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CHIRALITY INVERSION OF THE 1,3-GLYCOL SYSTEM AND ITS APPLICATION TO THE SYNTHESIS OF THE CARBAPENEM INTERMEDIATE

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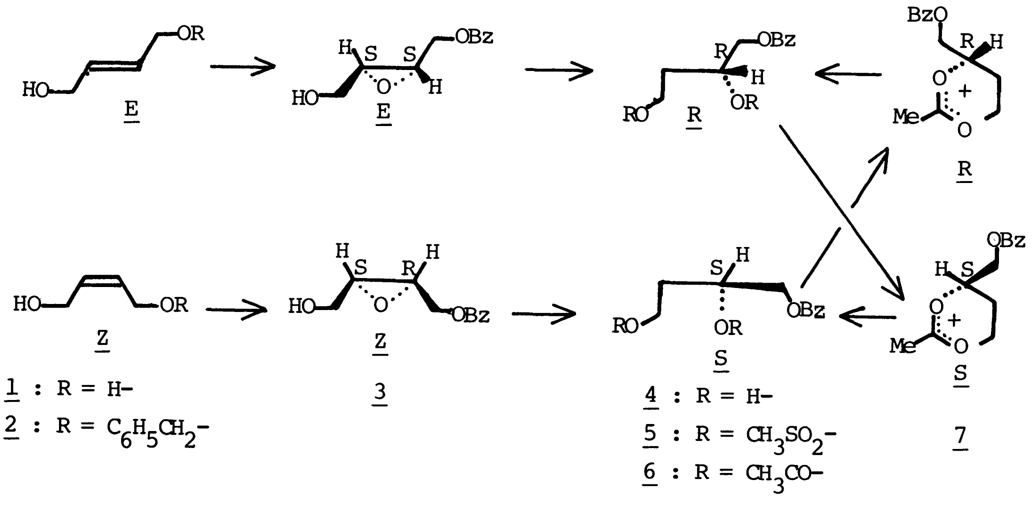
Novel chirality inversion of the butane-1,3-diol system (4) and its application to the synthesis of the carbapenem intermediate are described.

Recently, we developed a novel 1,2-glycol chirality inversion method[1] applicable to the enantioselective synthesis of both enantiomers of the aggregation pheromone sulcatol using a single chiral precursor[2]. Herein we describe our efforts on the development of chirality inversion of the 1,3-glycol system based on the same conception and its application to the synthesis of the key intermediate of the carbapenem antibiotics.

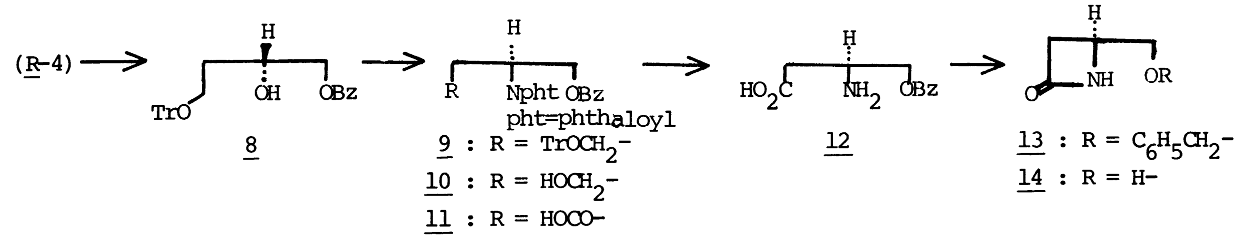
Both E(2S,3S)- and Z(2S,3R)- epoxides (3) were prepared in yield of 74.5 % ($[\alpha]_D^{14}$-20.3 (c = 6.40, $CHCl_3$) (lit., $[\alpha]_D^{25}$-22.0° (c = 0.50, $CHCl_3$)[3], $[\alpha]_D^{25}$-21° (c = 0.97, $CHCl_3$)[4]) and 77.6 % ($[\alpha]_D^{23}$-22.8° (c = 2.26, $CHCl_3$) (lit. $[\alpha]_D^{25}$-27° (c = 1.5, $CHCl_3$)), respectively, from the corresponding E[5]- and Z[6]-4-benzyloxy-2-butene-1-ols (2) by Sharpless method[3] using naturally abundant (+)-tartarate derivative as chirality control element. Upon reduction with bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran[7,8], E-isomer(E-3) gave (R)-1,3-glycol (R-4), $[\alpha]_D^{22}$+7.89° (c = 9.48, MeOH), in 84.8 % yield, while Z-isomer (Z-3) gave (S)-1,3-glycol (S-4), $[\alpha]_D^{23}$-7.56° (c = 3.65, MeOH), in 86.8 % yield. The each enantiomer was converted into the corresponding dimesylate (5) which was treated with potassium acetate in boiling acetic anhydride[1] to yield the inverted diacetate (6), respectively. Methanolysis of the each acetate (6)



Scheme 1

regenerated the 1,3-glycol (4) which possessed the opposite sign of optical rotation to that of the original one (4). Thus, the (R)-enantiomer (R-4) furnished the (S)-enantiomer (S-4), $[\alpha]_D^{19.5}$ -7.22°(c = 1.80, MeOH), in 59 % overall yield and the (S)-enantiomer (S-4) furnished the (R)-enantiomer (R-4), $[\alpha]_D^{24}$ $+7.66^{\circ}$ (c = 1.75, MeOH), in 60 % overall yield, respectively. We assume that the observed inversion may be resulted from the reaction sequence involving initial intermolecular substitution at the primary C-1 center by acetate and the following internal participation by the substituted group as has been shown in the reaction of 6-O-benzoyl-1,2-O-isopropylidene-5-O-tosyl-D-glucofuranose derivatives under the same conditions[9] (Scheme 1).

Conversion of the (R)-diol (R-4) into the β-lactam intermediate (14) was carried out in 37 % overall yield via 7 steps. Thus, (R-4) was converted into the imide (10), $[\alpha]_D^{22}$ $+14.6^{\circ}$ (c = 1.90, $CHCl_3$), in 78 % yield employing Mitsunobu's conditions[10] via the tritylate (8), $[\alpha]_D^{22}$ -6.18° (c = 2.2, $CHCl_3$). Oxidation of (10) using pyridinium dichromate in dimethylformamide[11] gave the acid (11), $[\alpha]_D^{22}$ $+19.7^{\circ}$ (c = 2.52, $CHCl_3$), in 87 %, which on hydrazinolysis, followed by cyclization[12] gave the β-lactam (13)[13], $[\alpha]_D^{23}$ $+41.7^{\circ}$ (c = 1.04, $CHCl_3$), in 63 % yield via the amino acid (12). Optical purity of (13) caluculated by ^{1}H-mnr spectroscopy using shift reagent $(Pr(tfc)_3)$ was 90 % ee. Hydrogenolysis of (13) furnished the known alcohol (14), $[\alpha]_D^{21}$ $+27.8^{\circ}$ (c = 0.460, MeOH), in 71 % yield, which has been prepared from L-aspartic acid in the synthesis of thienamycin by Merck group[14] (Scheme 2).



Scheme 2

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