Stereoselective Synthesis of (22*R*)- and (22*S*)-22-Methyl-1α,25-Dihydroxyvitamin D_3

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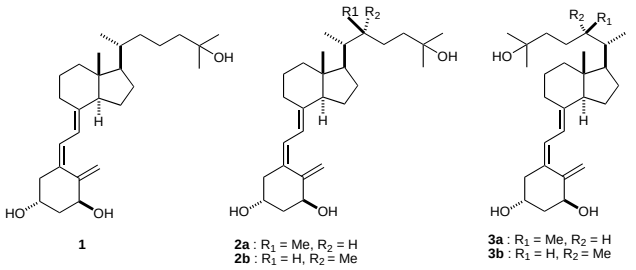
Abstract: An efficient, straightforward method for construction of the side chain of (22*R*)- and (22*S*)-22-alkyl-1α,25-dihydroxyvitamin D_3 is described. The title compounds were synthesized by Lythgoe's procedure.

Key words: 1α,25-dihydroxyvitamin D_3, stereoselective synthesis, alkylations, nitriles, 22-substituted analogue

It is now well established that regulation of gene transcription is among the mechanisms of action of 1α,25-dihydroxyvitamin D_3 (calcitriol, **1**) (Figure), the hormonally active metabolite of vitamin D_3.[1] This multifunctional hormone[2] controls the expression of various genes involved in calcium and phosphorus metabolism, cell differentiation and regulation of the immune system,[3] apparently by binding to the nuclear vitamin D receptor (VDR)[4].

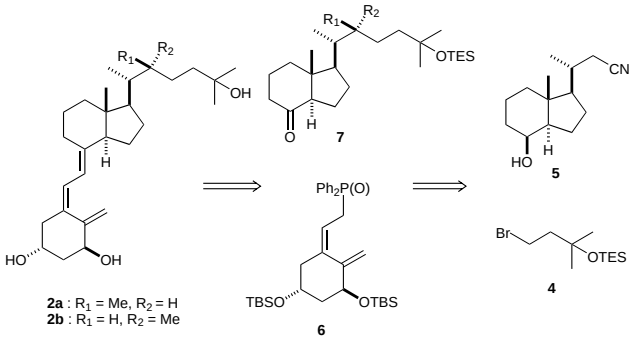


Figure

It is of crucial importance to find out the conformation that calcitriol must adopt in order to bind to VDR and to the equally vital transport protein, vitamin D binding protein (DBP). To that end, Yamada et al.[5,6] designed and synthesized analogues **2a**, **2b**, **3a** and **3b**. Structure-function studies of these compounds then showed that they are not only useful for studying calcitriol binding, but may also prove to be of therapeutical value. Yamada's synthesis of **2** and **3** was based on the stereoselective conjugate addition of organocuprate to steroidal *E*- and *Z*-22-en-24-ones, and suffers from the usual drawbacks of biomimetic approaches. Here we describe a convergent synthesis of **2a** and **2b**, based on the retrosynthetic analysis depicted in Scheme 1.

The synthesis of the key precursors bearing the 22 substituted side chains **7a** and **7b** is detailed in Scheme 2. Nitrile **5**,[7] readily obtained from the Inhoffen–Lythgoe diol **8**, was deprotonated with 2 equivalents of LDA in THF at –78 °C, a solution of bromide **4**[8] in THF was added, and the mixture was allowed to reach room temperature overnight, affording the cyanoalcohol **9**[9] (89%) as a mixture of inseparable diastereoisomers. Reaction of **9** with DIBAH in dichloromethane at –10 °C and subsequent acid work-up afforded the corresponding aldehyde, which was taken up in methanol and reacted with excess sodium borohydride, giving a 2:1.5 mixture of alcohols **10** and **11**. These colorless oils were cleanly separated by flash chromatography (15% EtOAc–hexanes) in yields of 40 and 24%, respectively; the stereochemistry at C22 was determined by X-ray crystallographic analysis of the triol resulting from deprotection of the TES group of diol **10**.[9]

Selective tosylation of the primary alcohols of **10** and **11** gave the corresponding tosylates **12** and **13** in 82% and 76% yield, respectively,[10] and treatment of these tosylates with LAH in ether at 0 °C to room temperature afforded the 22-methylated alcohols **14a** and **14b** in 80% and 84% yield, respectively. Pyridinium dichromate oxidation of alcohols **14a** and **14b** then afforded the ketones **15a** and **15b** in 90% and 91% yield, respectively, so setting the stage for the Wittig–Horner reaction with phosphine oxide **6**.[11] This coupling reaction, followed by removal of the silyl protecting groups, finally afforded the targets **2a**[12]and **2b**[13] in 72% and 75% yield, respectively. In conclusion, we have developed a convergent route to (22*R*)-



Scheme 1

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1437-2096,E;2001,0,10,1567,1568,ftx,en;D16801st.pdf.

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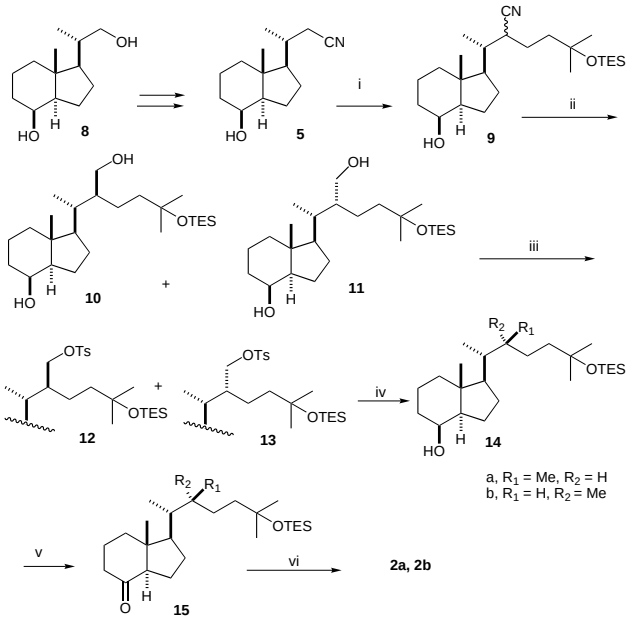

Scheme 2 (i) LDA, THF, –78 °C; **4** (89%); (ii) DIBAH, CH_2Cl_2, –10 °C; HCl; $NaBH_4$, MeOH (64% global yield **10**+**11**, two steps); (iii) TsCl, Pyr, 0 °C, 12 h; (iv) $LiAlH_4$, Et_2O, 0 °C to r.t.; (v) PDC, CH_2Cl_2, r.t. 5 h; (vi) (a) **6**; *n*-Buli, THF, –78 °C; (b) *n*-Bu_4NF, THF, r.t.

and (22*S*)-22-methyl-1α,25-dihydroxyvitamin D_3.[14] The new method is valid for multigram quantities and should allow convergent synthesis of a large number of vitamin D_3 analogues with restricted side chain conformations. Work is in progress for the synthesis of a series of such analogues.

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(12) Compound **2a**: ^1H NMR (300 MHz, $CDCl_3$), δ: 6.37 (1 H, d, *J* = 11.20 Hz, H-6 or 7), 6.01 (1 H, d, *J* = 11.27 Hz, H-6 or 7), 5.32 (1 H, d, *J* = 1.47 Hz, H-19), 4.99 (1 H, s, H-19), 4.42 (1 H, dd, *J* = 7.76 and *J* = 4.21 Hz, H-1), 4.22 (1 H, m, H-3), 2.60 (1 H, m), 2.31 (1 H, m), 1.25 (3 H, s, CH_3-26 or 27), 1.20 (3 H, s, CH_3-26 or 27), 0.78 (3 H, d, *J* = 5.96 Hz, CH_3-22), 0.72 (3 H, d, *J* = 6.72 Hz, CH_3-21), 0.54 (3 H, s, CH_3-18); ^{13}C NMR (CD_2Cl_2), δ: 147.67 (C-10), 143.18 (C-8), 132.90 (C-5), 124.96 (CH-6), 117.00 (CH-7), 111.70 (CH_2-19), 71.12 (C-25), 70.78 (CH-3), 66.83 (CH-1), 56.37, 54.20 (CH),45.99 (C-13), 45.25, 42.87, 42.17, 40.62 (CH_2), 39.00, 35.01 (CH), 30.25 (CH_2), 29.67 and 29.27 (CH_3-26 and 27), 29.10, 27.24, 23.62, 22.15 (CH_2), 13.09 (CH_3-18 or 21), 12.49 (CH_3-22), 11.93 (CH_3-18 or 21).
(13) Compound **2b**: ^1H NMR (300 MHz, $CDCl_3$), δ: 6.38 (1 H, d, *J* = 11.10 Hz, H-6 or 7), 6.03 (1 H, d, *J* = 11.15 Hz, H-6 or 7), 5.32 (1 H, s, H-19), 5.00 (1 H, s, H-19), 4.42 (1 H, m, H-1), 4.23 (1 H, m, H-3), 2.84 (1 H, m)2.60 (1 H, m), 2.31 (1 H, m), 1.22 (3 H, s, CH_3-26 or 27), 1.21 (3 H, s, CH_3-26 or 27), 0.87 (3 H, d, *J* = 6.72 Hz, CH_3-22), 0.72 (3 H, d, *J* = 6.74 Hz, CH_3-21), 0.54 (3 H, s, CH_3-18); ^{13}C NMR (CD_2Cl_2), δ: 147.66 (C-10), 143.28 (C-8), 132.83 (C-5), 125.03 (CH-6), 116.97 (CH-7), 111.75 (CH_2-19), 71.23 (C-25), 70.83 (CH-3), 66.88 (CH-1), 56.31, 54.20 (CH),45.91 (C-13), 45.27, 42.87, 42.80 (CH_2), 41.85 (CH), 40.58 (CH_2), 35.21 (CH), 29.69 (CH_2), 29.58 and 29.13 (CH_3-26 and 27), 29.05, 27.38, 23.60, 22.20 (CH2), 18.95 (CH_3-22), 13.17 and 11.93 (CH_3-18 and 21).
(14) A few mgs of compounds **2a** and **2b** are available upon request.