of compound **2**, on independent mass spectrometric analysis furnished molecular ions as a positive ion at m/e 1728 and a negative ion at m/e 1726. The expected molecular ion peak for $C_{76}H_{108}N_{16}O_{30}$ (compound **3**) is calculated as m/e 1725.82.

A linear gradient of acetonitrile (20–40% over 20 min) was run against 0.2 M triethylammonium phosphate buffer (pH 2.5) on a reverse-phase C-8 Zorbax analytical column (4.6 mm × 250 mm) maintained at 50 °C. The retention times (t_R) and k' values are summarized in Table III. Column eluent was detected at 214 nm. When a C-18 Zorbax analytical column (4.6 mm × 250 mm) with otherwise identical conditions was used, the retention times were somewhat longer. For example, compound 4 had a t_R of 9.84 min at a mobile-phase flow rate of 2 mL/min; the k' value was the same, within experimental error.

Registry No. **2**, 86846-53-9; **3**, 86853-41-0; **4**, 86853-43-2; Boc-Glu(OBzl)-OH, 13574-13-5; ammonium formate, 540-69-2; ACTH, 9002-60-2.

Cyclic Sulfur Esters as Substrates for Nucleophilic Substitution. A New Synthesis of 2-Deoxy-2-fluoro-D-glucose

Timothy J. Tewson

University of Texas Medical School at Houston, Division of Cardiology, Houston, Texas 77025

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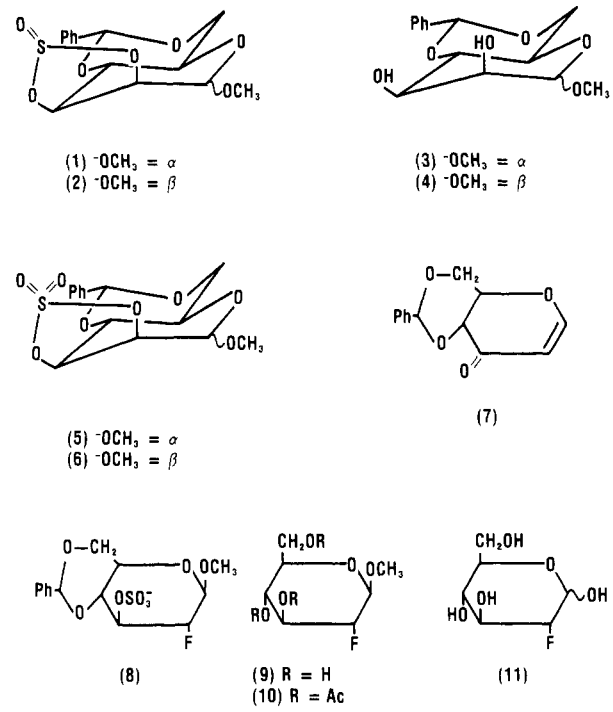
The 2,3-cyclic sulfites and sulfates of methyl 4,6-*O*-benzylidene-α- and -β-D-mannopyranoside were synthesized and examined as suitable substrates for the preparation of 2-deoxy-2-fluoro-D-glucose. Both sulfites on reaction with tetramethylammonium fluoride gave reaction products due to attack at sulfur by water. The methyl α-D-glycoside sulfate gave an α,β-unsaturated ketone (**7**). The β-methyl sulfate reacted cleanly with fluoride and other nucleophiles to give, after hydrolysis, the 2-substituted 2-deoxyglucose compounds.

2-Deoxy-2-fluoro-D-glucose-^{18}F has proved to be a useful radiopharmaceutical substance for studying glucose metabolism in man.[1,2] Because of the short half-life of fluorine-18 (110 min) both the radionuclide and the radiopharmaceutical compounds have to be freshly prepared for each study. However, the current synthesis, based upon F_2 addition to triacetal glucal,[3] is inefficient with respect to fluorine, which is the important criteria for evaluating yields with fluorine-18 reactions. Both 2-deoxy-2-fluoro-D-glucopyranosyl and -D-mannopyranosyl fluorides are formed and must be separated, and hydrolysis of the glycosyl fluoride leads to loss of half the remaining fluorine. As the production of fluorine-18 is very demanding on cyclotron time,[4] a synthesis of 2-deoxy-2-fluoro-D-glucose which can, in principal, utilize all the available fluorine-18 in the final product is desirable.

A synthetic route based upon fluoride ion displacement has the potential of utilizing all the available fluorine. High-yield reactions utilizing "no carrier added" fluorine-18 fluoride have been performed,[5–7] but nucleophilic displacement reactions at the 2-position of hexoses are difficult and normally give products other than those of direct displacement.[8]

Cyclic sulfur esters appeared to be attractive substrates to overcome these difficulties as the fully oxygenated sulfite or sulfate would be predicted to be a very good leaving group, and the transition states for alternative products would require highly strained tricyclic structures which should be unfavorable. However, after this work was completed the successful nucleophilic substitution of methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-[(trifluoromethyl)sulfonyl]-β-D-mannopyranoside at the 2-position was reported.[9] It appears that the nature and stereo-

Chart I



(1) Reivich, M.; Kuhl, D.; Wolf, A. P.; et al. *Circ. Res.* **1979**, *44*, 127.
(2) Ratib, O.; Phelps, M.; Huang, S. C.; Henze, E.; Selin, C. E.; Schelbert, H. R. *J. Nucl. Med.* **1982**, *23*, 577.
(3) Ido, T.; Wan, C.-N.; Cassella, V.; Fowler, J. S.; Wolf, A. P. *J. Labelled Compd. Radiopharm.* **1978**, *14*, 175.
(4) Nazaki, T.; Iwamoto, M.; Ido, T. *Int. J. Appl. Radiat. Isot.* **1974**, *25*, 393.
(5) Tewson, T. J.; Welch, M. J.; Raichle, M. E. *J. Nucl. Med.* **1979**, *19*, 1339.
(6) Tewson, T. J.; Welch, M. J. *J. Nucl. Med.* **1980**, *20*, 559.
(7) Gatley, S. J.; Hichwa, R.; Shaughnessy, W. J.; Nickles, J. R. *Int. J. Appl. Radiat. Isot.* **1981**, *32*, 211.
(8) Richardson, A. In "MTP International Review of Science: Organic Chemistry, Series One"; Aspinall, G. O., Ed.; University Park Press: Baltimore, MD, 1973; Vol. 7.
(9) Levy, S.; Elmaleh, D. R. *J. Chem. Soc., Chem. Commun.* **1982**, 972.

0022-3263/83/1948-3507$01.50/0

chemistry of the protecting groups at C-1 and C-3 and the stereochemistry of the leaving group at C-2 are the important factors for a successful reaction, rather than an intrinsic tendency for rearrangement.

The potential bifunctionality of the leaving group could be controlled by the use of manno derivatives where the departure of the axial oxygen at C-2 would be favored over the equatorial oxygen at C-3.

Reports on the use of cyclic sulfur esters as substrates for nucleophilic substitution are limited. Acid and base hydrolysis of both cyclic sulfites and sulfates are reported to give products arising from reaction at sulfur[10,11] and at carbon.[12,13] Grignard reagents react at sulfur (or oxygen)[14] while phenoxide[12] and fluoride[6] react at carbon.

The 2,3-cyclic sulfites of methyl 4,6-*O*-benzylidene-α- and -β-D-mannopyranosides were prepared by the reaction of the respective diols (**3** and **4**, Chart I) with thionyl chloride in carbon tetrachloride/pyridine. Both anomers crystalized as 1:1 diastereomeric mixtures (by gas chromatography) isomeric at sulfur.[15]

The methyl α- and β-D-glycoside cyclic sulfates (**5** and **6**) were prepared from the diols by reaction with sulfuryl chloride in triethylamine/ethyl acetate. The α compound gave a mixture of the disulfuryl chloride and the cyclic sulfate, but these could be separated by chromatography on Florisil.

All fluorination reactions were performed by using tetramethylammonium fluoride tetrahydrate which was evaporated to dryness three times under vacuum in a rotary evaporator from acetonitrile, with 10 mL of acetonitrile/mmol of fluoride each time. This removes some, but not all, of the water present. However, this product reacts cleanly and rapidly with both 1,2:5,6-di-*O*-isopropylideneallofuranose 3-*O*-trifluoromethanesulfonate[5] and ethylene glycol sulfite[6] to give the appropriate fluoro compounds. This preparation of tetramethyl ammonium fluoride has also been used successfully with fluorine-18 fluoride.[16]

Reaction of the sulfites **1** and **2** with the solutions of tetramethylammonium fluoride in equimolar ratios gave the diols as the only detectable products and in isolated yields of >90%. In the presence of excess fluoride the same products were isolated, and no SOF_2 could be detected. In reactions with a fourfold excess of **1** over tetramethylammonium fluoride a compound with the correct molecular ion for a fluorohydrin from **1** could be detected by GC/MS. However, the reaction was slow (~3 h at reflux) and the yield low (~10% based on fluoride), and so it was unsuitable for the primary purpose of this work. Presumably the water present is reacting at sulfur rather than fluoride at carbon.

The reaction of the methyl α-D-glycoside cyclic sulfate **5** with tetramethylammonium fluoride gave initially a very polar product that did not migrate on silic gel TLC plates with nonaqueous solvents. However, on a reverse-phase HPLC column the major product eluted at ~90% acetonitrile in a 0.01 M ammonium acetate → acetonitrile gradient, which is inconsistent with the TLC data. The reaction product, on evaporation of the solvent and addition of water, dissolved and then immediately crystalized. This compound was run on a TLC plate (R_f 0.8) with methylene chloride as a solvent and had the same retention time on HPLC as the peak observed directly in the reaction mixture.

This product had a carbonyl absorption at 1690 cm^{-1} and none of the peaks around 1400 and 1200 cm^{-1} characteristic of the sulfates. The UV spectrum had λ_{max} at 268 (log ε 3.2) with none of the fine structure associated with the benzylidene compounds. The NMR spectrum showed the aryl protons, the benzyl proton, a two-proton AB quartet at δ 5.6, a complex four-proton multiplet between δ 4 and 5, and no signal for the methoxyl group at δ 3.5. In the mass spectrum there was a molecular ion *m/e* 232 with strong peaks *m/e* 204 (M − 28) and 190 (M − 42). The compound was pure by TLC and GC but lost benzaldehyde very readily on standing. The data are consistent with the compound being 4,6-*O*-benzylidene-1,2-dideoxy-D-*erythro*-hex-1-enopyranos-3-ulose (**7**).[16]

The methyl β-D-glycoside cyclic sulfate **6** reacts rapidly and cleanly with tetramethylammonium fluoride to give a very polar product which is almost certainly tetramethylammonium methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-D-glucopyranoside 3-sulfate (**8**). The reaction is complete in less than 5 min at reflux and is remarkably insensitive to water. Addition of 3 equiv of water has no apparent effect on the reaction. With 10 equiv of water the reaction is appreciably slower, requiring 10 min to reach completion, but the overall yield of the final product is unchanged. Attempts to characterize the sulfate salt were unproductive as it is both hygroscopic and readily hydrolyzed by water producing benzaldehyde. Acid hydrolysis of the reaction mixture (2% HCl/MeOH or 10% trifluoroacetic acid/H_2O) followed by acylation gives methyl 2-deoxy-2-fluoro-β-D-glucopyranoside triacetate in 84% isolated yield from the sulfate **10**. Examination of the reaction mixture by gas chromatography showed that **10** comprised more than 98% of the products formed.

Rapid removal of the glycosidic methyl group proved more difficult. Refluxing the fluorination reaction mixture for several hours in 2 N HCl followed by neutralization and crystallization gave 2-deoxy-2-fluoro-D-glucose (**11**) in 60% overall yield. GC analysis of the reaction mixture following acylation showed the presence of a second compound, which from the mass spectrum appeared to be 1,6-anhydro-β-D-glucopyranose triacetate. This compound was identical on TLC, GC, and GC/MS with the product obtained by acylation of authentic 1,6-anhydro-β-D-glucopyranoside and contained no fluorine by ^{19}F NMR. Neither compound could be crystalized. The same compound accompanied the fluoro-D-glucose when pure methyl-2-deoxy-2-fluoro-β-D-glucose was subjected to these hydrolysis conditions. The formation of 1,6-anhydro compounds has been previously observed in the acid hydrolysis of glycosides.[22] However, the time scale of this reaction was prohibitive. Refluxing in 6 N HCl reduced the hydrolysis time to 15 min but again the fluoro sugar was accompanied by formation of the 1,6-anhydro compound, reducing the isolated yield of the sugar **11** to 40%. Similar results were obtained with other strong aqueous acids. However, treatment of the fluoride reaction product with boron tris(trifluoroacetate) (1 M in TFA) for 10 min at room temperature gave an overall isolated yield of the fluoro sugar **11** of 70% with very minor formation of the anhydroglucose.

The cyclic sulfate **6** was also reacted with tetramethyl ammonium hydroxide and bromide. The reactions were clean but slower than with the fluoride, requiring 1 h at

(10) Bunton, C. A.; De La Mare, P. B. D.; Greaseley, P. M.; Llewellyn, D. R.; Pratt, N. H.; Tillet J. *J. Chem. Soc.* **1958**, 4751.
(11) Brimacombe, J. D.; Foster, A. B.; Hancock, E. B.; Overend, W. G.; Stacy, M. *J. Chem. Soc.* **1960**, 201.
(12) Carlson, W. W.; Cretcher, L. H. *J. Am. Chem. Soc.* **1947**, *69*, 1952.
(13) Garner, H. K.; Lucas, H. J. *J. Am. Chem. Soc.* **1950**, *72*, 5497.
(14) Szmant, H. H.; Emerson, W. *J. Am. Chem. Soc.* **1956**, *78*, 454.
(15) Wang, Y.; Hogenkamp, H. *Carbohydr. Res.* **1979**, *76*, 131.
(16) Gatley, S. J.; Shaughnessy, W. J. *Int. J. Appl. Radiat. Isot.* **1980**, *31*, 339.
(17) Collins, P. M. *Carbohydr. Res.* **1969**, *11*, 125.

reflux. Glucose and methyl 2-bromo-2-deoxy-β-D-glucopyranoside were both isolated in excellent yields, 90% and 85%, respectively, after acid hydrolysis. However, clean removal of the glycosidic methyl group in the bromo compound was difficult. Refluxing in 2 N HBr followed by acylation and chromatography gave a noncrystalline 2-bromo-2-deoxy-D-glucose tetraacetate in an overall yield of 20%.

Experimental Section

^{1}H NMR spectra were recorded on a Varian EM-360 spectrometer at 60 MHz in $CDCl_3$ with Me_4Si as an internal reference. IR spectra were recorded on a Perkin-Elmer 299B spectrophotometer in CCl_4 solutions. Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. Vapor-phase chromatography was performed on a Hewlett-Packard 5880A by using a 6-ft OV-101 column between 150 and 250 °C. Mass spectra were recorded on a Finnigan quadrapole mass spectrometer, and GC/MS data were obtained on a direct inlet capillary column coupled to a Finnigan spectrometer. HPLC was performed on a Waters chromatograph with a μ-Bondapack C_{18} column with a mobile phase of 0.01 M ammonium acetate changing to acetonitrile in a linear program in 10 min. The compounds were detected by the UV absorption at 267 nm. UV spectra were recorded on a Gilford 2600 spectrophotometer in acetonitrile solution. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Preparation of Methyl 4,6-*O*-Benzylidene-α-D-mannopyranoside 2,3-Cyclic Sulfite 1. Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[18] (2.84 g, 10 mmol) was dissolved in dry carbon tetrachloride (120 mL) and pyridine (1.6 g, 21 mmol). The solution was cooled to 0 °C, and thionyl chloride (1.29 g, 10 mmol) in carbon tetrachloride (20 mL) was added slowly. After 2 h the solution was brought to room temperature, filtered, and evaporated to dryness. Trituration with heptane gave 2.31 g of **1** (72%) as crystalline solid (mp 118 °C) that was a 1:1 mixture of epimers by GC.

Fractional crystallization from carbon tetrachloride/petroleum ether gave the later eluting compound as a crystalline solid <95% pure by GC; mp 122–125 °C. Fractional crystallization of the mother liquors from heptane gave the earlier eluting compound as a poorly crystalline solid ~85% pure by GC; mp 80–85 °C. The IR spectra of the two compounds were identical: 1230, 1140, 1130, 1095, 1080 (s) 1060 (m), 985, 970 cm^{-1}; NMR (higher melting isomer) δ 7.4 (5 H, aryl protons, m), 5.6 (1 H), benzyl proton s), 5.1 (1 H, anomeric proton, s), 4.9–3.6 (6 H, H-2, H-3, H-4, H-5, H-6, complex), 3.4 (3 H), OCH_3, s); NMR (lower melting isomer) similar except the anomeric proton is at δ 4.7 (s); mass spectrum, *m/e* 328 (M^+), 327 (M − 1), both isomers by GC/MS.

Preparation of Methyl 4,6-*O*-Benzylidene-β-D-mannopyranoside (4). The standard procedure using methyl β-D-mannopyranoside,[19] benzaldehyde dimethyl acetal, tosic acid, and DMF was followed.[20] The product was chromatographed on silica to separate the mono- and dibenzylidene products and gave 38% of methyl 4,6-*O*-benzylidene-β-D-mannopyranoside[21] (**4**) crystallized from ethyl acetate: mp 178–9 °C; NMR δ 7.5 (5 H, aryl protons, m), 5.6 (1 H, benzyl proton, s), 4.6 (1 H, H-1 s), 4.5–3 (6 H, H-2, H-3, H-4, H-5, H-6, 3.4 (3 H, OCH_3, s), 2.8 (2 H, OH, br s that disappears on addition of D_2O); mass spectrum, *m/e* 282 (M^+), 281 (M − 1). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.38. Found: C, 59.64; H, 6.41.

Preparation of Methyl 4,6-*O*-Benzylidene-α-D-mannopyranoside 2,3-Cyclic Sulfate 5. Compound **3** (2.84 g, 10 mmol) was dissolved in freshly distilled ethyl acetate (150 mL) containing triethylamine (5.05 g, 50 mmol). The system was flushed with dry argon and sulfuryl chloride (2.7 g, 20 mmol) in ethyl acetate was run in slowly. After 2 h, the solution was filtered, evaporated to dryness, and chromatographed on silica, eluting with methylene chloride. The first compound off the column was crystalized from petroleum ether and gave 800 mg of crystals of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside-2,3-*O*-disulfuryl chloride: mp 114 °C; IR 1430 (s), 1375 (m), 1200, 1190, 1130, 1100, 1075, 985 (s) cm^{-1}; NMR δ 745 (5 H, aryl protons, m), 5.6 (1 H, benzyl proton, s), 5.1 (1 H, H-1, s), 4.95 (1 H, H-2, s), 4.3–3.7 (5 H, H-3, H-4, H-5, m), 3.4 (3 H), OCH_3, s); mass spectrum, *m/e* 478 (M^+, two-chlorine cluster with strong M − 1 peaks), 344 (M − SO_2Cl_2). Anal. Calcd for $C_{14}H_{16}S_2O_{10}Cl_2$: C, 35.08; H, 3.34; S, 13.36; Cl, 14.81. Found: C, 35.17; H, 3.34; S 13.57; Cl, 14.82.

The second compound off the column crystalized from heptane to give 2.1 g of crystals of **5**: mp 98 °C; IR 1410, 1220 (s) 1140, 1130 (m) 1100, 1085 990 (s) cm^{-1}; NMR δ 7.5 (5 H, aryl, m), 5.6 (1 H, benzyl proton, s), 5.1 (1 H, H-1, s), 5.0 (1 H, H-2, d, *J* = 1 Hz), 4.5–3.8 (5 H, H-3, H-4, H-5, H-6, m), 3.4 (3 H, s, OCH_3); mass spectrum, *m/e* 344 (M^+), 343 (M − 1). Anal. Calcd for $C_{14}H_{16}SO_8$: C, 48.83; H, 4.65; S, 9.30. Found: C, 48.83; H, 4.73; S, 9.32.

Preparation of Methyl 4,6-*O*-Benzylidene-β-D-mannopyranoside 2,3-Cyclic Sulfate 6. With the same procedure as for **5**, 2.8 g of sugar gave after chromatography on Florisil and crystallization from CCl_4 2.2 g of **6**: mp 157–159 °C dec; IR 1410, 1218, 1185, 985 (s); NMR δ 7.4 (5 H), aryl protons, m), 5.5 (1 H, benzyl proton, s), 5.1 (1 H, H-2, d, *J* = 1 Hz), 5.05 (1 H, H-1, s), 4.8 (1 H, H-3, d, *J* = 1 Hz), 4.7–3.9 (4 H, H-4, H-5, H-6, m), 3.7 (3 H, OCH_3, s); mass spectrum, *m/e* 344, (M^+), 343 (M − 1). Anal. Calcd for $C_{14}H_{16}O_8S$: C, 48.83; H, 4.65; S, 9.3. Found: C, 49.04; H, 4.93; S, 9.40.

Reaction of Methyl 4,6-*O*-Benzylidene-α-D-mannopyranoside 2,3-Cyclic Sulfite 1 with Tetramethylammonium Fluoride. Tetramethylammonium fluoride (165 mg, 1 mmol) was partially dissolved in freshly distilled acetonitrile and evaporated to dryness at 70 °C. This was repeated twice, and the resultant glassy solid was kept under high vacuum for 15 min. Acetonitrile (10 mL) and **1** (328 mg, 1 mmol) were added. The solution was refluxed under dry argon for 1 h, the solvent was evaporated, and the residue was dissolved in methylene chloride, washed with water, dried with sodium sulfate, and evaporated. Crystalization from ethyl acetate gave **3**.

Reaction of Methyl 4,6-*O*-Benzylidene-α-D-mannopyranoside 2,3-Cyclic Sulfate 5 with Tetramethylammonium Fluoride. Tetramethylammonium fluoride (165 mg, 1 mmol) was treated as before and dissolved in acetonitrile, and **5** (344 mg, 1 mmol) was added. The solution was refluxed for 3 h, when TLC showed total consumption of **5**. The solution was evaporated to dryness and water added. On gentle warming the residue dissolved and then immediately crystalized to give **7**: 110 mg; mp 125–127 °C;[17] IR 1690 cm^{-1}; (s); NMR δ 7.5 (5 H, aryl protons, m), 5.8 (1 H, benzyl proton, s), 5.6 (2 H, H-1, H-2, AB q), 5.4 (4 H, H-4, H-5, H-6, m); mass spectrum, *m/e* 232 (M^+), 204 (M − 28), 190 (M − 42).

Reaction of Methyl 4,6-*O*-Benzylidene-β-D-mannopyranoside 2,3-Cyclic Sulfate 6 with Tetramethylammonium Fluoride. Tetramethylammonium fluoride (165 mg, 1 mmol) was treated as before and then dissolved in acetonitrile (10 mL), **6** (344 mg, 1 mmol) was added, and the solution was refluxed for 10 min. The acetonitrile was then evaporated under vacuum to give **8** as a hygroscopic foam.

Hydrolysis of Methyl 4,6-*O*-Benzylidene-2-deoxy-2-fluoro-β-D-glucopyranoside 3-Sulfate. (a) The foam was dissolved in 10 mL of 2% HCl/MeOH and was refluxed for 10 min. The solvent was evaporated, and the residue was redissolved in water and neutralized with Dowex MR-3, followed by evaporation, to give a noncrystalline solid (200 mg). This was dissolved in acetic anhydride/pyridine (1:1) and kept at room temperature for 3 h. Evaporation and crystallization from ethanol gave **10**: 270 mg (84%); mp 128–129 °C; NMR δ 3.4 (3 H, OMe, s), 2.1 (6 H, OAc, s), 2.0 (3 H, OAc, s), 5.5–3.6 (complex). Mass spectrum, *m/e* 291 (M − OCH_3). Anal. Calcd for $C_{13}H_{19}FO_8$: C, 48.45; H, 5.9; F, 5.9. Found: C, 48.51; H, 6.08; F, 5.79.

(b) The foam was gently warmed with 6 N HCl until it dissolved and was then refluxed for 15 min. The solution was evaporated, and the residue was dissolved in water and desalted with Dowex MR-3. The water was evaporated and the resultant oil crystalized

(18) Robertson, G. *J. Chem. Soc.* **1934**, 330.
(19) Bott, H. G.; Haworth, W. N.; Hirst, E. E. *J. Chem. Soc.* **1930**, 2653.
(20) Evans, M. "Methods in Carbohydrate Chemistry"; Academic Press: New York, 1980; Vol 8.
(21) Garegg, P. *Ark. Kemi* **1965**, *23*, 255.
(22) Miller, J. N. *Adv. Carbohydr. Chem.* **1967**, *22*, 25.

from methanol/ethyl acetate to give 2-deoxy-2-fluoro-D-glucose: 80 mg (40%); mp 157–168 °C (lit. mp[23] 160–165 °C). This melting point was unchanged on mixing with authentic 2-deoxy-2-fluoro-D-glucose.

(c) The foam was treated with boron tris(trifluoroacetate) (5 mL; 1 M in TFA acid) for 5 min at room temperature. The TFA was evaporated, and the residue was dissolved in water and desalted with Dowex MR-3. Evaporation and crystallization gave 2-deoxy-2-fluoro-D-glucose (130 mg, 70%).

(23) Adamson, J.; Foster, A. B.; Hall, L. D.; Johnson, R. N.; Hesse, R. H. *Carbohydr. Res.* **1970**, *15*, 351.

Registry No. 1 (isomer 1), 86747-78-6; 1 (isomer 2), 86747-79-7; 2 (isomer 1), 86747-80-0; 2 (isomer 2), 86747-81-1; 3, 65530-26-9; 4, 86783-81-5; 5, 86747-82-2; 6, 86747-83-3; 7, 66183-24-2; 8, 86747-85-5; 10, 39110-57-1; 11, 86783-82-6; methyl 2-bromo-2-deoxy-β-D-glucopyranoside, 2880-98-0; 2-bromo-2-deoxy-D-glucose tetraacetate, 86783-83-7; methyl 4,6-*O*-benzylidene-α-D-mannopyranoside-2,3-*O*-disulfuryl chloride, 86747-86-6; methyl β-D-mannopyranoside, 22277-65-2.

A Simple and Efficient Synthesis of Chiral Acetic Acid of High Optical Purity

Koji Kobayashi,[†,§] Prabhakar K. Jadhav,[‡] Thomas M. Zydowsky,[†,§] and Heinz G. Floss*[†,§]

Department of Medicinal Chemistry and Pharmacognosy and Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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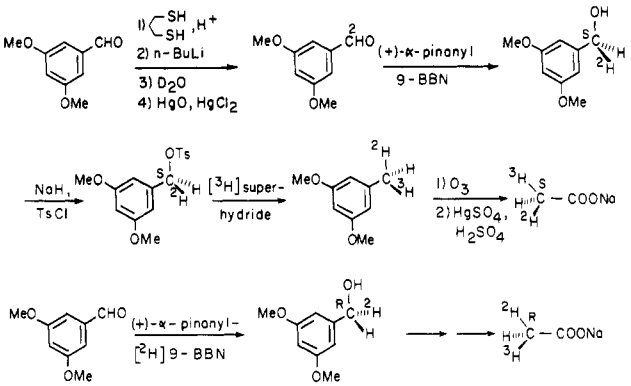
(*R*)- and (*S*)-[2-^{2}H,2-^{3}H]acetic acid of high chiral purity was synthesized in over 50% radiochemical yield. Reduction of 3,5-dimethoxy-[7-^{2}H]benzaldehyde with optically pure (+)-α-pinanyl-9-BBN and reduction of the unlabeled aldehyde with deuterated (+)-α-pinanyl-9-BBN gave 3,5-dimethoxy-(7*S*)- and -(7*R*)-[7-^{2}H]benzyl alcohol, respectively. Conversion to the tosylate and displacement with tritiated Superhydride gave 3,5-dimethoxy-(7*S*)- and -(7*R*)-[7-^{2}H,7-^{3}H]toluene, which was ozonized to produce *S* and *R* chiral acetic acid. Within the limits of detection, all the reaction steps proceeded completely (>98%) stereospecifically.

Chiral acetic acid, i.e., (*R*)- and (*S*)-[2-^{2}H,2-^{3}H]acetic acid has been synthesized by several enzymatic and chemical routes and by combinations of chemical and enzymatic reaction sequences.[1] An efficient synthesis should allow the generation of material of high chiral purity and high specific activity, the chiral purity of intermediates should be readily monitored, and radioactivity should be introduced late in the reaction sequence from an easily handled source of tritium. Most of the published routes do not meet one or more of these criteria. With this in mind we developed a new synthesis along the route outlined in Scheme I.

The general approach involved the sequential conversion of an aldehyde group into a stereospecifically deuterated hydroxymethyl group and then into a chiral methyl group[2-5] followed by oxidation to give chiral acetic acid. Dimethoxybenzaldehyde was selected as the starting material to facilitate the final oxidation step; the 3,5-substituted compound was chosen over the 3,4- and 2,4-isomers because the latter substitution significantly increased the reactivity of the benzylic position, producing very unstable benzyl tosylates. Conversion to the dithiane,[6] generation of the anion, quenching with D_2O, and treatment with mercuric oxide/mercuric chloride[4] produced the deuterated aldehyde (>98% ^{2}H) in 65% overall yield. Reduction of this aldehyde with (+)-α-pinanyl-9-borabicyclo[3.3.1]nonane (-BBN)[7] gave 3,5-dimethoxy-(7*S*)-[7-^{2}H]benzyl alcohol (83% yield, >98% ^{2}H). An aliquot of this material was converted to the (−)-camphanic acid ester and analyzed by proton NMR spectroscopy in the presence of shift reagent.[8] The absence of any detectable signal for the benzylic *pro-S* proton indicated that the material

Scheme I



contained a high (estimated ≳ 95%) enantiomeric excess of the *S* isomer. The optical purity of the product depends only on the degree of deuteration and the optical purity of the α-pinene used to generate the α-pinanyl-9-BBN; the reduction itself is completely stereospecific within the limits of detection. Optically pure (+)-α-pinene (100% ee) was prepared from commercial material (92% ee) by a

(1) For reviews, see: (a) Floss, H. G.; Tsai, M.-D. *Adv. Enzymol.* **1979**, *50*, 243–302. (b) Floss, H. G. *Methods Enzymol.* **1982**, *87*, 126–159. Floss, H. G.; Tsai, M.-D., Woodard, R. W. *Top. Stereochem.*, in press.

(2) The same general principle has been used before, e.g., by Lüthy et al.,[3] by Golding et al.,[4] and by Caspi and co-workers,[5] in different forms of implementation.

(3) Lüthy, J.; Retey, J.; Arigoni, D. *Nature (London)* **1969**, *221*, 1213–1215.

(4) Golding, B. T.; Ioannou, P. V.; Eckhard, I. F. *J. Chem. Soc., Perkin Trans.* 1 **1978**, 774–780.

(5) Caspi, E.; Shapiro, S.; Piper, J. *Tetrahedron* **1981**, *37*, 3535–3543.

(6) Seebach, D. *Synthesis* **1969**, 17–36.

(7) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352–2355.

(8) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274–275.

[†] Department of Medicinal Chemistry and Pharmacognosy.
[‡] Department of Chemistry.
[§] Present address: Department of Chemistry, The Ohio State University, Columbus, OH 43210.

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