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# SYNTHESIS OF NON-CONJUGATED 19-NOR-CALCITRIOLS

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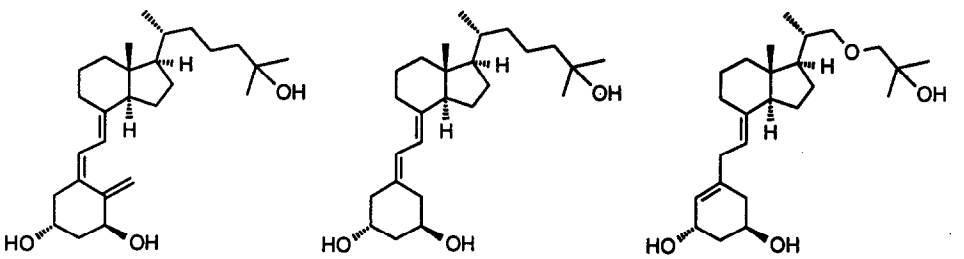
*Summary:* A simple synthetic approach to 19-nor-calcitriol **2**, bearing a deconjugated diene system is described.

1α,25-Dihydroxyvitamin $D_3$ (calcitriol), the biologically active metabolite of vitamin $D_3$, has long been known for it's ability to mediate calcium and phosphorous homeostasis [1] in vivo. More recently, it was discovered that calcitriol strongly influences proliferation and differentiation of certain cell types such as keratinocytes or cancer cells. [2] Meanwhile a number of structurally modified calcitriol analogs have been synthesized. Some of them are claimed to exhibit powerful activities in controlling cell growth but having reduced calcemic action. [3] This dissociation of effects could potentially lead to a new class of drugs for the treatment of psoriasis [4] and cancers. [5]




Calcitriol 19-Nor-calcitriol **1** **2**

Figure 1.

In extension of our work in the vitamin D field [6] we wish to describe an approach to a new series of 19-nor-calcitriol derivatives having a deconjugated diene system.

Regarding structure/activity relationships in the vitamin D area the conjugated triene system was thought to be crucial for biological activity. For the first time DeLuca et al. synthesized calcitriol analogs lacking the C-19 position. [7] This remarkable structural

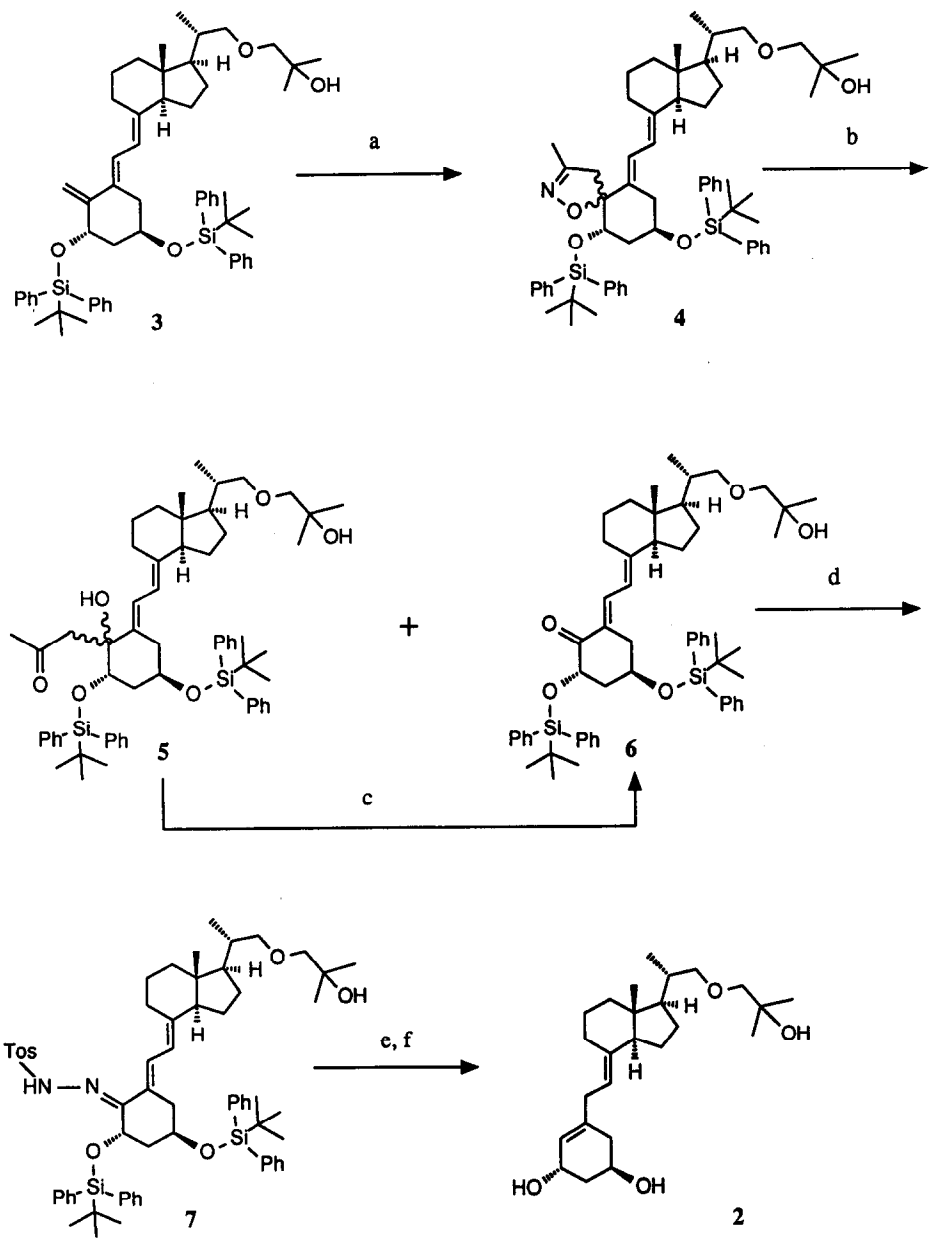
modification of the vitamin D skeleton did not result in a loss of agonistic potential. The parent compound of this series, 19-nor-calcitriol (**1**), for instance is as potent as calcitriol. Stimulated by these findings we started own work in the 19-nor series. Detailed inspections of molecular models indicated that deconjugation of the 5,6-double bond into the 5,10-position (**2**) should not dramatically change the geometry of the molecule. For reliable evaluations of the biological properties it was necessary to introduce a side chain known to contribute to an agonistic activity profile. Because of the facile chemical synthesis and the promising biological properties [8] we selected the 23-oxa side chain for this project.

The synthesis of the starting material **3** was previously published in a slightly different version (t-butyldimethylsilyl groups instead of t-butyldiphenylsilyl groups). [6] In an earlier study Reischl demonstrated that nitrile oxides, generated in situ according to Mukaiyama's procedure, add selectively to the 10(19)-double bond of vitamin $D_3$ acetate. [9] We applied this method to 23-oxa analog **3** (scheme 1). Even in the presence of the bulky t-butyldiphenylsilyl ether in the C-1 position the reaction proceeded cleanly yielding separable epimeric isoxazolines **4**.

For cleavage of the heterocycle several methods are available. Usually a Raney-nickel reduction leading to β-hydroxy ketones is performed. [10] In our case we had to avoid severe reductive conditions due to the instability of the diene unit. Therefore, following Reischl's approach, we used a metal assisted ring opening reaction and subsequent retro aldol cleavage with $Mo(CO)_6$ in acetonitrile. When dry acetonitrile was applied as the solvent the yield of ketone **6** did not exceed 30%. It is assumed that in anhydrous media the highly active molybdenum species could cause side reactions like polymerisations or degradations of the sensitive unsaturated ketone **6**. Thus, we turned our attention to a modification of this procedure. Following literature examples, [11] in the presence of water the initially formed imino alcohol, generated by isoxazoline cleavage, should immediately hydrolyze to hydroxy ketone **5** which is considered to be more stable towards reaction conditions. However, in our hands a mixture of **5** and **6** arose in an excellent yield. Furthermore, hydroxy ketone **5** could quantitatively be converted to **6** in a retro aldol reaction. Consequently, the degradation of isoxazoline **4** to ketone **6** could be accomplished very efficiently.

For the elimination of the carbonyl group in C-10 position we generated tosylhydrazone **7** by using standard conditions. As expected, reduction with $NaBH_4$ in acetic acid cleanly afforded the deconjugated diene system. Subsequent cleavage of the silyl groups with tetrabutylammonium fluoride produced 19-nor-calcitriol derivative **2** in a fair yield. [12]

In conclusion, a convenient synthetic approach to this new vitamin D series was established. Investigation of the biological properties by using standard in vitro-models (vitamin D receptor binding affinity, [13] differentiation of HL 60 cells [14]) showed significantly reduced agonistic activities. These results indicate that a conjugated diene system might be essential for the biological action.




Scheme 1.

Reaction conditions:
a: PhNCO, $EtNO_2$, toluene (77%); b: $Mo(CO)_6$, $CH_3CN$, $H_2O$ (**5**: 36%, **6**: 50%); c: LDA, THF (100%); d: $TosNHNH_2$, $CH_3COOH$ (79%); e: $NaBH_4$, $CH_3COOH$ (71%); f: TBAF, THF (67%).

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12. NMR spectra (300 MHz, $CD_3OD$):
    **2**: $\delta$= 0.63 ppm (s, 3H, H-18); 1.08 (d, J=7 Hz, 3H, H-21); 1.20 (s, 6H, H-26 and H-27); 2.74 (dd, J=16, 8.5 Hz, 1H, H-6); 2.82 (dd, J=16, 8.5 Hz, 1H, H-6'); 3.17 (d, J=9.5 Hz, 1H, H-24); 3.19 (dd, J=9.5, 9 Hz, 1H, H-22); 3.26 (d, J=9.5 Hz, 1H, H-24'); 3.47 (dd, J=9.5, 4.5 Hz, 1H, H-22'); 4.06 and 4.29 (2x m, 1H each, H-1 and H-3); 4.97 (t, J= 7.5 Hz, 1H, H-7); 5.52 (m, 1H, H-10).
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