%) as a viscous liquid. IR (neat): 3325, 2926, 2861, 1717 (vw), 1621 (vw), 1447, 1369 (vw), 1136 (vw), 1029, 780 cm^{-1}. ^1H NMR ($CDCl_3$), δ (ppm): 0.53 (3H, s), 3.80 (1H, m), 4.64 and 4.93 (2H, s), 5.83 (1H, d, J = 11.4 Hz), 6.46 (1H, d, J = 11.4 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 149.3, 145.0, 135.0, 121.2, 116.0, 108.5, 69.2, 56.8, 56.7, 46.1, 46.0, 40.7, 37.3, 36.7, 34.9, 34.1, 31.4, 29.3, 29.2, 27.9, 26.2, 23.8, 23.2, 22.5, 20.0, 19.2, 19.1, 12.3, 12.2. Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.33; H, 12.10.

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1α-Hydroxy-3β-triethylsilyloxy-9,10-*seco*-stigmasta-5(*E*),7(*E*),10(19)-triene (18). A solution of *N*-methylmorpholine *N*-oxide monohydrate (2.8 g, 23.9 mmol) in dichloromethane (30 mL) was dried over anhydrous sodium sulfate for 30 min then transferred into a solution of **17** (2.8 g, 5.3 mmol) in 1,2-dichloroethane (30 mL). The reaction mixture was heated to reflux for 15 min, and a solution of selenium dioxide (0.59 g, 5.3 mmol) in dry methanol (30 mL), which was stirred at room temperature for 45 min, was added. The reflux was continued for an additional 2 h. The orange reaction mixture was cooled, diluted with dichloromethane (100 mL), washed with saturated sodium bicarbonate and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and chromatographed on silica gel using hexanes/ethyl acetate 9:1 as the eluent to give the desired product (1.81 g, 63%). IR (neat): 3421, 2950, 2875, 1597 (vw), 1458, 1373 (vw), 1234 (vw), 1072, 1007, 733 cm^{-1}. ^1H NMR ($CDCl_3$), δ (ppm): 0.56 (3H, s), 4.20 (1H, m), 4.50 (1H, m), 4.95 and 5.09 (2H, s), 5.88 (1H, d, J = 11.4 Hz), 6.53 (1H, d, J = 11.4 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 152.6, 144.8, 134.1, 122.7, 116.3, 108.9, 71.4, 66.5, 56.7, 56.7, 46.2, 46.0, 42.9, 40.7, 37.5, 36.7, 34.1, 29.3, 29.3, 27.9, 26.2, 23.8, 23.3, 22.4, 20.0, 19.2, 19.1, 12.2, 12.2, 7.1, 5.0. MS *m/z*: 542 (M^+) for $C_{35}H_{62}O_2Si$. HRMS: found 542.451592, calcd 542.451910.

1α-Hydroxy-3β-triethylsilyloxy-9,10-*seco*-stigmasta-5(*Z*),7(*E*),10(19)-triene (19). A solution of **18** (1.6 g, 29 mmol) and phenazine (20% with respect to the substrate) in dry benzene (150 mL) was irradiated for 30 min with a Hanovia medium-pressure mercury lamp fitted with an uranium glass filter. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel using hexanes/ethyl acetate 90:1 as the eluent to afford the *cis*-derivative (1.33 g, 83%). IR (neat): 3421, 2950, 2875, 1597 (vw), 1458, 1373 (vw), 1234 (vw), 1072, 1007, 733 cm^{-1}. ^1H NMR ($CDCl_3$), δ (ppm): 0.56 (3H, s), 4.20 (1H, m), 4.96 and 5.27 (2H, m), 6.02 (1H, d, J = 11.4 Hz), 6.33 (1H, d, J = 11.4 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 147.7, 142.6, 133.7, 124.5, 117.4, 112.7, 72.1, 67.1, 56.6, 56.5, 46.4, 45.98, 45.96, 43.6, 40.7, 36.6, 34.0, 29.3, 29.2, 27.8, 26.2, 23.7, 23.2, 22.4, 20.9, 19.2, 19.1, 12.2, 12.1, 7.0, 5.0. MS *m/z*: 542 (M^+) for $C_{35}H_{62}O_2Si$. HRMS: found 542.451436, calcd 542.451910.

1α,3β-Dihydroxy-9,10-*seco*-stigmasta-5(*Z*),7(*E*),10(19)-triene (1).[1a] A solution of triethylsilyl ether derivative **19** (1.2 g, 2.21 mmol) in tetrahydrofuran (20 mL) was treated with 1 M tetrabutylamonium fluoride in tetrahydrofuran (5.5 mL, 5.5 mmol) at room temperature for 45 min. The reaction mixture was quenched with water and extracted three times with ethyl acetate. The organic phase was washed with water and brine and dried over anhydrous sodium sulfate. After solvent evaporation under reduced pressure, the residue was chromatographed on silica gel using hexanes/ethyl acetate 6:4 to 4:6 as the eluent to give the deprotected derivative (0.7 g, 75%) as a solid. The solid (a mixture of 1α-hydroxy- and 1β-hydroxyvitamin D5 4:1) was crystallized three times from anhydrous methyl formate to afford pure 1α-hydroxyvitamin D_5 (0.200 g, 28%). Mp: 153−154 °C. $[\alpha]^{20}_D$: +29.3, (c 0.5, $CHCl_3$). IR (neat): 3386, 2947, 2866, 1697 (vw), 1457, 1373, 1043, 891 cm^{-1}. ^1H NMR ($CDCl_3$), δ (ppm): 0.54 (3H, s), 4.23 (1H, m), 4.43 (1H, m), 5.0 and 5.33 (2H, s), 6.02 (1H, d, J = 11.4 Hz), 6.38 (1H, d, J = 11.4 Hz). ^{13}C NMR ($CDCl_3$), δ (ppm): 147.8, 143.5, 133, 125.2, 117.2, 112.0, 70.9, 67.0, 56.7, 56.5, 46.2, 46.0, 45.4, 43.0, 40.7, 36.7, 34.0, 29.3, 29.3, 27.8, 26.2, 23.2, 23.2, 22.5, 20.0, 19.2, 19.1, 12.19, 12.18. Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.14; H, 11.30.

Supporting Information Available: Listing of the ^1H spectrum of compound **1** and ^{13}C spectra of compounds **1**, **8**, and **13**−**18**, as well as the experimental details for the synthesis of compounds **7**−**9** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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