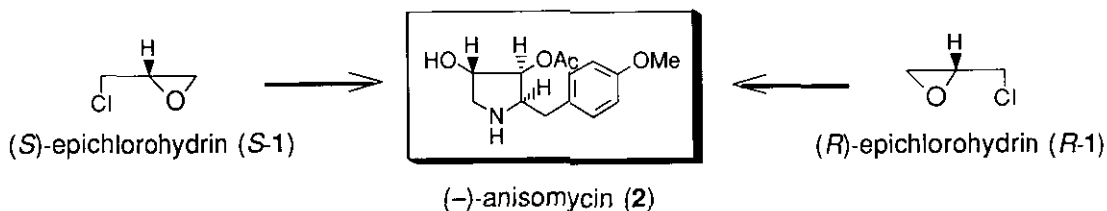


AN ENANTIOCONVERGENT ROUTE TO (-)-ANISOMYCIN FROM BOTH (S)- AND (R)-ENANTIOMERS OF EPICHLOROHYDRIN

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**Abstract** — An enantioconvergent route to (-)-anisomycin, an antibiotic isolated from *Streptomyces* species, has been established starting from both (R)- and (S)-enantiomers of epichlorohydrin.

Although both (S)- and (R)-enantiomers of epichlorohydrin (1) may be obtained from *D*-mannitol,<sup>1</sup> the latter enantiomer became more readily available by recent development of biotechnological method.<sup>2</sup> As a part of our on going project<sup>3</sup> utilizing optically active glycerol derivatives as key chiral building blocks for the construction of a variety of natural products, optically active epichlorohydrin (1) is being used as a chiral glycerol equivalent.<sup>4</sup> We report here a new enantioconvergent synthesis of (-)-anisomycin<sup>5</sup> (2) employing the method utilizable (S)- and (R)-enantiomers of epichlorohydrin (1) as starting material (Scheme 1).

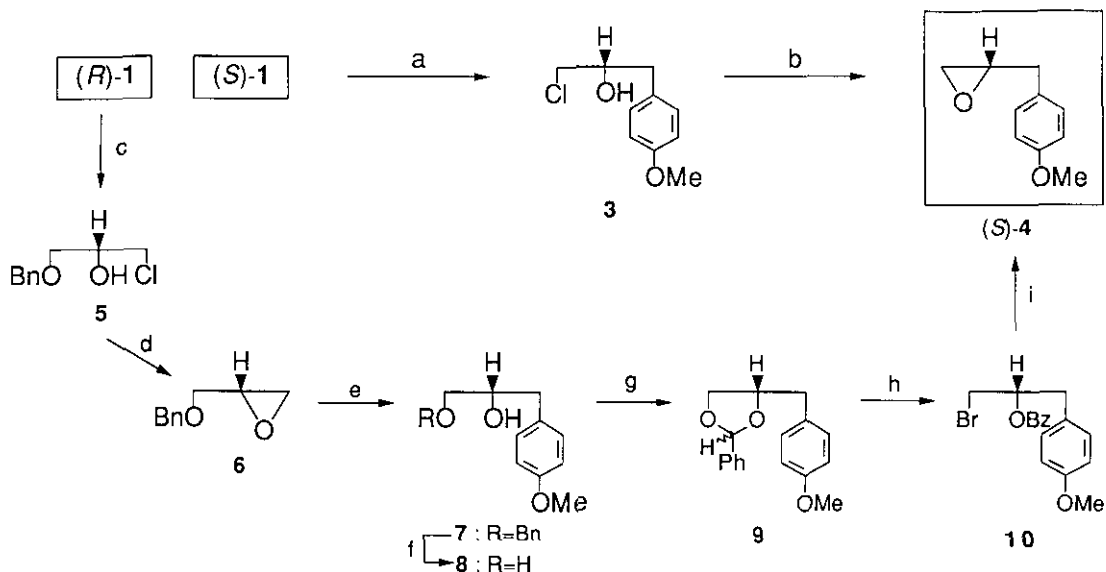


Scheme 1

Treatment of (S)-epichlorohydrin<sup>1</sup> (S-1) with 4-methoxyphenyllithium in the presence of copper(I) cyanide<sup>6</sup> afforded the chlorohydrin 3 which was immediately exposed to methanolic potassium carbonate to give (S)-(4-methoxybenzyl)oxirane (4),  $[\alpha]_D^{23} +0.8^\circ$  (c 1.01,  $\text{CHCl}_3$ ), in 74% overall yield.

On the other hand, (R)-epichlorohydrin<sup>7</sup> (S-1), more readily available counterpart, was first transformed to (R)-O-benzylglycidol<sup>8</sup> (6) in 60% overall yield by treatment with benzyl alcohol in the presence of boron trifluoride etherate followed by alkaline cyclization of the resulted chlorohydrin 5. Then, 6 was treated with *p*-methoxyphenyllithium as above to give the secondary alcohol 7 (98%) which on catalytic debenzoylation furnished the 1,2-glycol (8) (99%). Transformation of 8 into (S)-(4-methoxybenzyl)oxirane (S-4) could be carried out in a satisfactory overall yield by employing a sequence of three steps of reactions which we have

developed.<sup>9</sup> Thus, **8** was first converted into the benzylidene acetal (**9**) which in turn was treated with *N*-bromosuccinimide (NBS) followed by methanolysis of the resulted bromobenzoate (**10**) in the presence of potassium carbonate to afford the epoxide (**S**)-**4** in 67% overall yield (Scheme 2).

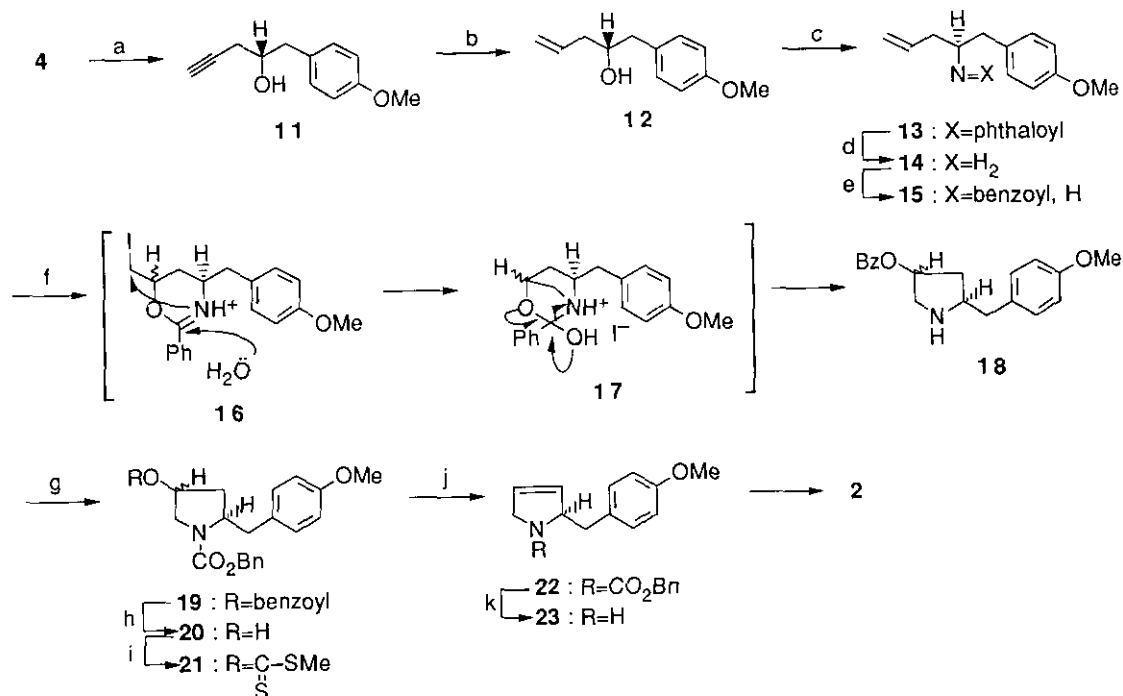


Scheme 2

a, *p*-bromoanisole, <sup>n</sup>BuLi, CuCN, THF, -78 °C; b, K<sub>2</sub>CO<sub>3</sub>, MeOH, r.t.; c, BF<sub>3</sub>·OEt<sub>2</sub>, BnOH, 50 °C; d, NaOH, H<sub>2</sub>O-Et<sub>2</sub>O; e, *p*-bromoanisole, <sup>n</sup>BuLi, CuCN, THF, -78 °C; f, H<sub>2</sub>, Pd(OH)<sub>2</sub>, MeOH; g, PhCHO, *p*-TsoH, benzene, reflux; h, NBS, CCl<sub>4</sub>; i, K<sub>2</sub>CO<sub>3</sub>, MeOH.

Having developed the synthesis of the same epoxide (**S**)-**4** from both enantiomers of epichlorohydrin (**1**), we next attempted its conversion into the key intermediate for the construction of natural (-)-anisomycin (**2**). Treatment of (**S**)-**4** with lithium acetylide ethylenediamine complex<sup>10</sup> afforded the acetylene alcohol<sup>11</sup> **11**,  $[\alpha]_D^{23} +3.84^\circ$  (c 1.04, CHCl<sub>3</sub>), in 85% yield, which was transformed into the vinyl alcohol (**12**),  $[\alpha]_D^{22} -11.1^\circ$  (c 1.06, CHCl<sub>3</sub>), quantitatively, by partial hydrogenation using Lindlar catalyst. Employing the Mitsunobu reaction<sup>12</sup> **12** was transformed into the phthalimide (**13**),  $[\alpha]_D^{26} +147.7^\circ$  (c 1.01, CHCl<sub>3</sub>), with inversion of chirality, which was converted into the benzamide (**15**),  $[\alpha]_D^{22} -6.66^\circ$  (c 0.36, CHCl<sub>3</sub>), in 64% overall yield via the primary amine (**14**) by sequential deacylation and benzoylation (Scheme 3).

When the amide (**15**) was exposed to three equivalents of iodine in aqueous acetonitrile (1:1 v/v) at room temperature,<sup>13,14</sup> slow (3 days) but neat reaction took place to give 2-(4-methoxybenzyl)-4-benzoyloxypyrrolidine (**18**) in 90% yield in a single step as a 2:1 mixture of epimers at C<sub>4</sub>-center. We presume that the reaction proceeded through the initial formation of the dihydro-oxazinium salt (**16**) which was sequentially transformed into the benzoate (**18**) via the bicyclic



Scheme 3

a, lithium acetylide ethylenediamine complex, DMSO, r.t.; b, H<sub>2</sub>, Pd/CaCO<sub>3</sub>, AcOEt; c, phthalimide, diisopropyl azodicarboxylate, PPh<sub>3</sub>, THF, -20 °C; d, H<sub>2</sub>NNH<sub>2</sub>, EtOH, reflux; e, BzCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; f, I<sub>2</sub> (3 equiv), H<sub>2</sub>O-MeCN (1:1); g, BnOCOCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; h, K<sub>2</sub>CO<sub>3</sub>, MeOH; i, CS<sub>2</sub>, NaOH, <sup>n</sup>Bu<sub>4</sub>NHSO<sub>4</sub>, then MeI, benzene; j, ODB, reflux; k, NaOH, (CH<sub>2</sub>OH)<sub>2</sub>, 120 °C.

salt (17) under the conditions as shown in Scheme 3. Without separation the resulted mixture was sequentially N-protected and debenzoylated to give the hydroxy-carbamate (20) which was converted into the xanthate (21) in 87% overall yield. Upon thermolysis<sup>15</sup> in *o*-dichlorobenzene (ODB) at reflux, 21 furnished a 6.2:1 mixture of the 3,4-dehydro- and the 4,5-dehydropyrrolidines from which the desired former isomer (22), mp 49-50 °C, [ $\alpha$ ]<sub>D</sub><sup>24</sup> -190.4° (c 1.0, CHCl<sub>3</sub>), could be obtained in 70% yield after separation by silica gel column chromatography. Alkaline hydrolysis of 22 furnished the known secondary amine (23), [ $\alpha$ ]<sub>D</sub><sup>24</sup> -101.2° (c 1.44, THF) [lit: [ $\alpha$ ]<sub>D</sub> +9.26° (c 0.55, THF) for the enantiomer;<sup>5g</sup> [ $\alpha$ ]<sub>D</sub> -89.3° (c 1.26, THF)<sup>5j</sup>],<sup>16,17</sup> in 89% yield. Since 23 has been converted into natural (-)-anisomycin (2) stereoselectively in good yield,<sup>5g,18</sup> the present synthesis constitutes a formal acquisition of this antibiotic (Scheme 3).

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- 11) During the reaction sequence some depression of enantiomeric integreties was observed. Optical purities of each acetylenic alcohol (11) obtained from (S)- and (R)-epichlorohydrins (1) were determined respectively by measurement of <sup>1</sup>H-nmr (500 MHz) spectra of the corresponding MTPA (both (S)- and (R)) esters: >90% ee from (S)-1 and >88% ee from (R)-1.
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