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Synthesis of Optically Active 2,3-Methanopipecolic Acid

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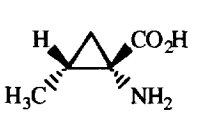
Abstract: The title compound was synthesized in enantiomerically pure form, starting from *L*-glutamic acid.

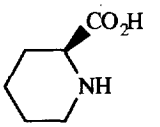
A growing interest in 2,3-methanoaminoacids has appeared in recent years due to the biological activities exhibited by these compounds[1]. However, their asymmetric synthesis are limited by the lack of easily available optically pure precursors. In our program toward the synthesis of optically active cyclopropane aminoacids[2,3], we recently reported the synthesis of (-)-(1*S*,2*S*)-allonorcoronamic acid **1**, using a chiral cyclic sulfate as precursor.

The proline homologue, pipecolic acid **2**, is a non proteinogenic aminoacid, naturally occuring in plants. This molecule, which asymmetric synthesis is still under investigation[4], is of special interest in the synthesis of peptide[5], enzyme inhibitors[6] and as a constituent of the immunosuppresant FK-506[7].

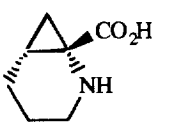
We now wish to report the first asymmetric synthesis of the optically active 2,3-methano analog of pipecolic acid **3**, starting from *L*-glutamic acid.



(1*S*, 2*R*)-**1**



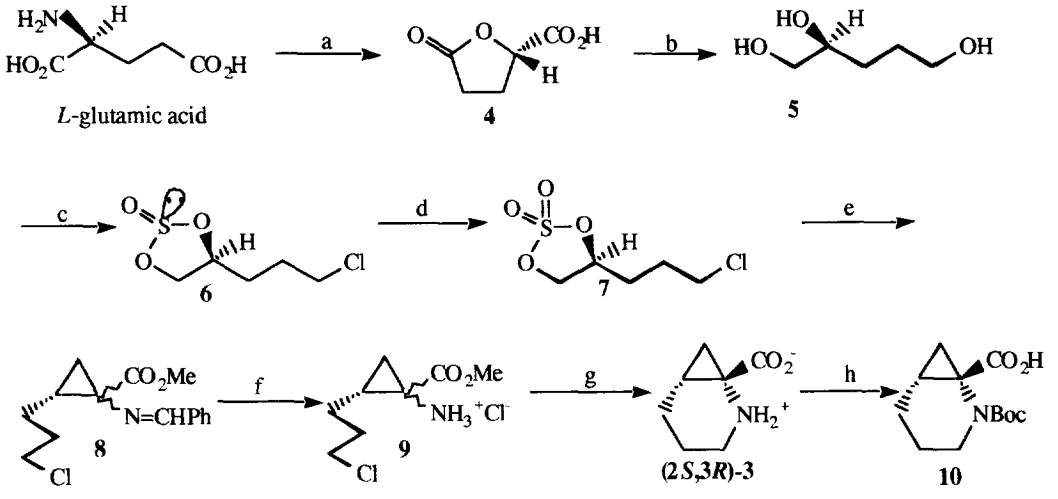
(*S*)-**2**



(2*S*,3*R*)-**3**

Thus, lactone **4**, obtained from *L*-glutamic acid by the reported procedures[8], was converted to triol **5** by treatment with BMS in chloroform. Crude pentanetriol **5**, when reacted with $SOCl_2$ in refluxing CCl_4, afforded pure cyclic sulfite **6** after flash chromatography. This sulfite was oxidized to sulfate **7**[9], using the Sharpless procedure[10]. Crude sulfate **7** was pure enough to be used in the next step without further purification.

Scheme1



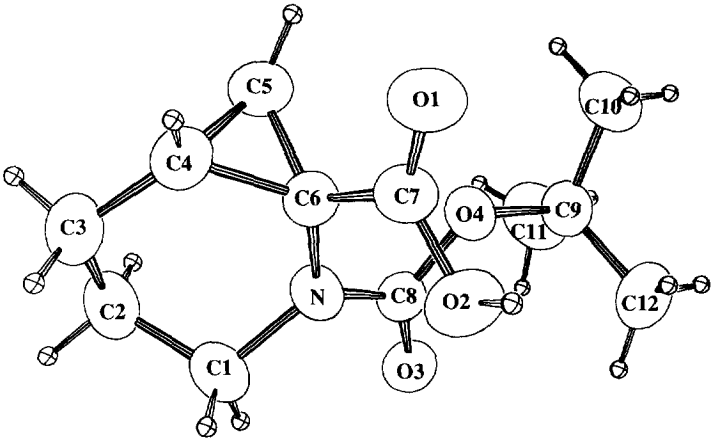
(a) HNO_2, 68%. (b) BH_3-Me_2S, 1.2 eq., $CHCl_3$, reflux, 3h; MeOH, 78%. (c) $SOCl_2$, 3 eq., CCl_4, reflux 3h, 72%. (d) $NaIO_4$, $RuCl_3.3H_2O$, 96%. (e) $PhCH{=}NCH_2CO_2Me$, 1 eq.; NaH, 2 eq., DME, rt, 4h, 99%. (f) 1N/Et_2O, HCl ,30 mn, 86%. (g) 1N NaOH, 1h ; 6N HCl refl. 4h ; Dowex 50X8; 59%. (h) Boc_2O, 1 eq., t-BuOH, 81%.

Alkylation of methylbenzylideneglycinate performed at room temperature in DME, using two equivalents of NaH as base, gave the alkylated imine **8** in 99% yield[11]. The reaction is diastereospecific, no trace of the second isomer was detected in the crude product. Hydrolysis of the imino protective group gave the hydrochloride aminoester **9**[12] that cyclised to the desired piperidine when treated with a stoechiometric amount of 1N sodium hydroxyde. Free aminoacid **3**[13] was then obtained after hydrolysis with 6N HCl and treatement with Dowex 50X8.

In order to ensure the cis configuration of the bicylic structure of **3**, we realized an X-ray structure determination. Suitable crystals could not be obtained from the aminoacid, so we prepared the N-Boc derivative **10**. The ORTEP plot given on Figure 1 confirms the proposed cis bicylic structure of the aminoacid[14].

This work represents the first synthesis of (2*S*, 3*R*)-methanopipecolic acid. Since *D*-glutamic acid is commercially available, this procedure can lead to both enantiomers of methanopipecolic acid.

Figure 1



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REFERENCES AND NOTES

1. For recent reviews see: (a), Stammer C. H., *Tetrahedron*, **1990**, *46*, 2231-2254. (b) Alami A., Calmes M., Daunis J. and Jacquier R., *Bull. Soc. Chim. Fr.*, **1993**, *130*, 5-24. (c) Burgess K., Ho K. K. and Moye-Sherman D., *Synlett*, **1994**, 575-583.
2. Le Corre M., Hercouët A. and Bessières B., *Tetrahedron: Asymmetry*, **1995**, *6*, 683-684.
3. Hercouët A., Bessières B. and Le Corre M., *Tetrahedron: Asymmetry*, **1996**, *7*, 283-284.
4. a) Hockless D. C. R., Mayadunne R. C. and Wild S. B., *Tetrahedron: Asymmetry*, **1995**, *6*, 3031-3037. b) Pauly, R., Sasaki, N.A. and Potier, P. *Tetrahedron Lett.*, 1994, 35, 237-240. c) Berrien, J. F., Royer, J. and Husson, H.-P.,*J. Org. Chem.* 1994, 59, 3769-3774. d)Fernandez-Garcia, C. and McKervey, M.A.. *Tetrahedron: Asymmetry*, **1995**, 6, 2905-2906.
5. Copeland T. D., Wondrack E. M., Tozser J., Roberts M. M. and Oroszlan S., *Biochem. Biophys. Res. Commun.*, **1990**, *169*, 310-311.
6. Flynn G. A., Giroux E. L. and Dage R.C., *J. Am. Chem. Soc.*, **1987**, *109*, 7914-7915.
7. Jones T. K., Mills S. G., Reamer R. A., Askin D., Desmond R., Volante R. P. and Shinkai I., *J. Am. Chem. Soc.*, **1989**, *111*, 1157-1159.

8. (a) Gringore O. H. and Rouessac F. P., *Organic Syntheses*, **1985**, *63*, 121. (b) Larchevêque M. and Lalande J., *Tetrahedron*, **1984**, *40*, 1061-1065.

9. (S)-(-)-4-chloropropyl-2,2-dioxo-1,3,2-dioxathiolane **7** $[\alpha]_D^{20}$ -15 (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.96-2.06 (m, 4H), 3.59-3.64 (m, 2H); 4.39 (dd, J = 7.9 / 8.7 Hz, 1H), 4.77 (dd, J = 6.0 / 8.7 Hz, 1H) and 5.00-5.06 (m, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 27.70, 29.73, 43.85, 72.72 and 82.40.

10. Gao Y. and Sharpless K. B., *J. Am. Chem. Soc.*, **1988**, *110*, 7538-7539.

11. **Alkylation Procedure.** A 250 mL three-necked round bottomed flask equipped with reflux condenser, $CaCl_2$ drying tube, nitrogen inlet and rubber septum was charged with NaH (63 mmol, 2.52 g of a 60% suspension in mineral oil) and dry DME (100 mL). Cyclic sulfate **7** (30 mmol, 6.01 g) and methyl benzylideneglycinate (30 mmol, 5.31 g) in dry DME (50 mL) were added in one portion via NH_4Cl and chloroform (90 mL) was added. The two phases were separated, the aqueous layer extracted with chloroform (90mL), the organic layer dried over $MgSO_4$, and the solvents evaporated to give the crude alkylated imine **8** in nearly quantitative yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13-1.18 (m, 1H), 1.50-1.58 (m, 2H), 1.68-1.92 (m, 3H); 3.48-3.54 (m, 3H), 3.69 (s, 3H); 7.38-7.42 (m, 3H), 7.75-7.79 (m, 2H) and 8.52 (s, 1H).

12 Compound **9** : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54-1.58 (m, 1H), 1.62-1.72 (m, 1H); 1.72-2.11 (m, 5H), 3.63 (t, J = 6.2Hz, 2H), 3.73 (s, 3H) and 9.20 (br, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.75, 24.52, 25.81 ,32.00, 38.52, 44.19, 53.31 and 169.5.

13. Aminoacid **3** : $[\alpha]_D^{20}$ -57.5 (c 1, MeOH); m.p. : 200°C (dec.). ^1H NMR (D_2O, 300 MHz) δ 1.11-1.16 (m, 1H), 1.37-1.49 (m, 2H), 1.66-1.95 (m, 4H), 2.74-2.83 (m, 1H) and 3.06-3.13 (m, 1H). ^{13}C NMR (D_2O, 75.5 MHz) δ 17.91, 18.41, 20.86, 21.07, 42.14, 43.89 and 178.19. Mass spectrum calcd. for $C_7H_{11}NO_2$: $[M\cdot]^+$ 141.0790; Found 141.0797.

14. Crystal of **10** : $C_{12}H_{19}NO_4$, 0.24 x 0.26 x 0.32 mm, monoclinic, a = 9.220(3), b = 11.457(4), c = 6.365(9) Å, β = 102.52(7), V = 1656(1)$Å^{-3}$, space group $P2_1$, and Z = 2.

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