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A NITRILE APPROACH TO THE SYNTHESIS OF THE SIDE CHAIN OF VITAMIN D METABOLITES AND ANALOGUES

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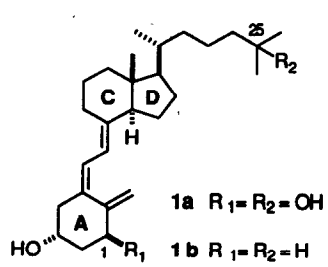
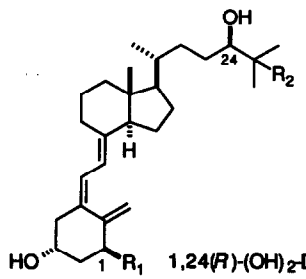
Abstract: An efficient new method for the construction of vitamin D hydroxylated side chains is described which is based on the alkylation and opening of epoxides by the α-anions derived from nitriles **6** and **7**.

1α,25-Dihydroxyvitamin D_3 (**1a**,1α,25-$(OH)_2$-D_3, calcitriol), the hormonally active form of vitamin D_3 (**1b**, calciferol), plays an important role in calcium homeostasis[1] and is associated with normal cell proliferation and differentiation.[2] However, the clinical utility of 1,25-$(OH)_2$-D_3 is limited, due to its potent calcemic effects.[3] Research is now directed towards the synthesis of analogues of **1a** with high cell differentiating ability and low calcemic action.[4] For example, 1α,24(*R*)-dihydroxyvitamin D_3 (**2**)[5] and several 26,27-dialkylated[2,6] and homologated[7] derivatives of **1a** combine potent induction of the differentiation of malignant cells with low calcemic activity, and are promising as possible therapeutic agents for the treatment of certain cancers and psoriasis.[2]



1a $R_1 = R_2 = OH$

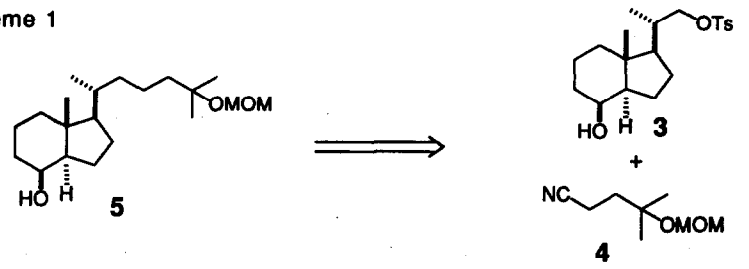
1b $R_1 = R_2 = H$



1,24(*R*)-$(OH)_2$-D_3 (**2**)

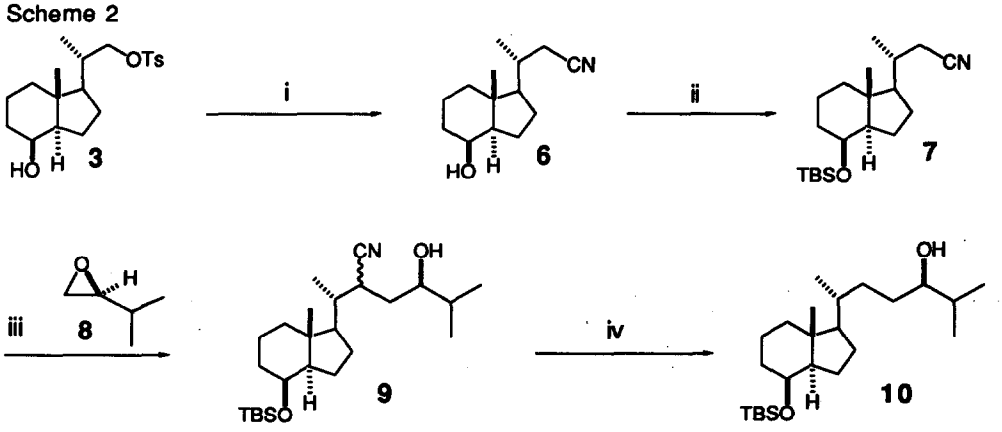
We have recently reported an efficient method for the construction of the 25-hydroxylated side chain of the hormone **1a** in multigram quantities.[8] This method is based on the reaction of an excess of the anion of nitrile **4** with the bicyclic tosylate **3** (Scheme 1).

Scheme 1



We now describe a more general method which not only allows the preparation of hydroxylated vitamin D_3 side chains via alkylation but also via the opening of epoxides (Scheme 2).

Scheme 2

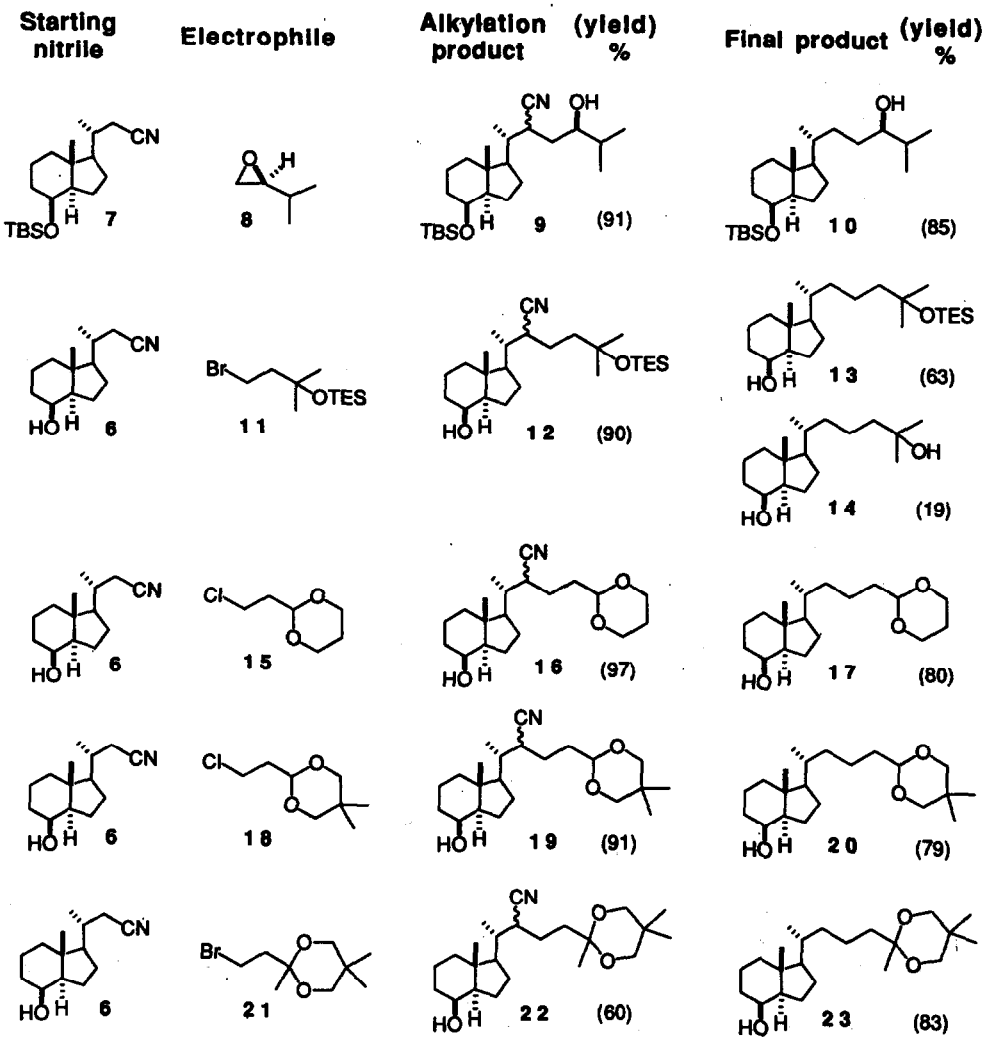


(i) NaCN, DMSO, 90 °C, 4h (90%). (ii) TBSCl, imidazole, DMF, CH_2Cl_2, reflux 48 h (98%). (iii) LDA/ THF, -78 °C, HMPA, **8** (91%). (iv) *t*-BuOH (2 equiv), HMPA (5 equiv), Et_2O (30 equiv), 0 °C, K in portions (7 equiv), rt 12 h (85%).

Nitrile **7** (readily obtained from tosylate **3**[9]) was deprotonated with LDA in THF at -78°C and added to a solution of epoxide **8** (derived from L-valine)[10] in THF/HMPA at -78°C. The mixture was allowed to reach rt to afford cyano alcohol **9**[11] (91%), which upon treatment with a mixture of potassium and HMPA in the presence of *t*-BuOH as the proton source[12] provided alcohol **10**[11] (85%). Alcohol **10** can be used as an intermediate in the synthesis of 1,24(*R*)-$(OH)_2$-D_3[5] by known procedures.[13]

Nitrile **6** can also be successfully used to prepare other side-chain modified analogues of the hormone **1a**. The results are illustrated in Fig 1. As an example, nitrile **6** was treated with LDA (2 eq) to give the corresponding dianion, which was reacted with chloride **15** to afford **16** (97%). Removal of the nitrile group as above provided the desired alcohol **17** (80%).

Fig 1



Compounds **17**, **20** and **23** are suitable intermediates for furher functionalization or radiolabelling.[14] In the literature there are many examples of vitamin D side chain formation by alkylation of a sulphone followed by reductive desulphonylation.[15] Reductive alkylation of a selenoacetal has also been used.[16] This new approach can be favourably compared with the others (excellent yields with fewer steps) and furthermore can lead to a whole range of analogues, as the intermediate nitrile can be transformed into various functional groups. Work is in progress on the synthesis of other vitamin D side chain analogues.

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