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An efficient stereoselective synthesis of enantiomerically pure mono- and di-*O*-hexadecyl-β-D-glucosylglycerol ethers by epoxidation of an allyl β-D-glucopyranoside asymmetrically induced by the glucide moiety †

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Abstract: 1-*O*-Hexadecyl and 1,2-di-*O*-hexadecyl-3-*O*-(β-D-glucopyranosyl)-*sn*-glycerol ethers were obtained by regiospecific opening of the oxirane ring of the 2′,3′-epoxypropyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside synthetized by stereoselective epoxidation of the corresponding allyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside asymmetrically induced by the glucide moiety. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Introduction

Glycosylglycerols are an important class of organic compounds widely distributed in Nature. They have been found[1] in plants, animals and bacteria with different biological functions. Recently attention towards these compounds is increasing owing to the biological activities shown, in particular, by the compounds in which the sugar is β linked to the primary position of glycerol.[2] Only small amounts of glycosylglycerols can be obtained, however, from natural sources, and consequently the development of efficient synthetic methods for the preparation of these compounds is becoming a timely problem in synthetic chemistry and biochemistry.

Two different synthetic procedures are generally followed to obtain glycosylglycerols in diastereomerically pure form, the coupling of the proper glycosyl donor a) with an optically pure glycerol derivative[3] or b) with a racemic glycerol derivative, followed by enzymatic separation of the diastereoisomeric products.[4]

On the other hand, it has been recently shown that carbohydrates can be used as efficient chiral auxiliaries for asymmetric synthesis,[5] and, although their multiple stereogenic centres and multifunctionality may introduce complications in the selective formation of derivatives, proper regio- and stereoselective functionalization allows one to obtain structural variations which can improve the diastereoselection. In particular, it has been shown that 3,4,6-tri-*O*-benzyl-β-D-glucose can be used as an efficient chiral template for the bromination of the unsubstituted allylic aglycon[6] and for the cyclopropanation[7] or epoxidation[8] of substituted allylic ones.

In this work we are reporting a simple procedure to prepare lipophilic mono- and di-*O*-hexadecyl-β-D-glucosylglycerol ethers in a diastereomerically pure form by epoxidation of an allylic β-D-glucopyranoside precursor asymmetrically induced by the glucide moiety.

Results and discussion

The suitable allyl β-D-glucopyranoside used as starting material in this synthetic approach has been prepared from the corresponding glucal **1** by epoxidation with MCPBA–KF in anhydrous CH_2Cl_2, which has been shown[9] to give the corresponding *anti* and *syn* epoxidation products, **2** and **3**, with

† Dedicated to the memory of Professor Giuseppe Bellucci (d. March 3, 1996).
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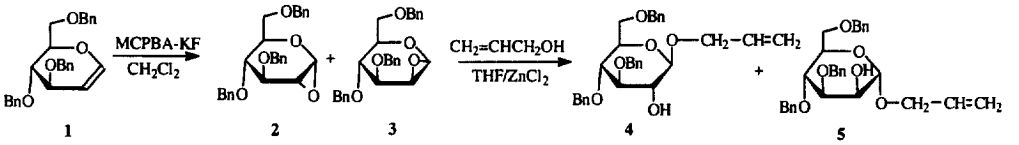
a high prevalence of the former (Scheme 1). The mixture of epoxides was then subjected to oxirane ring opening by treatment with allyl alcohol in the presence of $ZnCl_2$. Although 1,2-anhydro sugar derivatives have proved to be very good glycosyl donors for oligosaccharide and other glycoside syntheses,[10] it has recently been reported[11] that solvent, catalyst and order of reagents addition can have a significant influence on the results. In order to achieve higher yields[6] of the compound **4**, the reaction was carried out in THF at −78°C, in the presence of molecular sieves as a water scavenger, using the inverse addition order of the reagents reported by Kong.[11] The two products **4** and **5** arising, respectively, from **2** and **3** by an anti stereospecific oxirane ring opening were obtained in a 90:10 ratio and 90% yield after purification by column chromatography.



1 2 3 4 5

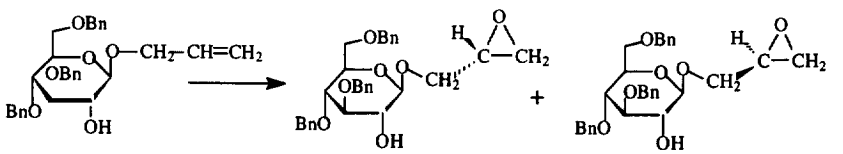
Scheme 1.

The allyl glycoside **4** was therefore subjected to epoxidation with anhydrous MCPBA in aprotic solvents of moderate polarity (1,2-dichloroethane, dichloromethane, chloroform and toluene) at −18°C (Table 1).

As shown in Table 1, the highest efficiency (conversion and diastereoselection) of the reaction was obtained in CH_2Cl_2. Owing to the poor reactivity of the allyl derivative the lower temperatures, which, in principle, would give an higher diastereoselection, could not be used. The (R) configuration of the oxirane carbon of **6** was determined on the basis of the absolute configuration of the products (see below) arising from the regiospecific oxirane ring opening.

The epoxidation of the corresponding 2-*O*-acetyl derivative of **4** was slower and practically non-diastereoselective showing that, in agreement with the bromination of allyl glycosides[6] and with the epoxidation of 1-*O*-*trans*-2-butenyl-3,4,5-tri-*O*-benzyl-β-D-glucopyranose,[8] the presence of a free hydroxy group at the 2-position was necessary for the enantioface selection. This, taking into account the absolute configuration of the prevalent diastereoisomer, suggests the formation of a hydrogen bond between the OH group and the peroxyacid which preferentially stabilizes the transition state related to the electrophilic addition to the *Re* face of the double bond. Furthermore, a possible role of the stereochemistry at the anomeric carbon and/or of the relative configuration at the C(1) and C(2)

Table 1. Epoxidation of **4** with MCPBA (1.2 eq) at −18°C



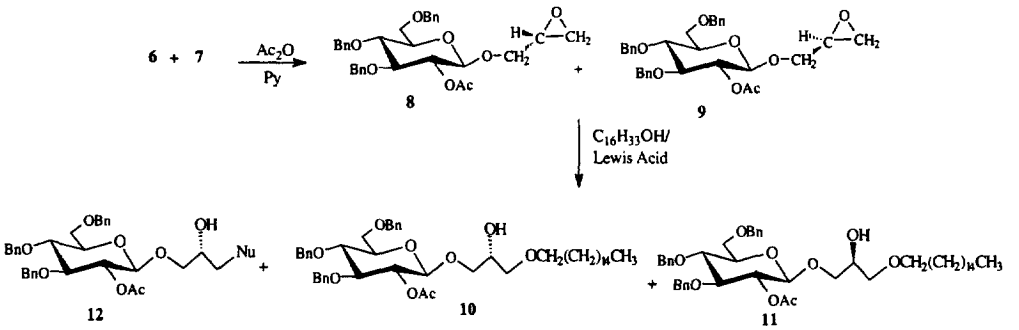
4 6 7

Solvent	Time (days)	Yield[a] %	Ratio (6:7)[b]
CH_2Cl_2	4	80[c]	90:10
$CHCl_3$	4	60[c]	80:20
$(CH_2Cl)_2$	8	10[c]	d
Toluene	7	<10[c]	d

[a]Determined after column chromathography. [b] Determined by ^1H and ^{13}C NMR. [c]The remaining material was unreacted **4**.[d] Undetermined.

carbons can be offered on the basis of the lower diastereoselection (around 60:40) observed when the epoxidation was carried out, under identical conditions, on the α-allyl glycoside **5**.

Once the 90:10 mixture of the diastereoisomeric epoxides **6** and **7** having the proper β-configuration at the glycosyl centre was obtained, the key step in our synthetic strategy was the regiospecific nucleophilic attack on the oxirane ring. In order to avoid a competition between the alkylation at the OH-2 of the glucosyl moiety and the attack at the secondary glycerol OH group in the subsequent step (Scheme 3), the mixture of epoxides **6+7**, before proceeding to the oxirane ring opening, was acetylated (Ac_2O/Py) to give a 90:10 mixture of epoxides **8+9**. The oxirane ring opening of the **8+9** mixture was then carried out with a long chain alcohol with different catalysts (Scheme 2).



Scheme 2.

Several protic and Lewis acids, that are known to accelerate the nucleophilic opening of epoxides with alcohols, were directly compared and Table 2 summarizes the obtained results.

The use of ferric chloride as the promoter in the reaction of epoxides with alcohols has been recently reported[12] as an efficient, simple and mild method for the regio- and stereoselective conversion of oxiranes into their corresponding β-alkoxy alcohols. Moreover, preliminary experiments, carried out on the **8+9** mixture using ethanol as nucleophilic solvent, have shown that the reaction occurs even on this substrate with a high regioselection giving the product arising from the nucleophilic attack on the less substituted carbon in a 60% yield (after purification by column chromatography) beside a lesser amount (around 30%) of compound **12** (Nu=Cl). However, when the reaction was conducted using 1-hexadecanol in THF practically only products arising from the incorporation of intermediate nucleophiles, formed by solvent polymerization, were isolated. On the other hand, more positive results were obtained in ethyl ether, where compound **10** was formed in *ca.* 20% yield. Also in this case, however, the main product, **12** (Nu=OEt), arose from the formation in the reaction media of ethanol,

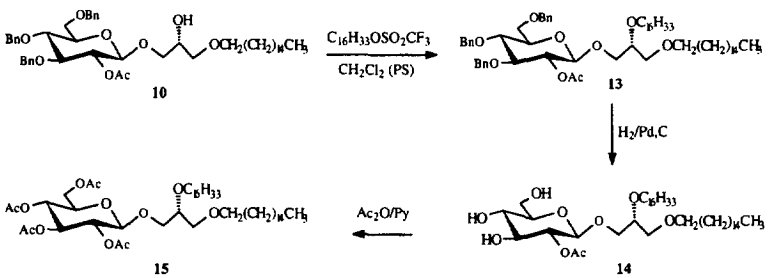
Table 2. Oxirane ring opening reactions with 1-hexadecanol

Catalyst	**10**[a] Yield, %[b]	**11**[a] Yield, %[b]	**12**[a] (Yield, %)[b]
$FeCl_3$/THF	--	--	Nu=O$(C_4H_8O)_n(CH_2)_{15}CH_3$ (30 %)
$FeCl_3/Et_2O$	21	--	Nu=OEt (31%)
$TsOH/CH_2Cl_2$	23	--	Nu=OTs (44%)
$TiCl_4$/THF	--	--	Nu=Cl (40%)
Sc(OTf)$_3$/Toluene	72	8	--

[a] Characterized by ^1H and ^{13}C NMR spectra.
[b] Determined after column chromatography.

or more probably of the ethoxylic radical formed through an electron transfer process involving the solvent and the catalyst. **10** was obtained in 20% yield in the reaction carried out in the presence of *p*-toluenesulfonic acid, where the main product arose from the incorporation of the promoter. No catalytic activity was observed using $TiCl_4$. A high yield (80%) was however observed using the mild catalyst[13] $Sc(OTf)_3$ in toluene. In this case the product **11**, arising from the regiospecific attack at the primary glycidol carbon of **9** was also isolated in 8% yield. Therefore, these reaction conditions were used to obtain **10**. It is noteworthy that independent of the products being formed the oxirane ring opening proceeds with complete regioselectivity, whatever the promoter and the nucleophile.

The subsequent alkylation of the C-2 position (Scheme 3) was carried out by heating with hexadecyl triflate in CH_2Cl_2 heating under reflux for six days and using 1,8-bis(dimethylamino)naphthalene (PS) as acid scavenger. Compound **13** was isolated in a 65% yield and characterized by ^1H and ^{13}C NMR spectra.



Scheme 3.

The stereochemistry at the C-2 carbon of the glycerol moiety of **13** was finally established by transformation in to the corresponding tetraacetyl derivative **15**, by debenzylation and acetylation. The comparison of the ^1H NMR spectrum, melting point and specific rotation[14] allowed us to assign the (R) configuration to this carbon and consequently to the C-2 carbon of **10**, **8** and **6**.

In conclusion, these results represent the first example of a synthesis of diastereoisomerically pure glucosylglycerols with the sugar moiety as the chiral inducer. Furthermore, the high diastereoselection, obtained in the epoxidation of the allylic aglycone, and the complete regiospecificity of the oxirane ring cleavage open the way to obtaining with this method a large class of diastereoisomerically pure differently substituted glycosyl glycerols.

Further work is in progress to explore the scope and limitations of this method in the synthesis of new compounds having potential biological activity.

Experimental

All melting points were taken on a Kofler apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ at 20±2°C with a Perkin–Elmer 241 polarimeter. NMR spectra were registered with a Bruker AC 200 instrument using tetramethylsilane as internal standard. All reactions were followed by TLC on Alugram® sil G/UV_{254} with detection by UV or with ethanolic 10% sulphuric acid and heating. Kieselgel Macherey–Nagel (70–230 or 230–400 mesh) was used for column and flash chromatography. Solvents were distilled and stored over 4Å molecular sievies activated by heating for 24 h at 400°C. Reactions in anhydrous conditions were carried out under an argon atmosphere.

The following standard procedure was used for acetylation: a solution of the proper compound in a 2:1 (v/v) mixture (15 ml/mmol) of pyridine and acetic anhydride was left at room temperature for 24 h, then repeatedly co-evaporated *in vacuo* with toluene and the residue was purified by chromatography on silica.

1,2-Anhydro-3,4,6-tri-O-*benzyl*-α-D-*glucopyranose* **2** *and 1,2-anhydro-3,4,6-tri*-O-*benzyl*-β-D-*mannopyranose* **3**

Anhydrous KF (2.10 g, 36 mmol, obtained by heating at 120°C and 0.1 mmHg for 2 h) was added to a dichloromethane solution (180 ml) of 70% *m*-chloroperoxybenzoic acid (4.41 g, 17.88 mmol), previously dried over Sikkon and $MgSO_4$, and the mixture was stirred at room temperature for 30 min. A solution of commercial tri-*O*-benzyl-D-glucal (**1**) (3.00 g, 7.2 mmol) in dry CH_2Cl_2 (10 ml) was added and the mixture was stirred for 24 h at room temperature. The insoluble complexes were then filtered off, and the solvent was removed under reduced pressure to give 2.95 g (95% yield) of a 9:1 mixture of epoxides **2** and **3**, which were identified on the basis of the ^1H and ^{13}C NMR spectra.[6]

Allyl 3,4,6-tri-O-*benzyl*-β-D-*glucopyranoside* **4** *and allyl 3,4,6-tri*-O-*benzyl*-α-D-*mannopyranoside* (**5**)

A suspension of powdered 4Å molecular sieves (300 mg) and allyl alcohol (2.0 ml, 29.4 mmol) in dry THF (10 ml) was stirred at room temperature. After 15 min the crude epoxidation product (**2+3**, 2.57 g, 5.95 mmol) was added, the mixture was cooled −78°C and then 1 M $ZnCl_2$ in ethyl ether (7 ml) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. After filtering, a solution of NaCl was added (30 ml) and the product was extracted with ethyl acetate (4 × 30 ml). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to obtain a residue, containing **4** and **5** in a 90:10 ratio, which was purified by flash-chromatography over silica gel (8:2 hexane/AcOEt) to give pure **4** (2.40 g, 81% yield) and **5** (0.32 g, 11% yield).

Allyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside **4**: syrup Rf=0.45 (7:3, hexane/AcOEt); $[\alpha]_D$=+29.3 (*c* 1.14, $CHCl_3$). Lit.[15] $[\alpha]_D$=+32.0 (c 3.18, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: from 3.48 to 4.56 (m, 12 H, allylic OCH_2, 2 benzylic CH_2, H-6, H-6′, H-5, H-4, H-3 and H-2), from 4.78 to 4.97 (m, 3 H, benzylic CH_2 and H-1); 5.24 (m, 2 H, $=CH_2$); 5.90 (m, 1 H, CH=); from 7.13 to 7.33 (m, 15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 69.31 (C-6); 70.62 (allylic OCH_2); 73.88, 75.40 and 75.60 (3 benzylic CH_2); 75.06 and 75.50 (C-2 and C-5); 78.01 (C-4); 85.03 (C-3); 102.25 (C-1); 118.33 ($=CH_2$); 1280.10–128.84 (15 aromatic C); 134.42 (=CH); 138.57, 138.57 and 139.14 (3 aromatic >C<). Anal. Calc. for $C_{30}H_{34}O_6$: %C=73.45, %H=6.99; Found: %C=73.28, %H=6.84. **5** was identified on the basis of the reported optical rotation and of the ^1H and ^{13}C NMR spectra.[16]

Allyl 2-O-*acetyl-3,4,6-tri*-O-*benzyl*-β-D-*glucopyranoside*

Compound **4** (350 mg, 0.715 mmol) was acetylated by the standard procedure. The crude product was purified by column chromatography over silica gel (6:4 hexane/AcOEt) to give 340 mg of pure allyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside: syrup, Rf=0.53 (hexane/AcOEt 6:4), $[\alpha]_D$=−1.4 (c 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.96 (s, 3 H, CH_3CO); from 3.45 to 4.83 (m, 14 H, allylic OCH_2, 3 benzylic CH_2, H-6, H-6′, H-5, H-4, H-1 and H-3), 5.04 (m, 1 H, H-2); 5.22 (m, 2 H, $=CH_2$); 5.84 (m, 1 H, CH=); from 7.14 to 7.33 (m, 15 H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ: 21.47 (MeCO); 69.24 (C-6); 70.09 (allylic OCH_2); 74.02, 75.57 and 75.68 (3 benzylic CH_2); 73.63 (C-2); 75.68 (C-5); 78.53 (C-4); 83.51 (C-3); 100.40 (C-1); 117.52 ($=CH_2$); 128.18–128.98 (15 aromatic C); 134.36 (=CH); 138.41, 138.71 and 138.71 (3 aromatic >C<): 170.07 (C=O). Anal. Calcd. for $C_{32}H_{36}O_7$: %C=72.16, %H=6.81. Found: %C=71.98, %H=6.74.

(2′R)- and (2′S)-2′,3′-Epoxypropyl 3,4,6-tri-O-*benzyl*-β-D-*glucopyranoside* **6** *and* **7**

Compound **4** (1.0 mmol) was added to a solution (5 ml) of 70% MCPBA (1.2 mmol) in the appropriate solvent (Table 1), previously dried for 20 min over Sikkon and $MgSO_4$ and filtered. The reaction mixture was left at −18°C for the time reported in Table 1, then diluted with CH_2Cl_2, washed with an aqueous solution of $NaHSO_3$ and $NaHCO_3$, dried ($MgSO_4$) and evaporated *in vacuo*. The residues were analyzed by ^1H NMR (C_6H_6) in order to evaluate the conversion from the ratio between the olefinic and oxirane protons, and the diastereoselectivity of the epoxidation, which was given by the ratio of signals for the diastereoisomeric oxirane H-3′ protons at δ 2.73 and 2.55. The crude residues were purified by flash-chromatography over silica gel (hexane/AcOEt, 7:3, containing

0.1% Et_3N) to obtain the starting glucoside **4** and a mixture of the two diastereoisomeric epoxides **6** and **7**. Yields and diastereoisomeric ratios are reported in Table 1. The mixture of epoxides **6** and **7**, obtained as a syrup, showed: Rf=0.18 (hexane/AcOEt 6:4), $[\alpha]_D$=−4.3 (c 1.27, $CHCl_3$). ^1H NMR (C_6D_6) for **6** δ: 2.73 (m, 2 H, H-3′); 3.17 (m, 1 H, H-2′); from 3.22 to 3.95 (m, 8 H, allylic OCH_2, H-6, H-6′, H-5, H-4, H-2 and H-3); from 4.27 to 4.99 (m, 7 H, 3 benzylic CH_2 and H-1), from 7.12 to 7.39 (m, 15 H, aromatic). Furthermore the ^1H NMR analysis allowed to attribute the signal at δ 2.55 (dd, 1 H, $J_{gem.}$=4.90 Hz, J_{trans}=2.65 Hz, H-3′) at the minor epoxide **7**. ^{13}C NMR (C_6D_6) for **6**, δ: 44.29 (C-3′); 50.38 (C-2′); 68.60 and 68.94 (C-6 and C-1′); 74.45 and 74.47 (C-2 and C-5); 73.22, 74.75 and 75.87 (3 benzylic CH_2); 77.17 (C-4); 84.36 (C-3); 103.05 (C-1); 127.43–128.17 (15 aromatic CH); 137.86, 137.86 and 138.48 (3 aromatic >C<). The following signals were attibuted to **7** δ: 50.57 (C-2′); 70.14 (C-6 or C-1′); 74.28 (C-2 or C-5), 102.61 (C-1). Anal. Calcd for $C_{30}H_{34}O_7$: %C=71.13, %H=6.76. Found: %C=70.96, %H=6.67.

(2′R)- and (2′S)-2′,3′-Epoxypropyl 2-O-acetyl-3,4,6-tri-O-benzyl-β-D-glucopyranoside 8 and 9

The 90:10 mixture of epoxides **6** and **7** (1.6 g) was acetylated by the standard procedure. The crude product was purified by column chromatography over silica gel (8:2 hexane/AcOEt, containing 0.1% Et_3N) to give 1.2 g of **8** and **9**, in a 90:10 diastereoisomeric mixture determined by ^1H NMR analysis on the basis signals related to the oxirane H-3′ protons at δ 2.43 and 2.04, respectively. $[\alpha]_D$=−0.8 (c 1.65, $CHCl_3$). ^1H NMR (C_6D_6) δ: 1.76 (s, 3 H, CH_3CO of **9**); 1.78 (s, 3 H, CH_3CO of **8**); 2.04 (dd, 1 H, $J_{gem.}$=5.03 Hz, J_{trans}=2.58 Hz, H-3′ trans of **9**); 2.23 (dd, 1 H, J_{cis}=4.38 Hz, H-3′ cis of **9**); 2.28 (dd, 1 H, $J_{gem.}$=5.44 Hz, J_{cis}=4.16 Hz, H-3′ cis of **8**); 2.43 (dd, 1 H, J_{trans}=2.53 Hz, H-3′ trans of **8**); 2.77 (m, 1 H, H-2′ of **8**); 2.89 (m, 1 H, H-2′ of **9**); from 3.21 to 3.92 (m, 7 H, allylic OCH2, H-6, H-6′, H-5, H-4 and H-3 of **8** and **9**); from 4.26 to 4.87 (m, 7 H, 3 benzylic CH_2 and H-1 of **8** and **9**), 5.41 (m, 1 H, H-2 of **8** and **9**); from 7.03 to 7.31 (m, 15 aromatic H of **8** and **9**). ^{13}C NMR (C_6D_6) δ: 20.80 (CH_3CO of **8** and **9**); 43.80 (C-3′ of **8** and **9**); 50.30 (C-2′ of **8**); 50.98 (C-2′ of **9**); 68.47 and 69.27 (C-6 and C-1′ of **8** and **9**); 73.63 (C-2 of **8** and **9**); 73.62, 74.99 and 75.74 (3 benzylic CH_2 of **8** and **9**); 75.74 (C-5 of **8** and **9**); 78.40 (C-4 of **84** and **9**); 83.39 (C-3 of **8** and **9**); 101.35 (C-1 of **9**); 101.78 (C-1 of **8**); 127.65–130.06 (15 aromatic CH of **8** and **9**); 138.94–139.10 (3 aromatic >C< of **8** and **9**): 169.19 (C=O of **8** and **9**). Anal. Calcd for $C_{32}H_{36}O_8$: %C=70.06, %H=6.61. Found: %C=70.32, %H=6.51.

Oxirane ring opening of compounds 8+9

All reactions were carried out on the 90:10 mixture of epoxides **8** and **9**.

With $FeCl_3$ in EtOH

Anhydrous $FeCl_3$ (40 mg, 0.25 mmol) was added to an ethanolic solution (5 ml) of **8+9** (120 mg, 0.2 mmol) and the solution was stirred at room temperature for 24h. The reaction was monitored by TLC and after 24 h the mixture was diluted with CH_2Cl_2, washed with an aqueous solution of NaCl, and dried ($MgSO_4$). Evaporation *in vacuo* of the solvent followed by column chromatogaphy on a silica gel column (65:35, hexane/AcOEt) gave the chlorohydrin **12** (Nu=Cl), 40 mg, (32% yield and the pure 3-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)1-*O*-ethyl-*sn*-glycerol (**12**, Nu=OEt), 76 mg, 60% yield. **12** (Nu=Cl): Rf=0.34 (6:4, hexane/AcOEt). ^1H NMR ($CDCl_3$) δ: 1.97 (s, 3 H, CH_3CO); from 3.42 to 4.01 (m, 11 H, CH_2Cl, H-6, H-6′, H-5, H-4, H-3, 3 glycerolic H); 4.39 (d, 1 H, $J_{1,2}$=7.93 Hz, H-1); from 4.49 to 4.95 (m, 6 H, 3 benzylic CH_2); 5.00 (m, 1 H, H-2); from 7.14 to 7.33 (m, 15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 21.54 (MeCO); 46.47 (CH_2Cl); 69.15 (C-6); 70.74 (CHCl); 72.65 (OCH_2); 73.62 (C-2); 74.16, 75.58 (C-3); 75.73 and 75.73 (3 benzylic CH_2); 78.49 (C-4); 102.18 (C-1); 128.46–129.09 (15 aromatic CH); 138.28, 138.28 and 138.65 (3 aromatic >C<); 170.34 (C=O). **12** (Nu=OEt): Rf=0.17 (6:4, hexane/AcOEt), m.p.=77–79°C (from hexane), $[\alpha]_D$=+4.6 (c 1.64, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.18 (t, 3 H, ethyl CH_3); 1.96 (s, 3 H, CH_3CO); 3.48 (q, 2 H, ethyl CH_2); from 3.61 to 3.96 (m, 10 H, H-6, H-6′, H-5, H-4, H-3, 5 glycerolic H); 4.40 (d, 1 H, $J_{1,2}$=7.98 Hz, H-1); 4.52–4.60 (AB system, 2 H, $J_{A,B}$=12.19 Hz, benzylic CH_2); 4.53–4.78 (AB system, 2 H, $J_{A,B}$=10.68

Hz, benzylic CH_2); 4.66–4.79 (AB system, 2 H, $J_{A,B}$=11.46 Hz, benzylic CH_2); 5.00 (m, 1 H, H-2); from 7.13 to 7.35 (m, 17 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 15.73 (CH_3); 21.52 (MeCO); 66.74 (ethyl OCH_2); 69.19 (C-6); 70.19 (C-2′); 71.90 (C-1′); 73.46 (C-3′); 73.74 (C-2); 74.03, 75.67 and 75.67 (3 benzylic CH_2); 75.56 (C-5); 78.49 (C-4); 83.45 (C-3); 102.35 (C-1); 128.32–129.05 (15 aromatic CH); 138.36, 138.50 and 138.74 (3 aromatic >C<); 170.18 (C=O). Anal. Calcd for $C_{34}H_{42}O_9$: %C=68.67, %H=7.12. Found: %C=69.12, %H=7.82.

With 1-hexadecanol and $FeCl_3$ in Et_2O

Anhydrous $FeCl_3$ (50 mg, 0.30 mmol) and 1-hexadecanol (120 mg, 0.48 mmol) were added to an ethyl ether solution (30 ml) of **8+9** (200 mg, 0.36 mmol) and the solution was stirred at room temperature. The reaction was monitored by TLC, and after 2 h the mixture was diluted with CH_2Cl_2, washed with an aqueous solution of NaCl, and dried ($MgSO_4$). Evaporation *in vacuo* of the solvent followed by colunm chromatogaphy on a silica gel column (7:3, hexane/AcOEt) gave pure 3-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-1-*O*-ethyl-*sn*-glycerol, 60 mg, 30% yield and the pure 3-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-1-*O*-hexadecyl-*sn*-glycerol, **10**, 60 mg, 21% yield. Rf=0.27 (7:3 hexane/AcOEt), m.p.=48–49°C (from EtOH/H_2O); $[\alpha]_D$=+3.4 (c 1.07, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.80 (m, 3 H, CH_3); from 1.17 to 1.45 (m, 28 H, 14 hexadecylic CH_2); 1.87 (s, 3 H, CH_3CO); 3.04 (br, 1 H, OH); from 3.31 to 3.85 (m, 12 H, H-6, H-6′, H-5, H-4, H-3, 5 glycerolic H and hexadecylic CH_2O); 4.32 (d, 1 H, $J_{1,2}$=8.00 Hz, H-1); from 4.41 to 4.74 (m, 6 H, 3 benzylic CH_2); 4.93 (m, 1 H, H-2); from 7.06 to 7.24 (m, 15 aromatic H); ^{13}C NMR ($CDCl_3$) δ: 14.75 (CH_3); 21.50 (MeCO); 23.30, 26.70, 29.96, 30.10, 30.29 and 32.53 (14 hexadecylic CH_2); 69.14 (C-6); 70.16 (C-2′); 72.10 and 72.29 (C-1′ and C-3′); 73.51, 75.65 and 75.65 (3 benzylic CH_2); 73.70 (C-2); 74.10 (hexadecylic -OCH_2); 75.57 (C-5); 78.47 (C-4); 83.43 (C-3); 102.36 (C-1); 128.43–129.02 (15 aromatic CH); 138.34, 138.46 and 138.71 (3 aromatic >C>); 170.11 (C=O). Anal Calcd for $C_{48}H_{70}O_9$: %C=72.88, %H=8.92. Found: %C=73.02, %H=8.82.

With 1-hexadecanol and $FeCl_3$ in THF

Anhydrous $FeCl_3$ (40 mg, 0.25 mmol) and 1-hexadecanol (60 mg, 0.25 mmol) were added to a THF solution (5 ml) of **8+9** (130 mg, 0.25 mmol) and the solution was stirred at room temperature. The reaction was monitored by TLC, and after 2 h the mixture was diluted with CH_2Cl_2, washed with aqueous NaCl, and dried ($MgSO_4$). Evaporation *in vacuo* of the solvent followed by column chromatogaphy on a silica gel column (8:2, hexane/AcOEt) gave 96 mg of the product **12** (Nu=$O(C_4H_8O)_n(H_{20})_{15}CH_3$). ^1H NMR ($CDCl_3$) δ: 0.85 (m, 3 H, CH_3); 1.25 (m, 26 H, 13 hexadecylic CH_2); 1.62 (m, 66 H, 1 hexadecylic CH_2 and 32 CH_2); 1.96 (s, 3 H, CH_3CO); from 3.41 to 3.89 (m, 12 H, H-6, H-6′, H-5, H-4, H-3, 5 glycerolic H, hexadecylic CH_2-O and 32 OCH_2); 4.39 (d, 1 H, $J_{1,2}$=8.02 Hz, H-1); from 4.49 to 4.82 (m, 6 H, 3 benzylic CH_2); 4.97 (m, 1 H, H-2); from 7.16 to 7.32 (m, 15 aromatic H); ^{13}C NMR ($CDCl_3$) δ: 14.64 (CH_3); 21.38 (MeCO); 23.17, 26.70, 29.84, 30.16, 32.40 (14 hexadecylic CH_2); 26.99 (32 CH_2); 69.03 (C-6): 71.05 (32 OCH_2); 70.00 (C-2′); 71.40 and 71.77 (C-1′ and C-3′); 73.32 (-OCH_2); 73.59 (C-2); 73.97, 75.50 and 75.50 (3 benzylic CH_2); 75.50 (C-5); 78.35 (C-4); 83.32 (C-3); 102.21 (C-1), 128.30–128.89 (15 aromatic CH); 138.24, 138.34 and 138.59 (3 aromatic >C<); 170.00 (C=O).

With 1-hexadecanol and TsOH

Anhydrous TsOH (35 mg) and 1-hexadecanol (260 mg, 1.05 mmol) were added to a dichloromethane solution (20 ml) of **8+9** (290 mg, 0.5 mmol) and the solution was stirred at room temperature. The reaction was monitored by TLC, and after 2 h the mixture was diluted with CH_2Cl_2, washed with an aqueous solution of $NaHCO_3$, and dried ($MgSO_4$). Evaporation *in vacuo* of the solvent followed by column chromatogaphy on a silica gel column (7:3, hexane/AcOEt) gave pure **10** (23%) and pure 3-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-1-*O*-tosyl-*sn*-glycerol (**12**, Nu=OTs), (44%): Rf=0.10 (7:3 hexane/AcOEt), $[\alpha]_D$=+7.0 (c 1.03, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.94 (s, 3 H, CH_3CO); 2.41 (s, 3 H, CH_3Ph); from 3.27 to 4.38 (m, 11 H, H-6, H-6′, H-5, H-4, H-3, 5 glycerolic H, OH); 4.36

(d, 1 H, $J_{1,2}$=7.94 Hz, H-1); from 4.46 to 4.81 (m, 6 H, 3 benzylic CH_2); 4.93 (m, 1 H, H-2); from 7.12 to 7.31 (m, 17 aromatic H); 7.77 (d, 2 H, J=8.2 Hz, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 21.46 (MeCO); 22.22 (MePh); 68.74 (C-2′); 69.04 (C-6); 71.05 and 72.13 (C-1′ and C-2′): 73.55 (C-2); 74.09, 75.64 and 75.64 (3 benzylic CH_2); 75.45 (C-5); 78.36 (C-4); 102.10 (C-1); 128.40–130.52 (19 aromatic CH); from 133.17 to 145.58 (5 aromatic >C<); 170.29 (C=O). Anal. Calcd for $C_{39}H_{44}O_{11}S$: %C=64.98, %H=6.15, %S=4.45. Found: %C=64.61, %H=6.10, %S=4.27.

With 1-hexadecanol and Sc(OTf)$_3$

$Sc(OTf)_3$ (80 mg. 0.16 mmol) and 1-hexadecanol (320 mg, 1.30 mmol) were added to a toluene solution (20 ml) of the 90:10 mixture of epoxides **8** and **9** (580 mg, 1.01 mmol) and the solution was stirred at room temperature. The reaction was monitored by TLC. After 24 h, 50 ml of an aqueous solution of NH_4Cl were added, the mixture was stirred for 30 min, then extracted with CH_2Cl_2 and the organic layer was dried over $MgSO_4$. Evaporation *in vacuo* of the solvent followed by column chromatogaphy on a silica gel column (7:3, hexane/AcOEt containing 0.1% Et_3N) gave pure **10**, (67%) and a mixture of **10** (5%) and **11** (8%). **11** showed ^1H and ^{13}C NMR spectra highly coincident with those of **10** with the exception of three CH_2 signals at δ 27.02 (hexadecylic CH_2), 71.15 and 71.64 (C-1′ and C-3′).

*3-O-(2-O-Acetyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-1,2-di-O-hexadecyl-*sn*-glycerol* ***13***

To a solution of **10** (281 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (6 ml) 1-hexadecyl triflate[17] (380 mg, 1 mmol) dissolved in the same solvent (3 ml), and 151 mg (0.7 mmol) of Proton Sponge were added. The mixture was heated under stirring at reflux for 6 days. When no further reaction progress was detected by TLC (7:3, hexane/AcOEt), the reaction mixture was diluted with CH_2Cl_2 (40 ml), washed with a 1 M HCl aqueous solution (2 × 20 ml), dried ($MgSO_4$), and evaporated *in vacuo*. The crude product (830 mg) was purified by flash chromatography (9:1, hexane:AcOEt) to give unreacted **10** and **13** in 26 and 65% yields, respectively.

13: Rf=0.15 (9:1, hexane/AcOEt), m.p.=42–44°C (from MeOH/H_2O); $[\alpha]_D$=+4.3 (c 1.18, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.88 (m, 6 H, 2 CH_3); from 1.26 to 1.53 (m, 56 H, 28 hexadecylic CH_2); 1.95 (s, 3 H, CH_3CO); from 3.41 to 3.90 (m, 14 H, H-6, H-6′, H-5, H-4, H-3, 5 glycerolic H and 2 hexadecylic CH_2-O); 4.40 (d, 1 H, $J_{1,2}$=7.76 Hz, H-1); from 4.51 to 4.81 (m, 6 H, 3 benzylic CH_2); 4.97 (m, 1 H, H-2); from 7.15 to 7.31 (m, 15 aromatic H); ^{13}C NMR ($CDCl_3$) δ: 14.73 (2 CH_3); 21.48 (CH_3CO); 23.29, 26.71, 29.97, 30.13, 30.31, 30.69 and 32.53 (28 hexadecylic CH_2); 69.20 (C-6); 71.05 and 71.25 (C-1′ and C-3′); 73.80 (C-2); 74.09 (2 -OCH_2); 75.60 (3 benzylic CH_2); 75.76 (C-5); 78.15 (C-2); 78.55 (C-4); 83.55 (C-3); 101.92 (C-1); 128.19–128.98 (15 aromatic CH); 138.51, 138.69 and 138.80 (3 aromatic >C<); 169.94 (C=O). Anal. Calcd. for $C_{64}H_{102}O_9$: %C=75.70, %H=10.12. Found: %C=76.2, %H=10.56.

*3-O-(2-O-Acetyl-β-D-glucopyranosyl)-1,2-di-O-hexadecyl-*sn*-glycerol* ***14***

To a solution of **13** (180 mg, 0.18 mmol) in AcOEt (25 ml), 50 mg of Pd/C (10%) were added and the mixture was stirred at room temperature under hydrogen. After 3 h, the suspension was filtered on Celite, washed with AcOEt and methanol and evaporated *in vacuo* to give **14** (130.4 mg, 97% yield), pure by NMR analysis. Rf=0.45 (1:9, hexane/AcOEt), m.p.=85–87°C; $[\alpha]_D$=−10.2 (c 1.28, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.82 (m, 6 H, 2 CH_3); from 1.19 to 1.46 (m, 56 H, 28 CH_2); 2.04 (s, 3 H, CH_3CO); from 3.31 to 3.76 (m, 15 H, H-6, H-6′, H-5, H-4, H-3, 5 glycerolic H, 2 hexadecylic CH_2-O and OH); 4.40 (br, 2 H, 2 OH); 5.22 (m, 1 H, H-2). ^{13}C NMR ($CDCl_3$) δ: 14.75 (2 CH_3) 21.70 (MeCO); 23.35, 26.81, 30.04, 30.40, 30.77, and 32.60 (28 hexadecylic CH_2); 61.90 (C-6); 69.77 (C-4); 70.60 and 71.20 (C-1′ and C-2′);72.47 and 72.47 (hexadecylic 2 -OCH_2); 74.70 (C-3); 75.40 (C-2); 76.45 (C-5); 101.88 (C-1); 171.90 (C=O). Anal. Calcd. for $C_{43}H_{84}O_9$: %C=69.31, %H=11.36. Found: %C=69.53, %H=11.13.

3-O-(2-3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-1,2-di-O-hexadecyl-sn-glycerol ***15***

70 mg (0.094 mmol) of **14** were acetylated by the standard procedure. The crude product (90 mg) was purified by flash-chromatography over silica gel (7:3, hexane/AcOEt) to give 77.5 mg (95%, yield) of pure **15**. Rf=0.38 (7:3, hexane/AcOEt), m.p=60–61°C (MeOH). $[\alpha]_D$=−9.3 (c 1.3, $CHCl_3$). Lit.[14] m.p.=62.5–63.5°C (MeOH), $[\alpha]_D$=−9.9° (c 5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.88 (m, 6 H, 2 CH_3); 1.26 (m, 52 H, 26 hexadecylic CH_2); 1.54 (m, 4 H, 2 CH_2-CH_2-O); 2.01, 2.03, 2.04 and 2.09 (4s, 12 H, 4 CH_3CO); from 3.38 to 3.55 (m, 6 H, 2 hexadecylic O-CH_2 and 2 glycerolic H-1); 3.54 (dd, 1 H, $J_{1,2}$=4.25 Hz, glycerolic H-2); 3.62 (m, 1 H, $J_{3',2}$=5.13 Hz, glycerolic H-3); 3.88 (m, 1 H, $J_{1,3'}$=10.05 Hz, glycerolic H-3); 3.67 (ddd, 1 H, $J_{5,6}$=4.74 Hz, $J_{5,6'}$=2.43 Hz, H-5); 4.13 (dd, 1 H, $J_{6,6'}$=12.32 Hz, H-6′); 4.28 (dd, 1 H, H-6); 4.56 (d, 1 H, $J_{1,2}$=7.80 Hz, H-1); 4.99 (dd, 1 H, $J_{2,3}$=9.28 Hz, H-2); 5.08 (dd, 1 H, $J_{4,5}$=10.45 Hz, H-4); 5.21 (dd, 1 H, $J_{3,4}$=9.49 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ: 14.76 (2 CH_3); 21.25 (CH_3CO); 23.32 (2 hexadecylic CH_2-CH_3); 26.74, 30.00, 30.16, 30.33 and 30.71 (24 hexadecylic CH_2); 32.56 (2 hexadecylic CH_2-CH_2-CH_3); 70.76, 72.40 (2 hexadecylic O-CH_2); 169.86, 170.04, 170.90 and 171.29 (4 C=O). Anal. Calcd. for $C_{49}H_{90}O_{12}$: %C=67.55, %H=10.41. Found: %C=67.30, %H=10.59.

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