A SIMPLE AND PRACTICAL PROCEDURE FOR THE CONVERSION OF (S)-4-HYDROXYMETHYL-4-BUTANOLIDE INTO ITS (R)-ENANTIOMER

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Abstract — A practical procedure for the conversion of (S)-4-hydroxymethyl-4-butanolide into its (R)-enantiomer is described.

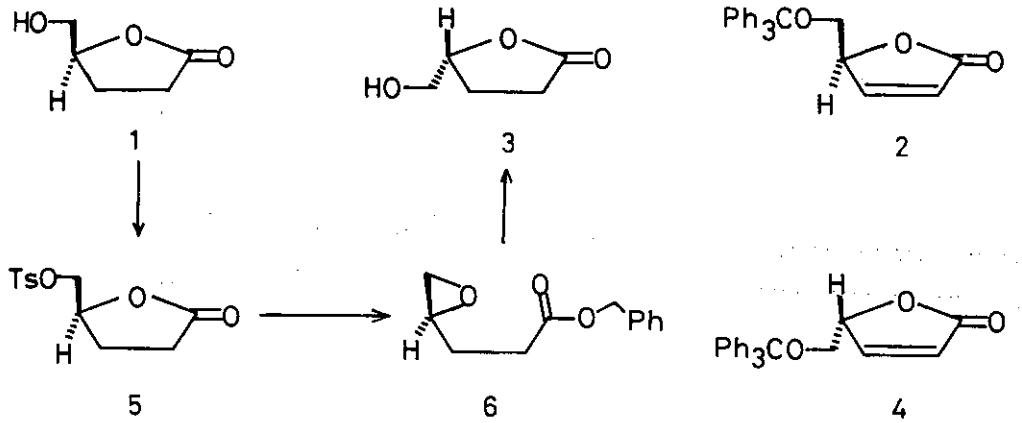
Optically pure (S)-4-hydroxymethyl-4-butanolide **1**[1] and its butenolide derivative **2**[2] are easily obtainable in quantity from L-glutamic acid, one of the most inexpensive commercially available optically active compounds, and have been shown to be highly useful in the asymmetric total synthesis of chiral natural products as chiral sources and at the same time as building blocks of the target molecules.[3] In connection with our program aimed at the asymmetric total synthesis of spatane diterpenes,[4,5] a large amount of **3** and **4**, enantiomers of **1** and **2**, were required. Although some procedures for the conversion of **1** into **3**[6a,b] and its trityl ether[6c] and the syntheses of **1-4** and their derivatives from optically active compounds other than L-glutamic acid have been reported,[7] these were found to be inadequate[6b] for the preparation of **3** and **4** in a preparative scale. Already we reported the conversion of **1** into **3** by using a simple and practical method,[4,8,9] and in this paper we describe a full accounts of the synthesis of **3** and **4** from **1**.

On treatment of the corresponding tosylate **5**[10] of **1** with lithium benzyloxide or sodium benzyloxide in tetrahydrofuran (THF), the epoxide **6** was obtained in a good yield. Catalytic hydrogenation of **6** in ether afforded **3** in an excellent yield. All data except for the sign of optical rotation were completely identical with those of **1**.[1] In this three-step procedure, **3** was obtained in 94% overall yield from **1**.

The synthesis of **4** from **3** was carried out using exactly the same procedure for

the preparation of 2.[2]

It is now shown that optically pure 1, 2 and their enantiomers 3, 4 are easily obtainable in quantity from L-glutamic acid for the asymmetric total synthesis of a variety of chiral natural products.



EXPERIMENTAL[11]

(S)-4-para-Toluenesulfonyloxymethyl-4-butanolide (5) --- Prepared from 1 in 96% yield according to the reported procedure.[10] Colorless prisms of mp 85.5-87°C (from benzene). $[\alpha]_D^{20}$+43.7°(c=1.58, $CHCl_3$).

(S)-Benzyl 4,5-epoxypentenoate (6) --- a) A hexane solution of n-BuLi (1.50 M, 37 ml, 55 mmol) was added to a solution of benzyl alcohol (5.7 ml, 55 mmol) in THF (25 ml) at -78°C and the whole was stirred for 20 min at -78°C. A solution of 5 (13.5 g, 50 mmol) in THF (100 ml) was added at -78°C and the whole was stirred for 1 h at 0°C. After the addition of satd. aq. NH_4Cl (30 ml) and satd. aq. NaCl (30 ml), the organic layer was separated and aqueous layer was extracted with benzene (30 ml x 2). The combined organic layers were washed successively with water, satd. $NaHCO_3$, and satd. NaCl, then dried over $MgSO_4$. Concentration in vacuo and chromatography (SiO_2, benzene-ether/4:1) afforded 6 (10.0 g, 100%) as a colorless oil. $[\alpha]_D^{20}$-13.4°(c=1.1, $CHCl_3$). IR (neat) cm^{-1}: 1730, 1160. NMR ($CDCl_3$) δ: 1.6-2.2 (2H, m), 2.2-2.9 (4H, m), 2.92 (1H, m), 5.09 (2H, s, OCH_2Ph),

7.28 (5H, s). MS m/z: 206 (M^+). HRMS Calcd for $C_{12}H_{14}O_3$: 206.0954. Found: 206.0944.

b) Benzyl alcohol (2.2 ml, 20 mmol) was added to a suspension of sodium hydride (0.5 g, 21 mmol) in THF (5 ml) at 0°C and the whole was stirred for 1 h at room temperature. A solution of **5** (4.8 g, 18 mmol) in THF (20 ml) was added at room temperature. Work up as described above and chromatography affoded **6** (3.7 g, 100%) as a colorless oil.

(R)-4-Hydroxymethyl-4-butanolide (**3**) --- A solution of **6** (7.6 g, 37 mmol) in ether (50 ml) was stirred in the presence of 5% Pd/C (0.4 g) under the atmosphere of hydrogen for 12 h and filtered. The filtrate was concentrated in vacuo and chromatographed (SiO_2, ether) to afford **3** (4.2 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ -33.5°(c=3.74, EtOH). Spectroscopic data, absolute value of optical rotation, and tlc behavior were completely identical with those of **1**.[1]

(R)-4-Trityloxymethyl-4-butanolide (**7**) --- Prepared from **3** according to the reported procedure for the enantiomer.[12] Colorless prisms of mp 151-151.5°C (from AcOEt). $[\alpha]_D^{20}$-26.5°(c=1.08, $CHCl_3$). Spectroscopic data, absolute value of optical rotation, and tlc behavior were completely identical with those of the enantiomer.

(R)-4-Trityloxymethyl-2-buten-4-olide (**4**) --- Prepared from **7** according to the reported procedure for the enantiomer (**2**).[2] Colorless prisms of mp 152-154°C (from benzene-hexane). $[\alpha]_D^{20}$+97.9°(c=1.12, $CHCl_3$). Spectroscopic data, absolute value of optical rotation, and tlc behavior were completely identical with those of **2**.

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8) See footnote 6 in reference 4, where we announced the preparatin of **3** from **1**.

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10) See references 3h and 6a,b.

11) Melting points were measured using Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a JASCO DIP-181 automatic polarimeter. Infrared (IR) spectra were taken with a JASCO Infrared Spectrometer Model DS-402 G and a JASCO IRA-I Grating Infrared Spectrometer. Proton nuclear magnetic resonance (NMR) spectra were taken with a JEOL FX-100 Spectrometer at 100 MHz, or with a Hitachi R-24B Spectrometer at 60 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (MS) were taken with a JEOL JMS DX-300 Mass Spectrometer.

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