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Synthesis of Novel Analogues of 1α,25-Dihydroxyvitamin D_3 with Side Chains at C-18

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Novel analogues of the hormone 1α,25-$(OH)_2$-D_3 with side chains attached to C-18 were synthesized by a versatile route in which key steps were the remote radical-induced functionalization of the 18-methyl by the C-8*β*-hydroxyl group and the introduction of the side chains by Wittig reactions on a C-18-aldehyde. The triene system of the novel analogues was constructed by the convergent Lythgoe−Hoffmann la Roche approach, which involves reaction of a phosphine oxide (the ring A fragment) with a ketone (the upper fragment).

Introduction

1α,25-Dihydroxyvitamin D_3 [1α,25-$(OH)_2$-D_3, calcitriol, **1a**, Figure 1], which is the hormonally active form of vitamin D_3 (cholecalciferol, **1b**), not only plays an important role in calcium homeostasis but also promotes cell differentiation and inhibits the proliferation of various tumor cells. Unfortunately, the therapeutic value of 1α,-25-$(OH)_2$-D_3 as an antitumor agent is severely limited by its potent calcemic effects.[1,2] Attempts are therefore being made to develop an analogue of 1α,25-$(OH)_2$-D_3 that acts against cancer and related skin diseases without causing calcium unbalance. To date, more than 3000 analogues have been synthesized, although only a few have reached the pharmaceutical market or advanced clinical trials.[3,4]

Until recently, the available information on the structure−activity relationships of 1α,25-$(OH)_2$-D_3 analogues was rather limited and the design of new compounds was essentially intuitive. However, it is now known that calcitriol acts in the cell nucleus through a multistep mechanism that includes its binding to the nuclear vitamin D receptor (VDR),[5] heterodimerization of the VDR with retinoid X receptor (RXR), and binding of the resulting complex to specific DNA sequences named vitamin D-responsive elements (VDRE).[1,6] The recent elucidation of the crystalline structure of a complex formed by 1α,25-$(OH)_2$-D_3 and a mutant VDR opens new possibilities for rational design of new vitamin D analogues with therapeutic potential.[7]

During the past decade, we have systematically synthesized a number of 1α,25-$(OH)_2$-D_3 analogues to study their structure−activity relationships.[8] One of our re-

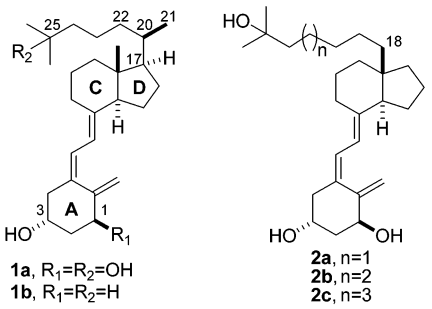

FIGURE 1. 1α,25-$(OH)_2$-D_3 and 20(17→18)-*abeo*-analogues.

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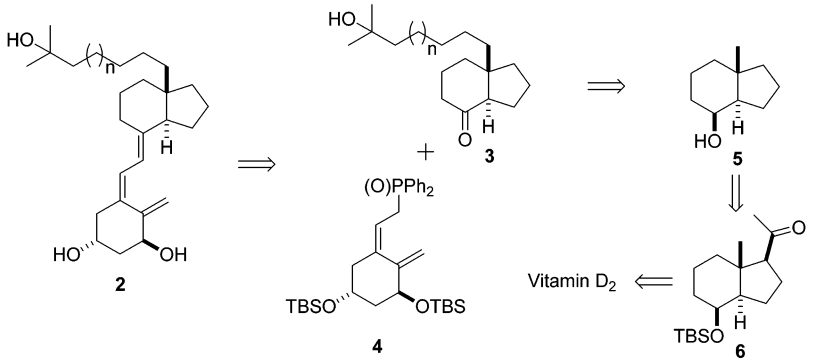
SCHEME 1. Retrosynthetic Analysis

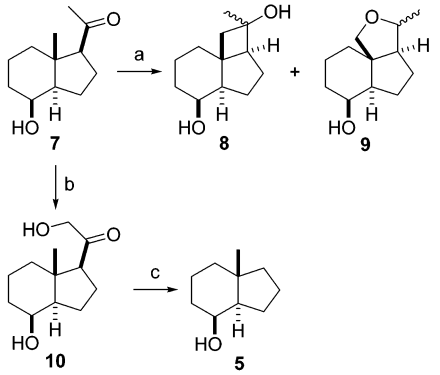


search programs was directed to the synthesis of 1α,25-$(OH)_2$-D_3 analogues with side chains attached to selected positions of the molecule, such as the angular C18 methyl group. A number of analogues modified at C-18 have already been reported by us[9] and others[10] including a series of analogues with side chains linked to C-18 through an oxygen atom.[11] Despite the fact that some of these compounds have promising therapeutic profiles,[11,12] only one analogue with a side chain linked to C-18 through a carbon−carbon bond has been reported to date.[13]

We describe here new synthetic approaches to 1α,25-$(OH)_2$-D_3 analogues with side chains at C-18 and the use of one of these strategies for the preparation of three novel 1α,25-$(OH)_2$-D_3 analogues in which side chains homologous to that of the natural hormone are linked to C-18 through a C−C bond (**2a**−**c**, Figure 1). The new analogues, unlike previously reported analogues with C-18 modifications, have no substituents on C-17.

Retrosynthesis. The mild, convergent Lythgoe−Hoffmann la Roche approach[1f,3c] was chosen for the introduction of the triene system of the target 1α,25-$(OH)_2$-D_3 analogues **2** (Scheme 1). Key elements of the synthetic plan involve the construction of the upper ketones **3** from alcohol **5**, which in turn might be prepared from ketone **6** using as key reaction the C-8-OH-induced[14] radical functionalization[15] of the C-18-methyl group. We considered that degradation of commercially available vitamin D_2 might provide convenient entry to alcohol **5**.

SCHEME 2. Irradiation of Ketones 7 and 10[a]



[a] Key: (a) *hν*, EtOH (**8**/**9** = 2:1), 73%; (b) (i) LDA, THF, −78 °C, then TMSCl, (ii) *m*-CPBA, hexanes, −20 °C, (iii) TBAF, THF, (iv) HF, H_2O, CH_3CN; (c) *hν*, EtOH, 28% (from **7**).

Synthesis of Alcohol 5. We envisaged the preparation of alcohol **5** by type I Norrish fragmentation of ketone **7** (Scheme 2). This compound was prepared by degradation of commercially available vitamin D_2 according to procedures optimized in these laboratories.[16] Unfortunately, irradiation of **7** in ethanol provided a 2:1 mixture of cyclic compounds **8** and **9** accordingly with previous results reported by Corey et al. on Quabain derivatives.[17] It was possible to induce the Norrish fragmentation of the hydroxy ketone **10**, but this alternative pathway furnished the desired alcohol **5** only in poor yield. We therefore decided to explore the preparation of alcohol **5** from protected methyl ketone **6** (Scheme 3).

Ketone **6** was converted to ketone **13** by Baeyer−Villiger oxidation using *m*-CPBA in phosphate buffer and CH_2Cl_2 followed by hydrolysis of the resulting acetate **11** and oxidation of the resulting alcohol **12**, as previously described.[16] Use of freshly purified *m*-CPBA in cyclohexane or CH_2Cl_2 instead of the biphasic mixture led to a significant improvement of the Baeyer−Villiger step. Attempts to deoxygenate C-17 by reduction of the tosylate of alcohol **12** gave only starting alcohol **12**, even though a wide variety of hydride reagents were tried. Treatment of the methylxanthate derivative of **12** with $HSnBu_3$−AIBN under conventional thermal or photochemical reaction conditions gave an intractable mixture of prod-

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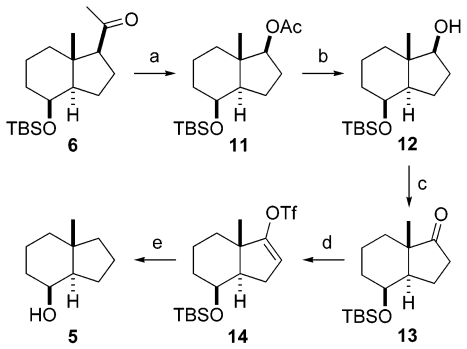
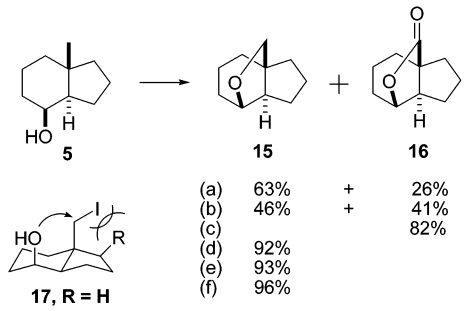
SCHEME 3. Synthesis of Alcohol 5[a]



[a] Key: (a) *m*-CPBA, cyclohexane, 95%; (b) K_2CO_3, MeOH, 99%; (c) PDC, CH_2Cl_2, 96%; (d) LDA, THF, −78 °C, then *N*,*N*-bis(trifluoromethanesulfonyl)-2-amino-5-chloropyridine, 93%; (e) (i) H_2, PtO_2, EtOH, (ii) HF, CH_3CN, 99%.

SCHEME 4. Irradiation of 5[a]



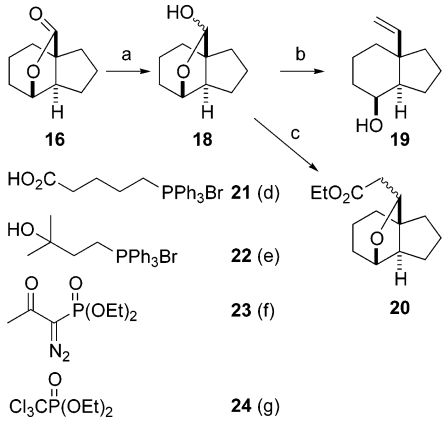
[a] Key: (a) (i) $Pb(OAc)_4$, I_2, $CaCO_3$, cyclohexane, *hν*, (ii) CrO_3, H_2SO_4, pyridine, acetone; (b) (i) $Pb(OAc)_4$, I_2, $CaCO_3$, cyclohexane, sonication, (ii) CrO_3, H_2SO_4, pyridine, acetone; (c) (i) $Pb(OAc)_4$, I_2, $CaCO_3$, cyclohexane, sonication, (ii) CrO_3, H_2SO_4, silica gel, THF, −10 °C; (iii) $RuO_2 \cdot H_2O$, $NaIO_4$, CCl_4, CH_3CN, buffer; (d) $Pb(OAc)_4$, benzene, *hν*; (e) DIB, I_2, cyclohexane, *hν*; (f) DIB, I_2, cyclohexane, sonication.

ucts. Wolff−Kishner reduction of ketone **13** also failed, as did related procedures. Eventually, we found that formation of enol triflate **14** from **13**, treatment of **14** with hydrogen in the presence of catalytic PtO_2, and final desilylation provided the desired alcohol **5** in 92% from **13**.

Functionalization of C-18. Our experiments on the functionalization of C18 started with irradiation of alcohol **5** in the presence of $Pb(OAc)_4$ and I_2 and oxidation of the resulting mixture with Jones' reagent, which furnished a mixture of the desired lactone **16** and, as the major product, cyclic ether **15** (Scheme 4, a). This trend is in contrast with previous observations where the irradiation of similar substrates with bulky substituents at C-17 afford the lactone as the major product.[9b] These results can be rationalized on a mechanistic basis. The presence of bulky substituents at C-17 prevents the C18−I bond orientation required for S_Ni cyclization with C-8-OH (Scheme 4).[18] The reaction pursues an alternative radical chain pathway that ends up with the formation of an α-iodoether and its oxidation to the lactone by Jone's reagent. Irradiation with light was advantageously replaced by sonication. Under these conditions, traces of

(18) Heusler, K.: Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525−538. (b) Kalvoda, J,; Heusler, K. *Synthesis* **1971**, 501−526.

SCHEME 5. Reactivity of Lactol 18[a]



[a] Key: (a) DIBAL-H, toluene, −80 °C, 88%; (b) CH_3PPh_3Br, KO-*t*-Bu, THF, Δ, 86%; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaOEt, EtOH, Δ, 30%; (d) **21**, KO-*t*-Bu, benzene, Δ, no reaction; (e) **22**, *n*-BuLi, Et_2O, Δ, no reaction; (f) **23**, K_2CO_3, MeOH, no reaction; (g) **24**, *n*-BuLi, THF, Et_2O, no reaction.

iodine **17** were also isolated (Scheme 4, b). Ether **15** can be converted to lactone **16** using catalytic RuO_2 and $NaIO_4$ (Scheme 4, c).

We next turned our attention to reactions known to provide cyclic ethers as the major products. Irradiation of alcohol **5** in benzene in the presence of $Pb(OAc)_4$ proceeded efficiently to deliver the cyclic ether **15** in excellent yield. To circumvent the toxicity of lead reagents and high dilution in benzene we explored the variant of the hypoiodite reaction developed by Suárez et al.[19] Thus, reaction of **5** with diacetoxyiodobenzene (DIB) and iodine under photochemical or sonochemical conditions in cyclohexane gave the desired ether **15** in excellent yield (Scheme 4, e,f). Ultrasounds allowed higher concentrations to be used.

Installation of the Side Chain. We initially attempted to introduce side chains at C18 by reaction of ylides with lactol **18**, which was prepared in 88% yield by reduction of **16** with DIBAL-H (Scheme 5). Unfortunately, most of these attempts failed, probably as the result of steric congestion at C-18. Only the simplest ylide ($Ph_3P{=}CH_2$) reacted efficiently with lactol **18**, providing olefin **19** in 86% yield. The simple phosphonate carbanion $(EtO)_2P(O)CHNaCO_2Et$ formed ester **20** by Horner−Wadsworth−Emmons reaction followed by hetero-Michael cyclization, but only in low yield (30%), while no reaction took place with the anions derived from **21**−**24** (Scheme 5).

In view of the above results, we investigated a different approach to the introduction of the side chain. Logan et al.[21] have reported that reaction of alkyl Grignard reagents with certain ester moieties adjacent to quaternary carbons can give rise to alkynes in moderate-to-good yields. Reaction of lactone **16** under Logan's conditions (MeMgCl, anisole, reflux) provided alkyne **25** (73%), tertiary alcohol **26** (15%), and lactol **27** (3%) (Scheme 6).

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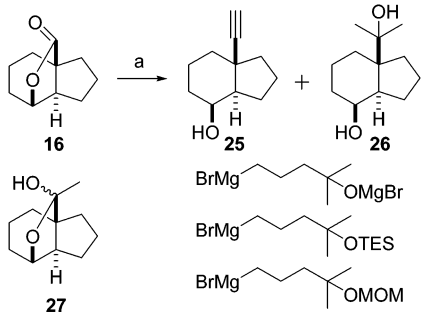
SCHEME 6. Synthesis of Alkyne 25[a]



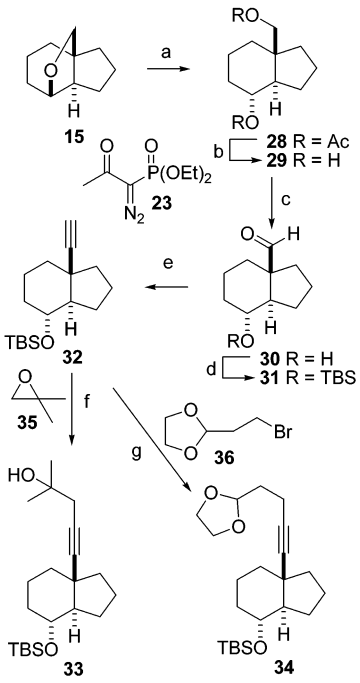
[a] Key: (a) MeMgCl, anisole, Δ, **25** (73%), **26** (25%), **27** (3%).

However, attempts to introduce alkynes with longer chains using Grignard reagents were unsuccessful. Unexpectedly, attempts of alkylation of **25** or its C-8-OTBS-protected derivative also failed.

The above failures to install the desired side chains led us to eliminate the steric hindrance at C-18 by inverting the configuration of the C-8-OH group. Cleavage of ether **15** in the presence of $BF_3{\cdot}OEt_2$ and Ac_2O using conditions reported by Okamura,[10] hydrolysis of the resulting diacetate **28** to diol **29**,[22] and selective oxidation of the latter with catalytic TEMPO and DIB as co-oxidant[23] afforded the key aldehyde **30** in 60% yield from **15** (Scheme 7). Disappointingly, it was not possible to convert the protected aldehyde **31** to the corresponding vinylic dibromide using Corey−Fuchs reaction conditions. Even more surprising was our inability to convert the tosylate or mesylate of the corresponding protected alcohol to its iodide by S_N2 displacement with NaI. To our delight, however, treatment of aldehyde **31** with diazophosphonate **23**[24] in the presence of K_2CO_3 afforded the desired alkyne **32** in 94% yield. The reaction of the organolithium reagent derived from alkyne **32** (*n*-BuLi) with 1,1-dimethyldioxirane (**35**) in the presence of $BF_3{\cdot}OEt_2$ provided the tertiary alcohol **33** in 87% yield. The lithium species derived from **32** also reacted with **36** to give alkyne **34** in 63% yield. Unfortunately, efforts to hydrogenate the triple bonds of **33** or **34** to the corresponding saturated derivatives were unsuccessful. Catalytic hydrogenation using PtO_2 (**33**) or Ni−Raney (**34**) furnished almost exclusively the corresponding alkenes, with only traces of the desired saturated compounds. These results further illustrate the low C-18 reactivity of *trans*-hydrindan systems due to the the severe steric congestion at this position.

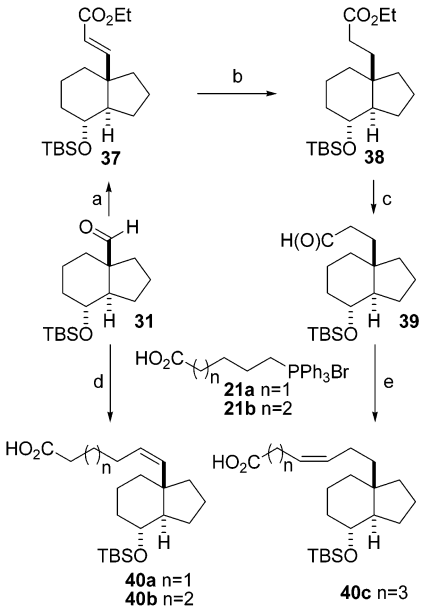
At this point, we back-tracked in our efforts to introduce side chains and took as the starting point aldehyde **31**, which upon Horner−Wadsworth−Emmons reaction with $(EtO)_2P(O)CH{=}CHCO_2Et$ provides the α,β-unsaturated ester **37** (Scheme 8). After catalytic hydrogenation of **37** to **38**, the latter was reduced with DIBAL-H, giving aldehyde **39** in 73% yield from **31**. Aldehydes **31** and **39** were then successfully coupled with the anions derived

SCHEME 7. Synthesis and Alkylation of Alkyne 32[a]



[a] Key: (a) $BF_3{\cdot}OEt_2$, Ac_2O, −20 °C, 62%; (b) K_2CO_3, MeOH, 99%; (c) TEMPO, DIB, CH_2Cl_2, CH_3CN, 97%; (d) TBSCl, imidazole, DMF, 98%; (e) **23**, K_2CO_3, MeOH, 94%; (f) *n*-BuLi, THF, then **35**, $BF_3{\cdot}OEt_2$, −50 °C, 87%; (g) *n*-BuLi, HMPA, THF, −30 °C, then **36**, 63%.

SCHEME 8. Coupling of Side Chains on Aldehydes 31 and 39[a]



[a] Key: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 93%; (b) H_2, Pd/C, EtOAc, 98%; (c) DIBAL-H, toluene, −80 °C, 81%; (d) **21a** or **21b**, KO-*t*-Bu, benzene, **40a** (79%) or **40b** (76%); (e) **21a**, KO-*t*-Bu, benzene, **40c** (71%).

from phosphonium salts **21a** and/or **21b**, affording the olefinic upper fragments **40a** (79%), **40b** (76%), and **40c** (71%).

(22) Attempts of selective deprotection of **28** or protection of **29** did not provide the selectivity reported for similar substrates.[10,11]

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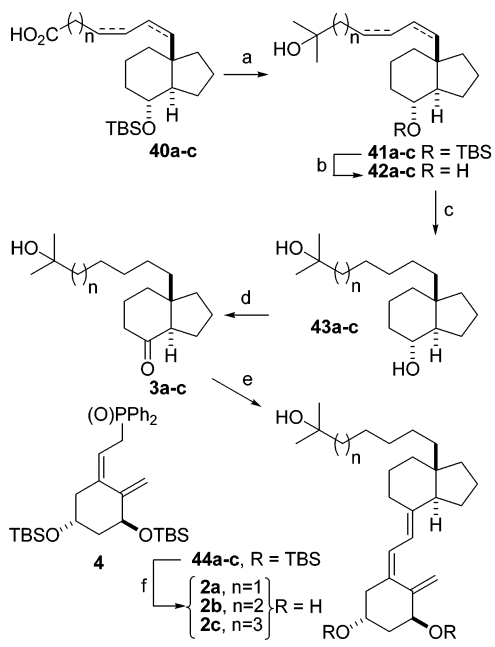
SCHEME 9. Synthesis of Calcitriol Analogues 2a−c[a]



[a] Key: (a) (i) MeLi, THF, −30 °C, (ii) MeLi, THF, −30 °C, **41a** (82%) or **41b** (80%) or **41c** (79%); (b) HF, H_2O, CH_3CN, **42a** (69%) or **42b** (63%) or **42c (**60%); (c) H_2, Pd/C, EtOAc, **43a** (98%) or **43b** (96%) or **43c** (98%); (d) PDC, CH_2Cl_2, **3a** (92%) or **3b (**90%) or **3c (**90%); (e) **4**, *n*-HexLi, THF, −30 °C, **44a** (87%) or **44b** (93%) or **44c** (96%); (f) TBAF, THF, **2a** (88%)or **2b** (81%) or **2c** (80%).

Synthesis of 1α,25-$(OH)_2$-D_3 Analogues. The upper ketones **3a−c** (Scheme 9) required for the preparation of the desired vitamin D analogues **2a−c** by the convergent Lythgoe−Hoffmann la Roche approach were synthesized in a straightforward manner from carboxylic acids **40a−c**. After reaction with MeLi, alcohols **41a−c** were desilylated (HF) and hydrogenated to provide diols **43a−c**, which upon oxidation (PDC) furnished the key ketones **3a−c** in 50% average yield from **40a−c**. Coupling **3a−c** with the anion of phosphine oxide **4**[25] provided, after desilylation (*n*-Bu_4NF, THF), the desired 1α,25-$(OH)_2$-D_3 analogues **2a** (76%), **2b** (75%), and **2c** (77%) (Scheme 9).

In summary, we have developed a versatile synthetic route to novel analogues of the hormone 1α,25-$(OH)_2$-D_3 in which side chains are attached to C-18 rather than C-17. The results of biological assays currently in progress will be published elsewhere.

Experimental Section

8*β*-[(*tert*-Butyldimethylsilyl)oxy]de-A,B-androstan-17*β*-yl Acetate (11).[16] *m*-CPBA (16 g, 92.7 mmol) was added to a solution of **6** (13 g, 41.9 mmol) in cyclohexane (260 mL). The reaction mixture, protected from direct light, was stirred for 168 h, supplementing 3 g per day of *m*-CPBA. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (200 mL). The aqueous layer was extracted with hexanes (3 × 150 mL). The combined organic fractions were dried, filtered, and concentrated. The residue was purified by flash chromatography (18 × 5 cm, 1% EtOAc/hexanes) to give **11** [13 g, 95%, R_f = 0.7 (5% EtOAc/hexanes), white solid, mp 47−49 °C]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.54 (1H, dd, *J* = 7.7 Hz, 9.0 Hz, H-17), 4.01 (1H, m, H-8), 2.03 (3H, s, H-21), 1.01 (3H, s, H-18), 0.89 (9H, s, *t*-BuSi), 0.002 (3H, s, Me_2Si), 0.003 (3H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 171.2 (CO), 82.7 (CH), 68.9 (CH), 47.6 (CH), 41.8 (C), 37.5 (CH_2), 34.2 (CH_2), 26.5 (CH_2), 25.6 (*t*-BuSi), 22.1 (CH_2), 21.0 (CH_3), 17.9 (C), 17.0 (CH_2), 13.6 (Me-18), −4.9 (Me_2Si), −5.3 (Me_2Si).

8*β*-[(*tert*-Butyldimethylsilyl)oxy]de-A,B-androstan-17*β*-ol (12).[16] K_2CO_3 (6.9 g, 49.9 mmol) was added to a solution of **11** (13 g, 39.8 mmol) in MeOH (200 mL). The reaction mixture was stirred for 16 h. The solution was concentrated. Hexanes were added to the residue, and the resulting suspension was filtered and concentrated. The residue was purified by flash chromatography (16 × 5 cm, 5% EtOAc/hexanes) to give **12** [11.3 g, 99%, R_f = 0.3 (15% EtOAc/hexanes), white solid, pf 69−71 °C]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.93 (1H, m, H-8), 3.50 (1H, t, *J* = 8.3 Hz, H-17), 1.97 (1H, m, H-14), 0.91 (3H, s, H-18), 0.85 (9H, s, *t*-BuSi), 0.02 (3H, s, Me_2Si), 0.04 (3H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 81.8 (CH), 69.1 (CH), 47.9 (CH), 42.0 (C), 37.3 (CH_2), 34.3 (CH_2), 29.5 (CH_2), 25.7 (*t*-BuSi), 22.1 (CH_2), 17.9 (C), 17.2 (CH_2), 12.5 (Me-18), −4.9 (Me_2Si), −5.3 (Me_2Si).

8*β*-[(*tert*-Butyldimethylsilyl)oxy]de-A,B-androstan-17-one (13).[14] Pyridinium dichromate (48 g, 127.6 mmol) was added to a solution of **12** (11 g, 38.7 mmol) in CH_2Cl_2 (300 mL). After 16 h, Et_2O (500 mL) was added. The reaction mixture was stirred for an additional 15 min and filtered through a silica gel layer. The residue obtained after concentration was purified by flash chromatography (18 × 5 cm, 2% EtOAc/hexanes) to give **13** [10.5 g, 96%, R_f = 0.4 (15% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.15 (1H, m, H-8), 2.42 (1H, m, H-16), 2.04−1.68 (2H, m, H-16, H-14), 1.10 (3H, s, H-18), 0.90 (9H, s, *t*-BuSi), 0.05 (6H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 221.9 (C-17), 69.8 (CH), 48.6 (CH), 47.4 (C), 35.2 (CH_2), 34.2 (CH_2), 32.1 (CH_2), 25.7 (*t*-BuSi), 21.2 (CH_2), 17.9 (C), 16.9 (CH_2), 16.4 (Me-18), −4.9 (Me_2Si), −5.2 (Me_2Si).

8*β*-[(*tert*-Butyldimethylsilyl)oxy]de-A,B-androst-16-ene-17-yl Trifluoromethanesulfonate (14). *n*-BuLi in hexanes (27.5 mL, 2.32 M) was added dropwise (20 min) to *i*-Pr_2NH (9.7 mL, 69.2 mmol) at −78 °C. Dry THF (10 mL) was added to the reaction mixture at 0 °C. The white precipitate formed was dissolved with THF (40 mL). The solution was stirred for 30 min and then cooled to −78 °C. A solution of **13** (14 g, 49.6 mmol) in THF (120 mL) was added dropwise to the LDA solution. After 45 min, a solution of *N*,*N*-bis(trifluoromethanesulfonyl)-2-amine-5-chloropyridine (29 g, 74.5 mmol) in THF (60 mL) was added. The reaction mixture was stirred at rt for 6 h and then filtered two times through silica gel (5 × 4 cm) eluting with 3% Et_2O/hexanes. The residue obtained after concentration was purified by flash chromatography (15 × 5 cm, 1% Et_2O/hexanes) to give **14** [19.2 g, 93%, R_f = 0.6 (hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.54 (1H, dd, *J* = 3.3, 1.7 Hz, H-16), 4.08 (1H, m, H-8), 2.37 (1H, ddd, *J* = 14.6, 11.5, 1.7 Hz, H-15*β*), 2.06 (1H, ddd, *J* = 14.6, 6.0, 3.3 Hz, H-15α), 1.22 (3H, s, H-18), 0.89 (9H, s, *t*-BuSi), 0.04, 0.03 (3H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 159.1 (C-17), 118.6 (CF3, q, *J* = 320 Hz), 113.7 (C-16), 68.5 (C-8), 52.1 (C-14), 44.5 (C-13), 34.2 (CH_2), 33.3 (CH_2), 28.4 (CH_2), 25.7 (CH_3, *t*-BuSi), 18.3 (C-18), 18.0 (C, *t*-BuSi), 17.4 (CH_2),-4.9 (Me_2Si), −5.2 (Me_2Si). MS [CI^+, *m*/*z*]: 415 (M^+ + H, 25), 414 (M^+, 15), 413 (M^+ − H, 37), 399 (M^+ − Me, 20), 357 (M^+ − *t*-Bu, 62), 283 (M^+ − OTBS, 59), 265 (M^+ − OTf, 73), 151 (27), 133 (100). HRMS (CI^+): calcd for $C_{17}H_{28}O_4F_3SiS$ 413.1430, found 413.1424.

De-A,B-androstan-8*β*-ol (5). PtO_2 (0.3 g, 0.03 equiv) was added to a solution of **14** (17 g, 41.1 mmol) in EtOH (300 mL).

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The resulting suspension was deoxygenated by alternating vacuum with H_2 bubbling and then stirred for 16 h under H_2 atmosphere (balloon pressure). H_2 was removed by Ar bubbling. The mixture was filtered through silica gel and concentrated. The residue was dissolved in CH_3CN (200 mL) and aqueous HF (2 mL, 48%) was carefully added. After 12 h, the reaction was quenched by addition of a saturated solution of $NaHCO_3$ (200 mL). CH_3CN was removed at the rotatory evaporator, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic fractions were concentrated. The residue was purified by flash chromatography (12 × 5 cm, 5% EtOAc/hexanes) to give **5** [6.3 g, 99%, $R_f = 0.3$ (5% EtOAc/hexanes), volatile colorless oil]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.08 (1H, m, H-8), 0.92 (3H, s, Me-18). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 68.6 (C-8), 50.6 (C-14), 41.4 (CH_2), 39.7 (C-13), 39.2 (CH_2), 33.7 (CH_2), 23.4 (CH_2), 19.6 (C18), 19.3 (CH_2), 17.4 (CH_2). MS [CI$^+$, *m*/*z*]: 155 ($M^+ + H$, 5), 154 (M^+, 2), 153 ($M^+ - H$, 12), 139 ($M^+ - Me$, 9), 137 ($M^+ - OH$, 100), 121 (10). HRMS (CI+): calcd for $C_{10}H_{17}O$ 153.1279, found 153.1287.

De-A,B-(8β)-8,18-epoxyandrostane (15). Pyridine (7 mL) and $Pb(OAc)_4$ (32 g, 72.2 mmol) were successively added to a solution of **5** (2.3 g, 14.9 mmol) in benzene (1 L) placed in a 1.5 L photochemical Pyrex glass reactor. The cooled suspension was irradiated for 150 min with a 450 W medium-pressure Hg lamp. The reaction mixture was filtered through a silica gel layer and concentrated. The residue was purified by flash chromatography (12 × 2 cm, 10% Et_2O/hexanes) to give **15** [2.1 g, 92%, $R_f = 0.4$ (5% EtOAc/hexanes), volatile colorless oil]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.21 (1H, dm, $J = 4.3$ Hz, H-8), 3.68 (1H, d, $J = 8.0$ Hz, H-18), 3.43 (1H, d, $J = 8.0$ Hz, H-18). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 79.8 (C-8), 75.2 (C-18), 56.1 (C-14), 52.1 (C-13), 35.9 (CH_2), 32.6 (CH_2), 32.4 (CH_2), 27.0 (CH_2), 22.5 (CH_2), 19.0 (CH_2). MS [CI$^+$, *m*/*z*]: 153 ($M^+ + H$, 36), 152 (M^+, 31), 151 ($M^+ - H$, 52), 135 ($M^+ - OH$, 100), 121 (36). HRMS (CI$^+$): calcd for $C_{10}H_{16}O$ 152.1201, found 152.1197.

De-A,B-(8β)-8,18-epoxyandrostane (15) and De-A,B-8β-hydroxyandrostan-18-oic Acid Lactone (16) (by Irradiation of 5). A stirred suspension of $CaCO_3$ (8 g, 79.9 mmol) and $Pb(OAc)_4$ (40 g, 90.2 mmol) in cyclohexane (400 mL) was heated to 80 °C, and the heating bath was removed. I_2 (6 g, 23.6 mmol) and a solution of **5** (2.6 g, 16.9 mmol) in cyclohexane (10 mL) were successively added. The cooled reaction mixture was irradiated with a 300 W tungsten lamp for 3 h. The mixture was filtered through a silica gel layer eluting with Et_2O and then washed successively with saturated aqueous $Na_2S_2O_3$ (200 mL) and H_2O (200 mL). The combined organic fraction was concentrated. Pyridine (2 mL) was added to a solution of the obtained residue in acetone (60 mL). A solution of Jones' reagent (22 mL) was added to the mixture at 0 °C. The reaction mixture was stirred, protected from direct light, for 20 h. The reaction was quenched by pouring the reaction mixture, in small portions, on cooled saturated aqueous NaOAc (200 mL). The acetone was removed at the rotatory evaporator, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic fraction was washed with saturated aqueous $NaHCO_3$ (200 mL), dried, and concentrated. The residue was purified by flash chromatography (12 × 2 cm, 6% EtOAc/hexanes) to give **15** [1.63 g, 63%, $R_f = 0.4$ (5% EtOAc/hexanes), volatile colorless oil] and **16** [0.7 g, 26%, $R_f = 0.3$ (5% EtOAc/hexanes), colorless oil].

De-A,B-(8β)-8,18-epoxyandrostane (15) and De-A,B-8β-hydroxyandrostan-18-oic Acid Lactone (16) (by Sonication of 5). A stirred suspension of $CaCO_3$ (0.42 g, 4.2 mmol) and $Pb(OAc)_4$ (2.22 g, 5.0 mmol) in cyclohexane (40 mL) was heated to 80 °C and the heating bath was removed. I_2 (0.33 g, 1.3 mmol) and a solution of **5** (0.15 g, 1.0 mmol) in cyclohexane (2 mL) were successively added. The reaction mixture was sonicated for 1 h. The mixture was filtered through a silica gel layer eluting with Et_2O and then washed successively with saturated aqueous $Na_2S_2O_3$ (50 mL) and H_2O (50 mL). The combined organic fraction was concentrated. Pyridine (3 drops, Pasteur pipet) was added to a solution of the obtained residue in acetone (10 mL). A solution of Jones' reagent (4 mL) was added to the mixture at 0 °C. The reaction mixture was stirred, protected from direct light, for 16 h. The reaction was quenched by pouring the reaction mixture, in small portions, on cooled saturated aqueous NaOAc (20 mL). The acetone was removed in vaccum, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic fraction was washed with saturated aqueous $NaHCO_3$ (50 mL), dried, and concentrated. The residue was purified by flash chromatography (8 × 0.5 cm, 6% EtOAc/hexanes) to give **15** [0.07 g, 46%, $R_f = 0.4$ (5% EtOAc/hexanes), volatile colorless oil] and **16** [0.07 g, 41%, $R_f = 0.3$ (5% EtOAc/hexanes), colorless oil].

De-A,B-8β-hydroxyandrostan-18-oic Acid Lactone (16). A stirred suspension of $CaCO_3$ (6 g, 60.0 mmol) and $Pb(OAc)_4$ (31.6 g, 71.3 mmol) in cyclohexane (130 mL) was heated to 80 °C, and the heating bath was removed. I_2 (5 g, 19.7 mmol) and a solution of **5** (2 g, 13.0 mmol) in cyclohexane (20 mL) were successively added. The reaction mixture was sonicated for 4 h with vigorous mechanical stirring. The mixture was filtered through a silica gel layer eluting with Et_2O and then washed successively with saturated aqueous $Na_2S_2O_3$ (100 mL) and AgOAc (100 mL) and with H_2O (50 mL). The combined organic fraction was concentrated. The residue was dissolved (60 mL) and cooled at −10 °C. Silica gel (13 g) and Jones' reagent (40 mL) were added. The reaction mixture was stirred, protected from direct light, for 20 h. After filtering, the solution was poured carefully on saturated aqueous $NaHCO_3$ (250 mL) at 0 °C. The aqueous fraction was extracted with Et_2O (2 × 100 mL). The combined organic fraction was dried, filtered and concentrated. The residue was dissolved in a mixture of CH_3CN and CCl_4 (160 mL, 1:1). A pH 7 buffer solution (120 mL of H_2O, 1.037 g of KH_2PO_4, and 0.182 g of NaOH) was added. $NaIO_4$ (14.4 g, 67.3 mmol)] and $RuO_2 \cdot H_2O$ (0.22 g, 1.5 mmol) were consecutively added to the biphasic mixture. The resulting yellow mixture was vigorously stirred for 172 h. The organic solvents were removed at the rotatory evaporator. The aqueous fraction was extracted with Et_2O (3 × 100 mL). The combined organic fraction was washed successively with saturated aqueous $Na_2S_2O_3$ (100 mL) and H_2O (100 mL) and then dried, filtered, and concentrated. The residue was purified by flash chromatography (18 × 2 cm, 6% EtOAc/hexanes) to give **16** [1.76 g, 82%, $R_f = 0.3$ (5% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.54 (1H, dm, $J = 4.4$ Hz, H-8). 13C NMR ($CDCl_3$, 63 MHz): δ 181.4 (C-18), 78.4 (C-8), 55.0 (C-13), 53.6 (C-14), 30.9 (CH_2), 30.8 (CH_2), 28.4 (CH_2), 26.8 (CH_2), 22.9 (CH_2), 18.2 (CH_2). MS [CI$^+$, *m*/*z*]: 167 ($M^+ + H$, 33), 166 (M^+, 60), 150 (46), 138 (45), 121 ($M^+ - CO_2$, 100). HRMS (CI$^+$): calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0997.

De-A,B-(8β)-8,18-epoxyandrostane (15) (by Irradiation of 5). (Diacetoxyiodo)benzene (8 g, 24.8 mmol) and I_2 (5.4 g, 21.3 mmol) were added to a mixture of cyclohexane (110 mL) and benzene (10 mL) placed in a 250 mL reaction tube. The resulting suspension was deoxygenated by Ar bubbling. A solution of **5** (2.5 g, 16.2 mmol) in cyclohexane (20 mL) was added. The cooled reaction mixture was irradiated with a medium-pressure Hg 450 W lamp for 40 min. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (150 mL). The aqueous layer was extracted with Et_2O (100 mL). The combined organic fraction was washed with H_2O (100 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (15 × 2 cm, 6% Et_2O/hexanes) to give **15** [2.3 g, 93%, $R_f = 0.4$ (5% EtOAc/hexanes), volatile colorless oil].

De-A,B-(8β)-8,18-epoxyandrostane (15) (by Sonication of 5). (Diacetoxyiodo)benzene (0.97 g, 3.0 mmol) and I_2 (0.65 g, 2.6 mmol) were added to a mixture of cyclohexane (50 mL) and benzene (5 mL) placed in a 250 mL reaction tube. The resulting suspension was deoxygenated by simultaneous Ar bubbling and sonication. A solution of **5** (0.30 g, 2 mmol) in cyclohexane (10 mL) was added. The reaction mixture was sonicated for 80 min. The reaction was quenched with satu-

rated aqueous $Na_2S_2O_3$ (100 mL). The aqueous layer was extracted with Et_2O (100 mL). The combined organic fraction was washed with H_2O (100 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (12 × 1 cm, 6% Et2O/hexanes) to give **15** [0.28 g, 96%, R_f = 0.4 (5% EtOAc/hexanes), volatile colorless oil].

De-A,B-8α,18-diacetoxyandrostane (28). BF_3·OEt_2 (22 mL, 174.8 mmol) was added dropwise (10 min) to a solution of **15** (2 g, 13.1 mmol) in Ac_2O (130 mL) at −30 °C. After 10 min, the cooling bath was removed and the reaction mixture was stirred for an additional 40 min. The reaction was quenched by carefully carefully the mixture on saturated aqueous $NaHCO_3$ (250 mL) at 0 °C. $NaHCO_3$ was poured in small portions, over 6 h, on the vigorously stirred mixture until CO_2 release ceased. The aqueous fraction was extracted with EtOAc (5 × 100 mL). The combined organic fraction was dried, filtered, and concentrated. The residue was purified by flash chromatography (16 × 2 cm, 10% EtOAc/hexanes) to give **28** [2.1 g, 62%, R_f = 0.3 (20% EtOAc/hexanes), white solid]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.79 (1H, dt, J = 11.0, 4.7 Hz, H-8), 4.12 (1H, dd, J = 11.2, 2.0 Hz, H-18), 3.80 (1H, d, J = 11.2 Hz, H-18), 2.04 (3H, s, OAc), 1.99 (3H, s, OAc). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 171.3, 170.6 (C, $C(O)CH_3$), 72.8 (C-8), 62.1 (C-18), 52.7 (C-14), 46.7 (C-13), 35.0 (CH_2), 32.5 (CH_2), 32.1 (CH_2), 25.0 (CH_2), 21.2 (CH_2), 21.0 (CH_3, $C(O)CH_3$), 20.9 (CH_3, $C(O)CH_3$), 19.7 (CH_2). MS [CI$^+$, m/z]: 255 (M^+ + H, 3), 253 (M^+, 1), 211 (M^+ − Ac, 4), 195 (M^+ − OAc, 40), 135 (100), 121 (22). HRMS (CI$^+$): calcd for $C_{14}H_{23}O_4$ 255.1596, found 255.1588.

De-A,B-8α,18-dihydroxyandrostane (29). K_2CO_3 (2.2 g, 15.9 mmol) was added to a solution of **28** (1.8 g, 7.0 mmol) in MeOH (100 mL). The suspension was stirred for 2 h, filtered, and concentrated. The residue was dissolved in EtOAc (20 mL), and silica gel (2 g) was added. The suspension was filtrated and concentrated. The residue was purified by flash chromatography (12 × 2 cm, 60% EtOAc/hexanes) to give **29** [1.29 g, 99%, R_f = 0.3 (60% EtOAc/hexanes), white solid]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.60 (1H, dd, J = 10.9, 1.7 Hz, H-18), 3.59 (1H, dt, J = 10.2, 4.7 Hz, H-8), 3.30 (1H, d, J = 10.9 Hz, H-18). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 70.3 (C-8), 60.0 (C-18), 55.8 (C-14), 48.2 (C-13), 36.0 (CH_2), 34.4 (CH_2), 32.0 (CH_2), 24.9 (CH_2), 21.3 (CH_2), 20.1 (CH_2). MS [CI$^+$, m/z]: 170 (M^+, 1), 169 (M^+ − H, 8), 153 (M^+ − OH, 37), 152 (M^+ − H_2O, 10), 136 (12), 135 (100), 133 (36), 121 (32). HRMS (CI$^+$): calcd for $C_{10}H_{17}O_2$ 169.1229, found 169.1229.

De-A,B-8α-hydroxyandrostan-18-al (30). (Diacetoxyiodo)benzene (0.50 g, 1.6 mmol) and 2,2,6,6-tetramethylpiperidinooxyl free radical (0.03 g, 0.2 mmol) were added to a solution of **29** (0.28 g, 1.6 mmol) in CH_2Cl_2/CH_3CN (16 mL, 1:1). The mixture, protected from direct light, was stirred for 5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (50 mL). The aqueous fraction was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic fraction was dried, filtered, and concentrated. The residue was purified by flash chromatography (12 × 1 cm, 35% EtOAc/hexanes) to give **30** [0.27 g, 97%, R_f = 0.5 (60% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 9.52 (1H, d, J = 1.8, H-18), 3.97 (1H, dt, J = 10.5, 4.7 Hz, H-8). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 205.1 (C-18), 70.2 (C-8), 59.2 (C-13), 54.9 (C-14), 35.5 (CH_2), 33.7 (CH_2), 31.6 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 20.6 (CH_2). MS [CI$^+$, m/z]: 169 (M^+ + H, 2), 168 (M^+, 5), 167 (M^+ − H, 54), 139 (31), 121 (100). HRMS (CI$^+$): calcd for $C_{10}H_{15}O_2$ 167.1072, found 167.1065.

8α-[(*tert*-Butyldimethylsilyl)oxy]-de-A,B-androstan-18-al (31). Imidazole (1.84 g, 27 mmol) and TBSCl (1.36 g, 9.0 mmol) were consecutively added to a solution of **30** (0.57 g, 3.4 mmol) in DMF (10 mL). The reaction mixture was stirred for 30 h. The reaction was quenched with H_2O (200 mL). The aqueous fraction was extracted with an Et_2O/hexanes mixture (3 × 60 mL, 10%). The combined organic fraction was washed with H_2O (3 × 50 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (12 × 2 cm, 7% EtOAc/hexanes) to give **31** [0.94 g, 98%, R_f = 0.7 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 9.54 (1H, s, H-18), 3.96 (1H, dt, J = 9.9, 4.6 Hz, H-8), 0.88 (9H, s, *t*-BuSi), 0.06, 0.05 (3H, s, Me_2Si). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 205.3 (C-18), 70.9 (C-8), 59.1 (C-13), 55.3 (C-14), 36.5 (CH_2), 34.0 (CH_2), 31.8 (CH_2), 26.1 (CH_2), 25.7 (CH_3, *t*-BuSi), 22.6 (CH_2), 20.5 (CH_2), 18.0 (C, *t*-BuSi), −4.5, −4.9 (Me_2Si). MS [CI$^+$, m/z]: 283 (M^+ + H, 14), 282 (M^+, 22), 281 (M^+ − H, 100), 267 (37), 253 (83), 151 (15), 121 (15). HRMS (CI$^+$): calcd for $C_{16}H_{30}O_2Si$ 282.2015, found 282.2004.

(18*Z*)-20(17→18)-*abeo*-8α-[(*tert*-Butyldimethylsilyl)oxy]-24-carboxyde-A,B-21-norchol-18-ene (40a). KO-*t*-Bu (1.00 g, 8.9 mmol) was added to a suspension of (4-carboxybutyl)-triphenylphosphonium bromide (1.30 g, 2.9 mmol) in dry benzene (50 mL). The resulting white suspension was refluxed for 2 h to give rise to a red mixture. A solution of **31** (0.25 g, 0.9 mmol) in benzene (12 mL) was added dropwise. The reaction mixture was stirred at rt for 12 h. The reaction was quenched with H_2O (50 mL) and acidified with HCl 5% until pH 3−4. The aqueous fraction was extracted with EtOAc (8 × 50 mL). The combined organic fraction was washed with saturated aqueous NaCl (200 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (16 × 2 cm, 35% EtOAc/hexanes) to give **40a** [0.26 g, 79%, R_f = 0.2 (30% EtOAc/hexanes), white solid]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.34 (1H, d, J = 12.7 Hz, H-18), 5.27 (1H, ddd, J = 12.7, 11.8, 7.0 Hz, H-20), 3.66 (1H, dt, J = 10.1, 4.7 Hz, H-8), 2.37 (2H, t, J = 7.5 Hz), 2.19 (2H, q, J = 7.2 Hz), 2.08 (2H, dt, J = 12.4, 2.8 Hz), 1.92−1.82 (2H, m), 1.69 (2H, qm, J = 7.5), 0.88 (9H, s, *t*-BuSi), 0.054, 0.052 (3H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 179.9 (C-25), 133.8 (C-18), 130,2 (C-20), 72.1 (C-8), 57.5 (C-14), 48.4 (C-13), 39.5 (CH_2), 37.2 (CH_2), 36.4 (CH_2), 33.5 (CH_2), 28.4 (CH_2), 25.9 (CH_3, *t*-BuSi), 25.7 (CH_2), 24.5 (CH_2), 22.6 (CH_2), 20.5 (CH_2), 18.1 (C, *t*-BuSi), −4.2, −4.6 (Me_2Si). MS [CI$^+$, m/z]: 367 (M^+ + H, 34), 366 (M^+, 11), 365 (M^+ − H, 22), 349 (M^+ − OH, 17), 309 (M^+ − *t*-Bu, 88), 235 (M^+ − OTBS, 100). HRMS (CI$^+$): calcd for $C_{21}H_{39}O_3Si$ 367.2669, found 367.2674.

(18*Z*)-20(17→18)-*abeo*-8α-[(*tert*-Butyldimethylsilyl)oxy]-de-A,B-21-norcholest-18-en-25-ol (41a). MeLi in Et_2O (2 mL, 1.25 M) was rapidly added to a cooled solution of **40a** (0.17 g, 0.46 mmol) in THF (6 mL) at 0 °C. The mixture was stirred at rt for 4 h. The reaction was quenched with H_2O (10 mL) and acidified with HCl 5% until pH 3−4. The aqueous fraction was extracted with EtOAc (5 × 15 mL). The combined organic fraction was washed with saturated aqueous NaCl (50 mL), dried, filtered, concentrated, and dried at high vacuum. The residue was dissolved in THF (6 mL), and MeLi in Et_2O (2 mL, 1.25 M) was added to the cooled solution at −20 °C. The mixture was stirred for 12 h. The reaction was quenched with H_2O (20 mL). The aqueous fraction was extracted with EtOAc (3 × 15 mL). The organic fraction was washed with saturated aqueous NaCl (30 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (12 × 0.5 cm, 6% EtOAc/hexanes) to give **41a** [0.15 g, 82%, R_f = 0.6 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.34−5.23 (2H, m, H-18, H-20), 3.65 (1H, dt, J = 10.1, 4.7 Hz, H-8), 2.12 (2H, m), 1.94−1.78 (2H, m), 1.19 (6H, s, H-26, H-27), 0.87 (9H, s, *t*-BuSi), 0.04 (6H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 132.8 (CH), 131,4 (CH), 72.0 (C-8), 70,9 (C-25), 57.5 (C-14), 48.3 (C-13), 43.5 (CH_2), 39.5 (CH_2), 37.2 (CH_2), 36.5 (CH_2), 29.4 (CH_2), 29.2 (C-26, C-27), 25.8 (CH_3, *t*-BuSi), 25.7 (CH_2), 24.3 (CH_2), 22.6 (CH_2), 20.5 (CH_2), 18.1 (C, *t*-BuSi), −4.2, −4.6 (Me_2Si). MS [CI$^-$, m/z]: 381 (M^+ + H, 5), 380 (M^+, 10), 379 (M^+ − H, 36), 378 (M^+ − 2H, 13), 265 (M^+ − TBS, 10). HRMS (CI$^-$): calcd for $C_{23}H_{43}O_2Si$ 379.3032, found 379.3022.

(18*Z*)-20(17→18)-*abeo*-De-A,B-8α,25-dihydroxy-21-norcholest-18-ene (42a). Aqueous HF (12 drops, Pasteur pipet, 48%) was slowly added to a solution of **41a** (0.14 g, 0.37 mmol) in CH_3CN (10 mL). The reaction mixture was stirred for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The CH_3CN was removed in the rotatory evaporator. The aqueous fraction was extracted with EtOAc (5 × 10 mL).

The combined organic fraction was dried, filtered, and concentrated. The residue was purified by flash chromatography (12 × 0.5 cm, 35% EtOAc/hexanes) to give **42a** [0.07 g, 69%, R_f = 0.4 (50% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.28−5.25 (2H, m, H-18, H-20), 3.66 (1H, dt, J = 10.5, 4.7 Hz, H-8), 2.15−2.08 (2H, m), 1.97−1.82 (2H, m), 1.18 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 132.3 (CH), 131,5 (CH), 71.3 (C-8), 70,8 (C-25), 57.4 (C-14), 48.5 (C-13), 43.5 (CH_2), 39.3 (CH_2), 37.1 (CH_2), 35.8 (CH_2), 29.4 (CH_2), 29.1 (C-26, C-27), 24.7 (CH_2), 24.3 (CH_2), 22.5 (CH_2), 20.7 (CH_2). MS [CI$^+$, *m*/*z*]: 267 (M^+ + H, 7), 266 (M^+, 9), 265 (M^+ − H, 7).

20(17→18)-*abeo*-De-A,B-8α,25-dihydroxy-21-norcholestane (43a). Pd on carbon (0.03 g, 5% Pd) was added to a solution of **42a** (0.07 g, 0.26 mmol) in EtOAc (6 mL). The resulting suspension was deoxygenated by alternating vacuum with H_2 bubbling and then stirred for 16 h under H_2 atmosphere (balloon pressure). H_2 was removed by Ar bubbling. The mixture was filtered through silica gel and concentrated. The residue was purified by flash chromatography (12 × 0.5 cm, 35% EtOAc/hexanes) to give **43a** [0.07 g, 98%, R_f = 0.4 (50% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.64 (1H, dt, J = 10, 5 Hz, H-8), 2.05−1.93 (2H, m), 1.17 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 71.0 (C-8), 70.7 (C-25), 56.9 (C-14), 45.7 (C-13), 43.9 (CH_2), 36.2 (CH_2), 35.9 (CH_2), 34.0 (CH_2), 31.2 (CH_2), 29.1 (C-26, C-27), 27.1 (CH_2), 24.44 (CH_2), 24.36 (CH_2), 23.5 (CH_2), 21.5 (CH_2), 20.2 (CH_2). MS [CI$^-$, *m*/*z*]: 269 (M^+ + H, 3), 268 (M^+, 16), 267 (M^+ − H, 100), 251 (M^+ − OH, 12). HRMS (CI$^-$): calcd for $C_{17}H_{31}O_2$ 267.2324, found 267.2325.

20(17→18)-*abeo*-De-A,B-25-hydroxy-21-norcholestan-8-one (3a). Pyridinium dichromate (0.300 g, 0.797 mmol) was added to a solution of **43a** (0.060 g, 0.224 mmol) in CH_2Cl_2 (6 mL). After 16 h, Et_2O (4 mL) was added. The reaction mixture was stirred for an additional 15 min and filtered through a silica gel layer. The residue obtained after concentration was purified by flash chromatography (12 × 0.5 cm, 20% EtOAc/hexanes) to give **3a** [0.055 g, 92%, R_f = 0.3 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.17 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 212.0 (C-8), 70.9 (C-25), 61.5 (C-14), 50.7 (C-13), 43.8 (CH_2), 41.0 (CH_2), 36.1 (CH_2), 33.9 (CH_2), 30.8 (CH_2), 29.1 (C-26, C-27), 27.6 (CH_2), 24.3 (CH_2), 23.6 (CH_2), 23.4 (CH_2), 20.2 (CH_2), 20.0 (CH_2). MS [FAB$^+$, *m*/*z*]: 289 (M^+ + Na, 5), 267 (M^+ + H, 7), 266 (M^+, 2), 265 (M^+ − H, 4), 249 (M^+ − OH, 100), 137 (46). HRMS (FAB$^+$): calcd for $C_{17}H_{30}O_2$ 266.2246, found 266.2243.

20(17→18)-*abeo*-3-(*tert*-Butyldimethylsilyl)-1α-[(*tert*-butyldimethylsilyl)oxy]-25-hydroxy-21-norvitamin D$_3$ (44a). *n*-Hexyllithium in hexanes (0.45 mL, 2.24 M) was added dropwise, over 10 min, to a cooled solution of **4** (0.600 g, 1.029 mmol) in THF (3 mL) at −78 °C. The intense red mixture was stirred for 40 min. A solution of **3a** (0.040 g, 0.150 mmol) in THF (4 mL) was slowly added. The mixture was stirred for an additional 2 h. The temperature was allowed to reach −20 °C. After 1 h, the reaction was quenched with H_2O (10 mL). The aqueous fraction was extracted with Et_2O (3 × 10 mL). The combined organic fraction was washed with aqueous saturated NaCl (20 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (10 × 0.4 cm, 12% Et_2O/hexanes) to give the protected analogue **44a** [0.080 g, 87%, R_f = 0.6 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 6.27, 6.04 (2H, AB, J = 11.3 Hz, H-6, H-7), 5.19 (1H, dd, J = 2.5, 0.8 Hz, H-19E), 4.86 (1H, d, J = 2.5 Hz, H-19Z), 4.38 (1H, dd, J = 6.4, 3.6 Hz, H-1), 4.20 (1H, tt, J = 7.5, 3.75 Hz, H-3), 2.87 (1H, dd, J = 12.5, 3.6 Hz, H-9β), 2.46 (1H, dd, J = 13.0, 3.8 Hz, H-4), 2.20 (1H, dd, J = 13.0, 7.5 Hz, H-4), 1.16 (6H, s, H-26, H-27), 0.88 (18H, s, *t*-BuSi), 0.07 (12H, s, $SiMe_2$). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 148.5 (C), 141.2 (C), 135.1(C), 123.2 (CH), 118.1 (CH), 111.3 (C-19), 72.2 (C-1), 70.8 (C-25), 67.7 (C-3), 56.0 (C-14), 46.5 (C-13), 46.1 (CH_2), 45.0 (CH_2), 44.1 (CH_2), 36.4 (CH_2), 35.4 (CH_2), 31.3 (CH_2), 29.1 (C-26, C-27), 28.8 (CH_2), 27.2 (CH_2), 25.8, 25.7 (*t*-BuSi), 24.6 (CH_2), 23.6 (CH_2), 23.3 (CH_2), 23.2 (CH_2), 20.2 (CH_2), 18.2, 18.1 (C, *t*-BuSi), −4.8, −4.9, −5.0, −5.2 ($SiMe_2$). MS [FAB$^+$, *m*/*z*]: 631 (M^+ + H, 1), 630 (M^+, 1), 629 (M^+ − H, 1), 615 (M^+ − Me, 1), 613 (M^+ − OH, 1), 573 (M^+ − *t*-Bu, 1), 515 (M^+ − TBS, 1), 499 (M^+ − OTBS, 1), 498 (1), 400 (M^+ − 2TBS, 3), 399 (3), 369 (4), 367 (2), 263 (4), 147 (100). HRMS (FAB$^+$): calcd for $C_{38}H_{70}O_3Si_2$ 630.4864, found 630.4875.

20(17→18)-*abeo*-1α,25-Dihydroxy-21-norvitamin D$_3$ (2a). A solution of tetrabutylammonium fluoride in THF (1 mL, 1 M) was added to a solution of **44a** (0.060 mg, 0.095 mmol) in THF (2 mL). The mixture, protected from direct light, was stirred for 16 h. H_2O (10 mL) was added, and the aqueous fraction was extracted with Et_2O (7 × 10 mL). The combined organic fraction was washed with aqueous saturated NaCl (20 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (6 × 0.4 cm, 12% *i*-PrOH/hexanes), to give the analogue **2a** [0.033 g, 88%, R_f = 0.2 (90% EtOAc/hexanes), white solid]. ^{1}H NMR(CD_2Cl_2, 250 MHz): δ 6.34, 6.12 (2H, AB, J = 11.2, H-6, H-7), 5.30 (1H, bs, H-19E), 4.97 (1H, bs, H-19Z), 4.37 (1H, m, H-1), 4.16 (1H, m, H-3), 1.18 (6H, s, H-26, H-27). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 148.1 (C), 142.8 (C), 133.6 (C), 124.7 (CH), 117.2 (CH), 111.9 (C-19), 70.85 (C-25), 70.8 (C-1), 66.6 (C-3), 56.0 (C-14), 46.9 (C-13), 45.9 (CH_2), 44.5 (CH_2), 43.3 (CH_2), 37.6 (CH_2), 35.7 (CH_2), 31.7 (CH_2), 29.6 (C-26, C-27), 29.6 (CH_2), 27.8 (CH_2), 25.1 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 20.6 (CH_2), 19.7 (CH_2). MS [CI$^+$, *m*/*z*]: 403 (M^+ + H, 1), 402 (M^+, 1), 401 (M^+ − H, 3), 385 (M^+ − OH, 3), 384 (3), 383 (7), 367 (M^+ − OH − H_2O, 5), 291 (6), 249 (8), 136 (3), 135 (30), 121 (26). HRMS (CI$^+$): calcd for $C_{26}H_{41}O_3$ 401.3056; found 401.3066.

(5-Carboxypentyl)triphenylphosphonium Bromide (21b). Ph_3P (26.80 g, 102.2 mmol) was added to a solution of 6-bromohexanoic acid (5.00 g, 25.6 mmol) in dry CH_3CN (17 mL). The reaction mixture, vigorously stirred, was refluxed over 24 h. The solution was concentrated. The residue was rinsed consecutively with benzene (3 × 20 mL), hexanes (20 mL), and Et_2O (2 × 20 mL). The crystalline white solid was dried to give **21b** (11.7 g, 99%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.80−7.68 (15H, m), 3.58 (2H, bs), 2.34−2.32 (2H, m), 1.63 (6H, bs). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 175.5 (C), 134.7 (CH, d, J = 2.4 Hz), 133.1 (CH, d, J = 10.0 Hz), 130.1 (CH, d, J = 12.5 Hz), 117.5 (C, d, J = 86.0 Hz), 33.6 (CH_2), 29.0 (CH_2, d, J = 16.2 Hz), 23.5 (CH_2), 22.3 (CH_2), 21.5 (CH_2). MS [CI, *m*/*z*]: 360 (M^+ − OH, 3), 359 (M^+ − H_2O, 11), 358 (M^+ − H_3O^+, 5), 262 (Ph_3P^+, 54), 185 (Ph_2P^+, 100), 81 (Br^+, 81), 79 (Br^+, 58).

(18*Z*)-20(17→18)-*abeo*-8α-[(*tert*-Butyldimethylsilyl)oxy]-24-carboxyde-A,B-22-homo-21-norchol-18-ene (40b). Following the same experimental procedure as for **40a**, the coupling of the aldehyde **31** (0.15 g, 0.5 mmol) with the ylide formed from Wittig salt **21b** (1.00 g, 2.2 mmol) and KO-*t*-Bu (0.75 g, 6.7 mmol) afforded, after purification by flash chromatography (16 × 2 cm, 35% EtOAc/hexanes), **40b** [0.15 g, 76%, R_f = 0.2 (30% EtOAc/hexanes), white solid]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.30−5.27 (2H, m, H-18, H-20), 3.66 (1H, dt, J = 10.2, 4.7 Hz, H-8), 2.36 (2H, t, J = 7.4 Hz), 2.18−2.15 (2H, m), 1.90−1.82 (2H, m), 0.88 (9H, s, *t*-BuSi), 0.05 (6H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 180.0 (C-25), 133.0 (CH), 131,0 (CH), 72.1 (C-8), 57.5 (C-14), 48.3 (C-13), 39.5 (CH_2), 37.2 (CH_2), 36.5 (CH_2), 34.0 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 25.9 (CH_3, *t*-BuSi), 25.7 (CH_2), 24.4 (CH_2), 22.6 (CH_2), 20.5 (CH_2), 18.0 (C, *t*-BuSi), −4.2, −4.6 (Me_2Si). MS [CI$^+$, *m*/*z*]: 381 (M^+ + H, 32), 380 (M^+, 7), 379 (M^+ − H, 15), 365 (M^+ − Me, 22), 363 (M^+ − OH, 21), 323 (M^+ − *t*-Bu, 81), 249 (M^+ − OTBS, 100). HRMS (CI$^+$): calcd for $C_{22}H_{41}O_3Si$ 381.2825, found 381.2826.

(18*Z*)-20(17→18)-*abeo*-8α-[(*tert*-Butyldimethylsilyl)oxy]-de-A,B-22-homo-21-norcholest-18-en-25-ol (41b). Following the same experimental procedure as for **41a**, the reaction of the carboxylic acid **40b** in two stages with MeLi in Et_2O (1.5 mL, 1.25 M) afforded, after purification by flash chromatography (12 × 0.5 cm, 6% EtOAc/hexanes), **41b** [0.07 g, 80%, R_f = 0.6 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.34−5.24 (2H, m, H-18, H-20), 3.66 (1H, dt, J =

10.1, 4.7 Hz, H-8), 2.16−2.10 (2H, m), 1.95−1.79 (2H, m), 1.20 (6H, s, H-26, H-27), 0.88 (9H, s, *t*-BuSi), 0.05 (6H, s, Me_2Si). ^{13}C NMR (CDCl3, 75.5 MHz): δ 132.6 (CH), 131,6 (CH), 72.0 (C-8), 71,0 (C-25), 57.5 (C-14), 48.3 (C-13), 43.9 (CH_2), 39.5 (CH_2), 37.3 (CH_2), 36.5 (CH_2), 30.1 (CH_2), 29.2 (C-26, C-27), 25.9 (CH_3, *t*-BuSi), 25.7 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 20.5 (CH_2), 18.1 (C, *t*-BuSi), −4.2, −4.6 (Me_2Si). MS [CI^-, *m*/*z*]: 395 (M^+ + H, 4), 394 (M^+, 8), 393 (M^+ − H, 33), 337 (M^+ − *t*-Bu, 4). HRMS (CI^-): calcd for $C_{24}H_{45}O_2Si$ 393.3189, found 393.3195.

(18*Z*)-20(17→18)-*abeo*-De-A,B-8α,25-dihydroxy-22-homo-21-norcholest-18-ene (42b). Following the same experimental procedure as for **42a**, the deprotection of **41b** (0.06 g, 0.15 mmol) with aqueous HF (9 drops, 48%) afforded, after purification by flash chromatography (10 × 0.4 cm, 35% EtOAc/hexanes), **42b** [0.027 g, 63%, R_f = 0.4 (50% EtOAc/hexanes), colorless oil]. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.34−5.23 (2H, m, H-18, H-20), 3.69 (1H, dt, *J* = 10.5, 4.6 Hz, H-8), 2.18−2.09 (2H, m), 2.00−1.80 (2H, m), 1.19 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 132.1 (CH), 131,7 (CH), 71.5 (C-8), 70,7 (C-25), 57.5 (C-14), 48.6 (C-13), 43.8 (CH_2), 39.3 (CH_2), 37.2 (CH_2), 35.9 (CH_2), 30.1 (CH_2), 29.2 (C-26, C-27), 24.7 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 20.7 (CH_2). MS [CI^-, *m*/*z*]: 281 (M^+ + H, 10), 280 (M^+, 8), 279 (M^+ − H, 10), 278 (M^+ − 2H, 23), 265 (M^+ − Me, 25), 263 (M^+ − OH, 100). HRMS (CI^-): calcd for $C_{18}H_{31}O_2$ 279.2324, found 279.2314.

20(17→18)-*abeo*-De-A,B-8α,25-dihydroxy-22-homo-21-norcholestane (43b). Following the same experimental procedure as for **43a**, the catalytic hydrogenation of **42b** (0.020 g, 0.071 mmol) with Pd on carbon (0.02 g, 5% Pd) afforded, after purification by flash chromatography (9 × 0.4 cm, 35% EtOAc/hexanes), **43b** [0.019 g, 96%, R_f = 0.4 (50% EtOAc/hexanes), colorless oil]. ^1H NMR ($CDCl_3$, 250 MHz): δ 3.68 (1H, dt, *J* = 10.5, 4.7 Hz, H-8), 2.06−1.97 (2H, m), 1.20 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 71.0 (C-25), 70.8 (C-8), 57.0 (C-14), 45.8 (C-13), 44.0 (CH_2), 36.3 (CH_2), 36.0 (CH_2), 34.1(CH_2), 30.7 (CH_2), 30.2 (CH_2), 29.2 (C-26, C-27), 27.1 (CH_2), 24.4 (CH_2), 24.3 (CH_2), 23.5 (CH_2), 21.5 (CH_2), 20.3 (CH_2). MS [CI^-, *m*/*z*]: 283 (M^+ + H, 12), 282 (M^+, 18), 281 (M^+ − H, 100). HRMS (CI^-): calcd for $C_{18}H_{33}O_2$ 281.2481, found 281.2474.

20(17→18)-*abeo*-De-A,B-25-hydroxy-22-homo-21-norcholestan-8-one (3b). Following the same experimental procedure as for **3a**, the oxidation of **43b** (0.015 g, 0.053 mmol) with PDC (0.060 g, 0.160 mmol) afforded, after purification by flash chromatography (9 × 0.4 cm, 20% EtOAc/hexanes), **3b** [0.013 g, 90%, R_f = 0.3 (20% EtOAc/hexanes), colorless oil]. ^1H NMR ($CDCl_3$, 250 MHz): δ 1.19 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 212.1 (C-8), 71.0 (C-25), 61.6 (C-14), 50.8 (C-13), 43.9 (CH_2), 41.0 (CH_2), 36.2 (CH_2), 33.9 (CH_2), 30.3 (CH_2), 30.1 (CH_2), 29.2 (C-26, C-27), 27.7 (CH_2), 24.3 (CH_2), 23.6 (CH_2), 23.4 (CH_2), 20.2 (CH_2), 20.1 (CH_2). MS [FAB^+, *m*/*z*]: 303 (M^+ + Na, 6), 281 (M^+ + H, 9), 280 (M^+, 2), 279 (M^+ − H, 4), 278 (M^+ − 2H, 12), 264 (M^+ − H_2O, 14), 263 (M^+ − H_3O^+, 69), 153 (94), 137 (100). HRMS (FAB^+): calcd for $C_{18}H_{31}O_2$ 279.2324, found 279.2324.

20(17→18)-*abeo*-3-(*tert*-butyldimethylsilyl)-1α-[(*tert*-butyldimethylsilyl)oxy]-25-hydroxy-22-homo-21-norvitamin D_3 (44b). Following the same experimental procedure as for **44a**, the coupling of **3b** (0.009 g, 0.032 mmol) with the phosphine oxide anion formed by reaction of **4** (0.130 g, 0.223 mmol) with *n*-HexLi in hexanes (0.10 mL, 2.24 M) afforded, after purification by flash chromatography (10 × 0.4 cm, 12% Et_2O/hexanes), the protected analogue **44b** [0.019 g, 93%, R_f = 0.6 (20% EtOAc/hexanes), colorless oil]. ^1H NMR (CD_2Cl_2, 250 MHz): δ 6.27, 6.04 (2H, AB, *J* = 11.3 Hz, H-6, H-7), 5.19 (1H, dd, *J* = 2.5, 0.8 Hz, H-19E), 4.86 (1H, d, *J* = 2.5 Hz, H-19Z), 4.38 (1H, dd, *J* = 6.4, 3.6 Hz, H-1), 4.20 (1H, tt, *J* = 7.5, 3.74 Hz, H-3), 2.86 (1H, dd, *J* = 12.5, 3.6 Hz, H-9β), 2.46 (1H, dd, *J* = 13.0, 3.8 Hz, H-4), 2.20 (1H, dd, *J* = 13.0, 7.5 Hz, H-4), 1.16 (6H, s, H-26, H-27), 0.88 (18H, s, *t*-BuSi), 0.07 (12H, s, $SiMe_2$). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 148.5 (C), 141.2 (C), 135.0(C), 123.2 (CH), 118.0 (CH), 111.3 (C-19), 72.2 (C-1), 70.7 (C-25), 67.6 (C-3), 56.0 (C-14), 46.4 (C-13), 46.1 (CH_2), 44.9 (CH_2), 44.1 (CH_2), 36.4 (CH_2), 35.3 (CH_2), 30.8 (CH_2), 30.4 (CH_2), 29.1 (C-26, C-27), 28.8 (CH_2), 27.2 (CH_2), 25.74, 25.71 (*t*-BuSi), 24.4 (CH_2), 23.6 (CH_2), 23.3 (CH_2), 23.2 (CH_2), 20.2 (CH_2), 18.2, 18.1 (C, *t*-BuSi), −4.8, −4.9, −5.0, −5.2 ($SiMe_2$). MS [FAB^+, *m*/*z*]: 645 (M^+ + H, 1), 644 (M^+, 2), 643 (M^+ − H, 3), 629 (M^+ − Me, 1), 627 (M^+ − OH, 1), 587 (M^+ − *t*-Bu, 1), 529 (M^+ − TBS, 2), 513 (M^+ − OTBS, 2), 512 (M^+ − HOTBS, 2), 511(5), 414 (M^+ − 2TBS, 1), 382 (M^+ − 2OTBS, 2), 381 (4), 380 (2), 367 (3), 277 (3), 147 (36), 137 (100). HRMS (FAB^+): calcd for $C_{39}H_{72}O_3Si_2$ 644.5020, found 644.5030.

20(17→18)-*abeo*-1α,25-Dihydroxy-22-homo-21-norvitamin D_3 (2b). Following the same experimental procedure as for **2a**, **44b** (0.007 g, 0.011 mmol) was deprotected with TBAF in THF (0.4 mL, 1 M) to afford, after purification by flash chromatography (6 × 0.4 cm, 12% *i*-PrOH/hexanes), the analogue **2b** [0.004 g, 81%, R_f = 0.2 (90% EtOAc/hexanes), white solid]. ^1H NMR ($CDCl_3$, 250 MHz): δ 6.36, 6.01 (2H, AB, *J* = 11.2 Hz, H-6, H-7), 5.30 (1H, bs, H-19E), 4.98 (1H, bs, H-19Z), 4.40 (1H, m, H-1), 4.19 (1H, m, H-3), 1.18 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 147.6 (C), 142.8 (C), 132.9 (C), 124.8 (CH), 117.1 (CH), 111.9 (C-19), 71.0 (C-1), 70.8 (C-25), 66.5 (C-3), 55.9 (C-14), 46.5 (C-13), 45.2 (CH_2), 43.9 (CH_2), 42.8 (CH_2), 36.3 (CH_2), 35.2 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 29.1 (C-26), 29.1 (C-27), 27.1 (CH_2), 24.2 (CH_2), 23.5 (CH_2), 23.2 (CH_2), 23.2 (CH_2), 20.1 (CH_2). MS [CI^+, *m*/*z*]: 417 (M^+ + H, 1), 416 (M^+, 1), 415 (M^+ − H, 2), 401 (M^+ − Me, 1), 399 (M^+ − OH, 2), 398 (3), 397 (5), 277 (3), 136 (3), 135 (8), 121 (2). HRMS (CI^+): calcd for $C_{27}H_{43}O_3$ 415.3212, found 415.3223.

Ethyl (18*E*)-20(17→18)-*abeo*-8α-[(*tert*-Butyldimethylsilyl)oxy]de-A,B-pregn-18-en-21-ate (37). A solution of diethyl ethoxycabonylmethylphosphonate (0.46 mL, 2.30 mmol) in THF (3 mL) was slowly added to a cooled suspension of NaH (0.05 g, 2.08 mmol) in dry THF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and at rt for 1 h. A solution of **31** (0.19 g, 0.67 mmol) in THF (6 mL) was added. The reaction mixture was quenched after 72 h by addition of H_2O (20 mL). The aqueous fraction was extracted with EtOAc (3 × 15 mL). The combined organic fraction was washed with saturated aqueous NaCl (20 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (10 × 1 cm, 3% EtOAc/hexanes) to give **37** [0.22 g, 93%, R_f = 0.5 (10% EtOAc/hexanes), colorless oil]. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.08 (1H, d, *J* = 16.1 Hz, H-18), 5.83 (1H, d, *J* = 16.1 Hz, H-20), 4.19 (2H, q, *J* = 7.1 Hz), 3.55 (1H, dt, *J* = 10.0, 4.4 Hz, H-8), 1.30 (3H, t, *J* = 7.1 Hz), 0.86 (9H, s, *t*-BuSi), 0.03 (6H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 167.0 (C-21), 152.4 (C-18), 120,3 (C-20), 71.7 (C-8), 60.2 (CH_2, CO_2Et), 56.8 (C-14), 49.5 (C-13), 39.7 (CH_2), 36.7 (CH_2), 36.0 (CH_2), 25.8 (CH_3, *t*-BuSi), 25.6 (CH_2), 22.0 (CH_2), 20.0 (CH_2), 18.1 (C, *t*-BuSi), 14.3 (CH_3, CO_2Et), −4.2, −4.7 (Me_2Si). MS [CI^+, *m*/*z*]: 253 (M^+ + H, 25), 352 (M^+, 8), 351 (M^+ − H, 28), 337 (M^+ − Me, 68), 307 (M^+ − OEt, 31), 221 (M^+ − *t*-Bu, 76), 221 (M^+ − OTBS, 100). HRMS (CI^+): calcd for $C_{20}H_{35}O_3Si$ 351.2355, found 351.2352.

Ethyl 20(17→18)-*abeo*-8α-[(*tert*-Butyldimethylsilyl)oxy]de-A,B-pregnan-21-ate (38). Pd on carbon (0.05 g, 5% Pd) was added to a solution of **37** (0.16 g, 0.45 mmol) in EtOAc (12 mL). The resulting suspension was deoxygenated by alternating vacuum with H_2 bubbling and then stirred for 20 h under H_2 atmosphere (balloon pressure). H_2 was removed by Ar bubbling. The mixture was filtered through silica gel and concentrated. The residue was purified by flash chromatography (9 × 1 cm, 3% EtOAc/hexanes) to give **38** [0.16 g, 98%, R_f = 0.5 (10% EtOAc/hexanes), colorless oil]. ^1H NMR ($CDCl_3$, 250 MHz): δ 4.11 (2H, q, *J* = 7.1 Hz), 3.64 (1H, dt, *J* = 10.0, 4.7 Hz, H-8), 2.18 (1H, dd, *J* = 10.5, 1.7 Hz, H-20), 2.14 (1H, d, *J* = 10.5 Hz, H-20), 1.24 (3H, t, *J* = 7.1 Hz), 0.85 (9H, s, *t*-BuSi), 0.02 (6H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 174.5 (C-21), 71.0 (C-8), 60.3 (CH_2, CO_2Et), 56.7 (C-14), 45.0 (C-13), 36.4 (CH_2), 36.1 (CH_2), 33.8 (CH_2), 29.1 (CH_2),

25.8 (CH_3, *t*-BuSi), 25.2 (CH_2), 22.3 (CH_2), 21.3 (CH_2), 19.8 (CH_2), 18.1 (C, *t*-BuSi), 14.2 (CH_3, CO_2Et), −4.2, −4.7 (Me_2-Si). MS [CI$^+$, *m*/*z*]: 355 (M^+ + H, 4), 354 (M^+, 5), 353 (M^+ − H, 19), 339 (M^+ − Me, 49), 309 (M^+ − OEt, 20), 297 (M^+ − *t*-Bu, 52), 223 (M^+ − OTBS, 100). HRMS (CI$^+$): calcd for $C_{20}H_{37}O_3Si$ 353.2512, found 353.2511.

20(17→18)-*abeo*-8α-[(*tert*-Butyldimethylsilyl)oxy]de-A,B-pregnan-21-al (39). A solution of diisobutylaluminum hydride in hexanes (0.40 mL, 1 M) was added dropwise over 40 min to a cooled solution of **38** (0.13 g, 0.37 mmol) in dry toluene (10 mL) at −80 °C. The reaction was quenched by rapid addition, via syringe, of cooled H_2O (0.5 mL, 0 °C) and aqueous NH_4Cl (20 mL, 10%). The aqueous fraction was extracted with Et_2O (4 × 10 mL). The combined organic fraction was washed with H_2O (20 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (9 × 1 cm, 5% EtOAc/hexanes) to give **39** [0.09 g, 81%, R_f = 0.5 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 9.81 (1H, t, J = 1.6 Hz, H-21), 3.64 (1H, dt, J = 10.1, 4.7 Hz, H-8), 2.34 (1H, d, J = 8.2 Hz, H-20), 2.31 (1H, dd, J = 8.2, 1.6 Hz, H-20), 0.86 (9H, s, *t*-BuSi), 0.03 (6H, s, Me2Si). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 202.9 (C-21), 71.0 (C-8), 56.6 (C-14), 45.0 (C-13), 39.0 (CH_2), 36.4 (CH_2), 36.2 (CH_2), 33.9 (CH_2), 25.8 (CH_3, *t*-BuSi), 25.2 (CH_2), 21.3 (CH_2), 19.8 (CH_2), 19.1 (CH_2), 18.1 (C, *t*-BuSi), −4.2, −4.7 (Me_2Si). MS [CI$^+$, *m*/*z*]: 311 (M^+ + H, 64), 310 (M^+, 5), 309 (M^+ − H, 18), 295 (M^+ − Me, 36), 253 (M^+ − *t*-Bu, 39), 179 (M^+ − OTBS, 74), 161 (100). HRMS (CI$^+$): calcd for $C_{18}H_{35}O_2Si$ 311.2406, found 311.2401.

(22*Z*)-20(17→18)-*abeo*-8α-[(*tert*-Butyldimethylsilyl)oxy]-24-carboxyde-A,B-22,23-dihomo-21-norchol-22-ene (40c). Following the same experimental procedure as for **40a**, the coupling of the aldehyde **39** (0.08 g, 0.26 mmol) with the ylide formed from Wittig salt **21a** (0.40 g, 0.90 mmol) and KO-*t*-Bu (0.30 g, 2.67 mmol) afforded, after purification by flash chromatography (12 × 2 cm, 35% EtOAc/hexanes), **40c** as a mixture of *Z*/*E* isomers [0.07 g, 71%, R_f = 0.2 (30% EtOAc/hexanos), white solid]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.48−5.27 (2H, m, H-22, H-22′), 3.64 (1H, dt, J = 10.5, 4.7 Hz, H-8), 2.37 (2H, t, J = 7.4 Hz), 0.87 (9H, s, *t*-BuSi), 0.03 (6H, s, Me_2-Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 131.8 (CH), 128,0 (CH), 71.3 (C-8), 56.8 (C-14), 44.5 (C-13), 36.5 (CH_2), 36.3 (CH_2), 34.0 (CH_2), 27.4 (CH_2), 26.3 (CH_2), 25.84 (CH_3, *t*-BuSi), 25.81 (CH_2), 25.4 (CH_2), 24.6 (CH_2), 21.6 (CH_2), 20.0 (C, *t*-BuSi), −4.2, −4.7 (Me_2Si). MS [CI$^+$, *m*/*z*]: 325 (M^+ + H, 23), 323 (M^+ − H, 4), 309 (M^+ − Me, 58), 291 (29), 279 (23), 267 (7). HRMS (CI$^+$): calcd for $C_{23}H_{41}O_3Si$ 393.2825, found 393.2827.

(22*Z*)-20(17→18)-*abeo*-8α-[(*tert*-Butyldimethylsilyl)oxy]-de-A,B-22,23-dihomo-21-norcholest-22-en-25-ol (41c). Following the same experimental procedure as for **41a**, the reaction of the carboxylic acid **40c** (0.05 g, 0.13 mmol) in two stages with MeLi in Et_2O (1 mL, 1.25 M) afforded, after purification by flash chromatography (10 × 0.5 cm, 6% EtOAc/hexanes), **41c** [0.04 g, 82%, *Z*/*E* isomers mixture, R_f = 0.6 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.40−5.29 (2H, m, H-22, H-22′), 3.63 (1H, dt, J = 9.6, 4.7 Hz, H-8), 1.20 (6H, s, H-26, H-27), 0.86 (9H, s, *t*-BuSi), 0.02 (6H, s, Me_2Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 130.8 (CH), 129,3 (CH), 71.2 (C-8), 70,9 (C-25), 56.8 (C-14), 45.5 (C-13), 43.5 (CH_2), 36.5 (CH_2), 36.4 (CH_2), 34.0 (CH_2), 29.2 (C-26, C-27), 27.5 (CH_2), 27.4 (CH_2), 25.8 (CH_3, *t*-BuSi), 25.4 (CH_2), 24.4 (CH_2), 21.6 (CH_2), 20.0 (CH_2), 18.1 (C, *t*-BuSi), −4.2, −4.7 (Me_2-Si). MS [CI$^-$, *m*/*z*]: 409 (M^+ + H, 10), 408 (M^+, 27), 407 (M^+ − H, 100), 406 (M^+ − 2H, 25), 349 (14), 393 (14). HRMS (CI$^-$): calcd for $C_{25}H_{47}O_2Si$ 407.3345, found 407.3347.

(22*Z*)-20(17→18)-*abeo*-De-A,B-8α,25-dihydroxy-22,23-dihomo-21-norcholest-22-ene (42c). Following the same experimental procedure as for **42a**, the deprotection of **41c** (0.030 g, 0.073 mmol) with aqueous HF (9 drops, 48%) afforded, after purification by flash chromatography (9 × 0.5 cm, 35% EtOAc/hexanes), **42c** [0.013 g, 60%, *Z*/*E* isomers mixture, R_f = 0.4 (50% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.43−5.27 (2H, m, H-22, H-22′), 3.75−3.60 (1H, m, H-8), 1.20 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 130.6 (CH), 129,4 (CH), 71.0 (C-25), 70,8 (C-8), 56.9 (C-14), 45.8 (C-13), 43.5 (CH_2), 36.2 (CH_2), 35.9 (CH_2), 34.0 (CH_2), 29.7 (CH_2), 29.2 (C-26, C-27), 27.5 (CH_2), 24.4 (CH_2), 21.5 (CH_2), 20.3 (CH_2). MS [FAB$^+$, *m*/*z*]: 295 (M^+ + H, 2), 294 (M^+, 2), 293 (M^+ − H, 7), 137 (100), 121 (13).

20(17→18)-*abeo*-De-A,B-8α,25-dihydroxy-22,23-dihomo-21-norcholestane (43c). Following the same experimental procedure as for **43a**, the catalytic hydrogenation of **42c** (0.010 g, 0.034 mmol) with Pd on carbon (0.01 g, 5% Pd) afforded, after purification by flash chromatography (6 × 0.4 cm, 35% EtOAc/hexanes), **43c** [0.010 g, 98%, R_f = 0.4 (50% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.68 (1H, dt, J = 10.5, 4.7 Hz, H-8), 1.20 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 71.0 (C-8), 70.9 (C-25), 57.0 (C-14), 45.8 (C-13), 44.0 (CH_2), 36.3 (CH_2), 36.0 (CH_2), 34.1(CH_2), 30.7 (CH_2), 30.2 (CH_2), 29.7 (CH_2), 29.2 (C-26, C-27), 27.1 (CH_2), 24.5 (CH_2), 24.3 (CH_2), 23.6 (CH_2), 21.6 (CH_2), 20.3 (CH_2). MS [CI$^-$, *m*/*z*]: 296 (M^+, 5), 295 (M^+ − H, 18), 278 (M^+ − H_2O, 2). HRMS (CI$^-$): calcd for $C_{19}H_{35}O_2$ 295.2637, found 295.2627.

20(17→18)*abeo*-De-A,B-25-hydroxy-22,23-dihomo-21-norcholestan-8-one (3c). Following the same experimental procedure as for **3a**, the oxidation of **43c** (0.009 g, 0.030 mmol) with PDC (0.040 g, 0.106 mmol) afforded, after purification by flash chromatography (6 × 0.4 cm, 20% EtOAc/hexanes), **3c** [0.008 g, 90%, R_f = 0.3 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 212.5 (C-8), 71.0 (C-25), 61.6 (C-14), 50.8 (C-13), 44.0 (CH_2), 41.0 (CH_2), 36.2 (CH_2), 34.0 (CH_2), 30.3 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 29.2 (C-26, C-27), 27.7 (CH_2), 24.3 (CH_2), 23.7 (CH_2), 23.4 (CH_2), 20.3 (CH_2), 20.1 (CH_2). MS [FAB$^+$, *m*/*z*]: 317 (M^+ + Na, 2), 295 (M^+ + H, 3), 294 (M^+, 1), 279 (M^+ − Me, 6), 278 (M^+ − O, 19), 277 (M^+ − OH, 19), 137 (100). HRMS (FAB$^+$): calcd for $C_{19}H_{35}O_2$ 295.2637, found 295.2633.

20(17→18)-*abeo*-3-(*tert*-Butyldimethylsilyl)-1α-[(*tert*-butyldimethylsilyl)oxy]-25-hydroxy-22,23-dihomo-21-nor-vitamin D_3 (44c). Following the same experimental procedure as for **44a**, the coupling of **3c** (0.004 g, 0.014 mmol) with the phosphine oxide anion formed by reaction of **4** (0.055 g, 0.094 mmol) with *n*-HexLi in hexanes (0.04 mL, 2.24 M) afforded, after purification by flash chromatography (6 × 0.4 cm, 12% Et_2O/hexanes), the protected analogue **44c** [0.009 g, 96%, R_f = 0.6 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 6.27, 6.04 (2H, AB, J = 11.3 Hz, H-6, H-7), 5.19 (1H, dd, J = 2.5, 0.8 Hz, H-19E), 4.85 (1H, d, J = 2.5 Hz, H-19Z), 4.38 (1H, dd, J = 6.4, 3.6 Hz, H-1), 4.20 (1H, tt, J = 7.5, 3.75 Hz, H-3), 2.88 (1H, dd, J = 12.6, 3.5 Hz, H-9β), 2.46 (1H, dd, J = 13.0, 3.8 Hz, H-4), 2.20 (1H, dd, J = 13.0, 7.5 Hz, H-4), 1.16 (6H, s, H-26, H-27), 0.88 (18H, s, *t*-BuSi), 0.06 (12H, s, $SiMe_2$). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 148.5 (C), 141.2 (C), 135.0(C), 123.2 (CH), 118.0 (CH), 111.2 (C-19), 72.2 (C-1), 70.7 (C-25), 67.6 (C-3), 56.0 (C-14), 46.4 (C-13), 46.1 (CH_2), 44.9 (CH_2), 44.1 (CH_2), 36.4 (CH_2), 35.3 (CH_2), 30.8 (CH_2), 30.4 (CH_2), 29.9 (CH_2), 29.1 (C-26, C-27), 28.8 (CH_2), 27.2 (CH_2), 25.71, 25.69 (*t*-BuSi), 24.4 (CH_2), 23.6 (CH_2), 23.3 (CH_2), 23.2 (CH_2), 20.2 (CH_2), 18.2, 18.1 (C, *t*-BuSi), −4.8, −4.9, −5.0, −5.3 ($SiMe_2$). MS [FAB$^+$, *m*/*z*]: 659 (M^+ + H, 3), 657 (M^+ − H, 5), 656 (M^+ − 2H, 2), 643 (M^+ − Me, 3), 641 (M^+ − OH, 2), 601 (M^+ − *t*-Bu, 2), 542 (3), 527 (M^+ − OTBS, 3), 526 (M^+ − HOTBS, 3), 525 (6), 428 (M^+ − 2TBS, 2), 396 (M^+ − 2OTBS, 4), 395 (8), 367 (6), 291 (4), 147 (100). HRMS (FAB$^+$): calcd for $C_{40}H_{74}O_3Si_2$ 658.5176, found 658.5187.

20(17→18)-*abeo*-1α,25-Dihydroxy-22,23-dihomo-21-nor-vitamin D_3 (2c). Following the same experimental procedure as for **2a**, **44c** (0.005 g, 0.008 mmol) was deprotected with TBAF in THF (0.1 mL, 1 M) to afford, after purification by flash chromatography (6 × 0.4 cm, 12% *i*-PrOH/hexanes), the analogue **2c** [0.003 g, 80%, R_f = 0.2 (90% EtOAc/hexanes), white solid]. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 6.35, 6.00 (2H, AB, J = 11.1 Hz, H-6, H-7), 5.31 (1H, bs, H-19E), 4.98 (1H,

bs, H-19Z), 4.38 (1H, m, H-1), 4.18 (1H, m, H-3), 1.18 (6H, s, H-26, H-27). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 147.6 (C), 142.8 (C), 132.9 (C), 124.8 (CH), 117.2 (CH), 111.8 (C-19), 71.1 (C-1), 70.7 (C-25), 66.6 (C-3), 55.9 (C-14), 46.4 (C-13), 45.1 (CH_2), 43.9 (CH_2), 42.7 (CH_2), 36.4 (CH_2), 35.2 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 29.1 (C-26), 29.1 (C-27), 28.9 (CH_2), 27.0 (CH_2), 24.2 (CH_2), 23.5 (CH_2), 23.2 (CH_2), 23.2 (CH_2), 20.1 (CH_2). MS [CI+, *m*/*z*]: 430 (M^+, 1), 429 ($M^+ - H$, 2), 415 ($M^+ - Me$, 1), 413 ($M^+ - OH$, 2), 412 ($M^+ - H_2O$, 2), 411(4), 291 (2), 290 (3), 136 (2), 135 (5), 121 (2). HRMS (CI^+): calcd for $C_{28}H_{45}O_3$ 429.3369, found 429.3380.

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Supporting Information Available: General methods and materials,[26,27] and spectral data (^{1}H and ^{13}C NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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