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Highly Enantioselective Rearrangement of a *meso*-Epoxide to an Allyl Alcohol for Carbocyclic Nucleoside Synthesis: an Internal Alkoxide Effect

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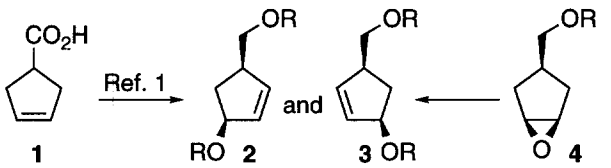
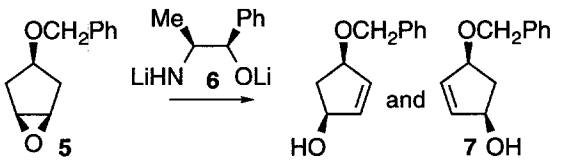
Abstract: *The synthesis of the enantiomeric cis-4-(hydroxymethyl)cyclopent-2-ene-1-ols* **2** *and* **3** *(R = H) via a highly enantioselective rearrangement of cis-6-oxabicyclo[3.1.0]hexane-3-methanol* **4** *(R = H) using the dilithium salts of (+)- or (-)-norephedrine is described.*

We recently communicated a racemic regio- and stereo-specific synthesis of the *cis*-diacetates **2** and **3** (R = Ac) from the acid **1** (Eq. 1) using a bromolactonisation strategy.[1] The *cis*-diacetates **2** and **3** are key intermediates in the convergent synthesis of carbocyclic nucleosides by way of palladium-catalysed coupling with purines or pyrimidines.[2] Compounds derived from the *cis*-diacetates **2** and **3** have been enzymatically resolved and used in the enantioselective syntheses of the anti-HIV agent carbovir[3] and *pseudo*-ribofuranoses.[4] Given the interest in preparing chiral carbocyclic nucleosides,[5] we sought to synthesise the enantiomeric *cis*-diacetates **2** and **3** individually, without recourse to a resolution procedure, *via* enantioselective rearrangement of the *meso*-epoxide **4** (Eq. 1).



(1)

The enantioselective rearrangement of *meso*-epoxides to allyl alcohols using chiral bases has been the focus of much research.[6] Milne and Murphy recently used the dilithium salts of (+)- or (-)-norephedrine to effect the closely studied rearrangement of the epoxide **5** (Eq. 2) in higher yields and enantiomeric excesses (e.e.s) than previously recorded with other chiral bases.[7] The highest e.e. reported, which gave predominantly (86% e.e.) the allylic alcohol **7**, was obtained by warming a mixture of dilithiated (1*R*,2*S*)-norephedrine **6** (3 equivs.) and the epoxide **5** in THF from -78 °C to 0 °C over 16 h.



(2)

In order to examine the enantioselective rearrangement strategy for preparing the *cis*-diacetates **2** and **3**, the *meso*-epoxide **4** (R = H) (previously synthesised as a 1:1 mixture with the *trans*-isomer)[8] was first made from the acid **1** by reduction[9] with $LiAlH_4$ followed by a highly stereoselective (*cis*:*trans* ≥ 97:3) hydroxyl-directed epoxidation[10] (Bu^tOOH, cat. $VO(acac)_2$, CH_2Cl_2, 98% yield). However, there was no reaction between the derived epoxy ethers **4** (R = trityl or CH_2Ph) and dilithiated (1*R*,2*S*)-norephedrine **6** (3 equivs.). The epoxy ether **4** (R = trityl) was also recovered unchanged (98%) from attempted reaction with LDA. In contrast, the unprotected *meso*-epoxide **4** (R = H) smoothly rearranged using dilithiated (1*R*,2*S*)-norephedrine **6** (3 equivs.) in benzene:THF (2:1 v/v) on warming from 0 °C to room temperature over 24 h, to give the *cis*-diol **2** (R = H) (66%) in 95% e.e., as determined by bis-Mosher's ester analysis [(*R*)-MPTA, DCC, cat. DMAP, CH_2Cl_2, 92%].[11] The enantiomeric *cis*-diol **3** (R = H) was similarly prepared (57%, 95% e.e.) using (1*S*,2*R*)-norephedrine. The absolute stereochemistry induced in the *cis*-diols **2** and **3** (R = H) was determined by measuring the direction of the optical rotations of the corresponding known monotritylated alcohols.[4,12] Finally, diacylation (Ac_2O, pyridine, cat. DMAP) of the *cis*-diol **3** (R = H) gave the *cis*-diacetate **3** (R = Ac) (95%).

It is interesting to note that the asymmetic induction found in the rearrangement of the *meso*-epoxide **4** (R = H) with the dilithium salts of (+)- or (-)-norephedrine is opposite to that observed with the epoxide **5**. In addition, the remarkably high e.e.s found for the rearrangement of the *meso*-epoxide **4** (R = H), which occur between 0 °C and room temperature, combined with the inertness of the epoxy ethers **4** (R = trityl or CH_2Ph) may indicate that the norephedrine serves to create a highly ordered transition state for the rearrangement to occur by way of an internal asymmetric deprotonation. We are currently investigating the ability of deprotonated sites within other *meso*-materials to act as aids for enhancing enantioselectivity in rearrangements. This strategy has the merit of avoiding protecting groups.

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12. Found for monotritylated **3**: $[\alpha]_D^{20}$ -73.9 (*c* 1.4 in $CHCl_3$). Lit.,[4] $[\alpha]_D^{24}$ -72 (*c* 1.2 in $CHCl_3$) for material determined (by NMR using a chiral shift reagent) to have a 95.5% e.e.

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