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PRACTICAL SYNTHESIS OF (R)-γ-AMINO-β-HYDROXYBUTANOIC ACID (GABOB) FROM (R)-EPICHLOROHYDRIN

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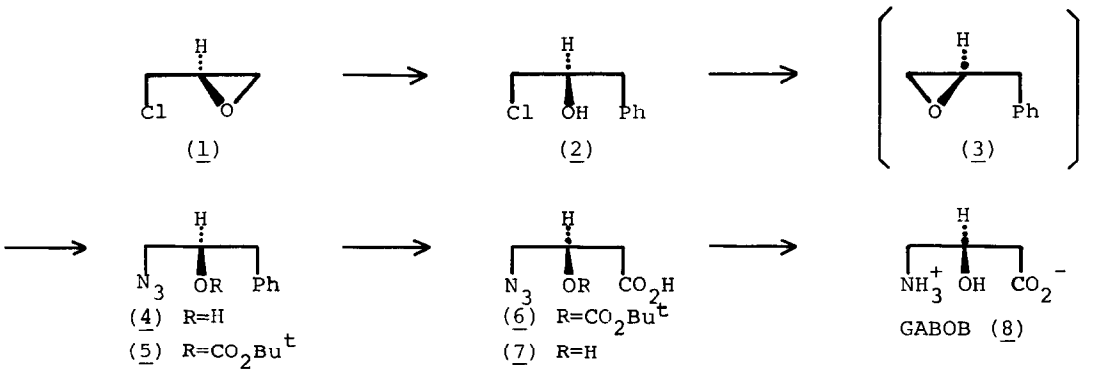
Summary: (R)-Epichlorohydrin has efficiently been converted to the hypotensive and antiepileptic compound, (R)-γ-amino-β-hydroxybutanoic acid (GABOB), in six steps in 57% overall yield.

(R)-Epichlorohydrin (1) has been readily available from racemic 2,3-dichloropropyl alcohol by microbial resolution followed by basic treatment.[1] As one indication of potential synthetic utility of this compound in the construction of optically active compounds, we report herein a six-step conversion of 1 into (R)-γ-amino-β-hydroxybutanoic acid (GABOB) (8) currently used as hypotensive and antileptic drug.[3] One of the practical problems of the synthesis of GABOB (8) is isolation of water-soluble low molecular intermediates as well as GABOB (8) itself. To avoid this problem, we designed to set phenyl group as carboxylic equivalent, azide as amino equivalent, and tertiary butoxy-carbonyl group as protecting group in the present synthesis.

Treatment of (R)-epichlorohydrin (1)[4] with phenyllithium in the presence of CuCN in THF[5] at -45°C gave the chlorohydrin (2),[6] $[\alpha]_D^{25}$ -3.72° (c 1.02, $CHCl_3$), in 93% yield. Reaction of 2 with sodium azide in dimethylformamide gave the azide (4), $[\alpha]_D^{24}$ +2.76° (c 2.1, $CHCl_3$), in 93% yield presumably via the epoxide intermediate (3). The secondary hydroxyl group of 4 was acylated with tert-butyl carbonic anhydride in methylene chloride in the presence of triethylamine to give the carbonate (5), $[\alpha]_D^{25}$ +18.28° (c 2.22, $CHCl_3$), in 88% yield. Oxidation



of 5 under Sharpless condition[7] afforded the carboxylic acid (6), $[\alpha]_D^{26}$ +13.12° (c 0.44, $CHCl_3$), in 81% yield. Removal of the protecting group of 6 could be effectively carried out in methylene chloride containing trifluoroacetic acid

(30%) to give rise to the carboxylic acid (7) quantitatively. The desired acid (7) could be obtained by simply evaporating the solvent and low volatiles from the reaction mixture. Catalytic reduction of 7 in aqueous methanol followed by evaporation of the solvent left a colorless crystalline solid which was recrystallized from aqueous ethanol to give pure (R)-γ-amino-β-hydroxybutanoic acid (GABOB) (8) in 92% yield as colorless prisms, mp 210-212°C (lit.[8] 212°C); $[\alpha]_D^{27}$ -23.17° (c 0.49, H_2O) (lit.[8] $[\alpha]_D^{25}$ -21.06° (c 2.2, H_2O)). The overall yield of 8 from 1 was 57% in six steps. Practically, the last two steps could be carried out in the same flask. Since methylation of GABOB (8) is known to produce carnitine (8:-$\overset{+}{N}H_3$=-$\overset{+}{N}Me_3$)[9] used for treatment of systemic and myopathic deficiencies,[10] the present synthesis also constitutes an alternative synthesis of the latter.

We believe that the present six-step synthesis of (R)-GABOB (8) from (R)-epichlorohydrin (1) is superior to the enantioselective syntheses described in the literature[11-17] from a view point of practical utility.

References and Notes

1. S. Takano, K. Ogasawara, Y. Sekiguchi, T. Kitamura, and N. Kasai, Japanese patent, to be opened: (R)-(1) was prepared in 73% yield by agitating (S)-2,3-dichloropropyl alcohol (obtained in ca. 40% yield by fermentation of racemic 2,3-dichloropropyl alcohol) with 1.5N-NaOH (1 eq.) in ether.
2. (R)-Epichlorohydrin (1) can also be prepared from D-mannitol, see: J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison, and D. E. McClure, J. Org. Chem., 43, 4876 (1978).
3. K. Ushikoba, Nippon Seirigaku Zasshi, 21, 616 (1959).
4. The material used in the present report was kindly provided by Osaka Soda Co., Ltd.: $[\alpha]_D^{25}$ -33.23° (c 5.814, MeOH) (lit.[2] $[\alpha]_D^{22}$ -34.3° (c 1.50, MeOH). Optical purity was reconfirmed by examination of ^{1}H-NMR spectrum (500 MHz) of MTPA ester derived from the azide (4).
5. (a) R. C. Elderfield and C. Ressler, J. Am. Chem. Soc., 72, 4059 (1950). (b) R. C. Elderfield, L. C. Craig, M. Lauer, R. T. Arnold, W. J. Gensler, J. D. Head, T. H. Bembry, H. R. Mighton, J. Tinker, J. Galbreath, A. D. Holley, L. Goldman, J. T. Maynard, and N. Picus, ibid., 68, 1516 (1946).
6. Satisfactory spectral (IR, NMR, Mass) and analytical (combustion and high resolution mass) data were obtained for all new compounds.
7. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, J. Org. Chem., 46, 3936 (1981).
8. M. Tomita and Y. Sendju, Hoppe-Seyler's Z. Physiol. Chem., 169, 263 (1927).
9. T. Kaneko and R. Yoshida, Bull. Chem. Soc. Japan, 35, 1153 (1962).
10. P. R. Borum, Nutr. Rev., 39, 385 (1981).
11. M. E. Jung and T. J. Shaw, J. Am. Chem. Soc., 102, 6304 (1980).
12. K. Bock, I. Lundt, and C. Pedersen, Acta Chem. Scand. B. 37, 344 (1983).
13. R. E. Rossiter and K. B. Sharpless, J. Org. Chem., 49, 3707 (1984).
14. A. S. Gopalan and C. S. Sih, Tetrahedron Lett., 25, 5235 (1984).
15. C. Fuganti, P. Grasselli, P. Casati, and M. Carmeno, ibid., 26, 101 (1985).
16. P. Renand and D. Seebach, Synthesis, 424 (1986).
17. C. Fuganti, P. Grasselli, P. Seneci, and P. Casati, Tetrahedron Lett., 27, 5275 (1986).

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