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A Convergent Route to Calcitriol Lactone via Reductive Cleavage of an Enantiopure Glycidyl Ether

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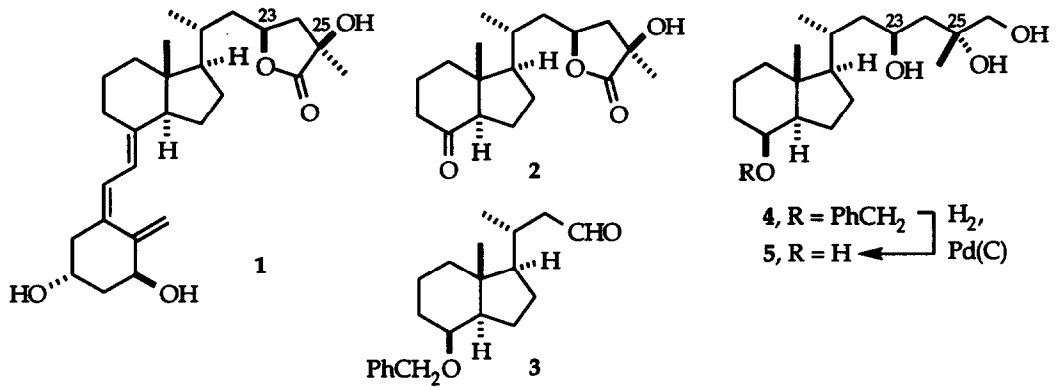
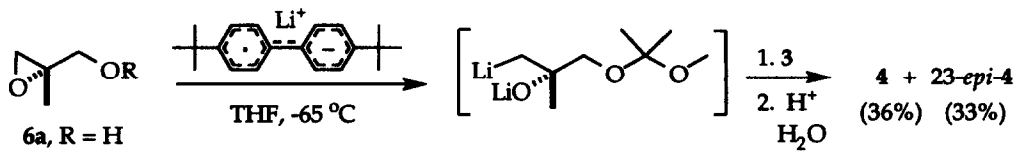
Abstract. *Reductive cleavage of the ((1-methyl-1-methoxy)ethyl) ether of (S)-2-methylglycidol with lithium 4,4'-di-t-butylbiphenylide, addition of aldehyde 3 to the resulting β-lithioalkoxide, followed by acidic hydrolysis, yields the advanced (23S,25R)-calcitriol lactone intermediate 4 plus its 23R epimer (~1:1, 69%).*

(23*S*,25*R*)-Calcitriol lactone (**1**), a major Vitamin D metabolite in man and other animals, has attracted attention due to its interesting biological activity profile, including stimulation of bone formation.[1] Natural sources yield only minute quantities of **1**, so a need exists for a practical synthesis.[2] The Hoffmann-LaRoche synthesis of **1** culminated in the coupling of keto lactone **2** (as its TMS ether) with a dienyl phosphine oxide anion.[3a,b] Johnson and Chan then reported a highly stereoselective synthesis of **2** via tetrol **4**, employing methallylation of a chiral acetal derived from aldehyde **3** to produce a homoallylic 23S alcohol, followed by iodocyclization of the derived *t*-butyl carbonate to establish the stereocenter at carbon 25.[4]



Herein is reported a concise synthesis of **4** in which the chiral butanediol segment comprising carbons 24-27 is derived from glycidyl ether **6b** and appended to **3** in one flask. Cohen has reported detailed studies on the reductive cleavage of epoxides with lithium di-*t*-butylbiphenylide (LiDBB) to produce synthetically useful β-lithioalkoxides.[5] The MOM ether of racemic glycidol undergoes the reaction satisfactorily.[5] Application of this method to an enantiopure glycidol, several of which are now produced commercially by catalytic Sharpless epoxidation,[6] appeared ideal for the present purpose. Thus, *(S)*-2-methylglycidol (**6a**)



6a, R = H
6b, R = CMe_2OMe

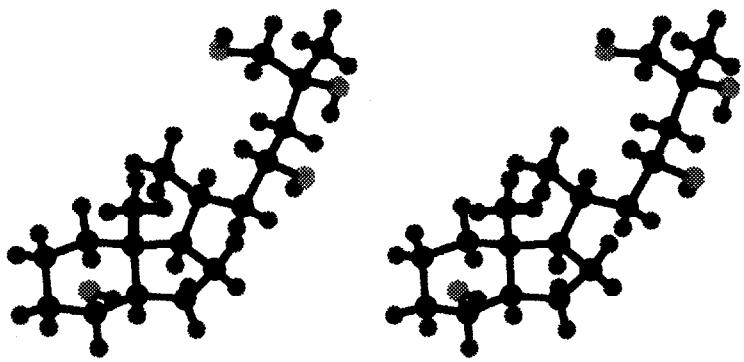
was protected as ether **6b**. Exposure of **6b** to LiDBB (2 mol eq) in THF at -65 °C, addition of aldehyde **3**,[4] and *in situ* deprotection with dilute aqueous acid gave a separable mixture of **4**[7] (36%) and its 23R epimer[7]

(33%). The yield of **4** from **3** is lower than that attained in the elegant, fully stereocontrolled synthesis (62%),[4] but seven steps are saved and gram quantities of **4** can be prepared in this way without difficulty. Hydrogenolysis[4] of **4** gave **5**, whose structure was confirmed by X-ray crystallography[8] and by comparison with an authentic sample and analytical data kindly provided by Professor Johnson and Dr. Chan.

(*R*)-2-((1-methyl-1-methoxy)ethoxy)methyl-2-methyloxirane (6b). $C_5H_5NH^+$ OTs^- (0.15 g, 0.60 mmol) was added to a stirred solution of 2-methoxypropene (8.0 mL, 83 mmol) and **6a** (Aldrich, 4.98 g, 56.6 mmol) in 20 mL of dry CH_2Cl_2 under Ar. A vigorous reflux ensued. Filtration through a Florisil pad (eluting with Et_2O), concentration and purification of the residue by flash chromatography on silica (1:1 Et_2O-hexane) afforded 7.29 g (80%) of **6b**[10a,c] as a volatile oil, $[\alpha]^{23}_D$ +4.7° (c = 1.4, MeOH).

(8*S*,23*S*,25*R*)-De-*A*,*B*-8-(benzyloxy)cholestan-23,25,26-triol (4). A stirred, ice-cooled solution of 4,4'-di-*t*-butylbiphenyl (8.5 g, 32 mmol) and 5 mg of 2,2'-bipyridyl in 90 mL of THF (distilled from K/Ph_2CO) under Ar was titrated to dryness with *n*-BuLi.[9] Lithium wire (1% Na, 0.21 g, 30 mmol, 0.3-cm pieces) was added, the mixture was stirred for 5.5 h, then cooled to -70 °C (internal). Epoxy ether **6b** (2.54 g, 16 mmol) was added (<-65 °C), followed after 6 min by a solution of **3** (2.43 g, 7.74 mmol) in 10 mL of anhydrous THF. The mixture was stirred for 4 h (to 8 °C), quenched with sat. aq. KH_2PO_4, and the separated organic solution stirred with 0.25 M aq. H_2SO_4 for 18 h. The product was isolated by extraction (EtOAc-H_2O) and purified by flash chromatography on silica (55% EtOAc-hexane→EtOAc) yielding 1.03 g (33%) of 23-*epi*-**4**,[10a] followed by 1.12 g (36%) of **4**.[10a]

(8*S*,23*S*,25*R*)-De-*A*,*B*-cholestan-8,23,25,26-tetrol (5). A sample of **4** (0.71 g) was hydrogenated (3 atm H_2, MeOH, 10% Pd(C))[4] for 24 h. Filtration through Celite and concentration gave 0.55 g (99%) of **5**. Recrystallization (*n*-BuCl/MeOH) gave the crystallographic sample of **5**[10a,b,c] (0.26 g), $[\alpha]^{23}_D$ +67.1° (c = 1, MeOH), colorless prisms, mp 181-183.5 °C, lit.[4] mp 178-180 °C.



Crystal structure of 5. Stereoview created in Alchemy III (Tripos Associates).

References and Notes

1. Seino, Y.; Ishizuka, S. *Drugs of the Future* **1992**, *17*, 655.
2. Hatakeyama, S.; Sugawara, M.; Kawamura, M.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1229, and cited references.
3. (a) Wovkulich, P.M.; Baggiolini, E.G.; Hennessy, B.M.; Uskokovic, M.; Mayer, E.; Norman, A.W. *J. Org. Chem.* **1983**, *48*, 4433. (b) Lythgoe, B. *Chem. Soc. Rev.* **1980**, *9*, 449.
4. Johnson, W.S.; Chan, M.F. *J. Org. Chem.* **1985**, *50*, 2598.
5. Cohen, T.; Jeong, I.-H.; Mudryk, B.; Bhupathy, M.; Awad, M.M.A. *J. Org. Chem.* **1990**, *55*, 1528.
6. Hanson, R.M. *Chem. Rev.* **1991**, *91*, 437; Shum, W.P., Eur. Pat. Appl. EP 454,463 (Chem. Abstr. *116:* P57582j); Dougherty, W.; Liotta, F.; Mondimore, D.; Shum, W. *Tetrahedron Lett.* **1990**, *31*, 4389.
7. Compounds **4** and 23-*epi*-**4** gave identical ketols[10a,b] upon silylation of the primary OH (*t*-$BuPh_2SiCl$, DMAP, imidazole, DMF, 50 °C) followed by oxidation (PCC, CH_2Cl_2).
8. Crystallography performed by Dr. V.M. Lynch, Chemistry Department, University of Texas, Austin.
9. Stork, G.; Rychnovsky, S.D. *J. Am. Chem. Soc.* **1987**, *109*, 1565 (Supplementary Material).
10. Structure determined by (a)IR and ^1H NMR (b)50-MHz ^{13}C NMR (c)C,H analysis (±0.1% of theory).

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