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Synthesis of a 'Reverse Ester' Analogue of 1,2-*sn*-Diglycerides from (*S*)-1,2-Di-*O*-Isopropylideneglycerol; Efficient, Stereospecific Nucleophilic Displacement *via* a Triflate at Glycerol C-2

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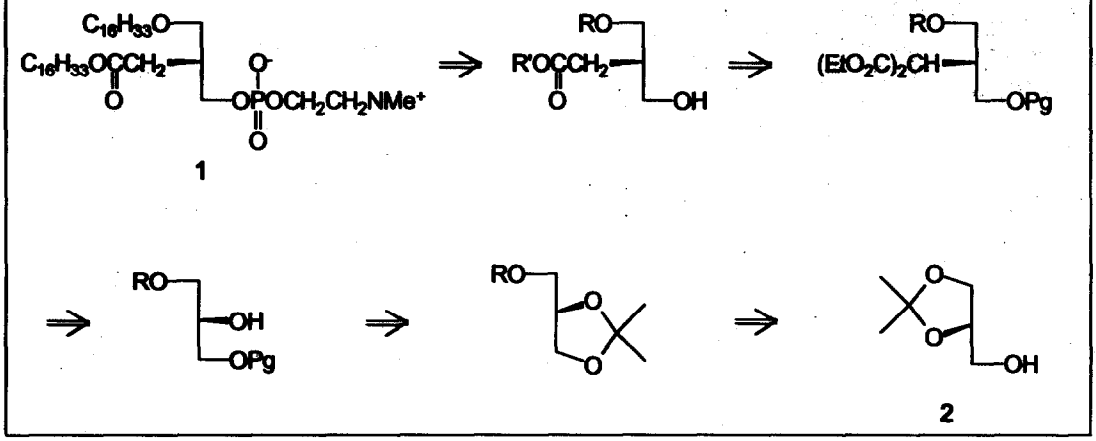
Abstract: An optically pure glyceride analogue in which the 2-*O*-ester grouping has been reversed was efficiently synthesised from (*S*)-di-*O*-isopropylideneglycerol by a sequence that featured an S_N2 displacement by the anion of diethyl malonate on a protected glycerol 2-*O*-triflate.

Current research on glycerol lipids concerns 1,2-*sn*-diglycerides in the context of their activation of protein kinase C,[1] platelet activation factors[2] (1-substituent alkyl), and inhibitors of phospholipase A_2 (PLA_2).[3] The latter enzyme catalyses the release of a fatty acid from the 2-*O*-position of membrane phospholipids. From crystallographic studies of enzymes from various sources, the mechanism of action of PLA_2 is believed to involve attack of a histidine-activated water molecule on an ester grouping polarised by co-ordination to Ca^{2+}.[4,5] Substances in which the 2-ester group of a conventional phospholipid has been reversed, *e.g.* **1** (Scheme 1), are isosteres of the natural systems and are of interest as potential inhibitors of PLA_2.[6,7] Indeed, 'reverse ester glycerides' are of interest in the context of all biologically active glycerols with a 2-*O*-acyl substituent. We will describe an efficient synthetic route from (*S*)-di-*O*-isopropylideneglycerol **2** to an optically pure 'reverse ester glyceride', which is a potential precursor of 'reverse ester' phospholipids. The key intermediate is a glycerol 2-*O*-trifluoromethanesulphonate, which undergoes S_N2 displacement with a variety of nucleophiles, including carbon nucleophiles. This strategy extends the usage of the chiral pool member **2** and is expected to have a variety of applications. Previous syntheses[6-8] of 'reverse ester glycerides' have used different strategies from those described here and have produced racemic materials.

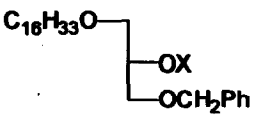
The synthesis of 'reverse ester glycerides' requires displacement of the oxygen functionality at the 2-position of glycerol by a carbon nucleophile and Scheme 1 shows a retrosynthetic analysis for the synthesis of a 'reverse ester glyceride' from **2**. Nucleophilic displacements at the 2-position of glycerol have been difficult to achieve without the incursion of neighbouring group participation.[9] Stereospecific inversion at C-2 leads to a 'reverse ester glyceride' having chirality corresponding to a 1,2-*sn*-glyceride provided the 3-*O*-position of **2** is initially acylated (or alkylated).

Scheme 1: Retrosynthetic analysis (R = $C_{16}H_{33}$, Pg = protecting group)



We have explored the use of the sulphonate leaving groups 2,2,2-trifluoroethanesulphonate[10,11] (tresylate) and trifluoromethanesulphonate (triflate)[11,12] as a means of achieving stereospecific inversion at C-2 of glycerol. Previous workers have used 4-nitrobenzenesulphonate for thiolate displacements, but the site of displacement and optical purity of products was not rigorously established.[13,14]

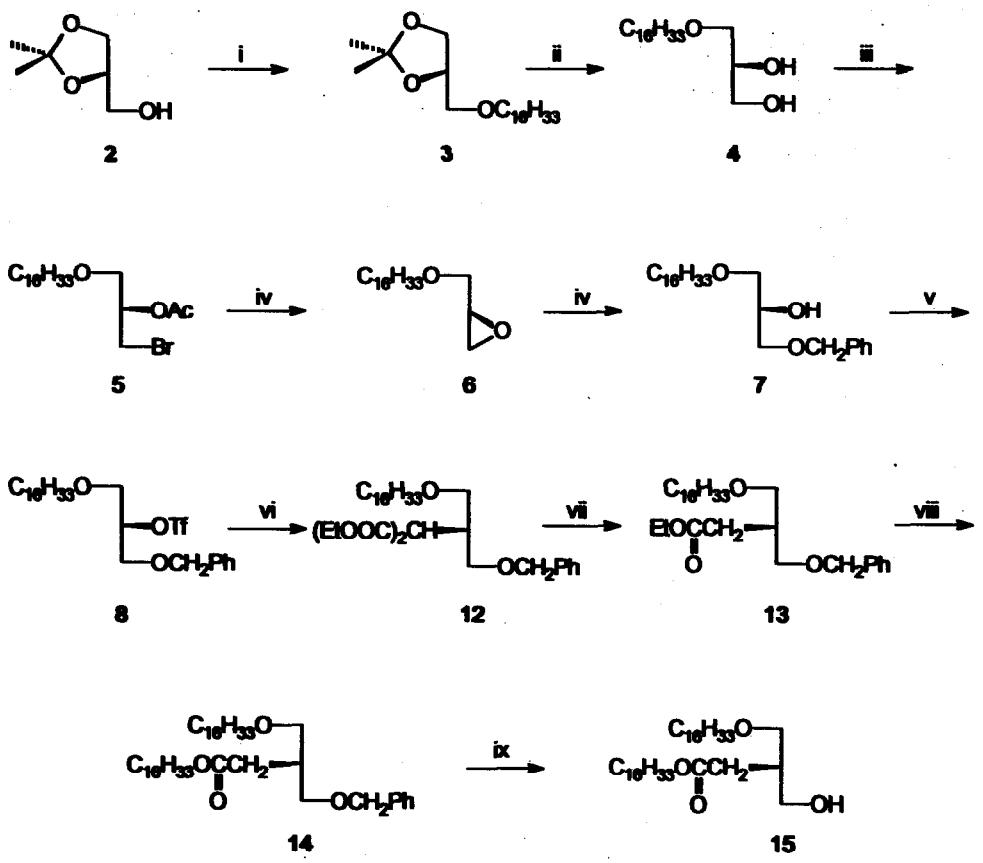
To enable the plan of Scheme 1 to be exemplified we prepared 1-*O*-benzyl-3-*O*-hexadecyl-*sn*-glycerol, 7 from **2** (*cf* Scheme 2). Thus, the alkoxide of **2** (prepared using sodium hydride in dimethyl sulphoxide; in our hands this gave more reliable results than NaH in tetrahydrofuran[13] or dimethylformamide,[15] both of which required heating) was alkylated with hexadecan-1-ol *O*-methanesulphonate to afford 3-*O*-hexadecyl-1,2-di-*O*-isopropylidene-*sn*-glycerol **3** (64%). This was quantitatively hydrolysed (1 M HCl in methanol) to the corresponding diol **4**, which gave the crystalline bromoacetate **5** (95%) when subjected to the HBA reaction[16] [45% HBr in acetic acid (3 equivalents HBr)]. Conversion of **3** into **5** was advantageously done in a 'one-pot' reaction using HBA[17] (89% overall). Treatment of **5** with 0.84 M sodium benzyloxide in benzyl alcohol (containing 3 equivalents NaOBn) gave, *via* epoxide **6**, compound **7** (94%). The same sequence was used to prepare *rac*-**7** from 'solketal' (*rac*-1,2-di-*O*-isopropylideneglycerol).



9 X = $CF_3CH_2SO_2$
10 X = CH_3CO
11 X = CH_3SO_2

Rac-**7** was initially used to define conditions for achieving nucleophilic displacements at its C-2 position and for obtaining *rac*-**1** from suitable intermediates. It was converted into the corresponding sulphonates, *rac*-**8** and *rac*-**9**, by standard methodology.[10-12] Whereas reaction of *rac*-**8** with tetra-*n*-butylammonium acetate in dry dichloromethane gave exclusively *rac*-acetate **10** (54%), the tresylate *rac*-**9** gave a mixture containing *inter alia* *rac*-acetate **10** and *rac*-mesylate **11** (20%, identical to a sample prepared by direct mesylation of *rac*-**7**[18]). Subsequent studies therefore utilised only the triflate.

Scheme 2: Synthesis of 'reverse ester glyceride' 15 from 2



Reagents and conditions

i NaH, DMSO, room temp, 0.5 h, $C_{16}H_{33}OSO_2CH_3$, 16 h; ii 1M HCl, MeOH, reflux, 1 h; iii 45% HBr in acetic acid, room temp, 0 °C, 5 min → room temp, 20 min.; iv 3equiv $PhCH_2ONa$, $PhCH_2OH$; v Triflic anhydride, dry pyridine, dry CH_2Cl_2; vi $(EtOOC)_2CH_2$/NaH, THF, room temp, 16 h; vii Bu_4NOAc, dry DMSO, 130°C; viii $C_{16}H_{33}OH$, 2 M BuLi, toluene, reflux with Dean-Stark, 4 h; ix H_2/Pd, THF, 2 h, room temp.

That the triflate → acetate conversion proceeds with inversion was demonstrated in the enantiomeric series. Thus, 3-*O*-benzyl-1-*O*-hexadecyl-*sn*-glycerol [prepared from (*R*)-1,2-di-*O*-isopropylideneglycerol] was converted (acetic anhydride/pyridine/4-dimethylaminopyridine catalyst) into the corresponding acetate (enantiomer of **10**; $[\alpha]_D$ + 1.54°, c 6 in benzene lit[15] +1.7° for the homologue with a C_{18} alkyl chain), and *via* the corresponding triflate (enantiomer of **8**) into acetate **10** ($[\alpha]_D$ - 1.77°, c 8.6 in benzene).

Triflate **8** undergoes nucleophilic displacement reactions with ammonia, the sodium salt of diethyl malonate, and sodium hexadecanethiolate. Diethyl malonate in tetrahydrofuran was treated with NaH followed by *rac*-**8**, to give *rac*-**12** (86%), which was converted into *rac*-**13** (79%) by heating with tetrabutylammonium acetate in dimethyl sulphoxide[19] (n.b. this gave better yields than heating with NaCl in DMSO containing 1,2 or

3 equivalents of water[20]). Transesterification of *rac*-13 to *rac*-14 (64%) was achieved by heating *rac*-13 in toluene with 1 mol equivalent of lithium hexadecan-1-olate (prepared *in situ* from hexadecan-1-ol and butyl lithium), using a Dean-Stark apparatus to remove ethanol. Hydrogenation (Pd/C, H_2 in tetrahydrofuran[21]) of *rac*-14 gave *rac*-15 quantitatively. Phosphorylation of *rac*-15 to *rac*-1 was accomplished using 2-chloro-2-oxo-1, 3,2-dioxaphospholane-2-oxide, followed by ring opening with trimethylamine.[22]

Application to 8 of the four-stage sequence described gave 15 in 22% overall yield. The optical integrity of 15 was proved by conversion into its Mosher ester, the ^{1}H NMR of which in $CDCl_3$ showed a single substance, whereas the ^{1}H NMR of the Mosher ester from *rac*-15 clearly indicated two diastereoisomers. It is assumed by analogy with the conversion of 8 into the enantiomer of 10 (see above), that the stereochemistry of 15 is as shown and therefore corresponds to natural glyceride stereochemistry.

n.b. All compounds gave analytical and spectroscopic data in accord with their assigned structure.

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