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# Synthesis of 24-Oxavitamin $D_3$ and 1α-Hydroxy-24-Oxavitamin $D_3$

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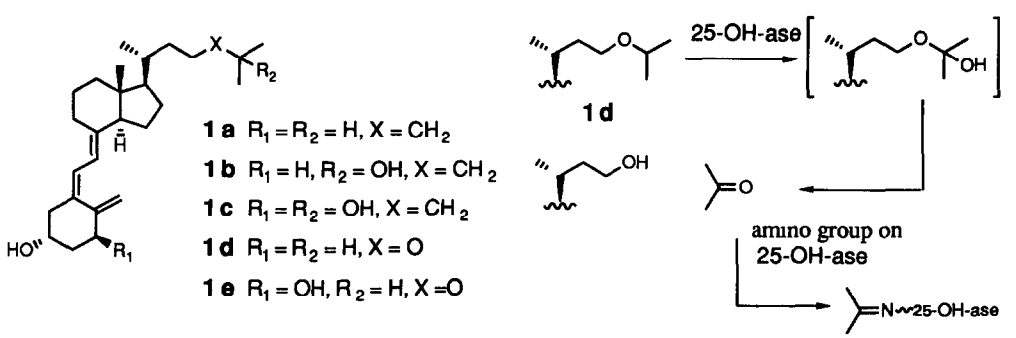
*Abstract* Coupling of the CD fragment, ketone **6** (obtained by partial synthesis from vitamin $D_2$), either directly (Horner-Wittig route) or *via* the derived enol triflate (dienyne route) with the appropriate A-ring fragment, phosphine oxide anion **7** or enyne **10**, is the key step in the syntheses of 24-oxavitamin $D_3$ (**1d**) and 1α-hydroxy-24-oxavitamin $D_3$ (**1e**), respectively

It is well established that vitamin $D_3$ (**1a**, Scheme 1), before functioning as a regulator of calcium homeostasis, must undergo two successive hydroxylations to produce 25-hydroxyvitamin $D_3$ (**1b**) and 1α,25-dihydroxyvitamin $D_3$ (**1c**) [1] It has been recently discovered that the latter metabolite **1c**, which is considered the hormonally active form of vitamin $D_3$, is also able to induce the differentiation and to inhibit the proliferation of malignant cells [2] Unfortunately the treatment of certain cancers and skin disorders with this hormone is limited due to its secondary strong calcemic effects [3] As a consequence, there has been enhanced interest in the development of modified analogs of the above hormone with high cell differentiating ability and low calcemic action

In an effort to find vitamin D analogs with these types of properties, we proceeded to synthesize the two vitamin D analogs 24-oxavitamin $D_3$ (**1d**) and 1α–hydroxy-24-oxavitamin $D_3$ (**1e**) [4] On the basis of the "oxa" concept introduced by Okamura in the vitamin D field,[5] it was also expected that compound **1d** could behave as an inhibitor of the 25-hydroxylase, the hepatic enzyme responsible for the hydroxylation at C-25, for example by the operation of the suicide inhibition mechanism proposed in Scheme 1 Thus **1d** could find use as an agent for lowering the biological production of the hormone **1c** For a study of the 25-hydroxylation of **1e**, see ref [6]

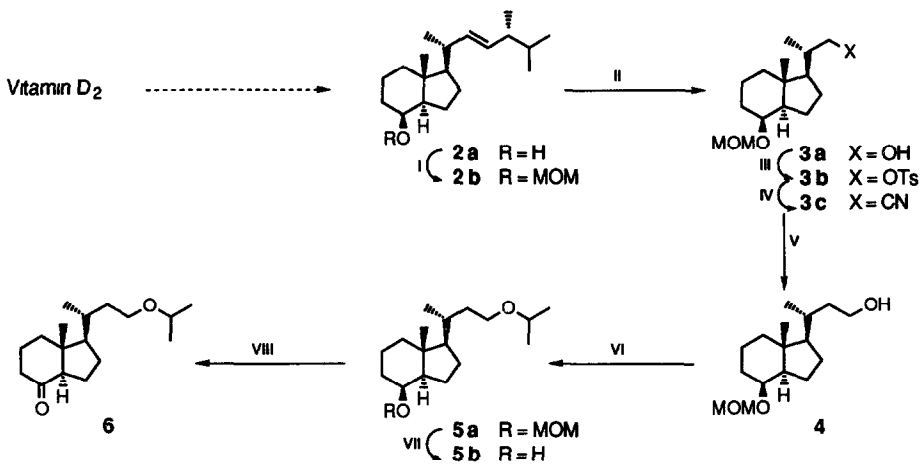



Scheme 1

For the synthesis of **1d** and **1e**, we have adopted the strategy of connecting a common upper (CD rings) fragment, having the required side chain in place, with the appropriate lower (ring A) fragment

***Synthesis of the upper fragment 6***

The starting material **2a**[7] used for the preparation of ketone **6** (Scheme 2) was prepared in 62% yield according to known procedures [8] Protection (MOMCl, *i*-$Pr_2NEt$, DMAP) of **2a**, followed by ozonolysis ($O_3$, MeOH-$CH_2Cl_2$-py) and *in situ* reduction ($NaBH_4$) of the resulting ether **2b** afforded **3a** in 85% yield (3 steps) Chain extension of the alcohol **4** was accomplished using a literature method [9] Thus, tosylation of **3a** and displacement of the resulting tosylate **3b** with NaCN afforded the nitrile **3c** which was sequentially treated with DIBAL-H and $NaBH_4$ to give **4** (46%, 4 steps) Deprotonation of **4** (NaH, DMF) followed by reaction of the resulting alkoxide with *i*-PrBr gave the ether **5a** in 72% Removal of the protecting group (AG 50W-X4) and oxidation of the resulting alcohol **5b** (PDC, PPTS) afforded the desired ketone **6** (95%, 2 steps)



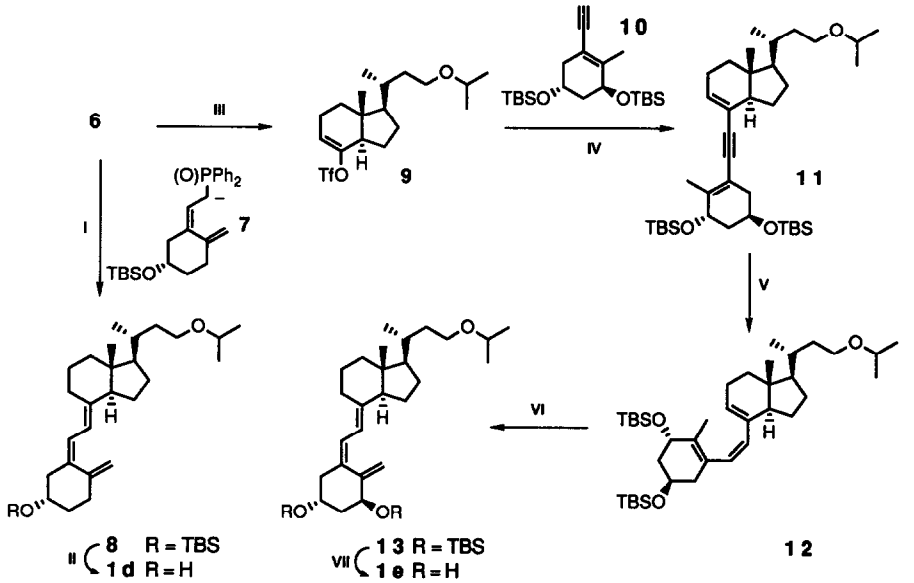

Scheme 2

(i) MOMCl (3 equiv), *i*-$Pr_2NEt$ (3 equiv), DMAP (0 3 equiv), $CH_2Cl_2$, rt, 16 h, 93% (ii) (a) $O_3$, -78 °C, MeOH $CH_2Cl_2$ py (25 3 1), (b) $NaBH_4$, rt, 4 h, 92% (iii) *p*-TsCl (1 1 equiv), py, 4 °C, 3 days, 90% (iv) NaCN (1 5 equiv), DMSO, 90 °C, 4 h, 95% (v) (a) DIBAL-H (3 5 equiv), $CH_2Cl_2$, -20 °C, 3 h, (b) $Et_2O$ 3 M HCl (1 1), 5 °C, 2 h, (c) $NaBH_4$, MeOH, 54% (vi) (a) NaH (5 7 equiv), DMF, rt, 1 h, (b) *i*-PrBr (14 2 equiv), 12 h, 72% (vii) AG 50W-X4, MeOH, rt, 4 days, 97% (viii) PDC (3 equiv), PPTS cat, $CH_2Cl_2$, rt, 12 h, 98%

**Abbreviations:** DMAP = 4-(*N,N*-dimethylamino)-pyridine, MOM = methoxymethyl, py = pyridine, TBS = *t*-butyldimethylsilyl Tf = trifluoromethanesulphonyl

***Synthesis of Vitamin D Analogues 1d and 1e***

The vitamin D analogue **1d** was straightforwardly synthesized following Lythgoe's approach[10] by Horner-Wittig coupling of the ketone **6** with the phosphine oxide anion **7** followed by deprotection (58% two steps) (Scheme 3)




Scheme 3

(i) **7** (1 9 equiv), THF, -78 °C, 1 h, rt, 3 h, 87% (ii) *n*-$Bu_4NF$ (1 5 equiv), THF, rt, 16 h, 67% (iii) (a) LDA (1 4 equiv), THF, -78 °C, 15 min, rt, 90 min; (b) $PhNTf_2$ (1 4 equiv), THF, -78 °C, rt, 10 h, 80% (iv) $Pd(Ph_3P)_2Cl_2$ (0 1 equiv), $Et_3N$ (3 7 equiv), DMF, 75 °C, 20 h, 94% (v) $H_2$, Lindlar, quinoline, hexane, 90 min, 87% (vi) isooctane, 100 °, 4 h, 75% (vii) *n*-$Bu_4NF$ (2 equiv), THF, rt, 16 h, 91%

The oxavitamin D analogue **1e** was synthesized by the dienyne route [11] Reaction of **6** with LDA and trapping of the resulting enolate with N-phenyltriflimide,[12] afforded triflate **9** (88%) Palladium catalyzed coupling between **9** and the known enyne **10**[11c,13] [$(Ph_3P)_2PdCl_2$, DMF, $Et_3N$] gave the dienyne **11** (94%) Partial hydrogenation ($H_2$, Lindlar, quinoline, hexane) of **11** and thermal isomerization of the resulting previtamin D (**12**), followed by deprotection (*n*-$Bu_4NF$) afforded the desired oxavitamin analogue **1e** (60%, 3 steps), identical with material prepared by an alternative route [6]

## EXPERIMENTAL SECTION

**General.** All dry solvents were distilled under Ar THF was distilled from sodium/benzophenone $CH_2Cl_2$ and DMF were distilled from $P_2O_5$, and DMF was stored under a Type 4Å molecular sieves Pyridine was distilled from KOH DMSO was purified by standing overnight with chromatographic grade alumina and

distillation from $CaH_2$ at low pressure, and stored under a Type 4Å molecular sieves Hexane and *i*-$Pr_2NH$ were distilled from $CaH_2$. All reactions were conducted under Ar unless otherwise stated. Boiling points (kugelrohr) are uncorrected, and refer to the external air bath temperature $^1H$ NMR and $^{13}C$ spectra were recorded at 250 and 62 83 MHz respectively, using $CDCl_3$ as solvent. Catalytic hydrogenations were carried out with a PARR 3915 hydrogenator Flash chromatography was performed by Still's method [14] TLC was performed on plates of silica gel (2 x 5 cm, 0 2 mm thickness) Components were located by observation of the plates under UV light and/or by treating the plates with a phosphomolybdic acid reagent followed by heating Concentrations were carried out in a rotary evaporator Dryings were carried out with anhydrous $Na_2SO_4$

**(8β,22*E*)-De-*A*,*B*-8-methoxymethyloxyergost-22-ene (2b).** *i*-$Pr_2NH$ (4 3 mL, 3 5 g, 26 98 mmol) and MOMCl (2 05 mL, 2 17 g, 26 98 mmol) were successively added to a cooled (0 °C) solution of **2a**[8] (2 50 g, 8 99 mmol) and DMAP (330 mg, 2 70 mmol) in dry $CH_2Cl_2$ (40 mL) The mixture was stirred for 16 h Water (30 mL) was added The organic phase was washed with HCl (1 M, 30 mL) and a saturated aqueous solution of $NaHCO_3$ (30 mL), filtered and concentrated The residue was purified by flash chromatography (0-5% EtOAc/hexanes) to afford 2 68 g of **2b** (93%, colorless liquid), TLC (10% EtOAc/hexanes) $R_f$ 0 90, IR (neat) 2965, 2930, 1260, 1093, 1025, 800 $cm^{-1}$, $^1H$ NMR δ 0 81 and 0 84 (2 d, $J$ = 4 0 Hz, 6 H, $CH_3$-26 and 27), 0 90 (s, 3 H, $CH_3$-18), 0 91 and 0 99 (2 d, $J$ = 6 7 Hz, 3 H, $CH_3$-21 and 28), 3 35 (s, 3 H, $OCH_3$), 3 85 (m, 1 H, H-8), 4 54 and 4 65 (AB, $J$ = 6 6 Hz, 2 H, $OCH_2O$), 5 18 (m, 2 H, H-22 and H-23), $^{13}C$ NMR δ 13 5, 17 6, 17 9, 19 6, 19 9, 20 8, 22 7, 27 6, 30 7, 33 1, 39 8, 40 6, 41 9, 42 8, 52 5, 55 0, 56 7, 75 0, 95 7, 131 8, 135 8, MS (EI, 20 eV) *m/z* 322 ($M^+$, 0 3), 292 (3), 281 (11), 262 (19), 225 (17), 175 (16), 163 (33), 155 (100), 137 (21), 135 (72), 122 (60), 108 (40), 95 (47), HRMS (EI) calcd for $C_{21}H_{38}O_2$ 322 2871 ($M^+$), found 322 2874

**(8β)-De-*A*,*B*-8-methoxymethyloxy-23,24-dinorcholan-22-ol (3a).** $N_2$ was bubbled through a cooled (-78 °C) solution of **2b** (2 57 g, 7 98 mmol) in dry MeOH $CH_2Cl_2$ py (25 3 1, 290 mL) for 15 min and then $O_3$ for 30 min The excess of $O_3$ was removed by $N_2$ (KI test) $NaBH_4$ (1 5 g, 39 5 mmol) was added in portions and the mixture was allowed to stir at rt for 4 h The reaction mixture was concentrated to small volume Water (70 mL) was added Extraction with $CH_2Cl_2$ (3 x 60 mL) gave an organic phase, which was dried, filtered and concentrated The residue was purified by flash chromatography (5-20% EtOAc/hexanes) to afford 1 62 g of **3a** (92 %, white oil), TLC (20% EtOAc/hexanes) $R_f$ 0 50, IR(neat) 3400, 2940, 1445, 1365, 1148, 1040 $cm^{-1}$, $^1H$ NMR δ 0 90 (s, 3 H, $CH_3$-18), 1 01 (d, $J$ = 6 6 Hz, 3 H, $CH_3$-21), 3 33 (dd, $J$ = 10 5 and 6 8 Hz, 1 H, CHH-22), 3 34 (s, 3 H, $OCH_3$), 3 60 (dd, $J$ = 10 5 and 3 2 Hz, 1 H, CHH-22), 3 84 (m, 1 H, H-8), 4 52 and 4 63 (AB, $J$ = 6 6 Hz, 2 H, $OCH_2O$), $^{13}C$ NMR δ 13 3, 16 6, 17 8, 22 7, 26 6, 30 6, 38 3, 40 4, 42 0, 52 1, 53 0, 55 0, 67 8, 74 8, 95 7, MS (EI, 20 eV) *m/z* 225 ($M^+$-$CH_2OH$), 213 (10), 211 (17), 194 ($M^+$-$CH_2OH$-$CH_3$), 181 (20), 179 (28), 155 (30), 147 (25), 135 (60), 125 (41), 111 (59), 107 (47), 97 (53), 95 (100), 85 (38), 81 (75), 69 (34), MS (FAB, Xe, 2-hydroxyethyl disulfide) *m/z* 255 ($M^+$-1, 4), 223 (5), 207 (16), 195 (100), 177 (97), 167 (36), 135 (72), HRMS (EI) calcd for $C_{15}H_{28}O_3$-$CH_3O$, 225 1854 ($M^+$-$CH_2OH$), found 225 1860

**(8β)-De-*A*,*B*-8-methoxymethyloxy-23,24-dinorcholan-23-yl 4-Toluenesulfonate (3b).** *p*-TsCl (685 mg, 3 60 mmol) was added to a cooled (0 °C) solution of **3a** (709 mg, 3,15 mmol) in dry pyridine (40 mL) The resulting mixture was kept in the refrigerator (4 °C) for 3 days, poured into $H_2O$ ice (50 mL) and extracted with $Et_2O$ (50 mL) The organic phase was washed with a saturated aqueous solution of $CuSO_4$ (3 x 15 mL), and water (30 mL), dried, filtered and concentrated to give a residue that was purified by flash chromatography (5-10% EtOAc/hexanes) to afford 1,16 g of **3b** (90%, oil), TLC (20% EtOAc/hexanes) $R_f$ 0 45, IR (neat) 3030, 2950, 1600, 1450, 1365, 1178, 1098, 1030, 950, 848, 815, 665 $cm^{-1}$, $^1H$ NMR δ 0 84 (s, 3 H, $CH_3$-18), 0 95 (d, $J$ = 6 6 Hz, 3 H, $CH_3$-21), 2 45 (s, 3 H, $CH_3$-Ar), 3 34 (s, 3 H, $OCH_3$), 3 80 (dd, $J$ = 9 2 and 6 4 Hz, 1 H, CHH-22), 3 84 (m, 1 H, H-8), 3 96 (dd, $J$ = 9 2 and 3 7 Hz, 1 H, CHH-22), 4 52 and 4 63 (AB, $J$ = 6 6 Hz, 2 H, $OCH_2O$), 7 34 and 7 78 (2 d, $J$ = 8 0 Hz, 4 H, H-Ar), $^{13}C$ NMR δ

13 2, 16 7, 17 7, 21 5, 22 5, 26 4, 30.4, 35 8, 40 2, 42 0, 52 0, 52.3, 55 1, 74.6, 75 6, 95 7, 127 9, 129.5, 133 3, 144 6, MS (EI, 20 eV) *m/z* 410 ($M^+$, 9), 378 (9), 367 (22), 365 (25), 349 (25), 348 (100), 321 (25), 313 (18), 223 (17), 217 (12), 194 (21), 193 (25), 177 (17), 155 (14), 95(18), HRMS (EI) calcd for $C_{22}H_{34}O_5S$ 410 2127 ($M^+$), found 410 2123

**(8β)-De-*A,B*-8-methoxymethyloxy-24-norcholane-23-nitrile (3c).** A solution of **3b** (1 42 g, 3 47 mmol) and NaCN (252 mg, 5 44 mmol) in dry DMSO (40 mL) was stirred at 90 °C (oil bath) for 4 h, cooled, and poured into water (100 mL) The mixture was extracted with $Et_2O$ (100 mL) and the organic phase washed with brine (75 mL), dried, filtered and concentrated The residue was purified by flash chromatography (10% EtOAc/hexanes) to afford 872 mg of **3c** (95 %, viscous white oil), TLC (20% EtOAc/hexanes) $R_f$ 0 50, IR (neat) 3020, 2950, 2245, 1468, 1375, 1230, 1148, 1098, 1040, 920, 760 $cm^{-1}$, $^1H$ NMR δ 0 91 (s, 3 H, $CH_3$-18), 1 15 (d, $J$ = 6 6 Hz, 3 H, $CH_3$-21), 2 24 (dd, $J$ =16 7 and 6 8 Hz, 1 H, CHH-22), 2 34 (dd, $J$ =16 7 and 4 0 Hz, 1 H, CHH-22), 3 35 (s, 3 H, $OCH_3$), 3 87 (m, 1 H, H-8), 4 54 and 4 64 (AB, $J$ = 6 6 Hz, 2 H, $OCH_2O$), $^{13}C$ NMR δ 13 3, 17 7, 19 1, 22 4, 24 5, 27 0, 30 3, 33 1, 40 1, 42 0, 52 1, 55 1, 55 2, 74 5, 95 7, 118 9, MS (EI, 70 eV) *m/z* 265 ($M^+$, 3), 250 (7), 220 (23), 204 (34), 176 (41), 163 (22), 155 (27), 135 (45), 127 (32), 119 (30), 107 (55), 93 (71), 71 (72), 85 (25), 81 (100), 79 (83), 69 (33), HRMS (EI) calcd for $C_{16}H_{27}NO_2$ 265 2042 ($M^+$), found 265 2037

**(8β)-De-*A,B*-8-methoxymethyloxy-24-norcholan-23-ol (4).** A solution of **3c** (780 mg, 2 94 mmol) in dry $CH_2Cl_2$ (7 mL) was slowly added to a cooled (-20 °C) solution of DIBAL-H in toluene (10 3 mL, 1 0 M, 10 3 mmol) and $CH_2Cl_2$ (5 mL) The mixture was stirred for 3 h and poured into a mixture of $Et_2O$ 3 M HCl (1 1, 60 mL) at 5 °C After stirring for 2 h, the aqueous layer was extracted with $CH_2Cl_2$ (2 x 40 mL) The combined organic phases were dried, filtered and concentrated The residue was dissolved in MeOH (30 mL) $NaBH_4$ (1 00 g, 26 32 mmol) was added in portions The mixture was stirred for 10 min Water (30 mL) was added and the mixture was extracted with $Et_2O$ (3 x 30 mL) The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (30 mL), dried, filtered, and concentrated The residue was purified by flash chromatography (0-10% EtOAc/hexanes) to yield 430 mg of **4** (54%, oil), TLC (20% EtOAc/hexanes) $R_f$ 0 53, IR (neat) 3420, 2950, 1230, 1045, 755 $cm^{-1}$, $^1H$ NMR δ 0 90 (s, 3 H, $CH_3$-18), 0 93 (d, $J$ = 6 6 Hz, 3 H, $CH_3$-21), 3 36 (s, 3 H, $OCH_3$), 3 70 (m, 2 H, $CH_2$-23), 3 85 (m, 1 H, H-8), 4 54 and 4 65 (AB, $J$ = 6 6, 2 H, $OCH_2O$), $^{13}C$ NMR δ 13 1, 17 8, 18 7, 22 6, 27 2, 30 5, 32 4, 38 7, 40 5, 42 0, 52 3, 55 0, 56 9, 60 7, 74 8, 95 6, MS (EI, 70 eV) *m/z* 270 ($M^+$, 0 2), 238 (32), 225 (45), 208 (100), 195 (10), 165 (11), 135 (12), 111 (27), 95 (17), 81 (22), 69 (12), HRMS (EI) calcd for $C_{16}H_{30}O_3$-$CH_4O$ 238 1933 ($M^+$-$H_2O$-$CH_2$), found 238 1932

**(8β)-De-*A,B*-8-methoxymethyloxy-24-oxacholestane (5a).** A solution of **4** (162 mg, 0 60 mmol) in dry DMF (10 mL) was added to a suspension of NaH (105 mg, 3 41 mmol, 80% dispersion in mineral oil, washed with hexane) in dry DMF (10 mL) The mixture was stirred for 1 h and *i*-PrBr (1 1 mL, 1 4 g, 12 mmol) was added After stirring for 12 h, more NaH (200 mg, 6 67 mmol, 80%, washed with hexane) and *i*-PrBr (0 8 mL, 1 5 g, 8 52 mmol) were successively added The mixture was stirred for 12 h Water (20 mL) was slowly added and the mixture was extracted with $CH_2Cl_2$ (2 x 25 mL) The combined organic phases were washed with brine (40 mL), dried, filtered and concentrated The residue was purified by flash chromatography (10-20% EtOAc/hexanes) to afford 41 mg of **4** and 135 mg of **5a** (72%, oil), TLC (30% EtOAc/hexanes) $R_f$ 0 80, IR (neat) 2940, 1735, 1460, 1375, 1040, 755 $cm^{-1}$, $^1H$ NMR δ 0 89 (s, 3 H, $CH_3$-18), 0 92 (d, $J$ = 6 6 Hz, 3 H, $CH_3$-21), 1 15 (d, $J$ = 6 6 Hz, 6 H, $CH_3$-26 and $CH_3$-27), 3 36 (s, 3 H, $CH_3O$), 3 45 (m, 3 H, $CH_2$-23 and H-25), 3 85 (m, 1 H, H-8), 4 54 and 4 65 (AB, $J$ = 6 6 Hz, 2 H, $OCH_2O$), $^{13}C$ NMR δ 13 2, 17 9, 18 9, 22 0, 22 2, 22 6, 27 2, 30 6, 33 0, 36 0, 40 6, 42 1, 52 4, 55 1, 57 0, 66 3, 71 2, 74 9, 95 7, MS (EI, 70 eV) *m/z* 312 ($M^+$, 0 8), 267 (23), 190 (45), 175 (24), 162 (41), 155 (22), 135 (90), 125 (40), 121 (54), 113 (96), 109 (81), 96 (92), 82 (100), 72 (99), 69 (46), HRMS (EI) calcd for $C_{19}H_{36}O_3$ 312 2664 ($M^+$), found 312 2665

**(8β)-De-*A,B*-24-oxacholestan-8-ol (5b).** A mixture of **5a** (144 mg, 0 46 mmol), AG 50W-X4 (1 7 g) and MeOH (20 mL) was stirred for 4 days, filtered and concentrated to small volume EtOAc (30 mL) and brine (30 mL) were added The organic phase was dried, filtered and concentrated Flash chromatography (0-10% EtOAc/hexanes) afforded 120 mg of **5b** (97%, oil), TLC (15% EtOAc/hexanes) $R_f$ 0 55, IR (neat) 3460, 2950, 1455, 1355, 1062, 755 $cm^{-1}$, $^1H$ NMR δ 0 91 (d, $J$ = 6 6 Hz, 3 H, $CH_3$-21), 0.93 (s, 3 H, $CH_3$-18), 1 15 (d, $J$ = 6 6 Hz, 6 H, $CH_3$-26 and $CH_3$-27), 3 45 (m, 3 H, $CH_2$-23 and H-25), 4 06 (m, 1 H, H-8), $^{13}C$ NMR δ 13.4, 17 4, 18 9, 22 1, 22 2, 22 5, 27 2, 32 9, 33 6, 36 0, 40 4, 41 9, 52 6, 57 0, 66 3, 69 4, 71 3, HRMS (EI) calcd for $C_{17}H_{32}O_2$ 268 2402 ($M^+$), found 268 2408

**De-*A,B*-24-oxacholestan-8-one (6).** PDC (350 mg, 0 93 mmol) and a trace of PPTS were successively added to a solution of **5b** (83 mg, 0 31 mmol) in dry $CH_2Cl_2$ (15 mL) The mixture was stirred for 12 h $Et_2O$ (15 mL) was added After stirring for 10 min, the mixture was filtered through celite, washed with $Et_2O$ (3 x 10 mL), and concentrated to small volume The residue was bulb-to-bulb distilled to afford 81 mg of **6** (98%, oil), bp (bulb-to-bulb) 135-140 °C (0 001 mmHg), TLC (15% EtOAc/hexanes) $R_f$ 0 60, IR (neat) 2930, 1735, 1458, 1375, 1150, 1130, 1075 $cm^{-1}$, $^1H$ NMR δ 0 65 (s, 3 H, $CH_3$-18), 0 97 (d, $J$ = 6 7 Hz, 3 H, $CH_3$-21), 1 15 (2 d, $J$ = 6 3 Hz, 6 H, $CH_3$-26 and $CH_3$-27), 3 45 (m, 3 H, $CH_2$-23 and H-25), $^{13}C$ NMR δ 12 4, 18 9, 19 0, 22 0, 22 2, 24 0, 27 4, 33 0, 35 9, 38 9, 40 9, 49 8, 57 0, 61 9, 66 0, 71 2, 211 8, HRMS (EI) calcd for $C_{17}H_{30}O_2$ 266 2246 ($M^+$), found 266 2248

**(3β,5*Z*,7*E*)-3-*t*-Butyldimethylsilyloxy-24-oxa-9,10-secocholesta-5,7,10(19)-triene (8).** A solution of *n*-BuLi in hexane (0 26 mL, 2 28 M, 0 58 mmol) was slowly added to a cooled (-78 °C) solution of **7**[7] (255 mg, 0 58 mmol) in dry THF (5 mL) The red solution was stirred for 30 min A solution of **6** (81 mg, 0 31 mmol) in dry THF (4 mL) was added The resulting solution was stirred at -78 °C for 1 h, and then at rt for 3 h A few drops of water were added and the mixture was concentrated to small volume The residue was diluted with hexane (30 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) The organic phase was dried, filtered and concentrated Flash chromatography (hexane) afforded 127 mg of **8** (87%, colorless oil), TLC (5% EtOAc/hexanes) $R_f$ 0 90, $^1H$ NMR δ 0 07 (s, 6 H, $Me_2Si$), 0 55 (s, 3 H, $CH_3$-18), 0 88 (s, 9 H, $Me_3CSi$), 0 90 (d, $J$ = 6 6 Hz, 3 H, $CH_3$-21), 1 15 (2 d, $J$ = 6 3 Hz, 6 H, $CH_3$-26 and $CH_3$-27), 3 45 (m, 3 H, $CH_2$-23 and H-25), 3 81 (m, 1 H, H-3), 4 78 (br s, 1 H, H-19*E*), 5 00 (br s, 1 H, H-19*Z*), 6 02 and 6 15 (AB, $J$ = 11 6 Hz, 2 H, H-6 and H-7)

**(3β,5*Z*,7*E*)-24-Oxa-9,10-secocholesta-5,7,10(19)-trien-3-ol (1d).** *n*-$Bu_4NF$ (100 mg, 0 38 mmol) was added to a solution of **13** (127 mg, 0 25 mmol) in dry THF (8 mL) The mixture was stirred in the dark for 16 h and concentrated to a small volume $Et_2O$ (30 mL) was added The organic phase was washed with water (30 mL), dried, filtered and concentrated The residue was purified by HPLC (Column Zorbax-Silica, 25 x 1 cm, 5% *i*-PrOH/hexane, 2 mL/min, $t_R$ 17 3 min) to afford 65 mg of **1d** (67%, yellowish oil), TLC (15% EtOAc/hexanes) $R_f$ 0 30, $^1H$ NMR δ 0 55 (s, 3 H, $CH_3$-18), 0 94 (d, $J$ = 6 4 Hz, 3 H, $CH_3$-21), 1 14 (2 d, $J$ = 6 3 Hz, 6 H, $CH_3$-26 and $CH_3$-27), 3 42 (m, 2 H, $CH_2$-23), 3 54 (m, 1 H, H-25), 3 94 (m, 1 H, H-3), 4 81 (br s, 1 H, H-19*E*), 5 05 (br s, 1 H, H-19*Z*), 6 03 and 6 22 (AB, $J$ = 10 6 Hz, 2 H, H-6 and H-7), MS (EI, 70 eV) *m/z* 386 ($M^+$, 11), 353 (10), 233 (11), 215 (14), 205 (15), 189 (35), 177 (30), 175 (30), 163 (32), 161 (44), 159 (38), 149 (47), 147 (47), 123 (37), 118 (54), 107 (67), 95 (85), 81 (100), 73 (48), 69 (64), HRMS (EI) calcd for $C_{26}H_{42}O_2$ 386 3185 ($M^+$), found 386 3189

**De-*A,B*-24-oxacholest-8-en-8-yl Trifluoromethanesulfonate (9).** *i*-$Pr_2NH$ (0 03 mL, 21 mg, 0 21 mmol) and dry THF (2 mL) were successively added to a solution of *n*-BuLi in hexane (0 07 mL, 2 67 M, 0 19 mmol), at -78 °C The solution was stirred at -78 °C for 10 min, and then at rt for 20 min After cooling to -78 °C, a solution of **6** (35 mg, 0 13 mmol) in THF (5 mL) was slowly added The mixture was stirred at the same temperature for 15 min, and at rt for 90 min After cooling at -78 °C, a solution of $PhNTf_2$ (66 mg, 0 19 mmol) in THF (4 mL) was slowly added The resulting solution was warmed to rt, and then stirred for 10 h

The reaction mixture was quenched by addition of MeOH (1 mL) Concentration gave a residue that was flash chromatographed (0-2% EtOAc/hexanes) to afford 42 mg of **9** (80%, colorless oil); TLC (10% EtOAc/hexanes) $R_f$ 0 70, IR (neat) 3020, 2960, 2360, 1410, 1210, 1140, 760 $cm^{-1}$, $^1H$ NMR δ 0 77 (s, 3 H, $CH_3$-18), 0 96 (d, $J$ = 6 5 Hz, 3 H, $CH_3$-21), 1 15 (d, $J$ = 6 1 Hz, 6 H, $CH_3$-26 and $CH_3$-27), 3 46 (m, 3 H, $CH_2$-23 and H-25), 5 57 (dd, $J$ = 6 9 and 3 5 Hz, 1 H, H-9), $^{13}C$ NMR δ 11 3, 18 9, 21 5, 22 1, 23 8, 28 3, 33 6, 34 9, 36 0, 45 3, 50 1, 54 6, 66 0, 71 4, 116 0, 149 9 HRMS (EI) calcd for $C_{18}H_{29}F_3O_4S$ 398 1739 ($M^+$), found 398 1742

**(1α,3β)-1,3-Bis(*t*-butyldimethylsilyloxy)-24-oxa-9,10-secocholesta-5(10),8-dien-6-yne (11).** A solution of **9** (37 mg, 0 10 mmol), **10**[11c](46 mg, 0 12 mmol), $Pd(Ph_3P)_2Cl_2$ (6 mg, 0 01 mmol), and $Et_3N$ (52 μL, 37 mg, 0 37 mmol) in dry DMF (8 mL) was heated at 75 °C (oil bath) for 20 h After cooling to rt, a mixture of $Et_2O$ hexane (1 1, 15 mL) and brine (10 mL) were added The organic phase was dried, filtered and concentrated to small volume The residue was purified by flash chromatography (0-1% EtOAc/hexanes) to afford 55 mg of **11** (94%, yellowish oil), TLC (5% EtOAc/hexanes) $R_f$ 0 60, IR (neat) 2960, 2860, 2360, 2240, 1255, 1185, 910, 735 $cm^{-1}$, $^1H$ NMR δ 0 09 (2 s, 12 H, 2 $Me_2Si$), 0 77 (s, 3 H, $CH_3$-18), 0 89 and 0 90 (2 s, 18 H, 2 $Me_3CSi$), 0 96 (d, $J$ = 6 5 Hz, 3 H, $CH_3$-21), 1 15 (d, $J$ = 6 1 Hz, 6 H, $CH_3$-26 and $CH_3$-27), 1 95 (br s, 3 H, $CH_3$-19), 3 36-3 57 (m, 3 H, $CH_2$-23 and H-25), 4 11 (m, 1 H, H-3), 4 19 (m, 1 H, H-1), 5 97 (br d, $J$ = 3 0 Hz, 1 H, H-9), $^{13}C$ NMR δ -4 8, -4 6, 11 0, 19 0, 19 1, 22 0, 22 2, 25 8, 25 9, 28 0, 29 7, 33 7, 35 9, 36 1, 39 6, 39 8, 41 3, 41 9, 50 2, 55 1, 64 3, 66 2, 69 7, 70 1, 71 3, 112 6, 115 6, 123 0, 128 5, 131 4, 133 3, HRMS (EI) calcd for $C_{38}H_{68}O_3Si_2$ 628 4707 ($M^+$), found 628 4712

**(1α,3β,5*Z*,7*E*)-1,3-Bis(*t*-butyldimethylsilyloxy)-24-oxa-9,10-secocholesta-5,7,10(19)-triene (13).** A solution of quinoline in hexane (0 03 mL, 0 042 M) was added to a solution of **11** (23 mg, 0 037 mmol) in dry hexane (12 mL) The reaction flask was purged with $H_2$ (3 x), and Lindlar catalyst (37 mg) was added The reaction mixture was hydrogenated (14 psi) for 90 min More Lindlar catalyst (26 mg) was added, and the hydrogenation was continued for 4 h Filtration through a short pad of celite, concentration and high vacuum drying gave 20 mg of **12** (87%) This crude (20 mg) was dissolved in isooctane (4 mL), and heated at 100 °C in the dark for 4 h Concentration gave a residue that was purified by flash chromatography (0-1% EtOAc/hexanes) to afford 15 mg of **13** (75%, yellow oil), TLC (5% EtOAc/hexanes) $R_f$ 0 65, $^1H$ NMR δ 0 09 (2 s, 12 H, 2 $Me_2Si$), 0 54 (s, 3 H, $CH_3$-18), 0 88 and 0 89 (2 s, 18 H, 2 $Me_3CSi$), 0 95 (d, $J$ = 6 4 Hz, 3 H, $CH_3$-21), 1 15 (d, $J$ = 6 1 Hz, 6 H, $CH_3$-26 and $CH_3$-27), 3 37-3 57 (m, 3 H, $CH_2$-23 and H-25), 4 19 (m, 1 H, H-3), 4 37 (m, 1 H, H-1), 4 87 (d, $J$ = 3 0 Hz, 1 H, H-19*E*), 5 17 (d, $J$ = 3 0 Hz, 1 H, H-19*Z*), 6 02 and 6 22 (AB, $J$ = 11 1 Hz, 2 H, H-7 and H-6), HRMS (EI) calcd for $C_{38}H_{70}O_3Si_2$ 630 4864 ($M^+$), found 630 4872

**(1α,3β,5*Z*,7*E*)-24-Oxa-9,10-secocholesta-5,7,10(19)-triene-1,3-diol (1e).** *n*-$Bu_4NF$ (10 mg, 0 038 mmol) was added to a solution of **13** (12 mg, 0 019 mmol) in THF (4 mL) The solution was stirred in the dark for 16 h and concentrated to a small volume Water (10 mL) was added The mixture was extracted with $Et_2O$ (10 mL) The organic phase was dried, filtered and concentrated The residue was flash chromatographed (50% EtOAc/hexanes) to afford 7 mg of **1e** (91%), TLC (EtOAc) $R_f$ 0 50, $^1H$ NMR δ 0 55 (s, 3 H, $CH_3$-18), 0 95 (d, $J$ = 6 4 Hz, 3 H, $CH_3$-21), 1 15 (d, $J$ = 6 1 Hz, 3 H, $CH_3$-26 and $CH_3$-27), 3 36-3 64 (m, 3 H, $CH_2$-23 and H-25), 4 23 (m, 1 H, H-3), 4 42 (m 1 H, H-1), 5 00 (br s, 1 H, H-19*E*), 5 33 (br s, 1 H, H-19Z), 6 02 and 6 37 (AB, $J$ = 11 4 Hz, 2 H, H-7 and H-6), HRMS (EI) calcd for $C_{26}H_{42}O_3$ 402 3134 ($M^+$), found 402 3139

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