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SYNTHESIS OF (2R) AND (2S)-BENZYL-2,3-EPOXYPROPYL ETHER FROM A COMMON PRECURSOR: O-BENZYL-L-SERINE

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Summary: The (2R) and (2S)-benzyl-epoxypropyl ether are obtained from commercially available O-benzyl-serine, via nitrosation and Mitsunobu reactions to afford the chiral precursors of the above epoxy ethers.

The highly-oxygenated three-carbon unit present in glycidol and related derivatives are important building blocks for a variety of biologically important molecules and for the synthesis of various natural products, including leukotriene derivatives[1], phospholipids[2], glycerides[3], etc.

Whilst (2R)-1-benzyloxy-2,3-propanediol, a precursor of (2S)-benzyl-2,3-epoxypropyl ether, is readily prepared from D-mannitol[4-6], L-serine[7] and other sources[8], via isopropylidene-glycerol, the (S) enantiomer is difficult to be obtained from chiral naturally occurring starting materials; notwithstanding few methods for the preparation of (2S)-1-benzyloxy-2,3-propandiol have been reported, e.g. starting from L-ascorbic acid[9,10] or via treatment of (2R)-1-benzyloxy-2,3-propandiol-bis-methane sulfonate with potassium acetate in boiling acetic anhydride.[11]

We now report here a simple means of preparing (2R) and (2S)-benzyl-2,3-epoxypropyl ether from O-benzyl-L-serine. Treatment of commercially available O-benzyl-L-serine with $NaNO_2/H_2SO_4$ at room temperature for 16 hr afforded crude (2S)-3-benzyloxy-2-hydroxy propanoic acid 2a, which was immediately converted to the corresponding methyl ester 2b by treatment with acidic MeOH followed by silica gel purification (70% yield; $[\alpha]_D$ = +4.5°; c = 8.34, $CHCl_3$).

Reduction of methyl-(2S)-3-benzyloxy-2-hydroxypropanoate 2b with 1.5 eq. of $LiAlH_4$ (1M, THF) gave: (2R)-1-benzyloxy-2,3-propandiol 3 in almost quantitative yield ($[\alpha]_D$ = +3.64°; c = 5, $CHCl_3$. Lit[6]: $[\alpha]_D$ = +3.71°; c = 19.9, $CHCl_3$).

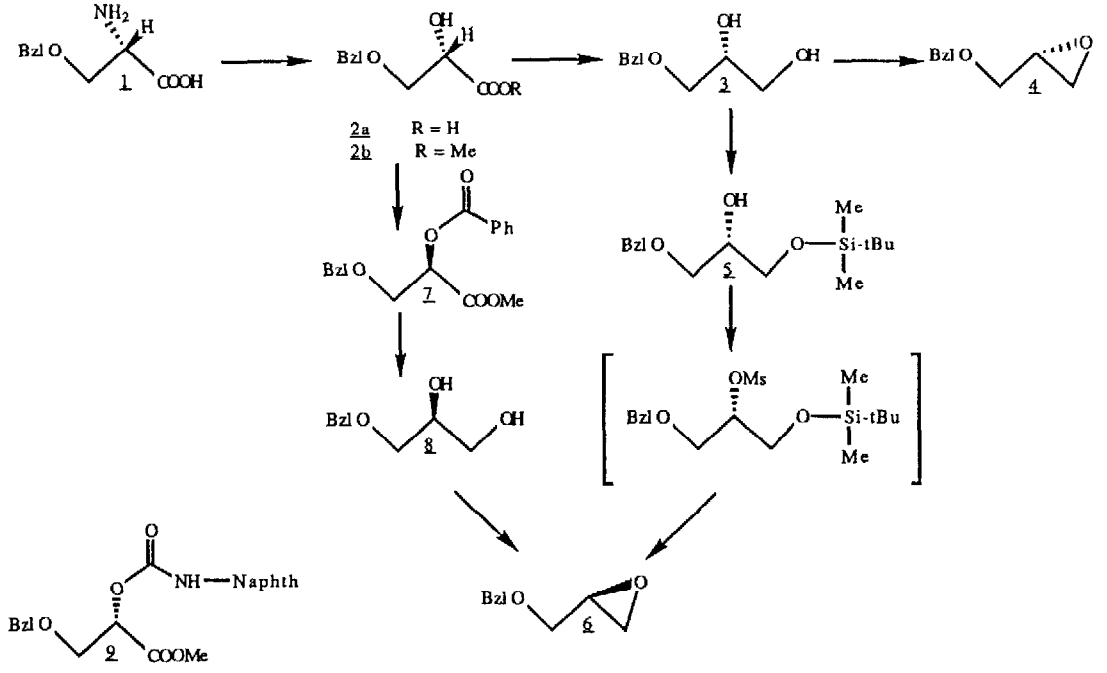
The conversion of 3 to (2S)-benzyl-2,3-epoxypropyl ether 4 was achieved, under usual conditions, by tosylation of the primary alcohol with p-toluenesulfonyl chloride (1 eq. in pyridine) followed by ring closure with sodium methoxide to afford (2S)-4 ($[\alpha]_D$ = -12.1°, neat; Lit[6]: $[\alpha]_D$ = -11.7°, neat) in 93% yield from 2b. When 3 was treated with t-butyl-dimethylsilylchloride/Et_3N in CH_2Cl_2, the silylated triol 5 was isolated in 83% yield ($[\alpha]_D$= +1.6°; c = 1 $CHCl_3$). The latter was mesylated (MsCl/Py) and treated with 1.5 eq. of TBAF 1M in THF to give the (2R)-isomer 6 ($[\alpha]_D$ = -13.2°, neat; Lit[11] : $[\alpha]_D$ = -13.9°, neat) in 76% yield from 3.

The synthesis of the same isomer can be also accomplished by Mitsunobu inversion[12] at the chiral center of 2b. When the methyl-(2S)-3-benzyloxy-2-hydroxypropanoate 2b was treated with an excess (20%) of Ph_3P/DEAD/benzoic acid, the methyl-(2R)-3-benzyloxy-2-benzoyloxy-propanoate 7 ($[\alpha]_D$ = +6.2°; c = 2, $CHCl_3$) was isolated in 83% yield after purification by silica gel chromatography.

The (2S)-1-benzyloxy-2,3-propandiol 8 ($[\alpha]_D$ = -3.63°; c = 8, $CHCl_3$. Lit[11] : $[\alpha]_D$ = -3.71°; c = 17.64, $CHCl_3$) was prepared in 90% yield by reduction of 7 with $LiAlH_4$ (2 eq.).

Using standard procedure (TsCl/Py then sodium methoxide) made the (2R)-6 isomer available in 71% yield from 2b ($[\alpha]_D$ = +13.2°; neat. Lit[11]:$[\alpha]_D$ = +13.9°, neat).

The enantiomeric purity of the key intermediate 2b was determined by HPLC of 9, obtained by refluxing 2b with 1-naphthylisocianate in toluene.



HPLC analysis of 9 using chiral stationary phases with both (S,S) and (R,R)-DACH-DNB[13] as selectors, showed that the enantiomeric excess of 2b was = 94%. The utilization of two chiral columns of opposite chirality made reliable the enantiomers identification also in the absence of reference compounds, because the inversion of the elution order only of the enantiomers was observed if passing from a column to the other. This result was confirmed by the analysis of the UV spectra obtained on line by a photodiode detector.

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