Efficient Synthesis of (R)-(-)-γ-Benzyloxymethyl-γ-butyrolactone from (D)-(+)-Mannitol

Seiichi TAKANO*, Emiko GOTO, Michiyasu HIRAMA, Kunio OGASAWARA
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract-----Efficient synthesis of (R)-(-)-γ-benzyloxymethyl-γ-butyrolactone(10) has been developed using (D)-(+)-mannitol(1) as starting material.

In recent years either (R)-(-)- and (S)-(+)- enantiomers of γ-hydroxymethyl-γ-butyrolactone derivatives have become of interest as valuable intermediates in the synthesis of various optically active natural products including carbohydrates[1], terpenes[2], lignans[3], and alkaloids[4]. Although they are synthesized most conveniently from glutamic acid with the corresponding chirality[1b,5], preparation of the enantiomer with (R)-configuration necessitates using the expensive unnatural (R)-glutamic acid as starting material. In connection with our recent chiral syntheses in indole alkaloid field[4], we have developed an alternative synthesis of (R)-(-)-γ-benzyloxymethyl-γ-butyrolactone(10) of high optical purity starting from naturally abundant and inexpensive (D)-mannitol(1).

The present synthesis consists a two step sequence from the known epoxide[7](8), however there includes some improvements for large scale preparation of (8), especially in treatments of highly racemizable(3) and water soluble(4) intermediates. Thus, cleavage of (D)-mannitol-1,2:5,6-diacetonide[8](2), obtained from (D)-mannitol (1), with sodium metaperiodate[9] in methanol containing a minimum amount of water, followed by reduction of the reaction mixture, which contained the highly racemizable product(3), with sodium borohydride in the same flask furnished the alcohol(4) in excellent yield with high optical purity. The overall yield of (S)-glycerol 1,2-acetonide(4) $[\alpha]_D$ +11.4° from (D)-mannitol-1,2:5,6-diacetonide(2) after distillation was 81 %. According to the literature procedure[9] (4) was converted into (R)-1-benzylglycerol(6) in overall 77 % yield through phase transfer catalyzed benzylation,

followed by acid catalyzed deacetonization. The diol(6) on selective esterification with p-toluenesulfonyl chloride(1 equimol) in pyridine, followed by treating with sodium methoxide[7b], gave (S)-1-benzyloxy-2,3-epoxypropane(8) in 97.5 % yield.

Reaction of (8) with diethyl malonate in ethanol in the presence of sodium ethoxide[2c] furnished the α-carbethoxy-γ-butyrolactone derivative (9) as a mixture of epimers in 84 % yield which on reflux with magnesium chloride[10] in wet dimethyl acetamide underwent smooth decarbethoxylation to give (R)-(-)-γ-benzyloxymethyl-γ-butyrolactone(10) $[\alpha]_D$ -18.5° of good optical purity in 90 % yield. Overall yield of the (R)-(-)-γ-benzyloxymethyl-γ-butyrolactone(10) from (D)-mannitol-1,2:5,6-diacetonide(2) via 8 steps was 46 %.

EXPERIMENTAL SECTION

All the reactions were carried out under Ar or N_2 atmosphere. IR spectra were measured with a Shimadzu IR-400 spectrometer. ^{1}H-NMR spectra were measured in $CDCl_3$ with a JEOL-PMX60 spectrometer using TMS as an internal reference. Mass spectra were measured with a JEOL-D300 spectrometer. Optical rotations were measured with a JASCO-PTP-SL automatic polarimeter.

(S)-(+)-Glycerol 1,2-acetonide(4) To a solution of (D)-mannitol-1,2:5,6-diacetonide[8](2)(32 g, 0.122 mol) in MeOH(150 ml) containing 5 % $NaHCO_3$ soln(40 ml) was added a saturated solution of $NaIO_4$(37.4 g, 0.174 mol in ca 130 ml of water) at 0 °C with stirring. After stirring at the same temperature for 1 h, the reaction mixture containing the aldehyde(3) was treated with $NaBH_4$(9.44 g, 0.25 mol) at 0∿10 °C with stirring. After the reduction was completed, MeOH(ca 150 ml) was added to the reaction mixture and the inorganic precipitate formed was removed by filtration using Celite. The filtrate was evaporated and the remaining water was stripped as the benzene azeotrope. The residue was extracted with ether, dried over Na_2SO_4, and evaporated to give the crude alcohol(4) which was purified by distillation: yield 26.2 g(81.3 %); bp 86∿87 °C/ 16 Torr(lit. bp 80∿90 °C/ 20 Torr); $[\alpha]_D$ +11.4°(C 5.29, MeOH)(lit.[7a] $[\alpha]_D$ +11.3°(C 5.175, MeOH).

(R)-(+)-1-Benzylglycerol(6) The alcohol(4)(20 g, 0.152 mol) was treated with benzyl bromide(32.4 ml, 0.272 mol) as described in ref. 9 using benzyltriethylammonium chloride(0.93 g) as a phase transfer catalyst[11] to give crude (R)-1-benzylglycerol(5), which without purification was refluxed with 1.5N H_2SO_4(120 ml) for 5 h to give (R)-(+)-1-benzylglycerol(6) after distillation: yield 21.3 g(77.2 % from (4)); bp 110∿120 °C/ 0.15 Torr(lit. 134 °C/ 0.6 Torr); $[\alpha]_D$ +3.71°(C 19.9, $CHCl_3$)(lit.[9]

$[\alpha]_D$ +5.72°(neat)).

(S)-(-)-Benzyl 2,3-epoxypropyl ether(8) To an ice-cooled solution of (6) (15.35 g, 84 mmol) in pyridine(45 ml) was added p-toluenesulfonyl chloride(16.0 g, 84 mmol) with stirring. After stirring for 1.5 h pyridine was removed by using a rotary pump and the residue was extracted with ether. The extract was washed throughly with 1N HCl, followed by 5 % $NaHCO_3$, dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the crude monotosylate(7), 23.8 g(84.1 % yield).

To a solution of the crude(7)(9.48 g, 28.2 mmol) in a mixture of MeOH(30 ml) and ether(15 ml) was added Na(0.65 g, 28.2 mmol) portionwise at 0 °C with stirring. After stirring for 2 h at the same temperature, CO_2 gas was introduced to the reaction mixture and water was then added and the reaction mixture was extracted with $CHCl_3$. The extract was washed, dried(Na_2SO_4), and the solvent was removed under reduced pressure to give the crude epoxide(8) which on purification by a silica gel chromatography gave the pure(8)(4.52 g, 97.5 %); $[\alpha]_D$ +1.79°(C 5.02, $CHCl_3$), -11.7°(neat) (lit.[7b] $[\alpha]_D^{21°}$ -15.3°(neat)).

(R)-(-)-γ-Benzyloxymethyl-(R/S)-α-carbethoxy-γ-butyrolactone(9) To a solution of NaOEt(prepared from Na(0.40 g, 0.0174 atom)) in EtOH(13 ml) was added diethyl malonate(2.84 ml, 18.7 mmol), followed by the epoxide(8)(2.4 g, 14.6 mmol) in EtOH(5 ml) dropwise at room temperature with stirring. After refluxing for 1 h, the reaction mixture was treated with 5 % HCl and was extracted with CH_2Cl_2 and the extract was washed with water, dried over Na_2SO_4. The solvent was removed under reduced pressure to leave the crude(9) which on purification by a silica gel chromatography to give the pure(9): yield 3.42 g(84 %); bp 180 °C/ 0.37 Torr; $[\alpha]_D$ -21.8° (C 5.16, MeOH); IR ν_{max}^{neat} (cm^{-1}) 1765, 1725; NMR($CDCl_3$) δ 7.6∿7.3(5H, m), 5.0∿4.7 (1H, m), 4.63(2H, d, J=2 Hz), 4.3(2H, q, J=7 Hz), 3.9∿3.6(3H, m), 2.9∿2.3(2H, m), 1.3(3H, t, J=7 Hz); MS(m/e) 279(M^++1), 278(M^+), 250, 172, 154, 129, 126, 111, 91 (100 %). Anal. Calcd for $C_{15}H_{18}O_5$ C, 64.73; H, 6.52. Found: C, 64.61; H, 6.47.

(R)-(-)-γ-Benzyloxymethyl-γ-butyrolactone(10) A mixture of (9)(2.0 g, 7.2 mmol) and $MgCl_2 \cdot 6H_2O$(7.3 g, 36 mmol) in dimethyl acetamide(16 ml containing 3 drops of H_2O) was refluxed for 2 h with stirring. After cooling, the reaction mixture was extracted with benzene and the extract was washed throughly with water and was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was distilled using a rotary pump to give the pure(10): yield 1.33 g(89.7 %); bp 160∿ 170 °C/ 0.4∿0.6 Torr(lit.[1b] bp 160∿164 °C/ 0.02 Torr); $[\alpha]_D$ -18.5°(C 5.18, EtOH)

(lit.[1b] $[\alpha]_D^{15°}$ +18.1°(C 2.70, EtOH).

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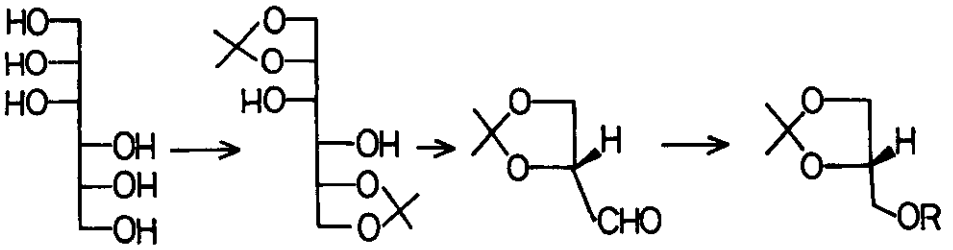
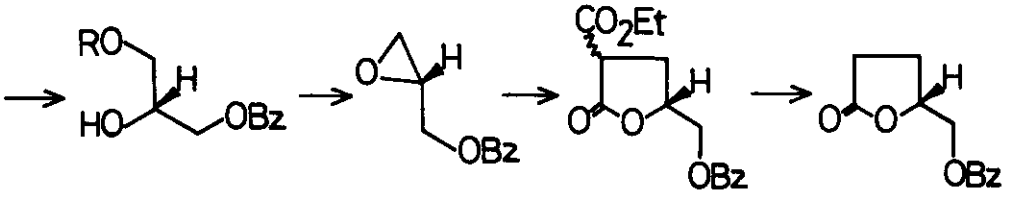


1 2 3 4: R=H

5: R=Bz



6: R=H 8 9 10

7: R=Ts

REFERENCES AND NOTES

1) (a) K. Koga, M. Taniguchi, and S. Yamada, Tetrahedron Lett., 263 (1971); (b) M. Taniguchi, K. Koga, and S. Yamada, Tetrahedron, 30, 3547 (1974); (c) M. Taniguchi, K. Koga, and S. Yamada, Chem. Pharm. Bull., 22, 2318 (1974).

2) (a) S. Iwaki, S. Marumo, T. Saito, M. Yamada, and K. Katagiri, J. Amer. Chem. Soc., 96, 7872 (1974); (b) K. Mori, Tetrahedron Lett., 2187 (1975); (c) K. Mori, Tetrahedron, 32, 1101 (1975); (d) K. Mori, Tetrahedron, 31, 3011 (1975); (e) U. Ravid and R.M. Silverstein, Tetrahedron Lett., 423 (1977); (f) U. Ravid, R.M. Silverstein, and L.R. Smith, Tetrahedron, 34, 1449 (1978); (g) L.R. Smith, H.J. Williams, and R.M. Silverstein, Tetrahedron Lett., 3231 (1978).

3) (a) K. Tomioka, H. Mizuguchi, and K. Koga, Tetrahedron Lett., 4687 (1978); (b) K. Tomioka, H. Mizuguchi, and K. Koga, Tetrahedron Lett., 1409 (1979); (c) K. Tomioka and K. Koga, Tetrahedron Lett., 3315 (1979); (d) K. Tomioka, T. Ishiguro, and K. Koga, J.C.S. Chem. Commun., 652 (1979); (e) K. Tomioka, and K. Koga, Heterocycles, 12, 1523 (1979); (f) K. Tomioka, T. Ishiguro, and K. Koga, Tetrahedron Lett., 21, 2973 (1980); (g) J.P. Robin, O. Gringore, and E. Brown, Tetrahedron Lett., 21, 2709 (1980).

4) (a) S. Takano, K. Chiba, M. Yonaga, and K. Ogasawara, J.C.S. Chem. Commun., 616 (1980); (b) S. Takano, M. Yonaga, K. Chiba, and K. Ogasawara, Tetrahedron Lett., 21, 3697 (1980).

5) Cf. L.R. Smith and H.J. Williams, J. Chem. Ed., 56, 696 (1979).

6) We have recently developed an efficient method converting (S)-(+)-γ-trityloxymethyl-γ-butyrolactone into the (R)-(-)-counterpart in an excellent yield both chemically and optically: S. Takano, M. Yonaga, and K. Ogasawara, to be published.

7) (a) M.M. Baizer, J.R. Clark, and J. Swidinsky, J. Org. Chem., 22, 1595 (1957). (b) A.K.M. Anisuzzaman, and L.N. Owen, J. Chem. Soc.(C), 1021 (1967).

8) E. Baer, Biochemical Preparations, 2, 31 (1952).

9) B.T. Golding and P.V. Ioannou, Synthesis, 423 (1977).

10) Cf. T. Sano, J. Toda, N. Kashiwaba, Y. Tsuda, Abstract Paper, 23rd Symposium of the Chemistry of Natural Products(Nagoya, 1980), p.343. Instead of using dimethyl sulfoxide as solvent which was described in the original report, we used dimethyl acetamide, thereby simplifying the isolation procedure.

11) In the original procedure[9], benzyltri-n-butylammonium bromide was used as a phase transfer catalyst.

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