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A New Approach to the Synthesis of the 25-Hydroxy-22-Oxa-Vitamin D_3 Side Chain

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Abstract: An efficient new method is described for the construction of the 25-hydroxy-22-oxavitamin D_3 side-chain, which is present in several analogues of calcitriol with antitumour activity.
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In recent years it has come to light that 1α,25-dihydroxyvitamin D_3 (**1**, calcitriol), the hormonally active form of vitamin D_3 in calcium homoeostasis,[1] can induce cell differentiation and inhibit cell proliferation, which suggests its possible use in the treatment of certain cancers and skin disorders.[2] Since 1α,25-dihydroxyvitamin D_3 itself is of limited therapeutic value due to its hypercalcemic effects,[2] interest in this field has focused on the development of analogues having strong cell differentiating and weak calcemic effects.[3] Hitherto, several interesting analogues with a modified side chain have been synthesized (Figure 1), among them 1α,25-dihydroxy-22-oxavitamin D_3 (**2b**),[4] which inhibits the growth of certain cancers[5] and is a potent immunomodulator *in vivo* but does not cause hypercalcaemia.[6] In this paper we report a rapid and practical method for the construction of the 25-hydroxy-22-oxavitamin D_3 side-chain which is present not only in **2b** but also in several other calcitriol analogues with antitumour activity.

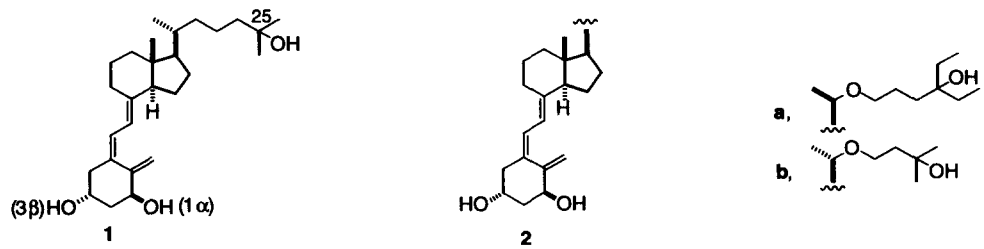
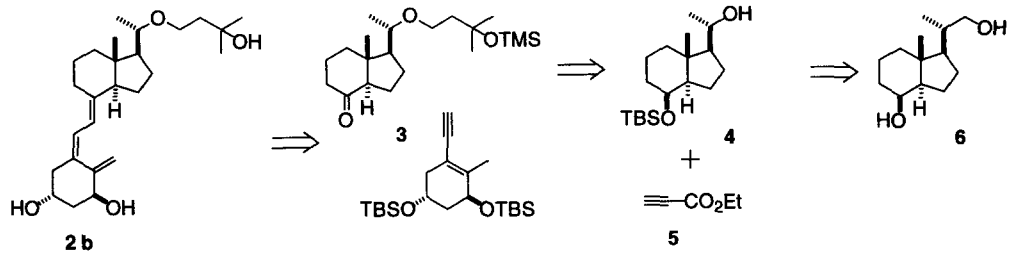


Figure 1. Structure of 1α,25-dihydroxyvitamin D_3 and some of its analogues modified at the side chain.

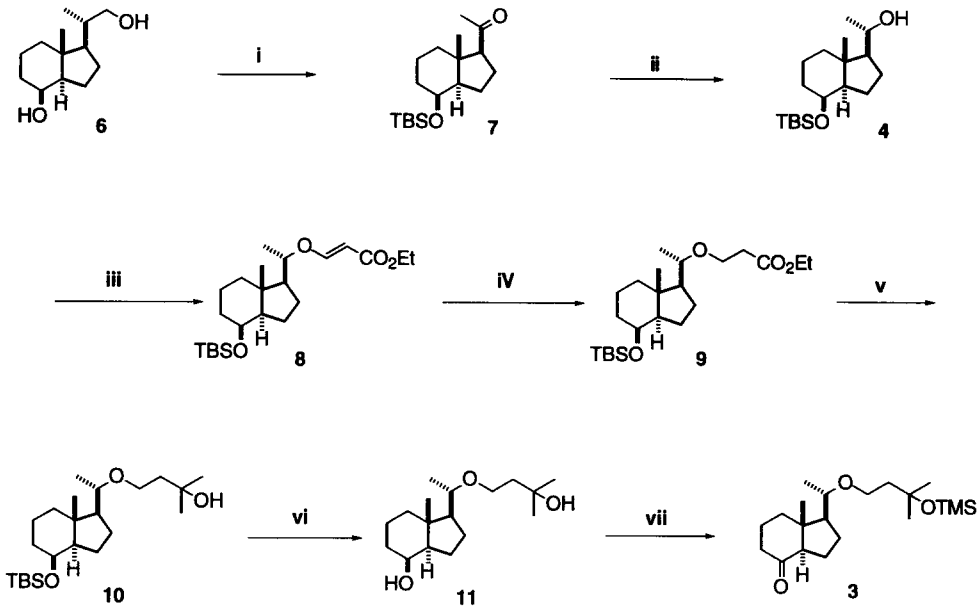
As outlined in Scheme 1, our synthetic approach to **2b** takes advantage of the readily available Inhoffen-Lythgoe diol (**6**) and makes use of the well-established convergent dienyne route to vitamin D analogues.[7] The success of the proposed synthesis hinged on the viability of the reaction between ethyl propiolate and the alcohol **4**, which was envisaged to afford **3**, the precursor of **2b**.



Scheme 1. Retrosynthetic plan.

Diol **6**, which was obtained by degradation of vitamin D_2,[8] was converted to ketone **7**[9] in 55% yield by sequential monotosylation, protection, conversion to the aldehyde by the modified Kornblum procedure,[9] and oxidation (Scheme 2). Ketone **7** was then stereoselectively reduced with an alkali metal to obtain alcohol **4**.[10] To our great satisfaction, room temperature reaction of alcohol **4** with ethyl propiolate in the presence of *N*-methylmorpholine in benzene[11] cleanly afforded the desired alkoxyacrylate **8**[12] in 85% yield. Conversion of **8** to the ester **9** (80%) by hydrogenation on Pd/C followed by treatment with methylmagnesium chloride (MeMgCl) in Et_2O gave an 80% yield of the tertiary alcohol **10**,[12] which bears the desired 25-hydroxy-22-oxavitamin D_3 side chain. The silyl protecting group of **10** was removed by reaction with HF in acetonitrile at room temperature to give the diol **11**[12] (91%). Oxidation of **11** with pyridinium chlorochromate, followed by overnight treatment with 1-(trimethylsilyl)imidazole in THF at room temperature, afforded the target compound **3**[12] (94% for the two steps, 15% from **6**), which can be converted to 1α,25-dihydroxy-22-oxavitamin D_3 (**2b**) by known synthetic routes.[8]

This new method for construction of the 25-hydroxy-22-oxavitamin D_3 side chain compares favourably with previous methods as regards to efficiency and rapidity. Furthermore, the ester **9** is a useful intermediate in the synthesis of other C-25 vitamin D analogues, the synthesis of which is in progress.



Scheme 2. Reaction conditions. (**i**) *p*-TsCl, py (95%); *t*-BuMe2SiCl, imidazole (83%); $NaHCO_3$ (1 equiv) DMSO, rt (85%); O_2, *t*-BuOK, *t*-BuOH, rt (82%). (**ii**) K, *i*-PrOH reflux (60%) (**iii**) Ethyl propiolate, *N*-methylmorpholine, PhH, rt, 12 h (85%). (**iv**) H_2, Pd/C, EtOH, (80%). (**v**) MeMgCl, Et_2O, -10 °C to rt (80%). (**vi**) HF, CH_3CN (91%). (**vii**) PCC, CH_2Cl_2, rt; TMS-imidazole, THF, rt, 12 h (94%).

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12. All new compounds were characterized by ^{1}H and ^{13}C NMR, combustion analysis and/or high resolution mass spectral data.

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