AN ALTERNATIVE SYNTHESIS OF (S)-(+)-γ-HYDROXYMETHYL-γ-BUTYROLACTONE FROM (D)-(+)-MANNITOL

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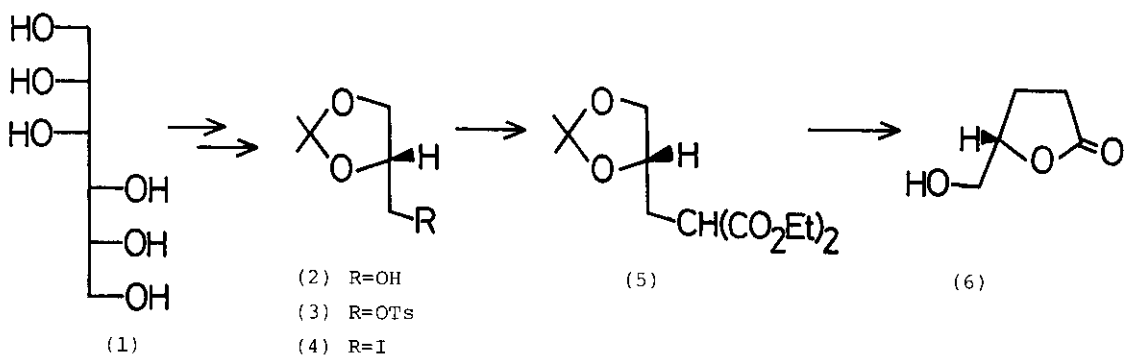
Abstract-----(S)-(+)-γ-Hydroxymethyl-γ-butyrolactone(6), which has been obtained from (S)-glutamic acid, is synthesized alternatively starting from (D)-(+)-mannitol(1).

Both (S)-(+)- and (R)-(-)-γ-hydroxymethyl-γ-butyrolactone derivatives have been widely used in the enantioselective synthesis of various natural products as chiral building blocks[1]. Both of the enantiomers have been obtained conveniently from glutamic acid[1b,2] with the corresponding chirality, though the formation of the enantiomers with (R)-(-)-configuration required use of less available unnatural (D)-glutamic acid as the progenitor. Recently we have developed new methodologies obtaining the less available lactones with (R)-(-)-configuration by the inversion reaction[3] and by using readily accessible (D)-(+)-mannitol(1) as starting material[4]. In relation to the latter methodology we describe here a complementary work which allows efficient synthesis of (S)-(+)-γ-hydroxymethyl-γ-butyrolactone(6) from a common progenitor, (D)-(+)-mannitol.

Treatment of (S)-glycerol 1,2-acetonide[4](2), obtained from (D)-mannitol(1) via a 3 step sequence with p-toluenesulfonyl chloride in pyridine gave the tosylate[5,6](3) in 96.6 % yield as half crystals. The tosylate(3) was then converted into the iodide[6](4) with sodium iodide in refluxing acetone. Reaction of the iodide(4) with diethyl malonate in dimethyl formamide in the presence of sodium hydride afforded the alkylated product[1h,7](5) in 50.1 % overall yield from the tosylate(3). To our surprise the compound(5) upon treatment with an equimolar amount of magnesium chloride[6,9] in refluxing dimethyl acetamide[4] furnished (S)-(+)-γ-hydroxymethyl-γ-butyrolactone(6) of excellent optical purity in one stage in 95 % yield with spontaneous loss of the ethoxycarbonyl and the acetonide groups.

In consequence it can now be said that we have developed an efficient methodology making production of both enantiomers of the lactone(6) from a single chiral progenitor, (D)-(+)-mannitol(1) possible, as the synthesis of the (R)-(-)-lactone from the same starting material has been reported in the preceding report[4].



(1) (2) R=OH (3) R=OTs (4) R=I (5) (6)

EXPERIMENTAL SECTION

All reactions were carried out under argon. Melting points are not corrected. IR spectra were measured with a Shimadzu IR 400 spectrometer and ^{1}H-NMR spectra were measured with a JEOL-PMX 60 spectrometer using tetramethylsilane as an internal reference. Mass spectra were measured with a JEOL-D300 spectrometer. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter.

(S)-(-)-4-(2-Dicarbethoxyethyl)-2,2-dimethyl-1,3-dioxolane(5) A solution of ethyl malonate(3.76 ml, 24.79 mmol) in 20 ml of N,N-dimethylformamide(DMF) was added to a slurry of hexane-washed sodium hydride(1.19 g, 24.79 mmol) in 20 ml of DMF at room temperature with stirring. After 15 min a solution of the iodide(4) (5.0 g, 20.66 mmol) in 20 ml of DMF was added and the mixture was heated at 100 °C for 3 hr with stirring. After cooling, the reaction mixture was treated with satulated NH_4Cl and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo to give a colorless oil. Purification by a Kugelrohr distillation(110-120 °C, 0.4 Torr) gave pure(5) as a colorless oil: yield 3.55 g(62.7 %); $[\alpha]_D$ -6.23°(C=3.79, MeOH); IR ν_{max}^{neat}(cm^{-1}) 1720; NMR($CDCl_3$) δ 1.2-1.5(12H, m), 2.05-2.5(2H, m), 3.5-3.8(2H, m), 4.0-4.5(6H, m); MS(m/e) 259(M^+-CH_3), 171, 72, 43(100 %).

Anal. Calcd for $C_{13}H_{22}O_6$ C, 56.92; H, 8.08. Found: C, 57.13; H, 8.29.

(S)-(+)-γ-Hydroxymethyl-γ-butyrolactone(6) A mixture of (5)(1 g, 3.65 mmol) and $MgCl_2 \cdot 6H_2O$(0.74 g, 3.65 mmol) in N,N-dimethyl acetamide(10 ml containing 2 drops of H_2O) was refluxed for 20 hr with stirring. After cooling, the solvent was removed under reduced pressure and then the residue was purified by a silica gel column chromatography to give an oil. Further purification by a Kugelrohr distillation gave pure(6) as a colorless oil: yield 0.40 g(95 %); bp 170-200 °C(11 Torr)(lit.[1b] bp 131-147 °C(7 Torr)); $[\alpha]_D$ +33.6°(C=3.16, EtOH)(lit.[1b] $[\alpha]_D$ +31.3°(C=2.92, EtOH)).

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9. Both chemical and optical yields were not much changed by amount of the catalyst used, though reaction time was greatly affected(5 equimol-2h; 0.5 equimol-48h; 0.1 equimol-very slow).

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