Pergamon

Tetrahedron, Vol. 53, No. 17, pp. 6163-6170, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00273-1

Synthesis of Stable Analogues of Glyceroglycolipids

Laura Cipolla, Francesco Nicotra*

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via Venezian 21, 20133 Milano

Elena Vismara

Dipartimento di Chimica, Politecnico di Milano, Via Mancinelli 7, 20131 Milano Italy

Marco Guerrini

Istituto di Chimica e Biochimica "Giuliana Ronzoni", V. G. Colombo 81, 20133 Milano, Italy

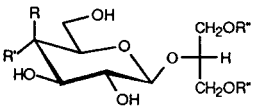
Abstract: Stable C-glycosidic analogues of 2-*O*-(β-D-glucopyranosyl)-*sn*-glycerol (**1a**), 2-*O*-(β-D-galactopyranosyl)-*sn*-glycerol (**1b**), 1-*O*-(β-D-glucopyranosyl)-*sn*-glycerol (**7**) and their dipalmitoyl ester have been synthesised starting from the corresponding 2,3,4,6-tetra-*O*-benzyl-glyconolactones **9**. The 2-*O*-derivatives **1** were obtained by methylenation of the lactone **9**, reaction of the obtained glycoexoenitol **10** with a malonyl radical, reduction of the malonyl derivative **11** and deprotection. The 1-*O*-derivative **7** was obtained by reaction of the lactone **9** with butenylmagnesium bromide, reduction of the obtained lactol **14**, osmylation and deprotection. © 1997 Elsevier Science Ltd.

Glycosyl glycerols (**1** and **3** in Figure 1) and glyceroglycolipids (**2** and **4** in Figure 1) of natural origin have recently shown interesting anti-tumor-promoting activities.[1] The glycidic part of these molecules consists of glucopyranosidic or galactopyranosidic units, linked at C-2 (**1** and **2**) or at C-1 (**3** and **4**) of glycerol with an α- or, more frequently, a β-glycosidic linkage. In glyceroglycolipids the glycerol is esterified with different fatty acids.

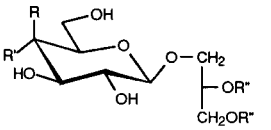
Like almost all O-glycosides, glycosylglycerols and glyceroglycolipids are easily hydrolyzed by glycosidases, this partially limiting their therapeutic utility. To enhance the metabolic stability of these compounds, looking for better therapeutic agents, one can substitute the glycosidic oxygen linking glycerol to the sugar, with a carbon atom. In this manner, the labile acetalic function is converted into an ether, and the sugar is converted into the corresponding stable C-glycoside (**5-8** in Figure 1).[2]

In this paper we describe the synthesis of **5a** and **6a**, the stable C-glycosidic analogues of 2-*O*-(β-D-glucopyranosyl)-*sn*-glycerol and its dipalmitoyl ester; **5b** and **6b**, the stable analogues of 2-*O*-(β-D-galactopyranosyl)-*sn*-glycerol and its dipalmitoyl ester, **7** and **8**, the stable analogues of 1-*O*-(β-D-glucopyranosyl)-*sn*-glycerol and its dipalmitoyl ester.

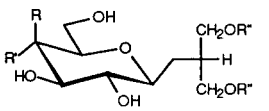
Figure 1



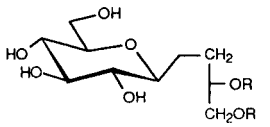
1a R=R"=H, R'=OH
1b R'=R"=H, R=OH
2a R=H, R'=OH, R"=CO(CH$_2$)$_n$CH$_3$
2b R'=H, R=OH, R"=CO(CH$_2$)$_n$CH$_3$



3a R=R"=H, R'=OH
3b R'=R"=H, R=OH
4a R=H, R'=OH, R"=CO(CH$_2$)$_n$CH$_3$
4b R'=H, R=OH, R"=CO(CH$_2$)$_n$CH$_3$



5a R=R"=H, R'=OH
5b R'=R"=H, R=OH
6a R=H, R'=OH, R"=CO(CH$_2$)$_{14}$CH$_3$
6b R'=H, R=OH, R"=CO(CH$_2$)$_{14}$CH$_3$

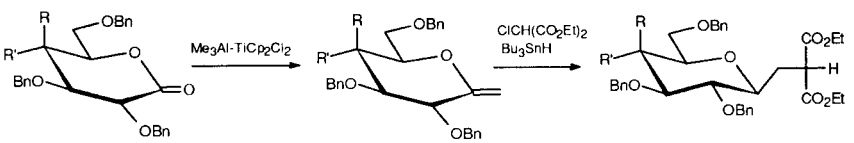


7 R=OH
8 R=CO(CH$_2$)$_{14}$CH$_3$

We envisaged that the synthesis of the analogues **5** can be easily effected by reduction of the corresponding malonate; so that our recently reported C-glycosidation procedure,[3] allowing the direct and stereoselective introduction of a β-oriented methylenemalonate group, can be used.

The synthesis exploits the reaction of a glycoexoenitol **10**, obtained by reaction of the corresponding lactone **9** with Tebbe's reagent,[4] with a malonyl radical (Scheme 1).

Scheme 1



9a R=H, R'=OBn
9b R=OBn, R'=H

10a R=H, R'=OBn
10b R=OBn, R'=H

11a R=H, R'=OBn
11b R=OBn, R'=H

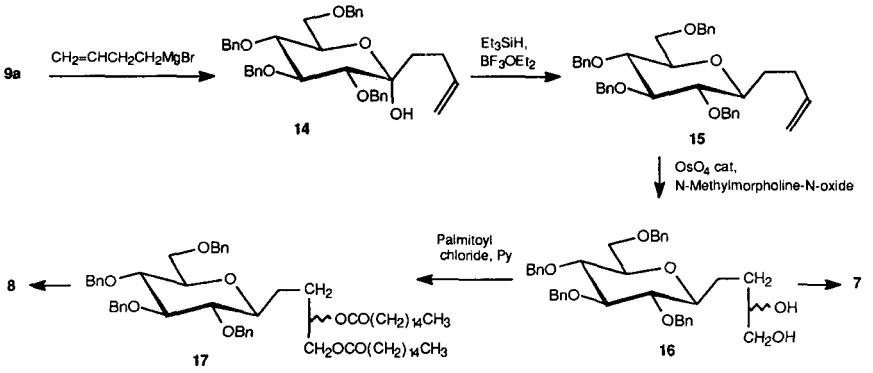
12a R=R"=H, R'=OBn
12b R=OBn, R'=R"=H

13a R=H, R'=OBn, R"=CO(CH$_2$)$_{14}$CH$_3$
13b R=OBn, R'=H, R"=CO(CH$_2$)$_{14}$CH$_3$

5a R=R"=H, R'=OBn
5b R=OBn, R'=R"=H
6a R=H, R'=OBn, R"=CO(CH$_2$)$_{14}$CH$_3$
6b R=OBn, R'=H, R"=CO(CH$_2$)$_{14}$CH$_3$

The stable C-glycosidic analogues of 1-*O*-(β-D-glucopyranosyl)-*sn*-glycerol and of its dipalmitoyl ester (**7** and **8**) have been synthesised according to Scheme 2.

Scheme 2



Reaction of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone **9a** with but-3-enylmagnesium bromide, at -78 °C in Et_2O, afforded the lactol **14**, the reduction of which, with triethylsilane and BF_3OEt_2 in MeCN at -20 °C, stereoselectively gave 1-(2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl)-3-butene[5] (**15**). The entiere C-glycosylation process occurs in 50 % overall yield, affording only the β-anomer in agreement with previous observations on the reduction of pyranosidic lactols.[6] The osmylation of the double bond of **15** afforded **16**, from which **7**, the analogue of 1-*O*-(β-glucopyranosyl)glycerol, was obtained by catalytic hydrogenation. Furthermore, esterification of **16** with palmitoyl chloride in Py afforded **17**, from which the glyceroglucolipid analogue **8** was obtained by catalytic hydrogenation.

The following in vitro tests have been effected to evaluate the antitumor activity of the obtained analogues of glycosylglycerols and glyceroglycolipids: 1) the % of survival vs control of HT29 human colon carcinoma cells has been tested at at 10 μM concentration; 2) the % adherent of bovine aortic endothelial adherent cells was tested at 20 μM concentration; 3) the antiproliferative activity was tested at 50 μM concentration on A 431 human epidermoid carcinoma; and 4) the inhibition of cellular tyrosine phosphorylation was tested at 100 μM concentration. No significant activity was detected in tests 1, 2 and 3; in the case of test 4, compound **5a** showed a 56.9 % inhibition (IC_{50} = 12.9 μM), and compounds **6a** and **6b** showed respectively an inhibition of 26.3 and 37.3 % (IC_{50} > 50 μM).

EXPERIMENTAL

General: ^1H NMR and ^{13}C NMR were recorded with TMS as internal reference. The signals of aromatic carbons are omitted in the ^{13}C NMR. $[\alpha]_D$ Values were measured at 20 °C and are given in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed with the flash procedure using silica gel 60 (230-400 mesh). TLC was performed on silica gel 60 F_{254} plates and visualised by spraying with a solution containing H_2SO_4 (31 mL), ammonium molybdate (21 g), and $Ce(SO_4)_2$ (1 g) in water (500 mL) and then heating at 110 °C for 5

min. Usual work-up refers to dilution with an organic solvent, washing with water to neutrality drying and evaporation under reduced pressure.

Diethyl [(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)methyl]malonate (11a). In a dry quarz tube containing **10a** (1.0 g), diethyl chloromalonate (300 μL) was added. The tube was purged with argon for 10 min and then dry THF (4 mL) was added to dissolve the substrate. The mixture was irradiated, under argon atmosphere, with an Hg-lamp and meanewhile a solution of Bu_3SnH (1 mL) in dry THF (3 mL) was slowly added (3 hr). After 15 min. of further irradiation, the solvent was evaporated, the residue was dissolved in MeCN and the solution was twice extracted with pentane to extract Sn salts. The MeCN solution was evaporated, the residue was dissolved in ethyl acetate, dryed with Na_2SO_4 and evaporated. Purification by flash-chromatography (hexane-ethyl acetate, 8:2) afforded unreacted **10a** (491 mg) and **11a** (648 mg, 50% yield). Mp. 95°C. $[\alpha]_D$ + 4.6 (c 0.5 in $CHCl_3$). MS, FAB: m/z 698 (M+1). ^{1}H NMR (500 MHz, C_6D_6): δ 0.90 (2t, 6 H, 2 OCH_2CH_3), 2.24 (ddd, 1 H, *J* = 5.6, 9.0 and 7.9 Hz, H-3), 2.87 (ddd, 1 H, *J* = 9.0, 2.8 and 1.6 Hz, H-3'), 3.23 (t, 1 H, *J* = 9.0 Hz, H-5), 3.30 (ddd, 1 H, *J* =10.0, 2.0 and 4.0 Hz, H-8), 3.47 (ddd, 1 H, *J* = 9.0, 7.9 and 1.6 Hz, H-4), 3.63 (dd, 1 H, *J* = 10.8 and 2.0 Hz, H-9), 3.64 (t, 1 H, *J* = 9.0 Hz, H-6), 3.67 (dd, 1 H, *J* = 10.8 and 4.0 Hz, H-9'), 3.77 (t, 1 H, *J* = 7.9 Hz, H-7), 3.95 (dd, 1 H, *J* = 5.6 and 2.8 Hz, H-2), 3.90-4.05 (4 H, 2 OCH_2CH_3), 4.35-4.90 (8 H, 4 OCH_2Ph), 7.00-7.40 (20 H, Ph-H). ^{13}C NMR (125.712 MHz, $CDCl_3$) δ 14.0 (q), 31.1 (t), 48.8 (d), 61.3 (t), 68.9 (t), 73.5 (t), 74.9 (t), 75.1 (t), 75.5 (t), 76.9 (d), 78.4 (d), 79.0 (d), 82.2 (d), 87.1 (d), 169.0 (s), 169.5 (s). Anal. Calcd for $C_{42}H_{48}O_9$: C, 72.39 %; H, 6.94 %. Found: C, 72.41 %; H, 6.89 %.

Diethyl [(2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl)methyl]malonate (11b). Following the same procedure described for the synthesis of **11a**, **10b** (800 mg) was converted into **11b** (362 mg, 35 % yield) (480 mg of unreacted starting material were recovered). Oil, $[\alpha]_D$- 5.0 (c 0.7 in $CHCl_3$). MS, FAB: m/z 698 (M+1). ^{1}H NMR (500 MHz, (C_6D_6) δ 1.15 (2t, 6 H, 2 OCH_2CH_3), 2.59 (ddd, 1 H, *J* 4.9, 14.5 and 9.7 Hz, H-3), 3.16 (ddd, 1 H, *J* = 14.5, 9.8and 2.5 Hz, H-3'), 3.65 (dd, 1 H, *J* = 9.4, 2.8 Hz, H-6), 3.72 (dd, 1 H, *J* = 8.4 and 5,5 Hz, H-8), 3.78 (dt, 1 H, *J* = 9.5, 2.5 Hz, H-4), 3.85 (dd, 1 H, *J* = 8.8 and 5.5 Hz, H-9), 3.99 (dd, 1 H, *J* = 8.8, 8.4 Hz, H-9'), 4.08 (t, 1 H, *J* = 9.5, H-5), 4.15-4.25 (4 H, 2 OCH_2CH_3), 4.21 (d, 1 H, *J* = 2.8 Hz, H-7), 4.27 (dd, 1 H, *J* = 9.8 and 4.9 Hz, H-2), 4.47-5.30 (8 H, 4 OCH_2Ph), 7.30-7.65 (20 H, Ph-H). ^{13}C NMR (125.712. MHz, $CDCl_3$) δ 12.0 (q), 30.0 (t), 47.0 (d), 59.0 (t), 67.0 (t), 67.0 (d), 70.0 (t), 71.0 (t), 73.0 (t), 72.5 (d), 75.0 (d), 75.5 (d), 83.0 (d), 170.0 (s). Anal. Calcd for $C_{42}H_{48}O_9$: C, 72.39 %; H, 6.94 %. Found: C, 72.11 %; H, 7.02 %.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-glucopyranosyl)-2-hydroxymethyl-3-propanol (12a). To a solution of **11a** (120 mg) in dry THF (2 mL), under N_2, a 1M solution of $LiAlH_4$ in THF (345 μL) was added. After the reaction was complete (TLC hexane-ethyl acetate 6:4 in order to check the consumption of the starting material, and CH_2Cl_2:MeOH 95:5 in order to visualise the reduction product), the reaction mixture was carefully diluted with ethyl acetate, washed sequentially with a 5% HCl solution and water to neutrality; the organic phase was then dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2:MeOH 20:0.5) and the diol **12a** obtained in quantitative

yield as a white hygroscopic solid. $[\alpha]_D$ + 6.8 (c 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.57-1.43 (m, 1 H, H-2), 1.84-2.02 (m, 2 H, H-1), 2.61 (bs, 2 H, OH), 3.28 (t, 1 H, *J* = 8.9 Hz, H-2'), 3.39 (t, 1 H, *J* = 8.9 Hz, H-3'), 3.44-3.48 (m, 1 H, H-5'), 3.58 (t, 1 H, *J* = 8.9 Hz, H-4'), 3.62-3.70 (m, 7 H, H-1', 2xH-6', 2xCH_2OH), 4,51-4.57 (m, 3 H, 3 OCHPh), 4.66 (d, 1 H, *J* = 11.0 Hz, OCHPh), 4.82 (d, 1 H, *J* = 11.0 Hz, OCHPh), 4.90 (bs, 2 H, OCH_2Ph), 4.90 (d, 1 H, *J* = 11.0 Hz, OCHPh), 7.48-7.22 (m, 20 H, Ph-H). ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 30.3 (t), 41.1 (d), 65.6 (2t), 69.8 (t), 74.1 (t), 75.6 (t), 76.0 (t), 76.2 (t), 78.7 (d), 79.1 (d), 82.8 (d), 87.8 (d). Anal. Calcd for $C_{38}H_{44}O_7$: C, 74.49%; H, 7.24%. Found: C, 74.43%; H, 7.35%.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-galactopyranosyl)-2-hydroxymethyl-3-propanol (12b). The same procedure described for the preparation of **12a** was followed for the reduction of **11b**. 350 mg of the methylenemalonate **11b** furnished, after purification (flash chromatography, eluent CH_2Cl_2:MeOH 20:0.5), 183 mg of **12b** (59%), as a white hygroscopic solid. $[\alpha]_D$ - 4.5 (c 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.62-1.51 (m, 1 H, H-2), 1.82-2.00 (m, 2 H, H-1), 2.74 (bs, 2 H, OH), 3.36 (t, 1 H, *J* = 9.5 Hz, H-2'), 3.44 (dd, 1 H, *J* = 9.5, 2.4 Hz, H-3'), 3.53-3.72 (m, 7 H), 3.93 (d, 1 H, *J* = 2.4 Hz, H-4'), 4.40 (d, 1 H, *J* = 11.8 Hz, OCHPh), 4.48 (d, 1 H, *J* = 11.8 Hz, OCHPh), 4.62-4.75 (m, 4H, 4 OCHPh), 4.95 (d, 1 H, *J* = 11.8 Hz, OCHPh), 4.97 (d, 1 H, *J* = 11.8 Hz, OCHPh), 7.52-7.25 (m, 20 H, Ph-H). ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 31.0 (t), 41.1 (d), 65.5 (t), 65.7 (t), 69.9 (t), 73.0 (t), 74.2 (t), 74.3 (d), 75.1 (t), 76.1 (t), 77.8 (d), 79.1 (d), 79.3 (d), 85.4 (d). Anal. Calcd for $C_{38}H_{44}O_7$: C, 74.49%; H, 7.24%. Found: C, 74.55%; H, 7.38%.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-glucopyranosyl)-2-hydroxymethyl-3-propanol dipalmitate (13a). 12a (150 mg) was dissolved in dry pyridine, and a catalytic amount of DMAP and palmitoyl chloride (268 μL) were added; the solution was warmed to reflux for 2 h. After completion (TLC CH_2Cl_2:MeOH 95:5 for the detection of the starting material and hexane-ethyl acetate, 75:25 for the detection of the acylation product), the reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed sequentially with a 5% HCl solution and water to neutrality. The organic phase was dried over Na_2SO_4, filtered and concentrated; the crude product was purified by flash chromatography (eluent hexane-ethyl acetate 9:1), furnishing 314 mg of the dipalmitoyl derivative **13a** (quantitative yield), as an amorphous solid. $[\alpha]_D$ + 0.2° (c 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 6 H, 2 CH_3), 1.02-1.60 (m, 54 H), 1.92 (m, 1 H, H-2), 2.20-2.35 (m, 4 H, 2 CH_2CO), 3.26 (t, 1 H, *J* = 7.5 Hz), 3.34 (t, 1 H, *J* = 7.5 Hz), 3.38 (m, 1 H), 3.62-3.78 (m, 4 H), 4.02-4.18 (m, 4 H), 4.52 (d, 1 H, *J* = 12.0 Hz, OCHPh), 4.57-4.69 (m, 3 H, 3 CHOPh), 4.82 (d, 1 H, *J* = 12.0 Hz, OCHPh), 4.85-5.00 (m, 3H, OCHPh), 7.15-7.40 (m, 20 H, Ph-H). ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 14.7 (q), 23.3-34.9 (triplets), 35.2 (d), 64.1 (t), 65.3 (t), 69.7 (t), 74.1 (t), 75.5 (t), 75.8 (t), 76.2 (t), 77.9 (d), 79.1 (d), 79.6 (d), 83.1 (d), 87.9 (d). Anal. Calcd for $C_{70}H_{104}O_9$: C, 77.16%; H, 9.62%. Found: C, 77.25%; H, 9.54%.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-galactopyranosyl)-2-hydroxymethyl-3-propanol dipalmitate (13b). The same procedure described for the preparation of **13a** was followed for the acylation of **12b**. The diol **12b** (40 mg) was treated under reflux with a catalytic amount of DMAP and 50 μL of palmitoyl chloride in dry

pyridine (2 mL). Purification of the crude product (flash chromatography, eluent hexane-ethyl acetate 9:1) afforded 67 mg of **13b** (94%), as a colourless oil. $[\alpha]_D$ - 2.3 (c 2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) d 0.89 (t, 6 H, *J* = 7.0 Hz, 2 CH_3), 1.20-1.65 (m, 54 H), 1.92 (m, 1 H, H-2), 2.23 (t, 2 H, *J* = 7.8 Hz, CH_2CO), 2.26 (t, 2 H, *J* = 7.9 Hz, CH_2CO), 3.29 (dt, 1 H, *J* = 8.4 and 1 Hz, H-5'), 3.50-3.60 (m, 4 H), 3.64 (t, 1 H, *J* = 9.1 Hz, H-2'), 3.97-4.14 (m, 5 H), 4.40 (d, 1 H, *J* = 11.8 Hz, OCHPh), 4.47 (d, 1 H, *J* = 11.8 Hz, OCHPh), 4.63 (d, 2 H, *J* = 11.4 Hz, OCHPh), 4.65 (d, 1 H, *J* = 11.6 Hz, OCHPh), 4.75 (d, 1H, *J* = 11.4 Hz, OCHPh), 4.93 (d, 1 H, *J* = 11.6 Hz, OCHPh), 4.95 (d, 1 H, *J* = 11.4 Hz, OCHPh), 7.20-7.45(m, 20 H, Ph-H). ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 14.5 (q), 23.2-34.8 (triplets), 35.3 (d), 64.2 (t), 65.4 (t), 69.8 (t), 73.0 (t), 74.2 (t), 74.9 (d), 75.2 (t), 75.9 (t), 77.8 (d), 78.3 (d), 79.9 (d), 85.7 (d), 174.1 (s). Anal. Calcd for $C_{70}H_{104}O_9$: C, 77.16%; H, 9.62%. Found: C, 77.22%; H, 9.64%.

1-(β-Glucopyranosyl)-2-hydroxymethyl-3-propanol (5a). **12a** (150 mg) dissolved in a mixture ethyl acetate-EtOH (1:1, 4 mL) was hydrogenated in the presence of $Pd(OH)_2$ as catalyst (15 mg). The suspension was stirred overnight under hydrogen atmosphere. After completion (TLC, CH_2Cl_2-MeOH 95:5 in order to visualise the starting material and ethyl acetate-PrOH-H_2O, 5:4:1 to observe the formation of the deprotected product) the suspension was filtered over a Celite pad, the solvent removed under reduce pressure; the residue was then dissolved in water, and lyophilised. **5a** was obtained as highly hygroscopic white solid, in quantitative yield. $[\alpha]_D$ + 12.1 (c 1, MeOH); ^1H NMR (300 MHz, D_2O) δ 1.78 (m, 1 H, H-2), 2.18 (ddd, 1 H, *J* ≈ 12, 8 and 1 Hz, H-1a), 2.30 (m, 1 H, H-1b), 3.50 (t, 1 H, *J* = 9 Hz, H-4'), 3.63-3.82 (m, 4 H), 3.90-4.05 (m, 5 H), 4.21 (broad d, 1 H, *J* = 12.0). ^{13}C NMR (75.43 MHz, D_2O) δ 30.2 (t), 39.4 (d), 61.5 (t), 62.0 (t), 63.2 (t), 70.5 (d), 74.3 (d), 77.8 (d), 77.8 (d), 79.9 (d). Anal. Calcd for $C_{10}H_{20}O_7$: C, 47.61%; H, 7.99%. Found: C, 47.73%; H, 7.78%.

1-(β-Galactopyranosyl)-2-hydroxymethyl-3-propanol (5b). Following the same procedure described for the deprotection of **5a**, 80 mg of **12b** were hydrogenated, affording 31 mg (quantitative yield) of **5b** as a white hygroscopic solid.. $[\alpha]_D$ + 1.8 (c 1.5, MeOH); ^1H NMR (300 MHz, D_2O) δ 1.59 (m, 1 H, H-2), 2.05 (m, 2 H, H-1a, H-1b), 3.48 (t, *J* = 9.2 Hz, H-2' or H-3'), 3.52 (t, *J* = 9.2 Hz, H-2' or H-3'), 3.70-3.90 (m, 8 H), 4.08 (d, 1 H, *J* = 3.3 Hz, H-4). ^{13}C NMR (75.43 MHz, D_2O) δ 30.8 (t), 40.0 (d), 62.3 (t), 62.5 (t), 63.7 (t), 70.1 (d), 72.2 (d), 74.9 (d), 78.8 (d), 79.4 (d). Anal. Calcd for $C_{10}H_{20}O_7$: C, 47.61%; H, 7.99%. Found: C, 47.54%; H, 7.91%.

1-(β-Glucopyranosyl)-2-hydroxymethyl-3-propanol dipalmitate (6a). **13a** (270 mg) dissolved in ethyl acetate (4 mL) was hydrogenated in the presence of $Pd(OH)_2$ as catalyst (27 mg); the reaction was monitored by TLC (eluent hexane-ethyl acetate to verify the disappearance of the starting material and CH_2Cl_2:MeOH 9:1 to check the formation of the reaction product). After 4 hours the reaction was recovered as already described for the previous hydrogenation, affording 179 mg of 6a as hygroscopic white solid, in quantitative yield. $[\alpha]_D$ - 4.1 (c 0.7, $CHCl_3$). ^1H NMR (300 MHz, DMSO) δ 0.88 (t, 6 H, *J* = 7.0 Hz, 2 CH_3), 1.27-1.62 (m, 54 H), 1.85 (m, 1 H, H-2), 2.28 (t, 4 H, *J* = 7.3 Hz, 2 CH_2CO), 3.40 (m, 1 H, H-6'a) , 3.68 (dd, 1 H, *J* = 11.5 and 5.5 Hz,

H-6'b), 3.95-4.15 (m, 5 H), 4.70 (m, 4 H, CH_2OCO). ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 14.0 (q), 22.6-34.3 (triplets), 34.7 (d), 62.2 (t), 63.8 (t), 64.5 (t), 70.5 (d), 74.1 (d), 77.6 (d), 78.6 (d), 79.4 (d). Anal. Calcd for $C_{42}H_{80}O_9$: C, 69.19%; H, 11.06%. Found: C, 69.33%; H, 11.15%.

1-(β-Galactopyranosyl)-2-hydroxymethyl-3-propanol dipalmitate (6b). **13b** (120 mg) was hydrogenated as previously described for **6a**; 79 mg of **6**b were recovered as a white hygroscopic solid, corresponding to a quantitative yield. $[\alpha]_D$ + 1.6 (c 1.2, $CHCl_3$); ^1H NMR (300 MHz, DMSO) δ 0.88 (t, 6H, *J* = 6.6 Hz, 2 CH_3); 1.34 (m, 52 H), 1.55 (t, 2 H, *J* = 6.8 Hz), 1.87 (m, 1 H, H-2), 2.28 (t, 4 H, *J* = 7.3 Hz, 2 CH_2CO), 3.48 (m, 2H), 3.72 (t, 1 H, *J* = 3.3 Hz, H-4'), 3.95-4.25 (m, 8 H). ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 14.0 (q), 22.6-34.3 (triplets), 34.8 (d), 63.3 (t), 63.9 (t), 64.6 (t), 70.6 (d), 71.8 (d), 75.4 (d), 77.8 (d), 78.0 (d). Anal. Calcd for $C_{42}H_{80}O_9$: C, 69.19%; H, 11.06%. Found: C, 69.24%; H, 10.98%.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-glucopyranosyl)-3-butene (15). To a solution of **9a** (2.0 g) in dry Et_2O (35 mL) but-3-enylmagnesium bromide (5.6 mL of a 1 M solution in Et_2O) was added at -78 °C under dry N_2 atmosphere. After 2 hs usual work-up and flash chromatography (hexane-ethyl acetate, 85:15) afforded pure **14** (1.94 g, 88% yield), which was dissolved in MeCN (30 mL), and treated at -18 °C, under N_2 atmosphere, with Et_3SiH (500 μL) and BF_3OEt_2 (400 μL) for 10 min. Usual work-up afforded pure **15** (1.82 g, 97 % yield) which crystallises from Et_2O. Mp 83-84 °C; $[\alpha]_D$ + 3 (c 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (m, 2 H, H-1a and H-1b), 2.23 (m, 2 H, H-2a and H-2b), 3.28 (m, 2 H, H-6'a and H-6'b), 3.39 (dt, 1 H, *J* = 9.2 and 3.3 Hz, H-1'), 3.68 (m, 4 H), 4.55 (d, 1 H, *J* = 11.5 Hz, OCHPh), 4.58 (d, 1 H, *J* = 10.7 Hz, OCHPh), 4.62 (s, 2 H, OCH_2Ph), 4.65 (d, 1 H, *J* = 10.7 Hz, OCHPh), 4.83 (d, 1 H, *J* = 11.5 Hz, OCHPh), 4.91 (s, 2 H, OCH_2Ph), 4.97 (broad d, 1 H, *J* = 10.3 Hz, H-4a), 5.08 (broad d, 1 H, *J* = 17.0, H-4b), 5.80 (ddt, 1 H, *J* = 17.0, 10.3 and 6.5 Hz, H-3), 7.15-7.40 (m, 20 H, Ph-H). ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 29.65 (t), 30.90 (t), 69.10 (t), 73.42 (t), 74.91 (t), 75.25 (t), 75.51 (t), 78.55 (d), 78.70 (d), 78.94 (d), 82.37 (d), 87.37 (d), 114.62 (t), 138.45 (d). Anal. Calcd for $C_{38}H_{42}O_5$: C, 78.86 %; H, 7.31 %. Found: C, 78.59 %; H, 7.30 %.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-glucopyranosyl)-2,3-butandiol (16). To a solution of **15** (1.75 g) in acetone-H_2O (8:1, 30 mL), *N*-methylmorpholine-*N*-oxide (819 mg) and OsO_4 (0.05 equivalents) were added. After 3 hs, ethyl acetate (30 mL) and $Na_2S_2O_3 \cdot 5\ H_2O$ were added and the mixture was stirred for 2 hs. The organic phase was then separated, washed with water, dryed and evaporated. Flash chromatography of the crude product (hexane-ethyl acetate, 4:6) afforded **16** (1.77 g, 95 % yield) as a white solid. **16** is a mixture of epimers at C-3. The ^{13}C NMR spectra showed 3:2 ratio; the predominant isomer showed the following signals: ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 28.2 (t), 29.5 (t), 66.8 (t), 69.3 (t), 72.1 (d), 73.5 (t), 75.0 (t), 75.4 (t), 75.6 (t), 78.7 (2d), 79.5 (d), 81.9 (d), 82.2 (d), 87.3 (d). Anal. Calcd for $C_{38}H_{44}O_7$: C, 74.48 %; H, 7.24 %. Found: C, 74.33 %; H, 7.31 %.

1-(β-D-Glucopyranosyl)-2,3-butandiol (7). **16** (140 mg) dissolved in ethyl acetate-EtOH (2:1, 5 mL) was hydrogenated overnight in the presence of $Pd(OH)_2/C$. Filtration of the reaction mixture quantitatively afforded **7** as an hygroscopic solid. ^{13}C NMR (75.43 MHz, D_2O), for the predominant isomer, δ 27.9 (t), 29.0 (t), 61.8

(t), 66.1(t), 70.9 (d), 72.5 (d), 74.2 (d), 78.2 (d), 79.6 (d), 80.2 (d). Anal. Calcd for $C_{10}H_{20}O_7 \cdot 2H_2O$: C, 41.64 %; H, 8.39 %. Found: C, 41.42 %; H, 8.54 %.

1-(2',3',4',6'-Tetra-O-benzyl-β-D-glucopyranosyl)-2,3-butandiol dipalmitate (17). A solution containing **16** (140 mg), pyridine (1.5 mL), dimethylaminopyridine (10 mg), and palmitoyl chloride (210 μL) was stirred at 100 °C under dry N_2 atmosphere for 3 hs. Usual work-up and flash chromatograpy afforded **17** (242 mg, 96 % yield). Oil, ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 14.09 (q), 22.7-34.4 (triplets), 64.9 (t), 69.1 (t), 71.0 (d), 73.5 (t), 74.9 (t), 75.2 (t), 75.5 (t), 78.6 (d), 79.0 (d), 82.0 (d), 87.3 (d). 173.4 (s). Anal. Calcd for $C_{70}H_{104}O_9$: C, 77.16 %; H, 9.62 %. Found: C, 76.89 %; H, 9.84 %.

1-(β-D-glucopyranosyl)-2,3-butandiol dipalmitate (8). Hydrogenation of **17** (200 mg), as described for the preparation of **7**, quantitatively afforded **8** (131 mg), as a white solid. ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 14.0 (q), 22.6-34.5 (triplets), 62.0 (t), 65.1 (t), 70.1 (d), 71.4 (d)73.8 (d), 78.5 (d), 78.9 (d), 79.4 (d), 173.8 (s). Anal. Calcd for $C_{42}H_{80}O_9$: C, 69.19 %; H, 11.06 %. Found: C, 68.84 %; H, 10.79 %.

Acknowledgements: We gratefully acknowledge MURST and CNR for the financial support and Pharmacia & Upjon, Nerviano Italy, for the biological assay.

REFERENCES AND NOTES

1 (a) Shirahashi, H.; Murakami, N.; Watanabe, M.; Nagatsu, A.; Sakakibara, J.; Tokuda, H.; Nishino, H.; Iwashima, A. *Chem. Pharm. Bull.* **1993**, 41, 1664. (b) Nagatsu, A.; Watanabe, M.; Ikemoto, K.; Hashimoto, M.; Murakami, N.; Sakakibara, J.; Tokuda, H.; Nishino, H.; Iwashima, A.; Yazawa, K. *Bioorg. Med. Chem. Lett.* **1994**, 4, 1619. (c) Morimoto, T.; Nagatsu, A.; Murakami, N.; Sakakibara, J. *Tetrahedron* **1995**, 51, 6443

2 For the synthesis of C-glycosides see (a) Levy, D.E.; Tang, C.: The Chemistry of C-Glycosides. in *Tetrahedron Organic Chemistry Series;* Baldwin, J.E.; Magnus, P.D. Eds, Pergamon, 1995; (b) Postema, M.H.D. C-Glycosides Synthesis, CRC Press; Boca Raton, 1995.

3 Cipolla, L.; Liguori, L.; Nicotra, F.; Torri, G.; Vismara, E. *J. Chem. Soc. Chem. Commun.* **1996**, 1253.

4 Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* **1978**, 100, 3611.

5 We named C-glycosides by semisystematic names generally accepted for this class of compounds; this allows an easier comparison with the parent sugar.

6 Lewis, M. D.; Kun Cha, J.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, 104, 4976.

(*Received in UK* 28 *January* 1997; *revised* 7 *March* 1997; *accepted* 13 *March* 1997)