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

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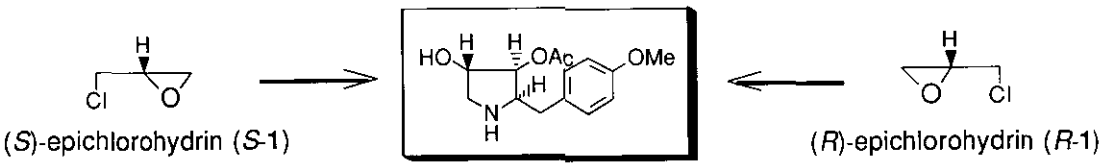
Abstract ——— An enantioconvergent route to (-)-anisomycin, an antibiotic isolated from Streptomyces species, has been established starting from both (R)- and (S)-enantiomers of epichlorohydrin.

Although both (S)- and (R)-enantiomers of epichlorohydrin (**1**) may be obtained from *D-mannitol*,[1] the latter enantiomer became more readily available by recent development of biotechnological method.[2] As a part of our on going project[3] 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.[4] We report here a new enantioconvergent synthesis of (-)-anisomycin[5] (**2**) employing the method utilizable (S)- and (R)-enantiomers of epichlorohydrin (**1**) as starting material (Scheme 1).

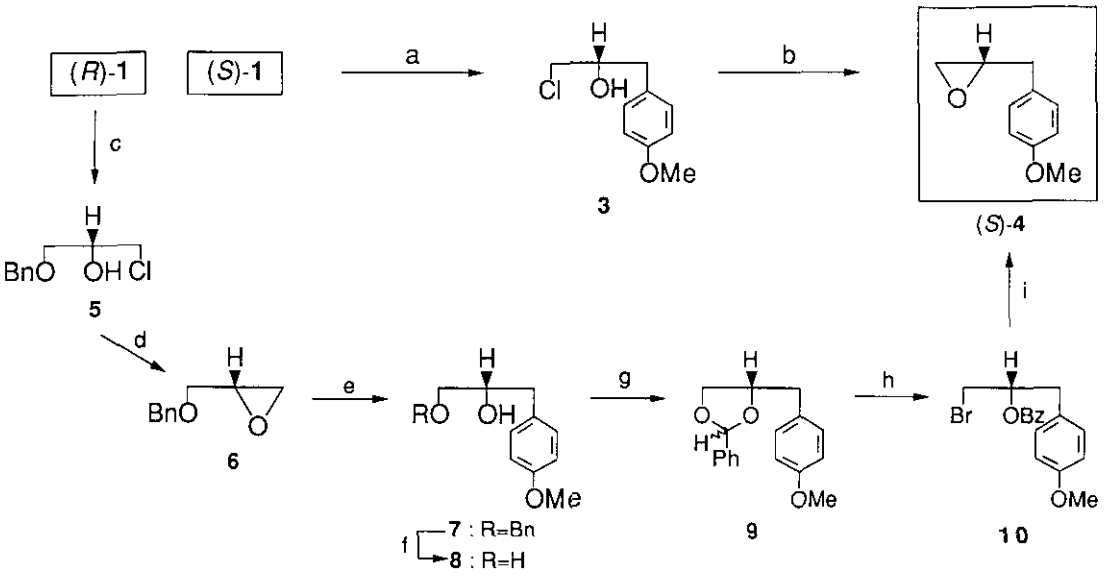


(–)-anisomycin (**2**)

Scheme 1

Treatment of (S)-epichlorohydrin[1] (S-**1**) with 4-methoxyphenyllithium in the presence of copper(I) cyanide[6] afforded the chlorohydrin **3** which was immediately exposed to methanolic potassium carbonate to give (S)-(4-methoxybenzyl)oxirane (**4**), $[\alpha]_D^{23}$ +0.8° (c 1.01, $CHCl_3$), in 74% overall yield.
On the other hand, (R)-epichlorohydrin[7] (S-**1**), more readily available counterpart, was first transformed to (R)-O-benzylglycidol[8] (**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 debenzylation 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.[9] 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).

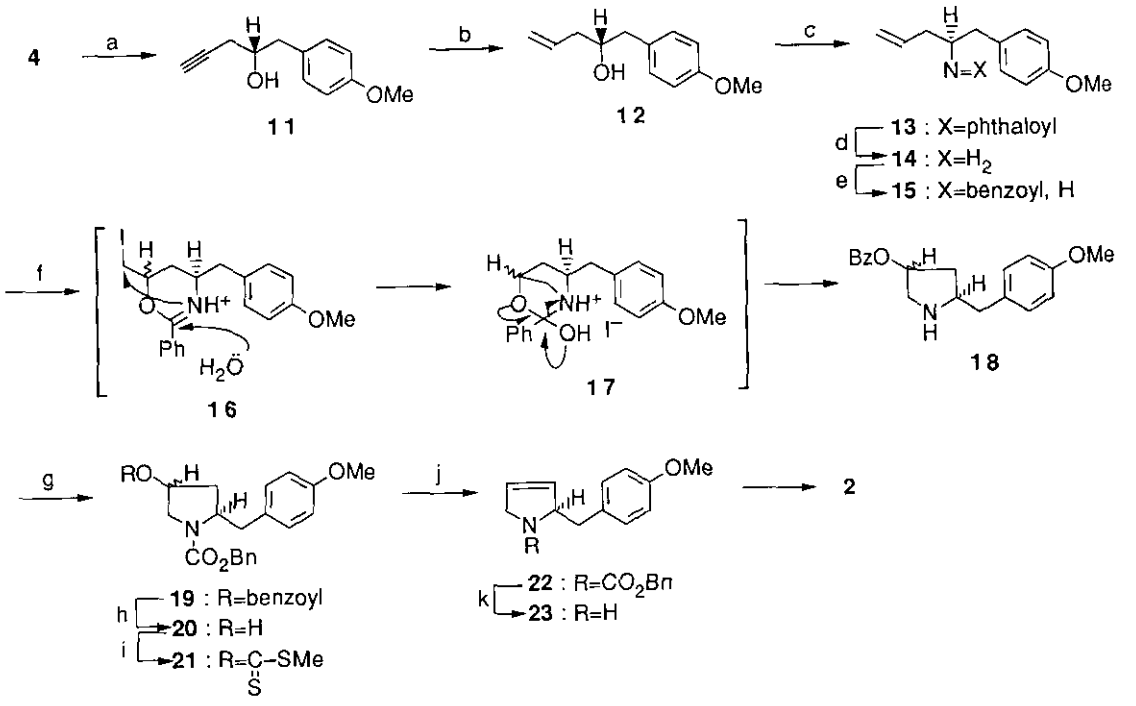


Scheme 2

a, p-bromoanisole, ^{n}BuLi, CuCN, THF, -78 °C; b, K_2CO_3, MeOH, r.t.; c, $BF_3{\cdot}OEt_2$, BnOH, 50 °C; d, NaOH, H_2O-Et_2O; e, p-bromoanisole, ^{n}BuLi, CuCN, THF, -78 °C; f, H_2, $Pd(OH)_2$, MeOH; g, PhCHO, p-TsOH, benzene, reflux; h, NBS, CCl_4; i, K_2CO_3, 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[10] afforded the acetylene alcohol[11] **11**, $[\alpha]_D^{23}$ +3.84° (c 1.04, $CHCl_3$), in 85% yield, which was transformed into the vinyl alcohol (**12**), $[\alpha]_D^{22}$ -11.1° (c 1.06, $CHCl_3$), quantitatively, by partial hydrogenation using Lindlar catalyst. Employing the Mitsunobu reaction[12] **12** was transformed into the phthalimide (**13**), $[\alpha]_D^{26}$ +147.7° (c 1.01, $CHCl_3$), with inversion of chirality, which was converted into the benzamide (**15**), $[\alpha]_D^{22}$ -6.66° (c 0.36, $CHCl_3$), 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,[13,14] 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_4-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_2, $Pd/CaCO_3$, AcOEt; c, phthalimide, diisopropyl azodicarboxylate, PPh_3, THF, -20 °C; d, H_2NNH_2, EtOH, reflux; e, BzCl, Et_3N, CH_2Cl_2; f, I_2 (3 equiv), H_2O-MeCN (1:1); g, BnOCOCl, Et_3N, CH_2Cl_2; h, K_2CO_3, MeOH; i, CS_2, NaOH, $^nBu_4NHSO_4$, then MeI, benzene; j, *ODB*, reflux; k, NaOH, $(CH_2OH)_2$, 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[15] 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, $[\alpha]_D$ -190.4° (c 1.0, $CHCl_3$), could be obtained in 70% yield after separation by silica gel column chromatography. Alkaline hydrolysis of **22** furnished the known secondary amine (**23**), $[\alpha]_D^{24}$ -101.2° (c 1.44, THF) [lit: $[\alpha]_D$ +9.26° (c 0.55, THF) for the enantiomer;[5g] $[\alpha]_D$ -89.3° (c 1.26, THF)[5j]],[16,17] in 89% yield. Since **23** has been converted into natural (-)-anisomycin (**2**) stereoselectively in good yield,[5g,18] the present synthesis constitutes a formal acquisition of this antibiotic (Scheme 3).

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7) (R)-Epichlorohydrin (R-**1**), $[\alpha]_D^{25}$ -33.23° (c 5.81, MeOH) (>98% ee) was used. We appreciate DAISO Co. Ltd. for kind donation of a substantial amount of (R)-epichlorohydrin (R-**1**).

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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 ^{1}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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16) Apparent large difference of $[\alpha]_D$ values between the preceding syntheses [5g and 5j] has been pointed out by the latter authors.

17) ^{1}H-Nmr spectrum (500 MHz) was identical with that reported in the preceding syntheses.[5g,18]

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Received, 30th June, 1989