Preparation of Glycerols protected at the 2-Hydroxy-group and their Application to the Synthesis of Lipids

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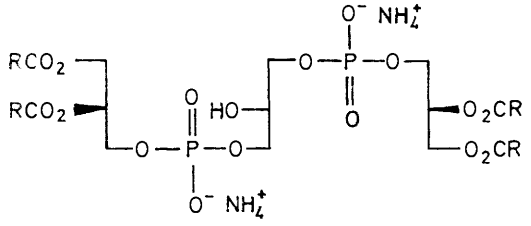
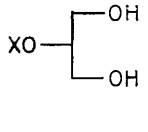
Several glycerols protected at the 2-hydroxy-group have been prepared and their advantages and disadvantages in the context of lipid synthesis (especially 1,3-diacylglycerols and certain phospholipids) have been examined.

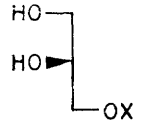
In our synthesis of cardiolipins (1),[1] the central glycerol unit was derived from the 2-*O*-substituted (2a). This precursor was chosen only after examining several possibilities. We provide here full details of the preparation of compound (2a), and compare its synthetic utility with that of other new protected glycerols (2b—d). In particular, the attempted application of (2a) to the synthesis of 1,3-diacylglycerols is described. Since we required cardiolipins and 1,3-diacylglycerols free of isomers, it was essential to develop a route which gave protected glycerols of type (2) free of 1-*O*-substituted isomers (3).



(1) R = *e.g.* n-$C_{15}H_{31}$



(2) a; X = $SiMe_2 \cdot CMe_3$
b; X = $CO_2CH_2 \cdot CCl_3$
c; X = 
d; X = CMe_3
e; X = CH_2Ph
f; X = $CMe_2 \cdot OMe$



(3) a; X = $SiMe_2 \cdot CMe_3$
b; X = $CO_2CH_2 \cdot CCl_3$

Previously, 2-*O*-benzylglycerol (2e) has been used as a precursor of 1,3-diacylglycerols,[2] but as catalytic hydrogenolysis is used to remove the benzyl group, this synthetic route is of limited application as yet, because it can only be directly applied to saturated 1,3-diacylglycerols.

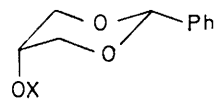
For ease of manipulation it was preferable that the protecting group X should confer crystallinity on the intermediate (2) and that (2) should be non-hygroscopic. Maximal versatility required that (2) should be stable to conditions for acylation and phosphorylation, and that X should be removable by reagents which would not perturb acyl, phosphoryl, and/or alkene groupings. None of the protecting groups examined fulfils all these demands. However, the dimethyl-t-butylsilyl (DMTBS) group in (2a) proved ideal for the synthesis of cardiolipins [1] (but not of 1,3-diacylglycerols—see below). The 2-*O*-(2,2,2-trichloroethoxycarbonyl)glycerol (2b) was crystalline, but was unstable in pyridine, making its application to the synthesis of glycerides and phospholipids risky and probably of restricted value. The 1-*O*-substituted isomer (3b), which is more stable in pyridine, has been recommended [3] for the synthesis of unsaturated 1,2-diacyl-*sn*-glycerols.

Preparation of 2-O-*Substituted Glycerols* (2a—d).—The title compounds were prepared either from *cis*-2-phenyl-1,3-dioxan-5-ol (4) [(2a—c)] or diethyl 2-hydroxymalonate [(2d and e)]. The syntheses of compounds (2b and c) were uneventful. [*N.B.* Although spectroscopic data were consistent with structure (2c), this compound did not give satisfactory analytical figures.] For the preparation of (2a), compound (4) was silylated [4] to afford (5a), which was hydrogenolysed to give crystalline (2a) in 81% overall yield. Crude (2a) was always accompanied by traces of glycerol (t.l.c.) an observation which conflicts with the claim [4] that the DMTBS group is stable to hydrogenolysis. Since (2a) is indeed stable to conditions (Pd–H_2; ethanol) used to hydrogenolyse (5a) to (2a), it is possible that the phenyl group in (5a) transports the otherwise unwilling DMTBS group to the catalyst 'surface' where cleavage to glycerol and dimethyl-t-butylsilane occurs. Since silanes react with alcohols in the presence of metallic catalysis to give silyl ethers,[5] (3a) could be formed during hydrogenolysis of (5a) by a palladium-catalysed recombination of glycerol with dimethyl-t-butylsilane. The presence of traces of (3a) in crude (2a) was indicated by ^1H n.m.r. spectroscopy. However, the contamination of crude (2a) by glycerol and (3a) hardly matters, since the crystallinity of (2a) (m.p. 64.5°) makes possible straightforward and effective purification by recrystallisation.

As the *O*-t-butyl derivative (2d) could not be prepared

[1] F. Ramirez, J. F. Maracek, P. V. Ioannou, G. H. Dodd, and B. T. Golding, submitted to *Tetrahedron*.
[2] A. J. E. Porck and B. M. Craig, *Canad. J. Chem.*, 1955, **33**, 1286.
[3] F. R. Pfeiffer, C. K. Miao, and J. A. Weisbach, (*a*) *J. Org. Chem.*, 1970, **35**, 221; (*b*) *Prep. Biochem.*, 1971, **1**, 221.
[4] E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, 1972, **94**, 6190.
[5] I. Ojima, T. Kogure, M. Nihonyanagi, H. Kono, S. Inaba, and Y. Nagai, *Chem. Letters*, 1973, 501, and references cited therein.

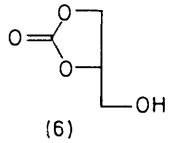
by the reaction of compound (4) with isobutene in the presence of a trace of concentrated sulphuric acid, owing to decomposition of (4) under these conditions, it was



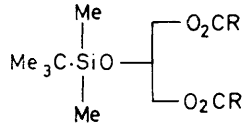
(4) X = H

(5) a; X = $SiMe_2 \cdot CMe_3$

b; X = $CO_2 \cdot CH_2 \cdot CCl_3$



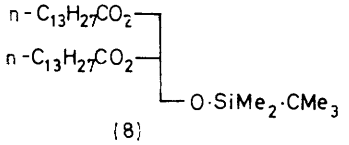
(6)



(7) a; R = n-$C_{13}H_{27}$

b; R = n-$C_{17}H_{35}$

(7)



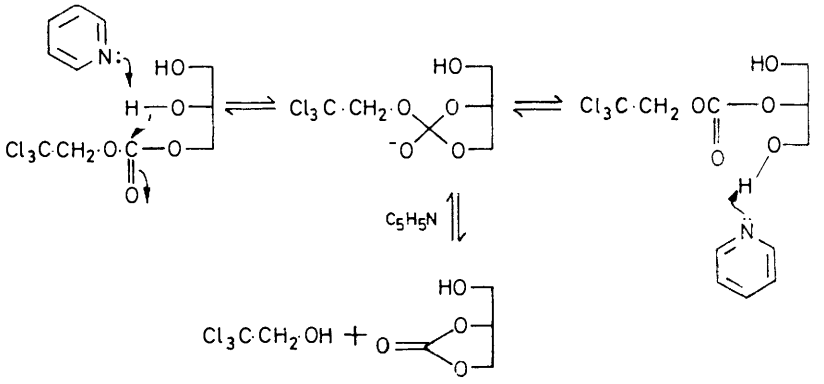
(8)

obtained from diethyl 2-hydroxymalonate. This diester was alkylated with isobutene under acidic catalysis to give the unstable oily diethyl 2-t-butoxymalonate, which was reduced to give (2d) in 12% overall yield from diethyl 2-hydroxymalonate. Compound (2d) was chromatographically pure and its spectroscopic data were consistent with the assigned structure, but it did not give satisfactory analytical figures.

The instability of diethyl 2-t-butoxymalonate is presumably due to its electron-withdrawing ester groups, which render it unstable with respect to loss of the t-butyl group. Attempts were made to prepare (2c) and (2f) *via* diethyl 2-hydroxymalonate. However, acid-catalysed reactions of diethyl 2-hydroxymalonate with either dihydropyran or 2-methoxypropene gave very low yields of alkylated products and so this approach was abandoned.

The promising nature of compound (2a) led us to investigate its isomer (3a). Initially, we attempted to prepare (3a) by direct silylation of glycerol, which was expected to be regioselective. However, even use of a 10-molar excess of glycerol gave, after fractional distillation, an oily mixture containing 90% (3a) and 10% (2a) (n.m.r. analysis) which could not be crystallised or further purified. We therefore prepared a sample of optically active (3a) from 1,2-dibenzyl-*sn*-glycerol (silylation followed by hydrogenolysis). The crude sample of (3a) was contaminated with glycerol (t.l.c.) and probably contained some (2a) (1.5—2.5% by n.m.r. analysis), both by-products probably arising in the manner discussed above for the case of the hydrogenation of (5a). Although *sn*-(3a) was obtained in >98% purity it could not be crystallised. We therefore disqualified this substance as a synthetic precursor of 1,2-diacyl-*sn*-glycerols.

Stability of Compounds (2a *and* b) *and* (3a *and* b).—Whereas compound (2a) is indefinitely stable at −20 °C, (2b) had partially (*ca.* 50%) decomposed to the cyclic carbonate (6) and trichloroethanol after 10 months at −20 °C. Compound (2a) is stable in pyridine at 20 °C (for at least 17 h) and can therefore be acylated and phosphorylated, at least under mildly basic conditions, without disturbing the silyl function. In contrast, (2b) rapidly decomposed in pyridine giving (6) and trichloroethanol, presumably by the mechanism shown in the Scheme. For a comparative study *rac*-(3b) was prepared.



SCHEME

The disappearance of (2b) and (3b) and appearance of (6) and trichloroethanol in [$^2H_5$]pyridine was followed by ^1H n.m.r. spectroscopy. Observation of the CH_2 signal from trichloroethanol showed that the half-time for production of this alcohol from (2b) was *ca.* 20 h, whereas from (3b) the half-time was *ca.* 50 h. The greater reactivity of (2b) is due to a statistical factor [two reacting hydroxy-groups as opposed to one in

(3b)] and perhaps to steric reasons [faster attack on C=O by less hindered primary hydroxy-groups in (2b)].

On heating the silyl ether (2a) in pyridine slow interconversion with (3a) appears to occur [n.m.r. analysis indicated the formation of *ca.* 11% (3a) and other unidentified compounds after 30 h at 118 °C]. Thermolysis (118 °C) of the neat (2a) also effects a slow equilibration [*ca.* 10% (3a) formed after 30 h]. Compound (2a) could not be applied to the synthesis of pure 1,3-diacylglycerols by way of (7a) and (7b) because of our failure to find conditions for the removal of the DMTBS group without causing acyl migration (*cf.* ref. 6). In (7a) and (7b) the silyl function is flanked by electron-withdrawing acyl groups which probably increase the susceptibility of the silicon atom to nucleophilic attack by F^-, but depress the rate of acidic hydrolysis (by reducing the equilibrium concentration of *O*-protonated silyl ether). Hence, recommended conditions [4,7] for the acidic hydrolysis of DMTBS ethers do not work on (7a) and (7b). More strongly acidic conditions, although partially effective for the removal of the DMTBS group, also cause acyl migration and deacylation. Fluoride-induced cleavage of the Si–O bond in (7b) and (8) by tetra-n-butylammonium fluoride ($Bu_4N^+F^-$) in tetrahydrofuran (THF) is very fast but, owing to very effective catalysis of acyl migration by F^-, an equilibrium mixture [8] of 1,2- (*ca.* 40%) and 1,3-diacylglycerol (*ca.* 60%) results (treating pure 1,2-distearoyl-*sn*-glycerol with $Bu_4N^+F^-$–THF rapidly generated the same equilibrium mixture). Adding 1 equiv. of acid to reaction mixtures in order to suppress acyl migration completely arrests desilylation, owing to the inactivation of highly nucleophilic ' naked ' F^- ion. These problems were overcome in our synthesis [1] of cardiolipins, by the circumstance that *in this case* the silyl group is removed *via* a remarkably effective and mild acidic catalysis by nearby $P{\rightarrow}O^-H^+$ groups.

EXPERIMENTAL

All solvents were either AnalaR (ether) or purified by standard methods.[9] Chloroform used for acylations and measurements of optical rotations was alcohol-free. In synthetic work, solvents were removed with a rotary evaporator (bath temperature <25°). Concentrations of solutions for ^1H n.m.r. spectroscopy (tetramethylsilane reference) were *ca.* 10%, and for i.r. spectroscopy *ca.* 2%. M.p.s were determined for samples in open capillaries and are corrected. Optical rotations were determined with a Bendix NPL automatic polarimeter 143D. Fisons silica gel (80—200 mesh) was used for column chromatography. Thin-layer plates were prepared from Machery and Nagel silica gel N. Spots were detected by spraying with 35% sulphuric acid and charring. Hydrogenolyses were performed with a Parr hydrogenator. Elemental analyses were carried out by CHN Analyses Ltd. or Bernhardt.

cis-2-Phenyl-1,3-dioxan-5-ol (4) [10] was prepared in 6—20% yield and was pure by t.l.c. and n.m.r. spectroscopy (devoid of dioxolan isomers [8]) after two recrystallisations from benzene–hexane (1 : 1); m.p. 80—81° (lit.,[11] 83.9°). It was stored at −20 °C (stable for at least 11 months) and was recrystallised just before use.

cis-2-*Phenyl*-1,3-*dioxan*-5-*yl Dimethyl-t-butylsilyl Ether* (5a).—A solution of *cis*-2-phenyl-1,3-dioxan-5-ol (16.5 g, 0.092 mol) and imidazole (15.6 g, 0.23 mol) in dimethylformamide (DMF) (50 ml) was slowly added at room temperature to dimethyl-t-butylsilyl chloride (16.6 g, 0.11 mol). The mixture was stirred at room temperature for 8½ h and was then extracted with n-hexane (6 × 80 ml). The combined extracts were washed with water (3 × 50 ml), dried (Na_2SO_4), and evaporated to give an oil which was distilled. The main faction was the *ether* (5a) (22.6 g, 84%), b.p. 136° at 0.4 mmHg, n_D^{20} 1.493 2; pure by t.l.c. [R_F 0.62 in ether–hexane (1 : 3)]; δ ($CDCl_3$) 0.11 (s, $SiMe_2$), 0.98 (s, CMe_3), 3.64 (m, $CH_2{\cdot}CH{\cdot}CH_2$), 4.00 (d, *J* 2.0 Hz, $CH_2{\cdot}CH{\cdot}CH_2$), 5.50 (s, PhC*H*), and 7.37 (m, Ph) (Found: C, 65.45; H, 9.15. $C_{16}H_{26}O_3Si$ requires C, 65.25; H, 8.9%); and stable for at least 3 months at −20 °C.

2-O-*Dimethyl-t-butylsilylglycerol* (2a).—Compound (5a) (3.0 g, 10.2 mmol) in ethanol (50 ml) containing 5% Pd–C (0.6 g) was hydrogenated for 2½ h (reduction was essentially complete after *ca.* 40 min.) The mixture was filtered through Celite, and the pad was washed with methanol. The solvents were removed and the residue was maintained under reduced pressure until solidification occurred. The solid was taken up in the minimum amount of ether; addition of hexane [or light petroleum (b.p. 40—60°)] until the mixture became opalescent and cooling to −20 °C for 3—4 h gave the *product* (2a) as white plates (2.0 g, 96%), m.p. 64.5°, pure by t.l.c. (R_F 0.55 in ether); δ ($CDCl_3$) 0.10 (s, $SiMe_2$), 0.92 (s, CMe_3), 2.67 (s, OH), and 3.63 (m, $CH_2{\cdot}CH{\cdot}CH_2$); δ (C_5D_5N) 0.15(s), 0.92(s), 3.85(m), and 5.04br(s); $\nu_{max.}$ (CCl_4) 3 430m, 2 955s, 2 930s, 2 895s, 2 860s, 1 471s, 1 463s, 1 390m, 1 360m, 1 255w, 1 215w, 1 115s, 1 050s, 1 005m, 980m, 960m, 835s, and 670w cm^{-1} (Found: C, 52.6; H, 10.6. $C_9H_{22}O_3Si$ requires C, 52.4; H, 10.75%).

The above-described hydrogenolysis of (5a) gave traces of glycerol as a by-product (identified by t.l.c. in five systems). Hydrogenolysis in methanol, tetrahydrofuran, ethyl acetate, or ethyl acetate containing 2% ethanol also gave these by-products. In all cases hydrogenolysis proceeded *via* an intermediate (detected by t.l.c. and ^1H n.m.r. spectra of incomplete reactions), probably *rac*-1-*O*-benzyl-2-*O*-dimethyl-t-butylsilylglycerol [δ (C_5D_5N) 4.58 (s, $PhCH_2$)]. Hydrogenolysis of (2a) for 8 h in ethanol or methanol under conditions similar to those described for (5a) did not produce glycerol.

1,2-*di*-O-*Benzyl*-sn-*glycerol* 3-*Dimethyl-t-butylsilyl Ether*.—To dimethyl-t-butylsilyl chloride (2.70 g, 18 mmol) was added dropwise with stirring at room temperature a solution of 1,2-di-*O*-benzyl-*sn*-glycerol [12] (4.10 g, 15 mmol) and imidazole (2.53 g, 37.5 mmol) in DMF (10 ml). The resulting solution was left for 8 h at room temperature. Extraction with hexane (5 × 25 ml), washing the extracts with water (3 × 30 ml), drying (Na_2SO_4), and evaporation

[6] G. H. Dodd, B. T. Golding, and P. V. Ioannou, *J.C.S. Chem. Comm.*, 1975, 249.
[7] K. K. Ogilvie, *Canad. J. Chem.*, 1973, **51**, 3799.
[8] B. Serdarevich, *J. Amer. Oil Chemists' Soc.*, 1967, **44**, 381.
[9] D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, ' Purification of Laboratory Chemicals,' Pergamon, Oxford, 1966.
[10] F. H. Mattson and R. A. Volpenhein, *J. Lipid Res.*, 1962, **3**, 281.
[11] R. Aneja and A. P. Davies, *J.C.S. Perkin I*, 1974, 141.
[12] H. Eibl, O. Westphal, H. Van Den Bosch, and L. L. M. Van Deenen, *Annalen*, 1970, **738**, 161; see also H. F. G. Beving, H. B. Boren, and P. J. Garegg, *Acta Chem. Scand.*, 1967, **21**, 2083; P. A. Gent and R. Gigg, *J.C.S. Perkin I*, 1975, 364.

gave a liquid (5.6 g), which was chromatographed on silica gel [250 g; elution with ether–hexane (1 : 5)]. Product was eluted in fractions 11—17 (25 ml fractions; 3 ml min^{-1} flow rate). Evaporation of these combined fractions gave an oil, pure by t.l.c. [R_F 0.60 in ether–hexane (1 : 5)], n_D^{17} 1.509 2 $[\alpha]_D^{20}$ +1.51° (*c* 4.3 in $CHCl_3$), δ (C_5D_5N) 0.09 (s, $SiMe_2$), 0.93 (s, CMe_3), 3.81 (m, $CH_2{\cdot}CH{\cdot}CH_2$), 4.58 (s, $PhCH_2{\cdot}O{\cdot}CH_2$), 4.78 (s, $PhCH_2{\cdot}O{\cdot}CH$), and 7.37 (m, 10 ArH) (Found: C, 71.45; H, 8.85. $C_{23}H_{34}O_3Si$ requires C, 71.45; H, 8.85%).

sn-*Glycerol* 3-*Dimethyl-t-butylsilyl Ether* (3a).—1,2-Di-*O*-benzyl-*sn*-glycerol DMTBS ether (2.5 g, 6.5 mmol) in ethanol (50 ml) containing 5% Pd–C (1.0 g) was hydrogenated for 2 h at 40 lb in^{-2}. Filtration through Celite, washing the Celite with ethanol, and removal of ethanol gave an impure liquid [t.l.c. (ether) R_F 0.75; impurity at R_F 0.00]. Short-column chromatography [silica gel (5 g); elution with ether] removed the impurity and gave an oil (1.073 g, 79%), n_D^{20} 1.437 0, δ (C_5D_5N) 0.10 (s, $SiMe_2$), 0.93 (s, CMe_3), 3.99 (m, $CH_2{\cdot}CH{\cdot}CH_2$), and 5.60br (2 × *OH*). [*N.B.* Impurity peaks were present at δ 0.06, 0.15 (2a), 0.23, and 0.95.] Hydrogenolysis of 1,2-di-*O*-benzyl-*sn*-glycerol DMTBS ether in ethyl acetate, ethanol, methanol, or ethyl acetate containing 2% ethanol gave (3a) always accompanied by glycerol (identified by t.l.c. in five systems) and (2a) (δ 0.15).

rac-*Glycerol* 3-*Dimethyl-t-butylsilyl Ether*.—A solution of glycerol (28.4 g, 0.32 mol) and imidazole (5.4 g, 0.08 mol) in DMF (30 ml) was added at room temperature to dimethyl-t-butylsilyl chloride (4.83 g, 0.032 mol) during 10 min. The mixture was stirred for 22 h at room temperature. Adding water and extracting the product with ether in the standard manner, followed by distillation, gave a liquid (3.45 g), b.p. 86—87° at 0.4 mmHg, n_D^{20} 1.445 0; pure by t.l.c. (R_F 0.73 in ether); δ (C_5D_5N) 0.10 (s, $SiMe_2$), 0.91 (s, CMe_3), 3.91 (m, $CH_2{\cdot}CH{\cdot}CH_2$), and 5.23 (s, 2 × OH) [peak due to (2a) (*ca.* 10%) at δ 0.15].

cis-2-*Phenyl*-1,3-*dioxan*-5-*yl* 2,2,2-*Trichloroethyl Carbonate* (5b).—A solution of 2,2,2-trichloroethoxycarbonyl chloride (15.1 g, 71 mmol) in alcohol-free chloroform (10 ml) was slowly added to a stirred, cooled (0 °C) solution of *cis*-2-phenyl-1,3-dioxan-5-ol (12.25 g, 68 mmol) in chloroform (25 ml) containing dry pyridine (5.9 g, 6.0 ml, 74.5 mmol). Stirring was continued for 23 h at room temperature. An excess of ether was added and the precipitated pyridinium hydrochloride was filtered off. The precipitate was washed with ether. The filtrate was washed with dilute hydrochloric acid (1 × 20 ml), water (1 × 20 ml), aqueous 5% potassium hydrogen carbonate (1 × 20 ml), and water (2 × 20 ml), dried (Na_2SO_4), and evaporated to leave a white solid. This was dissolved in warm ether; addition of petroleum (b.p. 40—60°) to turbidity and cooling overnight at 0 °C gave fine white *needles* (21.0 g, 88%) of (5b), pure by t.l.c. [R_F 0.47 in ether–hexane (1 : 1)], m.p. 91—92°; δ ($CDCl_3$) 4.20 (m, $CH_2{\cdot}CH{\cdot}CH_2$), 4.57 (m, $CH_2{\cdot}CH{\cdot}CH_2$), 4.78 (s, $CCl_3{\cdot}CH_2$), 5.50 (s, ArC*H*), and 7.42 (m, 5 × ArH); $\nu_{max.}$ 1 755s cm^{-1} (Found: C, 44.5; H, 3.65; Cl, 30.2. $C_{13}H_{13}Cl_3O_5$ requires C, 43.9; H, 3.65; Cl, 29.9%).

2-O-(2,2,2-*Trichloroethoxycarbonyl*)*glycerol* (2b).—The carbonate (5b) (7.11 g, 20 mmol) in ethyl acetate (85 ml) containing 10% Pd–C * (1.55 g) was hydrogenolysed (28 lb in^{-2}) for 1 h at room temperature. The mixture was filtered through Celite and the pad was washed with ether. Removal of solvents from the filtrate gave a white solid (5.21 g). Dissolution in the minimum of ether at room temperature, addition of petroleum (b.p. 40—60 °C) to turbidity, and cooling to −20° C overnight gave white crystals (2b) (4.67 g, 87%), pure by t.l.c. (R_F 0.47 in ether), m.p. 96—97°, δ (C_5D_5N; run immediately after dissolution) 4.24 (m, $CH_2{\cdot}CH{\cdot}CH_2$), 5.03 (s, $CCl_3{\cdot}CH_2$), 5.42 (m, $CH_2{\cdot}CH{\cdot}CH_2$), and 6.82 (s, OH); $\nu_{max.}$ (Nujol) 3 300s and 1 750s cm^{-1} (Found: C, 27.1; H, 3.45. $C_6H_9Cl_3O_5$ requires C, 26.95; H, 3.35%).

rac-*Glycerol* 1,2-*Carbonate* (6).—A small sample of *rac*-1-*O*-(2,2,2-trichloroethoxycarbonyl)glycerol (3b) [m.p. 67°; δ (C_5D_5N; run immediately) 4.13 (m, $CH_2{\cdot}OH$), 4.47 (m, CH), 4.84 (m, $CH_2{\cdot}O{\cdot}CO_2$), and 5.15 (s, $CH_2{\cdot}CCl_3$); prepared in the manner described [3a] for the *sn*-3-isomer]-was cyclised in pyridine at 95 °C (39 h). After pumping off the pyridine the residue was chromatographed on silica gel; the carbonate (6), eluted with methanol, was an oil homogeneous by t.l.c. (R_F 0.17 in 96 : 4 chloroform–methanol); δ (C_5D_5N) 3.91 (q of d, *J* 11 and 4 Hz, $CH_2{\cdot}OH$), 4.60 (m, $CH_2{\cdot}O{\cdot}CO$), 4.69 (m, CH), and 6.32br (OH); $\nu_{max.}$ (neat) 3 420m and 1 790s cm^{-1}.

Rates of Cyclisation of the Carbonates (2b) *and* (3b).—Solutions of (2b) (0.525M) and (3b) (0.562M) in [$^2H_5$]-pyridine were prepared. The cyclisation of each carbonate to (6) was followed at 37 °C by ^1H n.m.r. spectroscopy (increase in intensity of $Cl_3C{\cdot}CH_2OH$ signal and decrease of $Cl_3C{\cdot}CH_2{\cdot}O{\cdot}CO$ signal). Later spectra clearly showed the characteristic pattern due to the cyclic carbonate (6) and the absence of any compound other than trichloroethanol. The half-times for production of trichloroethanol were *ca.* 20 h from (2b) and *ca.* 50 h from (3b). These values were derived from plots (>22 measurements in each case) of the integral of the $Cl_3C{\cdot}CH_2{\cdot}OH$ signal against time.

2-O-*dimethyl-t-butylsilyl*-1,3-*di*-O-*myristoylglycerol* (7a).—To (2a) (0.345 g, 1.68 mmol) in chloroform (20 ml) at room temperature was added pyridine (1.0 ml, 1.24 mmol), followed (dropwise) by redistilled myristoyl chloride (1.13 g, 4.62 mmol) in chloroform (5 ml). This mixture was stirred for 4 days at room temperature. Ether was added to precipitate pyridinium hydrochloride, which was filtered off. The filtrate was washed with dilute hydrochloric acid, water, dilute aqueous potassium hydrogen carbonate, and water (twice). The final organic layer was dried (Na_2SO_4) and evaporated to give a semi-solid (1.235 g). This was chromatographed on silica gel (80 g) made up in n-hexane. Elution with increasing amounts of ether in hexane (flow rate 3 ml min^{-1}) gave the bulk of (7a) (0.72 g, 68%) in a fraction eluted by ether–hexane (30 : 70). The *product* (7a) was an oil at room temperature (m.p. *ca.* 17°), homogeneous by t.l.c. [R_F 0.63 in ether–hexane (1 : 5)], δ (CCl_4) 0.09 (s, $SiMe_2$), 0.88 (s, CMe_3 and 2 × Me), 1.25 (s, 22 × CH_2), 2.22 (m, 2 × $CH_2{\cdot}CO$), and 3.95 (s, $CH_2{\cdot}CH{\cdot}CH_2$); $\nu_{max.}$ (neat) 1 745 cm^{-1} (Found: C, 71.2; H, 12.1. $C_{37}H_{74}O_5Si$ requires C, 70.85; H, 11.9%).

1,2-*di*-*O*-*myristoyl*-rac-*glycerol* 3-*Dimethyl-t-butylsilyl Ether* (8) (*containing* ca. 10% 1,3-*Isomer*) *and* 1,3-*Di*-O-*stearoylglycerol* 2-*Dimethyl-t-butylsilyl Ether* (7b).—Prepared from *rac*-glycerol 3-dimethyl-t-butylsilyl ether [containing *ca.* 10% (2a)] and 2-*O*-dimethyl-t-butylsilylglycerol, respectively, essentially by the foregoing method, compound (8) was an oil [t.l.c. showed two spots, R_F 0.57 and 0.62 on silica gel N + 0.4M-H_3BO_3 in ether–hexane (1 : 5)]; and

* Catalyst from Johnson Matthey; using 10% Pd–C from another company gave an impure product owing to partial cyclisation to (6).

compound (7b) had m.p. 42—43° (Found: C, 73.2; H, 12.3. $C_{45}H_{90}O_5Si$ requires C, 73.1; H, 12.25%)

Removal of the Dimethyl-t-butylsilyl Group from Compounds (7a), (7b), *and* (8).—(a) *With* AcOH–H_2O–THF *at room temperature or reflux* (*cf. ref.* 4). Compound (7b) (50 mg) in AcOH–H_2O–THF (3 : 1 : 1 v/v) (675 μl) was kept at room temperature for 23 h and then refluxed for 3.5 h. At the end of this time, t.l.c. showed solely (7b).

(b) *With* 80% AcOH (cf. *ref.* 7).—Compound (7b) (10 mg) suspended in 80% acetic acid–water (2 ml) was heated at 100 °C for 15 min. No reaction took place (t.l.c.).

(c) *With boric acid* (cf. *ref.* 13). Refluxing trimethyl borate containing compound (7b) and boric acid for 3 h, or heating (7b) with boric acid in 2-ethoxyethanol at 100 °C for 16 h caused no change (t.l.c. of isolated material).

(d) *With hydrofluoric acid* (cf. *ref.* 14). Compound (7b) (12 mg, 0.016 mmol) in 1 : 1 ethanol–THF (2 ml) was treated with *ca.* 9% HF in 1 : 1 ethanol–water (*ca.* 0.45 mmol HF) and the solution was left at room temperature for 24 h. Addition of water and extraction with ether gave a solid which contained *ca.* 40% (7b), 40% 1,3-di-*O*-stearoylglycerol, 5—10% 1,2-di-*O*-stearoylglycerol, 5—8% stearic acid, and 5—8% mono-*O*-acylglycerols (t.l.c.: [15] 20 cm silica gel N plates + 0.4M-boric acid; 24 : 1 chloroform–acetone).

Exposure of compound (7a) to > 2 equiv. of $(HF)_x$ in pyridine–THF [16] for 14 h at room temperature gave mainly unchanged (7a), with 1,2- and 1,3-di-*O*-myristoylglycerol.

(e) *With hydrochloric acid.* Compound (7b) (47 mg, 0.064 mmol) in chloroform (1.0 ml) and methanol (1.0 ml) was treated with 2N-hydrochloric acid as follows: (i) 3 : 1 molar ratio [HCl : (7b)], 64 h; (ii) 9:1, 46 h; (iii) 33 : 1, 15 h. The same products as with hydrofluoric acid [see (d)] were obtained, but the mono-*O*-acylglycerols and fatty acid predominated.

(f) *With* $Bu_4N^+F^-$ *in* THF (*cf. ref.* 4). Compound (7b) (10 mg, 0.013 5 mmol) in THF (1.0 ml) was treated with 0.5M-$Bu_4N^+F^-$ in THF (54 μl, 0.027 mmol) for 5 min at room temperature. Ether and water were added. The mixture was acidified and was extracted with ether to give a product containing solely 1,2-di-*O*-stearoylglycerol (40%) and 1,3-di-*O*-stearoylglycerol (60%) (t.l.c.). A similar result was obtained with compound (8).

Treatment of compound (7b) with $Bu_4N^+F^-$ in THF containing 1 equiv. of concentrated H_2SO_4 resulted in no reaction (after 18 h at room temperature).

After 0.5 or 1.0 equiv. of $Bu_4N^+F^-$ in THF had reacted with (7b) for 5 min at room temperature, t.l.c. showed the presence of (7b) as well as 1,2- and 1,3-di-*O*-stearoylglycerol.

Control Experiments.—1,2-Di-*O*-stearoyl-*sn*-glycerol (10 mg, 0.016 mmol) in THF (0.4 ml) was treated with 0.5M-$Bu_4N^+F^-$ in THF (54 μl, 0.027 mmol) for 10 min at room temperature. An equilibrium mixture of 1,2- (60%) and 1,3-di-*O*-stearoylglycerol resulted (t.l.c.). Similar treatment of 1,2-di-*O*-stearoyl-*sn*-glycerol 3-benzyl ether had no effect.

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