A Combined Microbial/Chemical Synthesis of (+)-(R)-Methyloxirane
Having High Enantiomeric Excess1

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Closatonia thermoaccharoligolycum (ATCC 31960) converts glucose to (+)-(R)-propylene glycol; standard procedures transform this substance to (+)-(R)-methyloxirane (+(R)-propylene oxide) with enantiomeric excess >99%. This procedure is capable of generating this useful chiral synthon on a large scale.

Enantiomerically pure (+)-(R)-methyloxirane (4) is a valuable chiral synthon.3-4 This paper details a new method for the production of multigram quantities of optically pure (>99% ee) 4 from glucose (1) (Scheme I). Previous syntheses of this substance have started with ethyl (+)-(S)-lactate,5,8 alanine,7,8 propene,9 and acetol.10

Methods developed for butene oxide could also be applied to 4.11

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Fermentation of glucose in a glass carboy by the bacterium *Clostridium thermosaccharolyticum* (ATCC 31960)\(^{12}\) yielded an aqueous broth containing 7.9 g/L of (-)-(R)-1,2-propanediol (2). Concentration and filtration of the broth, continuous extraction into ether, and distillation yielded an aqueous broth containing (-)-(R)-1,2-propanediol (2) in the presence of Eu(tfc). Addition of racemic 1,2-propanediol (2) was monitored by \(^1\)H NMR spectroscopy in the presence of Eu(tfc)\(^{13}\). Reaction of 2 with hydrobromic acid in acetic acid afforded a mixture of acetoxymethopropanes, of which the major compound was 3. Treatment of this mixture with potassium pentanolate\(^{14}\) in pentan-1-ol generated the epoxide 4. The enantiomeric excess of 4, measured by \(^1\)H NMR spectroscopy in the presence of Eu(hfc), was >99% (Figure 1). The shift reagent studies were calibrated by the sequential addition of precisely determined amounts of either the opposite enantiomer or the racemic material to a known amount of the sample.

This procedure has several advantages over existing methods. The starting material, glucose, is readily available; other sugars such as xylose and mannose may also be used.\(^{12}\) The enantiomeric excess of the product is high. The procedure can be used to produce 4 on a large scale.

**Experimental Section**

**Materials and Methods.** Infrared spectra were recorded as neat films on NaCl plates. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer 241 polarimeter. The lanthanide shift studies were carried out with a Bruker AM 300 instrument. Concentrations of glucose, 1,2-propanediol, acetate, lactate, and ethanol in aqueous solution were measured by HPLC (column, AMINEX HPX57H, Bio-Rad Laboratories; solvent, 0.005 M H\(_2\)SO\(_4\); flow rate, 0.5 mL/min; column temperature, 45 °C; refractive index detection).

*C. thermosaccharolyticum* (ATCC 31960) is available from the American Type Culture Collection. This microorganism is non-pathogenic. Yeast extract was obtained from DIFCO. Deuteriated acetonitrile (1% Me\(_2\)Si) was purchased from ICN Biomedical, Inc. Eu(tfc) was dried in vacuo in a drying pistol at 50 °C and manipulated under a nitrogen atmosphere. All other chemicals and biochemicals were reagent grade and were used without further purification.

**Analysis of Optical Purity.** The splitting of enantiotopic protons of 2 in the presence of Eu(tfc) was monitored by \(^1\)H NMR spectroscopy, with CD\(_3\)CN as a solvent.\(^{15}\) Calibration of the shift study was as follows. Separate standard solutions of the sample and of the S enantiomer were made in volumetric flasks.

Precisely determined amounts of the standard solution containing the S enantiomer were then added by syringe; continued addition of the solution increased the intensity of the signals corresponding to the S enantiomer, which were resolved at the base line from those corresponding to the R enantiomer. Signals corresponding to the S enantiomer were not observed with the standard solution containing the sample but were observed when the ratio of the sample standard solution to the S enantiomer standard solution was 99.5:0.5. Drying the commercially obtained shift reagent enhanced resolution. For compound 4, Eu(hfc) in CDCl\(_3\) was used as the lanthanide shift reagent. Stepwise addition, as above, of precise amounts of racemic material calibrated the study.

**Fermentation of Glucose.**\(^{16}\) Solutions containing the following compounds were prepared in distilled water and were autoclaved at 121 °C for 30 min: (1) 7.0 g of NaCl, 10.44 g of MgCl\(_2\)-6H\(_2\)O, 0.9 g of CaCl\(_2\)-2H\(_2\)O, and 14 mg of sodium resazurin (a redox indicator) in a total volume of 0.7 L; (2) 2.0 g of yeast extract, 20.3 g of K\(_2\)HPO\(_4\), 10.5 g of KH\(_2\)PO\(_4\), 9.1 g of (NH\(_4\))\(_2\)SO\(_4\), 35 mg of FeSO\(_4\)-7H\(_2\)O in a total volume of 0.7 L; (3) 315 g of D-glucose in a total volume of 0.7 L; (4) 119 g of NaHCO\(_3\) and 3.5 g of L-cysteine hydrochloride in a total volume of 4.2 L.

Solution 4 was prepared in a 5-gal Pyrex carboy sealed with a three-hole rubber stopper containing three stainless steel tubes; one tube served as an entrance port for CO\(_2\), one was attached to a paraffin oil bubbler to allow the escape of H\(_2\) and CO\(_2\) during the fermentation, and one was a sampling port. The solutions were cooled to below 45 °C, and then the first three solutions were added aseptically to the carboy. The carboy was sparged with CO\(_2\) for 20 min or until the disappearance of the red color, due to the oxidized form of resazurin, indicated that the medium was free of oxygen. The carboy was then heated to 60 °C in an incubator and inoculated with 0.7 L of a vigorous culture of *C. thermosaccharolyticum* grown in an anaerobic flask\(^{15}\) containing...
the above medium. The fermentation was stopped after 37 h at which time analysis by HPLC indicated 7.9 g/L of 2, acetate, lactate, and ethanol were also produced. In practical use, the addition of resazurin and the analysis by HPLC are not necessary. To accommodate foaming, a 5-gal carboy should contain no more than 15 L of medium. The periodic addition of antifoam (FG-10, Dow-Corning, concentration 50.5 g/L) can control foaming.

Purification of (+)-HO-1-01 followed the literature1 to yield 6.8 g (121 mmol, 88%) of a clear, colorless liquid whose 1H NMR spectrum1 identified it as mainly 8; 1H NMR spectroscopy indicated the presence of approximately 6% of 1-acetox-2-bromopropanone. Conversion of the mixture (25.0 g, 138 mmol) to 4 by treatment with potassium pentanolate in pentanol-1-ol followed the literature14 to yield 6.8 g (121 mmol, 88%) of 4 as a clear, colorless liquid; bp 38-39 °C (lit.15 bp 34-35 °C); ee >99%; [α]D +18.0° (c 5.73, CCl4) [lit.15 [α]D +19.13° (c 5.66, CCl4)]; 1H NMR spectral data were in agreement with those in the literature.15

Registry No. 1, 50-99-7; 2, 4254-14-2; 3, 99457-42-8; 4, 15446-41-2; (S)-H3CCHBrCH20Ac, 109245-62-1.

(18) The fermentation was repeated on a 15-L scale with similar results.

**Synthesis of Functionalized Bicyclic Dioxopiperazines via Intramolecular Epoxide Opening**

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As part of a program directed at synthesizing and studying unnatural analogues of the natural antibiotic bicyclomycin,1 the carbocyclic bicyclo[3.2.2] and bicyclo[2.2.2] olefins 1 and 2 were chosen as potentially interesting targets. It was reasoned that omission of the bridging ether oxygen in the more highly strained bicyclo[3.2.2] and -[2.2.2] ring systems would impart both increased chemical stability2 and increased biological reactivity to these analogues. Since neither functionalized ring system has been reported in the literature,3,4 a new approach had to be devised that would produce useful quantities of 1 and 2. In this paper is described a convenient and practical synthesis of these unusual bicyclic dipeptides using an intramolecular enolate epoxide cyclization reaction.

(18) The fermentation was repeated on a 15-L scale with similar results.

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(2) Bicyclomycin is known to undergo under acidic catalyzed ring-opening reactions resulting from scission of bridging-ether linkage, see: Maag, H.; Blount, J. F.; Coffen, D. L.; Steppe, T. V.; Wong, F. J. Am. Chem. Soc. 1978, 100, 6786.
(4) Kemp et al. have used a bicycle[2.2.2] dioxopiperazine as an intermediate in the preparation of 8-turn-inducing dipeptide analogues, see ref 3a and Kemp, D. S.; McNamara, P. E.-J. Org. Chem. 1985, 50, 5834. Syntheses of the bicyclic materials reported herein have potential application in this area.

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