Enantioconvergent Preparation of the A-Ring Precursors of Calcitriol from Either (*R*)- or (*S*)-Epichlorohydrin

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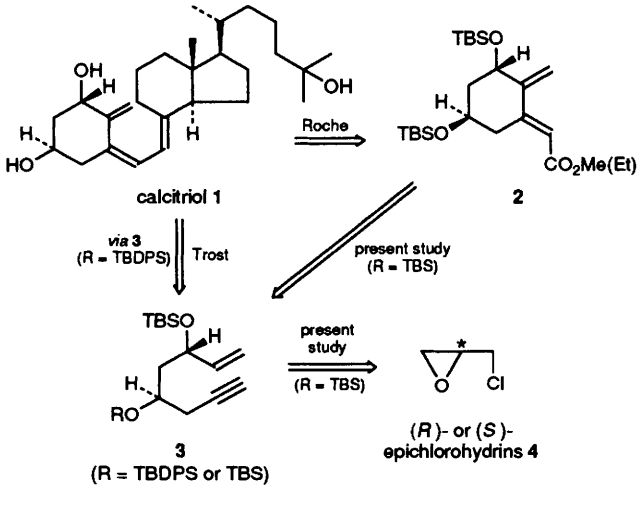
Linear and cyclic A-ring precursors of calcitriol have been prepared in both synthetically and enantiomerically convergent ways starting from either (*R*)- or (*S*)-epichlorohydrin.

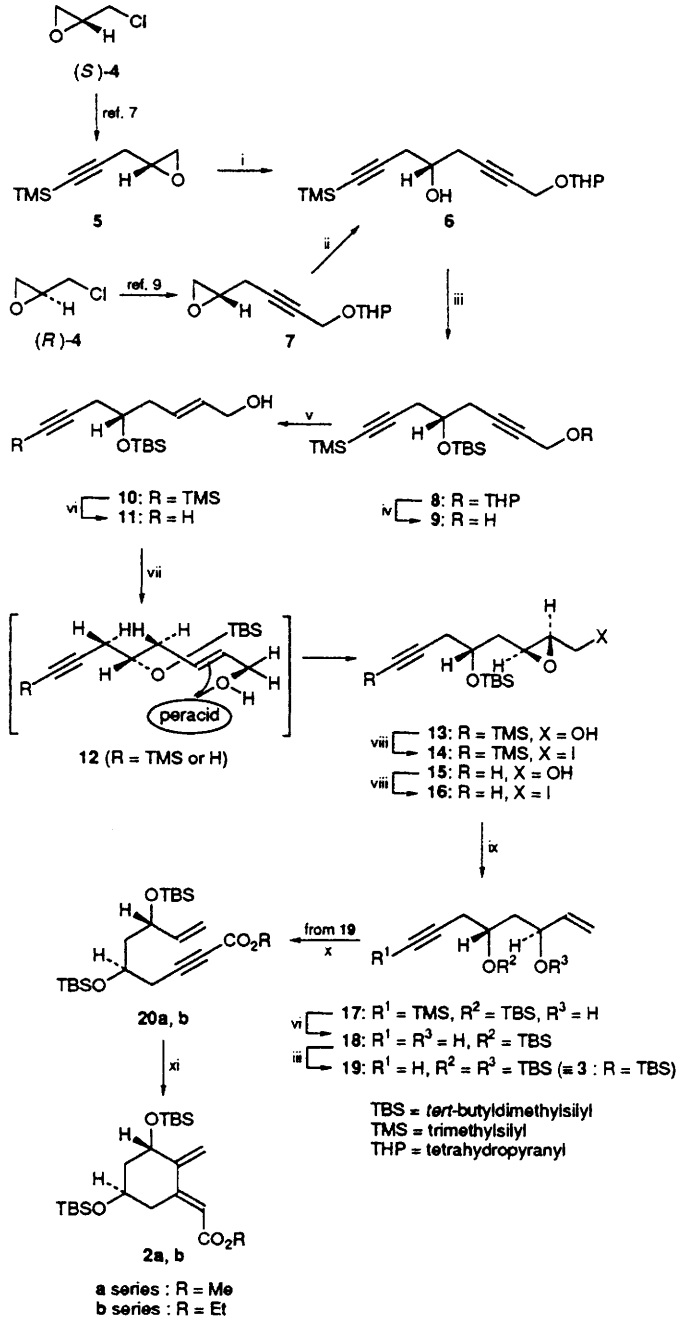
Medicinal importance of calcitriol **1** and the related vitamin D derivatives has stimulated a great deal of recent interest in development of synthetic routes to these molecules.[1,2] In particular, most of the synthetic efforts have been devoted to the construction of the A-ring moiety because of the difficulty of the conversion from the naturally occurring steroidal precursors.[3] Generally, the A-ring moiety has been elaborated from either cyclic precursors such as **2**[4] or linear precursors such as **3**[1a,5] though both have never been prepared from a common starting material.[6] Herein, we describe the first synthetically and enantiomerically convergent approach to the both types of the A-ring precursors of calcitriol **1** utilizing either (*R*)- or (*S*)-enantiomer of epichlorohydrin **4** (Scheme 1).

Exposure of the five-carbon chiral epoxyacetylene[7] **5**, obtained from (*S*)-epichlorohydrin [(*S*)-**4**], to the prop-1-ynyl ether in the presence of *n*-butyllithium and boron trifluoride etherate[8] gave the diynol† **6** in 67% yield. The same compound could also be prepared from (*R*)-epichlorohydrin [(*R*)-**4**] in four steps (>70% overall) *via* the six-carbon epoxyacetylene **7** on sequential reaction with prop-1-ynyl tetrahydropyranyl ether[9] and trimethylsilylacetylene. The diynol **6** was then transformed into the primary alcohol **9**, $[\alpha]_D^{30}$ + 9.0 (*c* 1.01, MeOH), in 88% yield *via* the silyl ether **8** on sequential protection and deprotection.[10] Treatment of **9** with an excess (≈5 equiv.) of sodium bis(2-methoxyethoxy)-aluminium hydride[11] in ether afforded a readily separable mixture of the (*E*)-allylic alcohols, **10**, $[\alpha]_D^{28}$ + 3.9 (*c* 0.92, MeOH), and **11**, $[\alpha]_D^{25}$ −6.0 (*c* 0.86, $CHCl_3$), in yields of 65 and 32%, the former of which was transformed into the latter (97%) on stirring with methanolic potassium carbonate.[12]

Very fortunately, the oxidation of **10** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane proceeded in a stereospecific way to give the desired β-epoxide **13**, $[\alpha]_D^{32}$ −43.3 (*c* 1.28, $CHCl_3$), in 73% yield accompanied by the separable α-epoxide in 7% yield. The observed stereochem-



Scheme 1



Scheme 2 *Reagents and conditions*: i, $HC{\equiv}CCH_2O$–THP, $LiBu^n$, $BF_3{\cdot}OEt_2$, THF, −78 °C, 2.5 h; ii, $TMSC{\equiv}CH$, $LiBu^n$, $BF_3{\cdot}OEt_2$, THF, −78 °C, 2.5 h; iii, TBS–Cl, imidazole, DMF, room temp., 6 h; iv, cat. PPTS, MeOH, room temp., 17 h; v, $Na(MeOCH_2CH_2O)_2AlH_2$, Et_2O, 0 °C → room temp., 1 h; vi, K_2CO_3, MeOH, 40 °C, 30 min. vii, MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h; viii, I_2, PPh_3, imidazole, THF–MeCN (4:1), room temp.; ix, activated Zn, cat. AcOH, MeOH, sonication, 40 °C, 1 h; x, **a**, $LiBu^n$ then $ClCO_2Me$, THF, −78 °C, 2h; **b**, Li^n . . then $ClCO_2Et$, THF, −78 °C, 2.5 h; xi, $[Pd_2(dba)_3]{\cdot}CHCl_3$ (2υ mol%), pivalic acid (50 mol%), $Ph_2PCH_2CH_2PPh_2$ (10 mol%), benzene, 50 °C, ≈22 h

ical outcome may be due to the bulky TBS ether at the homoallylic centre which forced the allylic hydroxy group to be the opposite face in the transition state **12**, directing the oxidant in a favourable way for the present purpose. Both diastereomeric epoxides could also be generated selectively from **10** by employing the Katsuki–Sharpless asymmetric epoxidation conditions:[13] thus, the β-epoxide **13** was formed selectively in quantitative yield in the presence of diisopropyl L-tartrate, while a 11 : 1 mixture of the α- and the β-epoxides was formed in an excellent total yield in the presence of diisopropyl D-tartrate.

Having introduced the requisite stereogenic centres, **13** was first transformed into the iodide **14**, $[\alpha]_D^{31}$ −26.3 (*c* 1.19, $CHCl_3$), in 85% yield on exposure to iodine in the presence of triphenylphosphine and imidazole.[14] The iodide **14** was then treated with activated zinc powder in methanol containing acetic acid (≈3%) under sonication to give rise to the enynol **17**, $[\alpha]_D^{28}$ −26.0 (*c* 1.06, $CHCl_3$), in 87% yield, which on detrimethylsilylation with methanolic potassium carbonate[12] afforded the terminal enynol **18**, $[\alpha]_D^{27}$ −32.3 (*c* 1.15, $CHCl_3$), in 97% yield. Finally, **18** was transformed into the di-TBS ether **19**, $[\alpha]_D^{30}$ −10.3 (*c* 1.50, $CHCl_3$), in 94% yield which may be taken as an equivalent of the Trost intermediate[1a,5] [3: R = *tert*-butyldiphenylsilyl (TBDPS)].

Quite similarly, the detrimethylsilyl product **11** could also be transformed into the terminal enynol **18** in a comparable overall yield. Thus, the oxidation of **11** with *m*-chloroperbenzoic acid afforded a separable mixture of the desired β-epoxide **15**, $[\alpha]_D^{27}$ −51.4 (*c* 1.04, $CHCl_3$), and the diastereomeric α-epoxide in yields of 74 and 5%. The major product **15** was transformed into the iodide **16**, $[\alpha]_D^{29}$ −26.9 (*c* 1.17, $CHCl_3$), in 84% yield as above, which on reductive treatment left **18** in 87% yield.

In order to transform the linear precursor **19** into the cyclic intermediate **2**, **19** was treated with methyl chlorocarbonate in the presence of *n*-butyllithium to give the methyl propiolate **20a**, $[\alpha]_D^{28}$ −4.7 (*c* 1.15, $CHCl_3$), in 78% yield. Similarly, the ethyl propiolate **20b**, $[\alpha]_D^{25}$ −3.5 (*c* 1.23, $CHCl_3$), could be obtained from **19** in 81% yield. After considerable examination employing palladium-based conditions,[1a,15] we have found that cycloisomerization of **20** could best be carried out in the presence of tris(dibenzylideneacetone)dipalladium–chloroform (1/1) $[Pd_2(dba)_3]\cdot CHCl_3$[16] (0.2 equiv.), ethylenebis(diphenylphosphine) (0.1 equiv.) and pivalic acid (0.5 equiv.) to give the desired dialkylidenecyclohexanes, **2a**, $[\alpha]_D^{25}$ −13.8 (*c* 0.86, $CHCl_3$) and **2b**, $[\alpha]_D^{26}$ −5.3 (*c* 0.56, EtOH) [lit.:[4b] $[\alpha]_D^{25}$ −4.7 (*c* 0.5, EtOH); $[\alpha]_D^{23}$ −4.9 (*c* 0.5, EtOH);[1b] $[\alpha]_D$ −4.2 (*c* 0.48, EtOH)[1c]], in yields of 64 and 69%, respectively (Scheme 2).

In conclusion, we have shown an efficient route to the linear and the cyclic A-ring precursors of calcitriol in both synthetically and enantiomerically convergent ways starting from either (*S*)- or (*R*)-enantiomer of epichlorohydrin.

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Footnote

† Satisfactory analytical (combustion and high resolution mass) and spectral (IR, ^1H NMR, Mass) data were obtained for all new isolable compounds.

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