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SYNTHESIS OF 23-OXA-CALCITRIOL DERIVATIVES

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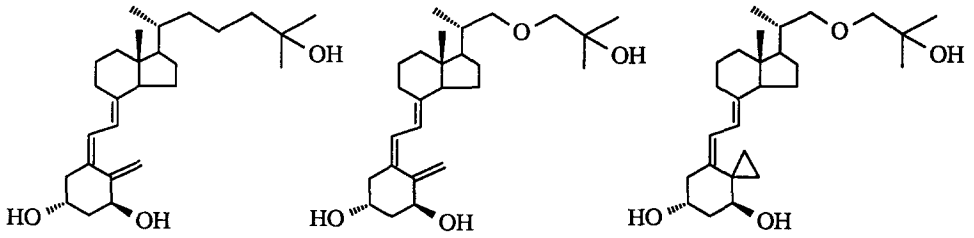
Summary: *A convenient synthetic strategy leading to 23-oxa-calcitriol and 23-oxa-10,19-methylene-calcitriol is disclosed.*

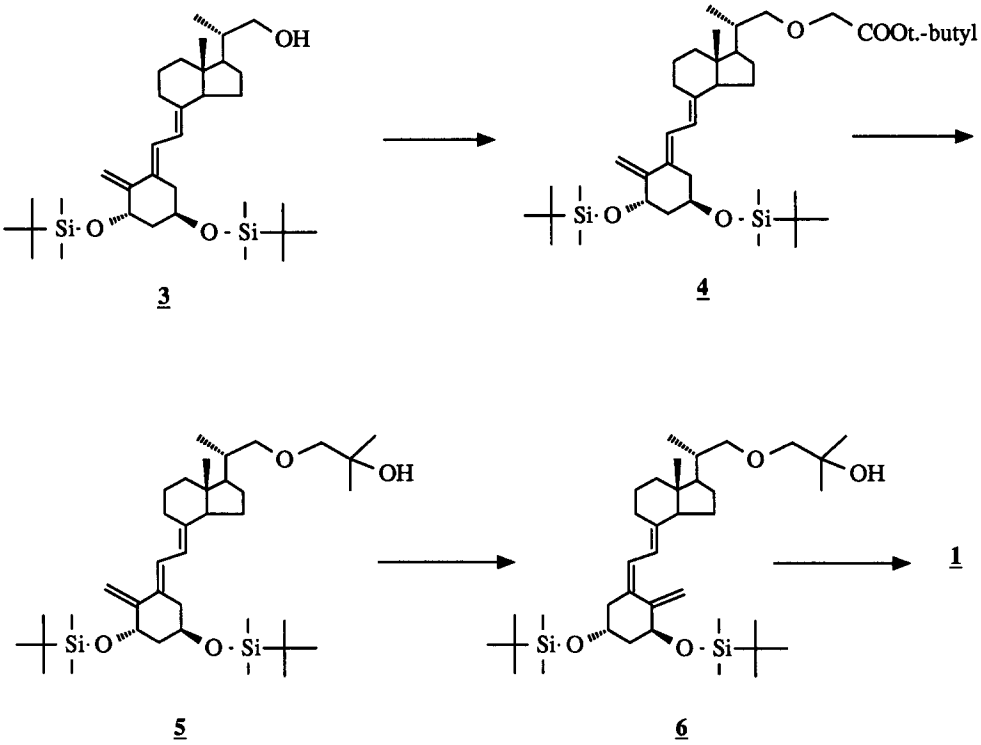
In recent years it has become evident that calcitriol (1α,25-dihydroxy-vitamin D_3), besides acting as a regulator of calcium homeostasis, exerts potent effects upon cell proliferation and cell differentiation [1]. A number of chemically modified calcitriols [2] have been claimed to show dissociation of effects making these derivatives potentially valuable drugs in the treatment of psoriasis [3] and cancers[4] without the risk of hypercalcemia. Although the mechanism of dissociation is not always clearly recognizable, the possibility of separating the various effects of calcitriol has enormously stimulated chemical activities in the vitamin D area.
We wish to report the synthesis of two calcitriol derivatives as a contribution to the ongoing efforts of establishing structure-activity relations in the vitamin D series.



Calcitriol **1** **2**

The calcitriol side chain is known to be the major site of metabolic attack [5]. Consequently, a great deal of work was concentrated upon side chain variations resulting in the discovery of potent analogues [6].
Replacement of a methylene group by an oxygen atom has often proven a successful strategy to modify a biologically active molecule without provoking dramatic structural changes[7]. Therefore, a 23-oxa calcitriol could be expected to retain receptor affinity. Assuming 24-hydroxylation to be the first degradative step of metabolism as in the natural compound, a hemiacetal situation, highly unstable in an aqueous medium, would result possibly giving rise to differences in biological action.
With this concept in mind, we began to look for synthetic strategies that would lead us to compounds **1** and **2**. Though a 23-oxa side chain was found to be part of several general patent claims [8], only one experimental procedure was detected describing nucleophilic

opening of 1,2-epoxy-2-methyl-propane with the alcohol 3 [8a]. As we were unable to reproduce the patent result, we turned our attention to a process successfully applied in the prostacyclin series. Skuballa [9] found that the well-known problems associated with the use of bromo acetates as O-alkylating agents can be overcome by reacting an alcohol with tert.-butyl bromo acetate under phase transfer conditions. The viability of this key step being ascertained we could synthesize compound 1 without difficulty (scheme 1).

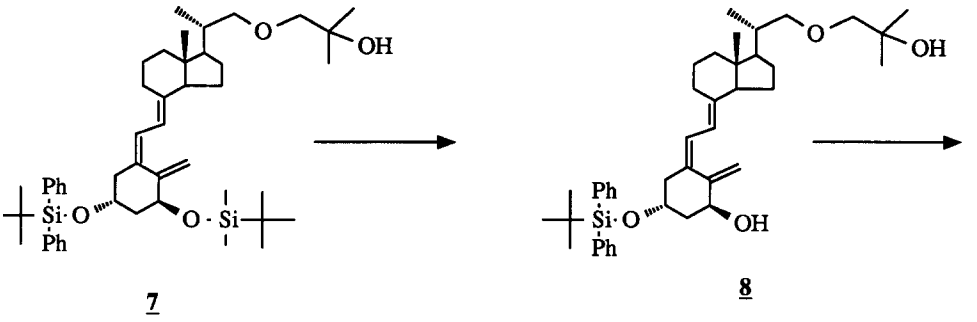


The starting material 3 is conveniently accessible by the route recently described in detail by Calverley [10]. Phase-transfer alkylation (t.-butyl bromoacetate, 25% NaOH, toluene, Bu_4NHSO_4) gives a 60% yield of ester 4. Although it is difficult to drive the reaction to completion, the only by-product is starting compound 3 that can be recycled. Standard Grignard reaction, photochemical isomerisation of the triene system and subsequent ether cleavage with tetrabutyl ammonium fluoride cleanly give target compound 1.

Our interest in calcitriol derivative 2 resulted from a recent observation made by DeLuca [8b,11]: Removal of C-19 to produce so-called 19-nor calcitriol appeared to favorably modulate calcitropic effects of calcitriol without affecting its ability to inhibit cell proliferation and to induce differentiation. We, therefore, reasoned that replacement of the 10,19-double bond by a spiro cyclopropane unit might produce compounds of interest.

Initially we hoped to synthesize compound 2 by a direct Simmons-Smith methylenation of precursor 1 expecting selective double bond attack under the well-known assistance of an allylic alcohol function. However, triol 1 could not be made to react under typical

Simmons-Smith conditions [12]. Success was achieved by using a partially protected intermediate (scheme 2).



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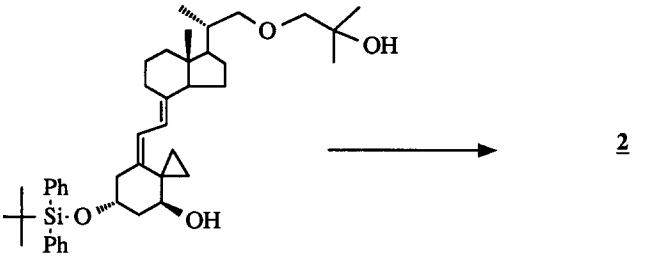

9 2

We made use of the different chemical stabilities observed for silyl ethers as protecting groups. Whereas a tert.butyl-diphenyl silyl ether remains stable under the conditions of mild acid treatment (1n-HCl, methanol, 25°C), a tert.-butyl-dimethyl silyl ether becomes smoothly cleaved.

The Calverley strategy conveniently allows to prepare precursor 7 with different protecting groups, acid cleavage liberates the allylic alcohol function to give intermediate 8 and subsequent Simmons-Smith methylenation results in a 65% yield of compound 9. Again it is difficult to achieve completion in the first run, but starting material can be recovered unchanged.

Thus, new calcitriol derivatives 1 and 2 were made accessible in gram quantities. Biological data will be reported elsewhere.

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NMR spectra (300 MHz, $CDCl_3$):

1: δ= 0,56 ppm (s, 3H, H-18); 1,04 (d, J=7 Hz, 3H, H-21); 1,22 (s, 6H, H-26 and H-27); 3,16 (d, J=9 Hz, 1H, H-24); 3,22 (m, 1H, H-22); 3,26 (d, J=9 Hz, 1H, H-24'); 3,43 (dd, J=9, 4,5 Hz, 1H, H-22'); 4,22 (m, 1H, H-3); 4,43 (m, 1H, H-1); 5,01 and 5,33 (s, 1H each, H-19); 6,03 and 6,39 (d, J=11 Hz, 1H each, H-6 and H-7).

2: δ= 0,53-0,68 ppm (m, 2H, Cyclopropyl); 0,56 (s, 3H, H-18); 0,85-1,01 (m, 2H, Cyclopropyl); 1,04 (d, J=7 Hz, 3H, H-21); 1,20 (s, 6H, H-26 and H-27); 3,18 (d, J=9 Hz, 1H, H-24); 3,21 (dd, J=9,5, 9 Hz, 1H, H-22); 3,26 (d, J=9 Hz, 1H, H-24'); 3,36 (m, 1H, H-1); 3,44 (dd, J=9,5, 9 Hz, 1H, H-22'); 4,10 (m, 1H, H-3); 6,09 and 6,29 (d, J=11 Hz, 1H each, H-6 and H-7).

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