Table III. Spectral Characterization

product	^{1}H NMR ($CDCl_3/Me_4Si$), δ
4b	8.27 (s, 2 CHO), 7.23 (s, C_6H_5), 3.52 (s, CH_2)
4e	8.10 (s, 2 CHO), 6.87 (s, 2 H), 2.25 (s, p-CH_3), 2.09 (s, 2 o-CH_3)
4f	8.60 (s, 2 CHO), 7.32 (s, C_6H_5)
4g[a]	9.20 (very br s, OH), 8.53 (s, 2 CHO), 7.87 (dd, J = 3.7 and 1.3 Hz, 1 H), 7.37 (dd, J = 5.0 and 1.3 Hz, 1 H), 7.05 (dd, J = 5.0 and 3.7 Hz, 4′-H)
4h	14.0 (very br s, OH), 8.48 (br d, 2 CHO), 1.20 (s, 3 CH_3)
4i	14.13 (t, J = 5.8 Hz, OH), 8.38 (d, J = 5.8 Hz, 2 CHO), 2.03 (br, 3 H), 1.77 (pseudo d, 6 CH_2)
5b[b]	9.01 (s, 1-H), 7.03 (s, C_6H_5), 6.65 (s, 3-H), 3.82 (s, OCH_3), 3.40 (s, CH_2)
6b	9.01 (s, CHO), 7.12 (s, C_6H_5), 6.69 (s, CHN), 3.79 (s, CH_2), 2.92 (s, NMe_2)
6c	8.80 (d, J = 2 Hz, CHO), 6.35 (s, CHN), 3.03 (s, NMe_2), 1.26 (d, J = 7 Hz, 2 CH_3)
6d[b]	8.77 (d, J = 1.7 Hz, CHO), 6.27 (s, CHN), 3.03 (s, NMe_2), 1.83 (br m, C_4H_7)
6e	8.88 (s, CHO), 6.72 (s, 3 H), 2.67 (s, NMe_2), 2.23 (s, p-CH_3), 2.03 (s, 2 o-CH_3)

[a] In CD_3COCD_3. [b] In CCl_4.

preparation[17] of the "dianions" **2a** and **2b** containing the unbranched propionic acid moiety is carried out as in procedure A, but the vacuum distillation must be omitted. The formylating reagent **3** (120 mmol, prepared in 40 mL of DMF as *solvent*) is added dropwise at −70 °C, and the mixture is stirred at −28 °C for 90 min and poured into the aqueous workup solution. If hydrolysis is carried out by stirring with iced 2 N hydrochloric chloric acid for 1 h, benzylmalonaldehyde (**4b**, 33%) can be isolated from the acidic product fraction. Working up at pH ca. 7.7 with aqueous phosphate buffer rather than with HCl yields 30% of the methyl ether **5b** by distillation of the neutral product fraction. 2-Benzyl-3-(dimethylamino)propenal (**6b**) is obtained if the reaction mixture is quenched with K_2CO_3 as in procedure A. After heating to 50 °C prior to workup, the resulting **6b** is produced in similar yield (33%) but is heavily contaminated by diisopropylformamide (from **3** and diisopropylamine).

Methylmalonaldehyde[24] (**4a**) is amphoteric[7,23] and hence difficult to isolate; the yield of its sodium salt was therefore determined by conversion to a vinamidinium perchlorate with 2 equiv of *p*-toluidine.

4-(Chloromethylene)morpholinium Chloride (9). Oxalyl chloride (0.86 mL, 10.0 mmol) is added dropwise at 0 °C to a solution of 4-formylmorpholine (1.00 mL, 10.0 mmol) in 10 mL of methylene chloride. Evolution of gases starts slowly, becomes vigorous, and ceases after a few minutes at room temperature; continued stirring for 30 min yields a colorless suspension.

N,N-Dimethylchloromethaniminium chloride[25] (**10**) is prepared from oxalyl chloride and DMF in the same manner.

2-(2,4,6-Trimethylphenyl)propanedial (4e). General Procedure C for Arylmalonaldehydes 4e–g from Enamines 7 and 8, Scheme II. A mixture of crude 4-[2-(2,4,6-trimethylphenyl)-1-ethenyl]morpholine[16] (**7e**, 5.2 mmol) and 4-(chloromethylene)morpholinium chloride (**9**, 6.0 mmol) in 20 mL of dichloromethane is kept in a refrigerator at 4 °C for 13–20 h. (Prolonged treatment at higher temperatures results in decomposition.) The dark red, clear solution is freed from the solvent by vacuum distillation, dissolved in 5 mL of 50% aqueous NaOH plus 10 mL of 1,2-dihydroxyethane, and heated at 65–100 °C for 9–24 h. The alkaline solution is diluted with 50 mL of water, extracted to remove impurities, and then acidified and extracted into methylene chloride. The residue recovered from the dried extracts crystallyzes on digestion with hot CCl_4 (5 mL) to give spectroscopically pure **4e** (Table III) with mp 166–175 °C. Repeated extraction with boiling diethyl ether leaves the analytically pure material (Table II) at the expense of great losses.

***tert*-Alkyl-Substituted Malonaldehydes 4h and 4i from Enamines, Scheme II.** Procedure (C) is followed but, omitting vacuum distillation, the reaction mixtures are stirred with ice for 8 h (**4h**) or 2 h (**4i**). The resulting acidic two-phase systems are treated with excess 2 N sodium hydroxide solution; after separation from nonacidic byproducts, **4h** and **4i** are obtained by acidification.[10,12] The crude (1-adamantyl)malonaldehyde (**4i**) is sufficiently pure to show ^{1}H NMR triplet splitting of its OH signal at room temperature.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for their generous support.

Registry No. **1a**, 79-09-4; **1b**, 501-52-0; **1c**, 503-74-2; **1d**, 6540-33-6; **1e**, 4408-60-0; **1f**, 103-82-2; **1g**, 1918-77-0; **1h**, 1070-83-3; **1i**, 4942-47-6; **3**, 21511-55-7; **4a**, 57325-58-3; **4b**, 88905-12-8; **4e**, 88905-13-9; **4f**, 4432-64-8; **4g**, 88905-14-0; **4h**, 88905-15-1; **4i**, 88905-16-2; **5b**, 88905-17-3; **6b**, 17773-58-9; **6c**, 87234-38-6; **6d**, 51007-69-3; **6e**, 88905-18-4; **7e**, 58047-49-7; **9**, 59611-75-5; **10**, 3724-43-4; dimethylformamide, 68-12-2; dimethyl sulfate, 77-78-1; oxalyl chloride, 79-37-8; 4-formylmorpholine, 4394-85-8.

Synthesis of Chiral Acetic Acid by Chirality Transfer from D-Glucose

Koji Kobayashi,† Katsumi Kakinuma,‡ and Heinz G. Floss*†

Department of Medicinal Chemistry and Pharmacognosy, Purdue University, West Lafayette, Indiana 47906, and Laboratory for Chemistry of Natural Products, Tokyo Institute of Technology, Nagatsuta-cho, Midori-ku, Yokohama 227, Japan

Received October 14, 1983

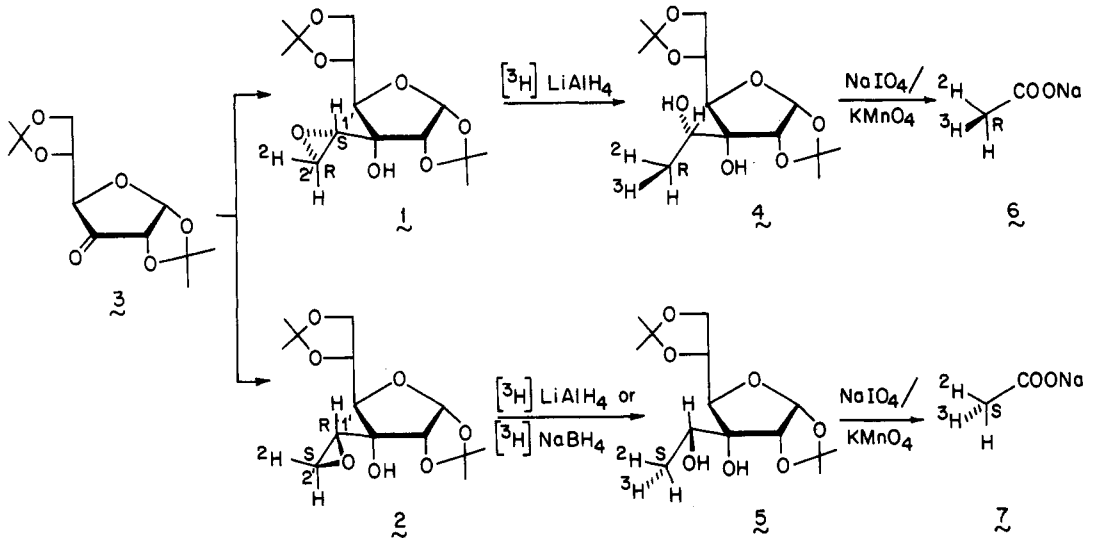
Although a number of approaches have been described,[1] there is still a need for more efficient methods for the synthesis of compounds containing chiral methyl groups of high configurational purity for studies on the cryptic stereochemistry of bioorganic reactions. One of us recently described[2] a new synthesis of chiral [2-^{2}H]glycine using D-glucose as chiral template. The key intermediates in the synthesis, (1′*S*,2′*R*)-**1** and (1′*R*,2′*S*)-**2**, were prepared from the readily available[3,4] 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-3-hexulofuranose (**3**) in four steps by stereoselective addition of acetylene, deuteration of the acetylenic hydrogen, stereospecific reduction to a deuterated (*E*)-ethenylcarbinol and epoxidation.[5] It was suggested[2] that the same intermediates could also be converted to chiral acetic acid. We now report the implementation of this suggestion.

Treatment of **1** or **2** with [^{3}H]$LiAlH_4$ in tetrahydrofuran (THF) gave the corresponding methylcarbinols **4** or **5** carrying a chiral methyl group, which were oxidized with permanganate/periodate[6] to acetic acid (Scheme I). Chirality analysis of the acetic acid by the method of Cornforth et al.[7] and Arigoni and co-workers[8] under the conditions described[9] gave F values[10] of 22.5 ± 0.3 for the material from the *S* epoxide **2**, indicating 95% ee of (*S*)-[2-^{2}H,^{3}H]acetate. The material from the *R* epoxide **1** had F = 79 ± 1.7, corresponding to 100% ee (*R*)-[2-^{2}H,^{3}H]acetate. Although the radiochemical yield is only modest (0.4–1% based on [^{3}H]$LiAlH_4$), owing undoubtedly to extensive decomposition of the tritiated metal hydride

* Present address: Department of Chemistry, The Ohio State University, Columbus, OH 43210.
† Purdue University.
‡ Tokyo Institute of Technology.

0022-3263/84/1949-1290$01.50/0

Scheme I



during the slow epoxide ring-opening reaction, the chiral purity of the resulting [2-^{2}H,^{3}H]acetic acid is excellent.

In view of the low radiochemical yield and the high cost of tritiated $LiAlH_4$, we explored the use of the less expensive [^{3}H]$NaBH_4$ for the epoxide ring opening. Reduction of *S* epoxide **2** with [^{3}H]$NaBH_4$ in Me_2SO at 50 °C[11] gave **5** in 10.6% radiochemical yield, together with a more polar compound containing 3% of the tritium. Chromatographic separation and permanganate/periodate oxidation of **5** produced acetic acid **7** (F = 21.8 corresponding to 97% ee *S* isomer) in 86% yield. Similarly, the (1′*R*,2′*R*)-[2′-^{2}H$_1$]epoxide[5] produced acetic acid **6** (F = 76.5, 91% ee *R* isomer) in 10.5% overall radiochemical yield.

Experimental Section

(a) Reduction with [^{3}H]$LiAlH_4$. To a solution of *R* epoxide **1** (80 mg, 0.265 mmol, 99% ^{2}H) in 1.5 mL of dry THF was added $LiAlH_4$ (1 mg) at 0 °C under an argon atmosphere. After stirring for 10 min, a suspension of [^{3}H]$LiAlH_4$ (2.4 mg, 11.1 mCi) in 0.5 mL of dry THF was added, and the mixture was stirred for 1.5 h at room temperature. $LiAlH_4$ (10.1 mg, 0.265 mmol) was then added and stirring was continued for 1 h at room temperature. The mixture was diluted with ether and excess reagent was decomposed with water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to leave a residue (175 μCi), which was purified by preparative layer chromatography (silica gel, *n*-hexane–ether, 7:3) to give the (*R*)-methyl glycol **4** (76.5 mg, 146 μCi). To 68.9 mg (131.4 μCi) of the latter in 112 mL of water was added 40 mg of K_2CO_3 and 28 mL of oxidation mixture (584 mg (2.73 mmol) of $NaIO_4$ and 11.1 mg (0.07 mmol) of $KMnO_4$). After stirring for 16 h at room temperature, 1 mL of concentrated H_2SO_4 was added, and the mixture was subjected to steam distillation. Neutralization of the distillate with 0.1 N NaOH and evaporation to dryness gave sodium (*R*)-[2-^{2}H,^{3}H]-acetate **6** (96.8 μCi).

Similarly, reduction of 100 mg of *S* epoxide **2** with [^{3}H]$LiAlH_4$ (13.9 mCi) gave 88 μCi of (*S*)-methyl glycol **5**, which was oxidized to produce 58.9 μCi sodium (*S*)-[2-^{2}H,^{3}H]acetate **7**.

(b) Reduction with [^{3}H]$NaBH_4$. To a solution of *S* epoxide **2** (75.8 mg, 0.25 mmol) in dry Me_2SO (0.66 mL) was added $NaBH_4$ (0.2 mg) under an argon atmosphere, and the mixture was stirred for 20 min at 50 °C. [^{3}H]$NaBH_4$ (12.5 mCi, 1.4 mg, specific activity 341 mCi/mmol) was then added. After stirring for 24 h at 50 °C, excess $NaBH_4$ (16.9 mg, 0.447 mmol) was added and stirring was continued for 6 h. The reaction mixture was diluted with ether (40 mL), washed four times with brine, dried over $MgSO_4$, and concentrated in vacuo to a residue, which was purified by preparative layer chromatography (silica gel, *n*-hexane/ether, 1:1, three developments) to give (*S*)-methyl glycol (29.0 mg, 1.32 mCi, 10.6% radiochemical yield) and a more polar compound (36.1 mg, 0.41 mCi). Oxidation of the glycol gave sodium (*S*)-[2-^{2}H,^{3}H] acetate **7** (1.13 mCi, 85.8% radiochemcial yield, F = 21.8).

Under identical conditions, reduction of (1′*R*,2′*R*)-[2-^{2}H]epoxide[5] (0.25 mmol) with [^{3}H]$NaBH_4$ (12.5 mCi) gave (*R*)-methyl glycol (32.6 mg, 1.52 mCi, 12.2% radiochemical yield), which was oxidized to produce sodium (*R*)-[2-^{2}H,^{3}H]acetate **6** (1.31 mCi) of F = 76.5 in 86.2% yield.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Science and Culture and by Research Grant GM 11728 from the U.S. Public Health Service. We thank Ms. Razi Yazdanparast and Mrs. Kyung Lee for the chirality analyses of the acetate samples.

Registry No. **1**, 89103-63-9; **2**, 82977-95-5; **3**, 2847-00-9; **4**, 89032-30-4; **5**, 89103-64-0; **6**, 62678-94-8; **7**, 62678-90-4.

(1) Floss, H. G.; Tsai, M. D. *Adv. Enzymol.* **1979**, *50*, 243–302.
(2) Kakinuma, K.; Imamura, N.; Saba, Y. *Tetrahedron Lett.* **1982**, *23*, 1697–1700.
(3) Yoshimura, J.; Sato, K.; Hashimoto, H. *Chem. Lett.* **1977**, 1327–1330.
(4) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561–562.
(5) Alternatively, (1′*S*,2′*S*)- and (1′*R*,2′*R*)-[2-^{2}H]epoxide were prepared in three steps from **3** by $LiAl^2H_4$ reduction of the undeuterated ethynyl carbinol intermediate.
(6) v. Rudloff, E. *Can. J. Chem.* **1956**, *34*, 1413–1418.
(7) Cornforth, J. W.; Redmond, J. W.; Eggerer, H.; Buckel, W.; Gutschow, C. *Eur. J. Biochem.* **1970**, *14*, 1–13.
(8) Lüthy, J.; Retey, J.; Arigoni, D. *Nature (London)* **1969**, *221*, 1213–1215.
(9) Floss, H. G. *Methods Enzymol.* **1982**, *87*, 126–159.
(10) For the definition of F values and the calculation of enantiomeric purity (ee) from them, see ref 9.
(11) Bell, H. M.; Vanderslice, C. W.; Spehar, A. *J. Org. Chem.* **1969**, *34*, 3923–3926.

An Improved Synthesis of *S*-Adenosylhomocysteine and Related Compounds

Kondareddiar Ramalingam and Ronald W. Woodard*

College of Pharmacy, The University of Michigan, Ann Arbor, Michigan 48109

Received July 25, 1983

In our study on the structural requirements of the active site of the enzyme 1-aminocyclopropane-1-carboxylic acid (ACC) synthase, we had the occasion to prepare several *S*-adenosyl-L-homocysteine (SAH) analogues. ACC synthase is the pyridoxal phosphate requiring enzyme that

0022-3263/84/1949-1291$01.50/0