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

Kazuki Tazumi and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

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 epoxyacetylene⁷ 5 obtained from (S)-epichlorohydrin [(S)-4], to the prop-1-ynyl ether in the presence of *n*-butyllithium and boron trifluoride etherate⁸ 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 ether⁹ 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 silvl ether 8 on sequential protection and deprotection.¹⁰ Treatment of 9 with an excess (\approx 5 equiv.) of sodium bis(2-methoxyethoxy)aluminium hydride¹¹ 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, CHCl₃), 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, CHCl₃), in 73% yield accompanied by the separable α -epoxide in 7% yield. The observed stereochem-





Scheme 2 Reagents and conditions: i, HC=CCH₂O-THP, LiBuⁿ, BF₃·OEt₂, THF, -78 °C, 2.5 h; ii, TMSC=CH, LiBuⁿ, BF₃·OEt₂, 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(MeOCH₂ CH₂O)₂AlH₂, Et₂O, 0 °C \rightarrow room temp., 1 h; vi, K₂CO₃, MeOH, 40 °C, 30 min. vii, MCPBA, NaHCO₃, CH₂Cl₂, 0 °C, 2 h; viii, I₂, PPh₃, imidazole, THF-MeCN (4:1), room temp.; ix, activated Zn, cat. AcOH, MeOH, sonication, 40 °C, 1 h; x, **a**, LiBuⁿ then ClCO₂Me, THF, -78 °C, 2h; **b**, Liⁿ. then ClCO₂Et, THF, -78 °C, 2.5 h; xi, [Pd₂(dba)₃]·CHCl₃ (2ω mol%), pivalic acid (50 mol%), Ph₂PCH₂CH₂PPh₂ (10 mol%), benzene, 50 °C, \approx 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, CHCl₃), 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 ($\approx 3\%$) under sonication to give rise to the enynol **17**, $[\alpha]_D^{28} - 26.0$ (*c* 1.06, CHCl₃), in 87% yield, which on detrimethylsilylation with methanolic potassium carbonate¹² afforded the terminal enynol **18**, $[\alpha]_D^{27} - 32.3$ (*c* 1.15, CHCl₃), in 97% yield. Finally, **18** was transformed into the di-TBS ether **19**, $[\alpha]_D^{30} - 10.3$ (*c* 1.50, CHCl₃), in 94% yield which may be taken as an equivalent of the Trost intermediate^{1*a*,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, CHCl₃), 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, CHCl₃), 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, CHCl₃), in 78% yield. Similarly, the ethyl propiolate 20b, $[\alpha]_D^{25} - 3.5$ (c 1.23, CHCl₃), could be obtained from 19 in 81% yield. After considerable examination employing palladium-based conditions,^{1*a*,15} we have found that cycloisomerization of 20 could best be carried out in the presence of tris(dibenzylideneacetone)dipalladium-chloroform (1/1) [Pd₂(dba)₃]-CHCl₃¹⁶ (0.2 equiv.), ethylene-bis(diphenylphosphine) (0.1 equiv.) and pivalic acid (0.5 equiv.) to give the desired dialkylidenecyclohexanes, 2a, $[\alpha]_D^{25} - 13.8$ (c 0.86, CHCl₃) and 2b, $[\alpha]_D^{26} - 5.3$ (c 0.56, EtOH); $[i]_D^{25} - 4.7$ (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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