Synthesis of 25-Hydroxycholecalcifer-16-en-23-ynol: A Potential Antipsoriatic Agent

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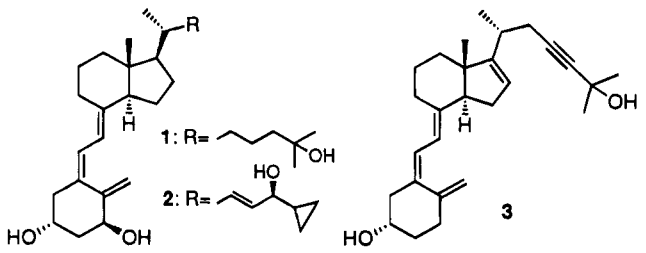
Received October 10, 1994

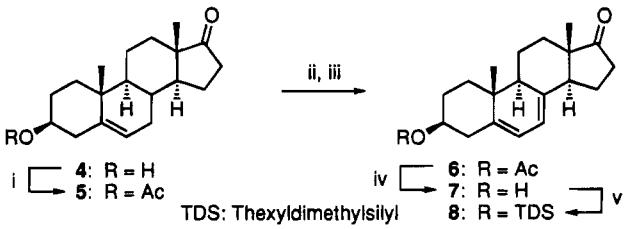
Introduction

It has been shown that 1α,25-dihydroxycholecalciferol (**1**)[1,2] or its analogs [1α-hydroxycholecalciferol,[2a] 1α,24-dihydroxycholecalciferol,[3] calcipotriol (**2**)[4]] have beneficial therapeutic effects in psoriasis, a hyperproliferative skin disorder.[5] However, their clinical use may be limited by



their potent effects on calcium homeostasis.[6] Therefore, the search for new analogs, which provide a greater margin of safety, would be important in the treatment of psoriasis. Among a large number of vitamin D_3 analogs prepared by the Uskoković group for a variety of therapeutic indications, 25-hydroxycholecalcifer-16-en-23-ynol (**3**) has been identified as a potential antipsoriatic agent with low calcemic effects[7] and as a consequence was selected for clinical development. In order to achieve a practical synthesis of **3**, we took a classical but direct approach starting from a commercially available steroid, dehydroepiandrosterone (**4**). Herein we describe the results of this study, which led to practical procedures

Scheme 1



[a] Key: (i) BF_3–OEt_2, Ac_2O, CH_2Cl_2; (ii) dibromantin, cyclohexane; (iii) Bu_4NF, THF; (iv) NaOMe, MeOH; (v) TDSCl, imidazole, CH_2Cl_2.

for the deoxygenation of propargylic alcohols and for the photolysis of provitamins (such as **14**).

Results and Discussion

Acetylation of **4** followed by bromination of **5** and dehydrobromination by Bu_4NF[8] afforded 5,7-diene acetate **6**, which was then converted to silyl ether **8** in 44.7% overall yield from **4** (Scheme 1). The side chain with the desired configuration at C-20 was then introduced[9] by a modification of the procedures described by Uskoković et al.,[7c] in which the ene reaction of steroidal *Z*-olefin **9** with acetylenic aldehyde **10** in the presence of Me_2AlCl[10] followed by Barton deoxygenation provides the complete side chain. Thus, Wittig reaction of **8** gave the requisite *Z*-olefin **9** in 93.7% yield with high stereoselectivity[11] (Scheme 2). The ene reaction proceeded well with complete stereocontrol at C-20 but with moderate selectivity at C-22, giving a 5:1 mixture of the C-22 epimeric alcohols **11**. The epimers were not separated. The mixture was subjected to Barton deoxygenation.[12] Deoxygenation of **11** using the phenoxy(thiocarbonyl) derivative and (thiocarbonyl)imidazole worked well, despite the presence of the diene function which is potentially sensitive under such conditions.[13] However, the reagents required, phenyl chlorothionoformate and (thiocarbonyl)-diimidazole, are too expensive for large scale application. Alternative derivatives which could be prepared by using relatively cheap reagents, including the corresponding xanthate and dimethyl thiocarbamate, were studied. To our pleasant surprise, the thionocarbamate **12** prepared from phenyl isothiocyanate, the cheapest reagent we studied, was found to be equally as efficient as the more expensive derivatives in giving the deoxygenation product **13** when treated with Bu_3SnH.[14] After deprotection, diol **14** (ca. 200 g, see Experimental Section) was thus obtained as a white solid in 47.5% overall yield from the *Z*-olefin **9**. **14** was then converted to acetate **15** in 89.8% yield.

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(6) Calcipotriol (**2**) is reported to be at least 100 times less active than **1** in its effects on calcium homeostasis in rats (see ref. 4). However, it is suggested that this is due to the rapid degradation of **2** in vivo (see ref 7b).

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(9) For a [2,3]-Wittig rearrangement approach, see: Granja, J. R. *Synth. Commun.* **1991**, *21*, 2033.

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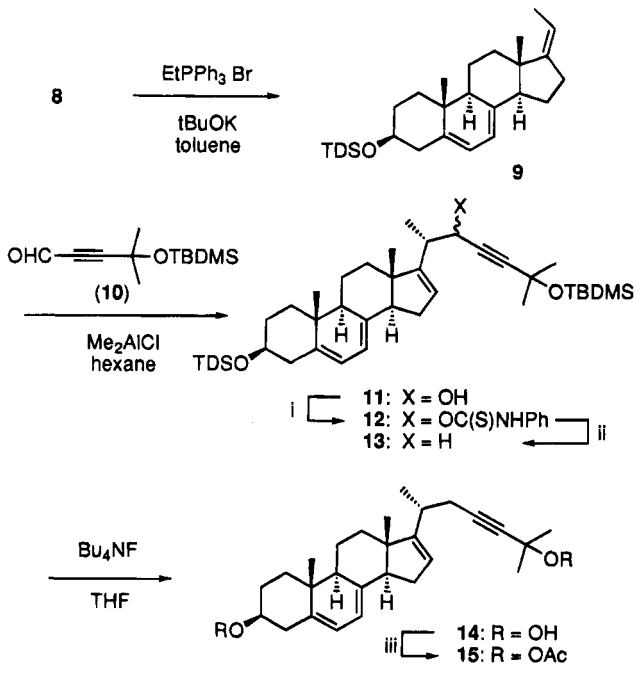
(12) For reviews, see: (a) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.

(13) After completion of this study, an additional example of the successful Barton deoxygenation in the presence of the ring B diene was reported. See ref 16e.

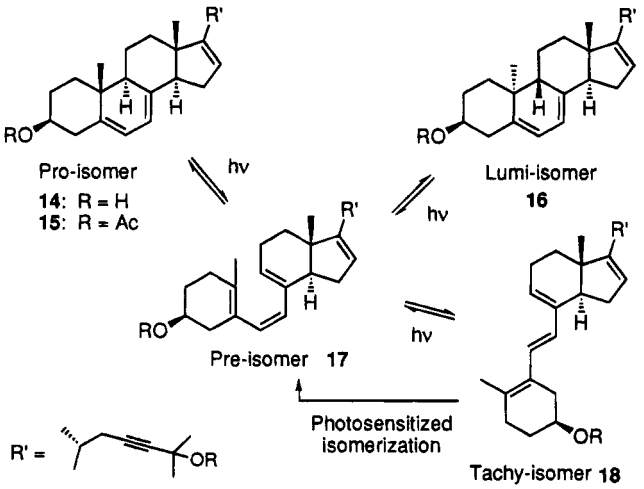
0022-3263/95/1960-0767$09.00/0

Scheme 2



[a] Key: (i) PhNCS, NaH, THF; (ii) Bu_3SnH, AIBN, hexane; (iii) Ac_2O, Et_3N, DMAP, CH_2Cl_2.

Scheme 3



The photolyses of provitamins (i.e., pro-isomer, such as **14**) to pre-isomers (such as **17**, Scheme 3) are usually carried out by using a high-pressure mercury lamp either in an inert solvent, such as ether and ethanol,[15] or in benzene.[16] The overall yields of vitamin D derivatives, after thermal isomerization of pre-isomers, are generally 15–30% (after HPLC purification, typically in a few milligram scale). Higher yields of pre-isomer have in the past been achieved by irradiating the pro-isomer with a narrow band of ca. 250 nm light (using a low-pressure mercury lamp or a laser) and then selective isomerization of the thus formed tachy-isomer into pre-isomer by irradiation at ca. 350 nm[17] or by the use of a photosensitizer.[18] Vitamin D_3 was then isolated in 50% after thermal isomerization.[17b] However, the use of high-intensity light sources, essential for a larger scale application, with narrow band spectra is prohibitive due to their high cost, and moreover, they require specialized equipment set-ups.

In order to achieve a practical synthesis which eventually would be used to produce several hundreds of grams of the vitamin D analog, we decided to use a medium-pressure mercury lamp, a cheap, high-intensity light-source. This lamp requires no specialized equipment. Also, it was essential to filter out the 300–315 nm light which promotes the ring-closure reaction to produce pro- and lumi-isomers (such as **15** and **16**, respectively).[17] We found that the addition of ethyl 4-(dimethylamino)-benzoate (**19**) as a filter fulfills this requirement.[19] When a mixture of **15** (16.4 g) and **19** (1.64 g) in *tert*-butyl methyl ether (1.7 L) was irradiated for 8 h with a 450 W medium-pressure mercury lamp it gave a near photo-equilibrium mixture (the ratio of **15**, **17**, and **18** was about 1:3:2). A uranium filter was then inserted to cut off <340 nm light, and the mixture was irradiated with the same lamp in the presence of 9-acetylanthracene as a sensitizer[20] to isomerize **18** to **17** (the ratio of **15**, **17**, and **18** became about 1:5:<0.1). After a simple chromatography and thermal isomerization of **17**,[21] the diacetate **20** of ca. 95% purity (together with ca. 5% of **15**) was obtained in 46.7% yield as a crystalline solid (Scheme 4). Fractional crystallization of this crude product gave analytically pure **20** (free from **15**) in 38.8% overall yield from **15** (the yield is not corrected for recovered starting material). Hydrolysis of **20** gave **3** as a crystalline solid in 90.9% yield.[22]

Conclusion

A practical synthesis of potential antipsoriatic agent **3** from commercially available steroid **4** was achieved in

(14) This new deoxygenation procedure may be limited to the system in which relatively stable radicals are produced, since it was recently reported that 2-decyl thionocarbamates prepared from 2-decanol and isothiocyanates, when treated with Bu_3SnH, gave decane only in 7% yield together with 2-decanol (49%). See: Nishiyama, K.; Oba, M. *Tetrahedron Lett.* **1993**, *34*, 3745. Similar results were obtained by André Hell (F. Hoffmann-La Roche Ltd.); private communication.

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(19) **19** has a strong, relatively sharp absorption at 305 nm (ϵ 32 500) and is fairly transparent in the region of 240–260 nm and above 330 nm, so the ring opening of **15** to **17** and photosensitized isomerization of **18** to **17** can be carried out effectively.

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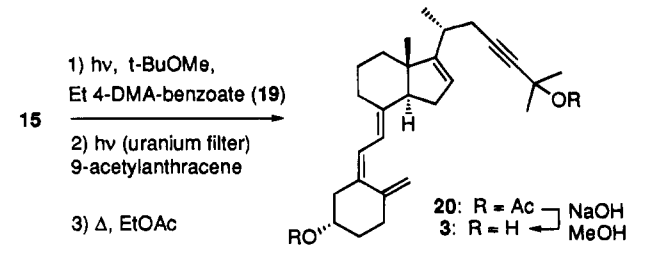
(21) See: Okamura, W. H.; Elnagar, H. Y.; Ruther, M.; Dobreff, S. *J. Org. Chem.* **1993**, *58*, 600 and references cited therein.

(22) The crystals of **3** obtained in this study are found to be quite sensitive toward oxygen. Detailed stability data of **3** are beyond the scope of this paper and will be published elsewhere. For stable pro-drugs, see ref 7d.

Scheme 4



6.3% overall yield involving only one simple chromatographic purification. One of the key steps of this synthesis involves the first successful use of a thionocarbamate prepared from phenyl isothiocyanate and a propargylic alcohol in a Barton deoxygenation. This new procedure using the cheap derivatizing agent, phenyl isothiocyanate, may be generally applicable to the system in which relatively stable radicals are produced.[14] The new protocol for the photolysis of a provitamin[23] described here can be carried out in a typical synthetic laboratory and should be applicable for the synthesis of a variety of vitamin D analogs. Application of this protocol in vitamin D_2 synthesis will be published elsewhere.

Experimental Section

Melting points are determined using a capillary melting point apparatus and are uncorrected. NMR spectra were recorded on Varian XL-200 and -400 instruments and are reported in ppm relative to Me_4Si. All moisture-sensitive reactions were carried out under a positive pressure of argon.

(3β)-3-(Acetyloxy)-5-androsten-17-one (5). To a suspension of **4** (144 g, 0.50 mol) in CH_2Cl_2 (250 mL) was added BF_3-OEt_2 (3 mL, 24 mmol) followed by Ac_2O (61.5 mL, 0.65 mol) over 15 min, keeping the temperature below 25 °C. After the mixture was stirred for 4 h, water was added, and the resulting mixture was stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, dried, and concentrated. The residue was dried at 50 °C under high vacuum to give 165 g (99.9% yield) of **5** as a white solid: mp 167–170 °C; IR (KBr) 1738, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (s, 3 H), 1.02 (m, 1 H), 1.05 (s, 3 H), 1.16 (m, 1 H), 1.30 (m, 2 H), 1.51 (m, 2 H), 1.60 (m, 1 H), 1.67 (m, 3 H), 1.87 (m, 3 H), 1.94 (m, 1 H), 2.04 (s, 3 H), 2.12 (m, 2 H), 2.35 (m, 2 H), 2.46 (dd, J = 20.4 and 8.9 Hz, 1 H), 4.61 (m, 1 H), 5.41 (d, J = 5.1 Hz, 1 H); MS m/z 270 ($M^+ - CH_3CO_2H$). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.19; H, 9.05.

Bromination of 5. A mixture of **5** (165 g, 499 mmol) and cyclohexane (1.5 L) was warmed to ca. 80 °C to obtain a clear solution. After the solution was cooled to 65 °C, 1,3-dibromo-5,5-dimethylhydantoin (dibromantin) (85.8 g, 300 mmol) was added and the mixture was heated to reflux. After being refluxed for 30 min, the suspension was cooled to 10 °C and diluted with 1.5 L of water. After being stirred for 1 h, the precipitate was collected by filtration and washed with water. After the solid was dissolved in CH_2Cl_2, the solution was washed with brine, dried, and concentrated. Drying at 30 °C under high vacuum afforded 175 g (85.9% yield) of crude 7α-bromo-3β-(acetyloxy)androst-5-en-17-one as a light brown solid. This crude material was used for the next step: ^1H NMR ($CDCl_3$) δ 0.90 (s, 3 H), 1.06 (s, 3 H), 2.04 (s, 3 H), 4.68 (m, 1 H), 4.76 (m, 1 H), 5.78 (d, J = 5.0 Hz, 1 H).

(3β)-3-Acetoxyandrosta-5,7-dien-17-one (6). A mixture of the crude bromide (175 g, 428 mmol) prepared above and 1.0 M Bu_4NF in THF (1.25 L, 1.25 mol) was stirred overnight. Then, the mixture was diluted with cyclohexane, washed with water, dried, and concentrated. Drying at 40 °C under high vacuum afforded 142 g (overweight) of crude **6** as a brown solid. This crude material was used for the next step. An analytical sample was prepared by chromatographic purification: mp 112–117 °C; IR (KBr) 1732 cm^{-1}; UV (EtOH) λ_{max} 271 (ε 10 530), 281 (ε 11 100), 293 (ε 6300) nm; ^1H NMR ($CDCl_3$) δ 0.82 (s, 3 H), 0.98 (s, 3 H), 1.38 (m, 2 H), 1.60 (m, 2 H), 1.74 (m, 3 H), 1.93 (m, 3 H), 2.05 (s, 3 H), 2.13 (m, 1 H), 2.20 (m, 2 H), 2.38 (bt, J = 13.1 Hz, 1 H), 2.52 (m, 2 H), 4.71 (m, 1 H), 5.57 (m, 1 H), 5.61 (m, 1 H); MS m/z 268 ($M^+ - CH_3CO_2H$). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.53; H, 8.61.

(3β)-3-Hydroxyandrosta-5,7-dien-17-one (7). To a suspension of crude **6** (142 g) prepared above in 1.25 L of methanol was added 25% (wt) NaOMe in MeOH (25 mL). After the mixture was stirred overnight, 1.0 L of water was added dropwise over 1 h. After the mixture was stirred for 2 h, the precipitate was collected by filtration, washed with MeOH–H_2O (1:2), and dried by suction for 3 h. Further drying at 40 °C under high vacuum afforded **7** (77.4 g, 54.2% from **5**) as a brown solid. This crude material was used for the next step. An analytical sample was prepared by recrystallization from aqueous methanol: mp 156–160 °C; IR (KBr) 1738 cm^{-1}; UV (EtOH) λ_{max} 270 (ε 10 150), 281 (ε 10 720), 292 (ε 6100) nm; ^1H NMR ($CDCl_3$) δ 0.83 (s, 3 H), 0.97 (s, 3 H), 1.35 (m, 2 H), 1.53 (m, 2 H), 1.74 (m, 3 H), 1.92 (m, 3 H), 2.07 (m, 2 H), 2.20 (m, 2 H), 2.31 (bt, J = 13.1 Hz, 1 H), 2.52 (m, 2 H), 3.67 (m, 1 H), 5.57 (m, 1 H), 5.62 (m, 1 H); MS m/z 286 (M^+). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.56; H, 9.38.

(3β)-3-[[(1,1,2-Trimethypropyl)dimethylsilyl]oxy]-androsta-5,7-dien-17-one (8). After a mixture of crude **7** (150 g, 523 mmol) and imidazole (56.9 g, 836 mmol) in CH_2Cl_2 (500 mL) was cooled to 3 °C, thexyldimethylsilyl chloride (144 mL, 732 mmol) was added dropwise over 90 min, keeping the temperature below 6 °C. After being stirred at rt overnight, the mixture was washed with water, and the aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, dried, and concentrated. The resulting solid was suspended in MeOH (700 mL) containing Et_3N (14 mL), and the suspension was refluxed for 20 min. After the suspension was cooled in a refrigerator overnight, the precipitate was collected by filtration, washed with MeOH–H_2O (9:1), and dried by suction for 2 h. Further drying at 40 °C under high vacuum afforded 185 g (82.5% yield) of **8** as a beige solid: mp 119–125 °C; IR (KBr) 1738 cm^{-1}; UV (EtOH) λ_{max} 271 (ε 10 000), 281 (ε 10 620), 293 (ε 6130) nm; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.82 (s, 3 H), 0.84 (s, 6 H), 0.89 (d, J = 6.8 Hz, 6 H), 0.96 (s, 3 H), 1.30 (m, 2 H), 1.51 (m, 1 H), 1.63 (quintet, J = 6.8 Hz, 1 H), 1.74 (m, 4 H), 1.90 (m, 2 H), 2.08 (m, 2 H), 2.20 (m, 2 H), 2.35 (m 2 H), 2.52 (dd, J = 20.0 and 8.1 Hz, 1 H), 3.59 (m, 1 H), 5.58 (m, 2 H); MS m/z 428 (M^+). Anal. Calcd for $C_{27}H_{44}O_2Si$: C, 75.64; H, 10.34; Si, 6.55. Found: C, 75.82; H, 10.29; Si, 6.72.

(3β,17Z)-(1,1,2-Trimethylpropyl)(pregna-5,7,17(20)-trien-3-yloxy)dimethylsilane (9). A mixture of ethyltriphenylphosphonium bromide (240 g, 647 mmol), potassium *tert*-butoxide (72.5 g, 647 mmol), and toluene (1 L) was stirred at rt for 1 h. Then, **8** (185 g, 430 mmol) was added. The temperature was kept below 25 °C by water cooling. After being stirred at rt overnight, the reaction was quenched with 24.5 mL (430 mmol) of AcOH. After the mixture was stirred for 1 h, the solid was removed by filtration and washed with toluene. The combined filtrate and washes were concentrated. Then, methanol was added, and the mixture was concentrated again. The residue was dissolved in a mixture of methanol (650 mL), water (65 mL), and hexane (650 mL). The methanol/water layer was back-extracted with hexane. The combined hexane layers were concentrated. Then, methanol was added, and the mixture was concentrated again. The resulting solid was suspended in MeOH (800 mL) containing Et_3N (8 mL), and the suspension was refluxed for 30 min. After the suspension was cooled in a refrigerator overnight, the precipitate was filtered, washed with cold MeOH, and dried by suction for 4 h. Further drying at 50 °C under high vacuum afforded 178 g (93.7% yield) of **9** as a pale yellow solid: mp 94–97 °C; $[\alpha]_D$ −62.8° (*c* 0.94, EtOH); IR (KBr) 1672, 1600 cm^{-1}; UV (EtOH) λ_{max} 271 (ε 10 980), 281 (ε 11 560), 293 (ε 6600) nm; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.84 (s, 9 H), 0.89 (d, J = 6.8 Hz, 6 H), 0.95 (s, 3 H), 1.28 (m, 1 H), 1.60 (m, 5 H), 1.68 (dt, J = 7.1 and 2.0 Hz, 3 H), 1.80 (m, 4 H), 2.02 (m, 2 H), 2.34 (m, 5 H), 3.59 (m, 1 H), 5.19 (bq, J = 7.1 Hz, 1 H), 5.47 (m, 1 H), 5.55 (m, 1 H); MS m/z 440 (M^+). Anal.

(23) Recently, the conversion of provitamin D_3 in an aqueous solution of antenna polyelectrolyte using solar light has appeared. See: Nowakowska, M.; Foyle, V. P.; Guillet, J. E. *J. Am. Chem. Soc.* **1993**, *115*, 5975.

Calcd for $C_{29}H_{48}OSi$: C, 79.02; H, 10.98; Si, 6.37. Found: C, 78.74; H, 11.23; Si, 6.50.

4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methyl-2-pentynal (10). To a solution of (1,1-dimethylethyl)[(1,1-dimethyl-2-propynyl)oxy]dimethylsilane (50.0 g, 252 mmol) in 200 mL of THF at −70 °C was added 112 mL (280 mmol) of 2.5 M BuLi in hexanes dropwise over 25 min, keeping the temperature below −55 °C. The mixture was stirred for 5 min. Then, 50 mL of DMF was added dropwise over 10 min. After 15 min, the reaction was quenched by the addition of 32 mL of AcOH (560 mmol). After the mixture was allowed to warm to −20 °C, hexane and water were added. The aqueous layer was back-extracted with hexane. The combined organic layers were washed with saturated NH_4Cl solution and then with brine. After drying, the solution was concentrated to dryness. Then the residue was distilled through a 10-cm Vigreux column to give 48.8 g (85.5% yield) of **10**: bp 50 °C (0.5 mmHg).[7c]

(3β)-25-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[[dimethyl(1,1,2-trimethylpropyl)silyl]oxy]cholesta-5,7,16-trien-23-yn-22-ol (11). A mixture of **9** (458 g, 1.04 mol), **10** (285 g, 1.20 mol), and hexane (6.4 L) was cooled to −55 °C. Then, 1 M Me_2AlCl in hexane (1.47 L, 1.47 mol) was added dropwise within 30 min, keeping the temperature below −40 °C. After the dark brown solution was stirred at −40 °C for 30 min, 4 L of 10% $Na_2HPO_4-7H_2O$ was added dropwise, and the mixture was allowed to warm to 5 °C. Then, 2.5 L of 2.87 N HCl was added dropwise at a temperature of 0−5 °C followed by 113 g of Celite. After 15 min, the solid was removed by filtration through a Celite pad and washed with hexane. The aqueous layer was extracted twice with hexane. The combined hexane solutions were washed successively with water, 10% $NaHCO_3$, and brine. The hexane layer was dried and concentrated to give 749 g (overweight) of crude **11** (ca. 5:1 mixture of epimers at C-22) as an orange oil. This crude material was used for the next step: IR (KBr) 3440, 2205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.16 (s, 6 H), 0.83 (s, 3 H), 0.84 (s, 6 H), 0.86 (s, 9 H), 0.89 (d, J = 6.9 Hz, 6 H), 0.97 (s, 3 H), 1.17 (d, J = 7.0 Hz, 3 H), 1.28 (m, 1 H), 1.44 (s, 6 H), 1.50 (m, 2 H), 1.62 (quintet, J = 6.9 Hz, 1 H), 1.80 (m, 5 H), 2.02 (m, 1 H), 2.22 (m, 3 H), 2.34 (m, 2 H), 2.47 (broad quintet, J = 7.0 Hz, 1 H), 3.59 (m, 1 H), 4.42 (m, 1 H of the minor isomer), 4.46 (t, J = 5.9 Hz, 1 H of the major isomer), 5.47 (m, 1 H), 5.57 (m, 1 H), 5.68 (bs, 1 H); MS m/z 666 (M^+).

Thionocarbamate 12. To a suspension of NaH (60% dispersion, 125 g, 3.12 mol) in 1 L of THF at 5 °C was added a solution of crude **11** (749 g) prepared above in 3.1 L of THF over 15 min. The resulting dark brown suspension was stirred at 5−15 °C for 2 h. Then, phenyl isothiocyanate (179 mL, 1.5 mol) was added, and the mixture was stirred at 10−20 °C for 2 h. The reaction was quenched by the dropwise addition of AcOH (119 mL) followed by water. After extraction with EtOAc, the organic phase was dried over Na_2SO_4 and concentrated to dryness. The residue was dissolved in hexane and 95% MeOH/H_2O. The hexane layer was washed with 95% MeOH, and the combined MeOH layers were extracted with hexane. The hexane solutions were combined, dried, and concentrated to dryness to give 943 g (overweight) of crude **12** as an orange oil. This crude material was used for the next step: IR (KBr) 3405 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H), 0.14 (s, 6 H), 0.84 (s, 18 H), 0.89 (d, J = 6.9 Hz, 6 H), 0.95 (s, 3 H), 1.18 (d, J = 6.9 Hz, 3 H), 1.28 (m, 1 H), 1.44 (s, 6 H), 1.50 (m, 2 H), 1.62 (quintet, J = 6.9 Hz, 1 H), 1.80 (m, 5 H), 2.02 (m, 1 H), 2.20 (m, 3 H), 2.34 (m, 2 H), 2.72 (broad quintet, J = 6.9 Hz, 1 H), 3.59 (m, 1 H), 5.44 (m, 1 H), 5.57 (m, 1 H), 5.64 (bs, 1 H), 6.19 (d, J = 6.6 Hz, 1 H of the major isomer), 6.30 (d, J = 6.1 Hz, 1 H of the minor isomer), 7.25 (m, 5 H), 8.18 (bs, 1 H); MS m/z 802 (M^+ + H).

[[(3β)-25-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]cholesta-5,7,16-trien-23-yn-3-yl]oxy]dimethyl(1,1,2-trimethylpropyl)silane (13). A mixture of the crude **12** (943 g) prepared above and Bu_3SnH (950 mL, 3.51 mol) in hexane (3 L) was heated to 50 °C, and AIBN (93.4 g, 0.57 mol) was added. After 2 h of refluxing, the mixture was cooled to rt and concentrated. The residual hexane was removed by coevaporation with MeOH several times. The residual oil was washed with MeOH several times and dried under high vacuum to give 1.06 kg (overweight) of crude **13** as an oil. This crude material was used in the next step. An analytical sample was obtained by chromatographic purification followed by crystallization from ethyl acetate/methanol (1:1): mp 62−66 °C; IR (KBr) 2235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.14 (s, 6 H), 0.81 (s, 3 H), 0.84 (s, 6 H), 0.86 (s, 9 H), 0.89 (d, J = 6.9 Hz, 6 H), 0.97 (s, 3 H), 1.13 (d, J = 6.6 Hz, 3 H), 1.29 (m, 1 H), 1.41 (s, 6 H), 1.45 (m, 2 H), 1.63 (quintet, J = 6.9 Hz, 1 H), 1.80 (m, 5 H), 2.02 (m, 1 H), 2.22 (m, 4 H), 2.34 (m, 4 H), 3.59 (m, 1 H), 5.41 (bs, 1 H), 5.46 (m, 1 H), 5.57 (m, 1 H); MS m/z 650 (M^+). Anal. Calcd for $C_{41}H_{70}O_2Si_2$: C, 75.62; H, 10.84; Si, 8.63. Found: C, 75.12; H, 10.77; Si, 8.55.

(3β)-Cholesta-5,7,16-trien-23-yne-3,25-diol (14). To a solution of crude **13** (1.06 kg) in 2 L of THF was added Bu_4NF-3H_2O (1.6 kg, 5.14 mol) with the aid of 3.4 L of THF. After being stirred at rt for 18 h, the mixture was diluted with EtOAc (4 L) and water (4 L). The organic layer was washed with water, and the aqueous layers were combined and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated to a beige sludge. This was suspended in EtOAc (2 L), and the suspension was stirred at 35 °C for 10 min prior to filtration. The collected solid was resuspended in EtOAc (2.2 L), and the mixture was refluxed for 30 min. Then, hexane (1.1 L) was added dropwise over 10 min. After the mixture was cooled to 10 °C, the precipitate was collected by filtration, washed with EtOAc/hexane (1:1), and dried to give 209 g of crude **14**. This was resuspended in MeOH (2.2 L), and the mixture was refluxed for 30 min. Then, water (440 mL) was added and reflux was continued for 10 min. After the mixture was cooled to 4 °C, the precipitate was collected by filtration, washed with MeOH/H_2O (1:1), and dried at 45 °C under high vacuum to give 195 g of **14** (47.5% overall yield from **9**) as a white solid: mp 185−192 °C; $[\alpha]_D$ −85.2° (c 1.1, EtOH); IR (KBr) 3325, 2225 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 0.80 (s, 3 H), 0.96 (s, 3 H), 1.12 (d, J = 6.6 Hz, 3 H), 1.28 (m, 1 H), 1.43 (s, 6 H), 1.47 (m, 2 H), 1.80 (m, 5 H), 2.02 (m, 1 H), 2.22 (m, 5 H), 2.34 (m, 2 H), 2.42 (m, 1 H), 3.52 (m, 1 H), 4.22 (d, J = 4.2 Hz, s-OH), 4.47 (s, t-OH), 5.41 (bs, 1 H), 5.43 (m, 1 H), 5.56 (m, 1 H); MS m/z 394 (M^+). Anal. Calcd for $C_{27}H_{38}O_2$: C, 82.18; H, 9.71. Found: C, 81.93; H, 9.74.

(3β)-Cholesta-5,7,16-trien-23-yne-3,25-diol Diacetate (15). To a cold suspension of **14** (75.3 g, 191 mmol) in 450 mL of CH_2Cl_2 were added Ac_2O (107 mL, 1.14 mol) and Et_3N (160 mL, 1.14 mol). After the suspension was cooled to 2 °C, DMAP (4.6 g, 38 mmol) was added, and the mixture was stirred at rt overnight. After the mixture was cooled with an ice−water bath, MeOH (30.7 mL, 758 mmol) was added, and the mixture was stirred at rt for 1.5 h. The mixture was washed with water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, dried, and concentrated to dryness. The residue was dissolved in 700 mL of warm 95% MeOH. After a seed crystal was added, the suspension was stored in a refrigerator overnight. The precipitate was filtered and washed with cold 90% MeOH. After the precipitate was dried under high vacuum, 82.05 g (89.8%) of **15** was obtained as a white solid: mp 98−101 °C; IR (KBr) 2240, 1742, 1728 cm^{-1}; UV (EtOH) λ_{max} 270 (ε 10 800), 281 (ε 11 400), 292 (ε 6070) nm; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H), 0.99 (s, 3 H), 1.12 (d, J = 6.5 Hz, 3 H), 1.36 (m, 1 H), 1.47 (m, 1 H), 1.57 (m, 1 H), 1.62 (s, 6 H), 1.80 (m, 5 H), 2.00 (s, 3 H), 2.04 (m, 1 H), 2.05 (s, 3 H), 2.22 (m, 5 H), 2.37 (m, 2 H), 2.52 (m, 1 H), 4.71 (m, 1 H), 5.41 (bs, 1 H), 5.46 (m, 1 H), 5.59 (m, 1 H); MS m/z 478 (M^+). Anal. Calcd for $C_{31}H_{42}O_4$: C, 77.79; H, 8.84. Found: C, 77.74; H, 8.88.

(3β,5Z,7E)-9,10-Secocholesta-5,7,10(19),16-tetraen-23-yne-3,25-diol Diacetate (20). A solution of **15** (16.4 g, 34.3 mmol) and ethyl 4-(dimethylamino)benzoate (**19**) (1.64 g) in 1.7 L of t-BuOMe at −20 °C was irradiated with a 450 W medium-pressure mercury lamp through a quartz immersion well. After 8 h of irradiation at 0 to −20 °C, a uranium filter was inserted in the arc housing, and then 66 mg of 9-acetylanthracene was added to the solution. After 1 h 45 min of irradiation through the filter at 0 to −20 °C, the solution was allowed to warm to rt overnight and then washed four times with a total of 400 mL of 3 N HCl. The organic layer was then washed with 200 mL of saturated $NaHCO_3$ and dried over Na_2SO_4. The solution was concentrated to dryness. Then the residual oil was purified by chromatography on silica gel (200 g), eluting with 3 L of 7% EtOAc in hexane. The desired fractions were combined and concentrated to give ca. 13 g of crude photoproduct as a clear oil, which contains **15**, **17**, **20**, and the sensitizer. A total of five

separate and comparable experiments produced 65 g (77%) of the crude photoproduct from 84 g of **15**.

A solution of the crude photoproducts (65 g, prepared above) in 1 L of EtOAc was refluxed for 4 h and then allowed to cool to rt overnight. The solution was concentrated. The residual semisolid was dissolved in 650 mL of hot 95% MeOH. The solution was cooled to rt and then stored in a refrigerator overnight. The crystalline material was collected by filtration and washed with cold 95% MeOH. The second crop was obtained in a similar manner and combined with the first crop. The crystalline solid was dried under high vacuum for 4 h to afford 38.4 g (46.9% from **15**) of crude **20** (ca. 95% pure, together with ca. 5% of **15**). Fractional crystallization from 95% MeOH gave 31.8 g (38.8% from **15**) of analytically pure **20**: mp 97–100 °C; $[\alpha]_D$ +14.88° (*c* 1.01, EtOH); IR (KBr) 2245, 1742 cm^{-1}; UV (EtOH) λ_{max} 264 (ϵ 13 150) nm; ^1H NMR ($CDCl_3$) δ 0.70 (s, 3 H), 1.12 (d, J = 6.7 Hz, 3 H), 1.50 (m, 1 H), 1.62 (s, 6 H), 1.75 (m, 5 H), 1.95 (m, 2 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 2.21 (m, 3 H), 2.37 (m, 5 H), 2.58 (m, 1 H), 2.81 (m, 1 H), 4.85 (bs, 1 H), 4.95 (m, 1 H), 5.07 (bs, 1 H), 5.38 (bs, 1 H), 6.12 (d, J = 11.4 Hz, 1 H), 6.20 (d, J = 11.4 Hz, 1 H); MS m/z 478 (M^+). Anal. Calcd for $C_{31}H_{42}O_4$: C, 77.79; H, 8.84. Found: C, 77.66; H, 8.93.

25-Hydroxycholecalcifer-16-en-23-ynol (3). A mixture of **20** (2.0 g, 4.18 mmol), EtOH (20 mL), and 10 N NaOH (2 mL, 20 mmol) was stirred at rt for 2.5 h. Then, the excess NaOH was quenched by the addition of AcOH (0.66 mL, 11.6 mmol). After 10 min of stirring, 14 mL of water was added dropwise followed by the addition of a seed crystal of **3**. After 1.5 h of stirring, 4 mL of water was added, and the suspension was stored in a refrigerator overnight. The white precipitate was filtered and washed with 6 mL of cold EtOH–H_2O (1:1) and with 24 mL of cold EtOH–H_2O (1:2). Drying at rt under 0.4 mmHg for 20 h afforded 1.5 g (90.9%) of **3** as a white solid:[22] mp 106–107 °C; IR (KBr) 2215 cm^{-1}; UV (EtOH) λ_{max} 262 (ϵ 13 750) nm; ^1H NMR ($CDCl_3$) δ 0.72 (s, 3 H), 1.12 (d, J = 6.5 Hz, 3 H), 1.48 (s, 6 H), 1.75 (m, 6 H), 1.92 (m, 1 H), 2.02 (m, 1 H), 2.30 (m, 8 H), 2.58 (m, 1 H), 2.81 (m, 1 H), 3.96 (m, 1 H), 4.83 (bs, 1 H), 5.06 (bs, 1 H), 5.38 (bs, 1 H), 6.12 (d, J = 11.2 Hz, 1 H), 6.22 (d, J = 11.2 Hz, 1 H); MS m/z 394 (M^+). Anal. Calcd for $C_{27}H_{38}O_2$ + 3/4H_2O: C, 79.46; H, 9.76. Found: C, 79.17; H, 9.89.

Acknowledgment. The encouragement and advice provided by Dr. David L. Coffen is greatly appreciated. The authors would like to acknowledge Mr. Anthony J. Laurenzano and his colleagues for the successful scale-up of this work.

JO9416980