

Synthesis of Novel Analogues of 1 α ,25-Dihydroxyvitamin D₃ with Side Chains at C-18

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Novel analogues of the hormone 1 α ,25-(OH)₂-D₃ 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

1 α ,25-Dihydroxyvitamin D₃ [1 α ,25-(OH)₂-D₃, calcitriol, **1a**, Figure 1], which is the hormonally active form of vitamin D₃ (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 1 α ,25-(OH)₂-D₃ as an antitumor agent is severely limited by its potent calcemic effects.^{1,2} Attempts are therefore being made to develop an analogue of 1 α ,25-(OH)₂-D₃ 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 1 α ,25-(OH)₂-D₃ analogues

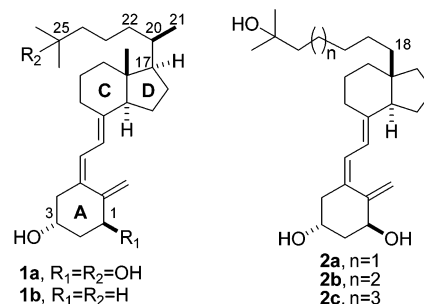


FIGURE 1. 1 α ,25-(OH)₂-D₃ and 20(17→18)-abeo-analogues.

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 1 α ,25-(OH)₂-D₃ 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 1 α ,25-(OH)₂-D₃ analogues to study their structure–activity relationships.⁸ One of our re-

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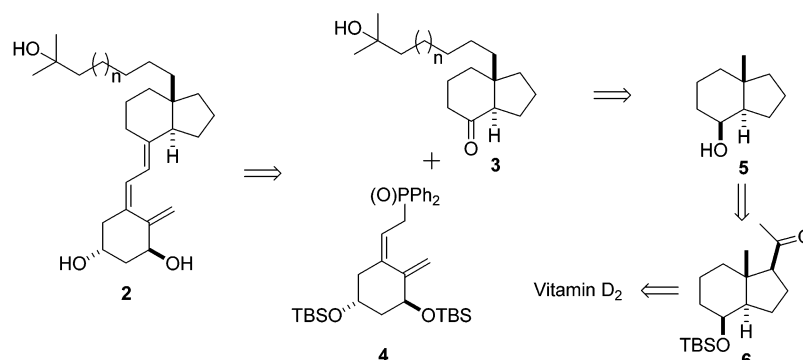
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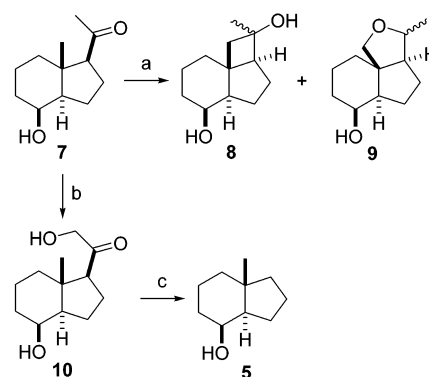
SCHEME 1. Retrosynthetic Analysis



search programs was directed to the synthesis of $1\alpha,25\text{-(OH)}_2\text{-D}_3$ 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 us⁹ and others¹⁰ 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 $1\alpha,25\text{-(OH)}_2\text{-D}_3$ analogues with side chains at C-18 and the use of one of these strategies for the preparation of three novel $1\alpha,25\text{-(OH)}_2\text{-D}_3$ 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 $1\alpha,25\text{-(OH)}_2\text{-D}_3$ 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-induced¹⁴ radical functionalization¹⁵ of the C-18-methyl group. We considered that degradation of commercially available vitamin D₂ 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, H₂O, CH₃CN; (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 D₂ 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 CH₂Cl₂ 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 CH₂Cl₂ 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 HSnBu₃–AIBN under conventional thermal or photochemical reaction conditions gave an intractable mixture of prod-

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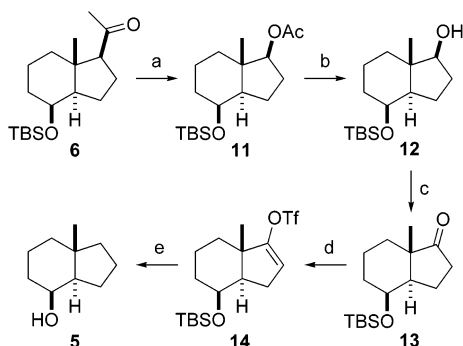
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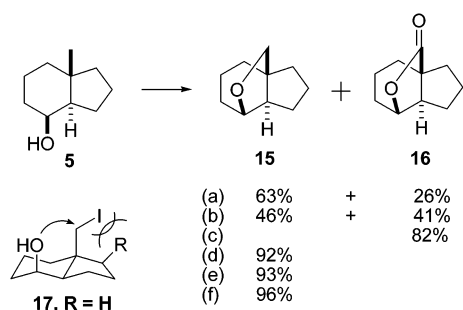
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SCHEME 3. Synthesis of Alcohol 5^a

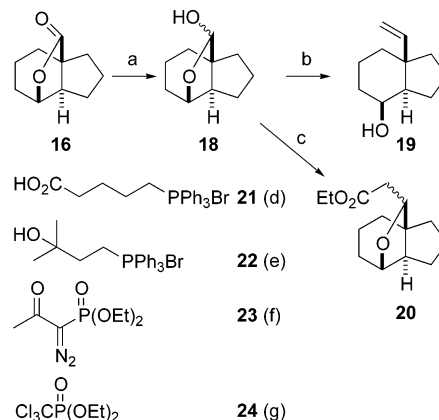
^a Key: (a) *m*-CPBA, cyclohexane, 95%; (b) K₂CO₃, MeOH, 99%; (c) PDC, CH₂Cl₂, 96%; (d) LDA, THF, -78 °C, then *N,N*-bis(trifluoromethanesulfonyl)-2-amino-5-chloropyridine, 93%; (e) (i) H₂, PtO₂, EtOH, (ii) HF, CH₃CN, 99%.

SCHEME 4. Irradiation of 5^a

^a Key: (a) (i) Pb(OAc)₄, I₂, CaCO₃, cyclohexane, *hν*, (ii) CrO₃, H₂SO₄, pyridine, acetone; (b) (i) Pb(OAc)₄, I₂, CaCO₃, cyclohexane, sonication, (ii) CrO₃, H₂SO₄, pyridine, acetone; (c) (i) Pb(OAc)₄, I₂, CaCO₃, cyclohexane, sonication, (ii) CrO₃, H₂SO₄, silica gel, THF, -10 °C; (iii) RuO₂·H₂O, NaIO₄, CCl₄, CH₃CN, buffer; (d) Pb(OAc)₄, benzene, *hν*; (e) DIB, I₂, cyclohexane, *hν*; (f) DIB, I₂, 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 PtO₂, 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 I₂ 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 Jones' reagent. Irradiation with light was advantageously replaced by sonication. Under these conditions, traces of

SCHEME 5. Reactivity of Lactol 18^a

^a Key: (a) DIBAL-H, toluene, -80 °C, 88%; (b) CH₃PPh₃Br, KO-*t*-Bu, THF, Δ , 86%; (c) (EtO)₂P(O)CH₂CO₂Et, NaOEt, EtOH, Δ , 30%; (d) **21**, KO-*t*-Bu, benzene, Δ , no reaction; (e) **22**, *n*-BuLi, Et₂O, Δ , no reaction; (f) **23**, K₂CO₃, MeOH, no reaction; (g) **24**, *n*-BuLi, THF, Et₂O, no reaction.

iodine **17** were also isolated (Scheme 4, b). Ether **15** can be converted to lactone **16** using catalytic RuO₂ and NaIO₄ (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 hypiodite reaction developed by Suárez et al.¹⁹ Thus, reaction of **5** with diacetoxiodobenzene (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 (Ph₃P=CH₂) reacted efficiently with lactol **18**, providing olefin **19** in 86% yield. The simple phosphonate carbanion (EtO)₂P(O)CHNaCO₂Et 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).

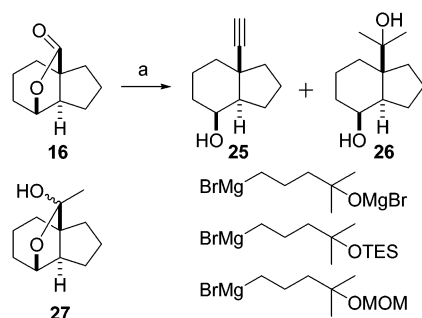
In view of the above results, we investigated a different approach to the introduction of the side chain. Logan et al.²¹ have reported that reaction of alkyl Grignard reagents with certain ester moieties adjacent to quaternary carbons can give rise to alkynes in moderate-to-good yields. Reaction of lactone **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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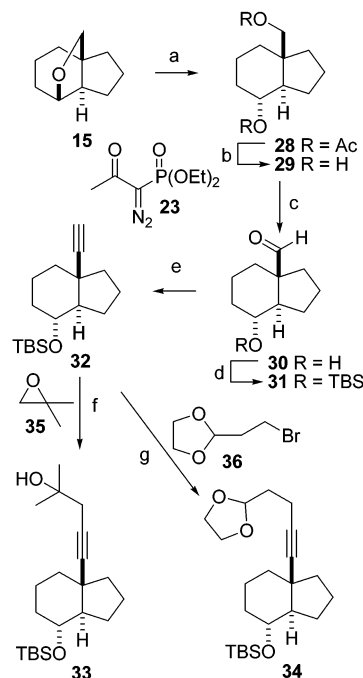
SCHEME 6. Synthesis of Alkyne **25**^a

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

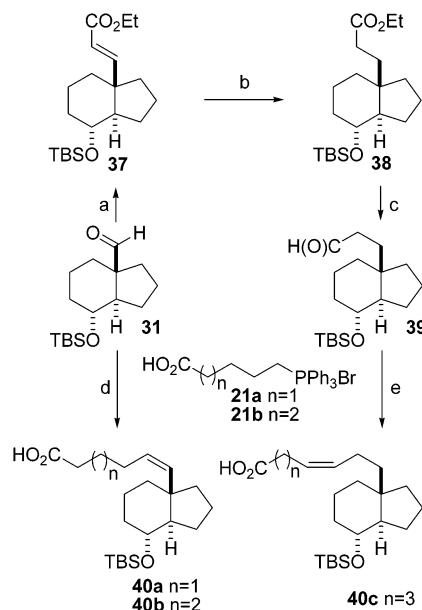
However, attempts to introduce alkynes with longer chains using Grignard reagents were unsuccessful. Unexpectedly, attempts of alkylation of **25** or its C-8-OTBS-protected derivative also failed.

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 $\text{BF}_3 \cdot \text{OEt}_2$ 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-oxidant²³ 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 $\text{S}_{\text{N}}2$ 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 $\text{BF}_3 \cdot \text{OEt}_2$ 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 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 $(\text{EtO})_2\text{P}(\text{O})\text{CH}=\text{CHCO}_2\text{Et}$ 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) $\text{BF}_3 \cdot \text{OEt}_2$, 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**, $\text{BF}_3 \cdot \text{OEt}_2$, -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

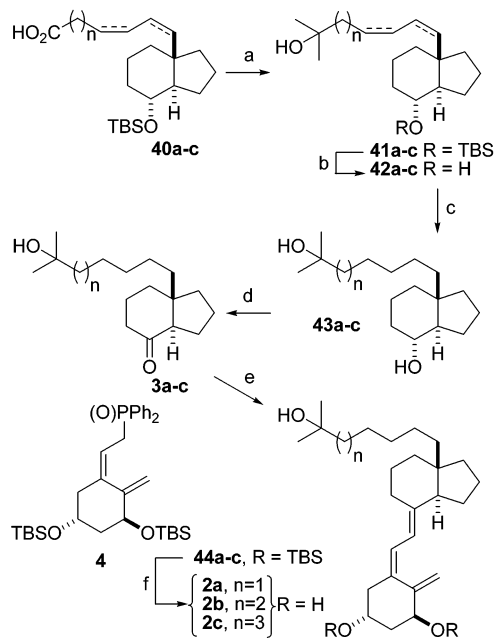
^a Key: (a) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, NaH, THF, 93%; (b) H_2 , Pd/C, EtOAc, 98%; (c) DIBAL–H, toluene, -80°C , 81%; (d) **21a** or **21b**, KO-*t*-Bu, benzene, **40a** (79%) or **40b** (76%); (e) **21a**, KO-*t*-Bu, benzene, **40c** (71%).

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, H₂O, CH₃CN, **42a** (69%) or **42b** (63%) or **42c** (60%); (c) H₂, Pd/C, EtOAc, **43a** (98%) or **43b** (96%) or **43c** (98%); (d) PDC, CH₂Cl₂, **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 1 α ,25-(OH)₂-D₃ 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*-Bu₄NF, THF), the desired 1 α ,25-(OH)₂-D₃ 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 1 α ,25-(OH)₂-D₃ 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 Na₂S₂O₃ (200 mL). The**

aqueous layer was extracted with hexanes (3 \times 150 mL). The combined organic fractions were dried, filtered, and concentrated. The residue was purified by flash chromatography (18 \times 5 cm, 1% EtOAc/hexanes) to give **11** [13 g, 95%, *R*_f = 0.7 (5% EtOAc/hexanes), white solid, mp 47–49 $^{\circ}\text{C}$]. ¹H NMR (CDCl₃, 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, Me₂Si), 0.003 (3H, s, Me₂Si). ¹³C NMR (CDCl₃, 62.89 MHz): δ 171.2 (CO), 82.7 (CH), 68.9 (CH), 47.6 (CH), 41.8 (C), 37.5 (CH₂), 34.2 (CH₂), 26.5 (CH₂), 25.6 (*t*-BuSi), 22.1 (CH₂), 21.0 (CH₃), 17.9 (C), 17.0 (CH₂), 13.6 (Me-18), -4.9 (Me₂Si), -5.3 (Me₂Si).

8 β -[(*tert*-Butyldimethylsilyl)oxy]de-A,B-androstan-17 β -ol (12**).¹⁶ K₂CO₃ (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 \times 5 cm, 5% EtOAc/hexanes) to give **12** [11.3 g, 99%, *R*_f = 0.3 (15% EtOAc/hexanes), white solid, mp 69–71 $^{\circ}\text{C}$]. ¹H NMR (CDCl₃, 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, Me₂Si), 0.04 (3H, s, Me₂Si). ¹³C NMR (CDCl₃, 62.89 MHz): δ 81.8 (CH), 69.1 (CH), 47.9 (CH), 42.0 (C), 37.3 (CH₂), 34.3 (CH₂), 29.5 (CH₂), 25.7 (*t*-BuSi), 22.1 (CH₂), 17.9 (C), 17.2 (CH₂), 12.5 (Me-18), -4.9 (Me₂Si), -5.3 (Me₂Si).**

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 CH₂Cl₂ (300 mL). After 16 h, Et₂O (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 \times 5 cm, 2% EtOAc/hexanes) to give **13** [10.5 g, 96%, *R*_f = 0.4 (15% EtOAc/hexanes), colorless oil]. ¹H NMR (CDCl₃, 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, Me₂Si). ¹³C NMR (CDCl₃, 62.89 MHz): δ 221.9 (C-17), 69.8 (CH), 48.6 (CH), 47.4 (C), 35.2 (CH₂), 34.2 (CH₂), 32.1 (CH₂), 25.7 (*t*-BuSi), 21.2 (CH₂), 17.9 (C), 16.9 (CH₂), 16.4 (Me-18), -4.9 (Me₂Si), -5.2 (Me₂Si).**

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 *t*-Pr₂NH (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 \times 4 cm) eluting with 3% Et₂O/hexanes. The residue obtained after concentration was purified by flash chromatography (15 \times 5 cm, 1% Et₂O/hexanes) to give **14** [19.2 g, 93%, *R*_f = 0.6 (hexanes), colorless oil]. ¹H NMR (CDCl₃, 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-15 α), 1.22 (3H, s, H-18), 0.89 (9H, s, *t*-BuSi), 0.04, 0.03 (3H, s, Me₂Si). ¹³C NMR (CDCl₃, 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 (CH₂), 33.3 (CH₂), 28.4 (CH₂), 25.7 (CH₃, *t*-BuSi), 18.3 (C-18), 18.0 (C, *t*-BuSi), 17.4 (CH₂), -4.9 (Me₂Si), -5.2 (Me₂Si). MS [C⁺, *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 (C⁺): calcd for C₁₇H₂₈O₄F₃Si 413.1430, found 413.1424.**

De-A,B-androstan-8 β -ol (5**).** PtO₂ (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 H₂ bubbling and then stirred for 16 h under H₂ atmosphere (balloon pressure). H₂ was removed by Ar bubbling. The mixture was filtered through silica gel and concentrated. The residue was dissolved in CH₃CN (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 NaHCO₃ (200 mL). CH₃CN was removed at the rotatory evaporator, and the aqueous layer was extracted with Et₂O (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]. ¹H NMR (CDCl₃, 250 MHz): δ 4.08 (1H, m, H-8), 0.92 (3H, s, Me-18). ¹³C NMR (CDCl₃, 63 MHz): δ 68.6 (C-8), 50.6 (C-14), 41.4 (CH₂), 39.7 (C-13), 39.2 (CH₂), 33.7 (CH₂), 23.4 (CH₂), 19.6 (C18), 19.3 (CH₂), 17.4 (CH₂). 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 C₁₀H₁₇O 153.1279, found 153.1287.

De-A,B-(8β)-8,18-epoxyandrostan-15 (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% Et₂O/hexanes) to give **15** [2.1 g, 92%, *R*_f = 0.4 (5% EtOAc/hexanes), volatile colorless oil]. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 63 MHz): δ 79.8 (C-8), 75.2 (C-18), 56.1 (C-14), 52.1 (C-13), 35.9 (CH₂), 32.6 (CH₂), 32.4 (CH₂), 27.0 (CH₂), 22.5 (CH₂), 19.0 (CH₂). 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 C₁₀H₁₆O 152.1201, found 152.1197.

De-A,B-(8β)-8,18-epoxyandrostan-15 (15) and De-A,B-8β-hydroxyandrostan-18-oi Acid Lactone (16) (by Irradiation of 5). A stirred suspension of CaCO₃ (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. I₂ (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 Et₂O and then washed successively with saturated aqueous Na₂S₂O₃ (200 mL) and H₂O (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 Et₂O (2 × 100 mL). The combined organic fraction was washed with saturated aqueous NaHCO₃ (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-epoxyandrostan-15 (15) and De-A,B-8β-hydroxyandrostan-18-oi Acid Lactone (16) (by Sonication of 5). A stirred suspension of CaCO₃ (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. I₂ (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 Et₂O and then washed successively with saturated aqueous Na₂S₂O₃ (50 mL) and H₂O (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 vacuum, and the aqueous layer was extracted with Et₂O (2 × 50 mL). The combined organic fraction was washed with saturated aqueous NaHCO₃ (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-oi Acid Lactone (16).

A stirred suspension of CaCO₃ (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. I₂ (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 Et₂O and then washed successively with saturated aqueous Na₂S₂O₃ (100 mL) and AgOAc (100 mL) and with H₂O (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 NaHCO₃ (250 mL) at 0 °C. The aqueous fraction was extracted with Et₂O (2 × 100 mL). The combined organic fraction was dried, filtered and concentrated. The residue was dissolved in a mixture of CH₃CN and CCl₄ (160 mL, 1:1). A pH 7 buffer solution (120 mL of H₂O, 1.037 g of KH₂PO₄, and 0.182 g of NaOH) was added. NaIO₄ (14.4 g, 67.3 mmol) and RuO₂·H₂O (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 Et₂O (3 × 100 mL). The combined organic fraction was washed successively with saturated aqueous Na₂S₂O₃ (100 mL) and H₂O (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]. ¹H NMR (CDCl₃, 250 MHz): δ 4.54 (1H, dm, *J* = 4.4 Hz, H-8). ¹³C NMR (CDCl₃, 63 MHz): δ 181.4 (C-18), 78.4 (C-8), 55.0 (C-13), 53.6 (C-14), 30.9 (CH₂), 30.8 (CH₂), 28.4 (CH₂), 26.8 (CH₂), 22.9 (CH₂), 18.2 (CH₂). MS [CI⁺, *m/z*]: 167 (M⁺ + H, 33), 166 (M⁺, 60), 150 (46), 138 (45), 121 (M⁺ - CO₂, 100). HRMS (CI⁺): calcd for C₁₀H₁₄O₂ 166.0994, found 166.0997.

De-A,B-(8β)-8,18-epoxyandrostan-15 (15) (by Irradiation of 5). (Diacetoxyiodo)benzene (8 g, 24.8 mmol) and I₂ (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 Na₂S₂O₃ (150 mL). The aqueous layer was extracted with Et₂O (100 mL). The combined organic fraction was washed with H₂O (100 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (15 × 2 cm, 6% Et₂O/hexanes) to give **15** [2.3 g, 93%, *R*_f = 0.4 (5% EtOAc/hexanes), volatile colorless oil].

De-A,B-(8β)-8,18-epoxyandrostan-15 (15) (by Sonication of 5). (Diacetoxyiodo)benzene (0.97 g, 3.0 mmol) and I₂ (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 Na₂S₂O₃ (100 mL). The aqueous layer was extracted with Et₂O (100 mL). The combined organic fraction was washed with H₂O (100 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (12 \times 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-8 α ,18-diacetoxyandrostane (28). BF₃·OEt₂ (22 mL, 174.8 mmol) was added dropwise (10 min) to a solution of **15** (2 g, 13.1 mmol) in Ac₂O (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 NaHCO₃ (250 mL) at 0 °C. NaHCO₃ was poured in small portions, over 6 h, on the vigorously stirred mixture until CO₂ release ceased. The aqueous fraction was extracted with EtOAc (5 \times 100 mL). The combined organic fraction was dried, filtered, and concentrated. The residue was purified by flash chromatography (16 \times 2 cm, 10% EtOAc/hexanes) to give **28** [2.1 g, 62%, R_f = 0.3 (20% EtOAc/hexanes), white solid]. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 63 MHz): δ 171.3, 170.6 (C, C(O)CH₃), 72.8 (C-8), 62.1 (C-18), 52.7 (C-14), 46.7 (C-13), 35.0 (CH₂), 32.5 (CH₂), 32.1 (CH₂), 25.0 (CH₂), 21.2 (CH₂), 21.0 (CH₃, C(O)CH₃), 20.9 (CH₃, C(O)CH₃), 19.7 (CH₂). 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 C₁₄H₂₃O₄ 255.1596, found 255.1588.

De-A,B-8 α ,18-dihydroxyandrostane (29). K₂CO₃ (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 \times 2 cm, 60% EtOAc/hexanes) to give **29** [1.29 g, 99%, R_f = 0.3 (60% EtOAc/hexanes), white solid]. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 63 MHz): δ 70.3 (C-8), 60.0 (C-18), 55.8 (C-14), 48.2 (C-13), 36.0 (CH₂), 34.4 (CH₂), 32.0 (CH₂), 24.9 (CH₂), 21.3 (CH₂), 20.1 (CH₂). MS [CI⁺, m/z]: 170 (M⁺, 1), 169 (M⁺ – H, 8), 153 (M⁺ – OH, 37), 152 (M⁺ – H₂O, 10), 136 (12), 135 (100), 133 (36), 121 (32). HRMS (CI⁺): calcd for C₁₀H₁₇O₂ 169.1229, found 169.1229.

De-A,B-8 α -hydroxyandrostane-18-ol (30). (Diacetoxy-iodo)benzene (0.50 g, 1.6 mmol) and 2,2,6,6-tetramethylpiperidinoxyl free radical (0.03 g, 0.2 mmol) were added to a solution of **29** (0.28 g, 1.6 mmol) in CH₂Cl₂/CH₃CN (16 mL, 1:1). The mixture, protected from direct light, was stirred for 5 h. The reaction was quenched with saturated aqueous Na₂S₂O₃ (50 mL). The aqueous fraction was extracted with CH₂Cl₂ (2 \times 50 mL). The combined organic fraction was dried, filtered, and concentrated. The residue was purified by flash chromatography (12 \times 1 cm, 35% EtOAc/hexanes) to give **30** [0.27 g, 97%, R_f = 0.5 (60% EtOAc/hexanes), colorless oil]. ¹H NMR (CDCl₃, 250 MHz): δ 9.52 (1H, d, J = 1.8, H-18), 3.97 (1H, dt, J = 10.5, 4.7 Hz, H-8). ¹³C NMR (CDCl₃, 63 MHz): δ 205.1 (C-18), 70.2 (C-8), 59.2 (C-13), 54.9 (C-14), 35.5 (CH₂), 33.7 (CH₂), 31.6 (CH₂), 25.1 (CH₂), 22.5 (CH₂), 20.6 (CH₂). MS [CI⁺, m/z]: 169 (M⁺ + H, 2), 168 (M⁺, 5), 167 (M⁺ – H, 54), 139 (31), 121 (100). HRMS (CI⁺): calcd for C₁₀H₁₅O₂ 167.1072, found 167.1065.

8 α -[(*tert*-Butyldimethylsilyloxy)]-de-A,B-androstan-18-ol (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 H₂O (200 mL). The aqueous fraction was extracted with an Et₂O/hexanes mixture (3 \times 60 mL, 10%). The combined organic fraction was washed with H₂O (3 \times 50 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (12 \times 2 cm, 7% EtOAc/hexanes) to give **31** [0.94 g, 98%, R_f = 0.7 (20% EtOAc/

hexanes), colorless oil]. ¹H NMR (CD₂Cl₂, 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, Me₂Si). ¹³C NMR (CD₂Cl₂, 63 MHz): δ 205.3 (C-18), 70.9 (C-8), 59.1 (C-13), 55.3 (C-14), 36.5 (CH₂), 34.0 (CH₂), 31.8 (CH₂), 26.1 (CH₂), 25.7 (CH₃, *t*-BuSi), 22.6 (CH₂), 20.5 (CH₂), 18.0 (C, *t*-BuSi), –4.5, –4.9 (Me₂Si). 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 C₁₆H₃₀O₂Si 282.2015, found 282.2004.

(18Z)-20(17–18)-abeo-8 α -[(*tert*-Butyldimethylsilyloxy)]-24-carboxyde-A,B-21-norchole-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 H₂O (50 mL) and acidified with HCl 5% until pH 3–4. The aqueous fraction was extracted with EtOAc (8 \times 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 \times 2 cm, 35% EtOAc/hexanes) to give **40a** [0.26 g, 79%, R_f = 0.2 (30% EtOAc/hexanes), white solid]. ¹H NMR (CDCl₃, 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, Me₂Si). ¹³C NMR (CDCl₃, 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 (CH₂), 37.2 (CH₂), 36.4 (CH₂), 33.5 (CH₂), 28.4 (CH₂), 25.9 (CH₃, *t*-BuSi), 25.7 (CH₂), 24.5 (CH₂), 22.6 (CH₂), 20.5 (CH₂), 18.1 (C, *t*-BuSi), –4.2, –4.6 (Me₂Si). 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 C₂₁H₃₉O₃Si 367.2669, found 367.2674.

(18Z)-20(17–18)-abeo-8 α -[(*tert*-Butyldimethylsilyloxy)]-de-A,B-21-norchole-18-en-25-ol (41a). MeLi in Et₂O (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 H₂O (10 mL) and acidified with HCl 5% until pH 3–4. The aqueous fraction was extracted with EtOAc (5 \times 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 Et₂O (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 H₂O (20 mL). The aqueous fraction was extracted with EtOAc (3 \times 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 \times 0.5 cm, 6% EtOAc/hexanes) to give **41a** [0.15 g, 82%, R_f = 0.6 (20% EtOAc/hexanes), colorless oil]. ¹H NMR (CDCl₃, 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, Me₂Si). ¹³C NMR (CDCl₃, 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 (CH₂), 39.5 (CH₂), 37.2 (CH₂), 36.5 (CH₂), 29.4 (CH₂), 29.2 (C-26, C-27), 25.8 (CH₃, *t*-BuSi), 25.7 (CH₂), 24.3 (CH₂), 22.6 (CH₂), 20.5 (CH₂), 18.1 (C, *t*-BuSi), –4.2, –4.6 (Me₂Si). 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 C₂₃H₄₃O₂Si 379.3032, found 379.3022.

(18Z)-20(17–18)-abeo-De-A,B-8 α ,25-dihydroxy-21-norchole-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 CH₃CN (10 mL). The reaction mixture was stirred for 3 h. The reaction was quenched with saturated aqueous NaHCO₃ (10 mL). The CH₃CN was removed in the rotatory evaporator. The aqueous fraction was extracted with EtOAc (5 \times 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]. ^1H 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 (CH₂), 39.3 (CH₂), 37.1 (CH₂), 35.8 (CH₂), 29.4 (CH₂), 29.1 (C-26, C-27), 24.7 (CH₂), 24.3 (CH₂), 22.5 (CH₂), 20.7 (CH₂). MS [CI^+ , m/z]: 267 ($\text{M}^+ + \text{H}$, 7), 266 (M^+ , 9), 265 ($\text{M}^+ - \text{H}$, 7).

20(17→18)-abeo-De-A,B-8 α ,25-dihydroxy-21-norcholestan-3-one (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]. ^1H 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 (CH₂), 36.2 (CH₂), 35.9 (CH₂), 34.0 (CH₂), 31.2 (CH₂), 29.1 (C-26, C-27), 27.1 (CH₂), 24.44 (CH₂), 24.36 (CH₂), 23.5 (CH₂), 21.5 (CH₂), 20.2 (CH₂). MS [CI^+ , m/z]: 269 ($\text{M}^+ + \text{H}$, 3), 268 (M^+ , 16), 267 ($\text{M}^+ - \text{H}$, 100), 251 ($\text{M}^+ - \text{OH}$, 12). HRMS (CI^+): calcd for $\text{C}_{17}\text{H}_{31}\text{O}_2$ 267.2324, found 267.2325.

20(17→18)-abeo-De-A,B-25-hydroxy-21-norcholestan-3-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]. ^1H 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 (CH₂), 41.0 (CH₂), 36.1 (CH₂), 33.9 (CH₂), 30.8 (CH₂), 29.1 (C-26, C-27), 27.6 (CH₂), 24.3 (CH₂), 23.6 (CH₂), 23.4 (CH₂), 20.2 (CH₂), 20.0 (CH₂). MS [FAB^+ , m/z]: 289 ($\text{M}^+ + \text{Na}$, 5), 267 ($\text{M}^+ + \text{H}$, 7), 266 (M^+ , 2), 265 ($\text{M}^+ - \text{H}$, 4), 249 ($\text{M}^+ - \text{OH}$, 100), 137 (46). HRMS (FAB^+): calcd for $\text{C}_{17}\text{H}_{30}\text{O}_2$ 266.2246, found 266.2243.

20(17→18)-abeo-3-(tert-Butyldimethylsilyl)-1 α -[(tert-butyldimethylsilyl)oxy]-25-hydroxy-21-norvitamin D₃ (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]. ^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, $J = 7.5, 3.75$ Hz, H-3), 2.87 (1H, dd, $J = 12.5, 3.6$ Hz, H-9 β), 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, SiMe₂). ^{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 (CH₂), 45.0 (CH₂), 44.1 (CH₂), 36.4 (CH₂), 35.4 (CH₂), 31.3 (CH₂), 29.1 (C-26, C-27), 28.8 (CH₂), 27.2 (CH₂), 25.8, 25.7 (*t*-BuSi), 24.6 (CH₂), 23.6 (CH₂), 23.3 (CH₂), 23.2 (CH₂), 20.2

(CH₂), 18.2, 18.1 (C, *t*-BuSi), $-4.8, -4.9, -5.0, -5.2$ (SiMe₂). MS [FAB^+ , m/z]: 631 ($\text{M}^+ + \text{H}$, 1), 630 (M^+ , 1), 629 ($\text{M}^+ - \text{H}$, 1), 615 ($\text{M}^+ - \text{Me}$, 1), 613 ($\text{M}^+ - \text{OH}$, 1), 573 ($\text{M}^+ - t\text{-Bu}$, 1), 515 ($\text{M}^+ - \text{TBS}$, 1), 499 ($\text{M}^+ - \text{OTBS}$, 1), 498 (1), 400 ($\text{M}^+ - 2\text{TBS}$, 3), 399 (3), 369 (4), 367 (2), 263 (4), 147 (100). HRMS (FAB^+): calcd for $\text{C}_{38}\text{H}_{70}\text{O}_3\text{Si}_2$ 630.4864, found 630.4875.

20(17→18)-abeo-1 α ,25-Dihydroxy-21-norvitamin D₃ (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]. ^1H 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 (CH₂), 44.5 (CH₂), 43.3 (CH₂), 37.6 (CH₂), 35.7 (CH₂), 31.7 (CH₂), 29.6 (C-26, C-27), 29.6 (CH₂), 27.8 (CH₂), 25.1 (CH₂), 24.0 (CH₂), 23.9 (CH₂), 20.6 (CH₂), 19.7 (CH₂). MS [CI^+ , m/z]: 403 ($\text{M}^+ + \text{H}$, 1), 402 (M^+ , 1), 401 ($\text{M}^+ - \text{H}$, 3), 385 ($\text{M}^+ - \text{OH}$, 3), 384 (3), 383 (7), 367 ($\text{M}^+ - \text{OH} - \text{H}_2\text{O}$, 5), 291 (6), 249 (8), 136 (3), 135 (30), 121 (26). HRMS (CI^+): calcd for $\text{C}_{26}\text{H}_{41}\text{O}_3$ 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%). ^1H 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 (CH₂), 29.0 (CH₂, $d, J = 16.2$ Hz), 23.5 (CH₂), 22.3 (CH₂), 21.5 (CH₂). MS [CI^+ , m/z]: 360 ($\text{M}^+ - \text{OH}$, 3), 359 ($\text{M}^+ - \text{H}_2\text{O}$, 11), 358 ($\text{M}^+ - \text{H}_3\text{O}^+$, 5), 262 (Ph_3P^+ , 54), 185 (Ph_2P^+ , 100), 81 (Br^+ , 81), 79 (Br^+ , 58).

(18Z)-20(17→18)-abeo-8 α -[(tert-Butyldimethylsilyl)oxy]-24-carboxyde-A,B-22-homo-21-norchole-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]. ^1H 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, Me₂Si). ^{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 (CH₂), 37.2 (CH₂), 36.5 (CH₂), 34.0 (CH₂), 29.0 (CH₂), 28.8 (CH₂), 25.9 (CH₃, *t*-BuSi), 25.7 (CH₂), 24.4 (CH₂), 22.6 (CH₂), 20.5 (CH₂), 18.0 (C, *t*-BuSi), $-4.2, -4.6$ (Me₂Si). MS [CI^+ , m/z]: 381 ($\text{M}^+ + \text{H}$, 32), 380 (M^+ , 7), 379 ($\text{M}^+ - \text{H}$, 15), 365 ($\text{M}^+ - \text{Me}$, 22), 363 ($\text{M}^+ - \text{OH}$, 21), 323 ($\text{M}^+ - t\text{-Bu}$, 81), 249 ($\text{M}^+ - \text{OTBS}$, 100). HRMS (CI^+): calcd for $\text{C}_{22}\text{H}_{41}\text{O}_3\text{Si}$ 381.2825, found 381.2826.

(18Z)-20(17→18)-abeo-8 α -[(tert-Butyldimethylsilyl)oxy]-de-A,B-22-homo-21-norchole-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]. ^1H 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, Me₂Si). ¹³C 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 (CH₂), 39.5 (CH₂), 37.3 (CH₂), 36.5 (CH₂), 30.1 (CH₂), 29.2 (C-26, C-27), 25.9 (CH₃, *t*-BuSi), 25.7 (CH₂), 24.1 (CH₂), 22.6 (CH₂), 20.5 (CH₂), 18.1 (C, *t*-BuSi), –4.2, –4.6 (Me₂Si). MS [CI⁺, *m/z*]: 395 (M⁺ + H, 4), 394 (M⁺, 8), 393 (M⁺ – H, 33), 337 (M⁺ – *t*-Bu, 4). HRMS (CI⁺): calcd for C₂₄H₄₅O₂Si 393.3189, found 393.3195.

(18Z)-20(17→18)-abeo-De-A,B-8 α ,25-dihydroxy-22-homo-21-norcholestan-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 \times 0.4 cm, 35% EtOAc/hexanes), **42b** [0.027 g, 63%, *R*_f = 0.4 (50% EtOAc/hexanes), colorless oil]. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 (CH₂), 39.3 (CH₂), 37.2 (CH₂), 35.9 (CH₂), 30.1 (CH₂), 29.2 (C-26, C-27), 24.7 (CH₂), 24.1 (CH₂), 22.6 (CH₂), 20.7 (CH₂). 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 C₁₈H₃₁O₂ 279.2324, found 279.2314.

20(17→18)-abeo-De-A,B-8 α ,25-dihydroxy-22-homo-21-norcholestan-8-one (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 \times 0.4 cm, 35% EtOAc/hexanes), **43b** [0.019 g, 96%, *R*_f = 0.4 (50% EtOAc/hexanes), colorless oil]. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 63 MHz): δ 71.0 (C-25), 70.8 (C-8), 57.0 (C-14), 45.8 (C-13), 44.0 (CH₂), 36.3 (CH₂), 36.0 (CH₂), 34.1 (CH₂), 30.7 (CH₂), 30.2 (CH₂), 29.2 (C-26, C-27), 27.1 (CH₂), 24.4 (CH₂), 24.3 (CH₂), 23.5 (CH₂), 21.5 (CH₂), 20.3 (CH₂). MS [CI⁺, *m/z*]: 283 (M⁺ + H, 12), 282 (M⁺, 18), 281 (M⁺ – H, 100). HRMS (CI⁺): calcd for C₁₈H₃₃O₂ 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 \times 0.4 cm, 20% EtOAc/hexanes), **3b** [0.013 g, 90%, *R*_f = 0.3 (20% EtOAc/hexanes), colorless oil]. ¹H NMR (CDCl₃, 250 MHz): δ 1.19 (6H, s, H-26, H-27). ¹³C NMR (CDCl₃, 63 MHz): δ 212.1 (C-8), 71.0 (C-25), 61.6 (C-14), 50.8 (C-13), 43.9 (CH₂), 41.0 (CH₂), 36.2 (CH₂), 33.9 (CH₂), 30.3 (CH₂), 30.1 (CH₂), 29.2 (C-26, C-27), 27.7 (CH₂), 24.3 (CH₂), 23.6 (CH₂), 23.4 (CH₂), 20.2 (CH₂), 20.1 (CH₂). 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⁺ – H₂O, 14), 263 (M⁺ – H₃O⁺, 69), 153 (94), 137 (100). HRMS (FAB⁺): calcd for C₁₈H₃₁O₂ 279.2324, found 279.2324.

20(17→18)-abeo-3-(*tert*-butyldimethylsilyl)-1 α -[(*tert*-butyldimethylsilyl)oxy]-25-hydroxy-22-homo-21-norvitamin D₃ (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 \times 0.4 cm, 12% Et₂O/hexanes), the protected analogue **44b** [0.019 g, 93%, *R*_f = 0.6 (20% EtOAc/hexanes), colorless oil]. ¹H NMR (CD₂Cl₂, 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-9 β), 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, SiMe₂). ¹³C NMR (CD₂Cl₂, 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 (CH₂), 44.9 (CH₂), 44.1 (CH₂), 36.4 (CH₂), 35.3 (CH₂), 30.8 (CH₂), 30.4 (CH₂), 29.1 (C-26, C-27), 28.8 (CH₂), 27.2 (CH₂), 25.74, 25.71 (*t*-BuSi), 24.4 (CH₂), 23.6 (CH₂), 23.3 (CH₂), 23.2 (CH₂), 20.2 (CH₂), 18.2, 18.1 (C, *t*-BuSi), –4.8, –4.9, –5.0, –5.2 (SiMe₂). 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 C₃₉H₇₂O₃Si₂ 644.5020, found 644.5030.

20(17→18)-abeo-1 α ,25-Dihydroxy-22-homo-21-norvitamin D₃ (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 \times 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 (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 (CH₂), 43.9 (CH₂), 42.8 (CH₂), 36.3 (CH₂), 35.2 (CH₂), 30.1 (CH₂), 30.1 (CH₂), 29.6 (CH₂), 29.1 (C-26), 29.1 (C-27), 27.1 (CH₂), 24.2 (CH₂), 23.5 (CH₂), 23.2 (CH₂), 23.2 (CH₂), 20.1 (CH₂). 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 C₂₇H₄₃O₃ 415.3212, found 415.3223.

Ethyl (18E)-20(17→18)-abeo-8 α -[(*tert*-Butyldimethylsilyl)oxy]de-A,B-pregn-18-en-21-ate (37). A solution of diethyl ethoxycarbonylmethylphosphonate (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 H₂O (20 mL). The aqueous fraction was extracted with EtOAc (3 \times 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 \times 1 cm, 3% EtOAc/hexanes) to give **37** [0.22 g, 93%, *R*_f = 0.5 (10% EtOAc/hexanes), colorless oil]. ¹H NMR (CDCl₃, 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, Me₂Si). ¹³C NMR (CDCl₃, 63 MHz): δ 167.0 (C-21), 152.4 (C-18), 120.3 (C-20), 71.7 (C-8), 60.2 (CH₂, CO₂Et), 56.8 (C-14), 49.5 (C-13), 39.7 (CH₂), 36.7 (CH₂), 36.0 (CH₂), 25.8 (CH₃, *t*-BuSi), 25.6 (CH₂), 22.0 (CH₂), 20.0 (CH₂), 18.1 (C, *t*-BuSi), 14.3 (CH₃, CO₂Et), –4.2, –4.7 (Me₂Si). 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 C₂₀H₃₅O₃Si 351.2355, found 351.2352.

Ethyl 20(17→18)-abeo-8 α -[(*tert*-Butyldimethylsilyl)oxy]de-A,B-pregn-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 H₂ bubbling and then stirred for 20 h under H₂ atmosphere (balloon pressure). H₂ was removed by Ar bubbling. The mixture was filtered through silica gel and concentrated. The residue was purified by flash chromatography (9 \times 1 cm, 3% EtOAc/hexanes) to give **38** [0.16 g, 98%, *R*_f = 0.5 (10% EtOAc/hexanes), colorless oil]. ¹H NMR (CDCl₃, 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, Me₂Si). ¹³C NMR (CDCl₃, 63 MHz): δ 174.5 (C-21), 71.0 (C-8), 60.3 (CH₂, CO₂Et), 56.7 (C-14), 45.0 (C-13), 36.4 (CH₂), 36.1 (CH₂), 33.8 (CH₂), 29.1 (CH₂),

25.8 (CH₃, *t*-BuSi), 25.2 (CH₂), 22.3 (CH₂), 21.3 (CH₂), 19.8 (CH₂), 18.1 (C, *t*-BuSi), 14.2 (CH₃, CO₂Et), -4.2, -4.7 (Me₂-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 C₂₀H₃₇O₃Si 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 H₂O (0.5 mL, 0 °C) and aqueous NH₄Cl (20 mL, 10%). The aqueous fraction was extracted with Et₂O (4 × 10 mL). The combined organic fraction was washed with H₂O (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]. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 63 MHz): δ 202.9 (C-21), 71.0 (C-8), 56.6 (C-14), 45.0 (C-13), 39.0 (CH₂), 36.4 (CH₂), 36.2 (CH₂), 33.9 (CH₂), 25.8 (CH₃, *t*-BuSi), 25.2 (CH₂), 21.3 (CH₂), 19.8 (CH₂), 19.1 (CH₂), 18.1 (C, *t*-BuSi), -4.2, -4.7 (Me₂Si). 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 C₁₈H₃₅O₂Si 311.2406, found 311.2401.

(22Z)-20(17→18)-abeo-8α-[(*tert*-Butyldimethylsilyl)oxy]-24-carboxyde-A,B-22,23-dihomo-21-norchole-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/hexanes), white solid]. ¹H NMR (CDCl₃, 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, Me₂-Si). ¹³C NMR (CDCl₃, 75.5 MHz): δ 131.8 (CH), 128.0 (CH), 71.3 (C-8), 56.8 (C-14), 44.5 (C-13), 36.5 (CH₂), 36.3 (CH₂), 34.0 (CH₂), 27.4 (CH₂), 26.3 (CH₂), 25.84 (CH₃, *t*-BuSi), 25.81 (CH₂), 25.4 (CH₂), 24.6 (CH₂), 21.6 (CH₂), 20.0 (C, *t*-BuSi), -4.2, -4.7 (Me₂Si). 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 C₂₃H₄₁O₃Si 393.2825, found 393.2827.

(22Z)-20(17→18)-abeo-8α-[(*tert*-Butyldimethylsilyl)oxy]de-A,B-22,23-dihomo-21-norchole-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 Et₂O (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]. ¹H NMR (CDCl₃, 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, Me₂Si). ¹³C NMR (CDCl₃, 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 (CH₂), 36.5 (CH₂), 36.4 (CH₂), 34.0 (CH₂), 29.2 (C-26, C-27), 27.5 (CH₂), 27.4 (CH₂), 25.8 (CH₃, *t*-BuSi), 25.4 (CH₂), 24.4 (CH₂), 21.6 (CH₂), 20.0 (CH₂), 18.1 (C, *t*-BuSi), -4.2, -4.7 (Me₂-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 C₂₅H₄₇O₂Si 407.3345, found 407.3347.

(22Z)-20(17→18)-abeo-De-A,B-8α,25-dihydroxy-22,23-dihomo-21-norchole-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]. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 (CH₂), 36.2 (CH₂), 35.9 (CH₂), 34.0 (CH₂), 29.7 (CH₂), 29.2 (C-26, C-27), 27.5 (CH₂), 24.4 (CH₂), 21.5 (CH₂), 20.3 (CH₂). 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-norchole-22-ene (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]. ¹H NMR (CDCl₃, 300 MHz): δ 3.68 (1H, dt, *J* = 10.5, 4.7 Hz, H-8), 1.20 (6H, s, H-26, H-27). ¹³C NMR (CDCl₃, 75.5 MHz): δ 71.0 (C-8), 70.9 (C-25), 57.0 (C-14), 45.8 (C-13), 44.0 (CH₂), 36.3 (CH₂), 36.0 (CH₂), 34.1 (CH₂), 30.7 (CH₂), 30.2 (CH₂), 29.7 (CH₂), 29.2 (C-26, C-27), 27.1 (CH₂), 24.5 (CH₂), 24.3 (CH₂), 23.6 (CH₂), 21.6 (CH₂), 20.3 (CH₂). MS [CI⁺, *m/z*]: 296 (M⁺, 5), 295 (M⁺ - H, 18), 278 (M⁺ - H₂O, 2). HRMS (CI⁺): calcd for C₁₉H₃₅O₂ 295.2637, found 295.2627.

20(17→18)-abeo-De-A,B-25-hydroxy-22,23-dihomo-21-norchole-22-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]. ¹H NMR (CDCl₃, 300 MHz): δ 1.20 (6H, s, H-26, H-27). ¹³C NMR (CDCl₃, 75.5 MHz): δ 212.5 (C-8), 71.0 (C-25), 61.6 (C-14), 50.8 (C-13), 44.0 (CH₂), 41.0 (CH₂), 36.2 (CH₂), 34.0 (CH₂), 30.3 (CH₂), 30.1 (CH₂), 29.6 (CH₂), 29.2 (C-26, C-27), 27.7 (CH₂), 24.3 (CH₂), 23.7 (CH₂), 23.4 (CH₂), 20.3 (CH₂), 20.1 (CH₂). 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 C₁₉H₃₅O₂ 295.2637, found 295.2633.

20(17→18)-abeo-3-(*tert*-Butyldimethylsilyl)-1α-[(*tert*-butyldimethylsilyl)oxy]-25-hydroxy-22,23-dihomo-21-norvitamin D₃ (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% Et₂O/hexanes), the protected analogue **44c** [0.009 g, 96%, *R*_f = 0.6 (20% EtOAc/hexanes), colorless oil]. ¹H NMR (CD₂Cl₂, 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, SiMe₂). ¹³C NMR (CD₂Cl₂, 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 (CH₂), 44.9 (CH₂), 44.1 (CH₂), 36.4 (CH₂), 35.3 (CH₂), 30.8 (CH₂), 30.4 (CH₂), 29.9 (CH₂), 29.1 (C-26, C-27), 28.8 (CH₂), 27.2 (CH₂), 25.71, 25.69 (*t*-BuSi), 24.4 (CH₂), 23.6 (CH₂), 23.3 (CH₂), 23.2 (CH₂), 20.2 (CH₂), 18.2, 18.1 (C, *t*-BuSi), -4.8, -4.9, -5.0, -5.3 (SiMe₂). 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 C₄₀H₇₄O₃Si₂ 658.5176, found 658.5187.

20(17→18)-abeo-1α,25-Dihydroxy-22,23-dihomo-21-norvitamin D₃ (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]. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 (CH₂), 43.9 (CH₂), 42.7 (CH₂), 36.4 (CH₂), 35.2 (CH₂), 30.6 (CH₂), 30.1 (CH₂), 29.6 (CH₂), 29.1 (C-26), 29.1 (C-27), 28.9 (CH₂), 27.0 (CH₂), 24.2 (CH₂), 23.5 (CH₂), 23.2 (CH₂), 23.2 (CH₂), 20.1 (CH₂). MS [CI⁺, *m/z*]: 430 (M⁺, 1), 429 (M⁺ - H, 2), 415 (M⁺ - Me, 1), 413 (M⁺ - OH, 2), 412 (M⁺ - H₂O, 2), 411(4), 291 (2), 290 (3), 136 (2), 135 (5), 121 (2). HRMS (CI⁺): calcd for C₂₈H₄₅O₃ 429.3369, found 429.3380.

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

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