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Stereoselective synthesis of vitamin D_3 analogues with cyclic side chains

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Abstract

The synthesis of a new class of vitamin D analogues having a cyclic side chain is described. Readily available starting material, a short sequence with high yielding steps are key features of the synthesis. Alcohols **12c** and **12d** were readily separable by flash chromatography and the stereochemistry at C22 was established unambiguously by X-ray diffraction analysis of **12c**.

The importance of 1α,25-dihydroxyvitamin D_3 [Calcitriol, 1α,25-$(OH)_2$-D_3, **1**] the hormonally active metabolite of vitamin D_3 is presently well recognized.[1] It exhibits control over the expression of various genes which are involved in calcium and phosphorus metabolism, cellular differentiation and regulation of the immune system.[2] 1α,25-$(OH)_2$-D_3 is a multifunctional hormone[3] which is believed to exert its activities by a mechanism mediated by the nuclear vitamin D receptor (VDR).[4] In the expression of vitamin D function, two proteins play important roles: the specific nuclear receptor protein (vitamin D receptor, VDR) and the transport protein (vitamin D binding protein, DBP). It is of crucial importance to find out the conformation of 1α,25-$(OH)_2$-D_3 responsible for the binding to those proteins. For that purpose, Yamada et al.[5,6] designed the synthesis of four new vitamin D analogues (**2a**,**2b**,**3a**,**3b**) with restricted side chain conformation.

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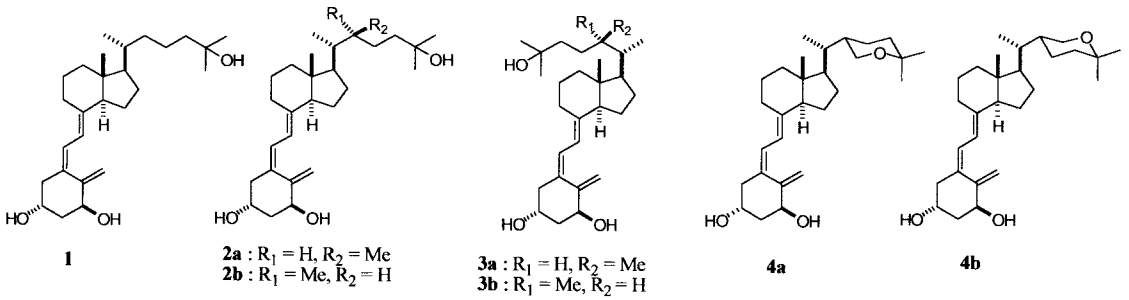
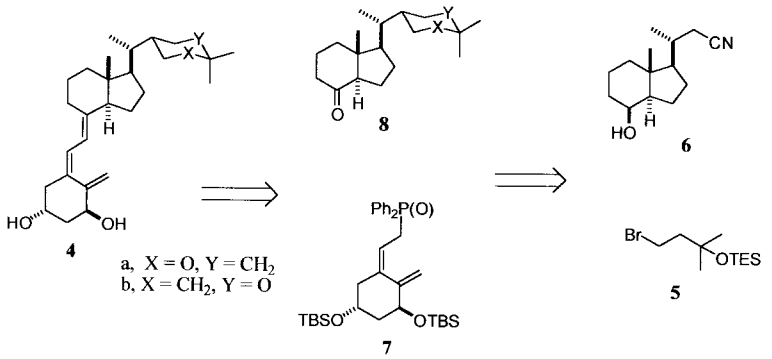


The structure and function studies of these active vitamin D analogues showed that they are indeed of extreme importance not only as potentially useful therapeutic drugs, but also as a tool for studying the molecular mechanism of vitamin D mediated gene expression. This prompted us to release our preliminary results on the synthesis of vitamin D analogues such as **4a** and **4b** with restricted side chain conformation, based on the retrosynthetic analysis depicted in Scheme 1.

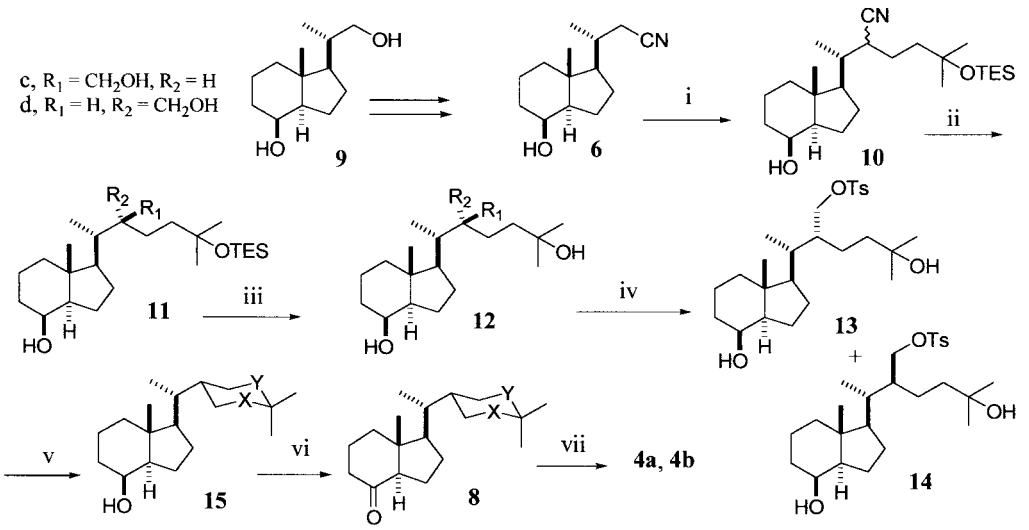


Scheme 1.

The synthesis of key precursors **8a** and **8b** bearing a cyclic side chain is detailed in Scheme 2.

The nitrile **6**,[7] readily obtained from the Inhoffen–Lythgoe diol **9** was deprotonated with 2 equivalents of LDA in THF at –78°C. A solution of the bromide **5**[8] in THF was added and the mixture allowed to reach room temperature overnight, affording the cyanoalcohol **10**[9] (89%) as a mixture of unseparable diastereoisomers. Reaction of the nitrile **10** 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 of sodium borohydride[10] to afford a 2:1.5 mixture of alcohols **11c** and **11d** which were cleanly separated by flash chromatography (15% EtOAc–hexanes) as colorless oils (40 and 24%, respectively). At this stage of the synthesis the stereochemistry of both compounds at C22 was unknown. Deprotection of the TES group gave the corresponding triols **12c** and **12d** in 92 and 90% yield, respectively, as white solids. Recrystallization of **12c**[11] from dichloromethane–methanol afforded crystals which were subjected to X-ray crystallographic analysis, thus establishing the structure to be that shown in Fig. 1.

Selective tosylation of the primary alcohol of **12c** and **12d** gave the corresponding tosylates **13** and **14** in 80 and 84% yield, respectively. The tosylates **13** and **14** were individually treated with



Scheme 2. *Reagents and conditions*: (i) LDA,THF, –78°C; **5** (89%); (ii) DIBAH,CH_2Cl_2, –10°C; HCl; $NaBH_4$, MeOH (64% global yield **11c+11d**, two steps); (iii) nBu$_4$NF, THF, rt; (iv) TsCl, Pyr, 0°C, 12 h; (v) NaH, DMF, rt (61%); (vi) PDC, CH_2Cl_2, rt 5 h; (vii) (a) **7**; nBuLi, THF, –78°C; (b) nBu$_4$NF, THF, rt

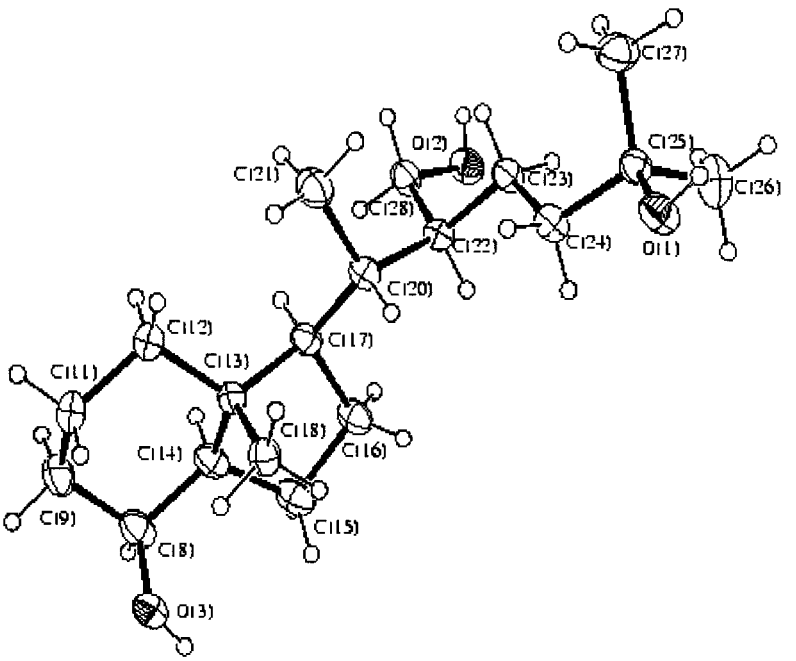


Figure 1. Molecular structure of **12c**

sodium hydride, in DMF at rt to afford the corresponding alcohols **15b** and **15a** bearing a cyclic side chain. Pyridinium dichromate oxidation of the alcohols **15a** and **15b** afforded the ketones **8a** and **8b** in 90 and 95% yield, respectively. With these key precursors in hand the stage was set for the Wittig–Horner reaction using phosphine oxyde **7**.[12] Coupling reaction of **8a** and **8b** with **7**,

and subsequent removal of the silyl protecting groups, afforded the corresponding targets **4a**[13] and **4b**[14] in 75 and 78% yield, respectively. In conclusion, we have developed a convergent route to a new class of vitamin D analogues having a cyclic side chain. This approach is also useful for the preparation of other vitamin D analogues modified at the side chain including Yamada's type compounds.[5] Work is in progress for the synthesis of those analogues.

Acknowledgements

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13. Compound **4a**: ^{1}H NMR (300 MHz, CD_2Cl_2), δ: 6.34 and 5.99 (2H, AB, J = 11.2, H-6 and 7), 5.27 (1H, br s, H-19), 4.94 (1H, br s, H-19), 4.36 (1H, m), 4.15 (1H, m), 3.51 (1H, dd, J = 11.0, 2.3, H-28), 3.41 (1H, t, J = 11.0, H-28), 2.83 (1H, dd, J = 12.0, 3.6), 2.53 (1H, dd, J = 12.3, 3.5), 2.24 (1H, dd, J = 13.4, 6.7), 1.12 (3H, s, CH_3-26), 1.11 (3H, s, CH_3-27), 0.87 (3H, d, J = 6.5, CH_3-21), 0.51 (3H, s, CH_3-18); ^{13}C NMR (CD_2Cl_2), δ: 148.80 (C=), 143.57 (C=), 134.29 (C=), 125.29 (CH=), 117.93 (CH=), 112.25 (=CH_2), 71.61 (C-25), 71.56, 67.49, 62.46 (CH_2), 57.01, 54.82, 46.63 (C-13), 46.13 (CH_2), 43.72 (CH_2), 41.32 (CH_2), 40.18, 39.40, 37.94 (CH_2), 31.99, 29.78 (CH_2), 28.15 (CH_2), 25.77 (CH_2), 24.36 (CH_2), 22.94 (CH_2), 21.99, 15.12, 12.05. HRMS calcd for $C_{28}H_{44}O_3$: 428.3290; found: 428.3318.
14. Compound **4b**: ^{1}H NMR (300 MHz, CD_2Cl_2), δ: 6.34 and 5.99 (2H, AB, J = 11.2, H-6 and 7), 5.27 (1H, br s, H-19), 4.94 (1H, br s, H-19), 4.35 (1H, m), 4.15 (1H, m), 3.53 (1H, t, J = 11.2, H-28), 3.32 (1H, dd, J = 11.2, 4.0, H-28), 2.82 (1H, dd, J = 12, 3.3), 2.52 (1H, dd, J = 13.3, 3.0), 2.26 (1H, dd, J = 13.3, 6.6), 1.13 (3H, s, CH_3-26), 1.11 (3H, s, CH_3-27), 0.84 (3H, d, J = 6.6, CH3-21), 0.53 (3H, s, CH_3-18); ^{13}C NMR (CD_2Cl_2), δ: 148.85 (C=), 143.51 (C=), 134.38 (C=), 125.23 (CH=), 117.94 (CH=), 112.18 (=CH_2), 71.87 (C-25), 71.47, 67.49, 66.51 (CH_2), 57.09, 54.48, 46.49 (C-13), 46.09 (CH_2), 43.72 (CH_2), 41.40 (CH_2), 39.28, 37.58, 37.50 (CH_2), 31.98, 29.79 (CH_2), 28.17 (CH_2), 24.38 (CH_2), 22.91 (CH_2), 22.02, 19.71 (CH_2), 15.44, 12.24. HRMS calcd for $C_{28}H_{44}O_3$: 428.3290; found: 428.3278.