

## A Facile Stereoselective Route to a C/D-Ring Synthon for 20-Epi-22-oxavitamin D<sub>3</sub> Analogues

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An efficient method for the preparation of a C/D-ring synthon for 20-epi-22-oxavitamin D<sub>3</sub> analogues is developed based on Me<sub>3</sub>SiOSO<sub>2</sub>CF<sub>3</sub> catalysed reductive etherification of a ketone with an alkoxytrimethylsilane in the presence of triethylsilane.

1 $\alpha$ ,25-Dihydroxyvitamin D<sub>3</sub> **1**, the hormonally active metabolite of vitamin D<sub>3</sub>, has long been known as a regulator in calcium and phosphorus homeostasis.<sup>1</sup> Recent studies have demonstrated that it also plays a vital role in the regulation of immune responses<sup>2</sup> as well as in the cell proliferation and differentiation.<sup>3</sup> The discovery of these new biological functions of **1** have prompted considerable efforts directed towards the synthesis of its structural analogues in order to separate and improve each inherent biological activity.

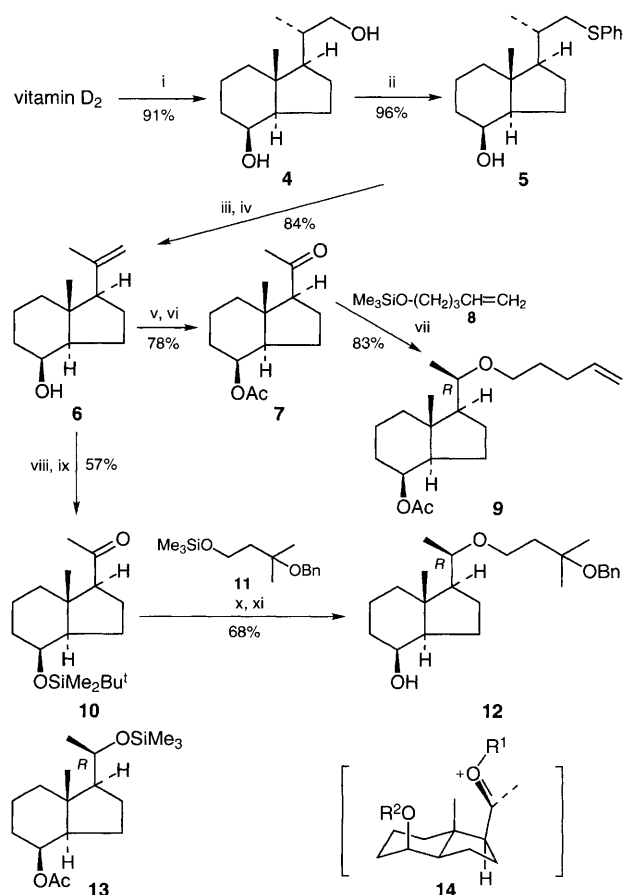
Among the analogues prepared to date, 20-epi-22-oxavitamin D<sub>3</sub> derivatives **2** have attracted much attention because of their potent immunosuppressive activities, which suggest a potential utility for the prevention of graft rejection and the treatment of autoimmune diseases.<sup>4</sup> For example, KH 1060 **2** [R = (CH<sub>2</sub>)<sub>2</sub>C(OH)Et]<sup>5</sup> developed by Leo Pharmaceutical Products was reported to be several orders of magnitude more active than cyclosporin A, a representative immunosuppressive agent, in the inhibition of T-lymphocyte proliferation induced by interleukin-1 or alloantigen.

We recently reported<sup>6</sup> an efficient method for the preparation of ethers by the trimethylsilyl trifluoromethanesulfonate (Me<sub>3</sub>SiOSO<sub>2</sub>CF<sub>3</sub>) catalysed reaction<sup>7</sup> of carbonyl compounds with alkoxytrimethylsilanes in the presence of triethylsilane. We report here a facile stereoselective route to a C/D-ring synthon **3** required for the convergent synthesis<sup>8</sup> of 20-epi-22-oxavitamin D<sub>3</sub> analogues based on this reductive etherification.

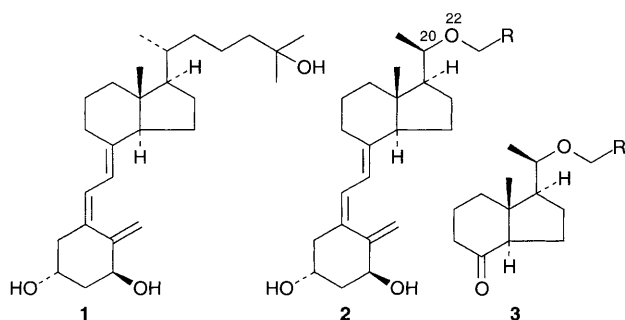
Reaction of the Inhoffen–Lythgoe diol **4**, prepared<sup>9</sup> from vitamin D<sub>2</sub>, with diphenyldisulfide in the presence of tributylphosphine<sup>10</sup> gave the sulfide **5**,<sup>†</sup> [ $\alpha$ ]<sub>D</sub><sup>24</sup> +75.3 (c 1.30, CHCl<sub>3</sub>). Oxidation of **5** with 30% aqueous hydrogen peroxide followed by thermolysis of the resulting sulfoxide afforded the alkene **6**, [ $\alpha$ ]<sub>D</sub><sup>23</sup> +34.3 (c 0.86, CHCl<sub>3</sub>), in good overall yield. The alkene **6** was then converted to the methyl ketone **7**, [ $\alpha$ ]<sub>D</sub><sup>22</sup> +100.4 (c 1.15, CHCl<sub>3</sub>), by sequential acetylation and ozonolysis. Upon reaction of **7** with 4-pentenyltrimethylsilane **8** in the presence of Me<sub>3</sub>SiOSO<sub>2</sub>CF<sub>3</sub> and triethylsilane, reductive etherification took place with complete diastereoselectivity to give the 20 (*R*)-ether **9**, [ $\alpha$ ]<sub>D</sub><sup>22</sup> -3.9 (c 1.47, CHCl<sub>3</sub>), as the sole product. The structure of **9** was confirmed by comparison with the authentic sample prepared (56% yield) by the reductive etherification of 4-pentenal with the trimethylsilyl ether **13**<sup>‡</sup> having 20- (*R*) configuration.<sup>§</sup> Similarly, the reductive etherification of the ketone **10**, [ $\alpha$ ]<sub>D</sub><sup>22</sup> +108.1 (c 1.00, CHCl<sub>3</sub>), prepared

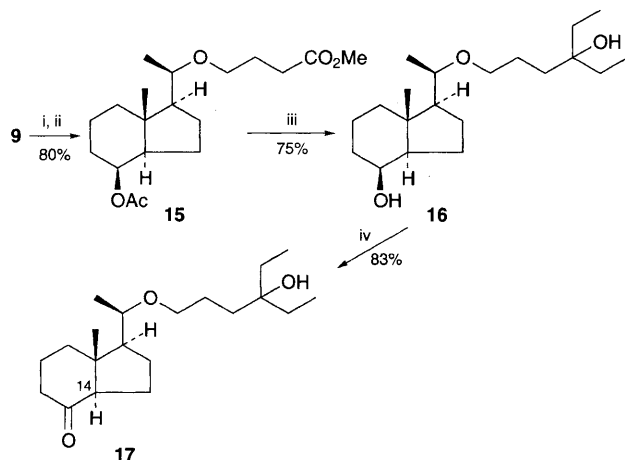
from **6** by silylation followed by ozonolysis, with the trimethylsilyl ether **11** was found to proceed with excellent diastereoselectivity and the ether **12**,<sup>||</sup> [ $\alpha$ ]<sub>D</sub><sup>22</sup> +6.4 (c 0.54, CHCl<sub>3</sub>), was obtained exclusively after desilylation.<sup>||</sup> The stereochemical outcome of these etherifications can be interpreted by assuming **14** as the most favourable conformer of the oxonium ion intermediate where the triethylsilane reduction occurs from the *si* face predominantly for steric reasons.

The ether **9** thus obtained was converted into the C/D-ring synthon of KH 1060 **17** as follows. Oxidative cleavage<sup>11</sup> of **9** with Jones reagent in the presence of a catalytic amount of osmium tetroxide followed by esterification with diazomethane gave the methyl ester **15**, [ $\alpha$ ]<sub>D</sub><sup>24</sup> -5.1 (c 1.42, CHCl<sub>3</sub>). Treatment of **15** with ethylmagnesium bromide provided the diol **16**, [ $\alpha$ ]<sub>D</sub><sup>22</sup> -5.1 (c. 1.12, CHCl<sub>3</sub>), which, upon oxidation with tetra-



**Scheme 1** Reagents and conditions: i, O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH (4 : 1), -78 °C, then NaBH<sub>4</sub>, -78 to -25 °C (cf. ref. 9); ii, PhSSPh, Bu<sub>3</sub>P, pyridine, 50 °C; iii, 30% H<sub>2</sub>O<sub>2</sub>, MeOH; iv, CaCO<sub>3</sub>, toluene, reflux; v, Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP (cat.), CH<sub>2</sub>Cl<sub>2</sub>; vi, O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH (4 : 1), -78 °C, then Me<sub>2</sub>S; vii, **8** (1.3 equiv.), Me<sub>3</sub>SiOSO<sub>2</sub>CF<sub>3</sub> (1 equiv.), Et<sub>3</sub>SiH (1 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to room temp.; viii, Bu<sup>t</sup>Me<sub>2</sub>SiOSO<sub>2</sub>CF<sub>3</sub>, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>; ix, as vi; x, **11** (1.3 equiv.), Me<sub>3</sub>SiOSO<sub>2</sub>CF<sub>3</sub> (1 equiv.), Et<sub>3</sub>SiH (1 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, -78 to -25 °C; xi, 46% HF, MeCN





**Scheme 2** Reagents and conditions: i,  $\text{OsO}_4$  (0.1 equiv.),  $\text{H}_2\text{CrO}_4$  (9 equiv.), acetone; ii,  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ ; iii,  $\text{EtMgBr}$ , THF,  $0^\circ\text{C}$ ; iv,  $\text{Pr}_4\text{NRuO}_4$  (0.05 equiv.), NMO (1.5 equiv.),  $\text{CH}_2\text{Cl}_2$

propylammonium perruthenate (TPAP),<sup>12</sup> furnished **17**,  $[\alpha]_{\text{D}}^{22} -78.4$  (c. 0.75,  $\text{CHCl}_3$ ). It is noteworthy that the TPAP catalysed oxidation did not cause any epimerisation of the C-14 asymmetric centre.

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### Footnotes

† All new compounds exhibited satisfactory spectra ( $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR) and HRMS analytical data.

‡ Prepared from **7** by the following sequence: (i)  $\text{NaBH}_4$ ,  $\text{Pr}^i\text{OH}$ , then chromatographic separation of epimers [20-(*R*):20-(*S*) = 3:1]; (ii)  $\text{Me}_3\text{SiCl}$ ,  $\text{Et}_3\text{N}$ , THF.

§ The stereochemistry of the C-20 position was assigned to be *R* on the basis of X-ray crystallographic analysis of the corresponding 20-(*N-p*-bromophenyl)carbamoyloxy derivative prepared by the reaction of the parent alcohol with *p*-bromophenyl isocyanate:  $[\alpha]_{\text{D}}^{22} -5.5$  (c. 1.04,  $\text{CHCl}_3$ ); mp  $167-169^\circ\text{C}$ . Crystal data for  $\text{C}_{21}\text{H}_{28}\text{O}_4\text{NBr}$ ,  $M = 438.00$ , orthorhombic, space group  $P2_12_12_1$ ,  $a = 13.459(6)$ ,  $b = 14.443(5)$ ,  $c = 11.023(5)$  Å,  $U = 2143(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_m = 1.30$ ,  $D_c = 1.36$  g cm<sup>-3</sup>;  $F(000) = 912$ ; Cu-K $\alpha$

radiation ( $\lambda = 1.54178$  Å),  $\mu(\text{Cu-K}\alpha) = 26.23$  cm<sup>-1</sup>; 1949 reflections measured, 1870 unique, 1750 used in refinement;  $R = 0.048$ ,  $R_w = 0.056$ . Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

¶ The 20-(*R*) stereochemistry was tentatively determined by the close similarity of the chemical shift and coupling constant of the C-21 methyl ( $\delta$  1.07, d,  $J$  5.9 Hz) to those of compounds **9** ( $\delta$  1.05, d,  $J$  5.9 Hz), **15** ( $\delta$  1.05, d,  $J$  5.9 Hz) and **16** ( $\delta$  1.07, d,  $J$  5.9 Hz) in their  $^1\text{H}$  NMR (500 MHz) spectra.

|| In order to aid purification desilylation was carried out after reductive etherification.

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