SYNTHESIS OF THE MONODEOXYMONOFLUOROGLYCEROLS*‡

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ABSTRACT

The three monodeoxymonofluoroglycerols have been synthesised stero-specifically. 2-Deoxy-2-fluoroglycerol (**4**) was prepared in four steps from glycerol by using a fluoride-ion displacement of the sulphonyloxy group from 2-*O*-*p*-tolylsulphonyl-1,3-di-*O*-tritylglycerol. 1-Deoxy-1-fluoro-D- and L-glycerol (**8** and **13**) were synthesised in five and eight steps, respectively, from D-mannitol. 1-Deoxy-1-fluoro-D-glycerol (**8**) resulted from fluoride-ion displacement of the sulphonyloxy group from 2,3-*O*-isopropylidene-1-*O*-*p*-tolylsulphonyl-D-glycerol (**6**), followed by acid hydrolysis. 1-Deoxy-1-fluoro-L-glycerol (**13**) was prepared from its enantiomer (**8**) by inversion of configuration at C-2 in a sequence involving *p*-toluenesulphonylation, benzoate-ion exchange, and hydrolysis of benzoate groups.

INTRODUCTION

The three monodeoxymonofluoroglycerols in each of which a single hydroxyl group of glycerol is replaced by fluorine were required for isolated enzyme studies[1]. 2-Deoxy-2-fluoroglycerol† (**4**) has previously been obtained by Taylor and Kent[2]. By using simple aliphatic precursors, they performed a total synthesis of 2-deoxy-2-fluoro-DL-glyceraldehyde. In the course of a structural proof, they reduced this aldehyde to the fluoroglycerol **4**, which they obtained as a syrup and characterised as crystalline 2-deoxy-2-fluoro-1,3-di-*O*-*p*-tolylsulphonylglycerol (**5**). The di-*p*-toluenesulphonate **5** has also been reported by Pattison *et al.*[3], who applied bromine monofluoride addition to allyl bromide, and obtained a mixture of 1,2-dibromo-3-fluoropropane and 1,3-dibromo-2-fluoropropane. After reaction of this mixture with silver *p*-toluenesulphonate, crystalline di-ester **5** was isolated. We report here a convenient, four-step synthesis of crystalline 2-deoxy-2-fluoroglycerol (**4**), in 20% overall yield from glycerol.

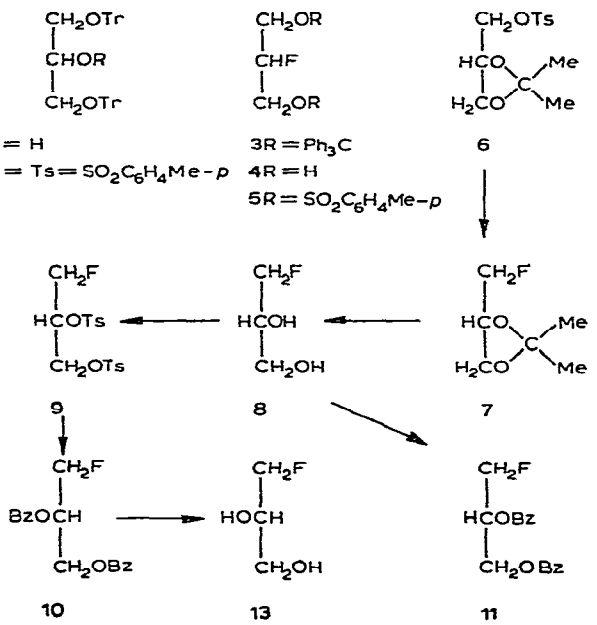
1-Deoxy-1-fluoro-DL-glycerol was first prepared[4] by hydrolysis of epifluorohydrin. Kun and Dummel have since described improved syntheses. In one method of

*Dedicated to Dr. Nelson K. Richtmyer in honour of his 70th birthday.
‡A preliminary account of this work has been published[1].
†The monohalo compounds are named throughout as glycerol derivatives.

preparation[5], the epoxide ring of glycidol was opened by reaction with potassium hydrogen difluoride, to give 1-deoxy-1-fluoro-DL-glycerol. Another route[6] involved displacement of the primary *p*-tolylsulphonyloxy group from 1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulphonyl-DL-glycerol by means of potassium fluoride in diethylene glycol, and subsequent hydrolytic removal of the isopropylidene group from the product. The present report describes use of a similar fluoride-ion displacement in the stereospecific synthesis of the enantiomeric 1-deoxy-1-fluoro-D- and L-glycerols, starting from D-mannitol.

RESULTS AND DISCUSSION

When 2-*O*-*p*-tolylsulphonyl-1,3-di-*O*-tritylglycerol[7] (**2**) was treated with a 1.4 molar excess of tetrabutylammonium fluoride in boiling acetonitrile, a crystalline precipitate separated from the reaction mixture. Preparative, layer chromatographic (p.l.c.) analysis showed this precipitate to be 2-deoxy-2-fluoro-1,3-di-*O*-tritylglycerol (**3**) containing ~6% of 1,3-di-*O*-tritylglycerol (**1**). The yield of crude, fluorinated derivative was 85%. Purification was conveniently effected by column chromatography on alumina, pure fluoro compound **3** being eluted with benzene. Removal of contaminating hydroxy compound **1** by crystallisation procedures was complicated by its persistent co-crystallisation with the fluoro analogue **3**. Similar tendencies of fluorinated carbohydrates to form isomorphous mixtures with corresponding hydroxy compounds have been reported[8]. That the hydroxy compound **1** should appear at all as a reaction product is probably a consequence of the difficulty of removing residual water from the amorphous, tetrabutylammonium fluoride reagent[9,10]. Acid hydrolysis removed the trityl ether protecting groups from the



purified fluoro derivative **3**, and distillation of the resulting syrup gave pure, crystalline 2-deoxy-2-fluoroglycerol (**4**). *p*-Toluenesulphonylation afforded the known[2], crystalline di-*O*-*p*-tolylsulphonyl derivative (**5**).

2,3-*O*-Isopropylidene-D-glycerol was prepared by cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol with lead tetraacetate, followed by reduction of the aldehyde with sodium borohydride[11]. *p*-Toluenesulphonylation gave 2,3-*O*-isopropylidene-1-*O*-*p*-tolylsulphonyl-D-glycerol[12] (**6**). Fluoride-ion displacement of the sulphonyloxy group from compound **6** was accomplished either with potassium fluoride in diethylene glycol or tetrabutylammonium fluoride in butanone. The scales and times of reaction were varied under both sets of conditions, and, in all experiments, a pure product, 1-deoxy-1-fluoro-2,3-*O*-isopropylidene-D-glycerol (**7**) with the same optical rotation ($[\alpha]_D$ +20°) was obtained. In the reaction involving potassium fluoride, compound **7** was continuously removed by distillation as the reaction progressed. When tetrabutylammonium fluoride in butanone was used, the product remained in contact with the reagents throughout the reaction period (2 to 4 days). The constancy of optical rotation of fluoro compound **7** suggests that proton abstraction from C-2 (leading to partial racemisation) does not occur under either set of conditions, and that product **7** is optically pure. No fraction corresponding to the olefin 1,2-*O*-isopropylidene-2-propene-1,2-diol (b.p. 104–106°) was obtained on distillation of the crude, fluorinated compound. Acid hydrolysis of **7** gave laevorotatory 1-deoxy-1-fluoro-D-glycerol (**8**), identical in all respects except optical activity with the racemic product[6].

p-Toluenesulphonylation of the fluoroglycerol **8** gave a syrup that was purified by p.l.c. to give chromatographically homogeneous di-ester **9**. Inversion of configuration at C-2 of **9** was caused by action of sodium benzoate in *N*,*N*-dimethylformamide; both sulphonyloxy groups of compound **9** were displaced, to give crystalline, laevorotatory 2,3-di-*O*-benzoyl-1-deoxy-1-fluoro-L-glycerol (**10**). That the displacement had occurred with 100% inversion of configuration at C-2 was confirmed by direct benzoylation of 1-deoxy-1-fluoro-D-glycerol (**8**), to give dextrorotatory 2,3-di-*O*-benzoyl-1-fluoro-D-glycerol (**11**).

Lands and Zschocke[13] prepared 1-*O*-benzyl-L-glycerol from 1-*O*-benzyl-D-glycerol by using a similar displacement of sulphonyloxy groups with total inversion of configuration; they employed acetate ion in ethanol as the nucleophile. However, their displacement reaction was accompanied by some hydrolysis of the diacetate product, and application of their reaction conditions to our system likewise resulted in a complex mixture of products.

Treatment of the laevorotatory dibenzoate **10** with methanolic hydrogen chloride gave dextrorotatory 1-deoxy-1-fluoro-L-glycerol (**13**); the magnitude of its optical rotation was the same as that of its (laevorotatory) enantiomer **8**.

In the preparations described, 1-deoxy-1-fluoro-D-and L-glycerols were synthesised in 12% and 4% overall yield, respectively, from D-mannitol. All three monodeoxymonofluoroglycerols could be obtained in a high state of purity, suitable for enzyme studies.

EXPERIMENTAL

General. — Melting points are uncorrected. Thin-layer chromatography (t.l.c.) was performed on Silica Gel G (Merck), and detection was effected with conc. sulphuric acid. P.l.c. was performed on glass plates (40 × 20 cm), coated with a layer (1.3 mm) of Silica Gel PF_{254} (E. Merck). Components were detected as bands of fluorescence or quenching on exposure to u.v. radiation (254 nm). G.l.c. was conducted isothermally on a column (2 m) of Silicone Gum Rubber E-301 (2.5%) on AW-DMCS Chromosorb G (80–100 mesh). The carrier gas was nitrogen, and the chromatograph was a Perkin–Elmer F-11 instrument, fitted with a flame-ionisation detector. Trimethylsilyl derivatives of hydroxy compounds were prepared for g.l.c. by using B.S.A. reagent (Pierce Chemical Company). Optical rotations were determined with a Bellinger and Stanley (Model A) polarimeter, with a 1.0-dm tube. N.m.r. spectra were recorded with a Varian A-60 spectrophotometer. Pyridine and acetonitrile were dried by distillation from phosphorus pentaoxide. Concentrations were performed under diminished pressure with the bath temperature below 40°, unless otherwise stated.

*2-Deoxy-2-fluoro-1,3-di-*O*-tritylglycerol* (**3**). — A solution of compound **2** (40 g; m.p. 159–160°, lit.[7] m.p. 155–156°) and tetrabutylammonium fluoride (20 g, 1.4 molar proportions) in acetonitrile (200 ml) was boiled under reflux for 3 days. The crystalline precipitate (27 g) was removed from the cooled reaction mixture by filtration, and well washed with ether. P.l.c. analysis (benzene) of the precipitate showed it to be crude **3** containing ~6% of compound **1**. Purification was effected by column chromatography on alumina (Camag M.F.C., neutral, Brockman activity 1). Elution with benzene gave a chromatographically pure (t.l.c., benzene) fraction which was recrystallized from ethyl acetate to give compound **3** (21.5 g, 68%), m.p. 172–175°. N.m.r. data (chloroform-*d*): δ 3.42 (quartet, 4 protons, H-α, $J_{\alpha,\beta}$ 5 Hz, $J_{\beta,F}$ 21 Hz); 4.75 (decet, 1 proton, H-β, $J_{\alpha,\beta}$ 5 Hz, $J_{\beta,F}$ 50 Hz); and 7.2–7.6 (complex, 30 protons, Ph groups).

Anal. Calc. for $C_{41}H_{35}FO_2$: C, 85.14; H, 6.06; F, 3.29. Found: C, 85.08; H, 5.96; F, 3.31.

2-Deoxy-2-fluoroglycerol (**4**). — A solution of **3** (8 g) in acetone (400 ml) and 2M hydrochloric acid (80 ml) was boiled for 2 h under reflux. Concentration of the hydrolysis mixture removed the acetone and caused precipitation of crystalline triphenylmethanol (7.2 g, ~100%) from the aqueous solution. The solid was removed by filtration and well washed with water. The filtrate and washings were combined, and stirred with Deacidite FF (CO_3^{2-}) resin until neutral, the suspension was filtered, and the filtrate was evaporated to a syrup which was distilled, to give crystalline 2-deoxy-2-fluoroglycerol (**4**) (1.0 g, 77%), b.p. 96°/3 torr, m.p. 39–40°. G.l.c. (90°) of the trimethylsilyl derivative showed less than 0.1% of impurity. N.m.r. data (deuterium oxide): δ 3.75 (quartet, 4 protons, H-α, $J_{\alpha,\beta}$ 5 Hz, $J_{\alpha,F}$ 25 Hz); and 4.66 (decet, 1 proton, H-β, $J_{\alpha,\beta}$ 5 Hz, $J_{\beta,F}$ 50 Hz).

Anal. Calc. for $C_3H_7FO_2$: C, 38.30; H, 7.45; F, 20.22. Found: C, 38.36; H, 7.63; F, 20.32.

2-Deoxy-2-fluoro-1,3-di-O-p-*tolylsulphonylglycerol* (**5**). — A mixture of 2-deoxy-2-fluoroglycerol (**4**, 0.26 g) and *p*-toluenesulphonyl chloride (1.6 g, 3 molar proportions) in pyridine (5 ml) was kept for 16 h at room temperature, and poured into ice–water (50 ml). The resulting, crystalline mass was removed by filtration, well washed with water, and recrystallised from ethanol, to give yellow needles of di-*p*-toluenesulphonate **5** (0.77 g, 69%), m.p. 107–108°. Treatment with charcoal and recrystallisation from ethanol gave colourless needles, m.p. 111–112° (lit.[3] m.p. 111–112°).

1-Deoxy-1-fluoro-2,3-O-*isopropylidene*-D-*glycerol* (**7**). — *Method A.* This procedure is a modification of that described[6] for preparation of the DL mixture. A stream of dry nitrogen was bubbled through a rapidly stirred solution of anhydrous potassium fluoride (30 g) in freshly distilled diethylene glycol (100 ml) at 160–165°. 2,3-*O*-Isopropylidene-1-*O*-*p*-tolylsulphonyl-D-glycerol[12] (**6**, 100 g) was added, and the colourless distillate was collected in two successive traps maintained at 0° and −20°, respectively. On this scale, distillation was complete in ~1.5 h. A solution of the distillate in ether was washed successively with ice-cold 0.5M hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (magnesium sulphate), and evaporated at atmospheric pressure; the residual liquid was distilled twice, to yield compound **7** (20 g, 43%), b.p. 126–127°, $[\alpha]_D^{22}$ +20.0° (*c* 5.0, ether). The g.l.c. and i.r. data for the dextrorotatory enantiomer **7** were identical with those for the racemic modification[6].

Method B. A mixture of compound **6** (16 g) and tetrabutylammonium fluoride (22 g) in butanone (250 ml) was boiled for 2 days under reflux, cooled, concentrated at atmospheric pressure to remove most of the butanone, and the material partitioned between ether and water. The ether layer was washed with water, dried (magnesium sulphate), and evaporated at atmospheric pressure. Distillation of the residual liquid gave compound **7** (4 g, 53%), b.p. 123–127°, $[\alpha]_D^{22}$ +20.0° (*c* 10.0, ether). The yield and physical constants of the product (**7**) were unchanged when the reaction mixture was allowed to boil for 4 days.

1-Deoxy-1-fluoro-D-*glycerol* (**8**). — Compound **7** (18.6 g) was added to rapidly stirred M hydrochloric acid (50 ml) at room temperature; the mixture became homogeneous after 5 min. The solution was kept overnight at room temperature and made neutral with Deacidite FF (CO_3^{2-}); the suspension was filtered and the filtrate was evaporated to a viscous syrup. Distillation gave compound **8** (9.6 g, 74%), b.p. 55°/0.2 torr, $[\alpha]_D^{22}$ −8.2° (*c* 10.0, water). G.l.c. (at 90°) of the trimethylsilyl derivative of diol **8** showed less than 0.1% of impurity; it was identical with that of the derivative of the racemic modification[6]. The i.r. spectrum of the laevorotatory enantiomer **8** was identical with that of the racemic modification.

2,3-Di-O-*benzoyl-1-deoxy-1-fluoro*-L-*glycerol* (**10**). — A solution of compound **8** (2.0 g) and *p*-toluenesulphonyl chloride (17.2 g, 4.2 molecular proportions) in pyridine (50 ml) was stirred for 4 days at room temperature, and poured into ice–

water (500 ml). The mixture was extracted with chloroform, and the extract was successively washed with 0.5M hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (magnesium sulphate), and concentrated. Purification by p.l.c. (benzene) gave syrupy compound **9** (7.6 g, ~100%), ν_{max}^{film} 1360, and 1180 cm^{-1} (sulphonate); no peak assignable to OH. The syrup was chromatographically homogeneous by t.l.c. (R_F 0.5 in 10:1 benzene–methanol).

A mixture of di-*p*-toluenesulphonate **9** (7.5 g) and dry sodium benzoate (19 g, 7.1 molecular proportions), in *N*,*N*-dimethylformamide (200 ml) was boiled for 6 h under reflux, cooled, and poured into chloroform. The mixture was well washed with water, dried (magnesium sulphate), and concentrated. Purification by p.l.c. (10:1 benzene–methanol) gave a syrup which crystallised from aqueous ethanol to give compound **10** (2.6 g, 41%), m.p. 50–51°, $[\alpha]_D^{22}$ −20.5° (*c* 10.0, ethanol); ν_{max}^{KBr} 1730 cm^{-1} (C=O). N.m.r. data (chloroform-*d*): δ 4.63 (doublet, 2 protons, H-3, $J_{2,3}$ 5.5 Hz), 4.73 (quartet, 2 protons, H-1, $J_{1,2}$ 4 Hz, $J_{F,1}$ 48 Hz), 5.61 (broadened decet, 1 proton, H-2, $J_{1,2}$ ~5 Hz, $J_{2,3}$ ~5 Hz, $J_{F,2}$ 21 Hz), 7.2–7.6 (complex, 6 protons, $Ph_{m,p}$), and 7.9–8.2 (complex, 4 protons, Ph_o). The i.r. spectrum of compound **10** was identical with that of its enantiomer **11** and that of the racemic modification **12**.

Anal. Calc. for $C_{17}H_{15}FO_4$: C, 67.55; H, 4.97; F, 6.29. Found: C, 67.55; H, 4.94; F, 6.30.

*2,3-Di-*O*-benzoyl-1-deoxy-1-fluoro-*D*-glycerol* (**11**). — A solution of compound **8** (0.5 g) in pyridine (10 ml) was treated with benzoyl chloride (2.0 g, 2.7 molecular proportions) at room temperature. After 18 h, the mixture was poured into ice–water (100 ml), and extracted with chloroform; the extract was successively washed with 0.5M hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried (magnesium sulphate). Concentration, and crystallisation from aqueous ethanol, gave the dibenzoate **11** (1.2 g, 75%), m.p. 50–51°, $[\alpha]_D^{22}$ +20.5° (*c* 10.0, ethanol).

*2,3-Di-*O*-benzoyl-1-deoxy-1-fluoro-*DL*-glycerol* (**12**). — Benzoylation of 1-deoxy-1-fluoro-DL-glycerol[6] by the foregoing procedure gave compound **12**, m.p. 50–51°.

*1-Deoxy-1-fluoro-*L*-glycerol* (**13**). — A solution of laevorotatory dibenzoate **10** (9 g) in methanolic hydrogen chloride (5% w/w) was boiled for 6 h under reflux, cooled, made neutral with Deacidite FF (CO_3^{2-}), and partitioned between chloroform and water. The aqueous layer was well washed with chloroform, and evaporated to a syrup. Distillation gave compound **13** (1.42 g, 50%), b.p. 55°/0.2 torr, $[\alpha]_D^{22}$ +8.2° (*c* 10.0, water) .G.l.c. (at 90°) of the trimethylsilyl derivative of diol **13** showed less than 0.1% of impurity; it was identical with that of the derivative of enantiomer **8**. The i.r. spectra of the enantiomers **8** and **13** were identical.

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