A Facile Stereoselective Route to a C/D-Ring Synthon for 20-Epi-22-oxavitamin D_3 Analogues

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An efficient method for the preparation of a C/D-ring synthon for 20-epi-22-oxavitamin D_3 analogues is developed based on $Me_3SiOSO_2CF_3$ catalysed reductive etherification of a ketone with an alkoxytrimethylsilane in the presence of triethylsilane.

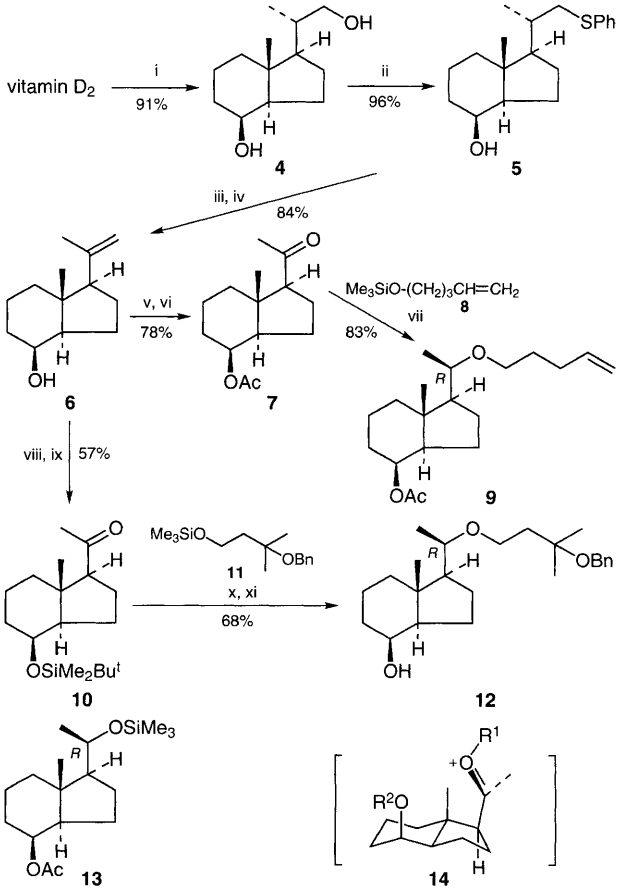
1α,25-Dihydroxyvitamin D_3 **1**, the hormonally active metabolite of vitamin D_3, has long been known as a regulator in calcium and phosphorus homeostasis.[1] Recent studies have demonstrated that it also plays a vital role in the regulation of immune responses[2] as well as in the cell proliferation and differentiation.[3] 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_3 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.[4] For example, KH 1060 **2** [R = $(CH_2)_2C(OH)Et_2$][5] 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.

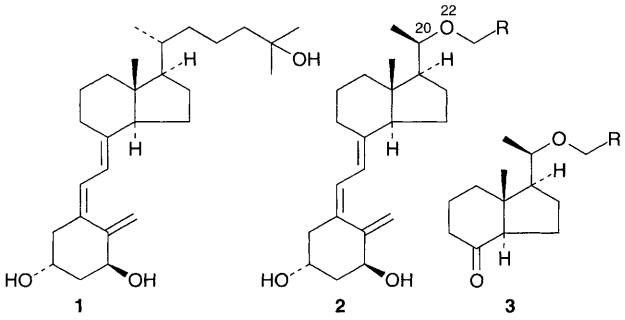
We recently reported[6] an efficient method for the preparation of ethers by the trimethylsilyl trifluoromethanesulfonate ($Me_3SiOSO_2CF_3$) catalysed reaction[7] of carbonyl compounds with alkoxytrimethylsilanes in the presence of triethylsilane. We report here a facile stereoselective route to a C/D-ring synthon **3** required for the convergent synthesis[8] of 20-epi-22-oxavitamin D_3 analogues based on this reductive etherification.

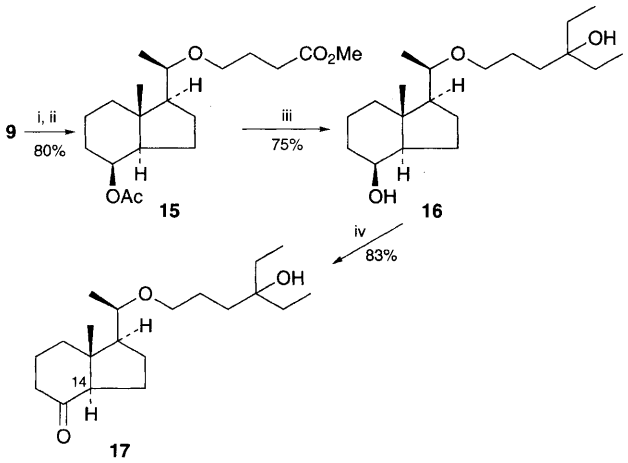
Reaction of the Inhoffen–Lythgoe diol **4**, prepared[9] from vitamin D_2, with diphenyldisulfide in the presence of tributylphosphine[10] gave the sulfide **5**,† $[\alpha]_D^{24}$ +75.3 (*c* 1.30, $CHCl_3$). Oxidation of **5** with 30% aqueous hydrogen peroxide followed by thermolysis of the resulting sulfoxide afforded the alkene **6**, $[\alpha]_D^{23}$ +34.3 (*c* 0.86, $CHCl_3$), in good overall yield. The alkene **6** was then converted to the methyl ketone **7**, $[\alpha]_D^{22}$ +100.4 (*c* 1.15, $CHCl_3$), by sequential acetylation and ozonolysis. Upon reaction of **7** with 4-pentenyloxytrimethylsilane **8** in the presence of $Me_3SiOSO_2CF_3$ and triethylsilane, reductive etherification took place with complete diastereoselectivity to give the 20 (*R*)-ether **9**, $[\alpha]_D^{22}$ −3.9 (*c* 1.47, $CHCl_3$), 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**‡ having 20-(*R*) configuration.§ Similarly, the reductive etherification of the ketone **10**, $[\alpha]_D^{22}$ +108.1 (*c* 1.00, $CHCl_3$), prepared from **6** by silylation followed by ozonolysis, with the trimethylsilyl ether **11** was found to proceed with excellent diastereoselectivity and the ether **12**,¶ $[\alpha]_D^{22}$ +6.4 (*c* 0.54, $CHCl_3$), was obtained exclusively after desilylation.‖ 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[11] 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**, $[\alpha]_D^{24}$ −5.1 (*c* 1.42, $CHCl_3$). Treatment of **15** with ethylmagnesium bromide provided the diol **16**, $[\alpha]_D^{22}$ −5.1 (*c*. 1.12, $CHCl_3$), which, upon oxidation with tetra-



Scheme 1 *Reagents and conditions*: i, O_3, CH_2Cl_2–MeOH (4 : 1), −78 °C, then $NaBH_4$, −78 to −25 °C (*cf.* ref. 9); ii, PhSSPh, Bu_3P, pyridine, 50 °C; iii, 30% H_2O_2, MeOH; iv, $CaCO_3$, toluene, reflux; v, Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2; vi, O_3, CH_2Cl_2–MeOH (4 : 1), −78 °C, then Me_2S; vii, **8** (1.3 equiv.), $Me_3SiOSO_2CF_3$ (1 equiv.), Et_3SiH (1 equiv.), CH_2Cl_2, −78 °C to room temp.; viii, $Bu^tMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2; ix, as vi; x, **11** (1.3 equiv.), $Me_3SiOSO_2CF_3$ (1 equiv.), Et_3SiH (1 equiv.), CH_2Cl_2, −78 to −25 °C; xi, 46% HF, MeCN





Scheme 2 *Reagents and conditions*: i, OsO_4 (0.1 equiv.), H_2CrO_4 (9 equiv.), acetone; ii, CH_2N_2, Et_2O; iii, EtMgBr, THF, 0 °C; iv, Pr_4NRuO_4 (0.05 equiv.), NMO (1.5 equiv.), CH_2Cl_2

propylammonium perruthenate (TPAP),[12] furnished **17**, $[\alpha]_D^{22}$ −78.4 (*c*. 0.75, $CHCl_3$). 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 (^1H and ^{13}C NMR, IR) and HRMS analytical data.

‡ Prepared from **7** by the following sequence: (i) $NaBH_4$, Pr^iOH, then chromatographic separation of epimers [20-(*R*):20-(*S*) = 3:1]; (ii) Me_3SiCl, Et_3N, 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: $[\alpha]_D^{22}$ −5.5 (*c* 1.04, $CHCl_3$); mp 167–169 °C. *Crystal data* for $C_{21}H_{28}O_4NBr$, 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^3, Z = 4, D_m = 1.30, D_c = 1.36 g cm^{-3}; $F(000)$ = 912; Cu-Kα radiation (λ = 1.54178 Å), μ(Cu-Kα) = 26.23 cm^{-1}; 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 (δ 1.07, d, *J* 5.9 Hz) to those of compounds **9** (δ 1.05, d, *J* 5.9 Hz), **15** (δ 1.05, d, *J* 5.9 Hz) and **16** (δ 1.07, d, *J* 5.9 Hz) in their ^1H NMR (500 MHz) spectra.

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

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