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Stereoselective synthesis of 22-oxacalcitriol (OCT) and analogues modified at C25

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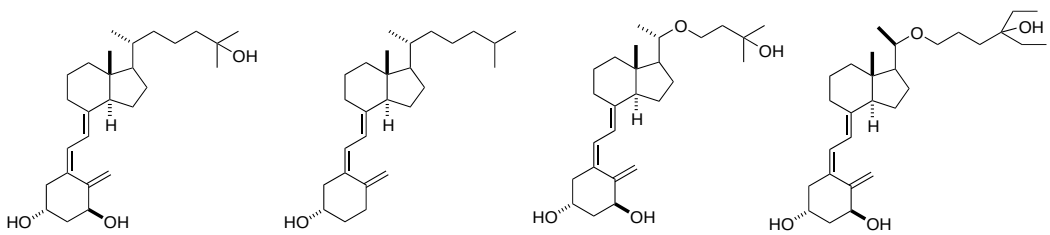
Abstract—The stereoselective synthesis of 22-oxacalcitriol (OCT) has been achieved. The triene system was introduced using the Lythgoe–Hoffmann La Roche convergent Wittig–Horner approach to couple ketoester **7** with A ring phosphine oxide **8**. The value of the resulting ester **6** for synthesis of C25-modified OCT analogues is exemplified by the synthesis of **5**. © 2002 Published by Elsevier Science Ltd.

Vitamin D and its metabolites continue to attract a great deal of interest owing to their potential for the treatment of rickets, osteoporosis, psoriasis, renal osteodystrophy, leukaemia, breast cancer, prostate cancer, Alzheimer's disease and AIDS.[1] 1α,25-Dihydroxyvitamin D_3 [**1**, 1α,25-$(OH)_2$-D_3, calcitriol], the hormonally active form of vitamin D_3[2] (**2a**, cholecalciferol), besides regulating the metabolism of calcium and phosphorus, promotes cell differentiation, inhibits the proliferation of tumour cells, and triggers certain biological functions related to the immunological system.[3] However, the clinical utility of the hormone in the treatment of cancers and skin disorders is limited by its hypercalcaemic effects. Accordingly, chemists have pursued the synthesis of analogues of **1** with high cell differentiating ability and weak calcaemic effects; known examples include **3** and **4** (Fig. 1). In particular, 1α,25-dihydroxy-22-oxavitamin D_3 (**3**, OCT)[4] inhibits the proliferation of certain cancers,[5] is a potent immunomodulator in vivo, and does not cause hypercalcaemia.[6]

Surprisingly, although many synthetic approaches to OCT have been developed,[4,7] few OCT analogues have been reported.[7a,c] This means that a synthesis of **3** that is both convergent and flexible has been lacking.

We have previously published a method for construction of the 25-hydroxy-22-oxavitamin D_3 side chain that compares favourably with previous methods as regards efficiency and rapidity.[7b] However, for the synthesis of OCT analogues modified at C25 we needed to develop another synthetic approach. This is outlined in Scheme 1.



1 **2a**, R = H; **2b**, R = OH **3** **4**

Figure 1. The structures of 1α,25-dihydroxyvitamin D_3 and some analogues with modified side chains.

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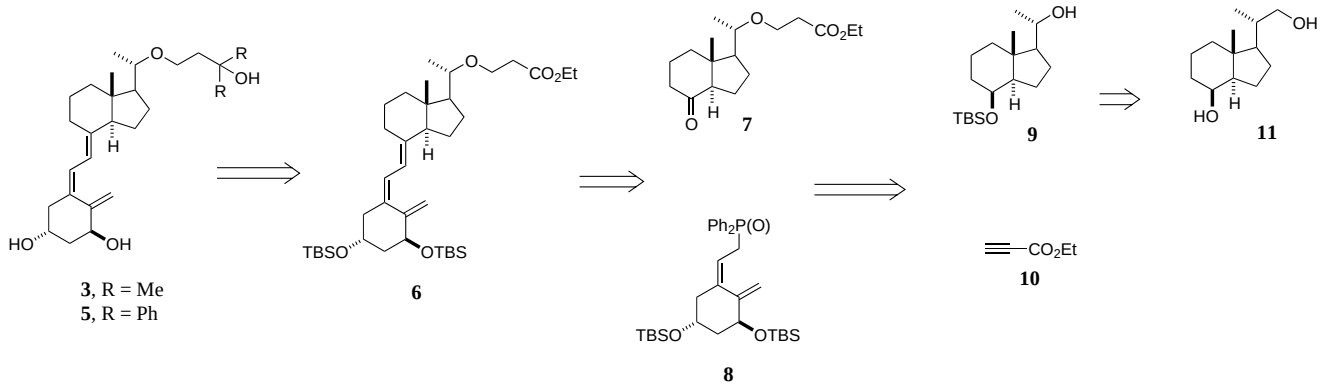

Scheme 1. Retrosynthetic plan.

The synthesis of key intermediate **6** is detailed in Scheme 2. Diol **11** obtained by degradation of vitamin D_2[8] was converted to ester **12** using our previously described procedure.[7b] Removal of the silyl protecting group of **12** by reaction with HF in acetonitrile at room temperature, gave alcohol **13**[9] (90%). Finally, oxidation of **13** with pyridinium dichromate afforded ketone **7**[9] (95%), so setting the stage for the Wittig–Horner reaction with phosphine oxide **8**.[10] This coupling reaction between **7** and **8** created the labile triene unit, affording key intermediate **6**[11] in 93% yield.

Reaction of **6** with MeLi at −78°C, followed by desilylation, afforded 22-oxacalcitriol (**3**)[12] in good yield, while its reaction with PhLi afforded the new OCT derivative **5**.[13] Preliminary biological evaluation of this new vitamin D_3 analogue has shown it to have very low affinity for VDR (0.5% that of calcitriol). Further biological evaluation is currently underway.

In conclusion, we have developed a convergent synthesis of key intermediate **6**, which contains both the vitamin D triene system and the OCT side chain skeleton. We are currently using compound **6** to prepare a broad range of OCT analogues modified at C25 for biological evaluation and SAR studies.

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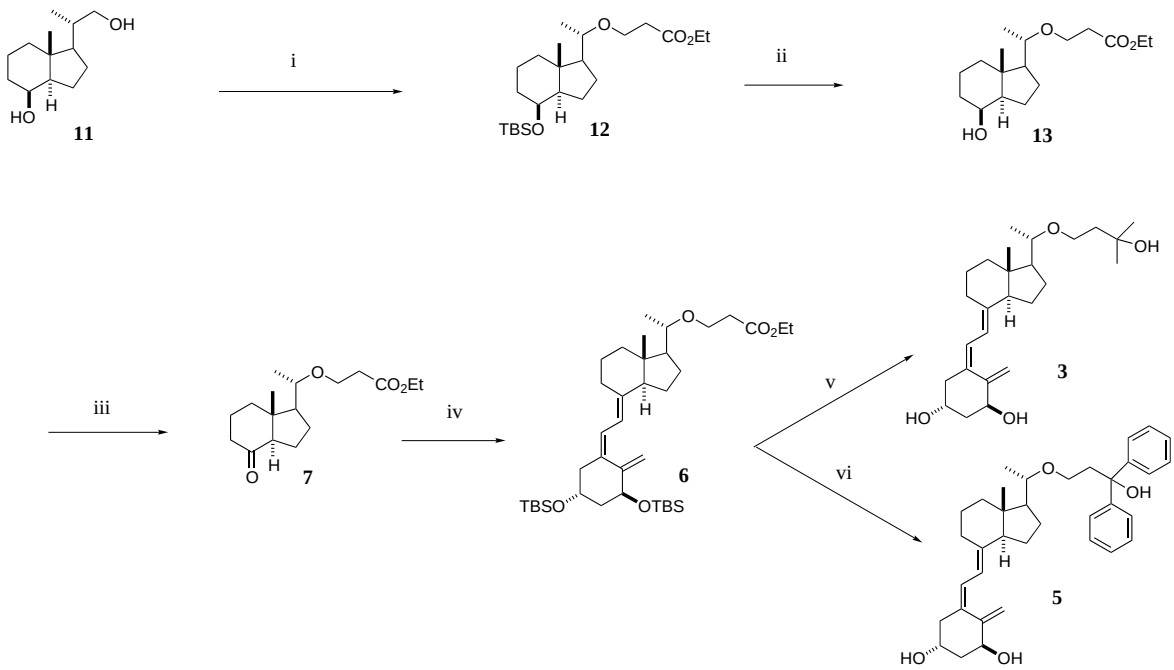

Scheme 2. *Reagents and conditions*: (i) see Ref. 7b; (ii) HF, CH_3CN, rt (90%); (iii) PDC, CH_2Cl_2, rt (95%); (iv) **8**; *n*BuLi, THF, −78°C (93%); (v) (a) MeLi/THF, −78°C (80%) (b) nBu_4NF, THF, rt (96%); (vi) (a) PhLi/THF, −78°C (b) nBu_4NF, THF, rt (73%).

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11. Compound **6** was prepared as follows: A solution of *n*-BuLi (2.25 M in hexane, 0.199 mL, 0.448 mmol) was added dropwise via syringe to a solution of the phosphine oxide **8** (0.436 mmol, 4.3 mL, 0.1 M) at −78°C. The resulting deep red solution was stirred at −78°C for 1 h followed by the slow addition of the ketone **7** (100 mg, 0.242 mmol) in THF (2 ml). The red solution was stirred in the dark at −78°C for 3 h and then warmed to −40°C over 2 h. The reaction was quenched with H_2O. The mixture was extracted with Et_2O and the combined organic fractions were washed with brine, dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (2% EtOAc/hexanes) to give 149 mg of **6** [93%, R_f = 0.72 (20% EtOAc/hexanes), colourless oil]. ^1H NMR (250 MHz, CD_2Cl_2): δ 6.24 and 6.02 (2H, AB, J = 11.2, H-6 and 7), 5.18 (1H, br s, H-19), 4.83 (1H, br s, H-19), 4.36 (1H, m), 4.17 (1H, m), 4.08 (2H, q, J = 7.1, $OC\underline{H}_2CH_3$), 3.78 (1H, m), 3.50 (1H, m), 3.25 (1H, m), 2.8 (1H, m), 2.44 (2H, t, J = 6.3), 2.20 (1H, m), 1.22 (3H, t, J = 7.1, $OCH_2C\underline{H}_3$), 1.12 (3H, d, J = 6.01, CH_3-21), 0.87 (9H, s, *t*-BuSi), 0.86 (9H, s, *t*-BuSi), 0.48 (3H, s, CH_3-18), 0.06 (6H, s Me_2Si), 0.05 (6H, s, Me_2Si); ^{13}C NMR (CD_2Cl_2): δ 172.26 (C=O), 149.04 (C=), 141.24 (C=), 135.88 (C=), 123.55 (CH=), 118.65 (CH=), 111.59 (=CH_2), 78.54, 72.46, 68.05, 64.20 (CH_2), 60.69 (CH_2), 57.79, 56.63, 46.43 (CH_2), 45.32 (CH_2), 45.00 (C-13), 40.09 (CH2), 36.11 (CH_2), 29.20 (CH_2), 26.04 (CH_3-*t*Bu), 25.61 (CH2), 23.64 (CH2), 22.48 (CH2), 19.39, 18.54 (C), 18.43 (C), 14.44, 12.70, −4.57 ($SiCH_3$), −4.68 ($SiCH_3$), −4.92 ($SiCH_3$). HRMS calcd for $C_{38}H_{68}O_5Si_2$: 660.4605; found: 660.4622.
12. Compound **3** was prepared as follows: To a solution of **6** (50 mg, 0.076 mmol) in THF (3 ml) at −78°C was added MeLi (0.142 ml, 0.228 mmol, 1.6 M in ether). The mixture was stirred at −78°C for 1 h and allowed to reach room temperature. The mixture was quenched with aqueous NH_4Cl solution and extracted with ether. The etheral extracts were dried, filtered, and concentrated in vacuo. The residue was dissolved in THF (3 ml) and treated with tetrabutylammonium fluoride (1.5 ml, 1.5 mmol, 1 M in THF). The mixture was stirred in the dark at rt overnight and concentrated in vacuo. Flash chromatography of the concentrate (1% EtOAc/hexanes) afforded 24 mg of **3** [77% from **6**, R_f = 0.27 (20% EtOAc/hexanes)]. ^1H NMR (300 MHz, $CDCl_3$): δ 6.31 and 5.98 (2H, AB, J = 11.2, H-6 and 7), 5.28 (1H, br s, H-19), 4.94 (1H, br s, H-19), 4.38 (1H, dd, J = 7.4, 4.3, H-1), 4.17 (1H, m, H-3), 3.8 (1H, dt, J = 9.2, 5.5, H-23), 3.44 (1H, dt, J = 9.2, 5.5, H-23), 3.21 (1H, m, H-20), 2.79 (1H, dd, J = 12.1, 3.9, H-14), 2.55 (1H, m, H-9), 1.2 (6H, s, CH_3-26 and CH_3-27), 1.16 (3H, d, J = 6.0, CH_3-21), 0.50 (3H, s, CH_3-18); ^{13}C NMR ($CDCl_3$): δ 147.58 (C-10), 142.33 (C-8), 133.23 (C-5), 124.79 (CH-6), 117.44 (CH-7), 111.91 (CH_2-19), 78.74 (CH-20), 70.83 (CH-1), 70.52 (C-25), 66.82 (CH-3), 65.55 (CH_2-23), 57.08 (CH-17), 56.06 (CH-14), 45.27 (CH_2-4), 44.79 (C-13), 42.80 (CH_2-2), 41.47 (CH_2-24), 39.54 (CH_2-12), 29.24 (CH_3-26), 29.10 (CH_3-27), 28.92 (CH_2-9), 25.60 (CH_2-16), 23.23 (CH_2-11), 22.20 (CH_2-15), 18.85 (CH_3-21), 12.63 (CH_3-18); LRMS: m/z (I, %): 418 (M+, 21), 400 (11), 382 (31), 364 (10), 314 (20), 296 (19), 278 (13), 134 (73), 59 (84), 45 (100).
13. Compound **5** was prepared according to the same procedure as above using PhLi (2 M in cyclohexane–Et_2O) instead of MeLi. [73% from **6**, R_f = 0.23 (40% EtOAc/hexanes)]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.15–7.45 (10H, m, Ar), 6.35 and 6.02 (2H, AB, J = 11.2, H-6 and 7), 5.33 (1H, br s, H-19), 4.99 (1H, br s, H-19), 4.42 (1H, m), 4.22 (1H, m), 3.68 (1H, m), 3.37 (1H, m), 3.11 (1H, m), 2.81 (1H, m), 1.02 (3H, d, J = 6.0, CH_3-21), 0.47 (3H, s, CH_3-18)); ^{13}C NMR ($CDCl_3$): δ 147.59 (C=), 147.04 (C=), 142.30 (C=), 133.28 (C=), 128.47 (CH=), 128.03 (CH=), 126.52 (CH=), 124.79 (CH=), 117.48 (CH=), 111.94 (CH_2=), 78.83 (C-25), 77.23, 70.85, 66.83, 65.67 (CH_2), 57.02, 56.07, 45.27 (CH_2), 44.79 (C-13), 42.82 (CH_2), 40.21 (CH_2), 39.51 (CH_2), 28.92 (CH_2), 25.38 (CH_2), 23.22 (CH_2), 22.23 (CH_2), 18.73, 12.58. HRMS calcd for $C_{36}H_{46}O_4$: 542.3396; found: 542.3412.