Tetrahedron Letters, Vol.22, No.37, pp 3555 - 3556, 1981
Printed in Great Britain

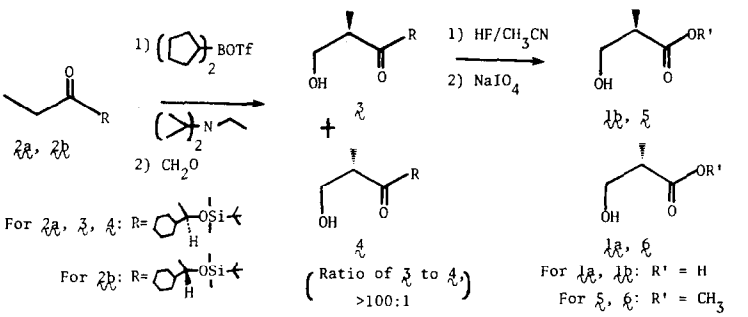
0040-4039/81/373555-02$02.00/0

ENANTIOSELECTIVE SYNTHESIS OF β-HYDROXYISOBUTYRIC ACID: A USEFUL SYNTHON IN THE SYNTHESIS OF POLYPROPIONATE-TYPE NATURAL PRODUCTS

William Choy, Philip Ma, and Satoru Masamune*
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Abstract: The aldol reaction of formaldehyde with the dicyclopentylborinyl enolate derived from S-(or R-) 1-tert-butyldimethylsilyloxy-1-cyclohexylbutan-2-one, followed by desilylation and sodium meta-periodate oxidation, provides R-(or S-) β-hydroxyisobutyric acid.

The utility of enantiomerically pure β-hydroxyisobutyric acid as a synthon has become evident in several recent syntheses of natural products, such as ionophore and macrocyclic antibiotics.[1] While the optically pure S-enantiomer (1a) is available by microbial oxidation of isobutyric acid,[2] derivatives corresponding to the pure R-enantiomer (1b) can only be prepared by propitious manipulation of the functionalities in 1a.[1d, 3] In view of the wide potential use of 1a and 1b we report herein that the synthesis of both pure enantiomers can be readily achieved via an aldol condensation, using a dialkylboron enolate derived from 1S-(or 1R-) tert-butyldimethylsiloxy-1-cyclohexylbutan-2-one (2a or 2b).[4]



The synthesis of 1b, in effect, followed the procedure described recently.[4] Thus, 2a is converted to its enolate with dicyclopentylborinyl trifluoromethanesulfonate[5] and diisopropylethylamine, and into this resulting enolate solution cooled to -78°C is introduced gaseous formaldehyde generated by pyrolysis of dry paraformaldehyde. After the usual workup, flash chromatography of the crude product provides a >100:1 mixture[6] of aldol diastereomers (3 and 4) in 90% yield. Successive treatments of the mixture (3 and 4) with hydrogen fluoride and sodium meta-periodate

afford 1b which is then methylated. The methyl ester 5 is, at minimum 98% optically pure,[7] identical (in IR, NMR, and R_f) with that derived from an authentic sample of S-β-hydroxyisobutyric acid.[8]

Use of 2b in the above sequence of reactions provides 1a with the equally high optical purity.

Procedure: To a cold (-78°C) dichloromethane (100 ml) solution of 1S-tert-butyldimethylsiloxy-1-cyclohexyl-2-butanone (2a) (5.0 g, 17.6 mmol) was added diisopropylethylamine (4.04 ml, 23.2 mmol) and then dicyclopentylborinyl trifluoromethanesulfonate (5.3 ml, 21.1 mmol). After stirring at 0°C for 2.5 h, the solution was cooled to -78°C. Gaseous formaldehyde, generated from paraformaldehyde (7.9 g, 264 mmol) at 140°C, was bubbled into the enolate solution with an argon stream. The reaction mixture was stirred at -60°C for 0.5 h and then warmed to 0°C. Methanol (50 ml), pH 7 phosphate buffer (50 ml), and 30% hydrogen peroxide (20 ml) were added in that order, and the resulting mixture was stirred for 0.5 h at room temperature. The usual workup including flash chromatography (300 ml silica gel 230-400 mesh; ether: petroleum ether, 35:65) afforded 3 (4.97 g, 90%) [^{1}H NMR (chloroform-d) δ 3.81 (d, J=3.8 Hz, 1H), 3.69 (dd, J=11.0 and 6.6 Hz, 1H), 3.57 (dd, J=11.0 and 4.4 Hz, 1H), 3.06 (m, 1H), 1.08 (t, J=7.3 Hz, 1H), 0.90 (s, 9H) and 0.06 (s, 6H), $[\alpha]_D^{25}$ = +15.03° (c 1.38 methanol)], contaminated with a small amount of 4 (<1%). This aldol product (3 and 4) was dissolved in cold (0°C) acetonitrile (50 ml) containing concentrated hydrogen fluoride (4 ml), and the resulting solution was stirred at room temperature for 4 h. After the addition of sodium bicarbonate (to pH~6), the extractive workup provided crude 1S-cyclohexyl-3R-methyl-1,4-dihydroxybutan-2-one (3.2 g, 100%), which was treated with sodium meta-periodate (6.8 g, 31.6 mmol) in 30% aqueous methanol (100 ml). The suspension was stirred at room temperature for 4 h. After removal of the neutral by-product (cyclohexylcarboxaldehyde), the acidic product represented chemically pure β-hydroxyisobutyric acid (1b) (1.6 g, 100%). Treatment of 1b (1.6 g) with ethereal diazomethane followed by distillation (60°C, 4 mm Hg) yielded 5 (1.6 g, 86%) [^{1}H NMR (chloroform-d) δ 3.72 (s, 3H), 3.70 (m, 2H), 2.70 (m, 1H), 2.36 (br s, 1H), 1.19 (d, J=7.4 Hz, 3H), $[\alpha]_D^{25}$ = -28.20° (c 1.34, methanol)]. The methyl ester of the S-acid (1a) obtained by microbial fermentation had $[\alpha]_D^{24}$ = +28.62° (c 1.23, methanol). In separate runs, all intermediates in the above sequence were purified and characterized in a standard manner.

Acknowledgments: We thank the National Institutes of Health (CA 28337) and Hoffmann-La Roche for financial support. P.M. is a National Cancer Institute Trainee (NCI, 2-T32-CA 09112-01). High resolution mass spectra were provided by the facility supported by NIH (Grant RR 00317).

References and Notes

1. (a) Monensin: Collum, D.B.; McDonald, J.H.; Still, W.C. J. Am. Chem. Soc., 1980, 102, 2117. 2118, 2120. (b) Ionophore antibiotic A-23187: Evans, D.A.; Sacks, C.E.; Kleschick, W.A.; Tabor, T.R.; ibid., 1979, 101, 6789. (c) Lasalocid A: Nakata, T.; Kishi, Y. Tetrahedron Lett., 1978, 2745. (d) α-Tocopherol: Cohen, N.; Eichel, W.F.; Lopresti, R.J.; Neukom, C.; Saucy, G. J. Org. Chem., 1976, 41, 3505.
2. Goodhue, C.T.; Schaeffer, J.R. Biotech., Bioeng., 1971, 13, 203.
3. (a) Branca, Q.; Fischli, A. Helv. Chem. Acta, 1977, 60, 925. Also see (b) Ohta, H.; Tetsukawa, H. Chem. Lett., 1979, 1379. (c) Sprecher, M.; Sprinson, D.R. J. Biol. Chem., 1966, 241, 868. (d) Retey, J.; Lynen, F. Biochem. Z., 1965, 342, 256.
4. Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. J. Am. Chem. Soc., 1981, 103, 1566.
5. Use of the 9-BBN or di-n-butylboron enolate in the aldol reaction resulted in inferior diastereoselection.
6. The ratio is based on the relative intensities of several sets of signals observed in the 250 MHz NMR spectrum of this mixture.
7. Determined from its optical rotation and from NMR using $Eu(hfbc)_3$.
8. Generously supplied by Dr. N. Cohen, Hoffmann-La Roche, N.J.

(Received in USA 3 June 1981)