Enantioselective Synthesis of a *C/D*-Ring Synthon for the Preparation of Vitamin D_3 Metabolites

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The hydrindanol (**2**), a *C/D*-ring synthon of vitamin D_3 metabolites, has been synthesized enantioselectively by the use of stereoselective epoxy alcohol-initiated polyalkene cyclisation as a key step.

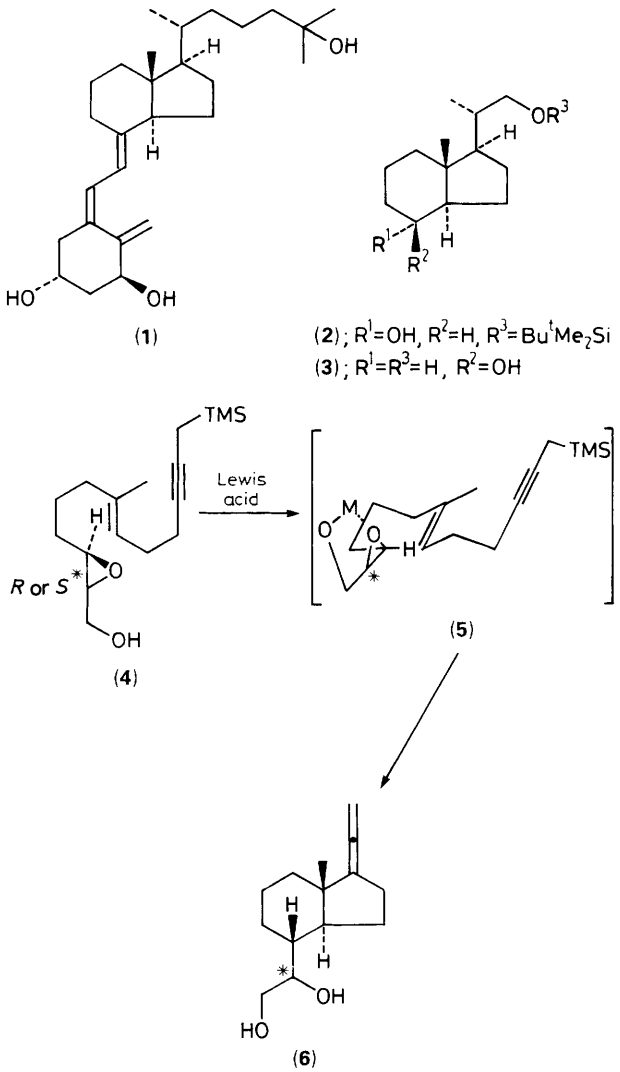
The discovery[1] of medicinally important vitamin D_3 metabolites such as 1α,25-dihydroxyvitamin D_3 (**1**) has spurred much research concerned with their partial and total syntheses.[2] Among the various synthetic routes developed, those based upon the Lythgoe's convergent methodology[2a] are particularly attractive because of their broad applicability to the synthesis of various analogues.

We have recently been able to develop efficient routes to *A*-ring synthons.[3] We now wish to report here a novel enantioselective synthesis of the *C/D*-ring synthon (**2**)[4] which constitutes a formal total synthesis of the Inhoffen–Lythgoe diol (**3**),[5] as well as vitamin D_3 and related metabolites.[6]

Our recent study[7] on intramolecular Lewis acid mediated nucleophilic opening of epoxy alcohols[8] prompted us to investigate the strategy based on the Johnson's cationic polyalkene cyclisation.[9] We assumed that Lewis acid catalysed reaction of a chiral epoxy alcohol (**4**) would proceed with a high degree of regio- and stereo-selectivity *via* a transition state resembling (**5**) to produce an allene diol (**6**), a promising precursor of the *C/D*-ring synthons, even though this type of cyclisation using a chiral epoxy alcohol as an initiating functionality was unprecedented (Scheme 1).

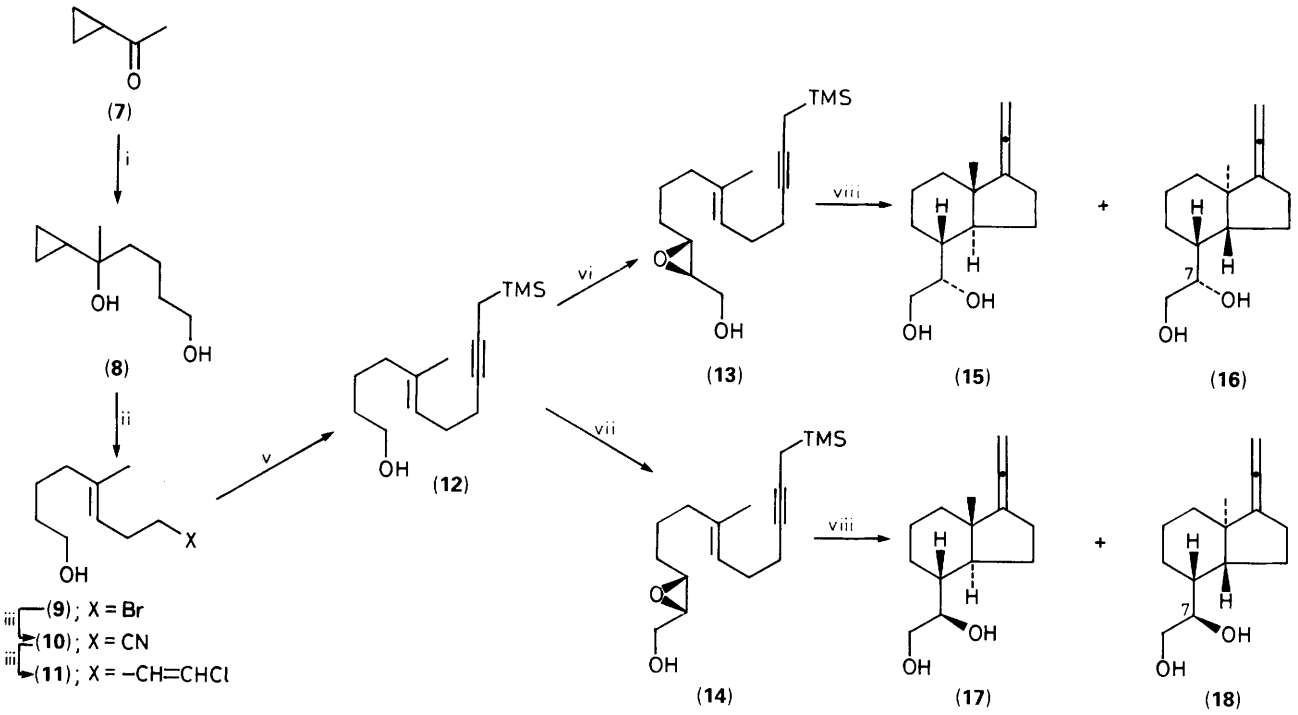
The synthesis started with commercially available cyclopropyl methyl ketone (**7**). Reaction of (**7**) with the Grignard reagent prepared from 4-chlorobutan-1-ol,[10] gave the diol (**8**)† which, upon treatment with hydrobromic acid according to Julia's method,[11] afforded the bromide (**9**). After conversion of (**9**) to (**10**), the nitrile (**10**) was sequentially subjected to reduction, Wittig reaction,[12] and protection to afford the chloroalkene (**11**). Treatment of (**11**) with n-butyl-lithium followed by *in situ* trimethylsilylmethylation[5c] using trimethylsilylmethyl triflate[13] and deprotection gave the alcohol (**12**).

The alcohol (**12**) was then transformed into the (*E*)-epoxy alcohol (**13**), $[\alpha]_D^{23}$ +20.4° (*c* 1.10, $CHCl_3$), and the (*Z*)-epoxy alcohol (**14**), $[\alpha]_D^{23}$ −1.2° (*c* 1.13, $CHCl_3$), by the combination of Swern oxidation, alkenation according to either Ireland's method[14] or Still's method,[15] di-isobutylaluminium hydride (DIBAL) reduction, and the Sharpless asymmetric epoxida-



Scheme 1. TMS = Me_3Si.

† All new isolated compounds exhibited satisfactory spectral (^1H NMR, IR, MS) and analytical data.



Scheme 2. *Reagents and conditions*: i, $ClMg(CH_2)_3OMgBr$, tetrahydrofuran (THF), −25 °C, 81%; ii, 48% HBr, −18 °C, 87%; iii, KCN, 18-crown-6 (catalyst), dimethylformamide (DMF), 89%; iv, (a) DIBAL, n-hexane–toluene–CH_2Cl_2 (3:3:1 v/v), −78 °C, (b) $Ph_3P{=}CHCl$, THF, 67% overall; (v) (a) 3,4-dihydro-2*H*-pyran (DHP), pyridinium toluene-*p*-sulphonate (PPTS) (catalyst), CH_2Cl_2, (b) 2.3 equiv. Bu^nLi, 1.5 equiv. $TMSCH_2OTf$ (TMS = tetramethylsilyl), THF, −70 °C, (c) PPTS (catalyst), MeOH, 82% overall; vi, (a) $(COCl)_2$ dimethyl sulphoxide (DMSO) Et_3N, CH_2Cl_2, −50 to 25 °C, then add $Ph_3P{=}CHCO_2Me$, *E*:*Z* = 8:1, (b) DIBAL, CH_2Cl_2, −78 °C, (c) 1.2 equiv. D-(−)-diethyl tartrate (DET), 1.1 equiv. $Ti(OPr^i)_4$, 2.5 equiv. Bu^tO_2H, CH_2Cl_2, −40 °C, 58% overall; vii, (a) $(COCl)_2$/DMSO/Et_3N, CH_2Cl_2, −50 °C to 25 °C, (b) $(TMS)_2NK$, 18-crown-6·MeCN, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF, −78 °C, *E*:*Z* = 1:9.4, (c) as in vi, (b), (d) 1.1 equiv. L-(+)-DET, 1.0 equiv. $Ti(OPr^i)_4$, 2.3 equiv. Bu^tO_2H, CH_2Cl_2, −40 °C, 61% overall; viii, 1.5 equiv. $SnCl_4$, CH_2Cl_2, −95 °C, 82% [(**15**):(**16**) = 2.4:1], 72% [(**17**):(**18**) = 5:1].

tion.[16] The optical purities of (**13**) and (**14**) were determined to be ≃100 and ≥90% enantiomeric excess (e.e.), respectively, by conversion to the corresponding α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) esters.‡ Upon treatment of the (*E*)-epoxy alcohol (**13**) with $SnCl_4$ at −95 °C in dichloromethane, instantaneous cyclisation took place to give the allene diol (**15**), $[\alpha]_D^{26}$ −17.8° (*c* 0.64, $CHCl_3$), and (**16**), $[\alpha]_D^{23}$ +19.0° (*c* 0.61, $CHCl_3$), in a ratio of 2.4:1 and in good yield. Conversely, cyclisation of the (*Z*)-epoxy alcohol (**14**) under the same conditions as mentioned above resulted in higher diastereoselection to give the allene diol (**17**), $[\alpha]_D^{23}$ +11.6° (*c* 0.60, $CHCl_3$), and (**18**), $[\alpha]_D^{24}$ +20.5° (*c* 0.84, $CHCl_3$), in a ratio of 5:1.§ It is interesting to note that this $SnCl_4$ mediated reaction of the corresponding acetate of (**13**) did not afford any hydrindan derivatives and that the $BF_3{\cdot}Et_2O$ mediated reaction of (**13**) failed to give either (**15**) or (**16**). These results suggest that tight complexation of the epoxy alcohol moiety to the metal centre not only makes this type of reaction feasible but also restricts the stereochemical course of cyclisation (Scheme 2).

Assembly of the requisite C-17 and C-20 chiral centres followed established methodology.[5c,17] After conversion of (**17**) to the acetate (**19**), $[\alpha]_D^{22}$ −13.4° (*c* 0.90, $CHCl_3$), (**19**) was subjected to semihydrogenation over Lindlar's catalyst and the $BF_3{\cdot}Et_2O$ catalysed ene reaction using paraformaldehyde to give exclusively the alcohol (**20**), $[\alpha]_D^{20}$ −28.9° (*c* 0.63, $CHCl_3$). Upon sequential hydrogenation, silylation, and methanolysis, (**20**) afforded the silyl ether (**21**), $[\alpha]_D^{21}$ −5.2° (*c* 0.96, $CHCl_3$), in good overall yield.

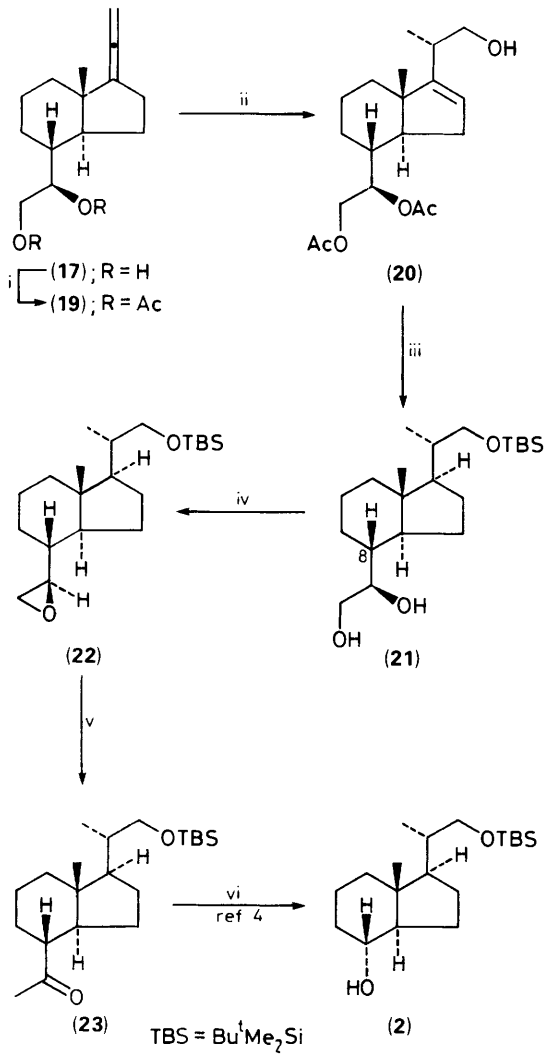
The silyl ether (**21**) was then converted to the epoxide (**22**), $[\alpha]_D^{24}$ +27.0° (*c* 0.62, $CHCl_3$), which, upon reduction with lithium triethylborohydride followed by Swern oxidation, gave the known ketone (**23**),[4,5d] $[\alpha]_D^{23}$ −1.3° (*c* 0.92, $CHCl_3$). According to the method reported by Trost and co-workers,[4] (**23**) was transformed into the alcohol (**2**) by Baeyer–Villiger oxidation followed by methanolysis. The synthetic substance, $[\alpha]_D^{23}$ +9.7° (*c* 1.34, CH_2Cl_2) [lit.[4] +7.6° (*c* 1.00, CH_2Cl_2)], was identical to the authentic sample, $[\alpha]_D^{27}$ +9.4° (*c* 0.60, CH_2Cl_2), prepared¶ from the Inhoffen–Lythgoe diol (**3**), by spectroscopic (^1H NMR, IR, MS) and chromatographic comparisons (Scheme 3). The objective *C/D*-ring synthon (**2**) was thus obtained from cyclopropyl methyl ketone (**7**) in 6.7% overall yield (25 steps).

Having an appropriate substituent with the diol functionality at the C-8 position, compound (**21**) itself has the capability of serving as a new type of *C/D*-ring synthon. Development of an efficient route to vitamin D_3 metabolites utilizing (**21**) as a *C/D*-ring synthon is now under investigation.

‡ Determined by 500 MHz ^1H NMR spectroscopic analysis, see: H. S. Mosher, J. A. Dale, and D. L. Dull, *J. Org. Chem.*, 1969, **34**, 2543.

§ Compounds (**15**) and (**16**) proved to be C-7 epimers of (**17**) and (**18**) respectively through degradation experiments (i, H_2/PtO_2; ii, $NaIO_4$; iii, $NaBH_4$).

¶ Prepared from (**3**) by 3 steps: i, selective silylation[18] [Bu^tMe_2SiCl, Et_3N, 4-dimethylaminopyridine (DMAP) (catalyst), CH_2Cl_2]; ii, oxidation [pyridinium chlorochromate (PCC), CH_2Cl_2]; iii, dissolving metal reduction (Li, NH_3–Bu^tOH).



Scheme 3. *Reagents and conditions*: i, Ac_2O, pyridine, DMAP (catalyst), 95%; ii, (a) H_2, 5% Pd–$CaCO_3$–Pb (catalyst), n-hexane, (b) $(CH_2O)n$, $BF_3{\cdot}Et_2O$ (catalyst), CH_2Cl_2, 82% overall; iii, (a) H_2, PtO_2 (catalyst), AcOEt, (b) TBSOTf, 2.6-lutidine, CH_2Cl_2, (c) K_2CO_3, MeOH, 90% overall; iv, (a) MsCl, pyridine, CH_2Cl_2, (b) NaOEt, EtOH, 90% overall; v, (a) $LiBHEt_3$, THF, −30 °C, (b) $(COCl)_2$/DMSO/Et_3N, CH_2Cl_2, −50 to 0 °C, 93% overall; vi, (a) 3-chloroperoxylbenzoic acid (*m*-CPBA), CH_2Cl_2, (b) NaOMe, MeOH, 90% overall.

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