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AN ALTERNATIVE CHIRAL ROUTE TO SULCATOL

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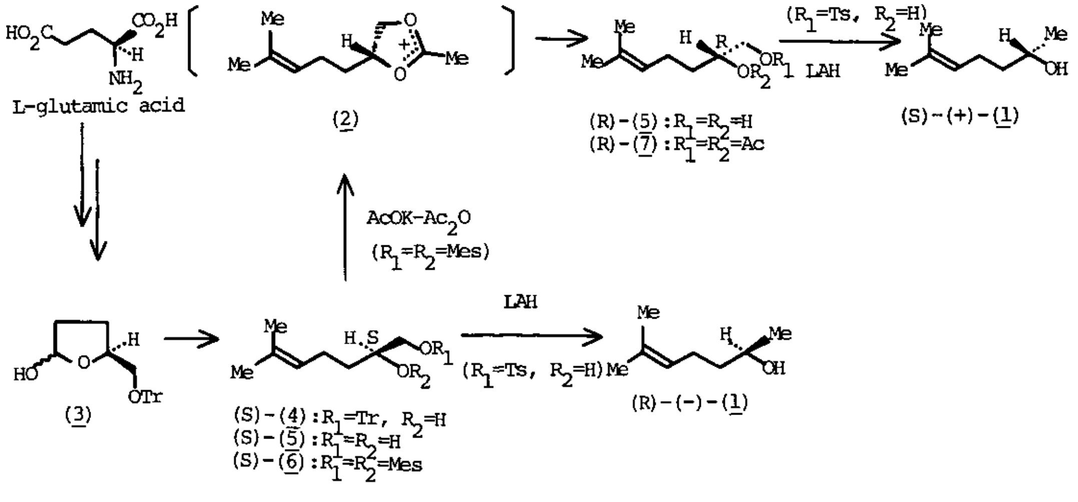
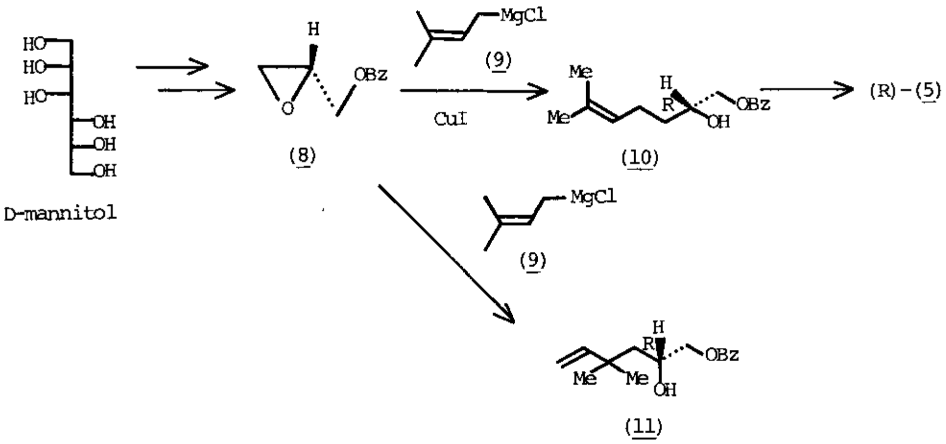
Abstract-----A key intermediate [(R)-(5)] for the enantioselective synthesis of both enantiomers of sulcatol (1), the aggregation pheromone of Gnathotrichus sulcatus, has been prepared from (S)-benzyl 2,3-epoxypropyl ether (8).

Recently, we developed an efficient enantioselective synthesis producing both enantiomers of sulcatol (1)[1], the aggregation pheromone of Gnathotrichus sulcatus and found as a 35(R) : 65(S) mixture of enantiomers in nature[2], utilizing a single chiral precursor [(S)-(5)] via the novel chirality inversion reaction[3,4] (Scheme 1). The method involved the solvolysis of the dimesylate [(S)-(6)] derived from the 1,2-diol [(S)-(5)] which allowed the efficient inversion of the secondary chiral center presumably by an anchimeric assistance of the acetoxy group substituted faster at the primary center to furnish the diacetate [(R)-(7)] via the transient intermediate (2) in excellent optical and chemical yields. We report herein an efficient method for preparation of the key diol [(R)-(5)] using (S)-benzyl 2,3-epoxypropyl ether (8)[3,5] as a chiral starting material.



Scheme 1

Since it has been reported that the reaction of Grignard reagents from unsymmetrical allylic halides shows the tendency to react at the internal carbon of the allylic system rather than at the terminal carbon without adding the copper catalyst$^{6-8}$, (S)-benzyl 2,3-epoxypropyl ether (8), obtained readily from D-mannitol^{3,5}, was reacted with prenylmagnesium chloride (9) in the presence of cuprous iodide. The reaction proceeded as expected to give the desired (R)-glycol monobenzyl ether (10) in an excellent yield. In absence of the copper catalyst, the reaction occurred at the internal position of the allylic system exclusively as reported to give the isomeric (R)-glycol monobenzyl ether (11) in an excellent yield. The former ether (10), upon reduction with lithium metal in liquid ammonia in the presence of ethanol as a proton donor, furnished the desired key intermediate [(R)-(5)], $[\alpha]_D$+18.46°, in 95.7% yield. Although we did not attempt the conversion with respect to the (R)-enantiomer [(R)-(5)] thus obtained, the same chirality inversion could be expected from the stereochemical outcome observed with its (S)-counterpart [(S)-(5)]^{1}.



Scheme 2

EXPERIMENTAL SECTION

IR spectra were measured with a JASCO A-102 spectrophotometer, NMR spectra with a JOEL PMX-60 spectrometer using tetramethylsilane as an internal reference, mass spectra with a JOEL JMX-D300 spectrometer, and optical rotations with a JASCO DIP-4 digital polarimeter.

(R)-Benzyl 2-Hydroxy-6-methylhept-5-enyl Ether (10) A solution of prenylmagnesium chloride (9), prepared from Mg 380mg (16.5mg atom) and prenyl chloride 1.57g (15.0mmol) in anhydrous THF (10ml), was added dropwise to a suspension of CuI 286mg (1.5mmol) in anhydrous THF (20ml) with stirring at -78°C under nitrogen and the stirring was continued for 10 min at the same temperature. To a stirred mixture, a solution of (S)-benzyl 2,3-epoxypropyl ether (8) 1.26g (7.7mmol) in anhydrous THF (5ml) was added dropwise at -78°C. After 10 min, a cooling bath was removed to raise reaction temperature gradually (ca. 30 min) to -15°C and the reaction was quenched by an addition of sat. aq. NH_4Cl. The mixture was filtered using Celite and the filtrate was evaporated under reduced pressure. The residue was taken into CH_2Cl_2, and the organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and evaporated under reduced pressure. The remaining oil was filtered through a silica gel column (n-hexane-AcOEt=4:1) to give a pure material, 1.63g (90.6%); $bp_{0.015}$ 95-100°C (Kugelrohr); $[\alpha]_D$+1.2° (c=9.172, MeOH); IR (neat) ν cm^{-1}: 3430, 1100; NMR ($CDCl_3$) δ: 1.25-1.70 (2H, m), 1.60 (3H, s), 1.67 (3H, s), 1.90-2.35 (2H, br.q), 2.47 (1H, br.s), 3.15-3.63 (2H, m), 3.65-4.05 (1H, m), 4.50 (2H, s), 5.10 (1H, br.t), 7.30 (5H, s); MS m/e: 234 (M^+), 91 (100%); Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.86; H, 9.56.

(R)-Benzyl 2-Hydroxy-4,4-dimethylhex-5-enyl Ether (11) To a solution of prenylmagnesium chloride (9), prepared from Mg 380mg (16.5mg atom) and prenyl chloride 1.57g (15.0mmol) in anhydrous THF (10ml), was added dropwise a solution of (S)-benzyl 2,3-epoxypropyl ether (8) 1.26g (7.7mmol) in anhydrous THF (10ml) with stirring at 0°C and the stirring was continued for 1 h at the same temperature. The reaction was quenched by an addition of sat. aq. NH_4Cl and the organic layer separated was evaporated under reduced pressure. The residue was taken into CH_2Cl_2, and the organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and evaporated under reduced pressure. The remaining oil was filtered through a silica gel column (n-hexane-Et_2O=4:1) to give a pure material, 1.61g (89.4%); $bp_{0.01}$100-105°C (Kugelrohr); $[\alpha]_D$+0.254° (c=7.872, MeOH); IR (neat) ν cm^{-1}: 3480, 1640, 1100, 910; NMR ($CDCl_3$) δ: 1.05 (6H, s), 1.35-1.55 (2H, m), 2.30 (1H, br.s), 3.20-3.50 (2H, m), 3.70-4.10 (1H, m), 4.52 (2H, s), 4.75-5.15 (2H, m), 5.88 (1H, dd, J=18, 10Hz), 7.28 (5H, s); MS m/e: 234 (M^+), 91, 69 (100%); Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.84; H, 9.26.

(R)-2-Hydroxy-6-methylhept-5-enol [(R)-(5)] Into a flask containing a solution of (10) 1.14g (4.87mmol) in anhydrous EtOH (1ml) ammonia (ca. 60ml) was condensed. To a mixture lithium (ca. 120mg) was added portionwise until the blue color persisted for 30 min. The reaction was quenched by addition of solid NH_4Cl and ammonia was evaporated. The residue was treated with sat. aq. NaCl and was extracted with CH_2Cl_2. The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and evaporated under reduced pressure. The remaining oil was filtered through a silica gel column ($CHCl_3$-MeOH=97:3) to give a pure material, 670mg (95.7%); $bp_{0.03}$85-90°C (Kugelrohr); $[\alpha]_D$+18.46° (c=4.96, EtOH) (lit.[1] for (S)-enantiomer; $[\alpha]_D$-17.8° (c=4.47, EtOH)). Spectral data were identical with those of an authentic material obtained from L-glutamic acid[1].

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