Tetrahedron: Asymmetry Vol. 1, No. 4, pp. 219-220, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

Enantioselective Syntheses of (2S) - 1 - Benzyloxy - 2,3 - propanediol and (2R) - 1 - Amino - 2,3 - propanediol from Glycerol

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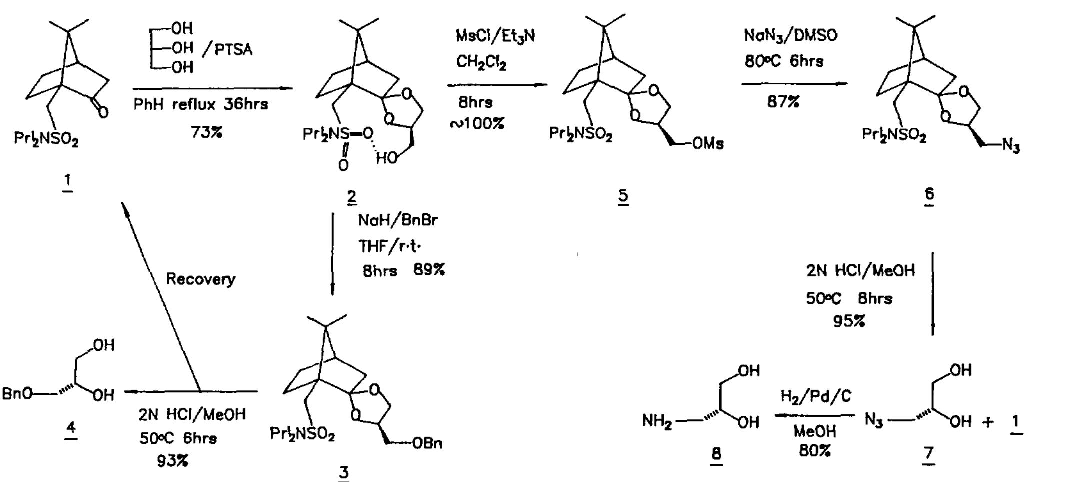
(*Received* 22 *February* 1990)

Abstract: Enantioselective syntheses of (2S) - 1 - benzyloxy - and (2R) - 1 - amino - 2,3 - propanediol from glycerol employing N,N - diisopropyl - 10 - camphorsulfonamide 1 as chiral auxiliary are described.

Propanediol derivatives are useful three carbon synthetic building blocks for the synthesis of various natural products. Optically active propanediol derivatives are generally obtained from carbohydrates through steps of chemical operations[1]. Herein we report an efficient synthetic method for the preparation of (2S) - 1 - benzyloxy - 2,3 - propanediol and (2R) - 1 - amino - 2,3 - propanediol from glycerol employing N,N - diisopropyl - 10 - camphorsulfonamide 1[2] as chiral auxiliary.

When a benzene solution containing 1 (1 equivalent), glycerol (1.2 equivalent), and a catalytic amount of *p* - toluenesulfonic acid was heated under reflux for 36 hours with removal of water, the major ketal **2**[3] was obtained by chromatography in 73% yield. The formation of the major ketal **2** presumably arose from the attack of the pro - R primary alcohol of glycerol to the carbonyl group from the endo position of 1 followed by a cyclization with the secondary alcohol of glycerol from the endo position with the reaction being driven by hydrogen bonding between the free OH and the sulfonamide group. Treatment of **2** with sodium hydride (1 equivalent) in THF followed by benzyl bromide (1.2 equivalent) gave benzylether **3**[3] in 89% yield. Hydrolysis of benzyl ether **3** in methanol with 2N hydrochloric acid afforded 1 - benzyloxy - 2,3 - propanediol **4**[3] in 93% yield and completely recovered 1. The $[\alpha]_D$ for **4** is -5.42°(neat)[4]. Therefore the absolute configuration at C_2 of **4** is the S conifiguration. Thus the



stereochemical assignments for compounds **2** and **3** were confirmed by this chemical correlation.

On the other hand, treatment of **2** with methanesulfonyl chloride (1.2 equivalent) and triethylamine (1.5 equivalent) in dichloromethane for 8 hours afforded the corresponding mesylate **5**[3]. Reaction of crude **5** with sodium azide in dimethylsulfoxide at 80°C for 6 hours gave azide **6**[3] in 87% yield. Hydrolysis of **6** in methanol with 2N HCl at 40-50°C for 8 hours liberated azidodiol **7**[3] in 95% yield and recovered **1** in nearly quantitative yield. Hydrogenation of azidodiol **7** in methanol with 10% Pd/C afforded 1-amino-2,3-propanediol **8**[3] in 80% yield. The $[\alpha]_D$ for **8** is 2.96° (c1,H_2O)[5], therefore an R configuration was assigned for C_2 of **8**. This is consistent with the previous observation. Thus a facile entry to optically acive propanediol derivatives from glycerol has been demonstrated.

Acknowledgement. This research was supported by the National Science Council of Republic of China. A generous gift of D-10-Camphorsulfonic acid, starting material of **1**, from China Camphor Co., LTD. is gratefully acknowledged.

References and Notes

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2. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5885.
3. **2**: mp 70°C; ^{1}H NMR ($CDCl_3$) δ 4.00 (dd, 1H, J=5.6, 5.6 Hz), 3.94-3.85 (m, 3H), 3.72 (dd, 1H, J=10.8, 2.0 Hz), 3.62 (heptet, 1H, J=6.8 Hz), 3.43 (dd, J=11.2,2.0 Hz), 3.36 and 2.50 (ABq, 2H, J=14.4 Hz), 2.20-2.18 (m, 1H), 2.05-1.93 (m, 1H) 1.70-1.68 (m, 2H), 1.37 (d, 1H, J=12.8Hz), 1.25 (m, 1H), 1.22 (d, 6H, J=6.8 Hz), 1.21 (d, 6H, J=6.8 Hz), 0.86 (s, 3H), 0.81 (s, 3H); IR ν($CHCl_3$) 3440 cm^{-1}; $[\alpha]_D^{20}$- 11.84° (c 1, $CHCl_3$). **3**: mp 76°C; ^{1}H NMR ($CDCl_3$) δ 7.30-7.21 (m, 5H), 4.58 and 4.51 (ABq, 2H, J=12.4 Hz), 4.13-4.09 (m, 1H), 3.97 (dd, 1H, J=8.0, 8.0 Hz) 3.69~3.61 (m, 4H), 3.(ABq, 2H, J=14 Hz), 2.20-2.18 (m, 1H), 2.13-2.10 (m, 1H) 2.01-1.96 (m, 1H), 1.74-1.68 (*m*, 2H), 1.42 (d, 1H, J=14.8 Hz), 1.26 (m, 1H), 1.22 (d, 12H, J=8 Hz), 1.00 (s, 3H), 0.97 (s, 3H); $[\alpha]_D^{20}$ 12.79° (c 1, $CHCl_3$). **4**: ^{1}H NMR ($CDCl_3$) δ 7.36-7.26 (m, 5H), 4.53 (s, 2H), 3.85 (m, 1H), 3.66 (m, 1H), 3.60-3.48 (m, 3H), 2.92 (bs, 1H), 2.45 (bs, 1H); IR ν($CHCl_3$) 3600-3100 (br) cm^{-1}. **5**: mp 104°C; ^{1}H NMR ($CDCl_3$) δ 4.40 (dd, 1H, J=7.2,7.2 Hz), 4.18-4.11 (m, 2H), 3.93 (dd, 1H, J=7.2,7.2 Hz), 3.59 (m, 3H), 3.13 and 2.50 (ABq, 2H, J=14 Hz), 3.00 (s, 3H), 2.13-2.06 (m, 1H), 1.92-1.74 (m, 2H), 1.64 (bs, 2H), 1.33 (d, 1H, J=12.8 Hz), 1.18 (d, 12H, J=7.2 Hz), 1.15 (m, 1H), 0.86 (s, 3H), 0.78 (s, 3H); $[\alpha]_D^{20}$ -13.87° (c 2, $CHCl_3$). **6**: mp 78°C; ^{1}H NMR ($CDCl_3$) δ 4.09-4.06 (m, 1H),3.96 (dd, 1H, J=7.2,7.2 Hz) 3.70-3.60 (m, 4H), 3.26 (dd, 1H, J=12.4,4.8 Hz), 3.16 and 2.69 (ABq, 2H, J=14 Hz), 2.21-2.18 (m, 1H), 2.01-1.95 (m, 2H), 1.80-1.69 (m, 2H), 1.41 (d, 1H, J=13.2 Hz), 1.26 (d, 12H, J=6.8 Hz), 1.22 (m, 1H), 0.96 (s, 3H), 0.91 (s, 3H); IR ν($CHCl_3$) 2080 cm^{-1}; $[\alpha]_D^{20}$ -19.07° (c 0.5, $CHCl_3$). **7**: ^{1}H NMR ($CDCl_3$) δ 4.16 (br,1H), 3.83 (br,1H), 3.80 (m, 1H), 3.64 (dd, 1H, J=11.6,3.2 Hz), 3.54 (dd, 1H, J=11.6, 6.4 Hz), 3.33 (m, 2H); IR ν($CHCl_3$) 2090 cm^{-1}; $[\alpha]_D^{20}$ 2.24° (c 0.5, $CHCl_3$). **8**: ^{1}H NMR (D_2O) δ 3.62-3.57 (m, 1H), 3.53 (dd, 1H, J=16.0, 4.4 Hz), 3.43 (dd, 1H, J=16.0, 6.8 Hz), 2.64 (dd, 1H, J=12.8, 4.4 Hz), 2.53 (dd, 1H, J=12.8, 7.6 Hz); MS (m/z, rel. intensity) 92 (M+1, 16%), 73 (48%), 60 (100%), 31 (89%).
4. For a sample of (2S)-1-benzyloxy-2,3-propanediol, $[\alpha]_D$-5.36° (neat): Baer, E.; Martin, F. *J. Biol. Chem.* **1951**, *193*, 835.
5. For a sample of (2S)-1-amino-2,3-propanediol, $[\alpha]_D$ -2.4° (c 5.09, H_2O): Sowden, J. C.; Fischer H.O. L. *J. Am. Chem. Soc.* **1942**, *64*, 1291.