Synthesis of 14,20-Bis-*epi*-1α,25-dihydroxy-19-norvitamin D_3 and Analogues

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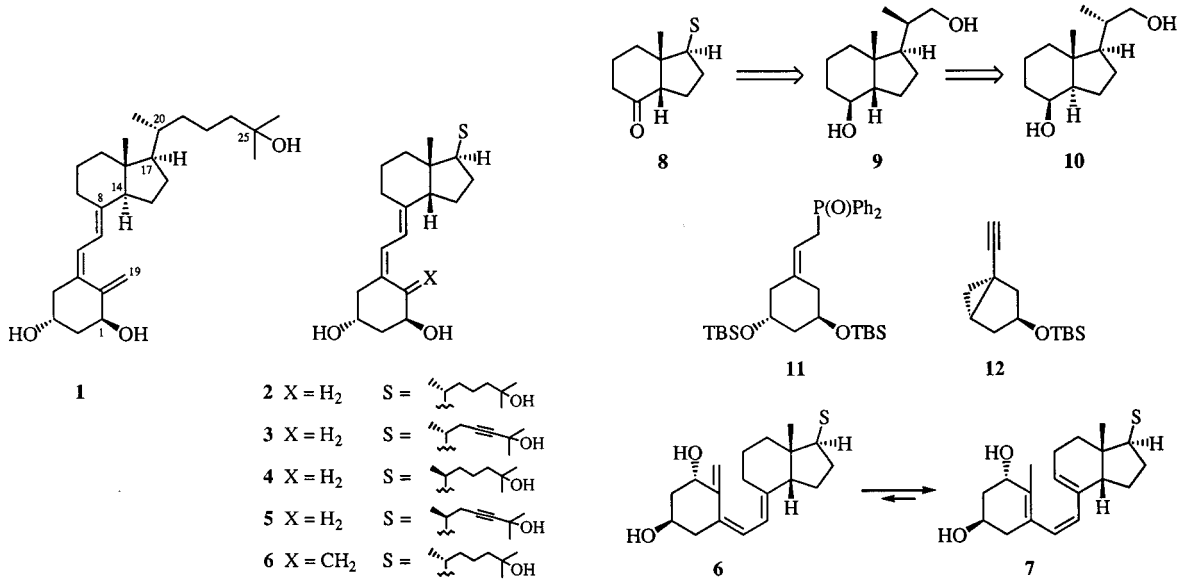
14,20-Bis-*epi*-1α,25-dihydroxy-19-norvitamin D_3 and side chain analogues thereof have been synthesised via the 14,20-bis-epi-Inhoffen–Lythgoe diol **9**. The synthesis of this precursor was performed via degradation of vitamin D_2 and by total synthesis starting from Hajos–Wiechert ketone **24**.

The observation that the metabolite 1α,25-dihydroxy-vitamin D_3 (**1**; calcitriol) is active in the regulation of cell proliferation and differentiation, next to its classical role in calcium-bone homeostasis, has led in recent years to the development of analogues capable of dissociating cell differentiating effects from calcemic effects.[1][2] Among the three fragments of the vitamin D skeleton structural modifications of the side chain and of the A-ring have been especially studied in the past.[3] Some years ago, we embarked on an extensive study of the structure-function relationship focussing on the least studied part of the module, i.e. the central CD-ring region.[4] In this context, we presently, describe a synthetic study of 14-*epi* analogues such as **2** and further side-chain modified analogues (e.g. **3**, **4**, **5**). Because of the *cis*-fused nature of the central hydrindane, these analogues should be of the 19-nor type (Scheme 1) in order to avoid the 1.7 sigmatropic rearrangement. Indeed, in contrast to the natural series[5] (e.g. **1**) this 1,7-sigmatropic rearrangement induced vitamin D − previtamin D equilibrium is largely shifted towards the latter structural isomer (e.g. **6**/**7**; ratio circa 5:95)[6] The previtamin triene structural unit in **7** (2 endocyclic double bonds) is thermodynamically more stable than the vitamin triene system (3 exocyclic double bonds). In the natural series this inherent stability is outweighed by tortional constraints imposed on *trans*-fused hydrindane, resulting in a less favourable position of an 8,9-double bond.[7]

Thus the CD-ring side chain precursors **8** have to be coupled with a 19-nor-A-ring precursor such as **11**[8] or **12**[9]. The *cis*-fused C-8 ketones **8** (steroid numbering) can be obtained bybase-catalysed equilibration of the corresponding *trans*-isomer: (*cis*/*trans* ratio circa 3:1). The *trans*-fused precursors are generally formed starting from the Inhoffen−Lythgoe diol **10**[10] (from ozonolysis of vitamin D_2 **17** in Scheme 3) via construction of the side-chain and oxidation of the 8-hydroxy group. This strategy, with subsequent



Scheme 1

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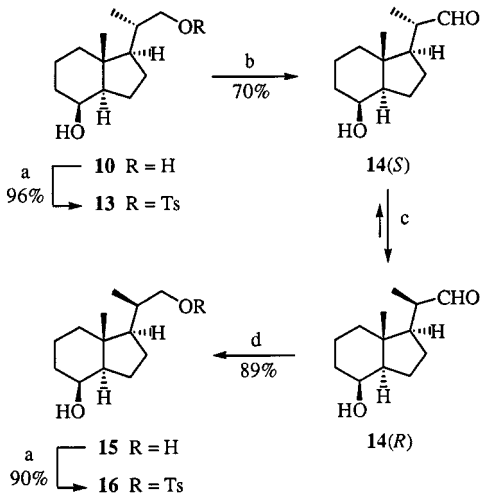


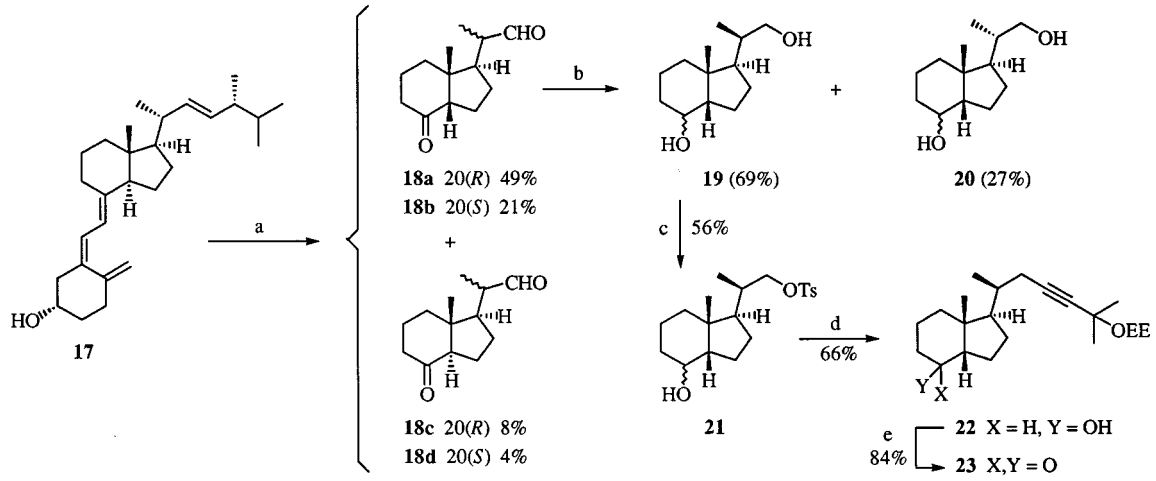
Scheme 2. a: TsCl, pyridine, 7°C, 16 h. b: 2,4,6-collidine, DMSO, 150°C, 30 min. c: HCl, MeOH, H_2O, room temp., 20 h. d: $NaBH_4$, MeOH, room temp., 30 min

coupling with the A-ring precursor is thus rather straightforward. However we were also interested in the synthesis of 14,20-bis-*epi* analogues such as **4** and **5** for which the 14,20-bis-*epi* Inhoffen−Lythgoe diol **9** would be an ideal precursor. Indeed it has been shown in the natural *trans*-fused CD-ring series that C-20 epimers can induce highly enhanced biological activities, further modulated by side-chain modifications.[11]

Our first route to the title compounds is a partial synthesis starting from vitamin D_2 and involving epimerisation at C-20 (Scheme 2). It is indeed known that the equilibrium at C-20 is moderately in favour of the unnatural configuration.[12] In order to minimise the use of protecting groups we decided to perform the Kornblum oxidation[13] of **13**, the monotosylate of the Inhoffen−Lythgoe diol (**10**). This oxidation led to the epimeric aldehydes **14**(*S*) and **14**(*R*) in a 3:1 ratio. Further equilibration led to an epimeric mixture, also moderately in favour of **14**(*R*) (ratio circa 1:3); HPLC separation was rather tedious at this stage and gave **14**(*R*) in an isolated yield of 54%. Finally, reduction provided **15**. Recycling of **14**(*S*), an inherent advantage of this approach, is however offset by the unpractical separation.

A more practical procedure involves reduction of the mixture of aldehydes **14** and a more facile separation of isomers **10** and **15** (41% overall yield from **10**). Monotosylation then gave **16**, the intermediate for introduction of the side chain (vide infra). As in a later stage epimerisation at C-14 has to be carried out as a separate step, we decided to investigate a protocol in which both epimerisations at C-14 and C-20 are performed simultaneously (Scheme 3). Therefore, ozonolysis of vitamin D_2 **17** was carried out without reductive work-up. The resulting crude keto-aldehyde was directly subjected to acid-catalysed equilibration, which afforded a mixture of the four isomers **18**. The respective structures were determined by ^{1}H-NMR spectroscopy. Column chromatography led to two fractions; the first one consisted of a mixture of **18a** and **18b** (2.4:1 ratio), while the second one was a mixture of **18c** and **18d** (circa 2:1). The *cis*-fusion of **18a** and **18b** was proved by the shift value for the angular methyl group (δ = 1.03 and 1.04, respectively) while for **18c** and **18d** values of δ = 0.64 and 0.68 were observed.

Reduction of the combined **18a**, **b** gave a mixture of the four epimeric diols; separation of the respective pairs of 20-epimers **19** and **20** was possible by HPLC. The unselective reduction is due to the fact that the *si*-face in a flexible *cis*-fused hydrindane is less hindered compared to the *trans*-isomer. As this selectivity is of no consequence for the final result we decided to pursue along this route. However we found that the subsequent monotosylation gave **21** in only 56% yield due to substantial formation of the ditosylate. This stands in contrast to the transformation of **15** into **16** where the axially oriented 8-hydroxy group is more sterically hindered. The low overall yield of **21** (19% from **17**) combined with as well a poor diastereoselectivity (steps a and b) and chemoselectivity (step c) led us to abandon this route. Only for sample preparation and structure identification (vide infra) it was continued to the key-intermediate

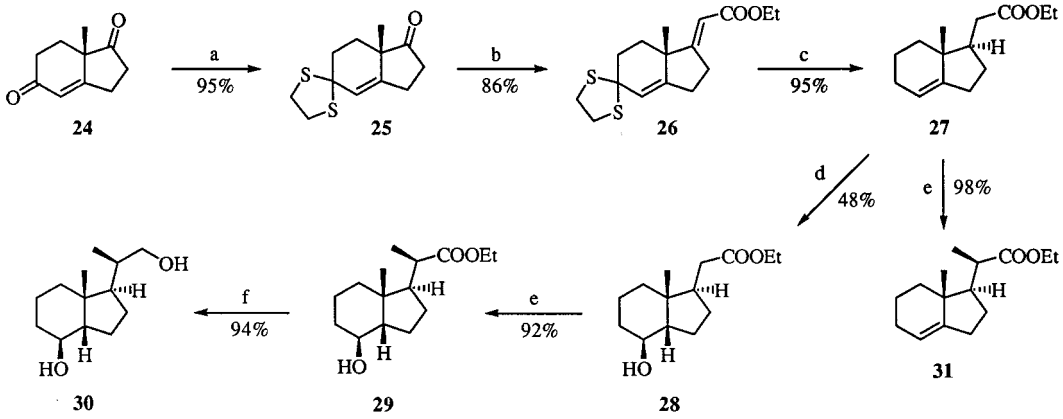


Scheme 3. a: (i) O_3, CH_2Cl_2/MeOH, 1:1, −78°C; (ii) Me_2S; (iii) 5% HCl, THF, 30°C, 36 h. b: $NaBH_4$, MeOH, room temp., 20 min. c: TsCl, pyridine, 0°C, 14 h. d: NaH, DMSO, 2-(ethoxyethyl)-2-methyl-3-butyn, room temp., 30 min. e: PDC, CH_2Cl_2, room temp., 4 h

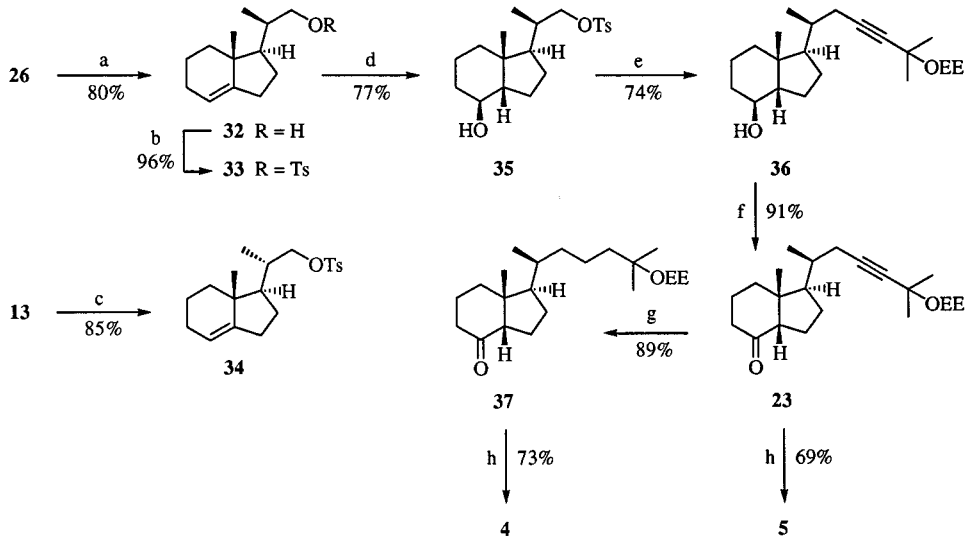
23 (compare **8**). In fact both approaches starting from vitamin D_2 suffer from low yields and cumbersome separations. Although the first route via **16**, is more acceptable we still have to carry out at a later stage the epimerisation at C-14 and a separation of the *cis*- and *trans*-fused hydrindanones.

We therefore decided to investigate a total synthesis, which could favourably compete with the partial synthesis, for the formation of the target key-intermediates C-8 ketones **8** via the 14,20-bis-*epi*-Inhoffen−Lythgoe diol **9** or derivative thereof. Our strategy centers on two essential transformations of the Hajos−Wiechert ketone **24**[14] which was selected as starting material. These transformations are (i) construction of the *cis*-fused hydrindane with an 8-hydroxy function and (ii) the somewhat problematic diastereoselective introduction of the side chain. Furthermore the route had to be short, with hopefully some "one-pot" reactions in order to offer a practical alternative to the above-described partial synthesis from vitamin D_2. In a first approach (Scheme 4) we decided to install the C-ring functionalities prior to attack the problem of the side-chain construction.

The dithioacetal **25**[15] was formed from **24** (99.8% ee)[16] and it was subjected to a Horner−Wadsworth−Emmons reaction leading to **26**. The conjugated double bond was reduced with simultaneous removal of the dithioacetal group. Hydroboration of **27** led in low yield to **28** next ca. 10% of the *trans*-fused isomer. For the methylation at C-20, we relied on the work of Wicha et al.[17], who have observed that, in steroids and *trans*-fused hydrindanes, this reaction leads, with complete diastereoselectivity, to the unnatural (*R*)-configuration. We found that this observation is also valid in the *cis*-fused series, as **29** was formed as the sole epimer. Reduction then gave the 14,20-bis-*epi*-Inhoffen−



Scheme 4. a: $HSCH_2CH_2SH$, AcOH, PTSA, room temp., 5 h. b: $(EtO)_2P(O)CH_2COOEt$, NaOEt, EtOH, reflux, 2.5 h. c: (i) Li, Ph_3CH, *t*BuBr, NH_3, THF, −78°C, 10 min; (ii) Li, **26**, THF, −78°C, 30 min; (iii) *t*BuBr, NH_4Cl. d: (i) $BH_3 \cdot THF$, THF, 0°C, 40 min; (ii) TAO, reflux, 2 h. e: (i) LDA, THF, −78°C, 1 h; (ii) MeI, −78°C, 2.5 h. f: $LiAlH_4$, Et_2O, 0°C, 2 h



Scheme 5. a: (i) Li, Ph_3CH, *t*BuBr, NH_3, THF, −78°C, 10 min; (ii) Li, **26**, THF, −78°C, 30 min; (iii) *t*BuBr; (iv) MeI, −78°C, 2 h; (v) Li, MeOH, −78°C, 15 min, reflux, 30 min; (vi) MeOH, NH_4Cl. b: TsCl, Et_3N, DMAP, CH_2Cl_2, room temp., 15 h. c: Ph_3P, DEAD, THF, reflux, 15 h. d. (i) $BH_3 \cdot THF$, THF, 0°C, 2 h; (ii) NaOH, H_2O_2, room temp., 50 min. e: NaH, DMSO, 2-(1-ethoxyethylether)-2-methyl-3-butyne, room temp., 2 h. f: TPAP, NMO, molec. sieves, CH_2Cl_2, room temp., 1 h. g: H_2 (1 atm), 5% Rh(Al), EtOAc, room temp., 3 h. h: (i) n-BuLi, **11**, THF, −78°C, 1 h; (ii) Amberlyst-15, MeOH/THF 1/1, room temp., 15 h

Lythgoe diol **30**. With respect to the low chemoselectivity of the monotosylation of **19** (Scheme 3), **30** is not a very adequate intermediate. Furthermore the transformation of **27** to **30** involves three separate steps with one (d) being low yielding. When we observed that also the methylation of **27** to **31** was completely diastereoselective, it became evident that a route to the target molecule **23** can considerably been shortened by simultaneous functional group transformations (Scheme 5).

Compound **26** is a suitable substrate for a "tandem" process. Initial treatment of **26** with lithium in liquid ammonia performed simultaneously the removal of the dithioacetal and reduction of the conjugated double bond. The resulting enolate was in situ methylated and the ester function was subsequently reduced upon adding methanol and fresh lithium. This "one pot" process let to **32** in an excellent overall yield of 80%; also ca. 10% of the C-17 epimer was isolated. In order to circumvent the unselective tosylation observed on the *cis*-fused diol **19** (Scheme 3), **32** was first transformed into tosylate **33**. At this stage the configuration at C-20 was proven; **33** is epimeric to **34,** obtained from **13**, the monotosylate of the Inhoffen−Lythgoe diol **10**. Finally, hydroboration gave the desired alcohol **35** (77%) next to some *trans*-fused isomer (7%).

Introduction of the complete side-chain upon alkylation of tosylate **35** afforded **36**, subsequent oxidation of wich led to **23**, identical to the compound described in Scheme 3, which provides additional structural proof. The overall yield of **23** starting from the Hajos−Wiechert ketone **24** is 33%. Lythgoe coupling of **23** with A-ring precursor **11** and subsequent deprotection gave the vitamin D analogue **5**. On the other hand hydrogenation of **23** gave **37**, the CD ring intermediate for the synthesis of 1α,25-dihydroxy-14,20-bis-*epi*-19-norvitamin D_3 **4**.

The biological activities of these analogues will be described in an appropriate journal.

Experimental Section

General: All reactions were carried out under argon atmosphere with magnetic stirring (unless otherwise specified). Reaction products were isolated (work-up) by the addition of water and extraction with the specified solvent. The combined extracts were washed with saturated brine and dried with $MgSO_4$. The solvent was removed from the filtered solutions on a rotary evaporator. − Column chromatography separations were performed on silica gel with hexane-EtOAc (ratio given between brackets) as eluent unless otherwise stated. HPLC separations were performed on a Knauer 64, a Waters 6000A or a Kontron 420 delivery system with RI detection using hexane-EtOAc (ratio given between brackets) as eluent unless otherwise stated. − Optical rotations were measured with a Perkin Elmer 421 polarimeter. − IR spectra were recorded on a Perkin Elmer FTIR-1600 spectrometer and mass-spectra on a Finnigan 4000 or HP-5988 spectrometer. − The ^{1}H-NMR spectra were recorded at 200 MHz (Varian-Gemini), 360 MHz or 500 MHz (WH-Brucker), the ^{13}C-NMR and DEPT spectra were recorded at 50 MHz (Varian-Gemini), the chemical shifts are expressed in ppm relative to TMS and coupling constants are in Hz. − All solvents were purified or dried according to standard procedures. − HRMS were performed on a Kratos MS-50TC. − Elemental analyses were carried out by ICHOR, Université Pierre et Marie Curie (Paris, France). − In small scale experiments, reagents were added with a 100-μL syringe.

De-A,B-8β-hydroxy-23,24-dinor-20-*epi*-cholan-22-al (14*R*): A solution of tosylate **13** (100 mg, 0.27 mmol) and 2,4,6-collidine (72 μL, 0.55 mmol) in dry DMSO (3 mL) was stirred under N_2 at 150 °C for 30 min. The reaction mixture was then allowed to reach room temp., diluted with water, extracted with Et_2O, followed by the usual work-up. HPLC separation (8:3) yielded a mixture of **14**(*S*) and **15**(*R*) in a 3:1 ratio (40 mg, 70%). A solution of this mixture (140 mg, 0.67 mmol) in 10% HCl (1.2 mL) and MeOH (4 mL) was stirred under N_2 at room temp. for 20 h. The residue obtained upon solvent concentration was diluted with Et_2O and washed with $NaHCO_3$. After the usual work-up, separation of the mixture by HPLC (85:15) afforded **14**(*S*) (38 mg, 27%) and **14**(*R*) (75 mg, 54%) as oils. **14**(*S*): R_f = 0.40 (hexane/EtOAc, 8:3). − IR (film): 3430, 2709, 1720 cm^{-1}. − ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.98 (3 H, s), 1.10 (3 H, d, *J* = 6.85 Hz), 1.15−1.98 (12 H, m), 2.37 (1 H, m), 4.11 (1 H, m), 9.58 (1 H, d, *J* = 3.22 Hz). **14**(*R*): R_f = 0.40 (hexane/EtOAc, 8:3). − IR (film): $\tilde{\nu}$ = 3439, 2707, 1720 cm^{-1}. − ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.95 (3 H, s), 1.02 (3 H, d, *J* = 6.8 Hz), 1.04 (1 H, m), 1.30−1.92 (11 H, m), 2.35 (1 H, m), 4.10 (1 H, m); 9.54 (1 H, d, *J* = 4.9 Hz).

20-*Epi*-Inhoffen−Lythgoe Diol (15): Method A − A solution of **14**(*R*) (70 mg, 0.33 mmol) and $NaBH_4$ (25 mg, 0.66 mmol) in dry MeOH (3 mL) was stirred under N_2 at room temp. for 30 min. After solvent evaporation, the residue was diluted with EtOAc, washed with 10% HCl, and with sat. $NaHCO_3$. Work-up and HPLC separation yielded **15** as white crystals (63 mg, 89%). R_f = 0.18 (hexane/EtOAc, 8:3). − M.p. 87 − 88 °C. − $[\alpha]_D^{20}$ = +31 (*c* = 1.14, $CHCl_3$). − ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.951 (3 H, d, *J* = 6.7 Hz), 0.952 (3 H, s), 1.10−1.90 (13 H, m), 3.45 (1 H, dd, *J* = 10.6, 6.9 Hz), 3.70 (1 H, dd, *J* = 10.6, 3.5 Hz), 4.08 (1 H, m). − MS *m/z* (%): 194 (3), 179 (4), 163 (3), 111 (100). − $C_{13}H_{24}O_2$: calcd C 73.52, H 11.41; found C 73.80, H 11.11.

Method B − A solution of tosylate **13** (1.1 g, 3.01 mmol) and 2,4,6-collidine (1.20 mL, 9.09 mmol) in dry DMSO (17 mL) was stirred 150 °C for 40 min. After cooling to room temp., the reaction mixture was poured in H_2O and extracted with CH_2Cl_2 washed with brine and dried ($MgSO_4$). After work-up and solvent concentration, the solution was treated with DBU (0.20 mL). The mixture was stirred at room temp. for 2 days. The residue obtained upon solvent evaporation was taken up in dry MeOH (10 mL). The solution was cooled to −20 °C, and $NaBH_4$ (300 mg, 7.89 mmol) was added; stirring was continued at −20 °C for 30 min and room temp. for 10 min. After removal of MeOH, the residue was diluted with Et_2O, washed with 10% HCl, and with sat. $NaHCO_3$. Work-up and HPLC separation (7:3) yielded diol **15** (250 mg) and diol **10** (260 mg) in 39% and 41% yield, respectively.

Tosylate 16: A solution of diol **15** (53 mg, 0.25 mmol) and TsCl (72 mg, 0.38 mmol) in dry pyridine (1.5 mL) was kept in a refrigerator for 16 h. The reaction mixture was poured in ice-water and extracted with EtOAc. Work-up and HPLC separation (7:3) yielded **16** (83 mg, 90%). R_f = 0.24 (hexane/EtOAc, 8:3). − IR (film): $\tilde{\nu}$ = 3430, 1598, 840 cm^{-1}. − ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.84 (3 H, s), 0.88 (3 H, d, *J* = 6.7 Hz), 1.01−1.84 (13 H, m), 2.45 (3 H, s), 3.79 (1 H, dd, *J* = 9.3, 7.1 Hz), 4.05 (1 H, m), 4.10 (1 H, dd, *J* = 9.3, 3.5 Hz), 7.78 (2 H, d, *J* = 8.1 Hz), 7.78 (2 H, d, *J* = 8.15 Hz). − MS *m/z* (%): 348 (0.5), 111 (100), 91 (82).

De-A,B-22-oxo-23,24-dinor-20-*epi*-cholestan-8-one (18a): A solution of vitamin D_2 **17** (2.0 g, 5.05 mmol) in dry MeOH (160 mL) and

pyridine (2 mL), at −78 °C, was treated with O_3 until the blue colour persisted. The excess O_3 was blown off with a N_2 stream, Me_2S was added and the mixture was concentrated. A solution of the residue in THF (30 mL) and a 5% HCl solution (10 mL, 14 mmol) was stirred for 36 h at 30 °C. After solvent evaporation, the residue was diluted with Et_2O. Work-up and column chromatography (8:2) led to a crystalline mixture of **18a** and **18b** (ratio 2.4:1) and an oily mixture (2:1) of **18c** and **18d**. HPLC separation (same eluent) of the first fraction gave **18a** (520 mg, 49%) next to **18b** (216 mg, 21%). **18a**: R_f = 0.46 (hexane/EtOAc, 7:3). − M.p. 83.5−84.5 °C. − IR (film): $\tilde{\nu}$ = 2937, 2877, 1698, 1454 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.04 (3 H, s), 1.05 (3 H, d, *J* = 5.9 Hz), 1.40 (1 H, m), 1.50−1.71 (4 H, m), 1.75−1.95 (3 H, m), 2.25−2.40 (5 H, m), 9.51 (1 H, d, *J* = 4.4 Hz). − MS *m/z* (%): 208 [M^+] (2), 193 (3), 151 (18), 124 (14), 111 (84), 82 (52), 55 (64), 41 (100).

Epimeric Diols 19: A mixture of **18a** and **18b** (200 mg, 0.96 mmol) and $NaBH_4$ (73 mg, 1.92 mmol) in MeOH (20 mL) was stirred at room temp. for 30 min; 10% HCl solution (8 mL) was then added. After 10 min, the solvent was evaporated and the residue was diluted with Et_2O. Work-up and HPLC separation (1:1 and MeOH 1.5%) of the residue gave **19** (140 mg, 69%) next to **20** (55 mg, 27%). **19**: R_f = 0.23 (hexane/EtOAc, 1:1). − ^1H NMR (360 MHz, $CDCl_3$): δ = 0.86 (3/2 H, d, *J* = 6.8 Hz), 0.89 (3/2 H, s), 0.93 (3/2 H, d, *J* = 6.8 Hz), 1.02 (3/2 H, s), 1.10−2.02 (13 H, m), 3.31−3.49 (2 H, m), 3.56 (1/2 H, dd, *J* = 4.9, 10.4 Hz), 3.90 (1/2 H, dt, *J* = 5.0, 10.2 Hz).

Tosylate 21: As described for **16**. Yield 56%. R_f = 0.40 (hexane/EtOAc, 1:1). − IR (film): $\tilde{\nu}$ = 3386, 2932, 1598, 1456, 1358, 1176, 1097, 1040, 962 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.81 (3/2 H, s), 0.82 (3/2 H, d, *J* = 5.8 Hz), 0.89 (3/2 H, d, *J* = 6.5 Hz), 0.94 (3/2 H, s), 1.02−2.08 (13 H, m), 2.46 (3 H, s), 3.21−3.36 (1/2 H, m), 3.70−3.96 (5/2 H, m), 7.34 (2 H, d, *J* = 8.3 Hz), 7.78 (2 H, d, *J* = 8.3 Hz). − MS *m/z* (%): 366 [M^+] (1), 348 (2), 306 (1), 275 (1), 229 (1), 194 (8), 176 (34), 135 (45), 111 (47), 91 (100), 55 (70), 41 (73).

De-A,B-25-(1-ethoxyethylether)-14,20-bis-*epi*-23-ynecholestan-8-one (23): From **21** as described for **23** from **35**. Yield for the 2 steps: 39 mg, 55% from 52 mg of **21**. Spectral data: vide infra.

(7a*S*)-5,5-(Ethylenedithio)-7a-methyl-1,2,3,5,6,7,7a-heptahydro-1-indenone (25): To a solution of **24** (1.00 g, 6.09 mmol) in glacial HOAc (2.6 mL) were added 1,2-ethanedithiol (0.632 g, 6.71 mmol), PTSA (0.46 g) and glacial HOAc (6.3 mL). The mixture was stirred at room temp. for 5 h, poured into H_2O, and stirred for another 15 min. The white solid was filtered off, washed successively with a dilute $NaHCO_3$ solution and H_2O. After drying, column chromatography (hexane/$CHCl_3$, 1:1) gave **25** (1.39 g, 95%) as white crystals. R_f = 0.25 (pentane/$CHCl_3$, 7:3). − M.p. 142 °C. − $[\alpha]_D^{20}$ = +370 (*c* = 1.1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 2910, 1737, 1662, 1449, 1434, 1380, 1326, 1272, 1234, 1150, 1099, 1057, 1009, 868, 839, 772, 681 cm^{-1}. − ^1H NMR: (500 MHz, $CDCl_3$): δ = 1.14 (3 H, s), 1.63 (1 H, dt, *J* = 4.8, 12.8 Hz), 1.84 (1 H, td, *J* = 3.4, 13.6 Hz), 2.23−2.34 (3 H, m), 2.50−2.60 (2 H, m), 2.69 (1 H, dtd, *J* = 2.1, 10.1, 14.8 Hz), 3.23 (1 H, m), 3.41 (3 H, m), 5.72 (1 H, bs). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 218.55 (C), 143.02 (C), 125.31 (CH), 64.88 (C), 47.24 (C), 40.52 (CH_2), 39.63 (CH_2), 38.01 (CH_2), 36.37 (CH_2), 29.30 (CH_2), 26.36 (CH_2), 21.10 (CH_3). − MS *m/z* (%): 240 [M^+] (30), 212 (14), 179 (7), 151 (12), 119 (20), 118 (100), 91 (23), 45 (34).

Unsaturated Ester 26: To a stirred solution of ketone 25 (0.950 g, 3.95 mmol) and triethyl phosphonoacetate (3.6 g, 16 mmol) in dry EtOH (20 mL) at 35−40 °C was added slowly a solution of NaOEt [from Na (0.350 g, 15.2 mmol) in EtOH (7 mL)]. The mixture was refluxed for 3 h, concentrated and diluted with H_2O. Work-up, column chromatography (20:1) and HPLC (25:1) gave 26 (1.05 g, 86%) as a crystalline product. R_f = 0.26 (isooctane/EtOAc, 100:6). − M.p. 69 °C. − $[\alpha]_D^{20}$ = +137 (*c* = 1.0, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 2966, 2920, 2851, 1704, 1646, 1418, 1369, 1277, 1256, 1232, 1210, 1177, 1042, 858 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.13 (3 H, s), 1.28 (3 H, t, *J* = 7.1 Hz), 1.69 (1 H, m), 1.90 (1 H, td, *J* = 3.4, 13.1 Hz), 2.34 (3 H, m), 2.52 (1 H, dtd, *J* = 2.52, 9.9, 15.3 Hz), 2.87 (1 H, dtd, *J* = 2.7, 9.4, 20.0 Hz), 3.03 (1 H, tq, *J* = 2.4, 10.4 Hz), 3.21 (1 H, m), 3.33−3.45 (3 H, m), 4.15 (2 H, q, *J* = 7.1 Hz), 5.56 (1 H, m), 5.63 (1 H, t, *J* = 2.6 Hz). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.93 (C), 147.56 (C), 143.59 (C), 123.96 (CH), 121.58 (CH), 65.04 (C), 60,41 (CH_2), 45.76 (C), 40.35 (CH_2), 39.32 (CH_2), 38.90 (CH_2), 35.91 (CH_2), 33.26 (CH_2), 31.86 (CH_2), 21.59 (CH_3), 13.98 (CH_3). − MS *m/z* (%): 310 [M^+] (47), 282 (42), 250 (32), 236 (9), 209(18), 189 (17), 175 (17), 143 (20), 128 (40), 91 (40), 69 (57), 45 (100). − $C_{16}H_{22}O_2S_2$: calcd C 61.84, H 7.09; found C 61.84, H 7.13.

Ethyl [(1*R*,7a*S*)-7a-methyl-1,2,3,5,6,7,7a-heptahydroindenyl]methylcarboxylate (27): To liq. NH_3 (20 mL) at −78 °C was added Ph_3CH (4 mg) in THF (0.5 mL) and Li (15 mg). 2-Bromo-2-methylpropane was added until the red colour persisted (ca. 160 μL).[18] Li (35 mg) was added, and the mixture was stirred for 15 min before adding **26** (100 mg, 0.32 mmol) in THF (3.5 mL). Stirring was continued for 0.5 h at −78 °C, then 2-bromo-2-methylpropane was added slowly until the solution became red, followed by NH_4Cl. The liq. NH_3 was evaporated and Et_2O was added. Filtration over silica gel and column chromatography (isooctane/Me_2CO, 100:2) afforded ester **27** (68 mg, 95%) as an oil. R_f = 0.18 (isooctane/Me_2CO, 100:2). − $[\alpha]_D^{20}$ = +54 (*c* = 1.2, $CHCl_3$). − IR (film): 2933, 1736, 1464, 1375, 1297, 1254, 1157, 1130, 1043 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (3 H, s), 1.13 (1 H, dt, *J* = 3.9, 13.0 Hz), 1.25 (3 H, t, *J* = 7.1 Hz), 1.41 (1 H, dtd, *J* = 7.1, 11.4, 23.8 Hz), 1.56−1.69 (3 H, m), 1.79−2.04 (4 H, m), 2.14−2.20 (1 H, m), 2.18 (1 H, dd, *J* = 9.8, 14.5 Hz), 2.33−2.43 (1 H, m), 2.39 (1 H, dd, *J* = 4.9, 14.6 Hz), 4.12 (2 H, q, *J* = 7.1 Hz), 5.29 (1 H, m). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.47 (C), 147.34 (C), 117.11 (CH), 60.10 (CH_2), 47.47 (CH), 41.76 (C), 35.24 (CH_2), 34.97 (CH_2), 27.68 (CH_2), 27.22 (CH_2), 25.03 (CH_2), 18.63 (CH_2), 18.03 (CH_3), 14.18 (CH_3). − MS *m/z* (%): 222 [M^+] (5), 199 (2), 177 (4), 134 (100), 119 (24), 105 (14), 91(28), 79 (20).

Alcohol 28: To a solution of olefin **27** (97 mg, 0.44 mmol) in dry THF (1 mL) was added at 0 °C 1M BH_3·THF solution (0.65 mmol). After 40 min at 0 °C trimethyl amine *N*-oxide (145 mg, 1.31 mmol) was added and stirring was continued at reflux for 2 h. The mixture was diluted with Et_2O and H_2O. Work-up, column chromatography (7:3) and HPLC (7:3) gave **28** (50 mg, 48%). R_f = 0.28 (hexane/EtOAc, 7:3). − $[\alpha]_D^{20}$ = +69 (*c* = 1.1, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3406, 2929, 1733, 1447, 1376, 1328, 1292, 1164, 1120, 1034, 934, 864 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): d = 0.80 (3 H, s), 1.14−1.22 (2 H, m), 1.25 (3 H, t, *J* = 7.1 Hz), 1.30−1.58 (5 H, m), 1.73 (1 H, ddd, *J* = 4.5, 10.1, 14.0 Hz), 1.82−1.93 (2 H, m), 2.05 (1 H, m), 2.06 (1 H, dd, *J* = 11.3, 15.7 Hz), 2.25 (1 H, m), 2.28 (1 H, dd, *J* = 4.2, 15.9 Hz), 3.35 (1 H, m), 4.12 (2 H, q, *J* = 7.1 Hz). − ^{13}C NMR (50 MHz, $CDCl_3$): d = 173.74 (C), 71.91 (CH), 60.25 (CH_2), 55.59 (CH), 44.87 (C), 38.09 (CH), 35.44 (CH_2), 35.07 (CH_2), 32.82 (CH_2), 28.18 (CH_2), 24.69 (CH_2), 24.03 (CH_3), 19.99 (CH_2), 14.29 (CH_3). − MS *m/z* (%): 222 (3), 195 (5), 176 (4), 151 (6), 134 (100), 111 (22), 93 (34), 81 (30), 79 (28).

Alcohol 29: To a solution of LDA (2 M, 0.092 mL, 0.18 mmol) in THF (0.1 mL) was added **28** (11 mg, 0.046 mmol) in THF (1 mL)

at −78 °C and the solution was stirred for 1 h. Then MeI (0.028 mL, 0.46 mmol) was added and stirring was continued for 2.5 h. After dilution with H_2O and Et_2O work-up and column chromatography (7:3) afforded **29** (10.7 mg, 92%). R_f = 0.30 (hexane/EtOAc, 7:3). − IR (film): 3405, 2935, 1732, 1459, 1376, 1251, 1160, 1097, 1064, 1039, 1017, 862, 804, 770 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3 H, s), 1.11 (3 H, d, *J* = 6.8 Hz), 1.15 (2 H, m), 1.25 (3 H, t, *J* = 7.1 Hz), 1.27−1.54 (5 H, m), 1.69 (1 H, m), 1.79 (1 H, m), 1.95 (2 H, m), 2.16 (1 H, q, *J* = 9.9 Hz), 2.28 (1 H, ddd, *J* = 6.8, 10.6, 13.6 Hz), 3.34 (1 H, dt, *J* = 4.0, 10.7 Hz), 4.08 (2 H, m).

14,20-Bis-*epi*-Inhoffen−Lythgoe Diol (30): A solution of **29** (8 mg, 0.031 mmol) in dry Et_2O (1 mL) and $LiAlH_4$ (12 mg, 0.31 mmol) was stirred at 0 °C for 2 h. Then a saturated Na_2SO_4 solution was added until white precipitate was formed. Filtration, work-up, and column chromatography (pentane/Me_2CO, 6:4) and HPLC (pentane/Me_2CO, 75:25) afforded **30** (6.2 mg, 94%). R_f = 0.23 (isooctane/EtOAc, 1:1). − M.p. 100 °C. − $[\alpha]_D^{20}$ = +43 (*c* = 1.2, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3335, 2927, 2869, 1450, 1376, 1077, 1031, 957, 865, 733 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3 H, s), 0.93 (3 H, d, *J* = 6.8 Hz), 1.11−1.96 (13 H, m), 3.36 (1 H, dt, *J* = 4.4, 10.4 Hz), 3.46 (1 H, dd, *J* = 6.5, 10.5 Hz), 3.56 (1 H, dd, *J* = 5.0, 10.5 Hz). − ^{13}C NMR (50 MHz, $CDCl_3$): δ 71.92 (CH), 67.72 (CH_2), 56.71 (CH), 45.47 (C), 41.98 (CH), 36.16 (CH), 34.92 (CH_2), 34.31 (CH_2), 25.38 (CH_2), 24.44 (CH_3), 24.35 (CH_2), 19.89 (CH_2), 16.01 (CH_3). − MS *m/z* (%): 194 (5), 179 (6), 163 (10), 135 (35), 125 (18), 111 (100), 97 (73), 81 (72), 67 (66).

Ester 31: To a solution of LDA (2M, 0.193 mL, 0.39 mmol) in THF (0.2 mL) was added ester **27** (43 mg, 0.19 mmol) in THF (0.5 mL) at −78 °C and the solution was stirred for 1 h. Then MeI (0.06 mL, 0.97 mmol) was added. After stirring for 2.5 h the mixture was diluted with H_2O and Et_2O. Work-up and column chromatography (100:4) afforded **31** (45 mg, 98%). R_f = 0.20 (isooctane/Me_2CO, 100:2). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (3 H, s), 1.14 (3 H, d, *J* = 6.9 Hz), 1.27 (3 H, t, *J* = 7.1 Hz), 1.35 (1 H, dq, *J* = 7.1, 11.7 Hz), 1.51 (1 H, td, *J* = 3.4, 12.5 Hz), 1.59 (2 H, m), 1.69 (1 H, dt, *J* = 7.9, 11.1 Hz), 1.87 (1 H, dddd, *J* = 3.2, 7.9, 9.9, 12.9 Hz), 1.94 (2 H, m), 2.13 (1 H, m), 2.37 (1 H, dd, *J* = 6.9, 10.7 Hz), 2.32−2.42 (2 H, m), 4.11 (2 H, q, *J* = 7.1 Hz), 5.27 (1 H, m). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.71 (C), 147.91 (C), 117.04 (CH), 59.86 (CH_2), 53.57 (CH), 42.02 (C), 40.94 (CH), 35.16 (CH_2), 26.96 (CH_2), 25.63 (CH_2), 24.84 (CH_2), 18.81 (CH_2), 17.86 (CH_3), 17.08 (CH_3), 14.06 (CH_3). − MS *m/z* (%): 236 [M^+] (3), 191 (3), 163 (8), 147 (10), 134 (100), 119 (22), 93(60), 77 (50) 55 (76).

Alcohol 32; One-Pot Process: To liq. NH_3 (30 mL) at −78 °C was added Ph_3CH (5 mg) in THF (0.5 mL) and Li (12 mg). 2-Bromo-2-methylpropane was added until the red colour persisted (ca. 150 μL)[18] Li (43 mg) was added, and the mixture was stirred for 15 min before adding **26** (147 mg, 0.47 mmol) in THF (5 mL). Stirring was continued for 0.5 h at −78 °C, then 2-bromo-2-methylpropane was added slowly until the solution became red. MeI (0.6 mL) was added and the mixture was stirred for 3 h. MeOH (0.3 mL) was added followed by Li until blue colour and stirring was continued for 0.5 h at −78 °C and under reflux for 1h. The excess Li was destroyed by adding MeOH. The liq. NH_3 was evaporated and NH_4Cl was added. Filtration over silica gel and column chromatography (5:1) and HPLC (7:1) afforded alcohol **32** (74 mg, 80%) as an oil. R_f = 0.42 (isooctane/EtOAc, 8:2). − $[\alpha]_D^{20}$ = +80 (*c* = 0.9, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3368, 2962, 2929, 1454, 1434, 1373, 1044, 1017, 985, 863, 801 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (3 H, s), 0.99 (3 H, d, *J* = 6.8 Hz), 1.20 (2 H, m), 1.30 (1 H, td, *J* = 8.3, 11.4 Hz), 1.45 (1 H, dq, *J* = 7.1, 11.9 Hz), 1.61−1.99 (6 H, m), 2.12 (1 H, m), 2.37 (1 H, m), 3.48 (1 H, bdd, *J* = 7.1, 10.5 Hz), 3.73 (1 H, bdd, *J* = 3.5, 10.5 Hz), 5.26 (1 H, m). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 148.66 (C), 116.81 (CH), 67.05 (CH_2), 52.61 (CH), 42.31 (C), 37.04 (CH), 36.77 (CH_2), 27.53 (CH_2), 25.86 (CH_2), 24.88 (CH_2), 18.96 (CH_2), 18.19 (CH_3), 16.21 (CH_3). − MS *m/z* (%): 194 [M^+] (8), 163 (5), 147 (4), 135 (100), 119 (10), 93 (40), 79 (36), 67 (18), 41 (23). − $C_{13}H_{22}O$: calcd C 80.29, H 11.32; found C 80.32, H 11.41.

Tosylate 33: To a stirred solution of 32 (64 mg, 0.33 mmol) and CH_2Cl_2 (2.8 mL) at 0 °C was added Et_3N (0.2 mL, 1.4 mmol), TsCl (0.129 g, 0.67 mmol) and DMAP (1 mg). The mixture was stirred overnight at room temp.. Solvent evaporation and column chromatography (isooctane/Me_2CO, 100:3) afforded tosylate **33** (110 mg, 96%) as white crystals. R_f = 0.19 (isooctane/Me_2CO, 100:3). − M.p. 42−43 °C. − $[\alpha]_D^{20}$ = +33 (*c* = 1.1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 2928, 1599, 1457, 1361, 1189, 1177, 1098, 1020, 956, 866, 816, 666, 616 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.81 (3 H, s), 0.92 (3 H, d, *J* = 6.7 Hz), 1.06 (1 H, m), 1.23 (1 H, m), 1.37 (1 H, dq, *J* = 7.0, 11.7 Hz), 1.53−1.61 (3 H, m), 1.72−1.96 (4 H, m), 2.08 (1 H, m), 2.33 (1 H, m), 2.45 (3 H, s), 3.81 (1 H, dd, *J* = 7.3, 9.3 Hz), 4.14 (1 H, dd, *J* = 3.8, 9.4 Hz), 5.24 (1 H, m), 7.35 (2 H, d, *J* = 8.2 Hz), 7.79 (2 H, d, *J* = 8.3 Hz). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.93 (C), 144.59 (C), 133.14 (C), 129.72 (2x CH), 127.90 (2x CH), 117.22 (CH), 74.34 (CH_2), 52.20 (CH), 42.17 (C), 36.60 (CH_2), 34.33 (CH), 27.36 (CH_2), 25.87 (CH_2), 24.75 (CH_2), 21.63 (CH_3), 18.89 (CH_2), 18.11 (CH_3), 16.36 (CH_3). − MS *m/z* (%): 348 [M^+] (1), 176 (28), 137 (80), 134 (60), 120 (20), 105 (22), 91 (100), 41 (37). − $C_{20}H_{28}O_3S$: calcd C 68.87, H 8.03; found C 68.95, H 8.08.

Tosylate 34: Diethyl azodicarboxylate (300 μL, 1.6 mmol) was added dropwise to a solution of **13** (200 mg, 0.55 mmol) and triphenylphosphine (400 mg, 1.6 mmol) in dry THF (13 mL). After refluxing for 24 h, the mixture was poured into Et_2O (75 mL) and brine (10 mL) was added. Work-up and column chromatography (isooctane/Et_2O, 1:9 → 2:3) gave **34** (162 mg, 85%) as an oil. R_f = 0.46 (isooctane/Et_2O, 1:1). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3 H, s), 1.00 (3 H, d, *J* = 6.7 Hz), 1.15−1.34 (3 H, m), 1.54−1.69 (3 H, m), 1.74 (1 H, m), 1.88 (1 H, td, *J* = 3.5, 13.0 Hz), 1.92 (2 H, m), 2.05 (1 H, m), 2.32 (1 H, m), 2.46 (3 H, s), 3.84 (1 H, dd, *J* = 6.4, 9.3 Hz), 4.01 (1 H, dd, *J* = 3.2, 9.3 Hz), 5.26 (1 H, m), 7.35 (2 H, d, *J* = 8.0 Hz), 7.80 (2 H, d, *J* = 8.0 Hz). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.77 (C), 144.57 (C), 132.91 (C), 129.70 (2× CH), 127.82 (2× CH), 117.23 (CH), 75.26 (CH_2), 52.29 (CH), 42.35 (C), 37.14 (CH_2), 33.46 (CH), 27.50 (CH_2), 26.16 (CH_2), 24.70 (CH_2), 21.56 (CH_3), 18.90 (CH_2), 17.71 (CH_3), 16.88 (CH_3).

Monotosylate of 14,20-Bis-*epi*-Inhoffen−Lythgoe Diol (35): To a solution of olefin **33** (54 mg, 0.155 mmol) in dry THF (1.2 mL) was added at 0 °C 1 M $BH_3 \cdot$ THF solution (0.31 mmol). After 2 h at 0 °C 3 N NaOH (80 μl) and 35% H_2O_2 (160 μL) were added and stirring was continued for 50 min. The mixture was diluted with Et_2O and H_2O. Work-up and column chromatography (7:3) afforded a 10:1 ratio of *cis*/*trans* alcohols (48 mg, 85%). Separation by HPLC (7:3) gave the desired alcohol **35** (43.6 mg, 77%). R_f = 0.36 (isooctane/EtOAc, 1:1). − $[\alpha]_D^{20}$ = +26 (*c* = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3400, 2928, 1598, 1451, 1358, 1188, 1176, 1097, 1039, 1020, 947, 835, 815, 733, 666 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ 0.80 (3 H, s), 0.88 (3 H, d, *J* = 6.2 Hz), 1.11−1.81 (13 H, m), 1.89 (1 H, m), 2.45 (3 H, s), 3.26 (1 H, m), 3.86 (1 H, dd, *J* = 5.6, 9.3 Hz), 3.93 (1 H, dd, *J* = 4.3, 9.3 Hz), 7.35 (2 H, d, *J* = 8.13 Hz), 7.78 (2 H, d, *J* = 8.27 Hz). − ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.68 (C), 133.09 (C), 129.74 (2x CH), 127.83 (2x CH), 74.69

(CH_2), 71.67 (CH), 56.64 (CH), 45.34 (C), 41.77 (CH), 34.87 (CH_2), 34.25 (CH_2), 33.44 (CH), 25.47 (CH_2), 24.20 (CH_2+CH_3), 21.61 (CH_3), 19.75 (CH_2), 16.12 (CH_3). − MS *m/z* (%): 366 [M^+] (0.3), 348 (2.3), 333 (1.4), 322 (2.3), 241 (2.4), 223 (1.4), 201 (2.6), 179 (20), 176 (22), 125 (26), 111 (63), 91 (100), 55 (72). − $C_{20}H_{30}O_4S$: calcd C 65.48, H 8.18; found C 65.42, H 8.16.

Alcohol 36: A mixture of NaH (60%, 34 mg, 1.4 mmol) and dry DMSO (1 mL) was stirred at 60 °C for 2 h. 2(1-Ethoxyethylether)-2-methyl-3-butyne (120 mg, 0.76 mmol) was added dropwise at room temp. and stirring was continued for 1 h. A solution of **35** (34 mg, 0.093 mmol) in dry DMSO (0.4 mL) was added dropwise and stirring was continued for 2 h. The mixture was poured in saturated aqueous NH_4Cl and extracted with Et_2O. Work-up, column chromatography (10:2) and HPLC (pentane/Me_2CO, 11:1) resulted in **36** (24 mg, 74%) as a colourless oil. R_f = 0.31 (pentane/Me_2CO, 9:1). − $[\alpha]_D^{20}$ = +16.5 (*c* = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3416, 2930, 2226, 1456, 1377, 1360, 1335, 1252, 1158, 1122, 1082, 1041, 975, 930, 850 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3 H, s), 0.97 + 0.98 (3 H, d + d, *J* = 6.7 + 6.7 Hz), 1.18 + 1.19 (3 H, t + t, *J* = 7.1 + 7.0 Hz), 1.25 (3 H, m), 1.32 + 1.33 (3 H, d + d, *J* = 5.3 + 5.3 Hz), 1.43 + 1.44 (3 H, s + s), 1.49 + 1.50 (3 H, s + s), 1.46−1.70 (5 H, m), 1.75−1.94 (5 H, m), 2.25 (2 H, d, *J* = 5.5 Hz), 3.34 (1 H, dt, *J* = 4.1, 10.4 Hz), 3.49 (1 H, m), 3.68 (1 H, m), 5.11 + 5.12 (1 H, q + q, *J* = 5.2 + 5.2 Hz). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 96.30 (CH), 84.29 (C), 83.33 + 83.29 (C), 71.75 (CH), 70.38 (C), 60.38 + 60.31 (CH_2), 57.36 (CH), 45.47 (C), 44.17 (CH), 35.00 (CH_2), 34.70 (CH_2), 33.56 (CH), 31.01 (CH_3), 30.40 + 30.33 (CH_3), 26.49 (CH_2), 25.99 (CH_2), 24.33 (CH_3), 24.06 (CH_2), 22.25 (CH_3), 20.24 (CH_2), 19.39 (CH_3), 15.33 (CH_3). − MS *m/z* (%): 291 (1), 277 (1), 259 (2), 243 (3), 227 (1), 217 (1), 201 (2), 187 (2), 161 (10), 127 (14), 109 (18), 73 (100), 45 (58). − ES: 373.1 (M^+ + Na).

Ketone 23: To a solution of **36** (15 mg, 0.043 mmol), NMO (20 mg, 0.17 mmol) in dry CH_2Cl_2 (0.6 mL) were added activated powdered molecular sieves (4 Å, 30 mL) and tetrapropylammonium perruthenate[19] (trace amount) and the solution was stirred for 1 h. The mixture was filtered trough a silica gel pad (pentane/Me_2CO, 1:1). After concentration, purification by HPLC (pentane/Me_2CO, 30:1) gave **23** (13.6 mg, 91%) as a colourless oil. R_f = 0.21 (pentane/Me_2CO, 100:4). − $[\alpha]_D^{20}$ = +21 (*c* = 1.1, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2974, 2936, 2875, 2235, 1708, 1462, 1379, 1249, 1158, 1122, 1080; 1051, 976 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (3 H, d, *J* = 6.7 Hz), 1.04 (3 H, s), 1.18 + 1.19 (3 H, t + t, *J* = 7.0 + 7.1 Hz), 1.32 (3 H, d, *J* = 5.2 Hz), 1.40 (1 H, m), 1.42 (3 H, s), 1.48 + 1.49 (3 H, s + s), 1.51−1.93 (8 H, m), 2.14−2.38 (6 H, m), 3.48 (1 H, m), 3.66 (1 H, m), 5.08 + 5.01 (1 H, q + q, *J* = 5.2 + 5.2 Hz). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.34 (C), 96.29 (CH), 84.42 (C), 83.19 + 83.15 (C), 70.32 (C), 61.00 (CH), 60.36 + 60.27 (CH_2), 48.54 (C), 48.31 (CH), 40.03 (CH_2), 35.57 (CH_2), 32.96 (CH), 30.92 (CH_3), 30.30 (CH_3), 26.37 (CH_2), 26.01 (CH_2), 23.45 (CH_3), 22.21 (CH_3), 21.42 (CH_2), 21.18 (CH_2), 18.76 (CH_3), 15.31 (CH_3). − MS *m/z* (%): 289 (10), 275 (27), 251 (100), 241 (3), 203 (5), 177 (8), 149 (6), 127 (30), 109 (22), 93 (9), 82 (30), 73 (100), 55 (25). − $C_{22}H_{36}O_3$: calcd. C 75.75, H 10.34; found C 75.80, H 10.40.

14,20-Bis-*epi*-23-yn-1α,25-dihydroxy-19-norvitamin D_3 (5): To a solution of **11** (50 mg, 0.09 mmol) in THF (1.4 mL) was added *n*BuLi (2.5 M in hexane, 57 μL, 0.14 mmol) at −78 °C. After stirring the resulting red suspension for 1 h, a solution of **23** (14 mg, 0.04 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture is stirred for 1 h at −78 °C, then the cooling bath was removed, H_2O was added slowly till the orange colour has completely disappeared and THF is evaporated off. After addition of Et_2O and sat. $NaHCO_3$ solution, the aqueous layer is extracted with Et_2O. The collected organic phases were filtered through silicagel; concentration and HPLC (8:2) gave 21 mg (75%) of the coupled product. A mixture of the crude product and Amberlyst-15 (35 mg) in MeOH/THF (1:1, 1.5 mL) was stirred for 15 h at room temp. Work-up and HPLC (CH_2Cl_2/MeOH, 95:5) afforded **5** (11 mg, 69%). R_f = 0.17 (CH_2Cl_2/MeOH, 95:5). − UV (MeOH): λmax = 250 nm. − IR (film): $\tilde{\nu}$ = 3360, 3040, 2930, 2233, 1647, 1611, 1452, 1376, 1237, 1165, 1048, 973, 946 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.93 (3 H, s), 0.94 (3 H, d, *J* = 6.6 Hz), 1.26 (3 H, m), 1.40 (2 H, m), 1.50 (6 H, s), 1.55−1.95 (10 H, m), 2.00−2.22 (5 H, m), 2.28 (1 H, m), 2.47 (2 H, m), 2.71 (1 H, m), 4.09(2 H, m), 6.04 (1 H, d, *J* = 11.2 Hz), 6.25 (1 H, d, *J* = 11.2 Hz). − MS *m/z* (%): 382 [M^+ − H_2O] (4): 342(3), 303(2), 285(3), 227(2), 187(6), 161(11), 133(15), 105(25), 91(36), 55(42), 43(100).

Precursor 37: A mixture of **23** (19 mg, 0.55 mmol), 5% Rh/Al_2O_3 (10 mg) in EtOAc (2 mL) was stirred under H_2 (1 atm) at room temp. for 3 h. Filtration over silica gel, solvent evaporation and HPLC (9:1) gave **37** (17 mg, 89%) as an oil. R_f = 0.50 (hexane/EtOAc, 8:2). − IR (film): $\tilde{\nu}$ = 2970, 2875, 1708, 1465, 1380, 1318, 1246, 1246, 1152, 1087, 1033, 971 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (3 H, d, *J* = 6.6 Hz), 1.02 (3 H, s), 1.17 (3 H, s), 1.17 (3 H, t, *J* = 6.9 Hz), 1.19 (3 H, s), 1.27 (3 H, d, *J* = 5.3 Hz), 1.25−1.50 (9 H, m), 1.65 (3 H, m), 1.80 (2 H, m), 1.90 (1 H, m), 2.15 (1 H, m), 2.28 (2 H, m), 2.37 (1 H, m), 3.42−3.56 (2 H, m), 4.87 (1 H, q, *J* = 5.3 Hz). − MS *m/z* (%): 386 [M^+ − H_2O] (3), 353 (1), 303(1), 289(3), 245(2), 189(2), 161(5), 133(11), 81(28), 73(37), 60(52), 45(100).

14,20-Bis-*epi*-1α,25-dihydroxy-19-norvitamin D_3 (4): From **37** as described for **5** from **23**. Yield 73%. R_f = 0.24 (CH_2Cl_2/MeOH, 95:5). − UV (MeOH): λmax = 249 nm. − IR (film): $\tilde{\nu}$ = 3360, 3036, 2932, 1649, 1610, 1452, 1377, 1214, 1049, 976, 939, 908 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (3 H, d, *J* = 6.6 Hz), 0.93 (3 H, s), 1.09 (1 H, m), 1.21 (6 H, s), 1.25 (3 H, m), 1.32−1.65 (13 H, m), 1.80 (3 H, m), 1.92 (1 H, m), 2.05 (1 H, m), 2.20 (2 H, m), 2.27 (1 H, m), 2.50 (2 H, m), 2.70 (1 H, m), 4.08 (2 H, m), 6.03 (1 H, d, *J* = 11.3 Hz), 6.26 (1 H, d, *J* = 11.3 Hz). − MS *m/z* (%): 386 (M^+ − H_2O, 3), 353(1), 303(1), 289(3), 245(2), 189(2), 161(5), 133(11), 81(28), 73(37), 60(52), 45(100).

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