Synthesis of 3-*O*-(α-D-Glucopyranosyl)-1,2-di-*O*-stearoyl-L-glycerol, a 'Glucosyl Diglyceride'

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3-*O*-(3,4-Di-*O*-benzyl-α-D-glucopyranosyl)-1,2-*O*-isopropylidene-L-glycerol was converted into 3-*O*-(α-D-glucopyranosyl)-1,2-di-*O*-stearoyl-L-glycerol, a 'glucosyl diglyceride.' 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose was converted by acetyl chloride and hydrogen chloride into 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranosyl chloride, which was condensed with 1,2-di-*O*-(but-2-enyl)-L-glycerol under conditions shown previously to give predominantly 1,2-*cis*-glycosidic linkages. The product was treated with potassium t-butoxide in dimethyl sulphoxide to give crystalline 3-*O*-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-L-glycerol, which was also prepared from 3-*O*-(3,4-di-*O*-benzyl-α-D-glucopyranosyl)-1,2-*O*-isopropylidene-L-glycerol. 3-*O*-(2,3,4-Tri-*O*-benzyl-α-D-glucopyranosyl)-L-glycerol was converted into the 'glucosyl diglyceride' and also into 3-*O*-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-1,2-di-*O*-stearoyl-L-glycerol, which should serve as an intermediate for the syntheses of a 'glucuronosyl diglyceride,' the 'plant sulpholipid,' and one of the phosphorylated 'glucosyl diglycerides' of *Streptococci*.

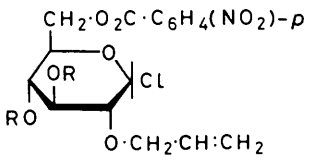
We have recently [1] described the synthesis of the crystalline **3**-*O*-(**3,4**-di-*O*-benzyl-α-D-glucopyranosyl)-**1,2**-*O*-isopropylidene-L-glycerol (**3**) from the intermediate (**2**). Compound (**2**) was prepared by condensation of the chloride (**1**), derived from the bis-*p*-nitrobenzoate of **2**-*O*-allyl-**3,4**-di-*O*-benzyl-D-glucopyranose,[2] with **1,2**-di-*O*-(but-2-enyl)-L-glycerol under conditions which we have described previously [3] for **1,2**-*cis*-glycoside synthesis. Compound (**3**) is suitably substituted for the synthesis of several of the neutral and phosphorylated glucosyl diglycerides which are present in the *Streptococci* [4] and other micro-organisms,[5] and in the present paper we describe the synthesis of **3**-*O*-(α-D-glucopyranosyl)-**1,2**-di-*O*-stearoyl-L-glycerol (**9**), a 'glucosyl diglyceride,' which is the parent compound of this series of glycolipids.

Benzylation of compound (**3**) gave the tetrabenzylglucopyranosyl derivative (**4**), which on acidic hydrolysis gave **3**-*O*-(**2,3,4,6**-tetra-*O*-benzyl α-D-glucopyranosyl)-L-glycerol (**7**). Acylation of compound (**7**) with octadecanoyl chloride in pyridine gave the stearoyl ester (**8**), from which the benzyl groups were removed by hydrogenolysis to give the glucosyl diglyceride (**9**).

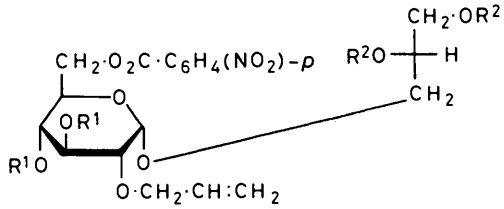
We subsequently discovered [6] that the reaction of acetyl chloride and hydrogen chloride with derivatives of **1,6**-anhydro-sugars gave the corresponding **6**-*O*-acylglycosyl chlorides. This indicated a more convenient route to the glucosyl diglyceride (**9**) by way of an intermediate which would also be valuable for the syntheses of other glycolipids derived from **3**-*O*-α-D-glucopyranosyl-L-glycerol.

The action of acetyl chloride containing hydrogen chloride on **1,6**-anhydro-**2,3,4**-tri-*O*-benzyl-β-D-glucopyranose (**19**) [7] gave the **6**-*O*-acetyl-**2,3,4**-tri-*O*-benzyl-D-glucopyranosyl chloride (**18**). Condensation of the chloride (**18**) with **1,2**-di-*O*-(but-**2**-enyl)-L-glycerol,[1] under the conditions described previously [3] for **1,2**-*cis*-glycoside

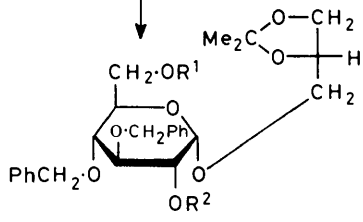
[1] P. A. Gent and R. Gigg, *Chem. Phys. Lipids*, 1976, **17**, 111.
[2] P. A. Gent and R. Gigg, *Carbohydrate Res.*, 1976, **49**, 325.
[3] P. A. Gent and R. Gigg, *J.C.S. Perkin I*, 1974, 1446, 1835; 1975, 361, 364, 1521, 1779; R. Gigg in A.C.S. Symposium Series No. 39, 1977, p. 253.
[4] W. Fischer in 'Lipids, Vol. 1: Biochemistry,' eds. R. Paoletti, G. Porcellati, and G. Jacini, Raven Press, New York, 1976, p. 255.
[5] N. Shaw, *Adv. Microbial Physiol.*, 1975, **12**, 141; R. H. Gigg in 'Rodd's Chemistry of Carbon Compounds,' ed. S. Coffey, Elsevier, Amsterdam, 1976, vol. 1E, p. 349.
[6] P. A. Gent, R. Gigg, and A. A. E. Penglis, *J.C.S. Perkin I*, 1976, 1395.
[7] G. Zemplén, Z. Csürös, and S. Angyal, *Ber.*, 1937, **70**, 1848.



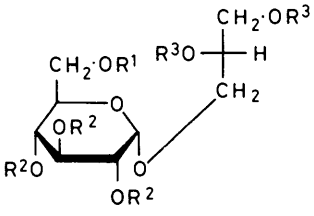
(1) R = CH_2Ph



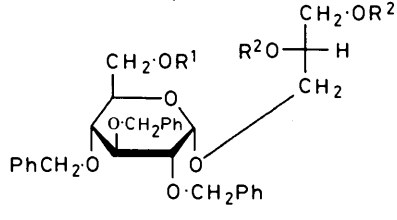
(2) $R^1 = CH_2Ph$, $R^2 = CH_2{\cdot}CH{:}CHMe$



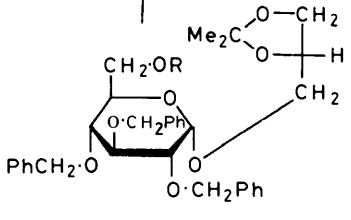
(3) $R^1 = R^2 = H$
(4) $R^1 = R^2 = CH_2Ph$
(5) $R^1 = CPh_3$, $R^2 = H$
(6) $R^1 = CPh_3$, $R^2 = CH_2Ph$



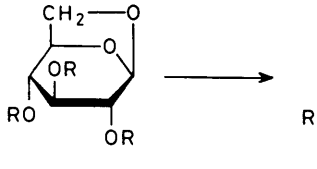
(7) $R^1 = R^2 = CH_2Ph$, $R^3 = H$
(8) $R^1 = R^2 = CH_2Ph$, $R^3 = CO{\cdot}[CH_2]_{16}Me$
(9) $R^1 = R^2 = H$, $R^3 = CO{\cdot}[CH_2]_{16}Me$
(10) $R^1 = CH_2{\cdot}CH{:}CH_2$, $R^2 = CH_2Ph$, $R^3 = H$
(11) $R^1 = CH{:}CHMe$, $R^2 = CH_2Ph$, $R^3 = H$
(12) $R^1 = CH{:}CHMe$, $R^2 = CH_2Ph$, $R^3 = CO{\cdot}[CH_2]_{16}Me$
(13) $R^1 = H$, $R^2 = CH_2Ph$, $R^3 = CO{\cdot}[CH_2]_{16}Me$



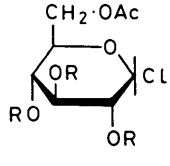
(14) $R^1 = Ac$, $R^2 = CH_2{\cdot}CH{:}CHMe$
(15) $R^1 = R^2 = H$



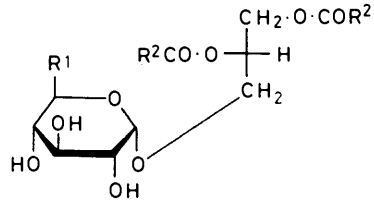
(16) R = H
(17) R = $CH_2{\cdot}CH{:}CH_2$



(19) R = CH_2Ph



(18) R = CH_2Ph



(20) $R^1 = CO_2H$
(21) $R^1 = CH_2{\cdot}O{\cdot}\overset{\overset{O}{\|}}{P}(OH){\cdot}OCH_2{\cdot}\overset{\overset{O{\cdot}COR^2}{|}}{C}H{\cdot}CH_2{\cdot}O{\cdot}COR^2$
(22) $R^1 = CH_2{\cdot}SO_3H$
R^2 = long-chain alkyl

synthesis, gave the crude 3-*O*-(6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-1,2-di-*O*-(but-2-enyl)-L-glycerol (14). Compound (14) was treated with potassium t-butoxide in dimethyl sulphoxide, which hydrolysed the acetyl group and removed [8] the but-2-enyl groups, to give the crystalline 3-*O*-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-L-glycerol (15).

The structure of compound (15) was confirmed by a further synthesis from the diol (3) whose structure was established previously.[1] Compound (3) was converted into the trityl ether (5), which was benzylated to give 3-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-glucopyranosyl)-1,2-*O*-isopropylidene-L-glycerol (6). Acidic hydrolysis of compound (6) removed the isopropylidene and trityl groups and gave the triol (15), identical with the material prepared as described above.

Compound (15) was converted into the isopropylidene derivative (16), which was benzylated; the resulting 3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-1,2-*O*-isopropylidene-L-glycerol (4) was converted into the ' glucosyl diglyceride ' as described above.

The isopropylidene derivative (16) was also converted into the allyl ether (17) and the isopropylidene group was removed to give 3-*O*-(6-O-allyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-L-glycerol (10). The allyl group was isomerised [9] with potassium t-butoxide in dimethyl sulphoxide to give the corresponding prop-1-enyl ether (11) and this was acylated with octadecanoyl chloride in pyridine to give the ester (12). The prop-1-enyl group was removed in the presence of mercury(II) chloride [10] to give the crystalline 3-*O*-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-1,2-di-*O*-stearoyl-L-glycerol (13).

Compound (13) should serve as a suitable intermediate for the synthesis of three other glycolipids: (*a*) the 1,2-di-*O*-acyl-3-*O*-(α-D-glucuronopyranosyl)-L-glycerol (20) which occurs in *Pseudomonas diminuta*,[11] should be available by oxidation of the primary hydroxy-group with chromic anhydride [12] and subsequent hydrogenolysis of the benzyl groups; (*b*) the phosphatidyl ' glucosyl diglyceride ' (21) of *Streptococci* [4] should be available by phosphorylation of compound (13) or its 6-deoxy-6-iodo-derivative; and (*c*) the ' plant sulpholipid ' (22),[13] which is a 6-deoxy-6-sulpho-derivative of a ' glucosyl diglyceride,' should also be available from the 6-deoxy-6-iodo-derivative of compound (13) by conversion into the sulphide and subsequent oxidation.

EXPERIMENTAL

Solvents were evaporated off under reduced pressure. Optical rotations were measured at 22—24° with a Bendix automatic polarimeter. T.l.c. was carried out on microscope slides coated with silica gel G.

3-O-(2,3,4-*Tri*-O-*benzyl*-α-D-*glucopyranosyl*)-L-*glycerol* (15).—(*a*) 3-*O*-(3,4-Di-*O*-benzyl-α-D-glucopyranosyl)-1,2-*O*-isopropylidene-L-glycerol (3) [1] (540 mg) and triphenylmethyl chloride (750 mg) were kept at 80 °C in dry pyridine until t.l.c. (toluene–acetone, 1 : 1) showed complete conversion of compound (3) (R_F 0.6) into the trityl ether (5) (R_F 0.9). Methanol was added to react with the excess of triphenylmethyl chloride; the mixture was then diluted with water and extracted with ether. The extract was washed with ice-cold N-hydrochloric acid and with saturated potassium chloride solution, dried (K_2CO_3), and evaporated; the crude product was treated with an excess of sodium hydride and benzyl chloride in *NN*-dimethylformamide at 20 °C for 20 min. T.l.c. (toluene–acetone, 3 : 1) then showed complete conversion of the alcohol (5) (R_F 0.6) into the benzyl ether (6) (R_F 0.9). Methanol was added to decompose the excess of sodium hydride, the solution was diluted with water, and the product was extracted with ether. The extract was dried (K_2CO_3) and evaporated and the crude product (6) was taken up in dioxan (45 ml) and N-hydrochloric acid (5 ml). The solution was heated under reflux for 15 min; t.l.c. (as above) then showed complete conversion of compound (6) (R_F 0.9) into the triol (15) (R_F 0.05). An excess of sodium hydrogen carbonate was added, the solvents were evaporated off, and the products were extracted with ether. The extract was dried and chromatographed on silica gel. Triphenylmethanol and benzyl chloride were eluted with ether and the *triol* (15) (480 mg, 80%) was eluted with ether–methanol (1 : 1) and crystallised from ether; m.p. 104—106°, $[\alpha]_D$ +41.1° (*c* 1 in $CHCl_3$) (Found: C, 68.5; H, 6.8. $C_{30}H_{36}O_8$ requires C, 68.7; H, 6.9%).

(*b*) 1,6-Anhydro-β-D-glucopyranose was prepared from penta-*O*-acetyl-β-D-glucopyranose (Koch–Light) by way of phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside as described [6] for the corresponding galacto-derivative. The crude product was acetylated with acetic anhydride–pyridine and the 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose was purified by crystallisation.[14] The 1,6-anhydro-β-D-glucopyranose was regenerated from the purified triacetate with sodium methoxide in dry methanol and was treated with an excess of benzyl chloride and sodium hydride in *NN*-dimethylformamide to give 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (19) [7] [m.p. 90—91° (from methanol)]. 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (19) (6 g) was dissolved in freshly distilled acetyl chloride (356 ml) and dry methanol (4.6 ml) was added. The solution was kept at 20 °C for 20 h; t.l.c. (toluene–acetone, 10 : 1) then showed conversion of compound (19) (R_F 0.65) into the chloride (18) (R_F 0.75). The acetyl chloride was distilled off and dry benzene was added to and evaporated from the residue to remove the last traces of acetyl chloride. A mixture of the crude chloride (18) (6.6 g), 1,2-di-*O*-(but-2-enyl)-L-glycerol [1] (5 g), dry tetraethylammonium chloride or bromide (2.1 g), and dry triethylamine (2.1 ml) in dry 1,2-dichloroethane (60 ml) was heated under reflux for 24 h. T.l.c. (as above) then showed complete conversion of the chloride (18) (R_F 0.75) into a major product (R_F 0.65) and other minor products, together with the excess of 1,2-di-*O*-(but-2-enyl)-L-glycerol. (R_F 0.3). The solution was cooled, washed with water, dried ($MgSO_4$), and evaporated. The crude

[8] P. A. Gent, R. Gigg, and R. Conant, *J.C.S. Perkin I*, 1972, 1535.
[9] J. Gigg and R. Gigg, *J. Chem. Soc.* (*C*), 1966, 82.
[10] R. Gigg and C. D. Warren, *J. Chem. Soc.* (*C*), 1968, 1903.
[11] S. G. Wilkinson, *Biochim. Biophys. Acta*, 1969, **187**, 492.
[12] E. Zissis and H. G. Fletcher, *Carbohydrate Res.*, 1970, **12**, 361; P. Kovac, *ibid.*, 1973, **31**, 323.
[13] A. A. Benson, *Adv. Lipid Res.*, 1963, **1**, 387; T. H. Haines, *Progr. Chem. Fats and Lipids*, 1971, **11**, 297.
[14] G. H. Coleman, *Methods Carbohydrate Chem.*, 1963, **2**, 397.

product was chromatographed on neutral alumina and the major product (14) (5.9 g, 66%), containing a small amount of by-product (R_F 0.7), was eluted with ether. The crude product (14) was added to a solution of potassium t-butoxide (10 g) in dry dimethyl sulphoxide (100 ml) and the solution was kept at 50 °C for 4 h. T.l.c. (toluene–acetone, 1 : 1) then showed conversion of compound (14) (R_F 0.9) into a major product [R_F 0.4, running concurrently with the triol (15)] together with small amounts of less polar materials. The solution was cooled, diluted with water, and extracted with ether (4 × 200 ml); the extract was dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica gel in toluene–acetone (1 : 1); after elution of some faster running impurities, the triol (15) [1.4—2.4 g, 20—35% from (19)] was eluted, and was recrystallised from ethyl acetate–light petroleum (b.p. 60—80°); m.p. and mixed m.p. 104—106°, $[\alpha]_D$ +41.0° (*c* 1 in $CHCl_3$) (Found: C, 68.8; H, 6.7%).

3-O-(α-D-*Glucopyranosyl*)-1,2-*di*-O-*stearoyl*-L-*glycerol* (9). —(*a*) The diol (3) (500 mg) was treated with an excess of sodium hydride and benzyl chloride in *NN*-dimethylformamide at 20 °C for 12 h. T.l.c. (toluene–acetone, 1 : 1) then showed complete conversion of the diol (3) (R_F 0.55) into the per-*O*-benzyl derivative (4) (R_F 0.9). Methanol was added to decompose the excess of sodium hydride and the solution was diluted with water and extracted with ether. The crude product (4) was taken up in dioxan (45 ml) and N-hydrochloric acid (5 ml) and heated at 100 °C for 10 min. T.l.c. (as above) then showed complete conversion of the isopropylidene derivative (4) into the diol (7) (R_F 0.5). An excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The product was extracted with ether and the extract dried (K_2CO_3) and evaporated to give the crude diol (7) (790 mg; still containing some benzyl chloride). The crude product (7) (150 mg) was treated with stearoyl chloride (600 mg) in dry pyridine (10 ml) at 20 °C for 2 h. T.l.c. (toluene–acetone, 10 : 1) then showed complete conversion of compound (7) (R_F 0) into the ester (8) (R_F 0.75). Water (0.3 ml) was added and the solution was kept at 20 °C for 3 h to convert any stearic anhydride into stearic acid. The solution was diluted with ice–water and 3N-hydrochloric acid was added (to pH 1). The product was extracted with ether and the extract was washed with water, dried ($MgSO_4$), and evaporated. The crude product (containing stearic acid) was chromatographed on neutral alumina in ether–toluene (1 : 1). The first fractions contained impurities (benzyl chloride) and the later fractions gave the pure ester (8) (140 mg, 50%), which crystallised but was not further characterised. The pure ester (8) (100 mg) was dissolved in ethyl acetate–methanol–acetic acid (2 : 2 : 1; 25 ml) and treated with hydrogen, at atmospheric pressure, in the presence of 10% palladium–charcoal, at 20 °C until t.l.c. (chloroform–methanol, 9 : 1) showed the presence of a single product (R_F 0.5). Filtration and evaporation left a crystalline product, which was recrystallised from methanol to give the *glucosyl diglyceride* (9) (50 mg, 70%), softening at 85 °C and forming a meniscus at 143 °C, $[\alpha]_D$ +49.6° (*c* 0.6 in chloroform–methanol, 1 : 1) (Found: C, 68.5; H, 11.25. $C_{45}H_{86}O_{10}$ requires C, 68.7; H, 11.0%).

(*b*) The triol (15) (100 mg) and toluene-*p*-sulphonic acid monohydrate (50 mg) were kept in dry acetone (75 ml) at 20 °C for 12 h. T.l.c. (toluene–acetone, 2 : 1) then showed complete conversion of the triol (15) (R_F 0.25) into the isopropylidene derivative (16) (R_F 0.75). Triethylamine (1 ml) was added and the solvent was evaporated off. Water was added to the residue and the product was extracted with ether; the extract was dried (K_2CO_3) and evaporated to give the isopropylidene derivative (16) as a syrup. Compound (16) was benzylated as described for compound (3) and the product (4) was converted into the glucosyl diglyceride as described in (*a*).

3-O-(2,3,4-*tri*-O-*benzyl*-α-D-*glucopyranosyl*)-1,2-*di*-O-*stearoyl*-L-*glycerol* (13).—The isopropylidene derivative (16) (1.3 g) was treated with an excess of allyl bromide and sodium hydride in *NN*-dimethylformamide at 20 °C for 1 h. T.l.c. (toluene–acetone, 2 : 1) then showed complete conversion of compound (16) (R_F 0.75) into the allyl ether (17) (R_F 0.9). The product was isolated in the usual way and treated with methanol (45 ml) and N-hydrochloric acid (5 ml) at reflux for 20 min. T.l.c. (as above) then showed complete conversion into the diol (10) (R_F 0.45). An excess of sodium hydrogen carbonate was added, the solvents were evaporated off, and the product (1.25 g) was extracted with ether. The extract was dried (K_2CO_3) and evaporated. The allyl ether (10) (500 mg) was treated with potassium t-butoxide (1 g) in dry dimethyl sulphoxide (20 ml) at 50 °C until t.l.c. (ether) showed complete conversion of the allyl ether (10) (R_F 0.3) into the prop-1-enyl ether (11) (R_F 0.45). The product (11) (490 mg) was isolated in the usual way [9,10] and treated with stearoyl chloride (2 g) in dry pyridine (25 ml) at 20 °C for 6 h. T.l.c. (toluene–acetone, 5 : 1) then showed complete conversion of the diol (11) (R_F 0.2) into the ester (12) (R_F 0.95). Water (1 ml) was added to the solution, which was then stirred at 20 °C for 3 h to convert any stearic anhydride into stearic acid. The solution was diluted with water and the product was extracted with ether. The extract was washed with ice-cold N-hydrochloric acid and with saturated potassium chloride solution, dried ($MgSO_4$), evaporated. The crude product (12) (containing stearic acid) was chromatographed on neutral alumina. The pure product (12) [194 mg, 20%; the low yield was due to hydrolysis of the acyloxy-groups by the presumed neutral alumina: partially acylated material and the diol (11) were subsequently eluted by methanol] was eluted with ether. The prop-1-enyl ether (12) (160 mg) was dissolved in ether (10 ml), acetone (10 ml), and water (1 ml), and mercury(II) chloride (100 mg) was added. After 30 min, t.l.c. (toluene–acetone 5 : 1) showed complete conversion of the prop-1-enyl ether (12) (R_F 0.95) into the alcohol (13) (R_F 0.7). The solution was diluted with potassium iodide solution and the product was extracted with ether. The extract was washed with potassium iodide solution, dried ($MgSO_4$), and evaporated, and the solid product was recrystallised from methanol–acetone (12 : 1) to give the *alcohol* (13) (100 mg), m.p. 60—61°, $[\alpha]_D$ +33.5° (*c* 1 in $CHCl_3$) (Found: C, 74.5; H, 10.1, $C_{66}H_{104}O_{10}$ requires C, 75.0; H, 9.9%).

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