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Design and Synthesis of 1α,25-Dihydroxyvitamin D3 Analogues with Fixed Torsion Angle C(16-17-20-22).

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Abstract

A series of semi-rigid analogues of the hormone 1α,25-dihydroxyvitamin D_3 have been designed in order to study the topology required for binding to the hormone receptor (VDR). The new vitamin D_3 analogues **2–5** possess a rigid C17–C20 bond and minimal structural modifications on the side-chain with respect to the hormone. Key steps for the introduction of the side-chains of the new analogues **2–5** from hydrindanone **6** involve a stereoselective Wittig reaction, olefin isomerization and dihalocyclopropanation.

Keywords: Hormone 1α,25-dihydroxyvitamin D_3, vitamin D receptor (VDR), molecular mechanics.

The steroid hormone 1α,25-dihydroxyvitamin D_3 [**1**, 1α,25-$(OH)_2$-D_3, Figure 1] is currently understood to induce a large number of biological responses via genomic pathways through binding to a ubiquitous nuclear receptor (VDR) that regulates the transcription of specific proteins related to calcium and phosphorus metabolism, cellular differentiation, or other biological functions [1,2]. This wide range of activities can be modulated by synthetic analogues of the above hormone, although the mechanism is unclear [3]. Some analogues may show different pharmacokinetics [4] or induce different conformational changes on the VDR upon binding, according to an induced fit model [5]. The topology of the binding site of the VDR is still unknown and has been considered as a hydrophobic cavity with the capacity to anchor the hormone through hydrogen bonds [6]. The hydroxyl groups of 1α,25-$(OH)_2$-D_3 are considered, therefore, to play an important role in the recognition and transduction events [1,2] although their relative topology upon binding to the VDR or other proteins is uncertain due to considerable conformational flexibility of the hormone.

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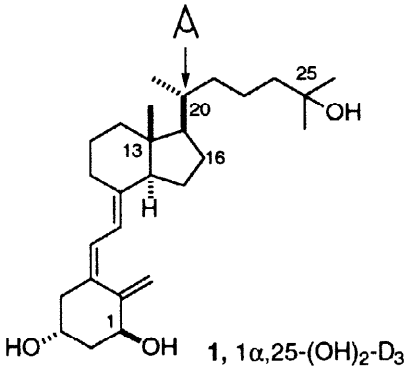
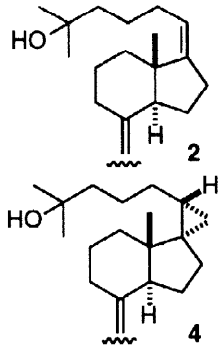
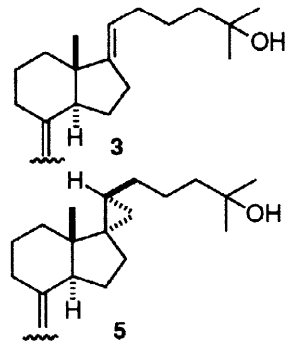
Despite the large number of side-chain modified analogues of 1α,25-(OH)$_2$-D$_3$ that have been synthesized, studies on their conformational behaviour have only been carried out recently [7]. Recent theoretical calculations suggest that the active side-chain conformation derived from the C(17-20-22-23) torsion angle seems to be anti (-178°) [8]. There is currently great interest in understanding the topology (or topologies) of the C25 hydroxyl group of the hormone 1α,25-(OH)$_2$-D$_3$ upon binding to its receptor (or receptors) in order to rationally design vitamin D$_3$ analogues with selective biological functions as potentially useful drugs for clinical purposes [1,6]. With this aim in mind, we wish to report our initial results in relation to the design, molecular mechanics analysis and synthesis of a series of analogues of the hormone 1α,25-(OH)$_2$-D$_3$ with a fixed torsion angle C(16-17-20-22) (Figure 1).

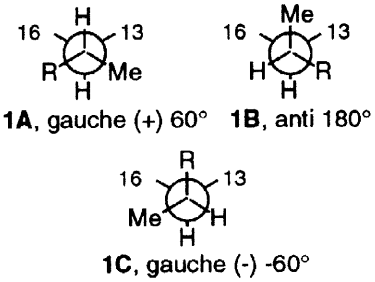
The side-chain conformers of analogues **2–5** were generated by energy minimisation using MMX force-field molecular mechanics calculations (Figure 1) [9]. The position of the 25-OH in all conformers found for each of the analogues **2–5** defines the occupancy volume of the side-chain [10]. No energy limitations were taken, although the energies of most of the conformers differed by less than 4 Kcal/mol from the minimum energy value. The side-chain conformers derived from fixed rotamers **1A**, **1B** and **1C** (see Figure 1) of hormone **1** were also analysed. The percentage values shown indicate the overlap of spatial regions corresponding to the side-chain conformers of analogues **2–5** with those of the three rotamers of the hormone **1**. It can be observed that a preference exists in each analogue for one or two of the regions defined by the three rotamers of **1**. This analysis suggests that the biological evaluation of our analogues **2–5** should provide some insight into the active side-chain conformation of the natural hormone.



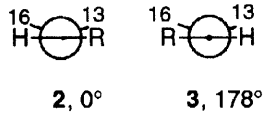
1, 1α,25-(OH)$_2$-D$_3$





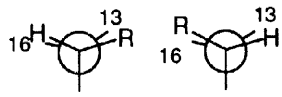


1A, gauche (+) 60° **1B**, anti 180°



2, 0° **3**, 178°

1C, gauche (-) -60°



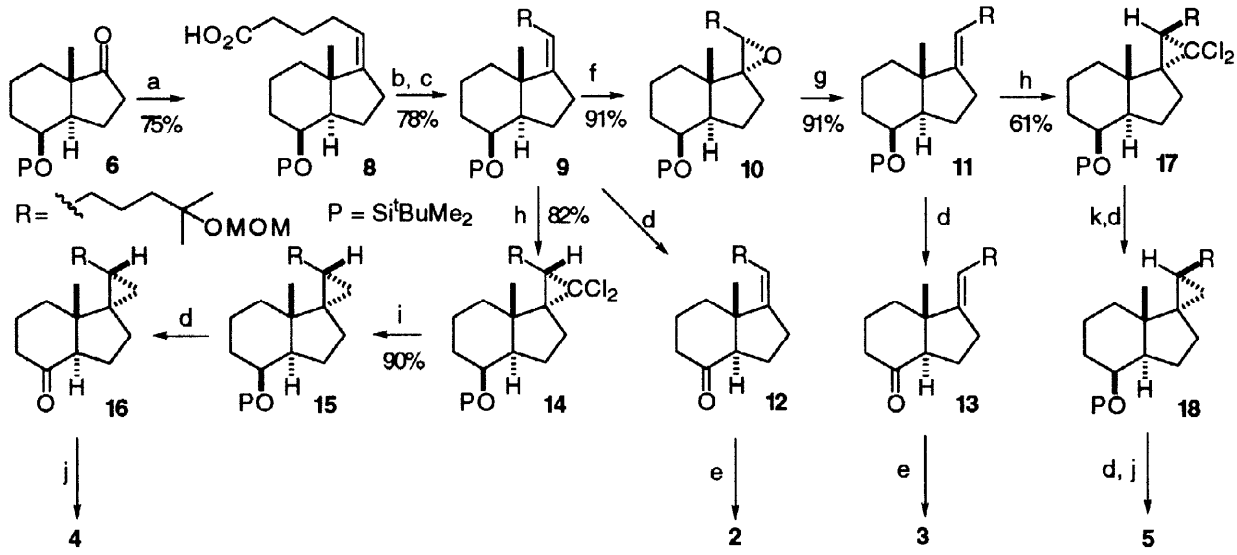
4, -2° **5**, -144°

Degree of overlapping of the spatial region occupied by the side chain of analogues **2-5** with that of each rotamer **1A**, **1B** or **1C** of the hormone **1**.

Analogue	1A Gauche (+)	1B Anti	1C Gauche (-)
2	20%	79%	29%
3	74%	34%	31%
4	15%	53%	57%
5	75%	23%	66%

Figure 1. Comparison of the spacial region accessible to the C25-OH of the semi-rigid analogues **2–5** and the three regions generated by rotamers **1A**, **1B**, **1C** of the hormone.

The triene unit of the target vitamin D analogues **2–5** was introduced by the Wittig–Horner approach or the dienyne route [11,12] (Scheme 1). The known hydrindanone **6** [13] was used as the starting material. The (Z)-olefinic side-chain of carboxylic acid **8** was constructed in 75% yield by reaction of **6** with the ylide derived from salt **7** [14]. Treatment of **8** with methyllithium, followed by protection, gave **9** [78%, ^{1}H NMR: δ = 1.08 (3 H, $C_{18}CH_3$)], which is the common precursor for analogues **2–5**.



Scheme 1. (a) $BrPh_3P(CH_2)_4CO_2H$ (7), *t*BuOK, PhH. (b) MeLi, THF, 0 °C; MeLi, THF, –78 °C. (c) CH_3OCH_2Cl, DMAP, *i*Pr_2NEt, CH_2Cl_2. (d) *n*Bu_4NF, THF; PDC, CH_2Cl_2. (e) Dienyne route [16]. (f) MCPBA, $NaHCO_3$, CH_2Cl_2/H_2O. (g) PPh_2Li, THF, 0 °C, then MeI. (h) $CHCl_3$, NaOH, *n*Bu_4NHSO_4. (i) Na, EtOH. (j) Wittig–Horner approach [19, 20]. (k) Na, *t*BuOH.

The (*E*)-olefinic side-chain of **11** [83%, ^{1}H NMR: δ = 0.98 (3 H, $C_{18}CH_3$)] was constructed by stereoselective epoxidation of **9** followed by deoxygenation of the resulting epoxide **10** using the Vedejs' method [15]. Compounds **9** and **11** were converted to the corresponding vitamin D analogues **2** and **3**, respectively, using the dienyne route [16]. These intermediates were also studied as possible precursors of the cyclopropanated vitamin D analogues **4** and **5**. Direct Simmons–Smith type methods, or the use of photochemically generated carbenes, gave poor conversion to the desired cyclopropanated compounds **15** and **18**. After considerable experimentation we found that the introduction of the desired cyclopropanic unit could satisfactorily be achieved in two steps by stereoselective addition of dichlorocarbene [17] followed by dehalogenation with sodium in the presence of an alcohol [18]. Cyclopropanic vitamin D analogues **4** and **5** were obtained in high yield from the respective ketones **16** and **19** using the Wittig–Horner approach [19,20].

In conclusion, we have designed and prepared four new vitamin D analogues with restricted rotation about their C17–C20 bond. The study of the structure/biological function relationships of the new analogues is underway.

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References and notes

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