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A Short and Efficient Synthesis of DE-A,B(22*E*,24S)-8ß-(benzoyloxy)-25-hydroxyergost-22-ene a Valuable Intermediate in the Total Synthesis of 25-Hydroxylated Vitamin D_2-Metabolites

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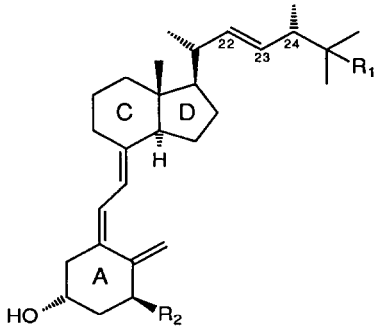
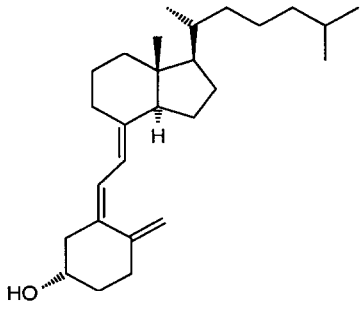
Abstract *The titel compound was synthesised in 8 steps starting from vitamin D_2. The side-chain was constructed using a chiral, stereoselective Wittig-reagent*

The unnatural vitamin D_2 (**1a**) is structurally related to its natural counterpart vitamin D_3 (**2**) The metabolism of both ergocalciferol (vitamin D_2) and vitamin D_3, according to the literature, are thought to be identical [1] First, the steroid has to be hydroxylated at the 25-position in the liver, followed by a hydroxylation at the 1-position in the kidney (**1b** and **1c** respectively).

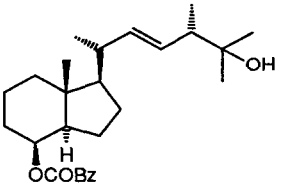




1a: R_1 =R_2 =H
b: R_1 =OH, R_2 =H
c: R_1 =R_2 =OH

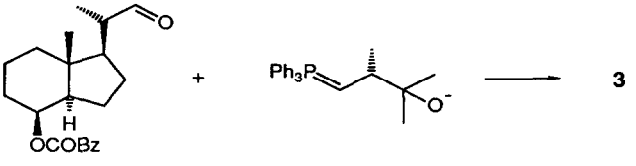
2

Due to the availability of several valuable methods for the preparation of synthetic vitamin D_2 metabolites, the biological significance of vitamin D_2 and its metabolites have received considerable attention.[2-7] The most efficient strategies are based on a coupling of Windaus-Grundmann's ketone,[8] or analogues ketones with modified side chains, with a suitable A-ring synthon. Clearly, the synthesis of **3**, a compound corresponding to a protected form of Windaus-Grundmann's ketone, is crucial in these strategies.



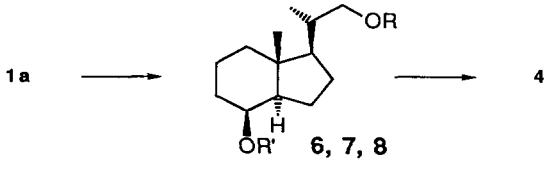
3

However, the syntheses published hitherto are, though very elegant, cumbersome and time-consuming. Moreover, these procedures are not always suitable for medium- or large scale synthesis. Therefore practical approaches are necessary and remain a special challenge.
We here report a practical and efficient method for the preparation of **3** (a protected form of the C_{19} ketone) based on the coupling of key intermediates **4** and **5**.



4 **5**

Aldehyde **4** was synthesised in a stereoselective way in 4 steps (1a→6→7→8→4) using ergocalciferol as the starting material with an overall yield of 75% after chromatography.

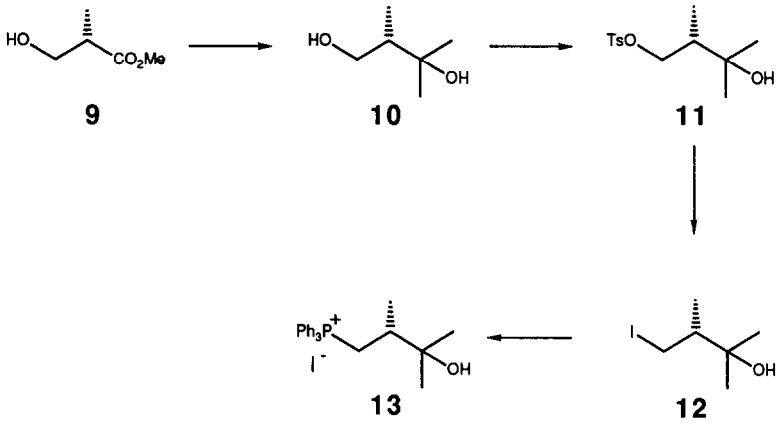


6, 7, 8

6: R =R' =H; 7: R =R' =benzoate; 8: R =OH, R' =benzoate

Diol **6** was readily obtained by ozonolysis of vitamin D_2 followed by reduction of the ozonides with sodium boriumhydride ($NaBH_4$) in a 85% yield after chromatography.[5a] The dibenzoate (**7**) was prepared, in a 100% yield, in pyridine with benzoylchloride, and dimethylaminopyridine (DMAP) as a catalyst, after which the monobenzoate of the secondary alcohol was prepared with potassium hydroxide in ethanol at room temperature (95%).[6] Oxidation of **8** with pyridinium chlorochromate rendered **4** in a 97% yield.[7]

The precursor of the ylid **5**, the phosphonium salt **13**, was prepared starting from commercially available S(+)-methyl-2-methyl-3-hydroxypropanoate **9**, which already contains the C-24 stereogenic centre (see **1**).



Treatment of **9** with excess methylmagnesium bromide in ether, followed by continuous extraction of the hydrolysed reaction mixture gave diol **10** in 87% yield after distillation.[9] Conversion of the diol into tosylate **11** was achieved in a 100% yield using p-toluenesulfonyl chloride in pyridine. Iodo-alcohol **12** was prepared in dry THF, using LiI (85% yield).[10] Reaction of **12** with triphenylphosphine gave the pure phosphonium salt **13** in a quantitative yield.[11] Treatment of **13** with two equivalents of methyllithium in ether at room temperature gave the stereoselective Wittig-reagent **5**.[12]

Finally, introduction of the 22(23)*E*-double bond was achieved by adding **4**, dissolved in ether, to ylid **5** at -40°C, after which the reaction mixture was stirred at that temperature for two hours.

The begotten yellow suspension was stirred for 20 hours at room-temperature, leading to the desired compound in a 45% yield after the usual work-up and chromatography. Some aldehyde (compound **4**), and the addition product of the aldehyde with methyllithium were retrieved.

The titel compound can be used as an intermediate in the synthesis of 25-hydroxy vitamin D_2 (**1b**) and 1,25-dihydroxy vitamin D_2 (**1c**) by known procedures, or in the synthesis of 25-hydroxylated vitamin D_2 A-ring analogues.

Acknowledgements

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