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Copper-Mediated Alkylation of Vitamin D C-Ring. Synthesis of C11-Functionalized 1α,25-Dihydroxyvitamin D_3.[1]

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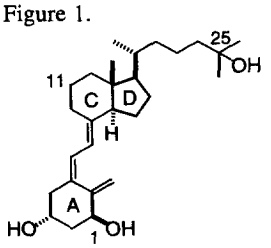
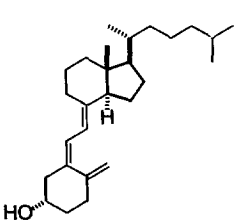
Abstract: This work describes our studies on the functionalization at C11 of CD-ring fragments of vitamin D_3 using organocopper reagents. As an application, an efficient, convergent synthesis of 11α-[3,3-(dimethoxy)propyl] calcitriol analogue **2**, which may be useful for the construction of affinity columns for the purification of 1α,25-$(OH)_2$-vitamin D_3 receptors, is described. © 1997 Elsevier Science Ltd.

In addition to its classical role in calcium homeostasis,[2] 1α,25-dihydroxyvitamin D_3 (**1a**, calcitriol, 1α,25-$(OH)_2$-D_3)-the hormonally active form of vitamin D_3 (**1b**, calciferol)-is also a potent inhibitor of cell-proliferation and can induce differentiation of a variety of malignant cells.[3] Unfortunately, the hormone **1a** has limited utility in the treatment of cancers and skin disorders owning to its hypercalcemic effect. Accordingly, there is much interest in the further design and synthesis of analogues of **1a** that might induce different or more selective biological responses.[4]

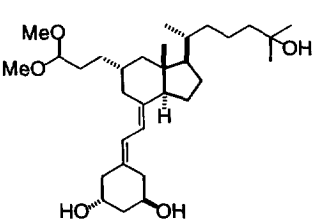
Figure 1.



1a



1b

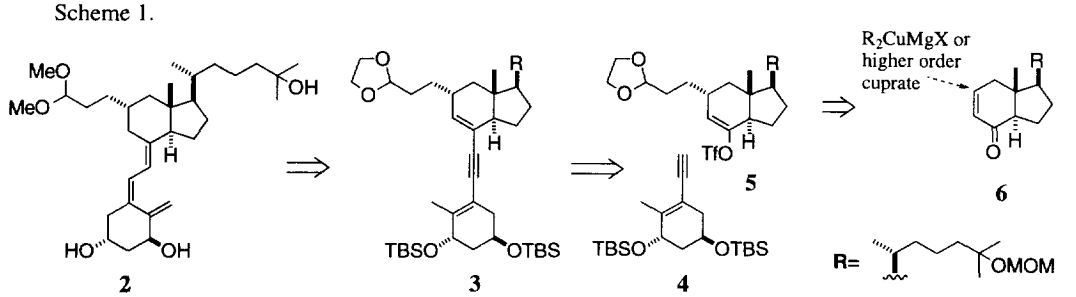


2

Many of the biological effects of 1α,25-$(OH)_2$-D_3 are mediated by its nuclear receptor (nVDR)[5] that belongs to the same superfamily of transactivating regulators of gene transcription that includes the receptors for other steroidal hormones and for retinoic acids.[6] There is evidence that nVDR forms either homodimers with itself or heterodimers with some other steroid receptors[7] and it has been suggested that binding of a particular ligand to a given steroid receptor induces distinct conformational changes that may be central to the ligand-receptor activation.[8] But little is known about the interaction of the vitamin D_3 hormone with its intracellular receptor, or about the structure of the binding site, which information is essential for rational design of 1α,25-$(OH)_2$-D_3 analogues.[9] In order to study these interactions and the topology of the receptor further, ligands are required for use in affinity columns for the isolation and purification of these receptors.[10]

In this work, we examined a synthetic route to C-ring modified analogues of 1α,25-$(OH)_2$-D_3 that might be useful for the construction of such affinity columns for the receptor of 1α,25-$(OH)_2$-D_3, or for the preparation of photoaffinity labels for studying the receptor. Our first target analogue of **1a** was acetal **2**, in which the latent aldehyde group is suitably remote from the three hydroxyl groups to fulfil the desired ends. When we started this work, very few synthesis of C-ring modified analogues bearing a 1α- and/or a 25-OH group had been reported.[11] In the course of our studies, however, Vandewalle and coworkers[12] reported the biological evaluation of several C11-alkylated analogues of **1a** that were synthesized using the Lythgoe-Roche phosphine oxide approach[13] for the assembly of the triene system.

Scheme 1.



For the synthesis of the desired analogue **2**, we chose the convergent dienyne route,[14] as shown in our retrosynthetic analysis in Scheme 1. It was envisaged that the required C11-substituted enol triflate **5** could be prepared by conjugate addition of organocopper reagents to enone **6**, which should take place preferentially from the less hindered side of the molecule, thus leading to α-substituents at C11.

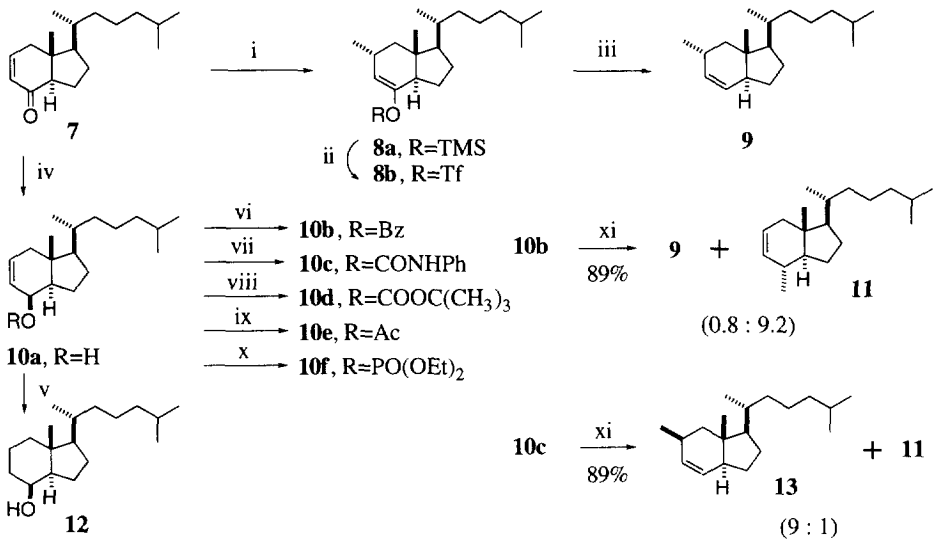
RESULTS AND DISCUSSION

Before starting the synthesis of the 25-hydroxylated enone **6**, we examined the stereoselectivity of the conjugate addition using model $\Delta^{9,11}$-C,D-ring-enone **7**[15] (Scheme 2).

Reaction of **7** with Me_2CuLi in THF, in the presence of chlorotrimethylsilane (to activate the conjugate addition[16] and as enolate trap), followed by metallation of the crude silyl enol ether **8a** with methyllithium and

treatment of the resulting enolate with *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$), gave enol triflate **8b** in 80% yield as the only reaction product. Much the same result was obtained when the organocopper reagent was derived from methylmagnesium bromide and catalytic copper (I) bromide - dimethylsulfide complex.

Scheme 2.



Reagents (i) Me_2CuLi, TMSCl, THF, -78 °C, 97%; (ii) MeLi, THF, 0 °C; $PhNTf_2$, -78 °C, 82%; (iii) $(Ph_3P)_2Pd(OAc)_2$ (10 mol%), HCO_2H, Et_3N, DMF, 65 °C, 74%; (iv) Dibal-H, THF, -78 °C, 87%; (v) H_2, Pd/C, EtOAc, EtOH, 26%; (vi) BzCl, DMAP, py, 5 °C, 96%; (vii) PhNCO, DMAP, py, 5 °C, 95%; (viii) $(CH_3)_3CCOCl$, DMAP, py, 90%; (ix) Ac_2O, py, 94%; (x) n-BuLi, Et_2O, $(EtO)_2POCl$, 86%; (xi) Me_2CuLi, Et_2O, 0 °C to rt.

To confirm the stereochemistry of the methyl group introduced at C11, we decided to reduce triflate **8b** to **9** and compare this compound with an authentic sample prepared by *anti*-S_N2' methylation of **10b**, and also with its diasteroisomer **13**, which was prepared by *syn*-S_N2' methylation of **10c**. Attempts to reduce **8b** with Bu_3SnH or Et_3SiH in the presence of $(Ph_3P)_4Pd$ and LiCl in THF[18] gave complex mixtures. However, reduction under Cacchi's conditions [HCO_2H, catalytic $(Ph_3P)_2Pd(OAc)_2$, Et_3N, DMF][17] gave compound **9** in 74% yield. The unsaturated alcohol **10a** was obtained in 87% yield by stereoselective reduction of the starting ketone **7** with diisobutylaluminum hydride (Dibal-H). The stereochemistry of **10a** was confirmed by hydrogenation to Grundmann's alcohol **12**.[19] Benzoylation of **10a** followed by treatment of the resulting benzoate **10b** with Me_2CuLi under Goering conditions[20] gave a mixture of the S_N2 and *anti*-S_N2' products in 89% combined yield. Structure **9** (*anti*-S_N2') was assigned to the minor compound on the basis of ^1H and ^{13}C NMR spectral analyses. *Syn*-S_N2' displacement[21] of the carbamate ester **10c** gave compound **13**[22] and a small amount of the S_N2 compound **11** in 89% combined yield.

The unexpectedly strong tendency of the semi-rigid system **10b**[23] to undergo S_N2 alkylation, led us to undertake a more detailed study of this reaction. Firstly we prepared pivaloate, acetate and phosphate derivatives **10d**, **10e** and **10f** (Scheme 2) in order to examine the influence of the leaving group. Reaction of these compounds with Me_2CuLi under the conditions described for benzoate **10b** gave similar results (Table 1, entries 1-3). Next, we examined the possibility of reversing the regioselectivity of the cuprate-mediated alkylation by the use of CuCN, as has been reported by Goering and co-workers.[23a,24] Pivaloate **10d** and acetate **10a** did not react with Me(CN)CuLi in Et_2O at 0 °C, and although in the reaction of phosphate **10f** with this cyanocuprate the **9/11** ratio was increased, **11** was still the major product (entry 6). Reaction of pivaloate **10d** with MeMgBr in the presence of a catalytic amount of CuCN (Et_2O, 0 °C) gave a 8:2 ratio of **9** and **11** in low yield, due to the competitive carbonyl attack (entry 7). High S_N2' regioselectivity was achieved by alkylating phosphate **10f** with MeMgBr in the presence of a catalytic amount of CuCN (Et_2O, 0 °C), which gave a 96:4 mixture of **9** and **11** in 98% combined yield (entry 8).

Table 1.

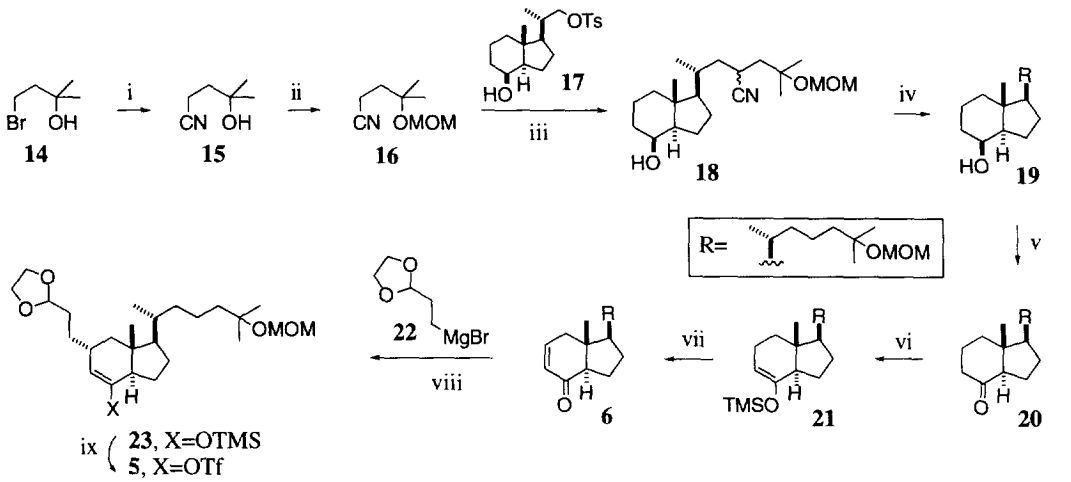
Entry	Substrate	Reagent	Yield	Ratio **9**:**11**
1	**10d**, R=$COC(CH_3)_3$	Me_2CuLi	98	0.8 : 9.2
2	**10e**, R=Ac	Me_2CuLi	77	0.9 : 9.1
3	**10f**, R=$PO(OEt)_2$	Me_2CuLi	96	0.9 : 9.1
4	**10d**, R=$COC(CH_3)_3$	Me(CN)CuLi	0	-
5	**10e**, R=Ac	Me(CN)CuLi	0	-
6	**10f**, R=$PO(OEt)_2$	Me(CN)CuLi	95	2.1 : 7.9
7	**10d**, R=$COC(CH_3)_3$	MeMgBr, CuCN	23	8 : 2
8	**10f**, R=$PO(OEt)_2$	MeMgBr, CuCN	98	9.6 : 0.4

After these preliminary studies, we turned our attention to the synthesis of the 25-hydroxylated enone **6**. For the construction of the 25-hydroxylated side-chain (present in most important vitamin D_3 metabolites)[25] we developed a new method based on coupling of the α-lithiated anion of nitrile **16** (Scheme 3) with the known tosylate **17**.[26] Nitrile **16** was prepared from bromoalcohol **14**.[27] Reaction of **14** with sodium cyanide gave nitrile **15** (76%), which was protected with chloromethyl methyl ether to give **16** (65%). Treatment of nitrile **16** with lithium diisopropylamide (LDA) followed by reaction of the resulting α-anion with tosylate **17** afforded a mixture of diastereomeric nitriles **18** (85%). Treatment of a solution of **18** in Et_2O-HMPA with potassium metal in portions using *tert*-butanol as proton source[28] to remove the cyano moiety, gave the desired alcohol **19** (90%). This procedure was easily carried out on up to a 10 g scale, and proved to be a general and efficient method applicable to the synthesis of various vitamin D side chains.[29]

Preparation of enone **6** continued with oxidation of **19** with pyridinium dichromate in the presence of a catalytic amount of pyridinium *p*-toluensulfonate (PPTS), which gave ketone **20** in excellent yield. The desired α,β-unsaturated ketone **6** was prepared from **20** by Saegusa's method,[30] which proved to be more efficient than the alternative two-step selenoxide-elimination procedure. Thus, addition of **20** to a solution of LDA in THF

gave the kinetic enolate, which was trapped with chlorotrimethylsilane. After work-up, the crude silyl enol ether **21** was immediately treated with palladium (II) acetate in acetonitrile to afford the desired enone **6** (94%).

Scheme 3.



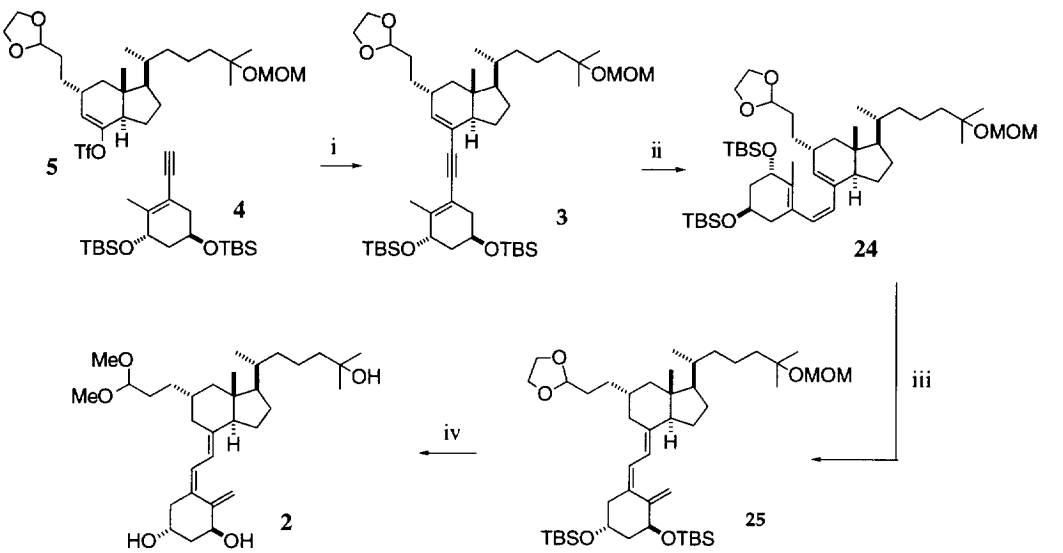
Reagents (i) NaCN, DMSO, 95 °C, 76%; (ii) NaH, DMF, 0 °C; MOMCl, 65%; (iii) LDA, THF, -70 °C; **17**, -70 °C to r.t., 84%; (iv) K, *t*-BuOH, HMPA, Et_2O, 0 °C to r.t., 90%; (v) PDC, PPTS, CH_2Cl_2, 99%; (vi) LDA, THF; TMSCl, -78 °C; (vii) $Pd(OAc)_2$, CH_3CN, 94% (from **20**); (viii) **22**, THF, -78 °C; CuBr•Me_2S, Me_2S; TMSCl, enone **6**; (ix) MeLi, THF, 0 °C; -78 °C, $PhNTf_2$, 70% (from **6**).

Conversion of **6** to **5** began by reaction of **6** with the organocopper reagent derived from the Grignard reagent **22**[31] and copper (I) bromide-dimethyl sulfide complex in the presence of chlorotrimethylsilane. The resulting crude silyl enol ether **23** was immediately metallated to form the kinetic enolate which was trapped with $PhNTf_2$ to afford the target vinyl triflate **5** (70% from **6**). The *R* configuration at C11 was confirmed by nOe difference experiments, which indicated the proximity of H-11β and CH_3-18. The attack of the copper reagent therefore took place from the less hindered α-face of the molecule, as expected from the experiments with model ketone **7**. As a shorter alternative, we examined the reaction of the organocopper reagent with **6** in the absence of TMSCl. In this case, the conjugate addition C11-alkylated ketone was obtained in low yield (40%), and the intermediate enolate could not be trapped with $PhNTf_2$. Subsequent treatment of the ketone with LDA in THF (-78 °C) and $PhNTf_2$ gave an inseparable 1:1 mixture of triflate **5** and the regioisomer resulting from removal by LDA of H-14 instead of H-9 in 55% yield.

Finally, we proceeded to assembly of the vitamin D triene system by palladium-catalysed coupling of vinyl triflate **5** with the known enyne **4**[15a,32] (Scheme 4), which gave dienyne **3** in 78% yield. Partial hydrogenation of **3** under a balloon pressure of H_2 in the presence of Lindlar palladium catalyst poisoned with quinoline in hexanes afforded previtamin D **24** (80%), which underwent thermal isomerization to vitamin D **25** via a thermal [1,7]-sigmatropic hydrogen shift (100% yield). Removal of the protecting groups of **25** by treatment with

AG 50W-X4 cation-exchange resin in methanol gave the desired 1α,25-$(OH)_2$-vitamin D_3 analogue **2** in 81% yield (25% overall yield, 11 steps).

Scheme 4.



Reagents (i) $(Ph_3P)_2PdCl_2$, Et_3N, DMF, 70-75 °C, 78%; (ii) H_2, Lindlar catalyst, quinoline, hexanes, 80%; (iii) isooctane, 100 °C, 100%; (iv) AG 50W-X4, MeOH, 81%.

In summary, we found that allylic esters derived from the semi-rigid bicyclic $\Delta^{9,11}$-8-hydroxy-CD-ring system (**10b** and **10d-f**) are biased towards S_N2 alkylation by cuprates, but highly selective *anti*-S_N2' alkylation can be achieved by reaction of phosphate ester **10f** with MeMgBr in the presence of CuCN (as catalyst). We also developed a practical and convenient procedure for the construction of the 25-hydroxylated vitamin D side-chain, that is easily generalized to the synthesis of other vitamin D side-chains. Finally, we developed an efficient synthesis of the C11-functionalized 1α,25-dihydroxyvitamin D_3 analogue **2**.

EXPERIMENTAL

General. All reactions involving oxygen- or moisture-sensitive compounds were carried out under a dry argon atmosphere. Reaction temperatures refer to external bath temperatures. All dry solvents were distilled under argon immediately prior to use. Tetrahydrofuran (THF) and ether (Et_2O) were distilled from Na/benzophenone. Dichloromethane (CH_2Cl_2) and acetonitrile were distilled from P_2O_5. Triethylamine (Merck), diisopropylamine (Merck), dimethylsulfide (Merck), and *tert*-butyl alcohol (Merck) were distilled from CaH_2. Dry dimethylformamide (DMF; Merck), hexamethylphosphoramide (HMPA; Aldrich) and dimethylsulfoxide (DMSO; Aldrich) were stored over type 4Å molecular sieves. Liquid reagents or solutions of reagents were added by syringe or cannula. Organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated with a rotary evaporator at aspirator pressure (20-30 mmHg). Reactions were monitored by thin layer

chromatography (TLC) using aluminium Merck 60 silica gel plates (0.2 mm thickness). After ultraviolet illumination at 254 nm, the plates were visualized by immersion in a solution of phosphomolibdic acid in MeOH (5%), followed by heating. Column chromatography was performed with Merck 60 (230-400 mesh) silica gel by Still´s method.[33] All NMR spectra were measured as solutions in $CDCl_3$ unless otherwise stated. Chemical shifts are reported as δ units (ppm) downfield from tetramethylsilane (δ 0.0) using residual solvent signal as an internal standard: δ 7.26 (^1H), 77.0 triplet (^{13}C). All coupling constants are measured in hertz units. DEPT was used to assign carbon types. Mass spectra were measured using electron impact ionization at 70 eV.

11α-Methyl-des-A,B-cholest-8-en-8-yl Trifluoromethanesulfonate (8b). Methyllithium [10.9 mL, 1.51 M in Et_2O, 16.6 mmol] was added to a suspension of CuI (1.7 g, 8.93 mmol) in THF (15 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and then the Me_2CuLi solution was cooled to -78 °C and TMSCl (1.14 mL, 9 mmol) followed by a solution of enone **7** (875 mg, 3.34 mmol) in THF (14 mL) were added. After stirring for 15 min, the reaction was quenched with drops of saturated $NaHCO_3$ solution. After warming to 0 °C, the mixture was poured into saturated $NaHCO_3$ solution (20 mL) and extracted with Et_2O (2x20 mL). The combined organic phases were washed with saturated NaCl (20 mL), dried, filtered and concentrated in vacuo. The residue was dried under high vacuum to give 1.14 g (97%) of crude silyl enol ether **8a** as a yellow liquid. Rf (15% EtOAc/hexanes): 0.9. This compound was immediately used in the next reaction.

Methyllithiym (3 mL, 1.51 M in Et_2O, 4.5 mmol) was added to a solution of crude **8a** (1.14 g, 3.25 mmol) in THF (10 mL) at 0 °C, and the mixture was stirred at rt for 30 min. The resulting deep yellow enolate solution was cooled to -78 °C and a solution of $PhNTf_2$ (1.6 g, 4.5 mmol) in THF (15 mL) was added. After stirring for 12 h, the reaction mixture was warmed to rt and then concentrated in vacuo. Flash chromatography (hexanes) of the concentrate afforded triflate **8b** (1.1 g, 82%) as a colorless liquid. Rf (hexanes): 0.6. **^1H NMR**: 5.46 (1H, d, *J*=2.8, H-9), 1.07 (3H, d, *J*=6.97, CH_3C-11), 0.95 (3H, d, *J*=6.36, CH_3-21), 0.88 (3H, d, *J*=6.61, CH_3-26), 0.87 (3H, d, *J*=6.58, CH_3-27), 0.78 (3H, s, CH_3-18). **^{13}C NMR**: 149.70, 121.56, 118.69 (c, $J_{C\text{-}F}$=320, CF_3), 54.26, 50.29, 46.55 (C-13), 44.89, 39.41, 36.00, 35.96, 30.69, 28.32, 27.95, 23.75, 22.68, 22.43, 21.50, 20.94, 18.60, 11.86. **LRMS** m/z (I,%): 410 (M^+, 26), 325 (1), 297 (39), 277 (63), 147 (100). **HRMS** calcd. for $C_{20}H_{33}O_3F_3S$, 410.2102; found, 410.2101.

11α-Methyl-des-A,B-cholest-8-ene (9). A mixture of **8b** (204 mg, 0.497 mmol), PPh_3 (21 mg, 0.08 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), DMF (3.5 mL), Et_3N (0.21 mL, 1.5 mmol) and formic acid (0.038 mL, 46 mg, 1 mmol) was stirred and heated at 60-70 °C for 45 min. The dark mixture was cooled to rt and diluted with hexanes (20 mL) and then washed with water (2x30 mL). The organic phase was dried, filtered and concentrated to a residue, which was purified by flash chromatography (hexanes) to afford 97 mg of **9** (74%, colorless liquid). Rf (hexanes): 0.9. **^1H NMR**: 5.56 (1H, dt, J_1=2.0, J_2=9.84), 5.44 (1H, dt, J_1=2.4, J_2=9.84), 1.01 (3H, d, *J*=7.03, CH_3C-11), 0.97 (3H, d, *J*=6.50, CH_3-21), 0.89 (3H, d, *J*=6.60, CH_3-26), 0.88 (3H, d, *J*=6.61, CH_3-27), 0.73 (3H, s, CH_3-18). **^{13}C NMR**: 132.72 (CH), 127.28 (CH), 54.46, 48.91,

46.72 (CH_2), 43.37 (C-13), 39.53 (CH_2), 36.24 (CH_2), 30.40, 28.59 (CH_2), 27.99, 24.81 (CH_2), 23.89 (CH_2), 22.77, 22.52, 21.68, 18.82, 11.51. **LRMS** m/z (I,%): 262 (M^+, 2.9), 261 (3), 247 (M^+-CH_3, 3), 149 (100). **HRMS** calcd. for $C_{19}H_{34}$, 262.2660; found, 262.2666.

Des-A,B-cholest-9(11)-en-8β-ol (10a). Dibal-H (19.4 mL, 1 M in hexanes, 19.4 mmol) was added dropwise to a solution of enone **7** (2.526 g, 9.63 mmol) in THF (70 mL) at -78 °C. After stirring for 15 min, the reaction was quenched with drops of water. Saturated NaCl (50 mL) and a solution of HCl (10%, 100 mL) were added and the mixture was extracted with Et_2O (2x75 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (50 mL), dried, filtered and concentrated. Purification of the resulting residue by flash chromatography (5-8% EtOAc/hexanes) gave allylic alcohol **10a** (2.22 g, 87%, colorless oil). Rf (20% EtOAc/hexanes): 0.5. **^{1}H NMR**: 5.86 (1H, m), 5.76 (1H, m,), 4.12 (1H, br s, H-8), 0.88 (3H, d, *J*=6.55, CH_3-21), 0.86 (3H, d, *J*=6.66, CH_3-26), 0.85 (3H, d, *J*=6.59, CH_3-27), 0.81 (3H, s, CH_3-18). **^{13}C NMR**: 129.81 (CH), 128.38 (CH), 66.50, 56.56, 50.39, 42.01(CH_2), 39.85 (C-13), 39.42 (CH_2), 35.93 (CH_2), 35.17, 27.91, 27.30 (CH_2), 23.74 (CH_2), 22.70, 22.44, 21.06 (CH_2), 18.16, 13.25. **IR** (film): 3395, 3030, 3960, 3880, 1470, 1385. **LRMS** m/z (I,%): 264 (M^+, 37), 249 (M^+-CH_3, 16), 206 (18), 161 (31), 151 (81), 109 (100). **HRMS** calcd. for $C_{18}H_{32}O$, 264.2453; found, 264.2446.

Hydrogenation of 10a. A mixture of **10a** (70 mg, 0.26 mmol) and Pd/C (10%, 35 mg) in EtOH (7 mL) and EtOAc (10.5 mL) was hydrogenated (50 psi) for 2 h. The mixture was diluted with Et_2O (50 mL) and filtered through a short pad of Celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography (4.5-5% EtOAc/hexanes) of the concentrate gave Grundmann´s alcohol (**12**, 18 mg, 26%, ^{1}H NMR spectrum and Rf were identical to those of an authentic sample). Rf (20% EtOAc/hexanes): 0.55. **^{1}H NMR**: 4.07 (1H, dd, J_1=5.7, J_2=2.8, H-8), 0.91 (3H, d, *J*=6.5, CH_3-21), 0.88 (3H, s, CH_3-18), 0.86 (6H, d, *J*=5.4, CH_3-26,27).

8β-Benzoyloxy-des-A,B-cholest-9(11)-ene (10b). Benzoyl chloride (0.6 mL, 5 mmol) was added to a solution of **10a** (280 mg, 1.05 mmol) and DMAP (10 mg) in pyridine (5 mL) at 0 °C. After 24h at ~5 °C, the mixture was poured into saturated $NaHCO_3$ solution (20 mL) and extracted with 1:3 EtOAc/hexanes (2x100 mL). The combined organic extracts were successively washed with 5% HCl solution (2x10 mL), H_2O (10 mL), saturated $CuSO_4$ solution (2x20 mL), H_2O (10 mL) and saturated $NaHCO_3$ solution (10 mL), and then dried, filtered and concentrated to a residue, which was purified by flash chromatography (1-2% EtOAc/hexanes) to give **10b** as a colorless oil (370 mg, 96%). Rf (15% EtOAc/hexanes): 0.85. **^{1}H NMR**: 8.06-7.38 (5H, m, Ar), 5.93 (2H, AB, *J*=10, H-9,11), 5.61 (1H, m, H-8), 0.99 (3H, s, CH_3-18), 0.95 (3H, d, *J*=6.38, CH_3-21), 0.90 (6H, d, *J*=6.61, CH_3-26,27). **^{13}C NMR**: 163.13 (CO), 132.62 (CH), 132.16 (CH), 130.75 (C), 129.54 (CH), 128.26 (CH), 124.43 (CH), 68.58, 56.30, 48.99, 41.89 (CH_2), 39.82 (CH_2), 39.35 (C-13), 35.83 (CH_2), 35.26, 27.86, 27.24 (CH_2), 23.71 (CH_2), 22.68, 22.42, 21.57 (CH_2),

18.23, 13.16. **LRMS** m/z (I,%): 368 (M^+, 3), 246 (4), 147 (2), 133 (22), 105 (100). **HRMS** calcd. for $C_{25}H_{36}O_2$, 368.2715; found, 368.2713.

8β-(Phenylcarbamoyl)oxy-des-A,B-cholest-9(11)-ene (10c). Phenylisocyanate (0.60 mL, 0.54 mmol) was added to a stirred solution of **10a** (260 mg, 0.983 mmol) and DMAP (10 mg) in pyridine (5 mL) at 0 °C. After 6 h at ~5 °C, the mixture was poured into a saturated $NaHCO_3$ solution and the resulting solid was filtered out and washed with small amounts of EtOAc/hexanes. The combined filtrates and washings were washed successively with 5% HCl solution (2x20 mL), H_2O (20 mL), saturated $CuSO_4$ solution (2x20 mL) and H_2O (10 mL). The organic phase was dried, filtered, concentrated to a small volume and diluted with hexanes, giving a white precipitate that was filtered off. The filtrate was concentrated and the residue was purified by flash chromatography (1.5-3% EtOAc/hexanes) to give carbamate **10c** as a white solid. (357 mg, 95%). Mp: 79-80 °C. Rf (15% EtOAc/hexanes): 0.7. **^{1}H NMR**: 7.41-7.01 (5H, m, Ar), 6.55 (1H, br s, NH), 5.88 (2H, m, H-9,11), 5.35 (1H, m, H-8), 0.92 (3H, d, *J*=6.14, CH_3-21), 0.873 (3H, d, *J*=6.61, CH_3-26), 0.869 (3H, d, *J*=6.63, CH_3-27), 0.83 (3H, s, CH_3-18). **^{13}C NMR**: 153.69 (CO), 138.15 (C), 132.16, 129.03, 124.68, 123.31, 118.79, 69.12, 56.36, 49.07, 41.92 (CH_2), 39.87 (C-13), 39.44 (CH_2), 35.93 (CH_2), 35.34, 27.94, 27.28 (CH_2), 23.76 (CH_2), 23.73, 22.47, 21.49 (CH_2), 18.28, 13.02. **LRMS** m/z (I,%): 383 (M^+, 0.9), 340 (4), 339 (14), 248 (16), 247 (84), 163 (34), 133 (45), 93 (100). **HRMS** calcd. for $C_{25}H_{37}NO_2$, 383.2824; found, 383.2827.

8β-[(2,2-Dimethylpropanoyl)oxy]-des-A,B-cholest-9(11)-ene (10d). Pivaloyl chloride (0.48 mL, 3.88 mmol) was added to a solution of **10a** (205 mg, 0.775 mmol) and DMAP (13 mg) in pyridine (13 mL) at 0 °C. The mixture was stirred at rt for 36 h and then poured into a 5% HCl solution (25 mL) and extracted with Et_2O (2x50 mL). The combined organic extracts were successively washed with 5% HCl solution (25 mL), saturated $CuSO_4$ solution (25 mL) and saturated $NaHCO_3$ solution (25 mL), and then dried, filtered and concentrated in vacuo. The concentrate was flash chromatographed (3% EtOAc/hexanes) to give pivaloate **10d** (242 mg, 90%, colorless oil). Rf (25% EtOAc/hexanes): 0.7. **^{1}H NMR**: 5.84 (1H, m), 5.76 (1H, m), 5.26 (1H, m, H-8), 1.18 [9H, s, $COC(CH_3)_3$], 0.90 (3H, d, *J*=6.43, CH_3-21), 0.86 (3H, d, *J*= 6.63, CH_3-26), 0.85 (3H, d, *J*=6.58, CH_3-27), 0.82 (3H, s, CH_3-18). **^{13}C NMR**: 178.17 (CO), 131.80 (CH), 124.60 (CH), 67.80, 56.43, 48.98, 42.00 (CH_2), 39.86 (C-13), 39.44 (CH_2), 38.90 [$\underline{C}(CH_3)_3$], 35.94 (CH_2), 35.33, 27.94, 27.29 (CH_2), 27.21 [$C(\underline{C}H_3)$], 23.77 (CH_2), 22.71, 22.47, 21.39 (CH_2), 18.29, 13.09. **LRMS** m/z (I,%): 348 (M^+, 14), 307 (3), 264 (9), 247 (21), 246 (23), 133 (50). **HRMS** calcd. for $C_{23}H_{40}O_2$, 348.3028; found, 348.3049.

8β-Acetoxy-des-A,B-cholest-9(11)-ene (10e). Acetic anhydride (0.5 mL, 5.3 mmol) was added to a solution of **10a** (340 mg, 1.29 mmol) in pyridine (6 mL) at 0 °C. After stirring for 3 days, TLC indicated that the reaction was incomplete, so further acetic anhydride was added (1.0 mL, 1.1 g, 10.6 mmol). The mixture

was stirred for one more day and then poured into water/ice (25 mL) and extracted with Et_2O (2x25 mL). The organic phase was washed with 10% HCl solution (30 mL) and saturated $CuSO_4$ solution (30 mL), dried, filtered and concentrated in vacuo. Flash chromatography (3% EtOAc/hexanes) of the concentrate gave 370 mg of acetate **10e** (94%) as a colorless oil. Rf (20% EtOAc/hexanes): 0.7. **^{1}H NMR**: 5.85 (1H, m), 5.76 (1H, m), 5.3 (1H, dt, J_1=4.4, J_2=2.2, H-8), 2.02 (3H, s, $COCH_3$), 0.89 (3H, d, J=6.46, CH_3-21), 0.85 (3H, d, J=6.58, CH_3-26), 0.85 (3H, d, J=6.58, CH_3-27), 0.78 (3H, s, CH_3-18). **^{13}C NMR**: 170.85 (CO), 132.02 (CH), 124.48 (CH), 68.15, 56.33, 48.78, 41.89, 39.85 (C-13), 39.42, 35.90, 35.30, 27.92, 27.25, 23.73, 22.71, 22.46, 21.51, 20.98, 18.25, 12.80. **LRMS** m/z (I,%): 306 (M^+, 6), 264 (27), 246 (41), 133 (100). **HRMS** calcd. for $C_{20}H_{34}O_2$, 306.2559; found, 306.2579.

Des-A,B-cholest-9(11)-en-8β-yl Diethyl Phosphate (10f). *n*-Butyllitium (0.39 mL, 2.61 M in hexanes, 1.0 mmol) was added dropwise to a stirred solution of alcohol **10a** (208 mg, 0.786 mmol) in Et_2O (8 mL) at -78 °C. After stirring at rt for 30 min, the solution was cooled at 0 °C and diethyl chlorophosphate (0.15 mL, 1.0 mmol) was added. The mixture was stirred at 0 °C for 1 h and then was warmed to rt and poured into water/ice (20 mL). The resulting mixture was extracted with Et_2O (2x20 mL) and the combined organic extracts were dried, filtered and concentrated in vacuo. The concentrate was purified by flash chromatography (5-40% EtOAc/hexanes) to give allylic phosphate **10f** (271 mg, 86%, colorless oil). Rf (30% EtOAc/hexanes): 0.3. **^{1}H NMR**: 5.86 (2H, m, H-9,11), 4.77 (1H, m, H-8), 4.05 [4H, m, J_1=7.04, J_2=3.55, $P(OC\underline{H}_2CH_3)_2$], 1.29 [6H, dt, J_1=7.04, J_2=0.67, $P(OCH_2C\underline{H}_3)_2$], 0.86 (3H, d, J=7.34, CH_3-21), 0.83 (6H, d, J=6.60, CH_3-26,27), 0.77 (3H, s, CH_3-18). **^{13}C NMR**: 132.17 (CH), 124.97 (CH), 72.65 (d, J=6.35, C-8), 63.34 [t, J=5.23, $P(O\underline{C}H_2CH_3)_2$], 56.40, 49.29 (d, J=6.49, C-14), 41.90, 39.76 (C-13), 39.37, 35.83, 35.16, 27.86, 27.14, 23.68, 22.65, 22.40, 21.32, 18.18, 16.02 [c, J= 3.22, $P(OCH_2\underline{C}H_3)_2$], 12.84. **LRMS** m/z (I,%): 401 (18), 400 (M^+, 90), 263 (4), 246 (15), 133 (100). **HRMS** calcd. for $C_{22}H_{41}O_4P$, 400.2742; found, 400.2731.

Reaction of 10c with Me_2CuLi. Methyllithium (2.95 mL, 1.45 M in Et_2O, 4.28 mmol) was added to a stirred suspension of CuI (408 mg, 2.14 mmol) in Et_2O (8.4 mL) at 0 °C. After 30 min a solution of compound **10c** (170 mg, 0.443 mmol) in Et_2O (7 mL) was cannulated into the cuprate solution. The mixture was slowly warmed to rt and stirred for 4 days. The reaction was quenched dropwise with saturated NH_4Cl solution (5 mL) and the mixture was stirred for 1 h and then filtered. The filtrate was extracted with EtOAc/hexanes (2x20 mL), and the organic extracts were combined and successively washed with 5% HCl solution (25 mL), H_2O (25 mL) and saturated $NaHCO_3$ solution (25 mL), and then dried, filtered and concentrated. Analysis of the crude residue (^{1}H NMR and ^{13}C NMR) showed a ~9:1 ratio of **13** and **11**. Purification by flash chromatography (hexanes) gave 104 mg (89%) of the mixture of **13** and **11**. Rf (hexanes): 0.9. An analytical sample of **13** was obtained by further purification by HPLC [column, Phenomenex Zorbasil (10x250 mm); eluent, hexane (1.5 mL/min)]. **13**. **^{1}H NMR**: 5.58 (1H, dt, J_1=2.2, J_2=9.7), 5.50 (1H, dt, J_1=2.6, J_2=9.7), 1.06 (3H, d, J=7.65,

CH_3C-11), 0.94 (3H, d, *J*=6.51, CH_3-21), 0.87 (3H, d, *J*=6.59, CH_3-26), 0.86 (3H, d, *J*=6.59, CH_3-27), 0.67 (3H, s, CH_3-18). **^{13}C NMR**: 133.28 (CH), 127.75 (CH), 55.58, 48.21, 44.63 (CH_2), 42.16 (C-13), 39.52 (CH_2), 36.15, 36.14 (CH_2), 29.66, 28.71 (CH_2), 27.98, 24.81 (CH_2), 23.88 (CH_2), 23.44, 22.76, 22.51, 18.68, 13.70. **LRMS** m/z (I,%): 262 (M^+, 1.9), 247 (M^+-CH_3, 3), 207 (2), 206 (4), 177 (5), 150 (13), 149 (100). **HRMS** calcd. for $C_{19}H_{34}$, 262.2660; found, 262.2652.

Reaction of 10b, 10d, 10e and 10f with Me_2CuLi. Following the procedure described above for **10c**, the reaction of these compounds with Me_2CuLi gave the following results. Reaction of **10b**: 89% combined yield of **11** and **9** (92:8 by GC); retention times 23.8 min and 23.5 min, respectively. Reaction of **10d**: 98% combined yield of **11** and **9** (92:8 by GC). Reaction of **10e**: 77% combined yield of **11** and **9** (91:9 by GC). Reaction of **10f**: 96% yield of **11** and **9** (91:9 by GC). An analytical sample of **11** was obtained by purification of a mixture of **11** and **9** by HPLC [column, Phenomenex Zorbasil (10x250 mm); eluent, hexanes (1.5 mL/min)]. **11**. **^{1}H NMR**: 5.53 (1H, m), 5.44 (1H, m), 0.96 (3H, d, *J*=6.85, CH_3C-8), 0.94 (3H, d, *J*=6.51, CH_3-18), 0.89 (3H, d, *J*=6.61, CH_3-26), 0.88 (3H, d, *J*= 6.61, CH_3-27), 0.68 (3H, s, CH_3-18). **^{13}C NMR**: 132.69 (CH), 125.61 (CH), 56.44, 53.39, 41.91 (CH_2), 41.57 (C-13), 39.54 (CH_2), 36.20 (CH_2), 35.66, 33.50, 28.00, 27.86 (CH_2), 25.13 (CH_2), 23.84 (CH_2), 22.78, 22.53, 19.62, 18.34, 11.78. **LRMS** m/z (I,%): 262 (M^+, 1.2), 247 (M^+-CH_3, 9), 221 (7), 193 (7), 149 (100), 107 (36). **HRMS** calc. for $C_{19}H_{34}$, 262.2660; found, 262.2642.

Reaction of 10f, 10d and 10e with Me(CN)CuLi. Following the procedure described above for the reaction of **10c** with Me_2CuLi, reaction of phosphate **10f** with Me(CN)CuLi [prepared by reaction of 1:1 MeLi/CuCN (Aldrich) in Et_2O at 0 °C; 30 min] gave a mixture of **11** and **9** (79:21 by GC) in 95% combined yield. Under the same conditions, esters **10d** and **10e** did not react with Me(CN)CuLi, only starting material was recovered.

Reaction of 10f and 10d with MeMgBr/CuCN. Methylmagnesium bromide (0.208 mL, 3 M in Et_2O, 0.625 mmol) was added slowly to a mixture of phosphate **10f** (28 mg, 0.070 mmol) and CuCN (4 mg, 0.045 mmol) in Et_2O (3 mL) at 0 °C. The mixture was stirred for 12 h and slowly allowed to warm to rt, whereupon saturated NH_4Cl solution (6 mL) was added to quench the reaction. After stirring for 1 h, the mixture was extracted with Et_2O (2x8 mL). The combined organic extracts were washed with saturated NaCl (8 mL), dried, filtered and concentrated. Analysis of the residue (^{1}H NMR, ^{13}C NMR and GC) showed a 4:96 ratio of **11** and **9**. Purification by flash chromatography (hexanes) gave 18 mg (98%) of the mixture of **9** and **11**. Rf (hexanes): 0.9. Reaction of pivaloate **10d** with MeMgBr/CuCN under the same conditions gave a 2:8 mixture of **11** and **9** in 23% yield, together with a 75% yield of recovered allylic alcohol **10a**.

4-Hydroxy-4-methylpentanenitrile (**15**). A mixture of 4-bromo-2-methylbutan-2-ol (**14**, 45.3 g, 271 mmol) and NaCN (25 g, 510 mmol) in DMSO (250 mL) was stirred at 90-100 °C for 1.5 h. The reaction

mixture was allowed to cool to rt and then poured into water (800 mL) and extracted with EtOAc (10x75 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. The concentrate was purified by flash chromatography (25-35% EtOAc/hexanes) to give **17** (23.2 g, 76%) as a yellowish liquid. Rf (60% EtOAc/hexanes): 0.4. **^{1}H NMR**: 2.46 (2H, t, *J*=7.8, CH_2-CN), 1.83 (2H, t, *J*=7.8, $C\underline{H}_2COH$), 1.25 (6H, s, $2CH_3$). **^{13}C NMR**: 120.41 (CN), 69.45 (COH), 38.43 ($\underline{C}H_2COH$), 28.81 (2 CH_3), 11.82 ($\underline{C}CN$). **IR** (film): 3420, 2970, 2240, 1370. **LRMS** m/z (I,%): 113 (M^+, 1), 111 (2), 107 (3), 98 (12), 70 (26), 59 (85), 43 (100). **HRMS** calcd. for $C_6H_{11}NO$, 113.0841; found, 113.0852.

4-[(Methoxymethyl)oxy]-4-methylpentanenitrile (16). An excess of NaH (80% dispersion in mineral oil, 6 g, ~200 mmol) was added portionwise to a cooled (0 °C) solution of nitrile **15** (15.22 g, 134.7 mmol) in DMF (75 mL). After the production of H_2 bubbles ceased, 1.5 h later, MOMCl (14.3 mL, 188 mmol) was slowly added and the reaction mixture was stirred at room temperature overnight. Then the mixture was cooled to 0 °C, water (150 mL) was carefully added, and the resulting mixture was extracted with Et_2O (4x100 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. The concentrate was flash chromatographed (9-13 % EtOAc/hexanes) to afford 13.81 g (65%) of the protected compound **16** as a colorless liquid. Rf (30% EtOAc/hexanes): 0.52. **^{1}H NMR**: 4.68 (2H, s, OCH_2O), 3.35 (3H, s, OCH_3), 2.44 (2H, t, *J*=7.8, CH_2CN), 1.86 (2H, t, *J*=7.8, $C\underline{H}_2COMOM$), 1.24 (6H, s, $2CH_3$). **^{13}C NMR**: 120.03 (CN), 90.73 (OCH_2O), 74.17 ($\underline{C}OMOM$), 54.84 (OCH_3), 37.36 ($\underline{C}H_2COMOM$), 25.34 (2 CH_3), 11.37 ($\underline{C}CN$). **IR** (film): 2970, 2930, 2240. **LRMS** m/z (I,%): 156 (M^+-H, 1), 142 (15), 126 (4), 112 (24), 103 (64), 96 (55), 45 (100). **HRMS** calcd. for $C_8H_{15}NO_2$, 157.1103; found, 157.1102.

8β-Hydroxy-25-[(methoxymethyl)oxy]-des-A,B-cholestan-23-carbonitrile (18). *n*-Butyllithium (48 mL, 2.5 M in hexanes, 120 mmol) was added to a solution of diisopropylamine (17 mL, 125 mmol) in THF (55 mL) at -70 °C. The mixture was stirred at -70 °C for 15 min, warmed to rt for 20 min, and then cooled to -78 °C, whereupon a solution of nitrile **16** (12.3 g, 78.3 mmol) in THF (100 mL) was cannulated dropwise. After 30 min a solution of tosylate **17** (14.15 g, 38.66 mmol) in THF (100 mL) was cannulated dropwise, and the solution was stirred at -78 °C for 1 h and then warmed to rt and stirred overnight. After quenching the reaction carefully with drops of saturated NH_4Cl solution, the mixture was poured into saturated NH_4Cl solution (200 mL) and extracted with Et_2O (3x100 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. The concentrate was purified by medium pressure liquid chromatography[34] on silica gel (13-20 % EtOAc/hexanes) to give 11.34 g (84 %) of **18** as a mixture of two diastereoisomers (oil). Rf (30% EtOAc/hexanes): 0.40. **^{1}H NMR**: 4.67-4.58 (2H, m, OCH_2O), 3.99 (1H, br s, H-8), 3.29 (3H, s, OCH_3), 2.78 (1H, m, H-23), 1.30, 1.21 and 1.20 (6H, 3s, CH_3-26,27), 0.92-0.88 (6H, m, CH_3-21,18). **^{13}C NMR**: 124.17 (CN), 123.00 (CN), 90.87 (OCH_2O), 74.96 (C-25), 74.95 (C-25), 68.79 (CH_2), 56.67 (CH_2), 56.57 (CH_2), 55.11 (CH_2), 55.00 (CH_2), 52.46 (CH_2), 52.34 (CH_2), 45.39, 44.26, 41.88 (C-13), 40.28, 40.19, 40.01, 33.65 (CH_2), 33.39, 27.14, 26.92, 26.61 (CH_2), 26.49 (CH_2), 25.75 (CH_2), 25.64 (CH_2), 23.74

(CH_2), 23.06 (CH_2), 22.28, 18.22 (CH_2), 17.87 (CH_2), 17.19, 13.35 (CH_2), 13.25 (CH_2). **IR** (film): 3510, 2940, 2880, 2230, 1460. **HRMS** calcd. for $C_{21}H_{37}NO_3$, 351.2773; found, 351.2770.

25-[(Methoxymethyl)oxy]-des-A,B-cholestan-8β-ol. (**19**). A solution of nitrile **18** (10.05 g, 28.64 mmol) and *tert*-butyl alcohol (4.8 mL, 52.2 mmol) in Et_2O (24 mL) was cannulated into a suspension of potassium (2.5 g, 64 mmol) in HMPA (24 mL) and Et_2O (24 mL) at 0 °C. As the potassium was consumed, additional amounts were added portionwise (in total 5 g, 128 mmol). The blue mixture was stirred and allowed to warm to rt over 12 h, during which time all the potassium was consumed. The reaction mixture was cooled to 0 °C, quenched with drops of water, and then diluted with water (200 mL) and extracted with Et_2O (3x100 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. The concentrate was purified by flash chromatography (5-10% EtOAc/hexanes) to give 8.42 g (90%) of **19** as a colorless oil. Rf (30% EtOAc/hexanes): 0.55. **^{1}H NMR**: 4.67 (2H, s, OCH_2O), 4.03 (1H, br s, H-8), 3.33 (3H, s, OCH_3), 1.18 (6H, s, CH_3-26,27), 0.90 (3H, s, CH_3-18), 0.87 (3H, d, *J*=6.5, CH_3-21). **^{13}C NMR**: 90.94 (OCH_2O), 76.30 (C-25), 69.30, 56.69, 54.95. 52.59, 42.22 (CH_2), 41.80 (C-13). 40.37 (CH_2), 36.22 (CH_2), 35.20, 33.56 (CH_2), 27.09 (CH_2), 26.29 (CH_3-26), 26.22 (CH_3-27), 22.44 (CH_2), 20.40 (CH_2), 18.44, 17.35 (CH_2), 13.42. **IR** (film): 3480, 2940, 2870, 1460, 1360. **LRMS** m/z (I,%): 325 (M^+-H, 0.1), 309 (2). 277 (3), 265 (23), 247 (50), 135 (40), 45 (100). **HRMS** calcd. for $C_{20}H_{38}O_3$, 326.2821; found, 326.2817.

25-[(Methoxymethyl)oxy]-des-A,B-cholestan-8-one (**20**). A mixture of **19** (5.35 g, 16.41 mmol), pyridinium dichromate (18.51 g, 49.2 mmol) and pyridinium tosylate (10 mg) in dry CH_2Cl_2 (95 mL) was stirred at 0 °C for 12h. After adding Et_2O (200 mL), the mixture was stirred at rt for 30 min and filtered through a short pad of Celite and silica gel. The solid residues were washed with Et_2O, and the combined filtrates and washings were concentrated to a residue which was chromatographed on a short column of silica gel (13% EtOAc/hexanes) to yield 5.24 g (99 %) of **20** as a colorless liquid. Rf (30% EtOAc/hexanes): 0.61. **^{1}H NMR**: 4.65 (2H, s, OCH_2O), 3.31 (3H, s, OCH_3), 1.17 (6H, s, CH_3-26,27), 0.92 (3H, d, *J*=6.09, CH_3-21), 0.59 (3H, s, CH_3-18). **^{13}C NMR**: 211.22 (C-8), 90.69 (OCH_2O), 75.83 (C-25), 61.62, 56.46, 54.64, 49.52 (C-13), 41.97 (CH_2), 40.58 (CH_2), 38.69 (CH_2), 36.00 (CH_2), 35.17, 27.18 (CH_2), 26.05 (CH_3-26), 25.98 (CH_3-27), 23.68 (CH_2), 20.11 (CH_2), 18.74 (CH_2), 18.38, 12.10. **IR** (film): 2950, 2870, 1710, 1460, 1375. **LRMS** m/z (I,%): 324 (M^+, 1), 309 (14), 266 (31), 263 (30), 262 (41). **HRMS** calcd. for $C_{20}H_{36}O_3$, 324.2664; found, 324.2656. **Anal.** calcd. for $C_{20}H_{36}O_3$, C 74.02, H 11.18%; found C 73.60, H 11.55%.

25-[(Methoxymethyl)oxy]-des-A,B-cholest-9(11)-en-8-one (**6**). A solution of lithium diisopropylamide was prepared by adding *n*-buthyllithium (1.55 mL, 2.46 M in hexanes, 3.80 mmol) to a solution of diisopropylamine (0.64 mL, 4.56 mmol) in THF at -78 °C and stirring for 20 min at rt. The LDA solution was recooled to -78 °C and a solution of freshly vacuum distilled ketone **20** (0.984 g, 3.04 mmol) in THF (14 mL) was cannulated dropwise. The mixture was stirred for 1 h at -78 °C and for 1 h at rt. After cooling to -78 °C

chlorotrimethylsilane (0.58 mL, 4.56 mmol) was added and the mixture was allowed to warm to rt overnight. The reaction mixture was cooled to 0 °C, quenched with drops of saturated $NaHCO_3$ solution, diluted with Et_2O (100 mL) and washed with a cold saturated $NaHCO_3$ solution (50 mL) and cold saturated NaCl (50 mL). The organic phase was dried and then filtered. After removal of solvent, the crude silyl enol ether **21** was dissolved in acetonitrile (70 mL) under argon, palladium (II) acetate (0.754 g, 3.4 mmol) was added and the mixture was stirred for 20 h. Then, the acetonitrile was removed under vacuum, the residue was suspended in Et_2O (50 mL), and the resulting mixture was filtered through a pad of Celite. The solids were washed with Et_2O (4 x 25 mL) and the combined filtrates and washings were washed successively with saturated $NaHCO_3$ solution (100 mL) and saturated NaCl (100 mL). The aqueous phases were re-extracted with Et_2O (100 mL), and the ethereal solutions were combined, dried, filtered and concentrated. Flash chromatography of the concentrate (9-12% EtOAc/hexanes) afforded 0.922 g (94% from **20**) of **6** as a colorless oil. Rf (30% EtOAc/hexanes): 0.56. **^{1}H NMR**: 6.71 (1H, ddd, J_1=2.3, J_2=5.7, J_3=10.0, H-11), 5.93 (1H, ddd, J_1=1.1, J_2=3.1, J_3=10.0, H-9), 4.65 (2H, s, OCH_2O), 3.31 (3H, s, OCH_3), 1.16 (6H, s, CH_3-26,27), 0.90 (3H, d, J=6.18, CH_3-21), 0.69 (3H, s, CH_3-18). **^{13}C NMR**: 201.62 (C-8), 147.27 (C-11), 129.54 (C-9), 90.92 (OCH_2O), 76.09 (C-25), 59.09, 56.68, 54.88, 47.36 (C-13), 42.87 (CH_2), 42.14 (CH_2), 36.07 (CH_2), 35.28, 27.32 (CH_2), 26.22 (CH_3-26) 26.16 (CH_3-27), 20.28 (CH_2), 19.27 (CH_2), 18.25, 11.78. **IR** (film): 2960, 2880, 1685, 1460, 1380. **LRMS** m/z (I,%): 322 (M^+, 1), 307 (23), 265 (11), 264 (58), 103 (100). **HRMS** calcd. for $C_{20}H_{34}O_3$, 322.2510; found, 322.2520. **Anal**: calcd. for $C_{20}H_{34}O_3$, C 74.49, H 10.63%; found, C 74.17, H 10.98%.

11α-[3,3-(Ethylenedioxy)propyl]-25-[(methoxymethyl)oxy]-des-A,B-cholest-8-en-8-yl Trifluoromethanesulfonate (**5**). Grignard reagent **22** was prepared by dropwise addition over 40 min of a solution of the precursor 2-(2-bromoethyl)-1,3-dioxolane (2.20 g, 12.2 mmol) and 1,2-dibromoethane (0.2 mL) in THF (4.3 mL) to a sonicated mixture of magnesium turnings (800 mg, excess) and THF (4.3 mL) at 20 °C. After further sonication for 20 min and posterior decantation of the solids, the supernatant solution of the Grignard reagent was transferred to another reaction flask and cooled to -78 °C. Then, a solution of copper (I) bromide-dimethyl sulfide complex (427 mg, 2.08 mmol) in Me_2S (3.6 mL) was added and the mixture was stirred for 45 min. TMSCl (0.47 mL, 3.72 mmol) was added, followed by a solution of enone **6** (543 mg, 1.69 mmol) in THF (8 mL), and the mixture was stirred for 2h. Then more TMSCl (0.5 mL, 3.94 mmol) was added, and the reaction was allowed to warm to rt overnight. The reaction mixture was concentrated to a small volume, cold saturated $NaHCO_3$ solution (50 mL) was added, and the resulting mixture was filtered and the solids were washed with cold Et_2O (5x75 mL). The two phases were separated, the organic layer was washed with cold water (50 mL) and the aqueous phase was extracted with Et_2O (2x25 mL). The ethereal extracts were combined and then dried, filtered and concentrated to give crude silyl enol ether **23**, which was dried under high vacuum and used immediately in the next reaction.

Methyllithium (2.76 mL, 1.46 M in Et_2O, 4.03 mmol) was added to a solution of crude silyl enol ether **23** in THF (7.2 mL) at 0 °C. The mixture was stirred at rt for 25 min, then cooled to -78 °C, and a solution of *N*-phenyltriflimide (1.44 g, 4.05 mmol) in THF (9.6 mL) was slowly added and the mixture was allowed to reach rt overnight. After evaporation of the solvent, the residue was flash chromatographed (6-12 % EtOAc/hexanes) to give vinyl triflate **5** (658 mg, 70 % from **6**) of the title as a colorless oil . Rf (30% EtOAc/hexanes): 0.64. **^{1}H NMR**: 5.48 (1H, br s, H-9), 4.82 (1H, t, *J*=4.4, OCHRO), 4.67 (2H, s, OCH_2O), 3.79-3.94 (4H, m, OCH_2CH_2O), 3.33 (3H, s, OCH_3), 2.44 (1H, br s, H-11), 1.18 (6H, s, CH_3-26,27), 0.91 (3H, d, *J*=6.3, CH_3-21), 0.74 (3H, s, CH_3-18). **^{1}H-^{1}H COSY**: coupling between 5.48 (H-9) and 2.44 (H-11). **^{1}H-^{1}H nOe** [irradiating ν= 185.7 (0.74 ppm, CH_3-18)]: nOe at 2.44 ppm (H-11β). **^{13}C NMR**: 150.07 (C-8), 119.87 (C-9), 118.66 (m, $J_{C\text{-}F}$=314, CF_3), 104.27 (OCHRO), 90.96 (OCH_2O), 76.15 (C-25), 64.82 ($O\underline{C}H_2\underline{C}H_2O$), 54.93, 54.29, 50.31, 46.33 (C-13), 42.36 (CH_2), 42.20 (CH_2), 36.22 (CH_2), 35.85, 35.46, 30.88 (CH_2), 29.52 (CH_2), 28.23 (CH_2), 26.21 (CH_3-26,27), 21.41 (CH_2), 20.34 (CH_2), 18.54, 11.87. **IR** (film): 2960, 2880, 2360, 1415, 1200. **LRMS** m/z (I,%): 556 (M^+, 0.1), 555 (0.4), 491 (1), 495 (4), 423 (4), 361 (26), 293 (20). **HRMS** calcd. for $C_{26}H_{43}O_7F_3S$, 556.2681; found, 556.2685.

1α-[(*tert*-Butyldimethylsilyl)oxy]-6,7-didehydro-11α-[(3,3-ethylenedioxy)propyl]-25-[(methoxymethyl)oxy]-previtamin D_3 *tert*-Butyldimethylsilyl ether (**3**). A mixture of enyne **4** (150 mg, 0.395 mmol), triflate **5** (193 mg, 0.347 mmol), Et_3N (0.136 mL, 0.968 mmol), and *bis*-triphenylphosphine palladium dichloride (7 mg, 0.010 mmol) in DMF (2.5 mL) was heated at 75 °C for 2 h and then cooled to rt. Et_2O (50 mL) was added and the resulting mixture was washed with water (2x30 mL). The aqueous washings were re-extracted with Et_2O (2x20 mL) and the combined organic extracts were dried, filtered and concentrated. Flash chromatography of the concentrate (2-6 % EtOAc/hexanes) afforded **12** (213 mg, 78 %) as a colorless oil. Rf (20% EtOAc/hexanes): 0.53. **^{1}H NMR** (CD_2Cl_2): 5.87 (1H, t, *J*= 3.0, H-9), 4.80 (1H, t, *J*= 4.6, OCHRO), 4.64 (2H, s, OCH_2O), 4.20 (1H, t, *J*= 3.7, H-1), 4.08 (1H, m, H-3), 3.76-3.94 (4H, m, OCH_2CH_2O), 3.29 (3H, s, OCH_3), 1.87 (3H, br s, CH_3-19), 1.16 (6H, s, CH_3-26,27), 0.94 (3H, d, *J*= 6.5, CH_3-21), 0.88 [9H, s, $(CH_3)_2CSi$], 0.87 [9H, s, $(CH_3)_2CSi$], 0.70 (3H, s, CH_3-18), 0.09 [6H, s, $(CH_3)_2Si$], 0.05 [6H, s, $(CH_3)_2Si$]. **^{13}C NMR** (CD_2Cl_2): 137.63 (C-9), 141.09 (C), 123.06 (C), 115.93 (C), 105.09 (OCHRO), 91.39 (OCH_2O), 92.93 (C), 88.80 (C), 76.48 (C-25), 70.42 (CHOTBS) 64.73 (CHOTBS), 65.29 ($O\underline{C}H_2\underline{C}H_2O$), 55.21, 51.01, 43.93 (C-13), 43.74 (CH_2), 42.68 (CH_2), 41.65 (CH_2), 40.24 (CH_2), 36.87 (CH_2), 36.62, 36.48, 31.70 (CH_2), 30.50 (CH_2), 28.45 (CH_2), 26.57 (CH_3-26), 26.53 (CH_3-27); 26.06, 26.01, 24.63 (CH_2), 20.89 (CH_2), 19.31, 18.97, 18.37 [$Si\underline{C}(CH_3)_3$], 18.29 [$Si\underline{C}(CH_3)_3$], 11.84, -4.24 (CH_3Si), -4.52 (CH_3Si), -4.58 (CH_3Si), -4.50 (CH_3Si). **IR** (film): 2960, 2860, 1460, 1360, 1250, 1140, 1040. **LRMS** m/z (I,%): 786 (M^+, 7), 725 (6), 724 (6), 656 (17), 655 (51), 654 (100). **HRMS** calcd. for $C_{46}H_{82}O_6Si_2$ - TBSOH, 654.4679; found, 654.4682.

1α-[(*tert*-Butyldimethylsilyl)oxy]-11α-[(3,3-ethylenedioxy)propyl]-25-[(methoxymethyl)-oxy]-previtamin D_3 *tert*-Butyldimethylsilyl ether (24). To a mixture of dienyne **3** (75 mg, 95.4 mmol) and Lindlar catalyst (66 mg, Aldrich) in hexane (27 mL) was added a 0.5% (v/v) solution of quinoline in hexane (0.09 mL), and the mixture was stirred under a hydrogen atmosphere (balloon pressure) and carefully monitored by TLC (15% EtOAc/hexanes) to avoid over hydrogenation. After 4.5 h all the starting material had been converted to a slightly less polar product. The reaction mixture was filtered through Celite, the filtrate was concentrated and the residue obtained was purified by flash chromatography (6% EtOAc/hexanes) to give 60 mg (80%) of previtamin **24**, which was immediately subjected to thermal isomerization. Rf (20% EtOAc/hexanes): 0.55. **^{1}H NMR** (CD_2Cl_2): 5.75 (2H, AB, H-6 and H-7), 5.41 (1H, br s, H-9), 4.75 (1H, t, *J*= 4.7, OCHRO), 4.64 (2H, s, OCH_2O), 4.05 (1H, br s, H-3), 4.11 (2H, br s, H-1), 3.74-3.90 (4H, m, OCH_2CH_2O), 3.29 (3H, s, OCH_3), 1.63 (3H, br s, CH_3-19), 1.16 (6H, s, CH_3-26,27), 0.94 (3H, d, *J*= 6.4, CH_3-21), 0.88 [9H, s, $(CH_3)_2CSi$], 0.86 [9H, s, $(CH_3)_2CSi$], 0.69 (3H, s, CH_3-18), 0.09 (3H, s, CH_3Si), 0.08 (3H, s, CH_3Si), 0.04 (3H, s, CH_3Si), 0.03 (3H, s, CH_3Si).

1α-[(*tert*-Butyldimethylsilyl)oxy]-11α-[(3,3-ethylenedioxy)propyl]-25-[(methoxymethyl)-oxy]-vitamin D_3 *tert*-Butyldimethylsilyl ether (25) Previtamin **24** (50 mg, 0.063 mmol) was dissolved in isooctane (7.5 mL) and the solution was refluxed in the dark for 5 h, and then concentrated at rt. The concentrate was purified by flash chromatography (5-6 % EtOAc/hexanes) to yield 50 mg (100%) of vitamin **25** as a transparent oil. Rf (20% EtOAc/hexanes): 0.55. **^{1}H NMR** (CD_2Cl_2): 6.02 and 6.26 (2H, AB, *J*=11.2, H-6,7), 5.17 (1H, br s, H-19) 4.83 (1H, br s, H-19), 4.79 (1H, t, *J*=4.8, OCHRO), 4.64 (2H, s, OCH_2O), 4.37 (1H, m, H-1), 4.17 (1H, m, H-3), 3.76-3.94 (4H, m, OCH_2CH_2O); 3.29 (3H, s, OCH_3), 1.16 (6H, s, CH_3-26,27), 0.92 (3H, d, *J*=6.2, CH_3-21), 0.85 [18H, br s, $2SiC(CH_3)_2$], 0.51 (3 H, s, CH_3-18); 0.05 [6H, s, $Si(CH_3)_2$], 0.04 [6H, s, $Si(CH_3)_2$]. **^{13}C NMR** (CD_2Cl_2): 149.05 (C), 140.74 (C), 135.78 (C), 123.53 (CH) 118.48 (CH), 111.58 (C-19), 105.31 (OCHRO), 91.37 (OCH_2O), 76.48 (C-25); 72.47 (COTBS), 68.05 (COTBS), 65.24 ($O\underline{C}H_2\underline{C}H_2O$), 57.02, 56.90, 55.15, 48.00 (CH_2), 46.40 (CH_2), 46.18 (C-13), 45.33 (CH_2), 42.68 (CH_2), 36.90 (CH_2), 36.58, 36.15 (CH_2), 35.13, 32.27 (CH_2), 32.18 (CH_2), 28.39 (CH_2), 26.52 (CH_3-26,27); 26.03 [2($\underline{C}H_3)_3CSi$], 22.38 (CH_2), 20.93 (CH_2), 19.12, 18.51 [$(CH_3)_3\underline{C}Si$], 18.40 [$(CH_3)_3\underline{C}Si$], 12.92, -4.59 (CH_3Si), -4.70 (CH_3Si), -4.92 (CH_3Si). **IR** (film): 2940, 2860, 2840, 1460, 1370, 1350, 1250. **LRMS** m/z (I,%): 789 (11), 788 (M^+, 18), 658 (11), 657 (40), 656 (62), 368 (19), 248 (100). **HRMS** calcd. for $C_{46}H_{84}O_6Si_2$ - TBSOH, 656.4836; found, 656.4837. **UV** (EtOH): λmax=265 nm, λmin=228 nm.

1α,25-Dihydroxy-11α-[(3,3-dimethoxy)propyl]-vitamin D_3 (2). A mixture of vitamin **25** (15 mg, 0.019 mmol) and AG 50W-X4 resin (700 mg, prewashed with MeOH) in MeOH (10 mL) was stirred at rt for 32 h in the dark. The resin was filtered out and washed with EtOAc (15 mL), and the combined filtrates and washings were concentrated. The residue was dissolved in EtOAc (15 mL) and the resulting solution was

washed with saturated NaCl (10 mL), dried, filtered and concentrated. The concentrate was purified by flash chromatography (30-50% EtOAc/hexanes) to give 8 mg (81%) of the desired compound **17** as a white solid. Rf (50% EtOAc/hexanes): 0.30. **^{1}H NMR**: 6.37 and 6.01 (2H, AB, *J*=11.4, H-6,7), 5.32 (1H, t, *J*=1.7, H-19*Z*), 4.99 (1H, br s, H-19*E*), 4.43 (1H, dd, J_1=4.4, J_2=8.0, H-1), 4.35 (1H, t, *J*= 5.7Hz, OCHRO), 4.23 (1H, m, H-3), 3.33 (6H, s, $2OCH_3$), 1.21 (6H, s, CH_3-26,27), 0.93 (3H, d, *J*=6.2, CH_3-21), 0.53 (3H, s, CH_3-18). **^{13}C NMR**: 147.82, 142.08, 133.27, 124.86, 117.27, 111.75, 104.97, 77.21, 71.07, 70.79, 66.87, 56.57, 56.36, 52.75, 47.49, 45.84, 45.26, 44.39, 42.88, 36.36, 36.05, 35.89, 34.80, 32.33, 30.32, 29.33, 29.18, 27.90, 22.01, 20.78, 18.86, 12.72. **IR** (film): 3370 (br), 2920, 1440, 1370, 1120, 1040. **LRMS** m/z (I,%): 520 (0.1), 519 (0.4), 518 (M^+, 1), 501 (3), 500 (8), 486 (25), 429 (309), 428 (100), 410 (44), 392.6 (71). **HRMS** calcd. for $C_{32}H_{54}O_5$, 518.3971; found, 518.3977. **UV** (EtOH): λmax=265 nm, λmin=228 nm.

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