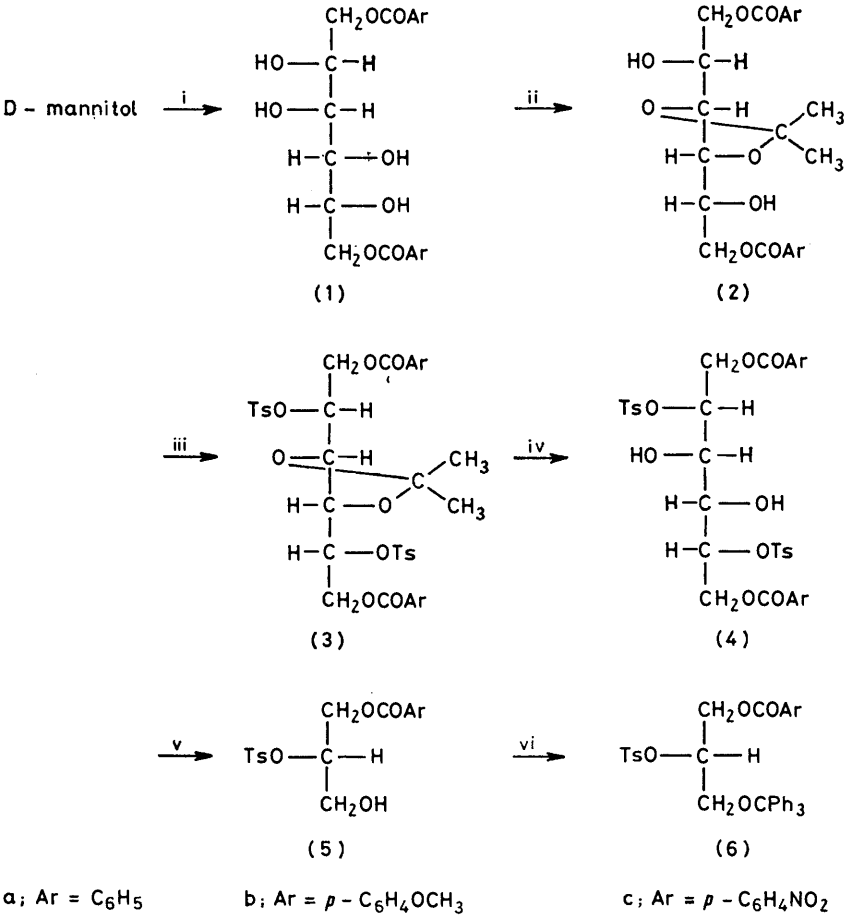
A Possible Model for a New Chiral Glyceride Synthesis. Part 1. Synthesis of 1-*O*-Aroyl-2-*O*-tosyl-*sn*-glycerols

By **Claude Morpain** * and **Madeleine Tisserand**, Institut de Chimie, Université de Besançon, 25000 Besançon, France

A procedure has been developed which permits the synthesis of mixed-acid 1,2-di-*O*-aroyl-*sn*-glycerols *via* 1,6-di-*O*-aroyl-2,5-di-*O*-tosyl-D-mannitol. The method was applied to the synthesis of some (*S*)-(+)-1-*O*-aroyl-2-*O*-tosyl-*sn*-glycerols. In order to check the structure and the optical purity of the 1,2-diglycerides, tritylation to give 3-trityl ethers was carried out. 1-Trityl ethers were prepared by a second method *via* 3-*O*-aroyl-*sn*-glycerols. The optical rotations of the 3- and 1-trityl ethers were compared. Oxidation of 1,6-di-*O*-aroyl-2,5-di-*O*-tosyl-D-mannitol at temperatures above 25 °C took place with complete or partial racemisation.

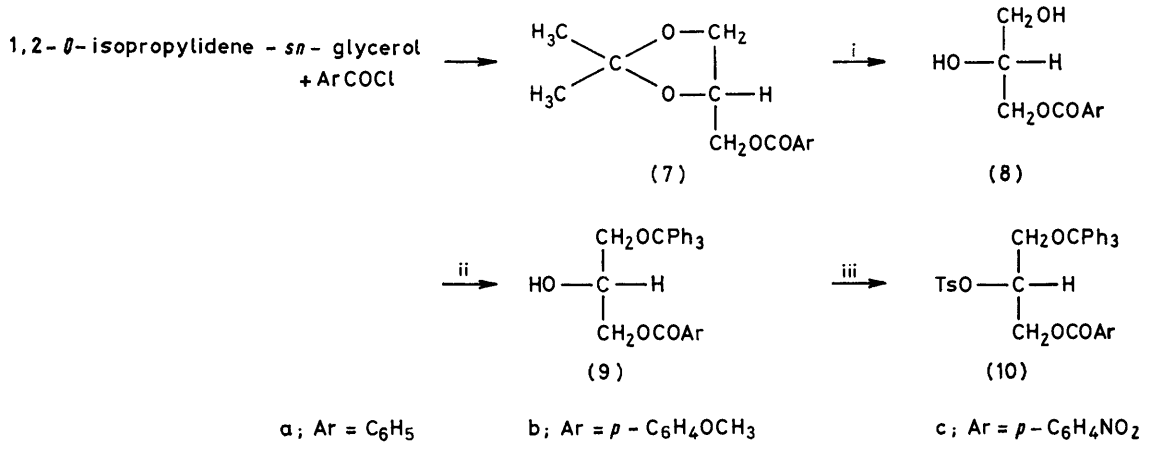
In connection with previous studies,[1,2] chiral mixed diglycerides † were required as intermediates in the synthesis of di-*O*-aroyl-*sn*-glycerol 2- or 3-iodohydrins. This paper describes a new preparation of 1-*O*-aroyl-2-*O*-tosyl-*sn*-glycerols, and the measurement of the optical purity of these compounds. Aromatic esters as protecting groups were chosen in the light of previous results, and the tosyl group was used in the preparation of 1,3-di-*O*-aroyl-*sn*-glycerol 2-iodohydrins. This model was very useful, and we think that it can be applied to true fatty acyl derivatives.

The method (Scheme 1) used D-mannitol as starting material which was then esterified in positions 1 and 6 with an acid chloride ArCOCl using the method of Brigl.[3] The alcohol functions at C(3) and (4) were protected by conversion into the isopropylidene derivative (2) with anhydrous copper sulphate and concentrated sulphuric acid. Compound (2) was then condensed with two moles of a different acid chloride Ar'COCl or TsCl and the isopropylidene group was



Scheme 1 Reagents: i, 2ArCOCl; ii, $CuSo_4$–H_2SO_4–Me_2CO; iii, 2 $ClSO_2C_6H_4CH_3$; iv, hydrolysis; v, $NaIO_4$–$NaBH_4$; vi, $ClCPh_3$

† The more usual term, 1,2-diglyceride, is used for 1-*O*-aroyl-2-*O*-tosyl-*sn*-glycerol.

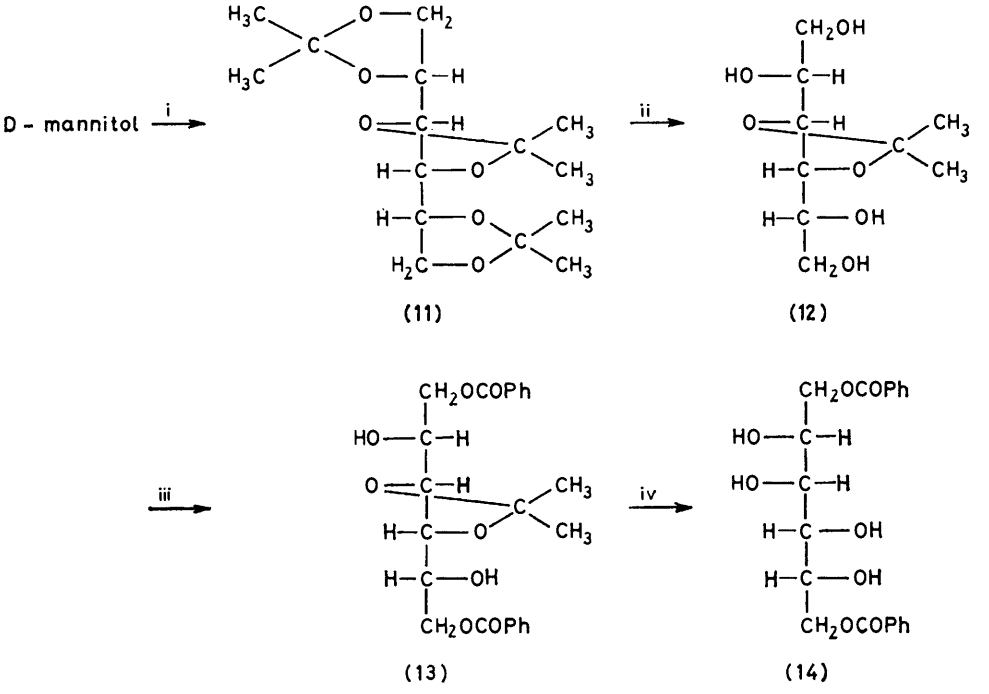


SCHEME 2 Reagents: i, 0.5N-HCl; ii, $ClCPh_3$; iii, TsCl

removed by hydrolysis in acetic acid. Compound (4) was oxidised either with sodium metaperiodiate in ethanol, or with lead(IV) acetate in ethyl acetate. Reduction of the resulting aldehyde with sodium borohydride gave the 1,2-di-*O*-aroyl-*sn*-glycerol.

DISCUSSION

Position of the Isopropylidene Group on C(3) *and* (4) *of* D-*Mannitol*.—This was established on the basis that the 1,2-diglycerides were isolated and by the sequence of reactions in Scheme 3. The conversion of 1,2;3,4;5,6-



SCHEME 3 Reagents: i, Me_2CO–H_2SO_4; ii, CH_3COOH; iii, 2 PhCOCl; iv, hydrolysis

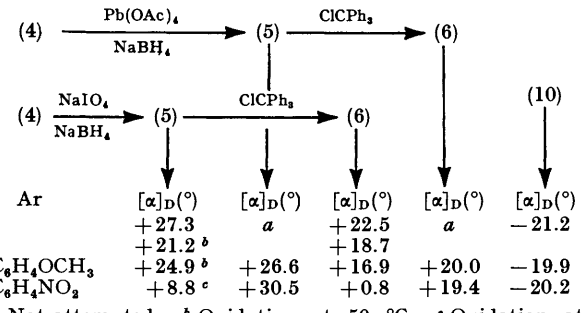
The optical purity of the 1,2-diglycerides required verification because transposition or partial or complete racemisation is always possible. For this purpose, the 1,2-diglycerides were treated with triphenylmethyl chloride. The rotations of the 3-trityl ethers thus prepared were examined in relation to those of 1-trityl ethers obtained by another method (Scheme 2) of established stereochemistry.[4]

tri-*O*-isopropylidene-D-mannitol (11) into 3,4-*O*-isopropylidene-D-mannitol (12) was by the method of Wiggings.[5] Condensation with benzoyl chloride gave 1,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-D-mannitol (13). This compound is identical with product (2) [analytical and spectroscopic data (n.m.r. and i.r.)]. This confirms that the 3,4-isopropylidene derivative was isolated. Moreover, hydrolysis of (13) with hydrochloric acid gave

1,6-di-*O*-benzoyl-D-mannitol (14), identical with (1).

Optical Rotations of the 1,2-*Diglycerides*.—Comparison of the rotations of the 3-trityl ethers (6) and the 1-trityl ethers is shown in Table 1. Oxidation with sodium

TABLE 1

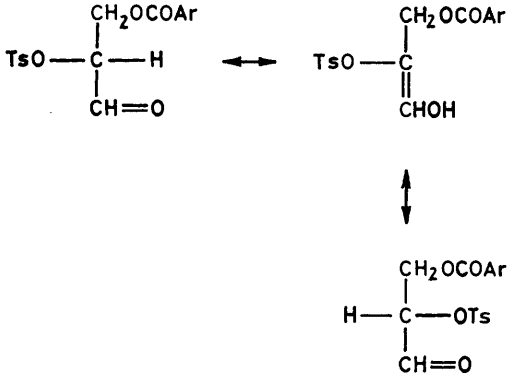


Ar	$[\alpha]_D$(°)	$[\alpha]_D$(°)	$[\alpha]_D$(°)	$[\alpha]_D$(°)	$[\alpha]_D$(°)
Ph	+27.3	*a*	+22.5	*a*	−21.2
	+21.2 [b]		+18.7		
p-$C_6H_4OCH_3$	+24.9 [b]	+26.6	+16.9	+20.0	−19.9
p-$C_6H_4NO_2$	+8.8 [c]	+30.5	+0.8	+19.4	−20.2

[a] Not attempted. [b] Oxidation at 50 °C. [c] Oxidation at 80 °C.

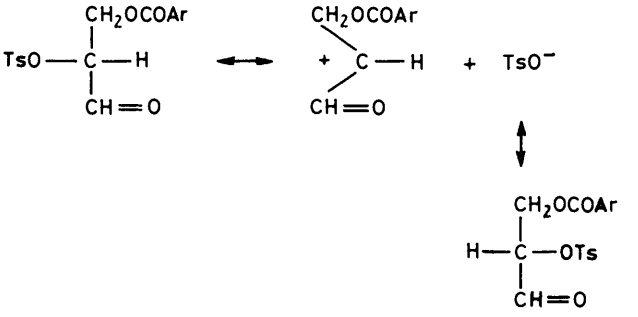
metaperiodiate in ethanol at 25 °C for (4a), at 50 °C for (4b), and 75 °C for (4c) showed that the temperature of oxidation influences whether complete or partial racemisation occurs.

In order to confirm this hypothesis, (4b and c) were oxidised with lead(IV) acetate at ambient temperature in ethyl acetate, and (4a) with $NaIO_4$ in ethanol at 50 °C for 2 h. The rotations of the 3-trityl ethers are for (4b) + 20.2°, for (4c) + 19.4°, and for (4a) + 18.7°. Under these conditions, the aldehyde can be converted into its enol form, which is a symmetric, conjugated system which should be planar. Return to the aldehyde form occurs with racemisation.



It is also possible that the tosyl group can be temporarily removed, giving a carbonium ion,[6] which is stabilised by transition into a planar form. The solvent will intervene in this case and 2-*O*-ethyl derivatives would be obtained. But the formation of by-products was not observed, and the yield was not influenced by the temperature and time of reaction.

Our method can be applied to the preparation of triacyl-*sn*-glycerides with three different fatty acyl substituents. The number of reactions to prepare the 1,2-diglycerides is less than those of previous methods.[7,8] There are only five steps. Moreover, the method avoids tritylation and detritylation.



EXPERIMENTAL

M.p.s were determined with a hot-stage apparatus. ^1H N.m.r. spectra were obtained for samples in deuteriochloroform with a Varian T 60 instrument (tetramethylsilane as internal standard), and i.r. spectra with a Perkin-Elmer 325 instrument (KBr disc). Analyses were performed by the Service Central Microanalyse du C.N.R.S., Thiais, France. Optical rotations were recorded with a Jouan micropolarimeter (accuracy ±5%). T.l.c. was carried out on silica gel F_{254} (Merck). Spots were detected by u.v. fluorescence. Organic solutions were dried over sodium sulphate and evaporated under reduced pressure below 40 °C. The physical and analytical characteristics of compounds (1)—(10) are recorded in Table 2.

1,6-*Di*-O-*aroyl*-D-*mannitol* (1).—The appropriate acid chloride (0.1 mol) in dry pyridine (0.5 mol) was added to a solution of D-mannitol (18.2 g, 0.1 mol) in dry pyridine (0.5 mol). The mixture was stirred at room temperature for 5 h. The reaction was then worked-up using the method of Brigl and Gruner.[3] The yield was raised to 45%.

1,6-*Di*-O-*aroyl*-3,4-O-*isopropylidene*-D-*mannitol* (2).—A mixture of compound (1) (0.1 mol) and dry acetone (800 ml) was stirred with anhydrous copper sulphate (8 g) and sulphuric acid (95%, 0.8 ml) for 36 h. The insoluble material was filtered off to remove unchanged starting product and anhydrous copper sulphate (2 g) was again added to the filtrate. The mixture was stirred for an additional 12 h and neutralised with sodium carbonate. Copper sulphate was filtered off. Evaporation of the solution gave a solid which was recrystallised from di-isopropyl ether to give (2a), from ethanol to give (2b and c) (yield 70%).

1,6-*Di*-O-*aroyl*-3,4-O-*isopropylidene*-2,5-*di*-O-*tosyl*-D-*mannitol* (3).—The isopropylidene derivative (2) (0.1 mol) in dry pyridine was stirred to 0 °C. The tosyl chloride (38.1 g, 0.2 mol) in dry pyridine was added dropwise during 20 min. The mixture was kept at room temperature for 48 h (except for Ar = *p*-$C_6H_4NO_2$ at 40 °C). Dilution with water, extraction with chloroform (750 ml), washing of the extract with sulphuric acid (2N), sodium hydrogencarbonate (10%), and water, drying, and evaporation gave a solid. Compounds (3a and b) were recrystallised from ethanol and (3c) from ethyl acetate (yield (75%).

1,6-*Di*-O-*aroyl*-2,5-*di*-O-*tosyl*-D-*mannitol* (4).—Concentrated hydrochloric acid (50 ml) was added to a stirred solution of compound (3) (20 g) in glacial acetic acid (500 ml). The mixture was warmed to 50 °C for (3b), to 60 °C for (3c), and maintained there for 1 h before cooling. The mixture was then stirred at room temperature for 4 h, and

TABLE 2

Physical and analytical data for compounds (1)—(10)

Compound	M.p. or b.p. (°C)	$[\alpha]_D$ (°)	$[\alpha]_J$ (°)	$[\alpha]_V$ (°)	$[\alpha]_B$ (°)	Solvent	Concentration	Formula	Found (%) C	H	N	S	Required (%) C	H	N	S
(1a)	182 [a]	+15.8	+16.2	+18.3	+31	Py	0.61	$C_{20}H_{22}O_8$	61.55	5.65			61.55	5.65		
(1b)	176 [b]	+15	+15.6	+17.7	+33.8	Py	1.07	$C_{22}H_{26}O_{10}$	58.65	5.85			58.65	5.8		
(1c)	198	+8.9	+9.1	+10.1	+17.3	Py	0.71	$C_{20}H_{20}N_2O_{12}$	50.05	4.1	5.85		50.0	4.15	5.85	
(2a)	96	+24.5	+25.8	+30	+46.7	Py	1.33	$C_{23}H_{26}O_8$	64.0	6.05			64.2	6.05		
(2b)	138	+20.6	+21.6	+24.4	+39.8	Py	0.99	$C_{25}H_{30}O_{10}$	61.35	6.15			61.2	6.1		
(2c)	160	+20	+20.7	+23.3	+37.8	Py	1.02	$C_{23}H_{24}N_2O_{12}$	53.05	4.75	5.2		53.1	4.6	5.2	
(3a)	99	+27	+28.1	+32.2		Chl	3.03	$C_{37}H_{38}O_{12}S_2$	60.15	5.25		8.05	60.15	5.15		8.65
(3b)	120	+20.8	+21.4	+24.2	+36.5	Chl	0.98	$C_{39}H_{42}O_{14}S_2$	58.6	5.25		7.75	58.65	5.25		8.0
(3c)	163	+17.3	+17.9	+20.2	+30.9	Chl	0.97	$C_{37}H_{36}N_2O_{16}S_2$	53.5	4.35	3.95	7.55	53.6	4.35	3.4	7.75
(4a)	123	−32.8	−34.1	−39.5		Chl	0.27	$C_{34}H_{34}O_{12}S_2$	58.5	5.1		9.25	58.45	4.85		9.15
(4b)	135	−55	−57.3	−67.3	−125.7	Chl	0.98	$C_{36}H_{38}O_{14}S_2$	56.7	5.05		8.35	57.0	5.0		8.45
(4c)	160	−40	−42	−48.8	−94.9	Chl	0.8	$C_{34}H_{32}N_2O_{16}S_2$	51.8	4.0	3.9	8.25	51.8	4.05	3.55	8.1
(5a)	88 [c]	+27.3	+29.3	+34.5	+56.8	Py	1.06	$C_{17}H_{18}O_6S$	57.75	5.2		9.1	58.3	5.15		9.15
(5b)	90 [d]	+26.6	+27.8	+31.2	+53	Py	1.02	$C_{18}H_{20}O_7S$	56.6	5.3		8.35	56.85	5.25		8.4
(5c)	99 [d]	+30.5	+31.6	+36	+59.8	Py	1.4	$C_{17}H_{17}NO_8S$	51.55	4.25	3.65	8.05	51.65	4.3	3.55	8.1
(6a)	167 [c]	+22.5	+23.5	+26.8	+46	Py	0.98	$C_{36}H_{32}O_6S$								
(6b)	121 [d]	+20.2	+21	+24.2	+40.1	Py	0.94	$C_{37}H_{34}O_7S$								
(6c)	184 [d]	+19.4	+20.2	+24	+37.9	Py	1.01	$C_{36}H_{31}NO_8S$								
(7a)	132 at 3 mmHg [e]	+8.6	+8.8	+9.7	+18.6	Chl	1.88	$C_{13}H_{16}O_4$								
(7b)	140 at 0.2 mmHg; 24	+13.1	+13.4	+15.6	+20.8	Py	1.12	$C_{14}H_{18}O_5$	63.0	6.85			63.15	6.75		
(7c)	160 at 0.4 mmHg; 36 [f]	+6.2	+6.6	+7.7	+14.3	Py	0.96	$C_{13}H_{15}NO_6$								
(8a)	66 [g]	−15.2	−16.1	−18.6	−31.8	Py	1.13	$C_{10}H_{12}O_4$	60.9	6.0			61.2	6.1		
(8b)	81	−13.8	−14.3	−16.9	−29.4	Py	1.36	$C_{11}H_{14}O_5$	58.9	6.1			58.4	6.2		
(8c)	88 [h]	−15.8	−16.3	−18.9	−34.4	Py	1.18	$C_{10}H_{11}NO_6$								
(9a)	90 [i]	−20.4	−21	−24.2	−41.8	Py	1.24	$C_{29}H_{26}O_4$	79.35	5.95			79.45	5.95		
(9b)	138	−15.1	−15.7	−17.2	−29	Py	0.69	$C_{30}H_{28}O_5$	76.8	6.05			76.9	6.0		
(9c)	136 [j]	−18.2	−19.2	−22.3	−37.5	Py	1.02	$C_{29}H_{25}NO_6$								
(10a)	167	−21.2	−22.2	−24.7	−42.2	Py	1.15	$C_{36}H_{32}O_6S$	72.95	5.55		5.45	72.95	5.4		5.4
(10b)	120	−19.4	−20.4	−22.3	−37.2	Py	0.9	$C_{37}H_{34}O_7S$	71.15	5.3		5.25	71.4	5.45		5.15
(10c)	183	−20.2	−21	−25.3	−39.6	Py	1.02	$C_{36}H_{31}NO_8S$	67.8	4.95	2.5	5.75	67.8	4.85	2.2	5.0

Py = pyridine, Chl = chloroform; D 589, J 578, V 546, B 436 nm

[a] Lit.,[3] m.p. 182°, $[\alpha]_D^{20}$ + 15.9° (pyridine). [b] Lit.,[9] m.p. 176°. [c] Oxidation with lead(IV) acetate. [d] Oxidation with $NaIO_4$. [e] Lit.,[10] b.p. 159—160.5° at 10.5 mmHg, $[\alpha]_D$ + 12.31° (neat). [f] Lit.,[4] m.p. 37°, $[\alpha]_D$ + 5.8° (pyridine). [g] Lit.,[11] m.p. 67°, $[\alpha]_D$ −15.3° (pyridine). [h] Lit.,[4] m.p. 88°, $[\alpha]_D$ − 16.4° (pyridine). [i] Lit.,[11] m.p. 90°, $[\alpha]_D$ − 22.1° (pyridine). [j] Lit.,[4] m.p. 136°, $[\alpha]_D$ − 5.7° (*s*-tetrachloroethane).

poured into water (4 l). The precipitate was filtered off and dried. Compounds (4a and b) were recrystallised from ethanol and (3c) from ethyl acetate (yield 75%).

1-O-*Aroyl*-2-O-*tosyl*-sn-*glycerol* (5).—(a) *Oxidation with sodium metaperiodiate.* Compound (4) (0.01 mol) was dissolved in ethanol (500 ml) under reflux. The solution was cooled to 75 °C for (4c), to 50 °C for (4b), to 25 °C for (4a), and a solution of $NaIO_4$ (2.14 g, 0.01 mol) in water (10 ml) was added. The temperature was maintained for 20 min. The solution was cooled to room temperature, and stirred for 2 h. The insoluble material was filtered off. The filtrate was evaporated. The oil was extracted into ethyl acetate. Upon drying the extract was converted into the alcohol.

(b) *Oxidation with lead*(IV) *acetate.* Lead(IV) acetate (4.45 g, 0.01 mol) was added to a solution of compound (4) (0.01 mol) in ethyl acetate (500 ml). The mixture was stirred for 16 h, but oxidation is not always complete after this time. Consequently, lead salts were filtered off, and ethyl acetate was evaporated. The oil was extracted into ethanol. Oxidation was achieved with $NaIO_4$ (see below).

(c) *Reduction.* The aldehyde (0.01 mol) in ethyl acetate (100 ml) was added to a suspension of sodium borohydride (0.57 g, 0.015 mol) in the same solvent (100 ml) at 5 °C. The mixture was stirred. After 20 min, water (2 ml) was added, and the mixture was stirred for a further 5 min. Excess of borohydride was destroyed by dropwise addition of dilute hydrochloric acid. The solvent was dried, and evaporated. Compound (5a) was recrystallised from carbon tetrachloride, (5b) from diethyl ether, and (5c) from ethanol (yield 70%).

On oxidation with $NaIO_4$, compound (5a) had m.p. 88°, $[\alpha]_D$ +27.3°; (5b) had m.p. 90°, $[\alpha]_D$ +24.9°; (5c) had m.p. 125°, $[\alpha]_D$ +8.8°. On oxidation with lead(IV) acetate, compound (5b) had m.p. 90°, $[\alpha]_D$ +26.6°; (5c) had m.p. 99°, $[\alpha]_D$ +30.5°

1-O-*Aroyl*-2-O-*tosyl*-3-O-*trityl*-sn-*glycerol* (6).—Triphenylmethyl chloride (2.8 g, 0.01 mol) and compound (5) (0.01 mol) were kept at room temperature in dry pyridine (0.1 mol) for 48 h. After dilution with water, the organic phase was extracted with chloroform (250 ml), washed, and dried. Evaporation of the solvent gave a product which was recrystallised from ethanol. On oxidation with $NaIO_4$, compound (6a) had m.p. 167°, $[\alpha]_D$ +22.5°; (6b) had m.p. 121°, $[\alpha]_D$ +16.9°; (6c) had m.p. 184°, $[\alpha]_D$ +0.8°. On oxidation with lead(IV) acetate, compound (6b) had m.p. 121°, $[\alpha]_D$ +20.2°; (6c) had m.p. 184°, $[\alpha]_D$ +19.4°.

1,2-O-*Isopropylidene*-3-O-*aroyl*-sn-*glycerol* (7).—This was prepared from D-mannitol, *via* 1,2;5,6-di-*O*-isopropylidene-D-mannitol, and *via* 1,2-*O*-isopropylidene-*sn*-glycerol, using the procedure of Baer.[10] The isopropylidene-*sn*-glyceraldehyde was reduced with sodium borohydride. Condens-

ation of the acid chloride gave compound (7) which was distilled under reduced pressure.

3-O-*Aroyl*-sn-*glycerol* (8).—A suspension of (7) (0.1 mol) in dilute hydrochloric acid (0.5N, 500 ml) was treated using the method of Baer.[4,11]

3-O-*Aroyl*-1-O-*trityl*-sn-*glycerol* (9).—The α-monglyceride (0.01 mol) was treated with triphenylmethyl chloride (2.8 g, 0.01 mol) in pyridine (0.1 mol). After 48 h, compound (9) was isolated after the usual procedure and recrystallised from ethanol.

3-O-*Aroyl*-2-O-*tosyl*-1-O-*trityl*-sn-*glycerol* (10).—The trityl ether (9) (0.01 mol) and tosyl chloride (1.90 g, 0.01 mol) in pyridine (0.1 mol) were kept at ambient temperature for 48 h. The usual work-up gave compound (10) which was recrystallised from ethyl acetate.

1,2;3,4;5,6-*Tri*-O-*isopropylidene*-D-*mannitol* (11).—A suspension of D-mannitol in acetone (1 l) was stirred for 2 h with sulphuric acid (96%, 8 ml). The solution was either poured into water, the precipitate filtered off and dried, or neutralised and acetone evaporated. The *solid* was recrystallised from ethanol (yield 75%), m.p. 70°, $[\alpha]_D$ +13.8°, $[\alpha]_J$ +14.3°, $[\alpha]_V$ +16.4°, $[\alpha]_B$ +25.8° (*c* 1.7 in chloroform) (Found: C, 59.4; H, 8.65. $C_{15}H_{26}O_6$ requires C, 59.6; H, 8.6%).

3,4-O-*Isopropylidene*-D-*mannitol* (12).—Compound (11) (10 g, 0.03 mol) in 70% acetic acid (200 ml)was stirred for 2 h at 40 °C. Distillation of acetic acid under reduced pressure (15—20 mmHg) gave a solid which was treated using the method of Wiggings,[5] m.p. 87°, $[\alpha]_D$ +18.7°, $[\alpha]_J$ +19.6°, $[\alpha]_V$ +22.4°, $[\alpha]_B$ +33.2° (*c* 1.52 in pyridine) (Found: C, 48.45; H, 8.3. Calc. for $C_9H_{18}O_6$: C, 48.65; H, 8.1%) (lit.,[5] m.p. 86—87°).

1,6-*Di*-O-*benzoyl*-3,4-O-*isopropylidene*-D-*mannitol* (13).—The isopropylidene derivative (2.22 g, 0.01 mol) in pyridine (8 ml) and benzoyl chloride (2.8 g, 0.02 mol) were stirred at 0 °C for 3 h. The mixture was poured onto ice–water, and the product extracted with chloroform. After the usual work-up, the solvent was evaporated to leave a syrup. The oil was cooled to −40 °C for 12 h. The crystalline *product* was filtered off and washed with ether–light petroleum (1 : 1), and recrystallised from di-isopropyl ether (yield 25%), m.p. 94°, $[\alpha]_D$ +24.1° (*c* 1.46 in pyridine) (Found: C, 64.15; H, 6.1. $C_{23}H_{26}O_6$ requires C, 64.2; H, 6.05%).

1,6-*Di*-O-*benzoyl*-D-*mannitol* (14).—Compound (13) was hydrolysed as described for compound (3). Work-up gave a solid, which was recrystallised from ethanol, m.p. 181°.

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