Stereoselective Convergent Synthesis of 24,25-Dihydroxyvitamin D_3 Metabolites: A Practical Approach

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Dedicated to Professor Dieter Seebach on the occasion of his 65th birthday

Abstract: Vitamin D_3 active metabolites 24*R*,25-$(OH)_2$-D_3, 24*S*,25-$(OH)_2$-D_3, and 1α,24*R*,25-$(OH)_3$-D_3 were synthesized by a convergent and stereoselective approach. In the synthetic route, the stereogenic center at C-24 was generated through ultrasonically induced aqueous conjugate addition of iodide **6** to Seebach's dioxolanone **5**, and the vitamin D triene system was constructed using the Lythgoe approach. The synthesis, which is both short (seven steps from iodide **6**) and efficient (32–40% overall yield), allows the preparation of large quantities of the metabolites and provides a novel example of a highly stereoselective reaction promoted by the zinc-copper couple in aqueous media.

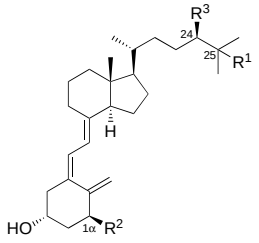
Keywords: asymmetric synthesis · Michael addition · vitamins

Introduction

Vitamin D_3 (**1a**, Figure 1) produces biological responses after transformation by successive stereospecific enzymatic hydroxylations into the major active metabolites 1α,25-$(OH)_2$-D_3 (**1b**, calcitriol) and 24*R*,25-$(OH)_2$-D_3 (**1c**, secalciferol).[1] These metabolites interact with specific protein vitamin D receptors (VDRs) in the cell nucleus (VDR_{nuc}) or in the membrane (VDR_{men}), and give rise to the biological responses through genomic or non-genomic pathways.[2] Calcitriol and secalciferol are involved in a wide range of biological functions such as calcium homeostasis, cellular differentiation and proliferation processes, and other functions related to the immune system. Once the biological responses have been produced, the metabolites are deactivated by further oxidations of the side-chain that lead to more polar metabolites.[3]

The major factor in the biological activity of vitamin D_3 has generally been attributed to calcitriol, while the functions of secalciferol have been relatively unexplored. In the last two decades,[4] intensive research aimed at elucidating the precise biological function of secalciferol and the utility of 24-hydroxy derivatives has been undertaken. As a consequence, a non-nuclear receptor specific for this vitamin D metabolite was discovered.[5] Secalciferol participates, in association with calcitriol, in the intestinal and bone absorption of calcium and phosphorus, but its role in cellular differentiation or proliferation processes is still not understood.[6] Nevertheless, 24-hydroxylated vitamin D analogues such as calcipotriol,[7] tacalcitol (24*R*-OH-D_3), and secalciferol itself, have been found to be effective as antipsoriatic or calcium-regulating agents.[8] The importance of the 24-hydroxy side-chain is also recognized by its presence in natural steroids.[9]

In response to the extraordinary biological activity of vitamin D, the synthesis of metabolites and analogues with



1a: $R^1 = R^2 = R^3 = H$; vitamin D_3
1b: $R^1 = R^2 = OH$, $R^3 = H$; 1α,25-$(OH)_2$-D_3
1c: $R^1 = R^3 = OH$, $R^2 = H$; 24*R*,25-$(OH)_2$-D_3

Figure 1. Vitamin D_3 (**1a**), calcitriol (**1b**), and secalciferol (**1c**).

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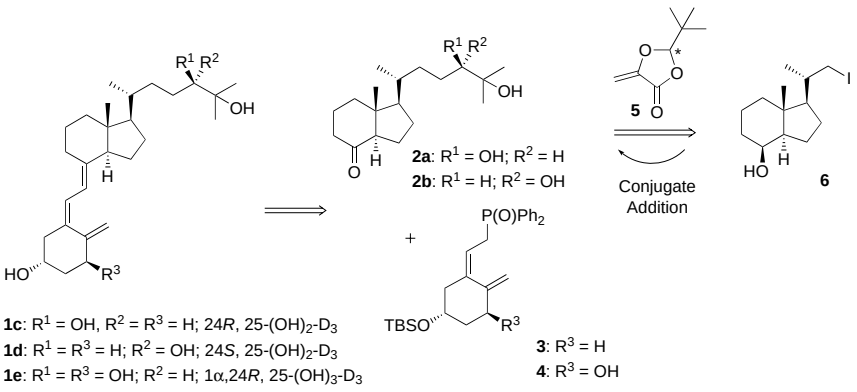
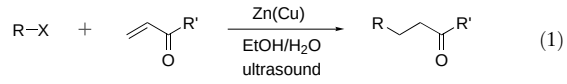
specific biological responses has been widely pursued.[10] In this sense, calcitriol and numerous 25-hydroxy analogues have been efficiently prepared following convergent synthetic approaches. However, the synthesis of secalciferol and its analogues has thus far involved low yielding linear approaches that use steroids as starting materials (biomimetic approach).[11] The resolution of complex diastereomeric mixtures is always necessary except in cases in which the C-24 stereogenic center is present in a synthetic intermediate.[12]



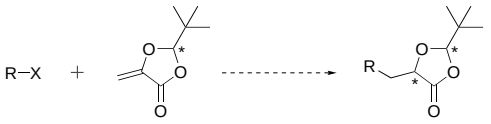
Scheme 1. Retrosynthetic analysis.

As part of our long-term program devoted to the synthesis of vitamin D analogues and metabolites, and to the rational understanding of related biological functions, we focused our attention on the development of an efficient and stereoselective approach to 24-hydroxyvitamin D_3 metabolites. Several years ago we reported an efficient synthesis of the calcitriol side-chain by means of an ultrasonically induced zinc-copper conjugate addition to α,β-unsaturated systems in aqueous media,[13] by application of reaction conditions developed by Luche in the eighties [Eq. (1)].[14] The method was employed for the synthesis of calcitriol and 25-dialkyl analogues. Herein we report the use of this methodology for the stereoselective synthesis of 24-hydroxyvitamin D metabolites.



(1)

The application of Luche's methodology in stereoselective synthesis is practically unknown, being limited to addition to a prochiral carbon in a very electron-deficient olefin.[15] For our synthesis, we envisioned the use of a chiral α-hydroxy Michael acceptor such as Seebach's dioxolanone **5**,[16] in this kind of reaction to obtain the required diastereoselectivity [Eq. (2)].

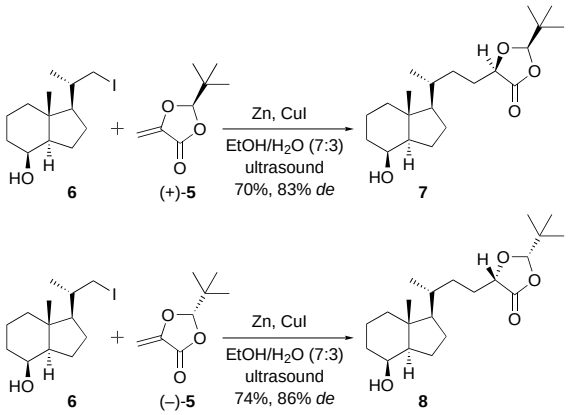


(2)

Results and Discussion

For the stereoselective synthesis of 24,25-dihydroxyvitamin D_3 metabolites (**1c–e**), we considered the retrosynthetic analysis depicted in Scheme 1. According to this scheme, the conjugated vitamin D triene system should be constructed following the Lythgoe approach[17] from 24,25-dihydroxylated ketone **2** and the known phosphane oxides **3** or **4**. The 24,25-dihydroxyketone **2** would be prepared by stereoselective Michael addition between the known iodide **6** and Seebach's dioxolanone **5**.

The synthesis starts with iodide **6**, which contains the CD rings of the vitamin D structure and can be obtained on a multigram scale from vitamin D_2 via the Inhoffen–Lythgoe diol.[18] Seebach's dioxolanone **5** was prepared as both enantiomers, (+)-**5** and (−)-**5**, from enantiomerically pure lactic acid according to the literature procedure.[16] To test our retrosynthetic analysis, we performed the aqueous zinc/copper sonochemically-induced conjugate addition of iodide **6** to the dioxolanone enantiomer (+)-**5**. Remarkably, the 1,4-conjugate addition product **7** was obtained as a *cis*:*trans* mixture of diastereomers in an 11:1 ratio (83% *de*) and 70% yield (Scheme 2). The stereochemistry of the major diastereomer was assigned *cis* (24*R*) on the basis of the NMR assignments described by Beckwith[19] for radical conjugate additions to chiral dioxolanones such as **5**. This stereochemical outcome is consistent with the results found in other 1,4-conjugate additions under classical radical conditions (nBu$_3$SnH/AIBN)[19] and with those obtained by Seebach for dioxolanone enolate alkylations.[20] According to the mechanism proposed by Luche for the zinc-copper conjugate addition, the final step occurs through the protonation of an enolate.[14]



Scheme 2. Diasteroselective Michael addition.

In an effort to determine whether the stereoselectivity of the reaction was due to the chirality of the iodide, the

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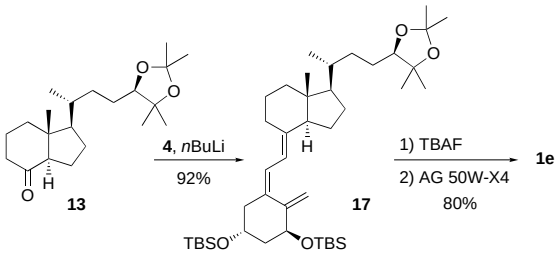
dioxolanone, or both (double stereodifferentiation), we performed the reaction with the dioxolanone enantiomer (−)-**5**. Under the same experimental conditions, the conjugate addition product **8** was obtained in similar yield (74%) and with a similar stereoselectivity (diastereomeric ratio of 13:1, 86% *de*), and the *cis* diastereomer was again the major product. This result proves that the stereoselectivity of the reaction is independent of the chirality of the iodide and that a remarkable, highly diastereoselective protonation of the enolate in aqueous media occurs.

At this point we studied the cleavage of the protected α-hydroxyacid in **7** and **8**, and the introduction of the C-26 and C-27 methyl groups of the vitamin D side-chain. Both objectives were achieved in one step. The reaction of dioxolanone **7** with methylmagnesium bromide afforded the triol **9** as a mixture of C-24 epimers in an 11:1 ratio (Scheme 3). At this point, the major stereoisomer (24*R*) was separated by chromatography (90% yield).[21] In a similar way, triol **10** (24*S*) (epimer of **9** at C-24) was obtained from **8** by reaction with MeMgBr and subsequent purification by crystallization (86% yield).

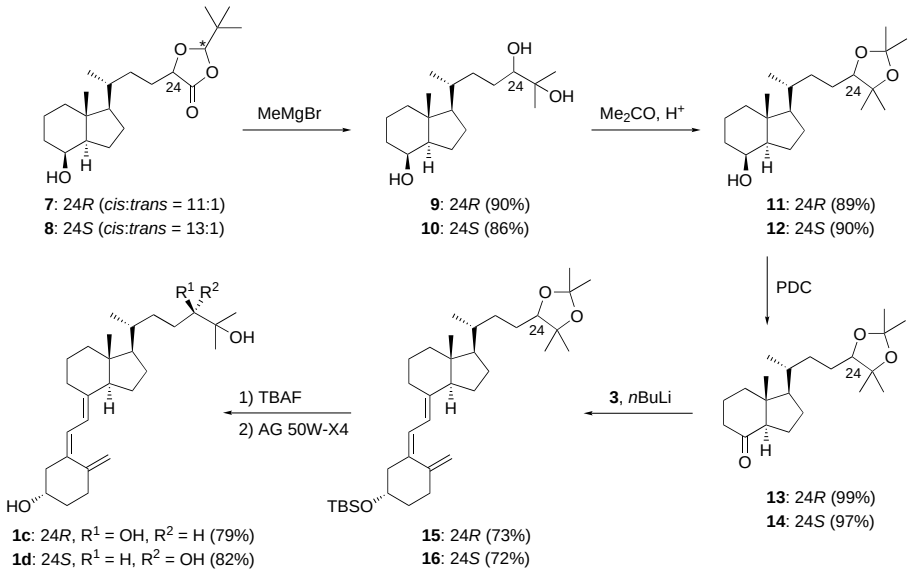
With the two optically pure triols **9** and **10** in hand, we turned our attention to their conversion into the 24*R*,25-$(OH)_2$-vitamin D_3 metabolite (**1c**, secalciferol) and its 24*S* epimer (**1d**). We first attempted the synthesis of secalciferol. Protection of the 24,25-diol unit as a ketal with acetone was achieved with the aid of ultrasound[22] (**9** → **11**), and subsequent oxidation of the hydroxyl group at the C-8 position afforded the ketone **13** in 87% overall yield. A Wittig–Horner reaction between ketone **13** and the anion of the phosphane oxide **3**,[23] which contained the A ring of vitamin D, generated by treatment with *n*BuLi at low temperature, yielded the protected vitamin **15** in 73% yield. Subsequent deprotection of **15** with tetrabutylammonium fluoride (TBAF) and the cationic resin AG 50W-X4 afforded the 24*R*,25-$(OH)_2$-D_3 (**1c**, secalciferol) in seven steps from iodide **6** and in 32% overall yield. The synthesis of 24*S*,25-$(OH)_2$-D_3 (**1d**) was achieved from triol **10** by following the same synthetic sequence (seven steps from iodide **6**, 33% overall yield). 24*S*,25-$(OH)_2$-D_3 (**1d**) is a naturally occurring vitamin D_3 metabolite that results from the enzymatic reduction of 24-oxo-25-hydroxyvitamin D_3. This metabolite (**1d**) exhibits lower affinity for the VDR and its biological activity is, in general, a few orders of magnitude below calcitriol and secalciferol.[5, 24] Nevertheless, its utility as an antitumor agent is patented.[25]

To further exploit the synthetic utility of this approach, we also synthesized the vitamin D_3 metabolite 1α,24*R*,25-$(OH)_3$-D_3 (**1e**). This is an active metabolite, generated in vivo from calcitriol and in vitro from secalciferol, that has preferential biological action in the transport of calcium in the intestine.[26] A Wittig–Horner reaction between ketone **13** and the anion of the 1α-hydroxylated phosphane oxide **4**,[27] generated at low temperature with *n*BuLi, afforded the protected metabolite **17** in 92% yield (Scheme 4). Deprotection with TBAF, followed by treatment with the resin AG 50W-X4 yielded the desired metabolite 1α,24*R*,25-$(OH)_3$-D_3 (**1e**) in 80% overall yield.



Scheme 4. Synthesis of 1α,24*R*,25-$(OH)_3$-D_3 (**1e**).

In summary, we describe here the first stereoselective convergent synthesis of the 24,25-dihydroxyvitamin D_3 metabolites 24*R*,25-$(OH)_2$-D_3 (**1c**), 24*S*,25-$(OH)_2$-D_3 (**1d**), and 1α,24*R*,25-$(OH)_3$-D_3 (**1e**). The synthetic approach is both short and efficient (seven steps from known iodide **6** and 32–40% overall yield) and is a practical method for the synthesis of these natural metabolites. A novel diastereoselective conjugate addition promoted by zinc/copper-assisted coupling in aqueous media was employed. This reaction should be of general use in organic chemistry, not only for the synthesis of other 24-vitamin D analogues, but also for many other chiral compounds such as α-hydroxyacids. Efforts to explore the scope of this reaction and the synthesis of new 24-vitamin D derivatives by using other chiral α,β-unsaturated systems are in progress.



Scheme 3. Synthesis of 24*R*,25-$(OH)_2$-D_3 (**1c**) and 24*S*,25-$(OH)_2$-D_3 (**1d**).

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Experimental Section

General materials and methods: Unless otherwise stated, all reactions were conducted in flame-dried glassware under a positive pressure of argon. Reaction temperatures refer to external bath temperatures. All dry solvents were distilled under argon immediately prior to use. Tetrahydrofuran (THF) was distilled from the sodium/benzophenone. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5. Absolute MeOH and EtOH were distilled from Mg turnings. Methyl acrylate was distilled under vacuum prior use. Zinc was purified as described in the literature.[28] Copper iodide was purified by recrystallization from saturated potassium iodide solution.[29] Sonications were carried out in a Kerry Pulsatron KC6 (38 kHz, 110 W) cleaning bath, filled with water and thermostated (18–20 °C) by running tap water through a stainless steel coil. Organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated using a rotary evaporator at aspirator pressure (20–30 mmHg). Thin-layer chromatography was carried out on Merck silica gel coated aluminium plates $60F_{254}$ (layer thickness 0.2 mm) and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid or *p*-anisaldehyde reagent followed by heating. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh) by Still's method.[30] $[\alpha]_D$: Jasco DIP-1000. UV: Kontron Uvikon 941. IR: Matson FTIR. ^{1}H NMR: 200 MHz, Bruker AC-200F. ^{13}C NMR: 50 MHz, Bruker AC-200F (DEPT was used to assign carbon types). MS: Fisons VG-Quattro. HRMS: VG Autospec M. The AG 50W-X4 resin was purchased from Bio-Rad, Hercules (California, USA) and used as received.

(2*S*,5*R*,8′*β*)-2-(*tert*-Butyl)-5-(de-*A*,*B*-8′-hydroxy-24′-norcholan-23′-yl)-1,3-dioxolan-4-one (7): CuI (182 mg, 0.96 mmol) and Zn (188 mg, 2.88 mmol) were added to a solution of dioxolanone (+)-**5**[16] (100 mg, 0.64 mmol) and **6**[13d] (310 mg, 0.96 mmol) in aqueous EtOH (5 mL, 70 %). The resulting black mixture was sonicated for 90 min until consumption of (+)-**5** was complete (by TLC). The mixture was diluted with EtOAc (8 mL) and filtered through a short pad of Celite, washing the solids with EtOAc (3 × 15 mL). The organic phase was washed with saturated NH_4Cl (30 mL) and NaCl (30 mL), dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20 % EtOAc/hexanes) to afford, after concentration and high vacuum drying, **7** (158 mg, 70 %, 24*R*/24*S* 11:1) as a white foam. $R_f = 0.34$ (30 % EtOAc/hexanes); IR (neat): $\tilde{\nu} = 3525$, 2935, 1796, 1197 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 0.93$ (d, $J = 4.5$ Hz, 3H), 0.95 (s, 3H), 0.98 (s, 9H), 4.07 (br s, 1H), 4.25 (m, 1H), 5.12 (d, $J =$ 1.4 Hz, 0.915H), 5.26 (d, $J = 1.4$ Hz, 0.085H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 13.5$ (CH_3), 17.4 (CH_2), 18.3 (CH_3), 22.5 (CH_2), 23.5 (3CH_3), 27.0 (CH_2), 27.1 (CH_2), 30.5 (CH_2), 33.6 (CH_2), 34.3 (C), 34.7 (CH), 40.3 (CH_2), 41.8 (C), 52.6 (CH), 56.1 (CH), 69.3 (CH), 75.2 (CH), 109.2 (CH), 173.6 (C); MS (FAB): *m*/*z* (%): 352 (8) [M^+], 334 (9) [$M^+ - H_2O$], 111 (100); HRMS (EI): *m*/*z*: calcd for $C_{21}H_{36}O_4$: 352.2614 [M^+]; found: 352.2618.

(2*R*,5*S*,8′*β*)-2-(*tert*-Butyl)-5-(de-*A*,*B*-8′-hydroxy-24′-norcholan-23′-yl)-1,3-dioxolan-4-one (8): Following the same experimental procedure used for **7**, dioxolanone (−)-**5**[16] (101 mg, 0.65 mmol) afforded, after purification (20 % EtOAc/hexanes), **8** (168 mg, 74 %, 24*R*/24*S* 1:13) as a white foam. $R_f = 0.36$ (30 % EtOAc/hexanes); IR (neat): $\tilde{\nu} = 3520$, 2946, 1749, 1194 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 0.92$ (d, $J = 4.4$ Hz, 3H), 0.94 (s, 3H), 0.98 (s, 9H), 4.08 (d, $J = 2.9$ Hz, 1H), 4.22 (m, 1H), 5.12 (d, $J = 1.5$ Hz, 0.93H), 5.25 (d, $J = 1.5$ Hz, 0.07H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 13.5$ (CH_3), 17.4 (CH_2), 18.3 (CH_3), 22.5 (CH_2), 23.4 (3CH_3), 27.0 (CH_2), 27.2 (CH_2), 30.9 (CH_2), 33.5 (CH_2), 34.2 (C), 43.9 (CH), 40.3 (CH_2), 41.8 (C), 52.5 (CH), 56.1 (CH), 69.2 (CH), 75.6 (CH), 109.2 (CH), 173.7 (C); MS (EI): *m*/*z* (%): 352 (5) [M^+], 334 (38) [$M^+ - H_2O$], 111 (100); HRMS (EI): *m*/*z*: calcd for $C_{21}H_{36}O_4$: 352.2614 [M^+]; found: 352.2611.

(8*β*,24*R*)-De-*A*,*B*-cholesta-8,24,25-triol (9):[21] MeMgBr in Et_2O (1.40 mL, 3.0 M, 4.20 mmol) was slowly added a solution of to a solution of **7** (178 mg, 0.50 mmol) in THF (10 mL) at −78 °C. The mixture was warmed to RT and stirred for 5 h. The reaction was quenched with few drops of MeOH, and the resulting mixture was concentrated to a small volume. The residue was dissolved in EtOAc (15 mL) and washed with saturated $NaHCO_3$ (15 mL) and NaCl (15 mL), dried, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (75 % EtOAc/hexanes) to afford, after concentration and high vacuum drying, **9** (134 mg, 90 %) as a colorless oil. $R_f = 0.10$ (30 % EtOAc/hexanes); $[\alpha]_D^{19} = +35.1$ ($c = 0.35$ in $CHCl_3$); IR (neat): $\tilde{\nu} = 3390$, 2922, 1377, 1071 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 0.92$ (d, $J = 6.5$ Hz, 3H), 0.94 (s, 3H), 1.18 (s, 3H), 1.20 (s, 3H), 3.33 (br s, 1H), 4.08 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta =$ 13.5 (CH_3), 17.4 (CH_2), 18.4 (CH_3), 22.5 (CH_2), 23.2 (CH_3), 26.6 (CH_3), 27.2 (CH_2), 28.1 (CH_2), 32.6 (CH_2), 33.5 (CH_2), 35.1 (CH), 40.4 (CH_2), 41.9 (C), 52.6 (CH), 56.6 (CH), 69.4 (CH), 73.2 (C), 78.8 (CH); MS (EI): *m*/*z* (%): 298 (3) [M^+], 280 (10) [$M^+ - H_2O$], 135 (100); HRMS (EI): *m*/*z*: calcd for $C_{18}H_{34}O_3$: 298.2508 [M^+]; found: 298.2512; elemental analysis calcd (%) for $C_{18}H_{34}O_3$ (298.5): C 72.44, H 11.48; found: C 72.15, H 11.63.

(8*β*,24*S*)-De-*A*,*B*-cholesta-8,24,25-triol (10):[21] Following the same experimental procedure used for **9**, dioxolanone **8** (120 mg, 0.35 mmol) afforded, after purification by flash chromatography (40 % EtOAc/hexanes), **10** (90 mg, 86 %) as a white solid. $R_f = 0.40$ (70 % EtOAc/hexanes); m.p. 89–91 °C (Et_2O/hexanes); $[\alpha]_D^{21} = +19.3$ ($c = 0.47$ in $CHCl_3$); IR (neat): $\tilde{\nu} =$ 3410, 2950, 1360, 1085 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 0.91$ (d, $J = 5.9$ Hz, 3H), 0.93 (s, 3H), 1.18 (s, 3H), 1.20 (s, 3H), 3.27 (dd, $J = 9.8$, 2.0 Hz, 1H), 4.06 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 13.5$ (CH_3), 17.4 (CH_2), 18.7 (CH_3), 22.5 (CH_2), 23.1 (CH_3), 26.5 (CH_3), 27.1 (CH_2), 28.3 (CH_2), 33.1 (CH_2), 33.5 (CH_2), 35.5 (CH), 40.4 (CH_2), 41.8 (C), 52.5 (CH_2), 56.6 (CH), 69.3 (CH), 73.2 (C), 79.5 (CH); MS (EI): *m*/*z* (%): 298 (4) [M^+], 270 (8) [$M^+ - C_2H_4$], 71 (100); HRMS (EI): *m*/*z*: calcd for $C_{18}H_{34}O_3$: 298.2508 [M^+]; found: 298.2505; elemental analysis calcd (%) for $C_{18}H_{34}O_3$ (298.5): C 72.44, H 11.48; found: C 72.70, H 11.57.

(8*β*,24*R*)-De-*A*,*B*-cholesta-8,24,25-triol cyclic 24,25-(1-methylethylidene acetal) (11): A solution of **9** (100 mg, 0.33 mmol) in acetone (10 mL) containing one drop of conc. H_2SO_4 was sonicated for 2.5 h. The mixture was concentrated to a small volume and the residue was dissolved in CH_2Cl_2 (20 mL). The organic phase was washed with water (15 mL), dried, filtered, and concentrated to afford **11** (100 mg, 89 %) as a colorless oil. $R_f = 0.70$ (70 % EtOAc/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta =$ 0.93 (s, 3H), 0.93 (d, $J = 5.6$ Hz, 3H), 1.11 (s, 3H), 1.26 (s, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 3.64 (dd, $J = 8.6$, 3.5 Hz, 1H), 4.09 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 13.5$ (CH_3), 17.4 (CH_2), 18.4 (CH_3), 22.5 (CH_2), 22.8 (CH_3), 25.9 (CH_2), 26.2 (CH_3), 26.8 (CH_3), 27.2 (CH_2), 28.6 (CH_3), 32.7 (CH_2), 33.6 (CH_2), 35.4 (CH), 40.4 (CH_2), 41.8 (C), 52.6 (CH), 56.4 (CH), 69.3 (CH), 80.2 (C), 83.7 (CH), 106.3 (C); MS (FAB): *m*/*z* (%): 337 (12) [$M^+ - H$], 323 (100) [$M^+ - CH_3$]; HRMS (EI): *m*/*z*: calcd for $C_{21}H_{38}O_3$: 338.2821 [M^+]; found: 338.2828.

(24*R*)-De-*A*,*B*-24,25-dihydroxycholestan-8-one cyclic 24,25-(1-methylethylidene acetal) (13): A mixture of **11** (96 mg, 0.28 mmol) and PDC (319 mg, 0.85 mmol) in CH_2Cl_2 (17 mL) was stirred for 6 h. Et_2O (10 mL) was added and the resulting mixture was stirred for 15 min. The mixture was filtered through Celite, and the solid was washed with Et_2O (5 × 10 mL). The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (30 % EtOAc/hexanes) to afford, after concentration and high vacuum drying, **13** (94 mg, 99 %) as a colorless oil. $R_f = 0.70$ (50 % EtOAc/hexanes); IR (neat): $\tilde{\nu} = 2950$, 1725, 1120 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 0.65$ (s, 3H), 0.99 (d, $J = 5.4$ Hz, 3H), 1.10 (s, 3H), 1.25 (s, 3H), 1.33 (s, 3H), 1.42 (s, 3H), 3.63 (dd, $J = 8.4$, 3.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 12.5$ (CH_3), 18.6 (CH_3), 19.0 (CH_2), 22.9 (CH_3), 24.0 (CH_2), 26.0 (CH_2), 26.2 (CH_3), 26.8 (CH_3), 27.5 (CH_2), 28.5 (CH_3), 32.7 (CH_2), 35.6 (CH), 39.0 (CH_2), 40.9 (CH_2), 49.9 (C), 56.5 (CH), 61.9 (CH), 80.1 (C), 83.6 (CH), 106.4 (C), 211.9 (C); MS (FAB): *m*/*z* (%): 337 (22) [M^++H], 321 (100) [$M^+ - CH_3$]; HRMS (EI): *m*/*z* calcd for $C_{21}H_{36}O_3$: 336.2664 [M^+]; found: 336.2659.

(3*β*,5*Z*,7*E*,24*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-9,10-secocholesta-5,7,10(19)-triene-24,25-diol cyclic 24,25-(1-methylethylidene acetal) (15): *n*BuLi in hexanes (0.125 mL, 2.39 M, 0.30 mmol) was added dropwise to a solution of phosphane oxide **3** (142 mg, 0.31 mmol) in THF (7 mL) at −78 °C. The red solution was warmed to 0 °C and, after 20 min, cooled again to −78 °C. A solution of **13** (43 mg, 0.13 mmol) in THF (3 mL) was then added by cannula. The mixture was warmed to RT and stirred for a further 5 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and then poured into a separating funnel with Et_2O (20 mL). The organic layer was washed successively with saturated solutions of NH_4Cl (10 mL) and NaCl (10 mL). The organic layer was dried, filtered, and concentrated, all with protection from light. The residue was purified by flash chromatography (45 % EtOAc/hexanes) to afford, after concentration and high vacuum drying, **15** (54 mg, 73 %) as a colorless oil. $R_f = 0.65$ (50 % EtOAc/hexanes); IR (neat): $\tilde{\nu} = 3031$, 2930, 1462, 1097 cm^{-1}; ^{1}H NMR (200 MHz, CD_2Cl_2, 25 °C): $\delta = 0.06$ (s, 3H), 0.07 (s, 3H), 0.56 (s, 3H), 0.87

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(s, 9H), 0.95 (d, $J = 5.9$ Hz, 3H), 1.05 (s, 3H), 1.20 (s, 3H), 1.28 (s, 3H), 1.35 (s, 3H), 3.61 (m, 1H), 3.86 (m, 1H), 4.76 (br s, 1H), 5.00 (br s, 1H), 6.01, 6.18 (2d, AB, $J = 11.2$ Hz, 2H); MS (EI): m/z (%): 570 (28) [M^+], 555 (36) [$M^+ - CH_3$], 193 (100); HRMS (EI): m/z: calcd for $C_{36}H_{62}O_3Si$: 570.4468 [M^+]; found: 570.4468.

(3β,5Z,7E,24R)-9,10-Secocholesta-5,7,10(19)-triene-3,24,25-triol [24R,25-dihydroxyvitamin D_3] (1c):[31] nBu$_4$NF·3H$_2$O (45 mg, 0.14 mmol) was added to a solution of **15** (33 mg, 0.06 mmol) in THF (10 mL), with protection from the light. The solution was stirred for 23 h, poured into a separating funnel with EtOAc (30 mL), and the organic layer was washed with a saturated solution of NH_4Cl (10 mL), dried, filtered, and concentrated in vacuo. The residue was dissolved in deoxygenated MeOH (10 mL), and AG 50W-X4 resin (175 mg) was added. The mixture was stirred for 24 h, filtered, the solids were washed with MeOH (4 × 5 mL), and concentrated in vacuo. The residue was purified by flash chromatography (85% EtOAc/hexanes) to afford, after concentration and high vacuum drying, **1c** (20 mg, 79%) as a white solid. $R_f = 0.5$ (EtOAc); $[\alpha]_D^{24} = +20.4$ ($c = 0.1$ in $CHCl_3$); IR (neat): $\tilde{\nu} = 3410, 3081, 2927, 1639, 1048$ cm^{-1}; UV (MeOH): $\lambda_{max} = 264, 215$ nm; ^{1}H NMR (200 MHz, CD_3OD, 25 °C): $\delta =$ 0.56 (s, 3H), 0.95 (d, $J = 5.9$ Hz, 3H), 1.12 (s, 3H), 1.15 (s, 3H), 3.21 (d, $J =$ 9.3 Hz, 1H), 3.75 (m, 1H), 4.74 (br s, 1H), 5.02 (br s, 1H), 6.02, 6.21 (2d, AB, $J = 11.2$ Hz, 2H); ^{13}C NMR (50 MHz, CD_3OD, 25 °C): $\delta = 12.3$ (CH_3), 19.2 (CH_3), 23.2 (CH_3), 24.5 (CH_2), 24.9 (CH_3), 25.6 (CH_2), 28.7 (CH_2), 29.9 (CH_2), 30.7 (CH_2), 33.6 (CH_2), 34.2 (CH_2), 36.6 (CH_2), 37.2 (CH), 41.9 (CH_2), 46.9 (C), 47.0 (CH_2), 57.5 (CH), 58.0 (CH), 70.5 (CH), 73.8 (C), 79.7 (CH), 112.6 (CH_2), 118.9 (CH), 122.6 (CH), 137.3 (C), 142.5 (C), 147.0 (C); MS (EI): m/z (%): 416 (100) [M^+], 398 (22) [$M^+ - H_2O$]; HRMS (EI): m/z: calcd for $C_{27}H_{44}O_3$: 416.3290 [M^+]; found: 416.3288.

(8β,24S)-De-A,B-cholesta-8,24,25-triol cyclic 24,25-(1-methylethylidene acetal) (12): Following the same experimental procedure used for **11**, triol **10** (62 mg, 0.21 mmol) afforded **12** (63 mg, 90%) as a colorless oil. $R_f = 0.75$ (70% EtOAc/hexanes); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 0.93$ (s, 3H), 0.93 (d, $J = 5.4$ Hz, 3H), 1.10 (s, 3H), 1.25 (s, 3H), 1.33 (s, 3H), 1.41 (s, 3H), 3.61 (dd, $J = 7.3$, 5.3 Hz, 1H), 4.08 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 13.5$ (CH_3), 17.4 (CH_2), 18.6 (CH_3), 22.5 (CH_2), 22.8 (CH_3), 25.9 (CH_2), 26.3 (CH_3), 26.8 (CH_3), 27.1 (CH_2), 28.6 (CH_3), 32.7 (CH_2), 33.5 (CH_2), 35.3 (CH), 40.4 (CH_2), 41.8 (C), 52.6 (CH), 56.4 (CH), 69.3 (CH), 80.1 (C), 84.0 (CH), 106.3 (C); MS (EI): m/z (%): 337 (1) [$M^+ - H$], 323 (58) [$M^+ - H_2O$], 111 (100); HRMS (EI): m/z: calcd for $C_{21}H_{38}O_3$: 338.2821 [M^+]; found: 338.2825.

(24S)-De-A,B-24,25-dihydroxycholestan-8-one cyclic 24,25-(1-methylethylidene acetal) (14): Following the same experimental procedure used for **13**, alcohol **12** (111 mg, 0.33 mmol) afforded, after purification (30% EtOAc/hexanes), **14** (107 mg, 97%) as a colorless oil. $R_f = 0.70$ (50% EtOAc/hexanes); IR (neat): $\tilde{\nu} = 2950, 1720, 1120$ cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 0.64$ (s, 3H), 0.98 (d, $J = 5.8$ Hz, 3H), 1.08 (s, 3H), 1.24 (s, 3H), 1.31 (s, 3H), 1.40 (s, 3H), 3.60 (dd, $J = 6.1$, 1.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta = 12.5$ (CH_3), 18.6 (CH_3), 19.0 (CH_2), 22.8 (CH_3), 24.0 (CH_2), 25.9 (CH_2), 26.2 (CH_3), 26.8 (CH_3), 27.5 (CH_2), 28.5 (CH_3), 32.8 (CH_2), 35.6 (CH), 39.0 (CH_2), 40.9 (CH_2), 49.9 (C), 56.5 (CH), 61.9 (CH), 80.1 (C), 83.9 (CH), 106.3 (C), 211.9 (C); MS (EI): m/z (%): 337 (3) [M^++H], 321 (100) [$M^+ - CH_3$]; HRMS (EI): m/z: calcd for $C_{21}H_{36}O_3$: 336.2664 [M^+]; found: 336.2667.

(3β,5Z,7E,24S)-3-[(tert-Butyldimethylsilyl)oxy]-9,10-secocholesta-5,7,10(19)-triene-24,25-diol cyclic 24,25-(1-methylethylidene acetal) (16): Following the same experimental procedure used for **15**, treatment of ketone **14** (46 mg, 0.14 mmol) with the anion formed from phosphane oxide **3** (81 mg, 0.18 mmol) and nBuLi in hexanes (0.092 mL, 2.24 M, 0.20 mmol) afforded, after purification by flash chromatography (40% EtOAc/hexanes), **16** (57 mg, 72%) as a colorless oil. $R_f = 0.74$ (30% EtOAc/hexanes); IR (neat): $\tilde{\nu} = 3030, 2940, 1450, 1100$ cm^{-1}; ^{1}H NMR (200 MHz, CD_2Cl_2, 25 °C): $\delta =$ 0.06 (s, 6H), 0.54 (s, 3H), 0.88 (s, 9H), 0.95 (d, $J = 5.9$ Hz, 3H), 1.05 (s, 3H), 1.20 (s, 3H), 1.27 (s, 3H), 1.35 (s, 3H), 3.59 (m, 1H), 3.84 (m, 1H), 4.76 (d, $J = 1.9$ Hz, 1H), 5.01 (d, $J = 1.0$ Hz, 1H), 6.01, 6.18 (2d, AB, $J = 11.2$ Hz, 2H); MS (EI): m/z (%): 570 (32) [M^+], 555 (45) [$M^+ - CH_3$], 193 (100); HRMS (EI): m/z: calcd for $C_{36}H_{62}O_3Si$: 570.4468 [M^+]; found: 570.4465.

(3β,5Z,7E,24S)-9,10-Secocholesta-5,7,10(19)-triene-3,24,25-triol [24S,25-dihydroxyvitamin D_3] (1d):[31] Following the same experimental procedure used for **1c**, compound **16** (40 mg, 0.07 mmol) afforded, after purification (90% EtOAc/hexanes), **1d** (24 mg, 82%) as a white solid. $R_f = 0.46$ (70% EtOAc/hexanes); $[\alpha]_D^{26} = +30.6$ ($c = 0.7$ in $CHCl_3$); IR (neat): $\tilde{\nu} = 3410, 3070, 2930, 1625, 1050$ cm^{-1}; UV (MeOH): $\lambda_{max} = 265, 215$ nm; ^{1}H NMR (200 MHz, CD_2Cl_2, 25 °C): $\delta = 0.54$ (s, 3H), 0.93 (d, $J = 5.9$ Hz, 3H), 1.11 (s, 3H), 1.16 (s, 3H), 3.22 (m, 1H), 3.87 (m, 1H), 4.79 (br s, 1H), 5.03 (br s, 1H), 6.02, 6.23 (2d, AB, $J = 11.2$ Hz, 2H); ^{13}C NMR (50 MHz, CD_2Cl_2, 25 °C): $\delta = 12.1$ (CH_3), 19.1 (CH_3), 23.4 (CH_3), 23.9 (CH_2), 26.6 (CH_3), 27.9 (CH_2), 28.7 (CH_2), 29.3 (CH_2), 30.0 (CH_2), 32.4 (CH_2), 33.6 (CH_2), 35.7 (CH_2), 36.7 (CH), 40.9 (CH_2), 46.1 (CH_2), 46.3 (C), 56.6 (CH), 56.8 (CH), 69.5 (CH), 73.3 (C), 79.9 (CH), 112.4 (CH_2), 117.9 (CH), 122.5 (CH), 135.8 (C), 142.4 (C), 145.8 (C); MS (EI): m/z (%): 416 (18) [M^+], 398 (3) [$M^+ - H_2O$], 136 (100); HRMS (EI): m/z: calcd for $C_{27}H_{44}O_3$: 416.3290 [M^+]; found: 416.3290.

(1α,3β,5Z,7E,24R)-1,3-Di[(tert-butyldimethylsilyl)oxy]-9,10-secocholesta-5,7,10(19)-triene-24,25-diol cyclic 24,25-(1-methylethylidene acetal) (17): Following the same experimental procedure used for **15**, treatment of ketone **13** (50 mg, 0.15 mmol) with the anion formed from phosphane oxide **4** (128 mg, 0.22 mmol) and nBuLi in hexanes (0.10 mL, 2.13 M, 0.21 mmol) afforded, after purification by flash chromatography (40% EtOAc/hexanes), **17** (96 mg, 92%) as a colorless oil. $R_f = 0.76$ (50% EtOAc/hexanes); ^{1}H NMR (200 MHz, CD_2Cl_2, 25 °C): $\delta = 0.06$ (s, 12H), 0.53 (s, 3H), 0.87 (s, 18H), 0.95 (d, $J = 5.9$ Hz, 3H), 1.05 (s, 3H), 1.20 (s, 3H), 1.28 (s, 3H), 1.35 (s, 3H), 3.61 (dd, $J = 8.8$, 2.9 Hz, 1H), 4.18 (m, 1H), 4.38 (t, $J =$ 5.4 Hz, 1H), 4.84 (d, $J = 2.4$ Hz, 1H), 5.18 (d, $J = 2.0$ Hz, 1H), 6.02, 6.26 (2d, AB, $J = 11.2$ Hz, 2H); ^{13}C NMR (50 MHz, CD_2Cl_2, 25 °C): $\delta = -4.9$ (CH_3), −4.7 (CH_3), −4.64 (CH_3), −4.61 (CH_3), 11.1 (CH_3), 12.1 (CH_3), 18.4 (C), 18.9 (CH_3), 22.5 (CH_2), 23.1 (CH_3), 23.9 (CH_2), 26.0 (6CH_3), 26.4 (CH), 27.0 (CH_3), 28.0 (CH_2), 28.8 (CH_3), 29.2 (CH_2), 33.3 (CH_2), 36.6 (CH), 39.2 (C), 40.9 (CH_2), 45.2 (CH_2), 46.1 (C), 46.3 (CH_2), 56.7 (CH), 67.9 (CH), 72.3 (CH_3), 80.4 (C), 84.0 (CH), 106.5 (C), 111.4 (CH_2), 118.2 (CH), 123.4 (CH), 135.5 (C), 141.5 (C), 148.8 (C); MS (FAB): m/z (%): 701 (29) [M^+], 686 (24) [$M^+ - H_2O$], 568 (100); HRMS (EI): m/z: calcd for $C_{42}H_{76}O_4Si_2$: 700.5282 [M^+]; found: 700.5288.

(1α,3β,5Z,7E,24R)-9,10-Secocholesta-5,7,10(19)-triene-1,3,24,25-tetrol [1α,24R,25-trihydroxyvitamin D_3] (1e):[31] nBu$_4$NF·3H$_2$O (171 mg, 0.54 mmol) was added to a solution of **17** (95 mg, 0.13 mmol) in THF (10 mL), with protection from the light. The solution was stirred for 22 h, poured into a separating funnel with EtOAc (30 mL), and the organic layer was washed with a saturated solution of NH_4Cl (10 mL), dried, filtered, and concentrated in vacuo. The residue was dissolved in deoxygenated MeOH (10 mL) and AG 50W-X4 resin (370 mg) was added. The mixture was protected from light and stirred for 22 h. The solids were filtered, washed with MeOH (4 × 6 mL), and the resulting solution was concentrated in vacuo. The crude product was purified by flash chromatography (5% MeOH/EtOAc) to afford, after concentration and high vacuum drying, **1e** (47 mg, 80% over two steps) as a white solid. $R_f = 0.3$ (EtOAc); $[\alpha]_D^{18} = +38.2$ ($c = 0.85$ in MeOH); IR (neat): $\tilde{\nu} = 3426, 2924, 1639, 1364, 1046$ cm^{-1}; UV (MeOH): $\lambda_{max} = 266, 215$ nm; ^{1}H NMR (200 MHz, CD_3OD, 25 °C): $\delta = 0.57$ (s, 3H), 0.96 (d, $J = 5.9$ Hz, 3H), 1.12 (s, 3H), 1.15 (s, 3H), 3.21 (d, $J = 9.3$ Hz, 1H), 4.11 (m, 1H), 4.35 (t, $J = 5.9$ Hz, 1H), 4.89 (d, $J =$ 2.0 Hz, 1H), 5.28 (d, $J = 1.0$ Hz, 1H), 6.08, 6.32 (2d, AB, $J = 11.2$ Hz, 2H); ^{13}C NMR (50 MHz, CD_3OD, 25 °C): $\delta = 12.4$ (CH_3), 19.3 (CH_3), 23.3 (CH_2), 24.6 (CH_2), 25.0 (CH_3), 25.6 (CH_3), 28.7 (CH_2), 30.0 (CH_2), 30.7 (CH_2), 34.2 (CH_2), 37.2 (CH), 41.9 (CH_2), 43.7 (CH_2), 46.1 (CH_2), 46.7 (C), 57.6 (CH), 58.1 (CH), 67.4 (CH), 71.4 (CH), 73.9 (C), 79.7 (CH), 112.0 (CH_2), 119.0 (CH), 124.9 (CH), 135.6 (C), 142.5 (C), 149.8 (C); MS (EI): m/z (%): 432 (9) [M^+], 414 (100) [$M^+ - H_2O$]; HRMS (EI): m/z: calcd for $C_{27}H_{44}O_4$: 432.3240 [M^+]; found: 432.3240.

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