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Synthesis of 17-*epi*-Calcitriol from a Common Androstane Derivative, Involving the Ring B Photochemical Opening and the Intermediate Triene Ozonolysis

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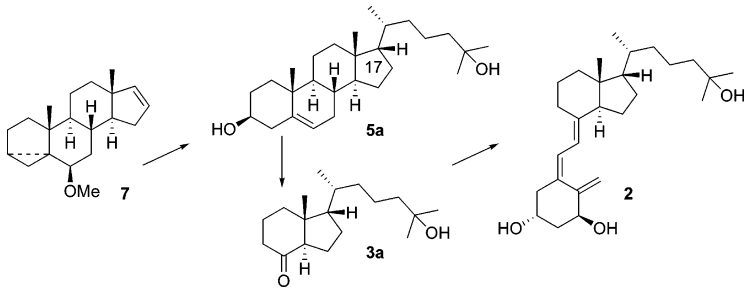

An efficient synthesis of 17-*epi*-calcitriol **2**, an epimer of natural hormone, via 17-*epi*-cholesterol **5a** is described. Synthesis of **5a** includes palladium-catalyzed cyclopropanation of the common androstane derivative **7** with an alkyl diazoacetate, reductive fission of the less shielded side of cyclopropane carboxylic acid esters **6**, oxidation of the products into acid **11a**, and alkylation of ester **11b**. Photolysis of 7,8-dedydro-17-*epi*-25-hydroxycholesterol **19b** and consecutive thermal rearrangement gave a mixture of several products that was subjected to ozonolysis to provide, after chromatography, hydroxy ketone **3a**. The silyl derivative **3b** was coupled with the respective ring A building block.

Introduction

Calcitriol **1** (Scheme 1), the hormonally active metabolite of calciol (vitamin D_3), shows a broad spectrum of biological activities.[1,2] Its primary function consists of controlling calcium transport and skeletal mineralization. A great deal of attention has recently been given to secondary noncalcemic activities of **1** affecting various metabolic processes. Calcitriol and its analogues have successfully been applied in the treatment of human bone, skin, and immune system metabolic disorders[3] and certain types of cancer,[4] stimulating the search for new compounds with better therapeutic indexes.[5,6]

A considerable part of the structure-activity studies on vitamin D compounds has concentrated on the side-chain modifications and the spatial orientation of the side chain.[1] During this line of research, interesting properties were recorded for 20-*epi*-calcitriol,[7] the "double side-chain" analogue,[5,8] and some CD-rings-modified analogues.[9]

As a continuation of our study on synthesis and biological evaluation of calcitriol stereoisomers,[10] we became interested in 17-*epi*-calcitriol **2**. Comparison of

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(2) (a) Beckman, M. J.; DeLuca, H. F. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Oxford, A. W., Eds.; Elsevier: Amesterdam, 1998; Vol. 35, pp 1−56. (b) Markus, R.; Feldman, D.; Kelsey, J. In *Osteoporosis*; Feldman, D., Malloy, P. J., Gross, C., Eds.; Academic Press: San Diago, 1996.

(3) (a) Nordin, B. E. C.; Morris, H. A. *J. Cell. Biochem.* **1992**, *49*, 19−25. (b) Kerkhof, P. C. M. v. d. *Br. J. Dermatol.* **1995**, *132*, 675−682. (c) Tsoukas, C. D.; Provvedini, D. M.; Manolagas, S. C. *Science* **1984**, *224*, 1438−1440.

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(6) Recent works include: (a) Shi, B. F.; Wu, H.; Yu, B.; Wu, J. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4324−4327. (b) Shimizu, H.; Shimizu, K.; Uchiyama, Y.; Sugita, A.; Mikami, T.; Yamauchi, T.; Kato, M.; Morikawa, K. *Tetrahedron Lett.* **2004**, *45*, 7837−7841. (c) Posner, G. H.; Jeon, H. B.; Sarjeant, A.; Riccio, E. S.; Doppalapudi, R. S.; Kapetanovic, I. M.; Saha, U.; Dolan, P.; Kensler, T. W. *Steroids* **2004**, *69*, 757−762. (d) Demin, S.; Van Haver, D.; Vandewalle, M.; De Clercq, P. J.; Bouillon, R.; Verstuyf, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3885−3888. (e) Moman, E.; Nicoletti, D.; Mourino, A. *J. Org. Chem.* **2004**, *69*, 4615−4625. For a recent review, see: Posner, G. H.; Kahraman, M. *Eur. J. Org. Chem.* **2003**, 3889−3895.

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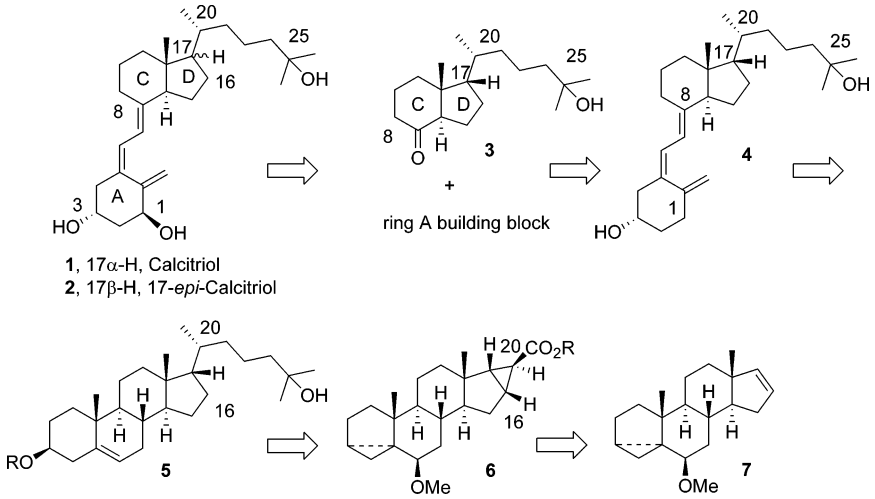
SCHEME 1. Structures of Calcitriol and 17-e*pi*-Calcitriol and an Outline of the Synthetic Route



molecular models for calcitriol **1** and **2** indicated a general similarity in molecules shape with a distinct difference in the side chains conformational preferences. No reports on synthesis of sterols or sterol analogues with 17α orientation of the side chain have been recorded.[11]

It was anticipated that the key intermediate in synthesis of **2**, 17-*epi*-cholesterol derivative **5**, would be obtained from alkyl 16α,20-cyclo-17α-pregnane-21-carboxylates **6** by reductive fission of the C-16(20) bond followed by side-chain elaboration. The intermediate **6**, in turn, should be accessible by diazocarboxylate-based cyclopropanation of the common androst-16-ene derivative **7**. Transformation of 17-*epi*-25-hydroxycholesterol **5** into 17-*epi*-calcidiol **4**, by dehydrogenation into the respective 5,7-diene derivative and the ring B photochemical opening,[12] was projected as the final sequence.

Hydroxylation of **4** in the 1α-position leading to **2** could be accomplished in principle by one of the known multistep procedures.[13,14] Since purification of vitamin D derivatives generated in photochemical reactions is known to be notoriously tedious and yields of any of the hydroxylation procedures are low, an alternative approach to **2** from **4** was considered. It was thought that the mixture of products furnished by the photolysis (and the thermal isomerization of the respective previtamin,[15] vide infra) containing **4** could be subjected to ozonolysis to afford ketone **3** along with several more polar products. Then, **3** can be separated and coupled[16] with the appropriate ring A precursor readily available by synthesis.[17]

In the present paper, we report the synthesis of **2**, which includes virtually diastereoselective construction of the side chain starting from **7** and new and versatile methodology for constructing the triene ring A moiety.[18]

Results and Discussion

The starting material olefin **7** was prepared by reduction of 17-iodo-3α,5-cyclo-5α-androst-16-ene with sodium in ethanol.[19] Initial experiments on cyclopropanation of **7** with alkyl diazoesters and various catalysts indicated that palladium(II) acetate[20] compares well with the more often used catalyst rhodium(II) acetate[21] so it was applied in all further work.

Treatment of **7** in dichloromethane (DCM) with ethyl diazoacetate (5 molar equiv) and catalyst (3 mol %) afforded a mixture of diastereomeric cyclopropane derivatives **6a** and **8a** (Scheme 2) in a ratio 7:1 (^{1}H NMR), contaminated with side products derived from the diazoester (ca. 5%). Since separation of the epimers by column chromatography was difficult, epimerization of

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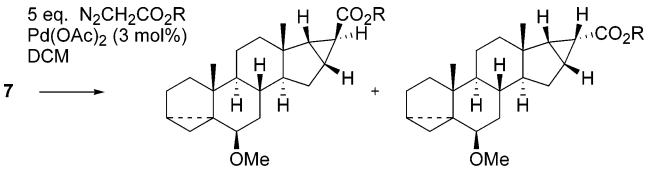
SCHEME 2



6a, R = Et
6b, R = Me
6c, R = *tert*-Bu

8a, R = Et
8b, R = Me

R	Product(s)	Epimer ratio	Yield (%)
Et	**6a**/**8a**	7:1	**6a**, 87[a]
Me	**6b**/**8b**	7:1	**6b**, 92[b]
tert-Bu	**6c**	only product	81[c]

[a] After equilibration of the mixture with EtONa/EtOH. [b]Crude product. [c]Estimated from the methanolysis product (**6a**), see the text.

the minor isomer (*endo*) was attempted. The crude mixture was heated in ethanol containing sodium ethoxide, and indeed, **6a** was obtained as the only steroid product affording easy purification.

Similarly, reaction of **7** with methyl diazoacetate in the presence of palladium(II) acetate afforded **6b** and its epimer to which the structure **8b** was assigned (92% yield; ca. 7:1). Treatment of **7** with *tert*-butyl diazoacetate and catalyst provided isomerically pure cyclopropane derivative **6c**, contaminated with side products (ca.. 5%). This crude product was used for further experiments; methanolysis of **6c** gave **6b** in 81% yield from **7**.

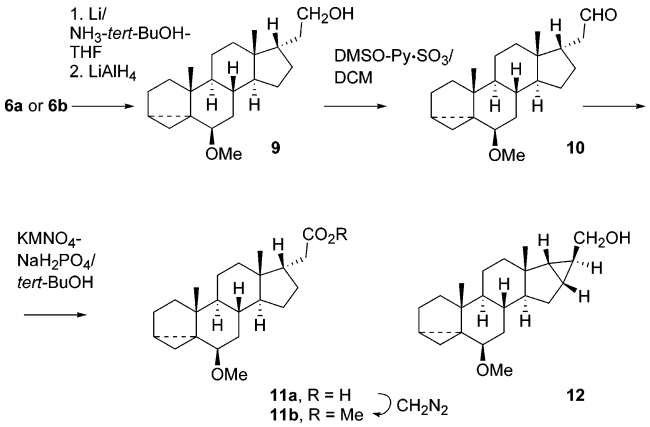
Treatment of **6a** or **6b** with lithium in liquid ammonia, in the presence of THF as a cosolvent and *tert*-butyl alcohol as a proton donor[22] gave a mixture of alcohols and aldehydes. The crude product was reduced with $LiAlH_4$ in ether to **9** contaminated with **12**. Under optimal conditions using a relatively large amount of *tert*-butyl alcohol (liq. ammonia:THF:*tert*-butyl alcohol, 4:1:1), over a 90% yield of **9** was obtained with ca. 5% of **12**.

Oxidation[23] of **9** with DMSO−Py·SO_3 afforded aldehyde **10** that was isolated and fully identified; however, this product decomposed in storage. Therefore aldehyde **10** was oxidized rapidly with potassium permanganate in *tert*-butyl alcohol in the presence of NaH_2PO_4 into crystalline acid **11a**, which was converted into methyl ester **11b** by diazomethane.

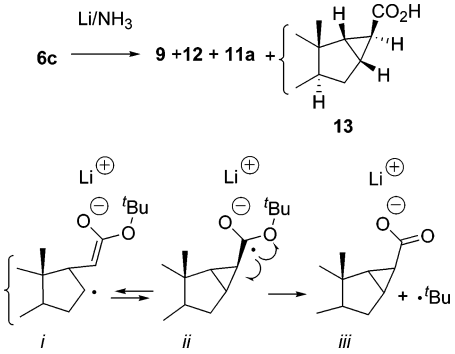
For larger scale routine preparations, olefin **7** was allowed to react with ethyl diazocarboxylate, then the crude product was subjected consecutively to methanolysis, lithium−liquid ammonia reduction, and two-step oxidation to give acid **11a** purified by flash chromatography and recrystallization if needed. After esterification **11b** was obtained in 60−68% overall yield.

Interestingly, lithium−liquid ammonia reduction of *tert*-butyl ester **6c** (Scheme 4) gave a mixture of alcohols **9** and **12** (ca. 40%) and an unexpectedly large acid

SCHEME 3



SCHEME 4



fraction (60%). The constituents of the acid fraction were identified as **11a** and **13** (ca. 2:3 ^{1}H NMR, Scheme 4). Here fragmentation of the intermediate anion radical *ii* takes place via two routes (1) to generate carboxylate anion *iii* and the stable *tert*-butyl radical[24] or (2) to form secondary radical *i* by carbon−carbon bond fission.

Alkylation of ester **11b** (Scheme 5) using LDA−methyl iodide−HMPA[25] gave an oily diastereomerically pure product **14** almost quantitatively. Structure **14** was assigned from a single-crystal X-ray analysis of its suitable derivative.[18]

Diastereoselective alkylation of pregnanoic acid ester **15**, which is the C-17 epimer of **11b**, has been reported from this laboratory some time ago.[26] Since then, asymmetric induction in ester alkylation has been well documented.[27,28] As illustrated in Scheme 5, alkylation of both esters **11b** and **15** afforded products of *like* configuration

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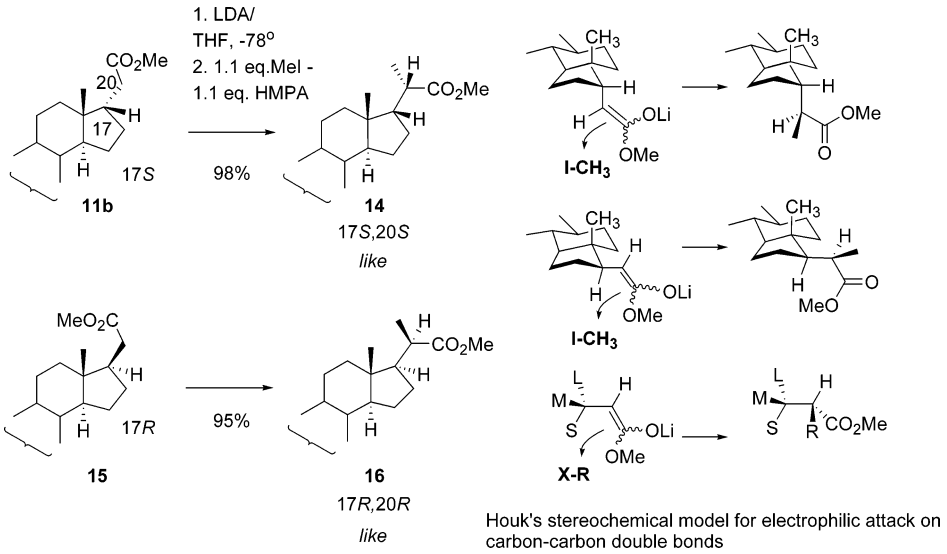
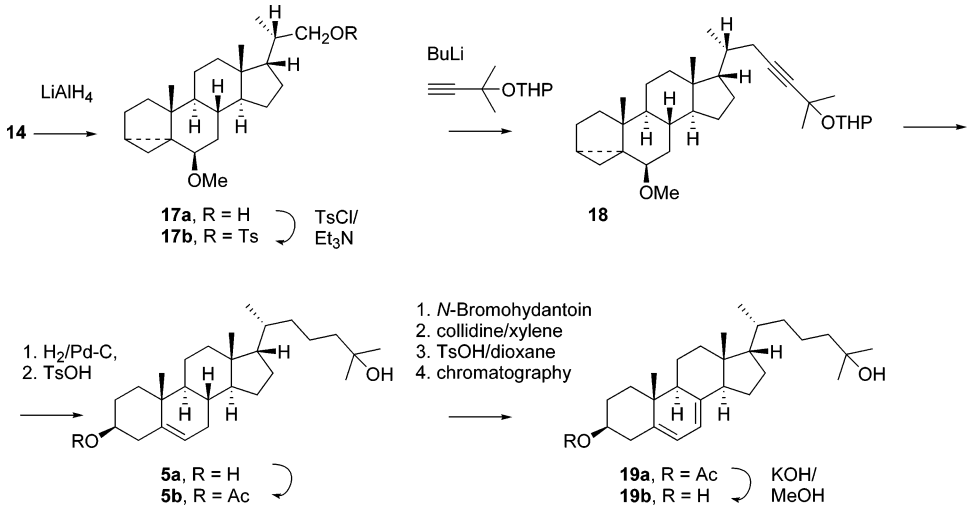
SCHEME 5



SCHEME 6



at C-17 and C-20, accordingly to the Houk stereochemical model for electrophilic addition to carbon−carbon double bonds.[28,29]

The side chain of **14** was extended using the known method.[30] Its ester was reduced to alcohol **17a** (Scheme 6), the respective tosylate **17b** allowed to react with the lithium derivative of 3-methyl-1-butyn-3-yl 2-tetrahydropyranyl ether, and the product **18** was subjected to catalytic hydrogenation followed by removal of the protective groups. 25-Hydroxy-17α-cholesterol[31] **5a** was obtained in over 81% yield from **14**. ^{1}H NMR spectra of **5a** and **5b** differ from those of 25-hydroxycholesterol and its acetate, respectively, in diagnostic signals of C-18 and C-21 protons, whereas signals for C-3, C-6, and C-19 protons practically superimpose (Table 1).

TABLE 1. Selected Physical and Spectroscopic Properties of 25-Hydroxycholesterol[30] and 25-Hydroxy-17α-cholesterol and the Respective Acetates

			^{1}H NMR	
compound	mp, °C	$[\alpha]_D$	C-18H(s)	C-21H(d)
25-hydroxycholesterol	179−181[a]	−38.4	0.67	0.93; J = 5.5 Hz
25-hydroxy-cholesteryl acetate	139−140	−41.4	0.67	0.92; J = 7.0 Hz
5a	181−183	−71.3	0.76	0.81; J = 6.4 Hz
5b	98−100	−72.0	0.77	0.82; J = 6.5 Hz

[a] A hydrate.

3-Monoacetate **5b** was brominated with 1,3-dibromo-5,5-dimethylhydantoin in hexanes at reflux temperature, and the product was refuxed with collidine in xylene.[12] The crude product consisting of the required 5,7-diene and its 4,6-isomer was treated with TsOH in dioxane.[32] After chromatography, 5,7-diene **19a** was isolated in 40%

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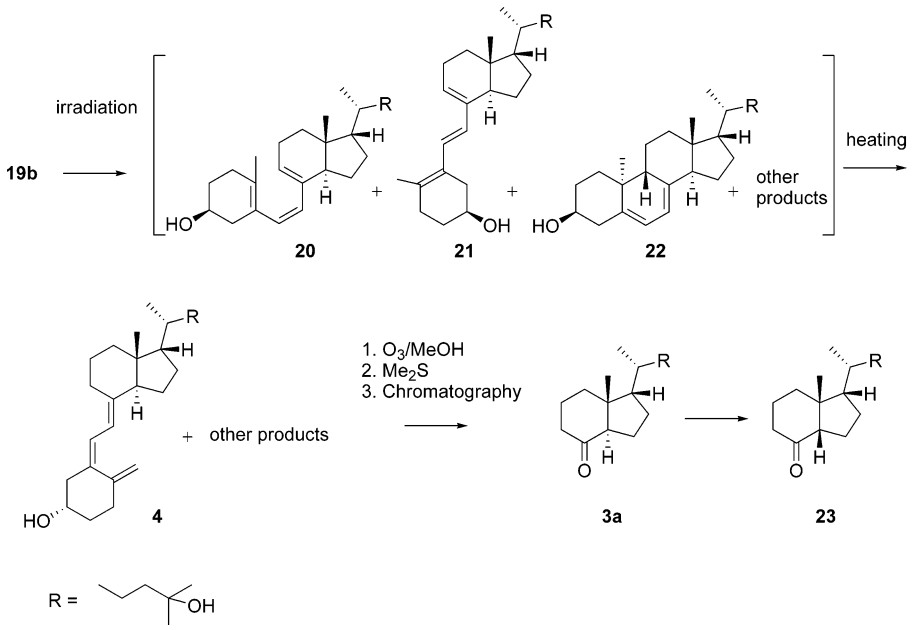
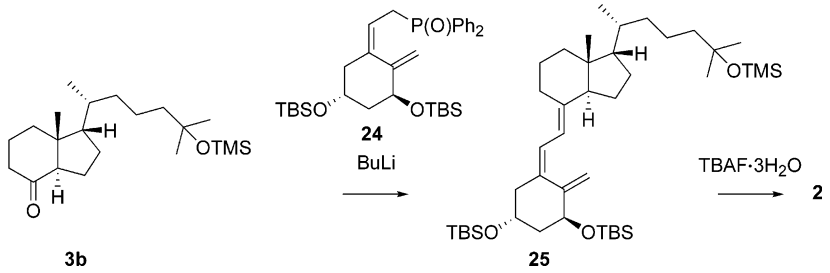
(31) In the present work, the orientation of the side chain is indicated as 17α (3*β*, 25-dihydroxy-17α-cholest-5-ene, 25-hydroxy-17α-cholesterol), in line with the IUPAC Nomenclature of Steroids, recommendations for derivatives with two alkyl substituents at C-17 (3S-2.7 and 3S-2.8). It should be noted that the generic name 5α,17α-cholestane comprises a discrepancy since the first numeral and letter (5α) relates to the hydrogen atom whereas the second (17α) to the carbon substituent.

SCHEME 7



SCHEME 8



yield. This product was hydrolyzed, and the dihydroxy diene **19b** was further used without purification.

Diene **19b** was dissolved in a mixture of methanol and toluene and the solution irradiated with a medium-pressure mercury lamp while monitoring progress by high-performance liquid chromatography (HPLC). After ca. 50% of the starting material was consumed, the mixture consisted of three major and several side products. Structures of the pre-vitamin D derivative **20**, 25-hydroxy-17-*epi*-tachysterol **21**, and 25-hydroxy-17-*epi*-lumicholesterol **22** were tentatively assigned to these major products from the analogous reaction of 7-dehydrocholesterol.[33] The solvent was removed under reduced pressure, and the residue was dissolved in ethanol, then heated under argon at 75 °C for 6 h in order to isomerize **20** into calcidiol **4**. Chromatography on a silica gel column and rechromatography on a preparative HPLC column gave 17-*epi*-calcidiol (17α-calcidiol) **4** in a 18.5% yield (96% pure by HPLC).

In further experiments, the crude product obtained after irradiation of **19b** and thermal isomerization was subjected to ozonolysis following by reductive workup. Hydroxy ketone **3a** was obtained along with more polar products that were easily removed by column chromatography. Under optimal conditions, the irradiation was carried out until 80−90% of the starting diene **19b** was consumed. After thermal isomerization, a mixture containing approximately 60% of 17-*epi*-calcidiol **4** was dissolved in methanol, treated with an excess of ozone at −78 °C and then with dimethyl sulfide.[34] The CD rings building block **3a** was obtained crystalline in 50% yield from **19b**. Since ketone **3a** is prone to epimerization, a reference sample of its *cis*-counterpart **23** was prepared by treating of **3a** with methanolic KOH.

The hydroxy ketone **3a** was silylated using imidazoyl trimethylsilane[35] and the derivative **3b** (Scheme 8) was allowed to react with an anion generated from phosphine oxide[36] **24** and butyllithium. The condensation reaction was slow under the conditions developed for the calcitriol synthesis (THF, −78 °C). The coupling of **3b** and **24** was eventually affected at −50 °C to give **25** as the only product (no products from the parallel reaction with **23** were detected). The crude product was treated with

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tertabutylammonium fluoride trihydrate in THF, and the free triol was purified by flash chromatography. 17-*epi*-Calcitriol (17α-calcitriol) **2** was obtained (98% pure by HPLC) in over 30% yield from 7-dehydro-17α-cholesteryl acetate **19a**.

Spectroscopic properties and high-resolution mass spectrometry (HRMS) of 17α-calcidiol **4** and 17α-calcitriol **2** fully confirmed their structures. When compared to **1** and the natural calcidiol,[14] respectively, the diagnostic signals for C-18 and C-21 protons in the spectra of **2** an **4** were shifted in analogous ways as those for 25-hydroxycholesterol and 25-hydroxy-17α-cholesterol.

In preliminary biological activity tests, 17-*epi*-calcitriol **2** exhibited about the same affinity to the vitamin D receptor as calcitriol **1** but was twice as potent as **1** in inhibiting proliferation of human breast cancer MCF-7 cells.

In conclusion, a facile synthetic approach to a new version of calcitriol and of cholesterol derivatives was developed. A sequence of highly selective transformations, including cyclopropanation of **7**, reductive cleavage of the C-16(17) bond in cyclopropanecarboxylic acid derivatives **6**, and alkylation of ester **11b**, has been accomplished. A method for efficient preparation of the C/D rings building block **3a** from **19b**, involving photochemical and thermal rearrangement, and ozonolysis of thus obtained crude product was also evolved.

Experimental Section

Ethyl 20(*S*)-6*β*-Methoxy-3α,5:16α,20(*S*)-dicyclo-5α,17α-pregnan-21-oate (6a). Ethyl diazoacetate (945 mg, 8.2 mmol) in DCM (10 mL) was added by means of a syringe pump, within 48 h, to a stirred solution of **7** (496 mg, 1.73 mmol) and $Pd(OAc)_2$ (12 mg, 0.05 mmol, 3 mol %) in DCM (20 mL). The mixture was set aside for 16 h, concentrated, diluted with hexanes (until it become cloudy), and filtered through a pad of silica gel. The solvent was evaporated, and the residue was chromatographed on silica gel (40 g, hexanes−EtOAc, 97:3) to give a mixture of **6a** and **8a** (580 mg, 90%, in a ratio of 7:1 by ^{1}H NMR), containing some diethyl fumarate. A mixture of **6a** and **8a** (1.65 g, 4.4 mmol) was dissolved in a solution of sodium ethoxide in ethanol, prepared from sodium (0.9 g) and ethanol (50 mL). The solution was heated at reflux for 5 h and cooled, and the bulk of the solvent was evaporated. The residue was diluted with hexanes (150 mL) and washed with water (3 × 50 mL). The organic extract was dried and evaporated. The residue was chromatographed on silica gel (35 g, hexanes−EtOAc, 97:3) to give **6a** (1.45 g, 87% yield): ^{1}H NMR (200 MHz) 4.05 (q, 2H, J = 7.1 Hz), 3.29 (s, 3H), 2.73 (t, 1H, J = 2.6 Hz), 1.85−0.50 (m, 18H) overlapping 1.22 (t, 3H, J = 7.1 Hz), 1.00 (s, 3H) and 0.90 (s, 3H), 0.7−0.5 (m, 1H) overlapping 0.62 (t, 1H, J = 5.1 Hz), 0.41 (dd, 1H, J = 8.1, 5.1 Hz); ^{13}C NMR (50 MHz) 174.2, 82.1, 60.1, 56.6, 48.7, 47.2, 43.5, 41.1, 38.2, 35.4, 35.2, 35.1, 33.2, 29.0, 27.1, 25.1, 24.9, 22.4, 21.4, 20.2, 19.9, 19.3, 14.3, 13.1. HRMS: calcd for $C_{24}H_{36}O_3$, 372.26645; found, 372.26498. **8a**: ^{1}H NMR (200 MHz) (from a mixture), 4.15 (q).

Methyl 20(*S*)-6*β*-Methoxy-3α,5:16α,20(*S*)-dicyclo-5α,17α-pregnan-21-oate (6b).

a. From **7**. Methyl diazoacetate (4.86 g, 47.6 mmol) in DCM (20 mL) was added by means of a syringe pump, within 48 h, to a stirred solution of **7** (2.595 g, 9.5 mmol) and $Pd(OAc)_2$ (64 mg, 0.29 mmol, 3 mol %) in DCM (50 mL). The mixture was set aside for 16 h, concentrated to ca. 15 mL, diluted with hexanes (until it become cloudy), and filtered through a pad of silica gel (10 g, in hexanes). The silica gel was washed with hexanes−EtOAc (9:1), and the combined filtrates were evaporated. The residue was chromatographed on silica gel (100 g, hexanes−EtOAc, 97:3) to give a mixture of **6b** and **8b** (3.145 g, 92% yield, in a ratio of 7:1 by ^{1}H NMR) contaminated with dimethyl fumarate (singlets at δ = 6.84 and 3.78 ppm, ca. 5 mol %) and a fraction of nonsteroid byproducts (459 mg) containing traces of 7.

b. From **6c**. Ester **6c** (960 mg, 2.4 mmol) was dissolved in a solution of sodium methoxide in methanol, prepared from sodium (660 mg) and methanol (25 mL). The mixture was heated at reflux for 8 h, cooled, and evaporated. The residue was diluted with hexanes (100 mL) and washed with water (3 × 30 mL). The solvent was evaporated, and the residue was chromatographed on silica gel (15 g, hexanes−EtOAc, 9:1) to give **6b** (804 mg, 93% yield): $[\alpha]^{25}_D$ = +40.7 (c = 1.1, $CHCl_3$); ^{1}H NMR (200 MHz) 3.61 (s, 3H), 3.29 (s, 3H), 2.73 (t, 1H, J = 2.6 Hz), 1.9−0.7 (m, 18H) overlapping 1.00 (s, 3H) and 0.90 (s, 3H), 0.7−0.5 (m, 1H) overlapping 0.62 (t, 1H, J = 5.1 Hz), 0.41 (dd, 1H, J = 8.1, 5.1 Hz); ^{13}C NMR (50 MHz) 174.6, 82.1, 56.5, 51.4, 48.6, 47.2, 43.5, 41.1, 38.3, 35.3, 35.2, 35.1, 33.2, 29.0, 27.0, 25.1, 24.8, 22.4, 21.3, 20.1, 19.7, 19.2, 13.0. HRMS: calcd for $C_{23}H_{34}O_3$, 358.25080; found, 358.25175. **8b**: ^{1}H NMR (200 MHz) (from the mixture), 3.67 (s).

***tert*-Butyl 20(*S*)-6*β*-Methoxy-3α,5:16α,20(*S*)-dicyclo-5α,17α-pregnan-21-oate (6c).** The reaction was carried out in an analogous way as described above, using **7** (1.102 g, 3.8) and $Pd(OAc)_2$ (26 mg, 0.12 mmol, 3 mol %) in DCM (40 mL) and di-*tert*-butyl diazoacetate (2.70 g, 19.2 mmol) in DCM (20 mL). The product was chromatographed on silica gel (80 g, hexanes−EtOAc, 97:3) to give **6c** containing some di-*tert*-butyl fumarate (1.35 g, 87%): ^{1}H NMR (200 MHz) 3.30 (s, 3H), 2.72 (t, 1H, J = 2.6 Hz), 1.90−0.70 (m, 18H) overlapping 1.41 (s, 9H), 1.01 (s, 3H) and 0.89 (s, 3H), 0.7−0.5 (m, 1H) overlapping 0.63 (t, 1H, J = 5.1 Hz), 0.41 (dd, 1H, J = 8.1, 5.1 Hz); ^{13}C NMR (50 MHz) 173.5, 82.2, 79.7, 56.6, 48.7, 47.3, 43.5, 41.0, 37.8, 35.34, 35.30, 35.25, 33.20, 29.0, 28.1, 28.0, 24.9, 24.6, 22.5, 21.4, 20.9, 20.2, 19.2, 13.1. HRMS: calcd for $C_{26}H_{40}O_3$, 400.29775; found, 400.29795.

Reduction of 6a with Lithium in Liquid Ammonia. Preparation of 6*β*-Methoxy-3α,5-cyclo-5α,17α-pregnan-21-ol (9) and 6*β*-Methoxy-3α,5:16α,20(*S*)-dicyclo-5α,17α-pregnan-21-ol (12). To a solution of lithium (57 mg, 8 mg-atom) in liquid ammonia (12 mL) was added a mixture THF−*tert*-butyl alcohol (1:1, 4 mL) followed by a solution of **6b** (139 mg, 0.39 mmol) in THF−*tert*-butanol (1:1, 2 mL). After 30 min, solid NH_4Cl was added to destroy the reagent excess. The ammonia was allowed to evaporate. The residue was diluted with ether (20 mL). Aqueous NaOH (3%, 20 mL) and hexanes (20 mL) were added. Organic layer was separated and washed consecutively with 3% aqueous NaOH (20 mL), water, and brine. The solvent was evaporated. The residue (127 mg) was dissolved in ether (3 mL), and $LiAlH_4$ (20 mg) was added. The mixture was stirred at room temperature for 15 min, and then the regent excess was destroyed with saturated aqueous Na_2SO_4. The mixture was diluted with ether (10 mL) and filtered. The solid was washed with a mixture of ether and hexanes. The combined filtrates were evaporated to give **9** (125 mg, 97% yield) contaminated with traces of **12** (less than 5%). Analytical samples of these products were purified by chromatography on a silica gel column.

9. ^{1}H NMR (400 MHz) 3.68 (ddd, 1H, J = 10.4, 8.3, 4.7 Hz), 3.58 (dt, 1H, J = 10.4, 7.4 Hz), 3.33 (s, 3H), 2.78 (t, 1H, J = 2.8 Hz), 2.00−1.89 (m, 2H), 1.81−1.07 (m, 16H), 1.03 (s, 3H), 0.92−0.75 (m, 4H) overlapping 0.82 (s, 3H), 0.65 (dd. J = 4.8, 4.0 Hz), 0.44 (dd, 1H, J = 7.8, 5.0 Hz); ^{13}C NMR (100 MHz) 82.4, 62.1, 56.5, 50.8, 48.0, 44.2, 43.5, 43.3, 35.6, 35.2, 35.1, 34.5, 33.4, 30.8, 28.0, 25.8, 24.9, 22.6, 21.5, 21.1, 19.3, 13.1. HRMS: calcd for $C_{22}H_{36}O_2$, 332.27153; found, 332.27012.

12. ^{1}H NMR (200 MHz) 3.37 and 3.34 (2d, 2H, J = 1.6 Hz), 3.31 (s, 3H), 2.75 (t, 1H, J = 2.9 Hz), 2.32−2.15 (m, 1H), 1.9−0.5 (m, 18H) overlapping 1.02 (s, 3H), 0.87 (s, 3H) and 0.64 (t, J = 4.9 Hz), 0.42 (dd, J = 8.1, 5.1 Hz); ^{13}C NMR (50 MHz) 82.3, 66.1, 56.6, 48.7, 47.9, 43.6, 40.5, 35.5, 35.4, 35.3, 33.5, 33.3, 29.2, 27.1, 24.9, 22.6, 21.5, 20.8, 20.5, 19.3, 19.2, 13.1. HRMS: calcd for $C_{22}H_{34}O_2$, 330.25588; found, 332.25429.

Reduction of 6c with Lithium in Liquid Ammonia. Preparation of 9,12,6β-Methoxy-3α,5-cyclo-5α,17α-pregnan-21-oic acid (11a) and 6β-Methoxy-3α,5:16α,20(*S*)-dicyclo-5α,17α-pregnan-21-oic acid (13). To a stirred solution of lithium (82 mg, 12 mg-atom) in liquid ammonia (17 mL) was added a mixture of THF−*tert*-butyl alcohol (1:1, 6 mL) followed by a solution of **6c** (228 mg, 0.57 mmol) in THF−*tert*-butanol (1:1, 3 mL). The mixture was refluxed for 30 min, and then solid NH_4Cl was added to destroy the reagent excess. The ammonia was allowed to evaporate, and the residue was diluted with ether (25 mL). Aqueous NaOH (3%, 30 mL) and hexanes (30 mL) were added. The mixture was vigorously agitated, and the layers were separated. The organic layer washed with 3% aqueous NaOH (2 × 30 mL, shaking for ca. 10 min was found necessary) and then with water and brine. The solvent was evaporated to give neutral products (77 mg). Aqueous layers were combined, acidified with AcOH, and extracted with ether (20 mL). The organic layer was separated, washed with water (4 × 30 mL) and brine, and evaporated to give the acid fraction (106 mg).

The neutral product was dissolved in ether (3 mL), and $LiAlH_4$ (20 mg) was added. The mixture was stirred at room temperature for 15 min, and the reagent excess was destroyed with saturated aqueous Na_2SO_4. The mixture was diluted with ether (10 mL) and hexane (20 mL) and filtered. The filtrate was evaporated to give alcohol **9** (76 mg) contaminated with traces of **12** (less than 5%). The acid fraction consisted of **11a** and **13** (2:3 based integration of C-18 proton signals in the NMR spectrum, s 0.84 and 0.91 ppm). Analytical samples of compounds **11a** and **13** were purified by chromatography on a silica gel column.

11a. mp 165−167 °C (acetone−hexanes); $[\alpha]^{24}_D = +10.5$ ($c = 1.06$, $CHCl_3$); ^{1}H NMR 3.31 (s, 3H), 2.77 (t, 1H, $J = 2.5$ Hz), 2.50−0.70 (m, 21H) overlapping 1.01 (s, 3H), 0.84 (s, 3H), 0.64 (t, 1H, $J = 4.8$ Hz), 0.43 (dd, 1H, $J = 7.9$, 5.1 Hz); ^{13}C NMR 179.6, 82.3, 56.5, 50.6, 47.9, 44.1, 43.4, 43.2, 37.4, 35.5, 35.2, 34.2, 33.4, 30.8, 28.5, 25.6, 24.9, 22.6, 21.5, 20.7, 19.3, 13.2. Anal. Calcd for $C_{22}H_{34}O_3$ (346.51): C, 76.26; H, 9.89. Found: C, 76.05; H, 9.77.

13. ^{1}H NMR (200 MHz) 3.31 (s, 3H), 2.76 (t, 1H, $J = 2.6$ Hz), 1.88−0.72 (m, 18H) overlapping 1.02 (s, 3H), 0.91 (s, 3H), 0.72−0.50 (m, 1H) overlapping 0.64 (t, 1H, $J = 4.9$ Hz), 0.43 (dd, 1H, $J = 7.9$, 5.1 Hz); ^{13}C NMR (50 MHz) 180.4, 82.1, 56.5, 48.6, 47.1, 43.6, 41.2, 39.2, 35.4, 35.2, 35.0, 33.2, 29.0, 27.1, 26.1, 24.9, 22.4, 21.4, 20.2, 19.8, 19.3, 13.2. HRMS: calcd for $C_{22}H_{32}O_3$, 344.23515; found, 344.23496.

6β-Methoxy-3α,5-cyclo-5α,17α-pregnan-21-al (10). a. $LiAlH_4$ (9 mg, 0.23 mmol) was added to a stirred solution of **11b** (32 mg, 0.09 mmol) in THF (2 mL). After 30 min, the reagent excess was destroyed with saturated aqueous Na_2SO_4. The mixture was diluted with hexanes (5 mL) and filtered. The solid was washed with hexanes (10 mL). The combined filtrates were evaporated to give **9** (30 mg). This product was dissolved in DCM (2 mL). The solution was cooled to 0 °C, and Dess−Martin reagent (56 mg, 0.13 mmol) was added. The mixture was stirred at 0 °C for 3.5 h and poured into water (20 mL). The product was extracted with hexanes (20 mL). The organic extract was washed with water (2 × 20 mL), and the solvent was evaporated. The residue was chromatographed on silica gel (2 g, hexanes−ethyl acetate 98:2) to give 10 (27 mg): ^{1}H NMR (200 MHz) 9.71−9.68 (m, 1H), 3.29 (s, 3H), 2.74 (t, 1H, $J = 2.7$ Hz), 2.56−2.38 (m, 1H), 2.3−0.7 (m, 20H) overlapping 1.0 (s, 3H) and 0.85 (s, 3H), 0.62 (t, 1H, $J = 4.9$ Hz), 0.41 (dd, 1H, $J = 8.1$, 5.1 Hz); ^{13}C NMR (50 MHz) 203.3, 82.2, 56.5, 50.8, 48.0, 47.4, 43.4, 43.2, 42.1, 35.5, 35.1, 34.6, 33.3, 30.8, 28.6, 25.6, 24.9, 22.5, 22.4, 20.7, 19.2, 13.0. HRMS: calcd for $C_{22}H_{34}O_2$, 330.25588; found, 330.25511. This product decomposed in storage.

b. To a stirred solution of **9** (81 mg, 0.24 mmol) in DCM (1.5 mL), DMSO (0.275 mL), and Et_3N (0.135 mL, 0.97 mmol) were added. After the solution cooled to 0 °C, Py·SO_3 (121 mg, 0.76 mmol) was added in two portions (with an interval of ca. 30 min). The mixture was left (at 0 °C) for 2 h, and then it was diluted with ether (10 mL) and hexanes (10 mL) and washed with water (2 × 15 mL). The organic extract was evaporated. The residue was chromatographed on silica gel (4 g, hexanes−ethyl acetate 98:2) to give **10** (74 mg) showing some contaminations (thin-layer chromatography (TLC)).

Oxidation of 10 into 11a with $KMnO_4$. To a stirred solution of **10** (74 mg, 0.22 mmol) in *tert*-butanol (2 mL), 5% aqueous NaH_2PO_4 (1.5 mL) was added. To this solution concentrated aqueous $KMnO_4$ was added until violet color persisted (ca. 1 mL). After 30 min, aqueous $Na_2S_2O_5$ (ca. 20 mL) was added and the mixture was extracted with a mixture of ether (15 mL) and hexanes (15 mL). The organic extract was washed with water (2 × 15 mL) and evaporated. The residue was chromatographed on silica gel (2 g, hexanes−EtOAc, 85:15) to give **11a** (69 mg).

A Procedure for the Synthesis of 11a from 7 without Purification of Intermediates. The cyclopropanation reaction was carried out in an analogous way as that described above, using ethyl diazoacetate (3.81 g, 33.4 mmol) in DCM (20 mL) and alkene **7** (1.91 g, 6.67 mmol) and $Pd(OAc)_2$ (45 mg, 0.20 mmol, 3 mol %) in DCM (40 mL). The crude product **6a** was filtered through silica gel (25 g, hexanes−EtOAc, 97:3). The filtrate was evaporated, and the residue was dissolved in methanolic sodium methoxide, prepared from methanol (50 mL) and sodium (1.2 g). The solution was heated under reflux for 5 h and cooled, and the bulk of the solvent was evaporated. The residue was diluted with hexanes (250 mL) and washed with water (2 × 100 mL). The organic extract was evaporated and the residue was chromatographed on silica gel (50 g, hexanes−EtOAc, 97:3) to give **6b** (2.13 g).

To a solution of lithium (0.59 g, 85 mg-atom) in liquid ammonia (125 mL) was added a mixture THF−*tert*-butanol (1:1, 40 mL) followed by a solution of **6b** (1.53 g, 4.3 mmol) in THF−*tert*-butanol (1:1, 20 mL). After 30 min, solid NH_4Cl was added in portions to destroy the reagent excess. The ammonia was allowed to evaporate. The residue was diluted with ether (100 mL). Water (150 mL) and hexanes (100 mL) were added. Organic layer was separated, washed with water and brine, and evaporated. The residue (1.45 g) consisted mainly of **9** and **10**.

This product was dissolved in DCM (25 mL). DMSO (5 mL) and Et_3N (2.45 mL, 17.6 mmol) were added, and the solution was cooled to 0 °C. Py·SO_3 (2.09 g, 13.2 mmol) was added in two portions (with the interval ca. 30 min). The mixture was stirred for 2 h at 0 °C, and then it was diluted with ether (50 mL) and hexanes (100 mL) and washed with water (2 × 100 mL). The organic extract was evaporated. The residue was dissolved in *tert*-butanol (35 mL) and 5% aqueous NaH_2PO_4 (24 mL) was added followed by concentrated aqueous $KMnO_4$ (ca. 15 mL, until the violet color persisted). After 30 min, aqueous $Na_2S_2O_5$ (ca.150 mL) was added, and the mixture was extracted with a mixture of ether (100 mL) and hexanes (100 mL). The organic extract was washed with water (2 × 100 mL) and evaporated. The residue was chromatographed on silica gel (75 g, hexanes−EtOAc, 85:15) to give **11a** (1.11 g, 76% yield from **6b**).

Methyl 6β-Methoxy-3α,5-cyclo-5α,17α-pregnan-21-oate (11b). An excess of diazometane in ether was added to a solution of **11a** (1.459 g) in ether (20 mL). The solvent was evaporated and the residue was chromatographed on silica gel (30 g, hexanes−EtOAc, 95:5) to give **11b** (1.384 g, 89%): $[\alpha]^{25}_D = +10.3$ ($c = 1.17$, $CHCl_3$); ^{1}H NMR (200 MHz) 3.63 (s, 3H), 3.30 (s, 3H), 2.74 (t, 1H, $J = 2.7$ Hz), 2.45−2.31 (m, 1H, $J = 13.2$, 4.8 Hz), 2.20−0.68 (m, 20H) overlapping 1.00 (s, 3H) and 0.83 (s, 3H), 0.62 (t, 1H, $J = 4.7$ Hz), 0.41 (dd, 1H, $J = 8.1$, 5.1 Hz); ^{13}C NMR (50 MHz) 174.2, 82.3, 56.5, 51.3, 50.7, 48.0, 44.4, 43.5, 43.2, 37.4, 35.6, 35.3, 34.1, 33.4, 30.8, 28.4, 25.6, 25.0, 22.6, 21.5, 20.7, 19.3, 13.1. HRMS: calcd for $C_{23}H_{36}O_3$, 360.26645; found, 360.26602.

Methyl 6β-Methoxy-3α,5-cyclo-23,24-bisnor-5α,17α-cholanoate (14). A solution of **11b** (1.059 g, 2.94 mmol) in THF

(20 mL) was added dropwise to a stirred at −78 °C solution of LDA [prepared from *n*-BuLi (2.5 M, 1.4 mL, 3.5 mmol) and (*i*-Pr)$_2$NH (0.485 mL, 3.5 mmol)] in THF (20 mL). After 30 min, MeI (0.22 mL, 3.5 mmol) and HMPA (0.615 mL, 3.5 mmol) were consecutively added. The mixture was stirred at −50 °C for 16 h and then diluted with hexanes (100 mL) and washed with water (2 × 50 mL). The solvent was evaporated, and the residue was chromatographed on silica gel (20 g, hexanes−EtOAc, 95:5) to give **14** (1.078 g, 98%): $[\alpha]^{25}_D$ = +49.7 (*c* = 1.04, $CHCl_3$); ^{1}H NMR (200 MHz) 3.65 (s, 3H), 3.31 (s, 3H), 2.76 (t, 1H, *J* = 2.8 Hz), 2.28 (dq, 1H, *J* = 10.5, 6.8 Hz), 2.10−0.70 (m, 19H) overlapping 1.09 (d, 3H, *J* = 6.8 Hz), 1.00 (s, 3H), 0.84 (s, 3H), 0.63 (t, 1H, *J* = 4.9 Hz), 0.42 (dd, 1H, *J* = 8.1, 5.1 Hz); ^{13}C NMR (50 MHz) 178.6, 82.9, 57.2, 52.6, 52.0, 51.1, 48.4, 44.3, 44.0, 42.1, 36.3, 35.9, 34.8, 34.0, 31.3, 26.5, 26.4, 25.6, 23.5, 22.1, 19.9, 17.9, 13.8. HRMS: calcd for $C_{24}H_{38}O_3$, 374.28210; found, 374.28173.

6*β*-Methoxy-3α,5-cyclo-23,24-bisnor-5α,17α-cholan-22-ol (17a). $LiAlH_4$ (150 mg, 3.59 mmol) was added in four portions to a solution of **14** (888 mg, 2.38 mmol) in THF (30 mL). The mixture was stirred at room temperature for 30 min, and the reagent excess was destroyed with saturated aqueous Na_2SO_4. The mixture was diluted with ether (30 mL) and then with hexanes (100 mL) and filtered. The filtrate was evaporated to give **17a** (821 mg, 100% yield): $[\alpha]^{25}_D$ = +12.8 (*c* = 1.19, $CHCl_3$); ^{1}H NMR (200 MHz) 3.46−3.18 (m, 2H) overlapping 3.30 (s, 3H), 2.74 (t, 1H, *J* = 2.7 Hz), 1.98−0.67 (m, 20H) overlapping 1.00 (s, 3H) and 0.86 (d, 3H, *J* = 6.6 Hz), 0.81 (s, 3H), 0.62 (t, 1H, *J* = 4.8 Hz), 0.41 (dd, *J* = 8.1, 5.1 Hz); ^{13}C NMR (50 MHz) 82.4, 68.3, 56.5, 52.5, 48.3, 48.1, 44.0, 43.4, 35.9, 35.6, 35.2, 34.1, 33.3, 30.9, 26.1, 24.9, 22.7, 22.3, 22.1, 21.4, 19.3, 14.0, 13.1. HRMS: calcd for $C_{23}H_{38}O_2$, 346.28718; found, 346.28651.

***O*-(Tetrahydropyran-2*ξ*-yl)-25-hydroxy-6*β*-methoxy-3α,5-cyclo-5α,17α-cho lest-23-yn (18).** To a stirred solution of **17a** (815 mg, 2.36 mmol) in DCM (20 mL) were added consecutively Et_3N (2.0 mL, 14.5 mmol), TsCl (1320 mg, 6.95 mmol), and DMAP (5 mg). The mixture was stirred for 16 h, and then saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was stirred for 1 h and poured into water. The product was extracted with hexanes (100 mL). The organic extract was washed with water and evaporated. The residue was chromatographed on silica gel (30 g, hexanes−EtOAc, 95:5 containing a few drops of Et_3N). Tosylate **17b** was obtained (1.257 g): ^{1}H NMR (200 MHz) 7.77 (d, 2H, *J* = 8.2 Hz), 7.33 (d, 2H, *J* = 8.2 Hz), 3.82 (dd, 1H, *J* = 9.3, 6.1 Hz), 3.66 (dd, 1H, *J* = 9.3, 7.3 Hz), 3.30 (s, 3H), 2.74 (t, 1H, *J* = 2.6 Hz), 2.45 (s, 3H), 2.10−0.63 (m, 20H) overlapping 1.00 (s, 3H), 0.84 (d, 3H, *J* = 6.7 Hz), 0.75 (s, 3H) and 0.63 (t, 1H, *J* = 4.9 Hz), 0.42 (dd, *J* = 8.1, 5.1 Hz); ^{13}C NMR (50 MHz) 144.5, 133.2, 129.7, 127.8, 82.2, 75.4, 56.5, 52.4, 47.9, 44.0, 43.4, 35.6, 35.2, 34.0, 33.3, 32.9, 30.9, 25.9, 24.9, 22.6, 22.3, 22.1, 21.6, 21.4, 19.2, 14.1, 14.0, 13.1.

n-BuLi (2.5 M in hexanes, 5.7 mL, 14.2 mmol) was added dropwise to a stirred at 5 °C solution of 3-methyl-3-(terahydropyran-2-yl)oxy-but-1-yne (2.40 g, 14.2 mmol) in dioxane (30 mL). After 30 min, the solution was added to a solution of **17b** (1.246 g) in dioxane (10 mL). The mixture was heated at the reflux temperature for 72 h, cooled, and partitioned between hexanes (100 mL) and water (100 mL). The organic layer was washed with water and evaporated. The residue was chromatographed on silica gel (100 g, hexanes−EtOAc, 98:2 and 95:5) to give **18** (1.025 g, 88% yield from **17a**) and unchanged **17b** (61 mg, 5%). **18**: ^{1}H NMR (200 MHz) 5.04 (dd, 1H, *J* = 6.0, 3.3 Hz), 3.99−3.88 (m, 1H), 3.54−3.42 (m, 1H), 3.31 (s, 3H), 2.75 (t, 1H, *J* = 2.7 Hz), 2.30−0.70 (m, 26H) overlapping 2.05 (t, 2H, *J* = 6.4 Hz), 1.49 (s, 3H), 1.45 (s, 3H), 1.02 (s, 3H), 0.93 (d, 3H, *J* = 6.4 Hz) and 0.82 (s, 3H), 0.64 (t, 1H, *J* = 4.8 Hz), 0.42 (dd, 1H, *J* = 8.1, 5.2 Hz); ^{13}C NMR (50 MHz) 96.2, 84.0, 83.4, 82.4, 71.4, 63.5, 56.5, 52.4, 51.8, 48.1, 44.0, 43.5, 35.7, 35.3, 34.3, 33.4, 32.1, 31.1, 30.9, 30.2, 27.0, 26.1, 25.4, 25.0, 22.8, 22.6, 22.4, 21.5, 20.7, 19.3, 17.0, 13.1. HRMS: calcd for $C_{33}H_{52}O_3$, 496.39165; found, 496.39121.

17α-Cholest-5-en-3*β*,25-diol (5a). Palladium-on-carbon (5%, 30 mg) and $NaHCO_3$ (50 mg) were added to a solution of **18** (1.006 g, 2.03 mmol) in EtOAc (30 mL). The suspension was vigorously stirred under hydrogen for 72 h and then filtered through a pad of Cellite. The Cellite was washed with EtOAc. The combined filtrates were vaporated to give *O*-(tetrahydropyran-2*ξ*-yl)-25-hydroxy-6*β*-methoxy-3α,5-cyclo-5α,17α-cholestane (1.011 g, 100%): ^{1}H NMR (200 MHz), 4.73−4.67 (m, 1H), 4.00−3.87 (m, 1H), 3.48−3.35 (m, 1H), 3.31 (s, 3H), 2.75 (t, 1H, *J* = 2.5 Hz), 1.98−0.68 (m, 32H) overlapping 1.18 (s, 3H), 1.17 (s, 3H), 1.01 (s, 3H), 0.81 (d, 3H, *J* = 6.6 Hz) and 0.79 (s, 3H), 0.62 (t, 1H, *J* = 4.8 Hz), 0.41 (dd, 1H, *J* = 8.1, 5.1 Hz); ^{13}C NMR (50 MHz), 93.9, 82.4, 63.4, 56.5, 52.7, 52.6, 52.4, 48.1, 43.9, 43.5, 42.1, 38.4, 35.7, 35.3, 34.1, 33.4, 32.9, 32.9, 32.6, 30.9, 26.8, 26.2, 26.1, 25.5, 24.9, 22.8, 22.6, 22.4, 21.9, 21.5, 20.9, 19.3, 17.0, 17.0, 13.1. HRMS: calcd for $C_{33}H_{56}O_3$, 500.42295; found, 500.42554.

Water (20 mL) and TsOH (250 mg) were added to a solution of this product (2.46 g, 4.9 mmol) in dioxane (80 mL). The mixture was stirred at 65 °C for 3 h, cooled, and the bulk solvent was evaporated. The residue was diluted with water (ca. 80 mL). The precipitate was collected and washed with water (2 × 25 mL) and then with hexanes (3 × 10 mL). Diol **5a** (1.83 g, 92% yield, 48% yield from **7**) was obtained: mp 181−183 °C (from EtOAc); $[\alpha]_D^{26}$ = −71.3 (*c* = 0.31, $CHCl_3$); ^{1}H NMR (200 MHz) 5.34 (d, 1H, *J* = 5.3 Hz), 3.61−3.43 (m, 1H), 2.28−0.70 (m, 29H) overlapping 1.21 (s, 6H), 1.01 (s, 3H), 0.81 (d, 3H, *J* = 6.4 Hz), 0.76 (s, 3H); ^{13}C NMR (50 MHz) 140.7, 121.7, 71.8, 71.1, 52.9, 52.6, 50.2, 44.2, 43.5, 42.3, 38.3, 37.3, 36.6, 33.6, 33.0, 32.5, 32.4, 31.7, 29.3, 26.3, 22.4, 22.3, 22.1, 21.1, 19.4, 16.9. Anal. Calcd for $C_{27}H_{46}O_2$ (402.65): C, 80.54; H, 11.51. Found: C, 80.33; H, 11.61.

3*β*,25-Dihydroxy-17α-cholest-5-ene 3-acetate (5b). Alcohol **5a** (0.33 g) was dissolved in a mixture of pyridine (6.4 mL) and acetic anhydride (2.8 mL) with slight warming. The solution was set aside for 20 h at room temperature, and then water (50 mL) was added. After 4 h, the precipitate was collected and air dried. This product (0.34 g) was chromatographed on silica gel (12 g, hexanes−acetone, 97:3) to give **5b** (0.31 g, 86% yield): mp 98−100 °C (from hexanes); $[\alpha]^{25}_D$ = −72.0 (*c* = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 5.39−5.36 (m, 1H), 4.64−4.56 (m, 1H), 2.36−2.27 (m, 2H), 2.03 (s, 3H), 1.90−1.80 (m, 2H), 1.80−1.10 (m, ca. 24H) overlapping 1.21 (s, 6H) and 1.02 (s, 3H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz) 170.5, 139.6, 122.6, 74.0, 71.0, 52.9, 52.7, 50.1, 44.3, 43.5, 38.4, 38.1, 33.0, 32.5, 32.3, 29.27, 29.26, 27.8, 26.3, 22.3, 22.1, 21.4, 21.1, 19.3, 17.0. Anal. Calcd for $C_{29}H_{48}O_3$ (444.67): C, 78.32; H, 10.88, Found: C, 78.37; H, 10.74.

3*β*,25-Dihydroxy-17α-cholesta-5,7-diene-3-acetate (19a). A mixture of **5b** (1.09 g, 2.45 mmol), powdered $NaHCO_3$ (1.05 g, 12.5 mmol), 1,3-dibromo-5,5-dimethylhydantoin (0.51 g, 1.77 mmol), and hexanes (35 mL) was stirred at reflux temperature for 30 min. After cooling, the solid was filtered off under argon and washed with hot hexanes. The combined filtrates were evaporated. To the residue xylene (35 mL) and collidine (3.5 mL) were added, and the mixture was heated under reflux for 1.5 h. After cooling, the mixture was poured into water and the product was extracted with ether (3 × 60 mL). Combined extracts were washed consecutively with cold 5% HCl (2 × 30 mL), water, saturated aqueous $NaHCO_3$, and brine. The solvent was evaporated on a rotary evaporator and then in high vacuum (xylene). The residue was dissolved in dioxane (35 mL), and TsOH (35 mg) was added. The solution was stirred at 55 °C for 4 h, whereupon it was poured into water and the product was extracted with ether. The crude product (1.28 g) was chromatographed on silica gel (45 g, acetone-hexanes, 97:3). Fractions containing 5,7-diene were collected to give **19a** (0.44 g, 40%): UV (EtOH) λ_{max} 271 nm (*ϵ* 8817), 281 nm (*ϵ* 9225), 292 nm (*ϵ* 5452); ^{1}H NMR (200 MHz) 5.61−5.50 (m, 1H), 5.47−5.35 (m, 1H), 4.80−4.60 (m, 1H), 2.04

(s, 3H), 1.21 (s, 6H), 0.95 (s, 3H), 0.83 (d, 3H, J = 6.3 Hz), 0.71 (s, 3H). HR MSIMS: calcd for $C_{29}H_{46}O_3Na$, 465.3339; found, 465.3367.

3*β*,25-Dihydroxy-17α-cholesta-5,7-diene (19b). A solution of **19a** (0.43 g) in EtOH (35 mL) containing 5% aqueous NaOH (2 mL) was stirred for 4 h, and the solvent was evaporated. The residue was taken in AcOEt (400 mL) and washed consecutively with 5% HCl, water, saturated aqueous $NaHCO_3$, and brine. Evaporation of the solvent gave alcohol **19b** (0.38 g, 97% yield, amorphous solid), which was used for the next step without purification.

(5*Z*,7*E*)-3S-9,10-Seco-17α-cholesta-5,7,10(19)-trien-3*β*,25-diol (4). A solution of **19b** (280 mg) in methanol−toluene (1:2, 300 mL), cooled in an ice−water bath, was irradiated with Heraeus TQ 150 medium-pressure mercury vapor lamp. After 20 min (ca. 50% of **19b** remained, by HPLC), the solvent was evaporated. The residue was dissolved in EtOH (40 mL), stirred at 75 °C for 6 h, and then the solvent was evaporated. The residue was chromatographed on silica gel (10 g, 6% hexanes−acetone, 94:6), and a fraction containing **4** (165 mg, ca. 50% by HPLC) was collected. This product was rechromatographed on a silica gel column and then was purified by HPLC (hexanes−2-propanol 88:12) to give **4** (54 mg, 18.5% yield, 96% pure): λ_{max} (EtOH) 264 nm; ^{1}H NMR (500 MHz, $CDCl_3$) 6.23 (d, 1H, J = 11.2 Hz), 6.05 (dt, 1H, J = 11.3, 1.0 Hz,), 5.05 (dt, 1H, J = 2.6, 1.3 Hz), 4.82 (d, 1H, J = 2.6 Hz,), 3.97−3.90 (m, 1H), 2.85−2.81 (m, 1H), 2.59−2.55 (m, 1H), 2.31−2.25 (m, 1H), 2.21−2.11 (m, 2H), 1.96−1.89 (m, 1H), 1.75−1.05 (m, ca. 24H) overlapping 1.54 (s, H_2O) and 1.21 (s, 6H), 0.86 (d, 3H, J = 6.6 Hz), 0.63 (s, 3H); EI MS 400 (26), 382 (19), 367 (20), 349 (17), 271 (18), 253 (18), 211 (15), 176 (22), 161 (18), 158 (60), 136 (100), 118 (98). HRMS: calcd for $C_{27}H_{44}O_2$, 400.3341; found, 400.3338.

(1*S*,3a*S*,7a*R*)-1-[(1*R*)-5-Hydroxy-1,5-dimethylhexyl]-7a-methyloctahydro-4*H*-i nden-4-one (3a). A stream of ozonized oxygen was passed through a cooled to −78 °C solution of **4** (obtained as described above, 17 mg, 86% pure by HPLC) in MeOH (2 mL). After ca. 5 min, gray-blue color appeared. Passing of ozone was continued for 10 min, and the solution was left at −78 °C for additional 10 min. Dimethyl sulfide (0.1 mL) was added, and the mixture was allowed to warm to room temperature. After 2 h, the mixture was diluted with ether (5 mL) and poured into water. The product was extracted with hexanes (20 mL). The organic extract was washed with water and dried, and the solvent was evaporated. The residue was chromatographed on silica gel (1 g, hexanes−ethyl acetate, 80:20) to give **3a** (8 mg) as colorless crystals: mp 38−40 °C (TLC, R_f = 0.6, hexanes−EtOAc, 50:50); ^{1}H NMR (400 MHz) 2.60 (dd, 1H, J = 10.7, 7.3 Hz), 2.16−2.32 (m, 2H), 2.09−1.09 (m, 16H) overlapping 1.22 (s, 6H), 0.88 (d, 3H, J = 6.8 Hz), 0.72 (s, 3H); ^{13}C NMR (100 MHz) 212.5, 71.0, 58.8, 52.6, 50.2, 44.1, 41.0, 37.9, 33.1, 32.9, 29.31, 29.29, 23.6, 22.8, 22.2, 21.5, 21.3, 16.2. HRMS: calcd for $C_{18}H_{30}O$, 262.22967; found, 262.22977.

(1*S*,3a*R*,7a*R*)-1-[(1*R*)-5-Hydroxy-1,5-dimethylhexyl]-7a-methyloctahydro-4*H*-i nden-4-one (23). Potassium hydroxide (24 mg) was added to a solution of **3a** (3.9 mg) in MeOH (2 mL), stirred under argon at room temperature. After 30 min, the mixture was poured into water and the product was extracted with CH_2Cl_2 (2 × 10 mL). The combined extract was dried and evaporated. The residue was chromatographed on silica gel (1 g, hexanes − EtOAc, 80:20 to give **23** (3.5 mg) (TLC, R_f = 0.65, hexanes−EtOAc, 1:1): ^{1}H NMR (400 MHz) 2.48 (ddd, 1H, J = 14.6, 13.9, 6.6 Hz), 2.29 (br. t, 1H, J = 9.8 Hz), 2.22−2.15 (m, 1H), 2.00−1.14 (m, 16H) overlapping 1.21 (s, 6H), 1.07 (s, 3H), 0.88 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz) 215.5, 71.0, 62.7, 56.2, 49.5, 44.1, 37.1, 32.9, 29.7, 29.3, 27.1, 26.9, 26.1, 25.1, 22.7, 21.4, 18.4. HRMS: calcd for $C_{18}H_{30}O$, 262.22967; found, 262.23009.

(5*Z*,7*E*)-9,10-*seco*-17α-Cholesta-5,7,10(19)-trien-1α,3*β*,25-triol (17-epi-calcitriol) (2). A solution of **19b** (160 mg) in toluene−methanol (2:1, 400 mL), cooled in a ice−water bath was irradiated with Heraeus TQ 150 medium-pressure mercury vapor lamp for 26 min (ca. 10% of the starting material remained, by HPLC). The solvent was evaporated, and the residue was dissolved in EtOH (40 mL). The solution was stirred at 75 °C for 6 h and cooled, and the solvent was evaporated to a residue (240 mg). A part of this product (121 mg) was dissolved in MeOH (5 mL). A stream of ozonized oxygen was passed through a solution at −78 °C for 20 min. The gray-blue solution was left at −78 °C for an additional 10 min, and then dimethyl sulfide (0.20 mL) was added. The mixture was set aside at room temperature for 2 h, diluted with ether (5 mL), and poured into water. The product was extracted with hexanes (25 mL). The organic extract was washed with water and dried, and the solvent was evaporated. The residue was chromatographed on silica gel (1 g, hexanes−EtOAc, 4:1) to give **3a** (26 mg).

This product was dissolved in THF (1.5 mL) and trimethylsilylimidazol (0.15 mL, 1 mmol) was added. The mixture was stirred for 16 h and then was partitioned between hexanes (20 mL) and water (10 mL). Organic layer was washed with water (2 × 10 mL), and the solvent was evaporated. The residue was dissolved in a mixture of hexanes and EtOAc (9:1) and filtered through silica gel deactivated with Et_3N. The filtrate was evaporated to give the trimethylsilyl derivative **3b** (31 mg, R_f = 0.35, hexanes−EtOAc, 9:1). This product was dissolved in THF (2 mL) and added to a solution of the salt prepared from phosphine oxide **24** (108 mg, 0.18 mmol) and BuLi (2.01 M in hexanes, 0.085 mL, 0.17 mmol) in THF (4 mL), at −50 °C. The mixture was stirred at −50 °C for 2.5 h, and then it was partitioned between hexanes (20 mL) and water (20 mL). The organic extract was washed with water and the solvent was evaporated. The residue was dissolved with THF (2 mL), and $Bu_4NF{\cdot}3H_2O$ (304 mg, 0.96 mmol) was added. The mixture was stirred at room temperature for 16 h, and then it was partitioned between EtOAc (35 mL) and water (15 mL). The organic extract was washed with water and the solvent was evaporated. The residue was chromatographed on silica gel (7 g, hexanes−EtOAc, 80:20 and 60:40) to give **2** (25 mg, 32% yield from **19b**, R_f = 0.5, EtOAc, λ_{max} (EtOH) 264 nm; ^{1}H NMR (500 MHz, $CDCl_3$) 6.37 (d, 1H, J = 11.2 Hz), 6.03 (d, 1H, J = 11.3 Hz), 5.32 (t, 1H, J = 1.6 Hz), 5.00 (t, 1H, J = 1.3 Hz), 4.46−4.41 (m, 1H), 4.25−4.20 (m, 1H), 2.87−2.81 (m, 1H), 2.63−2.57 (m, 1H), 2.34−2.28 (m, 1H), 2.18−2.12 (m, 1H), 2.05−1.98 (m, 1H), 1.96−1.89 (m, 1H), 1.75−1.05 (m, ca. 26H) overlapping 1.55 (s, H_2O) and 1.22 (s, 6H), 0.86 (d, J = 6.5 Hz, 3H), 1.15−1.05 (m, 1H), 0.63 (s, 3H); EI MS 398 (100), 380 (40), 365 (12), 362(7), 347(7), 269 (14), 251 (14), 223 (10), 209 (22), 195 (12), 181 (15), 176 (22), 159 (29), 145 (37), 131 (46), 119 (28), 105 (41), 91 (32), 81 (29). HR LSIMS: calcd for $C_{27}H_{44}O_3Na$ $(M + Na)^+$, 439.3183; found, 439.3207.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **6a**, **6b**, **6c**, **9**, **10**, **11b**, **12**, **13**, **14**, **17a**, **17b**, **18**, **3a**, and **23** and ^{1}H spectra of compounds **19a**, **4**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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