Preparation of Derivtives of (*R*)-1,2,4-Butanetriol from L-Ascorbic Acid

Kin-Chun Luk,* Chung-Chen Wei

Hoffmann-La Roche, Inc., Anti-Infective Chemistry, Chemistry Research Department, Nutley, NJ 07110, USA

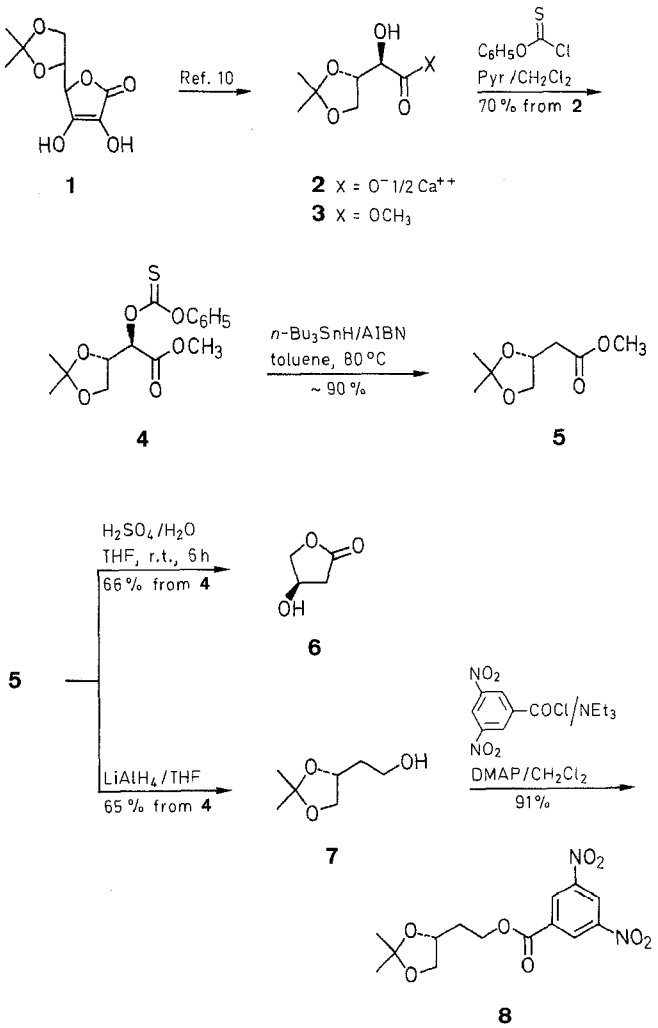
Methyl 3,4-*O*-isopropylidene L-threonate (**3**), obtained from L-ascorbic acid, was converted to its *O*-phenyl thiocarbonate **4**. Deoxygenation of **4** with tri-*n*-butyltin hydride gave the protected 3,4-dihydroxybutanoate **5**, which was converted to the (*R*)-1,2,4-butanetriol derivatives **6** and **7**.

Optically pure 1,2,4-butanetriol and a variety of derived analogues have proven useful as chiral starting materials in synthesis. For example, (+)-ipsdienol,[1] and fragments of okadaic acid[2] have been prepared from the *R*-series, while the *S*-series served as precursors in the synthesis of mevinolin,[3] compactin,[3] (*S*)-3-piperidinol,[4] tulipalin B,[5] avermectin $B_{1\alpha}$ aglycone,[6] dihydroxypentyluracil,[7] and Samuelsson's HETE.[8] To date, all reported preparations of 1,2,4-butanetriol and its derivatives have started from malic acid. Thus, in order to obtain the *R*-series, the expensive (*R*)-malic acid was required as starting material. Here an alternative route to a number of derivatives of (*R*)-1,2,4-butanetriol from inexpensive L-ascorbic acid (Vitamin C) is reported.[9]

The isopropylidene derivative **1**, obtainable from L-ascorbic acid in quantitative yield,[10] was converted to calcium 3,4-*O*-isopropylidene-L-threonate (**2**) (78% yield), and esterified to afford methyl 3,4-*O*-isopropylidene-L-threonate (**3**) in accord with known procedures.[10,11] Acylation of **3** with *O*-phenyl carbonochloridothioate[12] gave **4** in a 70% overall yield from **2**. Deoxygenation of **4** with tri-*n*-butyltin hydride[13] afforded **5** in greater than 90% isolated yield. Although the methyl ester **5** so obtained was contaminated with traces of phenol and tin-containing impurities which could be removed by chromatography, it was used in the subsequent steps without further purification. Treatment of **5** with aqueous acid led to the expected hydroxylactone **6** (66% from **4**), while reduction of **5** with lithium aluminum hydride gave the protected butanetriol **7** (65% from **4**).

The ^{1}H-NMR spectrum of **7** in the presence of tris-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) shift reagent as well as the formation of a single 3,5-dinitrobenzoate (**8**)[14] demonstrated that **7** was free of any 2,4-isopropylidene isomer.

The facile synthesis of **7** is of particular note, since except for a recent procedure which utilized enzymatic hydrolysis of (*S*)-malic acid diesters,[5] the reported preparation of **7** has required separation from the 2,4-*O*-isopropylidene isomer (41% from the mixture[14] and 33% overall from malic acid[3]). Recently, it has been shown that by utilization of a cyclohexylidene protecting group, pure (*S*)-1,2-*O*-cyclohexylidene-1,2,4-butanetriol can be isolated from the mixture of 1,2- and 2,4-isomers in 61% yield (51% from (*S*)-malic acid).[15] The procedure described in this report for the preparation of (*R*)-1,2-*O*-isopropylidene-1,2,4-butanetriol (**7**), obviates the need for this separation. Thus we have demonstrated that compounds **6** and **7**, both useful precursors from the chiral pool, can be readily prepared in six steps from L-ascorbic acid in an overall yield of 35%.[16]



Melting points were performed on a Thomas model 40 Micro Hot Stage melting point apparatus and are uncorrected. IR spectra were recorded on a Digilab FTS 14 spectrometer. Mass spectra were obtained on a Varian MAT CH5 spectrometer. ^{1}H-NMR were recorded on a Varian XL-200 instrument. UV spectra were recorded on a Cary-14 spectrophotometer. Silica gel 60 (230–400 mesh), obtained from EM Reagents, was used for flash chromatography.[17]

Methyl 3,4-*O*-isopropylidene-L-threonate (**3**) was prepared from calcium L-threonate according to the reported procedure (Method B in Ref. 2) and was used without further purification.

Methyl 3,4-*O*-isopropylidene-2-*O*-phenoxythiocarbonyl-L-threonate (4): Methyl ester **3** is dissolved in a mixture of dry CH_2Cl_2 (50 mL) and dry pyridine (50 mL) with cooling in an ice-water bath. *O*-Phenyl carbonochloridothioate (18.75 g, 0.11 mol) in CH_2Cl_2 (30 mL) is added dropwise with magnetic stirring under an argon atmosphere over 20 min. The mixture is stirred in an ice-water bath for an additional 2 h, followed by 2 h at room temperature. Water (250 mL) and aqueous 1 N NaOH (150 mL) are then added, and the mixture extracted with EtOAc (2 × 400 mL). The two EtOAc layers are independently washed with the same portion of 2 N HCl (400 mL) and sat. brine (400 mL). These two EtOAc layers are then combined, dried ($MgSO_4$), treated with charcoal, filtered through Celite and concentrated. The resultant residue is recrystallized from CH_2Cl_2/hexane to give **4** as colorless needles; yield: 28.21 g (70% from **2**, 84% from **3**); mp 102–103°C; $[\alpha]_D^{25}$ +4.16° (c = 0.9381, $CHCl_3$).

$C_{15}H_{18}O_6S$ (326.4) calc. C 55.20 H 5.56 S 9.82
found 55.13 5.76 9.82

IR ($CHCl_3$): ν = 1750, 1280, 1210, 1072 cm^{-1}.

UV (CH_3OH): λ_{max} = 235 (ε = 7800), 314 nm (40).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.40 (s, 3H); 1.47 (s, 3H), 3.87 (s, 3H) 4.10 (dd, 1H, J = 10, 8 Hz); 4.19 (dd, 1H, J = 10, 8 Hz); 4.68 (m, 1H) 5.63 (d, 1H, J = 6 Hz); 7.20 (m, 2H); 7.37 (m, 1H); 7.48 (m, 2H).

MS: m/z = 311(6), 295 (5), 251 (8), 237 (6), 172(82), 115(63), 114(100) 77(53), 43(83).

Methyl 3,4-*O*-isopropylidene-3,4-dihydroxybutanoate (5):
Tri-*n*-butyltin hydride (5.90 mL, 22 mmol) is added to a suspension of **4** (6.53 g, 20 mmol) and 2,2'-azobis(2-methylpropionitrile) (AIBN; 100 mg) in dry, degassed toluene (60 mL) at room temperature. The mixture is heated in an oil bath at 80 °C with magnetic stirring under an argon atmosphere for 50 min. After cooling to room temperature, the solvent is removed by evaporation on a rotary evaporator, and the residual oil fractionally distilled to give crude **5** as a colorless oil contaminated with trace amounts of a tin-containing compound and phenol; yield: 3.14 g (~ 90%); bp 57–58 °C/0.013 mbar.

IR ($CHCl_3$): ν = 1735, 1382, 1372, 1068 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.39 (s, 3 H); 1.44 (s, 3 H); 2.53 (dd, 1 H, J = 16, 7 Hz); 2.74 (dd, 1 H, J = 16, 7 Hz); 3.67 (dd, 1 H, J = 8, 7 Hz); 3.72 (s, 3 H); 4.19 (dd, 1 H, J = 8, 7 Hz); 4.50 (m, 1 H).

(*R*)-3-Hydroxy-γ-butyrolactone (6):
To a solution of crude **5** (from 6.53 g of **4**, 20 mmol) in THF (30 mL) is added 18 N aqueous H_2SO_4 (1.5 mL). This mixture is stirred at room temperature for 6 h. $NaHCO_3$ (10 g) is added in small portions and the suspension stirred at room temperature for 30 min. Gas evolution ceases and solution is no longer acidic to wet pH paper. The solid residue is filtered off and washed with EtOAc. Washing and filtrate are combined and concentrated to give an oil. This oil is purified by flash chromatography using EtOAc/CH_2Cl_2 (7:3) as solvent to give the desired product **6**, which is vacuum distilled; yield: 1.35 g (66% from **4**): bp 93–94 °C/0.007 mbar; (Lit.[1] bp 103–104 °C/0.5 mbar); $[\alpha]_D^{25}$ + 85.58° (c = 1.2888, EtOH) [Lit.[1] $[\alpha]_D^{23}$ + 77.3° (c = 2.0, EtOH)].

IR ($CHCl_3$): ν = 3605, 3430, 1780, 1170 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.52 (dm, 1 H, J = 20 Hz); 2.74 (dd, 1 H, J = 20, 7 Hz); 3.02 (d, 1 H, J = 4 Hz); 4.30 (dm, 1 H, J = 12 Hz); 4.42 (dd, 1 H, J = 12, 5 Hz); 4.67 (m, 1 H).

MS: m/z = 102 (3, M^+), 74 (7), 43 (100).

(*R*)-1,2-*O*-Isopropylidene-1,2,4-butanetriol (7):
Crude **5** (from 6.53 g of **4**, 20 mmol) is dissolved in dry THF (25 mL) and added dropwise to a suspension of $LiAlH_4$ (0.75 g, 20 mmol) in THF (25 mL) with cooling in an ice-water bath, magnetic stirring and under an argon atmosphere. The mixture is stirred in an ice-water bath for 1 h, then at room temperature for 1 h. The resultant mixture is again cooled in an ice-water bath and excess $LiAlH_4$ is destroyed by addition of EtOAc (25 mL). After stirring for another 1 h, sat. aqueous NH_4Cl solution (50 mL) is added, and the suspension filtered through Celite. The Celite cake is washed extensively with EtOAc. The washing and filtrate are combined, and the two phases are separated. The aqueous phase is extracted with EtOAc (100 mL). These two organic layers are combined, dried ($MgSO_4$), filtered, and concentrated. The resulting oil is purified by flash chromatography using EtOAc/hexane (55:45, v/v) as solvent, and vacuum distillation to give pure product **7** as a colorless oil; yield: 1.90 g (65% from **4**): bp 70–71 °C/0.2 mbar; $[\alpha]_D^{25}$ + 2.49° (c = 5.1205, MeOH) [Lit.[14] bp 55–61 °C/0.7 mbar; $[\alpha]_D^{23}$ − 2.23° (c = 9.8, MeOH, for *S*-isomer)].

$C_7H_{14}O_3$	calc.	C 57.51	H 9.65	
(146.2)	found	57.42	9.59	

IR ($CHCl_3$): ν = 3622, 3530, 1235 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.38 (s, 3 H); 1.45 (s, 3 H); 1.84 (m, 2 H); 2.32 (t, 1 H, J = 6 Hz); 3.63 (t, 1 H, J = 8 Hz); 3.83 (q, 2 H, J = 6 Hz); 4.12 (dd, 1 H, J = 8, 6 Hz); 4.31 (m, 1 H).

MS: m/z = 131 (40), 71 (88), 43 (100).

(*R*)-1,2-*O*-Isopropylidene-1,2,4-butanetriol-4-*O*-3,5-Dinitrobenzoate (8):
To the magnetically stirred, ice-water bath cooled solution of **7** (0.73 g, 5 mmol), Et_3N (2 mL) and 4-dimethylaminopyridine (0.1 g) in dry CH_2Cl_2 (20 mL) is added the solution of 3.5-dinitrobenzoyl chloride (2.38 g, 10 mmol) in dry CH_2Cl_2 (10 mL). After stirring for 2 h with cooling, the insoluble material is filtered off and washed with CH_2Cl_2 (70 mL). The washing is added to the filtrate and the mixture is washed with water (100 mL), 0.2 N aqueous H_2SO_4 (100 mL), and sat. aqueous $NaHCO_3$ solution (100 mL). The aqueous layers are washed with CH_2Cl_2 (100 mL). The two CH_2Cl_2 layers are combined, dried ($MgSO_4$), treated with charcoal, filtered through Celite and concentrated. The residue is recrystallized from ethanol to give pure **8** as white plates; yield: 1.54 g (91%); mp 60–61 °C; $[\alpha]_D^{25}$ + 12.78° (c = 1.5580, $CHCl_3$) [Lit.[14] mp 62.5–63 °C; $[\alpha]_D^{23}$ − 13.7° (c = 1.5, $CHCl_3$), for *S*-isomer].

$C_{14}H_{16}N_2O_8$	calc.	C 49.42	H 4.74	N 8.23
(340.3)	found	49.39	4.85	8.27

IR ($CHCl_3$): ν = 1738, 1552, 1348, 1290 cm^{-1}.

UV (CH_3OH): λ_{max} = 206 (ε = 27200), 225 (sh, 19500), 290 (sh, 690), 330 nm (200).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.38 (s, 3 H); 1.45 (s, 3 H); 2.09 (q, 2 H, J = 6.5 Hz); 3.66 (dd, 1 H, J = 8, 7 Hz); 4.16 (dd, 1 H, J = 8, 7 Hz); 4.31 (q, 1 H, J = 6.5 Hz); 4.61 (2 t, 1 H, each, J = 7 Hz); 9.20 (d, 2 H, J = 3 Hz); 9.26 (t, 1 H, J = 3 Hz).

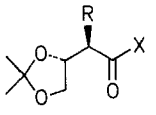
MS: m/z = 325 (30), 195 (17), 43 (100).

The authors wish to thank the members of the Physical Chemistry Department of Hoffmann-La Roche, Inc., for their assistance in measuring the various spectra, optical rotations and performing the microanalyses, and P. Weinert of Hoffmann-La Roche, Inc., for providing the calcium 3,4-O-isopropylidene-L-threonate used in this study.

Dedicated to Professor George Büchi on the occasion of his 65th birthday.

Received: 26 June 1987; revised: 20 October 1987

(1) Mori, K., Takigawa, T., Matsuo, T. *Tetrahedron* **1979**, *35*, 933.
(2) Isobe, M., Ichikawa, Y., Bai, D.-I., Goto, T. *Tetrahedron Lett.* **1985**, *26*, 5203.
(3) Guindon, Y., Yoakim, C., Bernstein, M.A., Morton, H.E. *Tetrahedron Lett.* **1985**, *26*, 1185.
(4) Olsen, R.K., Bhat, K.L., Wardle, R.B. *J. Org. Chem.* **1985**, *50*, 896.
(5) Papageorgiou, C., Benezra, C. *J. Org. Chem.* **1985**, *50*, 1144.
(6) Hanessian, S., Ugolini, A., Therien, M. *J. Org. Chem.* **1983**, *48*, 4427.
(7) Hayashi, H., Nakanishi, K., Brandon, C., Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749.
(8) Corey, E.J., Niwa, H., Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942.
(9) Since the completion of this work, two other procedures for preparing **6** have been reported.[18,19]
(10) Wei, C.-C., De Bernardo, S., Tengi, J.P., Borgese, J., Weigele, M. *J. Org. Chem.* **1985**, *50*, 3462.
(11) Abushanab, E. *Tetrahedron Lett.* **1984**, *25*, 3841.
(12) Miyazaki, M., Nakanishi, K. *Japanese Patent* 1322 (1957); *C.A.* **1958**, *52*, 4684.
(13) Robins, M.J., Wilson, J.S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
(14) Meyers, A.I., Lawson, J.P. *Tetrahedron Lett.* **1982**, *23*, 4883.
(15) Hanessian, S., Ugolini, A., Dube, D., Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146.
(16) Compound **3** can also be deoxygenated by first converting it to its mesylate **9**, followed by treatment with hydrazine hydrate[20,21] in methanol to give the corresponding hydrazide **10** in excellent yield.



9 R = OSO_2CH_3, X = OCH_3
10 R = H, X = $NHNH_2$

9: White needles from CH_2Cl_2/hexane, mp 113–116 °C; $[\alpha]_D^{25}$ + 38.50° (c = 1.065, $CHCl_3$).

$C_9H_{16}O_7S$	calc.	C 40.29	H 6.01	S 11.95
(268.3)	found	40.40	6.07	11.90

IR (KBr): ν = 1757, 1336, 1167 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.36 (s, 3 H); 1.45 (s, 3 H); 3.21 (s, 3 H); 3.58 (s, 3 H); 4.05 (dd, 1 H, J = 9, 6 Hz); 4.16 (dd, 1 H, J = 9, 7 Hz); 4.57 (m, 1 H); 5.02 (d, 1 H, J = 5 Hz).

MS: m/z = 253 (43), 193 (30), 115 (22), 101 (50), 55 (42), 43 (100).

10: Colorless oil; bp 117–118 °C/0.001 mbar; $[\alpha]_D^{25}$ + 18.78° (c = 2.029, $CHCl_3$).

$C_7H_{14}N_2O_3$ (174.2) calc. C 48.26 H 8.10 N 16.08
found 48.00 8.05 15.79

IR ($CHCl_3$): ν = 3445, 3440, 3330, 1673, 1628, 1500, 1382, 1372, 1225, 1158, 1055 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.37 (s, 3 H); 1.44 (s, 3 H); 2.05 (d, 2 H, J = 6 Hz); 3.60 (dd, 1 H, J = 8, 7 Hz); 3.90 (br s, 2 H); 4.11 (dd, 1 H, J = 8, 6 Hz); 4.40 (m, 1 H); 7.36 (br s, 1 H).

MS: m/z = 159 (9), 116 (69), 99 (31), 85 (24), 69 (25), 43 (99), 32 (100).

(17) Still, W.C., Kahn, M., Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(18) Seebach, D., Eberle, M. *Synthesis* **1986**, 37.
(19) Henrot, S., Larcheveque, M., Petit, Y. *Synth. Commun.* **1986**, *16*, 183.
(20) Paulsen, H., Stoye, D. *Chem. Ber.* **1966**, *99*, 908.
(21) Bock, K., Lundt, I., Pedersen, C. *Acta Chem. Scan. Sect. B* **1984**, *38*, 555.