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A key intermediate for the convenient synthesis of series of vitamin D_3 analogues with modified side chains

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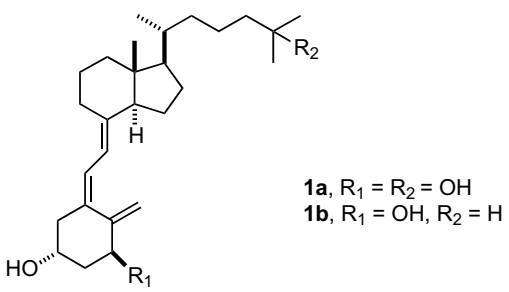
Abstract—Tosylate **1**, which features the vitamin D triene unit, was stereoselectively synthesized from commercially available starting materials. This key intermediate undergoes a very efficient one-pot, two-step reaction with tetrabutyl ammonium fluoride to afford vitamin D analogue **2**, which bears a cyclic side chain. Reaction of **1** with lithium aluminium hydride and removal of the silyl protecting groups affords the 22-methylated vitamin D analogue **3**.

1α,25-Dihydroxyvitamin D_3 (calcitriol, **4a**) (Fig. 1) is the hormonally active form of vitamin D_3 (**4b**). Besides regulating calcium homeostasis, it is also involved in other cellular processes, including cell differentiation, immune system regulation and gene transcription.[1] The latter function, mediated by the nuclear vitamin D receptor (found in more than thirty different tissues and cancer cell lines), raises the possibility of developing 1α,25-$(OH)_2$-D_3 analogues for specific therapeutic applications.

However, a rational design of such analogues requires information about the conformation of the hydroxylated side-chain in the structure binding to the VDR receptor(s).



1a, $R_1 = R_2 = OH$
1b, $R_1 = OH$, $R_2 = H$

Figure 1.

In initial studies aimed at determining the topography of the side chain of the receptor-bound hormone, Okamura and co-workers synthesized new vitamin D analogues possessing a side-chain made rigid by incorporation of an aromatic ring.[2] Later, Yamada and co-workers[3] synthesized a series of analogues with side chains with restricted orientations (Fig. 2).

We have recently synthesized analogues with restricted side chain conformations by a route based on the retrosynthetic analysis depicted in Scheme 1,[4] an approach that also allows preparation of other analogues with modified side chains, including Yamada's.[5]

However, since this strategy involves construction of the triene unit on the CD fragment following the introduction of the side chain, it is inconvenient if a lengthy series of analogues with modified side chains are to be prepared for systematic biological evaluation. We have therefore, now examined the possibility of preparing C22-modified analogues from a common intermediate, in which the labile triene system is already present, namely the tosylate **1.** Compound **1** was obtained by selective tosylation of the known diol **14** in 82% yield,[4] PDC oxidation of the resulting tosyl alcohol **15** to ketone **16** (75%), and formation of the vitamin D triene system in a 84% yield by reaction of ketone **16** with the ylide derived from phosphine oxide **17**,[6] (Scheme 2).

To test the utility of compound **1** as a key intermediate, we investigated its transformation in vitamin D analogues with cyclic and 22-methylated side chains (**2** and

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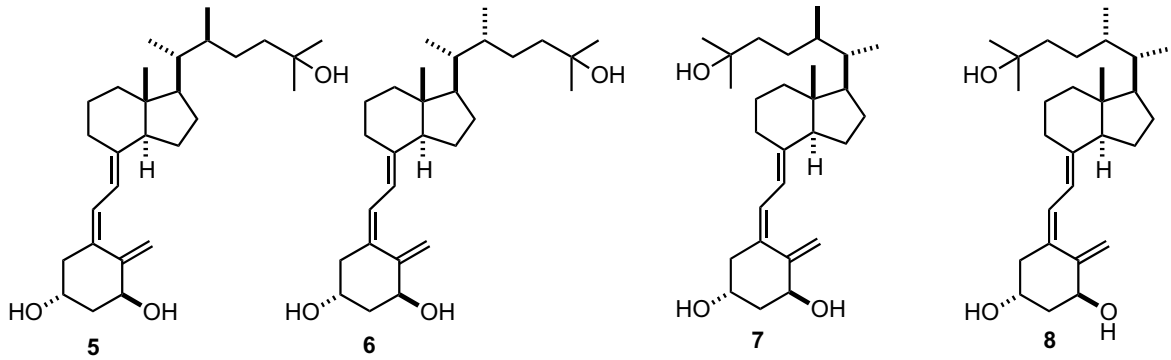
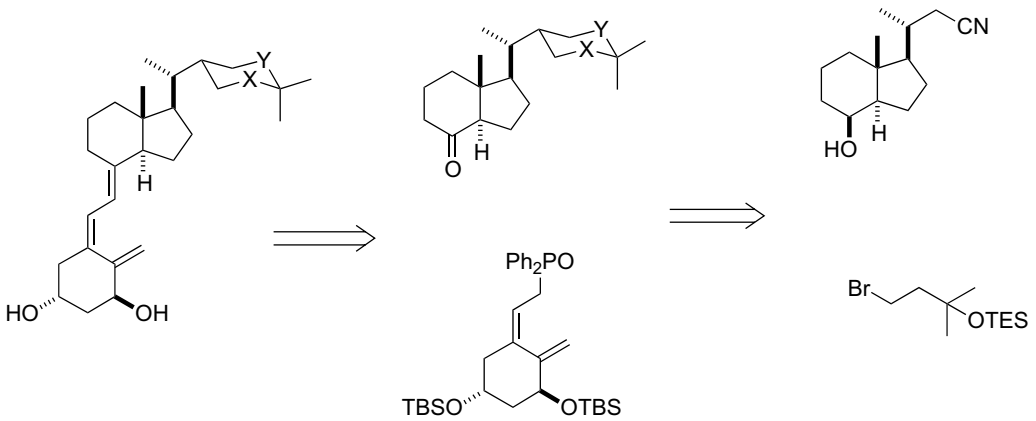
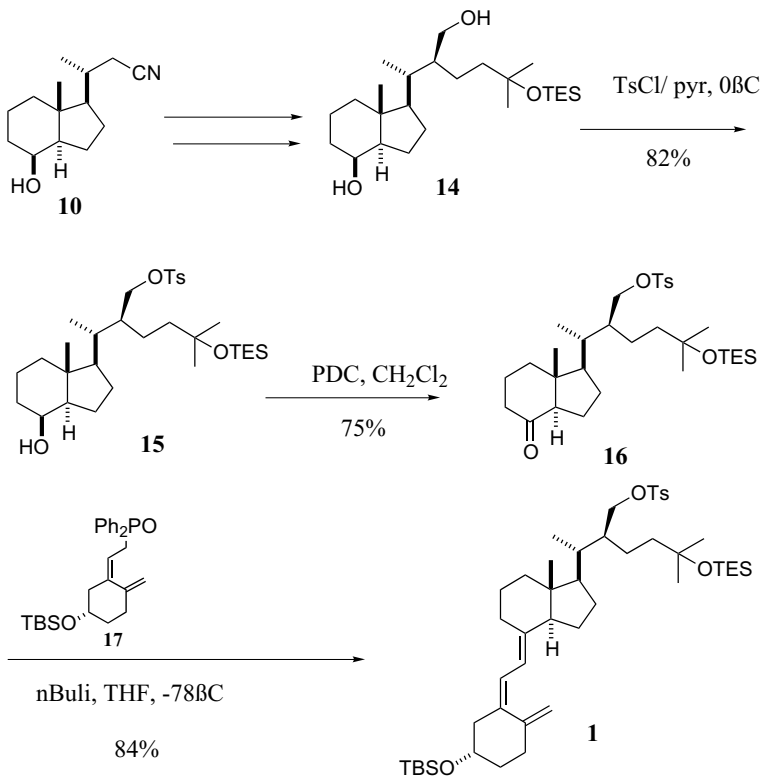


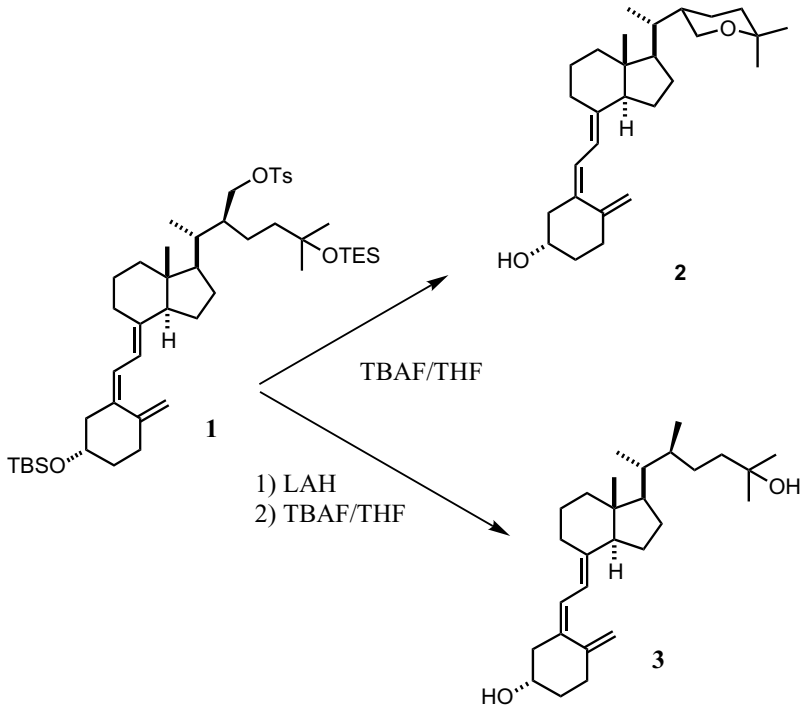
Figure 2. Yamada's type analogues.



Scheme 1. Retrosynthetic analysis for **13a** and **13b**.



Scheme 2. Synthesis of key intermediate **1**.



Scheme 3. Synthesis of vitamin D analogues **2** and **3**.

3, respectively; see Scheme 3). Gratifyingly, reaction of **1** with TBAF afforded **2**[7] in one pot and 70% yield through desilylation and in situ cyclization; while its reaction with LAH (10 equiv LAH, ether, 0°C to rt, overnight), followed by desilylation, afforded the (22*R*)-22-methyl analogue **3** (68% yield, two steps).

In conclusion, we have developed a potentially powerful method by which a large series of vitamin D analogues with modifications affecting C-22 can be synthesized from a common precursor in which the vitamin D triene system is already present. This method will undoubtedly facilitate investigation of the relationship between the structure of an analogue and its activity at vitamin D receptors, and we are currently using it to prepare a relevant series for biological evaluation. Finally, we note that tosylate **1** appears to be eminently suitable for the application of the solid support vitamin D synthesis procedures recently developed by Takahashi and co-workers,[8] and we are accordingly pursuing the synthesis of resin-bound **1**.

Acknowledgements

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