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# AN EFFICIENT ROUTE TO 1α,25-DIHYDROXYVITAMIN $D_3$ FUNCTIONALIZED AT C-11

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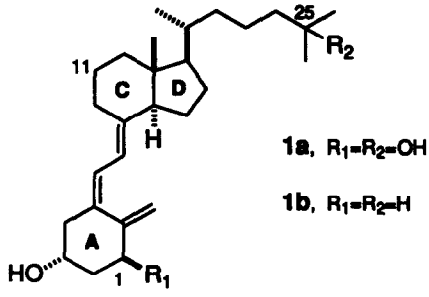
*Key Words*: 1α,25-Dihydroxyvitamin $D_3$; Analogues at C-11; 25-Hydroxylated Side Chain; Synthesis; Dienyne route.

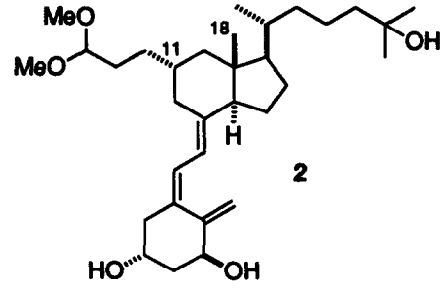
*Abstract:* An efficient route to vitamin $D_3$ analogues functionalized at C-11 is described. Key features of this synthesis are: (i) the development of a novel and efficient route for the introduction of the 25-hydroxylated side chain, present in the most important metabolites of vitamin $D_3$, and (ii) the stereoselective functionalization of the C-ring of 1α,25-$(OH)_2$-$D_3$ at C-11.

It has recently been discovered that 1α,25-dihydroxyvitamin $D_3$ [**1a**, 1α,25-$(OH)_2$-$D_3$, calcitriol], the hormonally active form of vitamin $D_3$ (**1b**, calciferol), in addition to its important role in calcium homeostasis,[1] is also associated with normal cell proliferation and differentiation.[2] The potential utility of 1α,25-$(OH)_2$-$D_3$ as a drug in the treatment of certain cancers and skin disorders has been restricted in part due to its potent calcemic effects.[3] As a consequence, there has been enhanced interest in the development of structurally modified analogs of this hormone with high cell differentiating ability and low calcemic action. In this connection a few remarkably interesting side-chain analogues of 1α,25-$(OH)_2$-$D_3$ with promising properties have been reported,[3] although very little has been done towards the synthesis of C-ring modified analogues possessing a 1α and/or a 25-OH group.[4]




**1a**, $R_1$=$R_2$=OH

**1b**, $R_1$=$R_2$=H

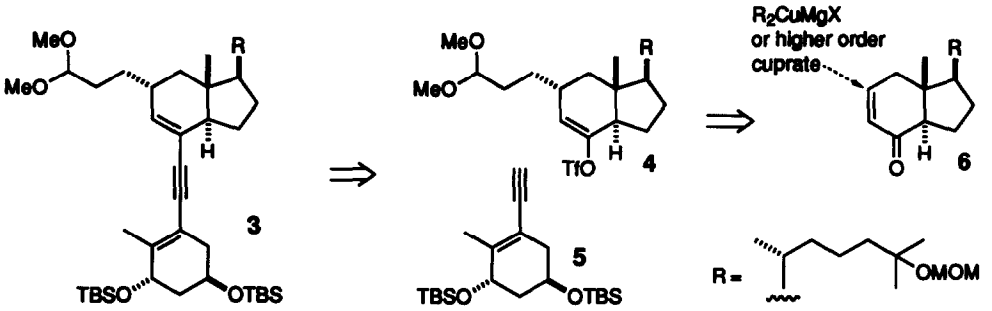



**2**

We chose the acetal **2** as the target analogue of 1α,25-$(OH)_2$-$D_3$ to further study the biochemical significance of α-substituents at C-11. The "latent" aldehyde, which is far away from the three hydroxyl groups, could also serve for the construction of potentially useful photoaffinity labels to study the active site of the receptor (or receptors[5]) of 1α,25-$(OH)_2$-$D_3$.

Retrosynthetic analysis suggested that the recently improved dienyne route to vitamin D metabolites and analogues[6] might be useful for the introduction of functionalized alkyl substituents at C-11 (Scheme 1). The conjugated addition of organocopper reagents to the α,β-unsaturated system of ketone **6** should take place from the less hindered side of the molecule leading to α - substituents at C-11.

Scheme 1

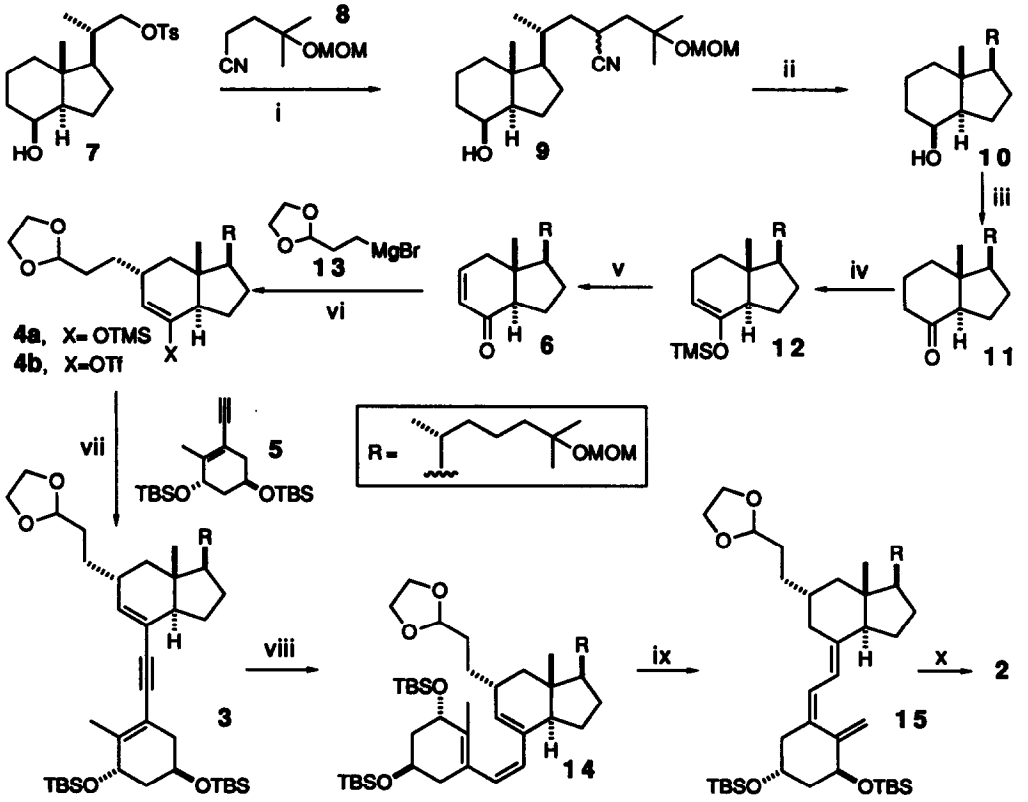



With this strategy in mind, we developed a general and efficient method for the introduction of the 25-hydroxylated side chain which is present in the most important metabolites of vitamin $D_3$.[7] We first prepared the α-lithio anion of nitrile **8** (Scheme 2) from ethyll 3-bromopropionate by succesive treatment with methyl magnesium bromide (4 equiv, $Et_2O$, r.t., 12 h)[8], sodium cyanide (2 equiv, DMSO, 90-100 °C, 1.5 h), chloromethyl methyl ether (1.3 equiv, DMF, NaH 1.5 equiv, r.t., 12 h), and LDA (1.5 equiv, THF, -78 °C, 30 min) (50 % overall yield).[9] Reaction of the above anion with the known tosylate **7**[10] afforded a diastereoisomeric mixture of nitriles **9**[9] (85 %) which upon treatment with potassium metal in portions[11] provided the alcohol **10**[9] with the desired protected side chain (90 %, 76 % over the two steps). This procedure was easily carried out on up to a 10 g scale and protection of the hydroxyl groups at C-8 was unnecessary.

Conversion of alcohol **10** into the ketone **11**[9] was accomplished by oxidation with pyridinium dichromate (99 %). Application of Saegusa's method[12] for the preparation of the α,β-unsaturated ketone **6**[9] from the silyl enol ether **12** was more efficient than the alternative two-step, selenoxide-elimination procedure. Addition of ketone **11** to a solution of LDA in THF and trapping of the resulting kinetic enolate with trimethylchlorosilane afforded, after work up, crude silyl enol ether **12**[9] which was immediately dissolved in acetonitrile and treated with palladium(II) acetate to give the desired ketone **6** in 94 % yield. Conjugate addition to ketone **6** at C-11 was carried out by the addition of ketone **6** to the organocopper reagent, derived from the Grignard reagent **13**[13] and copper(I) bromide-dimethyl sulfide complex in the presence of trimethylchlorosilane. The freshly elaborated crude silyl enol ether **4a** was metallated with methyllithium and the resulting kinetic enolate was treated with *N*-phenyltriflimide to give the desired vinyl triflate **4b**[9] (70% from ketone **6**). Attempts to obtain **4b** by trapping the enolate, generated by the organocopper reagent without TMSCl, were unsuccessful. The stereochemistry of **4b** at C-11 was assayed by nOe difference experiments, which indicated the proximity of H-11β and $CH_3$-18. Therefore, the attack of the copper reagent took place from the less hindered α-face of the molecule as expected.

With this phase of the synthesis complete, we next turned our attention to the construction of the dienyne **3**. This was accomplished in 78 % yield via palladium catalyzed coupling between the known A-ring fragment **5**[14], and the vinyl triflate **4b**. Partial hydrogenation gave previtamin D **14**[9] (80 %), which was subjected to thermal equilibration to afford, via a [1,7]-sigmatropic hydrogen shift,[7] the corresponding protected vitamin D **15**[9] quantitatively. The quantitative coversion of **14** to **15** may be accounted for by the interactions between the acetal moiety and the A ring of previtamin D **14**. Finally, treatment of **15** with AG 50W-X4 cation-exchange resin in methanol provided the desired vitamin $D_3$ analogue **2** in 81 % yield. (11 steps, 25 % overall yield).[15]

Scheme 2




(i) LDA, THF, -78 °C, Nitrile **8** (1.6 equiv), 30 min, then **7**, -78 °C, 1 h, r.t., 12 h (85 %). (ii) *t*-BuOH (2 equiv), HMPA (5 equiv), $Et_2O$ (30 equiv), 0 °C, K in portions (7 equiv), r.t., 10 h (90%). (iii) PDC (3 equiv), PPTS (trace), $CH_2Cl_2$ (99 %). (iv) LDA (1.5 equiv), THF, -78 °C, **11** (1 equiv), THF, 15 min, ---> r.t. 2 h; -78 °C, TMSCl (1.5 equiv), 15 min. (v) $Pd(OAc)_2$ (1 equiv), $CH_3CN$, r.t., 12 h (94 % over the two steps). (vi) **13** (7 equiv), THF, -78 °C, CuBr·$Me_2S$ (1 equiv), $Me_2S$ (40 equiv), 45 min; TMSCl (2.2 equiv), ketone **6** (1 equiv), THF, -78 °C, 2 h; TMSCl (2.3 equiv), r.t., 12 h.; work up; crude **12**, 0 °C, THF, MeLi (2.3 equiv), r.t., 25 min; -78 °C, $PhNTf_2$ (2.3 equiv), r.t., 12 h (70 %). (vii) **5**, $(Ph_3P)_2PdCl_2$ (3 mol %), $Et_3N$ (3 equiv), DMF, 70-75 °C, 2h (78 %). (viii) $H_2$ (balloon pressure), Lindlar catalyst, quinoline, hexanes, r.t., 4.5 h (80 %). (ix) Isooctane, 100 °C, 5 h (100 %). (x) AG 50W X4 cation exchange resin, MeOH, r.t., 32 h (81 %) (25 % overall yield from **7**).

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15. Biological testing of **2** and the synthesis of other related vitamin D analogues using this approach are in progress.

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