Practical Syntheses of (*S*)-4-Hydroxytetrahydrofuran-2-one, (*S*)-3-Hydroxytetrahydrofuran and Their (*R*)-Enantiomers

Yoshifumi Yuasa* and Haruki Tsuruta

Central Research Laboratory, Takasago International Corporation, 1-4-11 Nishiyawata, Hiratsuka City, Kanagawa 254, Japan

Received April 9, 1997

Keywords: Asymmetric hydrogenation / Cyclizations / Reductions / 4-Chloro-3-hydroxybutanoate / 4-Chloro-1,3-butanediol

Optically active 4-hydroxytetrahydrofuran-2-one (**3**) has been synthesized in good yield from optically active ethyl 4-chloro-3-hydroxybutanoate (**2**) by refluxing with dilute hydrochloric acid. In a similar manner, optically active 3-hydroxytetrahydrofuran (**5**) was prepared from optically active 4-chloro-1,3-butanediol (**4**), which was derived from **2** by $NaBH_4$ reduction. These new cyclizations proceed without racemization.

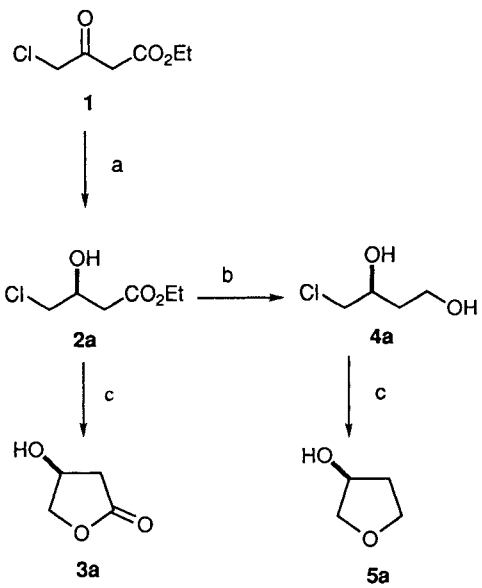
Optically active 4-hydroxytetrahydrofuran-2-one (**3**)[1] represents a versatile chiral source for the synthesis of natural products, and 3-hydroxytetrahydrofuran (**5**) is similarly expected to become part of the pool of available chiral compounds[2][3]. Many of the existing methods for preparing optically active **3** and **5** employ L- or D-malic acid as the starting material. However, these methods involve many steps and/or use expensive reagents. Therefore, they are rather unsuitable for large-scale preparations. We describe herein convenient and short syntheses of optically active **3** and **5** starting from **2** and **4**, respectively (Scheme 1).

Ethyl (*S*)-4-chloro-3-hydroxybutanoate (**2a**)[4] was obtained by the asymmetric hydrogenation of ethyl α-chloroacetoacetate (**1**), which is readily available in 94% *ee* using the Ru-(*R*)-*p*-tolyl-BINAP catalyst[5]. The (*R*)-enantiomer **2b** was likewise obtained by employing the Ru-(*S*)-*p*-tolyl-BINAP catalyst. Treatment of **2a** with 1 N HCl solution at refluxing temperature for 4 h gave **3a** in 83% yield. The progress of the cyclization, which was monitored by GC, is depicted in Figure 1. The structure of by-product (**7**) was determined by GC-MS and ^{1}H-NMR spectroscopy. An intermediate (**6**) could not be isolated, but its presence was inferred on the basis of GC-MS evidence[6]. The specific optical rotation of **3a** was found to be −79.53, indicating that its formation proceeded without racemization of the secondary alcohol function. The cyclization could also be performed using dilute sulfuric acid. Attempts to achieve a similar result under basic conditions were unsuccessful, leading only to the formation of complex mixtures of products.

In an alternative procedure, **2a** was reduced with one molar equivalent of $NaBH_4$ in THF at refluxing temperature to afford **4a** in 86% yield. Subsequent treatment of **4a** with 0.5 N HCl under reflux for 2 h gave **5a** in 79% yield, without racemization. The by-product was identified as 2,5-dihydrofuran (**8**)[7]. The enantiomeric excess of **5a** was determined to be 94.4%, by HPLC analysis[8] of the corresponding (*R*)-MTPA ester. The synthesis of the (*R*)-enantiomers **3b** (79%) and **5b** (75%) was accomplished from (*R*)-enantiomers **2b** and **4b** under similar reaction conditions. We presume the mechanism of the cyclization reaction to be that depicted in Scheme 2. To the best of our knowledge, these cyclizations of α-chlorobutanoate **2** and α-chlorobutanediol **4** have not previously been reported[9].

Scheme 1. Syntheses of optically active 4-hydroxytetrahydrofuran-2-one (**3**) and 3-hydroxytetrahydrofuran (**5**)

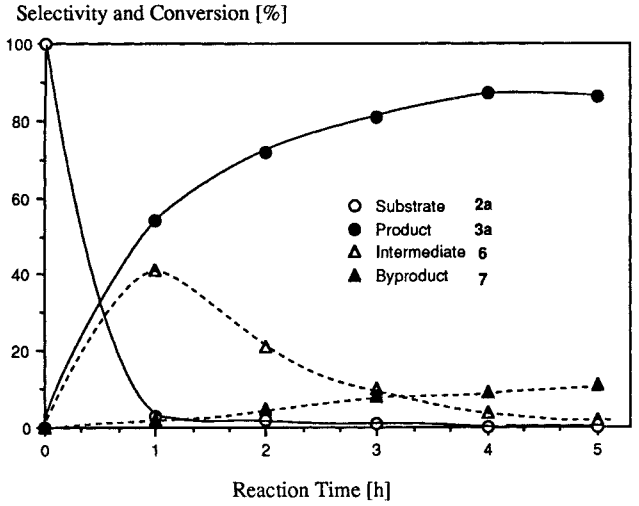
Reagents: (a) H_2, $Ru_2Cl_4[(R)$-*p*-tolyl-BINAP$]_2Et_3N$, EtOH, (96% of **2a** and 95% of **2b**). - (b) $NaBH_4$, THF, (86% of **4a** and 87% of **4b**). - (c) dil. HCl, (83% of **3a**, 79% of **5a**, 79% of **3b** and 75% of **5b**).



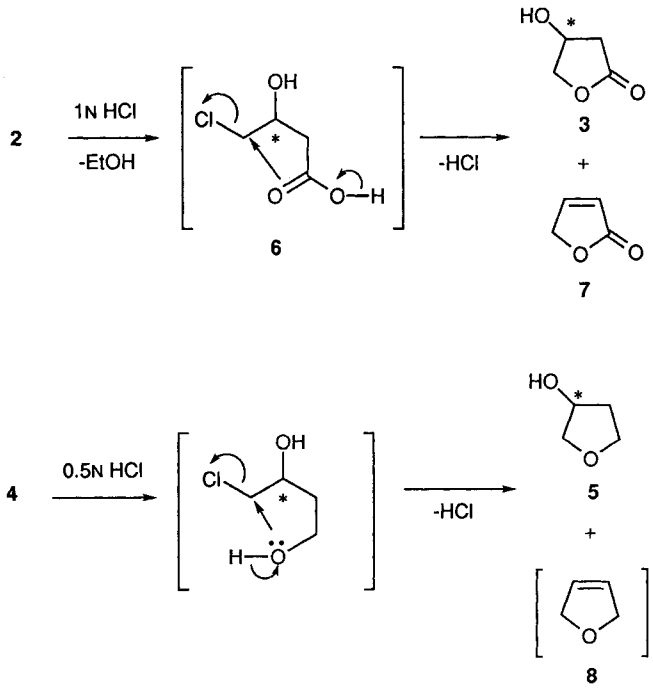
2b to **5b** refer to (*R*)-enantiomer

  0947–3440/97/0909–1877 $ 17.50+.50/0

Figure 1. Conversion of ethyl 4-chloro-3-hydroxybutanoate (**2a**) to 4-hydroxytetrahydrofuran-2-one (**3a**)



Scheme 2. Mechanisms of cyclization reactions leading to 4-hydroxytetrahydrofuran-2-one (**3**) and 3-hydroxytetrahydrofuran (**5**)



Experimental Section

^{1}H NMR: (TMS as internal standard): Bruker AM-400 (400 MHz). – ^{13}C NMR (TMS as internal standard): Bruker AM-400 (100 MHz). – MS: Hitachi M-80A mass spectrometer at 70 eV. – Optical rotations: Jasco DIP-4 digital polarimeter. – Gas chromatographic analysis was performed on a Hewlett Packard HP5890 II (column: Silicon Neutra Bond-1: 30 m × 0.25 mm, 0.25 μm, He gas; 1 kg/cm^2, oven temperature: 100–250°C, programmed increment 5°C/min., injection temperature: 250°C). – GC-MS was carried out on HP5870 and HP5890 II instruments (column: Silicon Neutra Bond-1: 30 m × 0.25 mm, 0.25 μm, He gas, 1 kg/cm^2, oven temperature 100–250°C, program rate 5°C/min.). – EI-MS were obtained at 70 eV. – Boiling points: uncorrected values.

Ethyl (S)-(−)-4-Chloro-3-hydroxybutanoate (**2a**): A 1-dm^3 autoclave was charged with ethyl 4-chloro-3-oxobutanoate (**1**) (200 g, 1.22 mol), MeOH (300 ml) and Ru_2Cl_4[(*R*)-(+)-*p*-tolyl-BINAP]$_2$·Et_3N (2.05 g, 1.22 mmol) under an atmosphere of N_2. The contents were heated to 100°C, and then stirred for 1 h under an atmosphere of H_2 gas at a pressure of 35 kg/cm^2. The vessel was then cooled and the reaction mixture was concentrated under reduced pressure. The residual oil was distilled under reduced pressure to afford **2a** (195 g, 96%) as a colorless oil, b.p. 95–96°C/3 Torr. – $[\alpha]_D^{24}$ = −19.08 (*c* = 7.7 in $CHCl_3$), {ref.[4] $[\alpha]_D^{21}$ = −20.3 (*c* = 8.11 in $CHCl_3$)}.

(S)-(+)-4-Hydroxytetrahydrofuran-2-one (**3a**): To **2a** (100 g, 0.6 mol) was added 1 N HCl (200 ml) and the mixture was distilled for about 1 h to remove ethanol as an azeotrope with water. Then, 40% NaOH (60 ml) was carefully added to the reaction mixture and reflux conditions were maintained for a further 3 h. The relative amounts of **3a**, the intermediate **6** and the by-product butenolide **7** were found to be 86%, 8% and 5% by GLC analysis. After cooling, the reaction mixture was adjusted to pH 4 with 50% NaOH solution and water was evaporated under reduced pressure. To the residue of salts and oily products, 2-propanol (100 ml) was added and the mixture was stirred. The salts were removed by filtration, and the filtrate was concentrated in vacuo. The residue was distilled under reduced pressure to give **7** (2.6 g, purity 96.6% by GLC) and **3a** (50.8 g, 83%, purity 99% by GLC).

7: b.p. 39°C/1 Torr. – ^{1}H NMR ($CDCl_3$): δ = 4.90 (dd, *J* = 1.7, 2.2 Hz, 2 H), 6.15 (dt, *J* = 2.2, 5.8 Hz, 1 H), 7.58 (dt, *J* = 1.7, 5.8 Hz, 1 H). – ^{13}C NMR ($CDCl_3$): δ = 72.31 (CH_2), 121.21 (CH=), 153.41 (CH=), 173.80 (C=O). – MS: *m/z* (%): 84 (M^+, 89), 55 (100), 29 (32).

3a: b.p. 140°C/ 1 Torr. – $[\alpha]_D^{24}$ = −79.53 (*c* = 2.07 in EtOH), {ref.[1b] $[\alpha]_D^{9}$ = −85.9 (*c* = 2.2 in EtOH)}. – ^{1}H NMR ($CDCl_3$): δ = 2.51 (dt, *J* = 1.4, 18 Hz, 1 H), 2.76 (dd, *J* = 6, 18 Hz, 1 H), 3.71 (br s, 1 H, OH), 4.31 (dt, *J* = 1.4, 10.3 Hz, 1 H), 4.42 (dd, *J* = 4.4, 10.3 Hz, 1 H), 4.65–4.69 (m, 1 H, C*H*-OH). – ^{13}C NMR ($CDCl_3$): δ = 7.81 (CH_2), 67.40 (CH), 76.41 (CH_2), 177.23 (CO). – MS: *m/z* (%): 102 (2) [M^+], 74 (23), 44 (100), 43 (60).

Ethyl (R)-(+)-4-Chloro-3-hydroxybutanoate (**2b**): Following a method similar to that described for **2a**, the (*R*)-enantiomer **2b** was prepared from ethyl 4-chloro-3-oxobutanoate **1** using Ru_2Cl_4[(*S*)-(−)-*p*-tolyl-BINAP]$_2Et_3N$ as the catalyst (95% yield). – $[\alpha]_D^{24}$ = +19.02 (*c* = 7.7 in $CHCl_3$).

(R)-(+)-4-Hydroxytetrahydrofuran-2-one (**3b**): Following a method similar to that described for **3a**, the (*R*)-enantiomer **3b** was prepared from ethyl (*R*)-(+)-4-chloro-3-hydroxybutanoate (**2b**) (79% yield). – $[\alpha]_D^{24}$ = +74.73 (*c* = 2.4 in EtOH), {ref.[1a] $[\alpha]_D^{23}$ = +77.3 (*c* = 2.0 in EtOH)}.

(S)-(−)-4-Chloro-1,3-butanediol (**4a**): To a suspension of $NaBH_4$ (23 g, 0.6 mol) in THF (400 ml), a solution of **2b** (100 g, 0.6 mol) in THF (400 ml) was added dropwise over a period of 1 h, and then the mixture was refluxed for 1 h. After cooling, the solvent was evaporated in vacuo, and the residue was treated with 4 N HCl (200 ml) with cooling and stirring. The reaction mixture was extracted with AcOEt and the combined extracts were washed with 10% aq. $NaHCO_3$ solution and saturated brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give (**4a**) as an oil (64.3 g, 86%), (the product decomposed upon attempted distillation). – $[\alpha]_D^{24}$ = −23.31 (*c* = 1.1 in MeOH). – ^{1}H NMR ($CDCl_3$): δ = 1.72–1.88 (m, 2 H), 2.87 (br s, 2 H, OH), 3.54 (dd, *J* = 6.7, 11.2 Hz, 1 H), 3.62 (dd, *J* = 4.4,

11.2 Hz, 1 H), 3.79–3.92 (m, 2 H), 4.02–4.11 (m, 1 H, C*H*-OH). – ^{13}C NMR ($CDCl_3$): δ = 35.62 (CH_2), 49.57 (CH_2), 60.22 (CH_2), 70.59 (CH). – MS: *m/z* (%): 107 (27), 87 (100), 75 (49), 57 (72).

(S)-(+)-3-Hydroxytetrahydrofuran (**5a**): To **4a** (50 g, 0.4 mol) was added 0.5 N HCl (100 ml), and the mixture was refluxed for 2 h. After cooling, the reaction mixture was neutralized with 50% aq. NaOH solution, and water was evaporated under reduced pressure. To the residue of salts and oily products, MeOH (80 ml) was added and the mixture was stirred. The salts were filtered off, and the filtrate was concentrated in vacuo. The residue was distilled under reduced pressure to afford **5a** as a coloress oil (31.9 g, 79%, purity 99.1% by GLC), b.p. 80°C/13 Torr. – $[\alpha]_D^{24}$ = +16.45 (*c* = 2.45 in MeOH), {ref.[2a] $[\alpha]_D^{22}$ = +16.23 (*c* = 2.427 in MeOH)}. – ^{1}H NMR ($CDCl_3$): δ = 1.88–1.92 (m, 1 H), 2.02–2.09 (m, 1 H), 3.65 (br s, 1 H, OH), 3.71–3.85 (m, 2 H), 3.95–3.97 (m, 1 H), 4.45–4.48 (m, 1 H, C*H*-OH). – ^{13}C NMR ($CDCl_3$): δ = 35.28 (CH_2), 66.63 (CH_2), 71.46 (CH), 75.33 (CH_2). – MS: *m/z* (%): 88 (11) [M^+], 70 (14), 58 (61), 57 (100).

(R)-(+)-4-Chloro-1,3-butanediol (**4b**): Following a method similar to that described for **4a**, the (*R*)-enantiomer **4b** was prepared from ethyl (*R*)-(+)-4-chloro-3-hydroxybutanoate **2b** (87% yield). – $[\alpha]_D^{24}$ = +23.54 (*c* = 1.2 in MeOH).

(R)-(–)-3-Hydroxytetrahydrofuran (**5b**): Following a method similar to that described for **5a**, the (*R*)-enantiomer **5b** was prepared from (*R*)-4-chloro-1,3-butanediol (**4b**) (75% yield). – $[\alpha]_D^{24}$ = –15.91 (*c* = 2.45 in MeOH), {(ref.[2a] $[\alpha]_D^{22}$ = –14.36 (*c* = 3.194 in MeOH)}.

[1] [1a] K. Mori, T. Takigawa, T. Masuo, *Tetrahedron* **1979**, *35*, 993–940. – [1b] S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, T. Moriwaki, *Chem. Lett.* **1984**, 1389–1392. – [1c] A. Tanaka, K. Yamashita, *Synthesis* **1987**, 570–572. – [1d] S. Henrot, M. Larchevêque, Y. Petit, *Synth. Commun.* **1986**, *16*, 183–190.

[2] [2a] V. K. Tandon, A. M. Leusen, H. Wynberg, *J. Org. Chem.* **1983**, *48*, 2767–2769. – [2b] H. C. Brown, J. V. N. Prasad, *J. Am. Chem. Soc.* **1986**, *108*, 2049–2054. – [2c] Y. Uozumi, T. Hayashi, *Tetrahedron Lett.* **1993**, *34*, 2335–2338.

[3] An example of available material: a component of the HIV aspartyl protease inhibitor KVX-478: R. D. Tung, M. A. Murcko, G. R. Bhisetti (Vertex Pharmaceutical Inc.), WO 9405639, **1994** [*Chem. Abstr.* **1995**, *122*, P81141j].

[4] M. Kitamura, T. Ohkuma, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1988**, *29*, 1555–1556.

[5] T. Ikariya, Y. Ishii, H. Kawano, T. Arai, M. Saburi, S. Yoshikawa, S. Akutagawa, *J. Chem. Soc., Chem. Commun.* **1985**, 922–924; [*p*-tolyl-BINAP = 2,2'-bis(di-*p*-tolylphosphanyl)-1,1'-binaphthyl].

[6] A peak at *m/z* 120 [M^+ – 18] was recorded in the GC-MS. (The author intends to prepare the acid **6** by an independent route for comparison).

[7] The proportion of **8** was determined to be 15% by GC and the structure was identified by comparison with an authentic sample purchased from the Aldrich Chemical Co.

[8] HPLC conditions: column: Cosmosil 5SL; eluent: 1:9 diethyl ether/hexane mixture; flow rate: 1 ml/min; detection: 254 nm light. The chromatogram showed two signals with t_r = 35.3 and 37.4 min, in a ratio of 2.8 : 97.2, assignable to the (*R,R*)- and (*R,S*)-diastereomer, respectively.

[9] With regard to the synthesis of α-butyrolactone, acid cyclizations after basic hydrolysis of esters are known; for example, F. F. Blicke, Jr. W. B. Wright, M. F. Zienty, *J. Am. Chem. Soc.* **1941**, *63*, 2488–2490.

[97119]