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TETRAHEDRON

Synthesis of Benzoyl and Dodecanoyl Derivatives from Protected Carbohydrates under Focused Microwave Irradiation

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Abstract: A microwave assisted phase transfer catalyzed transesterification in basic medium with methyl benzoate was studied for several carbohydrates. Small amounts of DMF were necessary to provide good yields (96-76%) within 15 minutes. This method was extended to the synthesis of dodecanoyl derivatives with 63-100% global yields within 15 to 30 minutes. Rate enhancements when compared to conventional heating in the same conditions and specific microwave activation were mostly evidenced when fatty compounds (less reactive) were involved.

INTRODUCTION

Long chains esters derived from carbohydrates and glycosides are well known as biodegradable surfactants.[1] Their preparation is at present rather long and expensive[2-4] and needs, as a consequence, serious improvements. Most of the syntheses were performed by esterifications from fatty acids or acyl halides but suffered from poor selectivities with numerous undesirable side products difficult to separate.[5-7] Base or acid-catalyzed transesterifications with methyl or ethyl esters proved to be more adapted for industrial applications.[8-9] α-D-Glucofuranose[10] or α-D-glucopyranoside[11] derivatives were thus selectively monobenzoylated in basic medium (K_2CO_3 or $NaOCH_3$) at 180-200 °C but the yields were low (≤ 40%).

We have previously shown[12] that transesterification of several substrates could be efficiently realized in solvent-free conditions under microwave activation either by phase transfer catalysis (PTC) or by supported reactions onto mineral oxides. This paper describes the results of base-catalyzed transesterifications activated by PTC and under microwaves applied to carbohydrates. Microwave assisted synthesis from carbohydrates was shown to be very efficient as we had already noticed for glycosylations.[13] Therefore, two typical cases were studied to synthesize aromatic or fatty esters including a variety of carbohydrates with either only one secondary (**1**), one primary (**2**) or two secondary hydroxyl groups (**3** and **4**) (Fig. 1).

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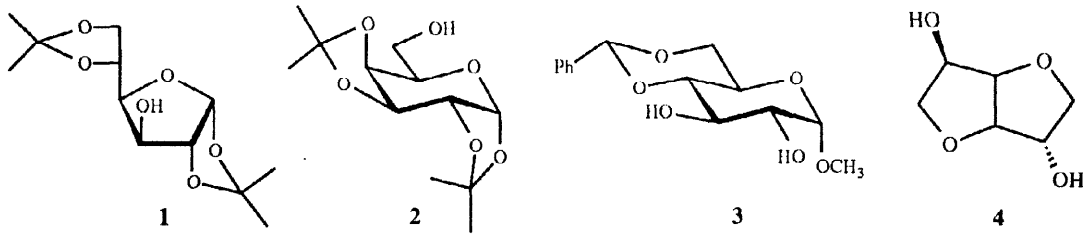


1 2 3 4

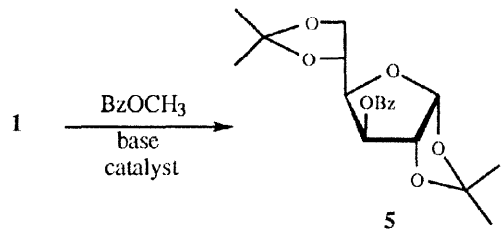
Fig. 1.

RESULTS AND DISCUSSION

Benzoylation by transesterification with methyl benzoate

As the selected substrates were not stable in acidic conditions, transesterification under basic conditions was considered using PTC either in the absence of solvent or in the presence of small amounts of various solvents.

3-*O*-Benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**) was obtained by transesterification from **1** with methyl benzoate using various phase transfer agents and bases (Scheme 1). The main results are given in Table 1.



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Scheme 1.

Table 1. Benzoylation of **1** (1.3 g, 5 mmol) in basic medium with methyl benzoate (2 equiv) and a phase transfer agent (4% molar equiv versus **1**). Microwave irradiation in a monomode reactor (P = 150-15 W). Reaction time = 15 minutes.

Entry	Base (equiv/1)	Catalyst	Solvent (2 mL)	Temperature(°C)	Yield (%)
1	K_2CO_3 (1)	Bu_4NBr	-	160	38
2	KOH (1)	Bu_4NBr	-	160	30
3	K_3PO_4 (1)	Bu_4NBr	-	160	31
4	K_2CO_3 (2)	Bu_4NBr	-	160	44
5	K_2CO_3 (2)	Bu_4NHSO_4 [a]	-	160	34
6	**K_2CO_3 (2)**	**Bu_4NBr**	**DMF**	**160**	**96**
7 [b]	K_2CO_3 (2)	Bu_4NBr	DMF	160	21
8	K_2CO_3 (2)	-	DMF	152	65
9	K_2CO_3 (2)	Bu_4NBr	Diglyme	148	71
10	K_2CO_3 (2)	Bu_4NBr	Mesitylene	150	17

[a] 10% of catalyst and reaction time = 45 min [b] Classical heating (thermostated oil bath): 15 min.

A weak and non nucleophilic base like potassium carbonate provided better yields than other stronger bases as potassium hydroxyde which probably induced the saponification of esters (entries 1 and 2). Moreover, 2 equiv of K_2CO_3 were preferable (entry 4). Longer reaction time and the use of Bu_4NHSO_4 as the catalyst did not improved the yield (entry 5).

Under solvent-free conditions, the best result was limited to 44% in yield (entry 4). The addition of a small amount of DMF (2 mL i.e. 5 equiv/**1**) led to a large improvement in yield which became nearly quantitative (entry 6) as yet evidenced in the case of Hantzsh synthesis of dihydropyridines.[14]

The presence of a polar solvent was largely favourable as DMF induced better yields (entry 6) than diglyme (entry 9) and much more than mesitylene (entry 10) in spite of very similar temperature profiles (Fig. 2). The specific role of DMF is not only due to its high dielectric constant but also to its high donicity[15] which implies a "drying effect"[16] as a strong acceptor of hydrogen bond from methanol.

During conventional heating, the temperature was measured all along the reaction with a thermocouple inside the reaction mixture and during microwave heating, with an infrared detector. No difference in temperature increase was noted between the two heating ways. As a consequence, strong specific microwave (non purely thermal) effects should be considered to rationalize the considerable improvement in yield when compared to conventional heating (96% versus 21%: entries 6, 7). This microwave specific activation has been evidenced several times in the literature.[17-23]

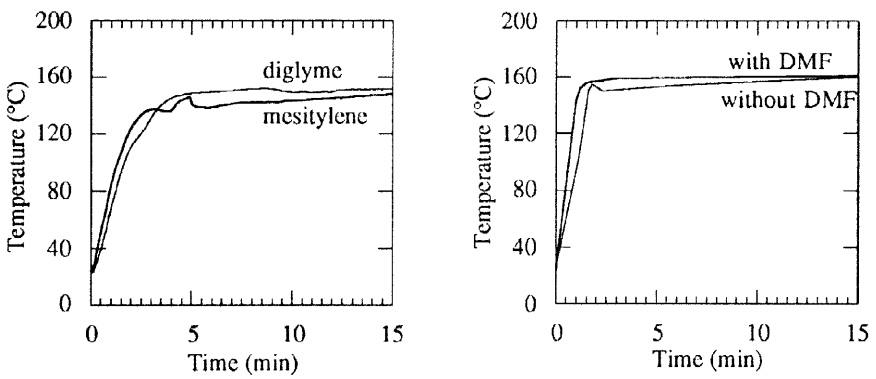
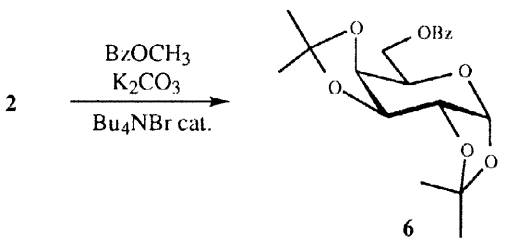


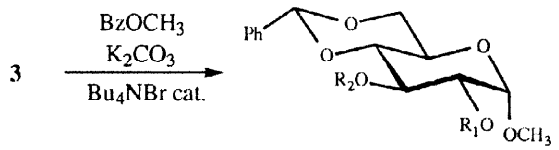
Fig. 2. Benzoylation of **1** under microwaves: curves of temperature increase in the case of solvent-free reaction, and comparison between different solvents.

The same conditions were applied to a monohydroxylated primary compound. From 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**), in the presence of K_2CO_3 (2 equiv) and Bu_4NBr (4%), a yield of 66% in **6** was obtained under solvent-free conditions within 4 minutes of irradiation (power 150-15 W, temperature 160 °C). When 2 mL (5 equiv) of DMF were added, the yield was increased up to 76% within 15 minutes (Scheme 2).



Scheme 2.

From the dihydroxylated secondary compound **3**, several attempts towards selective monobenzoylations as well as dibenzoylations were performed (Scheme 3). The main results are given in Table 2.



7a $R_1, R_2 = Bz$

7b $R_1 = Bz$ $R_2 = H$

7c $R_1 = H$ $R_2 = Bz$

Scheme 3.

Table 2. Benzoylation of **3** (705 mg, 2.5 mmol) by transesterification in basic medium (K_2CO_3) with methyl benzoate and Bu_4NBr (4%) in DMF (2 mL). Microwave power: P = 150-15 W. Reaction time: 15 minutes, T = 160 °C.

Entry	equiv K_2CO_3	equiv BzOMe	Total yield (%)	**7a** (%)	**7b** / **7c** (%)
1	**1.5**	**1.2**	**60**	10	**25 / 25**
2	3	3.5	74	70	3 / 1
3	**3**	**4**	**90**	**82**	7 / 1
4 [a)]	3	4	37	3	16 / 18

[a)] Conventional heating (thermostated oil bath) for 15 minutes at 160 °C.

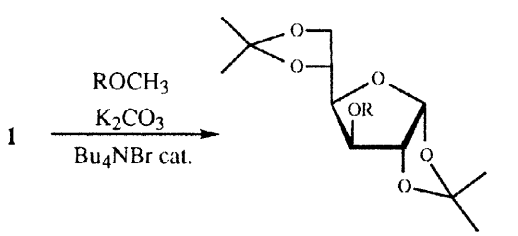
No selectivity was observed for monobenzoylation (entry 1). Using 4 equiv of methyl benzoate, a 82% yield of dibenzoylated compound (**7a**) was obtained within 15 minutes of irradiation (entry 3). Under classical heating (entry 4), the yield was very low with principally the monobenzoylated products **7b** and **7c** showing again a very significant specific microwave effect.

In the literature, one experiment was described with sodium methoxide as the base and only a 29% yield of **7b** + **7c** and a 4% yield of **7a** were obtained after 45 minutes at 200 °C.[11]

Long chain ester synthesis

Methyl laurate was selected as a typical fatty ester for the PTC transesterification in basic medium.

Transesterification of **1** (Scheme 4) was achieved with K_2CO_3 as the base and Bu_4NBr as the phase transfer catalyst. The main results are given in Table 3.



8 $R = CO(CH_2)_{10}CH_3$

Scheme 4.

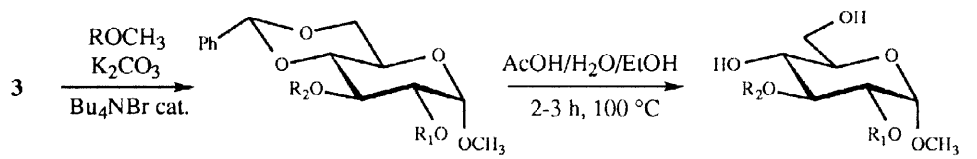
Table 3. Transesterification of **1** (1.3 g, 5 mmol) in basic medium (K_2CO_3) with methyl laurate (2 equiv) and Bu_4NBr (4%). Microwave power: P = 150-15 W. Reaction time: 15 minutes, T = 160 °C.

Entry	equiv K_2CO_3	Solvent (mL)	Yield (%)
1	2	DMF (2)	84
2	2	DMF (0.4)	32
3	**0.7**	**DMF (2)**	**88**
4	0.7	DMF (1)	64
5	1	-	15
6 [a)]	2	DMF (2)	0

a) Conventional heating (thermostated oil bath) for 15 minutes or 12 hours at 160 °C.

The best yield (88%, entry 3) was obtained in the presence of DMF (2 mL, 5 equiv) under microwaves with a very important specific effect of irradiation (entry 3 versus entry 6). This effect was greater with long chain compounds as yet observed during the synthesis of aromatic esters[20] or the saponification of hindered esters[24] i.e in the most difficult cases.[25]

From the dihydroxylated compound **3** (Scheme 5), selective monoesterifications as well as diesterifications were achieved, the main results are given in Table 4.



9a $R_1, R_2 = CO(CH_2)_{10}CH_3$ **10a** $R_1, R_2 = CO(CH_2)_{10}CH_3$

9b $R_1 = CO(CH_2)_{10}CH_3$ $R_2 = H$ **10b** $R_1 = CO(CH_2)_{10}CH_3$ $R_2 = H$

9c $R_1 = H$ $R_2 = CO(CH_2)_{10}CH_3$ **10c** $R_1 = H$ $R_2 = CO(CH_2)_{10}CH_3$

Scheme 5.

Table 4. Transesterification of **3** (705 mg, 2.5 mmol) with methyl laurate in basic medium (K_2CO_3) in the presence of Bu_4NBr (4%) and DMF (2 mL, 10 equiv). Microwave power: P = 150-15 W.

Entry	equiv K_2CO_3	equiv methyl laurate	Reaction time	Temperature (°C)	**9a / 9b / 9c (%)**
1	3	4	9 min	147	27 / 23 / 22
2	3	4	15 min	151	56 / 21 / 19
3	**3**	**4**	**30 min**	**147**	**77 / 12 / 11**
4 [a)]	3	4	9 min	147	0 / 2 / 1
5 [a)]	3	4	27 h	147	8 / 18 / 18
6	**1.5**	**1.5**	**15 min**	**150**	**24 / 26 / 15**

a) Conventional heating (thermostated oil bath)

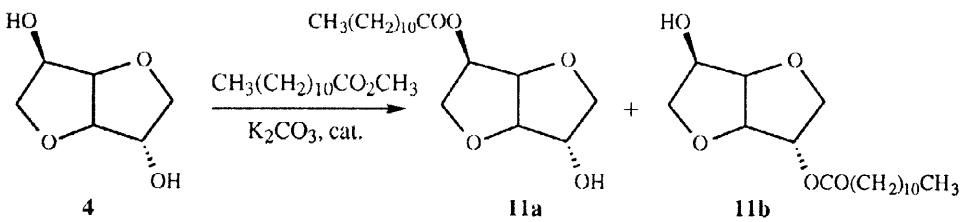
The diester **9a** was preferentially obtained within 30 minutes using 4 equiv of methyl laurate and 3 equiv of K_2CO_3 (77% yield, entry 3). After 9 minutes, the three possible products **9a-c** were isolated in rather similar proportions (entry 1). Conventional heating was by far less efficient (entries 4 and 5).

Among several attempts for monoesterification, the best one (entry 6) revealed rather poor selectivity.

Hydrolysis of compounds **9a**, **9b** and **9c** was performed at 100 °C in an ethanol/acetic acid/water (1/1/1) medium. Yields were quasi quantitative in a few hours (Scheme 5). Mono and 2,6-didodecanoyl derivatives of methyl glucoside have already demonstrated their high surface active properties and their utility as emulsifiers.[26]

1,4:3,6-Dianhydro-D-glucitol (isosorbide) (**4**) is an important by-product of the starch industry obtained by dehydration of D-glucitol[27], available in large quantities and of low cost. Isosorbide esterifications were very often described in the literature using long chain acids in acidic or basic medium at 230-240 °C during several hours but yields in isolated products were not mentioned as the products were not well defined and were probably mixtures.[28] Usual esterification reactions are directed toward the 5-endo position of higher reactivity, due to intramolecular hydrogen bonding.[5b] This property was used several times for selective acylations[29] but this regioselectivity was reversed using acid chloride in pyridine.[30]

Monoesterifications by transesterification with methyl laurate in the presence of K_2CO_3 and various phase transfer catalysts (4%) and solvents were achieved (Scheme 6), the main results are given in Table 5.



Scheme 6.

Table 5. Transesterification of **4** (1.46 g, 10 mmol) with methyl laurate (2 equiv) in the presence of K_2CO_3 (0.7 equiv) and a phase transfer catalyst (4%): A, Aliquat 336; B, Bu_4NBr. Microwave power: P = 20 W.

Entry	Cat.	Solvent (2 mL)	Reaction time	Temperature (°C)	Total Yield (%)	**11a / 11b (%)**
1	A	DMF	15 min	154	44	18 / 26
2	A	DMSO	15 min	174	47	25 / 22
3	**B**	**DMF**	**15 min**	**159**	**63**	**38 / 25**
4	B	DMSO	15 min	172	44	24 / 20
5	**B**	**DMSO**	**30 min**	**164**	**61**	**25 / 36**
6 [a)]	B	DMF	15 min	159	< 5	
			20 h	159	14	9 / 5

[a)] Conventional heating (thermostated oil bath)

Some experimental parameters were modified to provide the best results, for instance, only 0.7 equiv of K_2CO_3 and Bu_4NBr as the phase transfer catalyst were necessary to obtain a 63% total yield within 15 min (entry 3). If Aliquat 336 was used as the catalyst or DMSO instead of DMF, yields were lower (entries 1 and 2). The irradiation power had to be adjusted to a minimum value of 20 W in order to avoid an excessive heating due to the intrinsic polarity of the substrate. In order to optimize the yield in the presence of DMSO, 30 min under microwave irradiation were necessary. In that case 5-*O*- and 2-*O*-dodecanoyl derivatives (**11a** and **11b** respectively) were isolated in a 61% total yield (entry 5). With the same reagent proportions as in entry 3, but with oil bath heating, the reaction was much more difficult and even after 20 hours, the yield rose to only 14% (entry 6).

In conclusion, the synthesis by transesterification under basic PTC conditions from methyl esters and several carbohydrates were realized quasi quantitatively in the presence of small amounts of DMF. Specific activation by microwaves was largely evidenced and was more important when fatty compounds (i.e the less reactive ones) were involved.

EXPERIMENTAL SECTION

General methods. The microwave reactor was a monomode system (Synthewave 402 from Prolabo Society) with focused waves. All reactions were performed in a cylindrical pyrex vessel. The mixtures were introduced into the monomode reactor at the powers and times indicated in the tables and continuous mechanical stirring provided a good homogeneity of the materials. The temperature was controled all along the reaction and evaluated by an infrared detector which indicated the surface temperature (IR lecture was calibrated by according the emissivity factor using a thermocouple introduced inside the reaction mixture). Automatic control of the irradiation (power and temperature) as well as data processing were followed by a computer system.

Flash column chromatography was performed using 35-70 μ silica gel (60) purchased from S.D.S. company. TLC was run using DC-Plastikfolien, silica gel F_{254} (Schleicher and Schuell), detection by UV light (254 nm) and by heating after sulfuric acid treatment. ^1H and ^{13}C spectra were recorded at 250 MHz and 62.91 MHz and at 300 MHz and 75.49 MHz (Bruker WP 250, WP 300 respectively). Tetramethylsilane was the internal standard (δ = 0.00 ppm). Melting points were measured on a Reichert apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. For described compounds, ^1H and ^{13}C NMR values were in accordance with published ones. In addition, NMR values were given for some derivatives and $[\alpha]_D$ values were compared with literature data.

3-*O*-Benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5). 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1** (1.3 g, 5 mmol), K_2CO_3 (1.41 g, 10 mmol), Bu_4NBr (60 mg, 0.2 mmol) and methyl benzoate (1.36 g, 10 mmol) were mixed in 2 mL of DMF. This mixture was submitted to microwave irradiation for 15 min (P: 150-15 W, T: 160 °C), no coloration was observed after this time. After cooling, the reaction mixture was diluted with EtOAc, filtered through a pad of silica gel and the filtrate concentrated under vaccum. The residue was purified by flash chromatography (heptane/EtOAc 8/2) to give 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**) in 96% yield (1.74 g, 4.78 mmol). R_f 0.71 (heptane/EtOAc 1/1). Recrystallization from pentane; mp 63-65 °C Lit.[31] mp 63-64 °C; $[\alpha]_D$ - 48° (*c* 1.32, $CHCl_3$) Lit.[31] $[\alpha]_D$ - 50.2° (EtOH).

6-*O*-Benzoyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (6). 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **2** (1.33 g, 5 mmol) was diluted in DMF (2 mL), K_2CO_3 (1.41 g, 10 mmol), Bu_4NBr (60 mg, 0.2 mmol) and methyl benzoate (1.36 g, 10 mmol) were added and the mixture stirred under microwave irradiation over 15 min (P: 150-15 W, T: 160 °C). The reaction mixture was cooled, diluted with EtOAc, filtered through a pad of silica gel and the filtrate concentrated under vaccum. The residue was purified by flash chromatography (heptane/EtOAc 8/2) to give 6-*O*-benzoyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[32] (**6**) in 76% yield (1.39 g, 3.79 mmol). R_f 0.69 (heptane/EtOAc 1/1); $[\alpha]_D$ - 57° (*c* 1.26, $CHCl_3$).

Methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (7a). Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **3**[33] (705 mg, 2.5 mmol) was mixed in the flask with K_2CO_3 (1 g, 7.5 mmol), Bu_4NBr (36 mg, 0.1 mmol) and methyl benzoate (1.37 g, 10 mmol); DMF (2 mL) added and irradiation maintained during 15 minutes (P: 150-15 W, T: 160 °C). After cooling, the reaction mixture was filtered through a pad of silica gel and the filtrate concentrated under vaccum. The residue was purified by flash chromatography (heptane/EtOAc 8/2 then 7.5/2.5 and 4/6) to give methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**7a**)[34-36] in 82% yield (1.01 g, 2.06 mmol) and the monobenzoylated products **7b**[35,36] (7%, 65 mg, 0.17 mmol) and **7c**[35,36] (1%, 10 mg, 0.026 mmol). Rf 0.73 (heptane/EtOAc 1/1). Recrystallization from CH_2Cl_2/pentane; mp 153 °C Lit.[34] mp 148 °C (alcohol, H_2O); $[\alpha]_D$ + 92° (*c* 1.12, $CHCl_3$) Lit.[34] $[\alpha]_D$ + 96.9° (*c* 2.828, $CHCl_3$).

Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (7b) and methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (7c). Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **3**[33] (705 mg, 2.5 mmol) was mixed in the flask with K_2CO_3 (518 mg, 3.75 mmol), Bu_4NBr (36 mg, 0.1 mmol) and methyl benzoate (411 mg, 3 mmol); DMF (2 mL) added and irradiation maintained during 15 minutes (P: 150-15 W, T: 160 °C). After the same workup, the products were purified by column chromatography (heptane/EtOAc 8/2 then 7.5/2.5 and 4/6) to give 10% yield of **7a** (123 mg, 0.25 mmol) and 50% yield of the two monobenzoylated compounds: **7b** (25%, 234 mg, 0.61 mmol) and **7c** (25%, 232 mg, 0.61 mmol). All the products were recrystallized from CH_2Cl_2/pentane. **7b**; Rf 0.65 (heptane/EtOAc 1/1); mp 167-168 °C Lit.[35] mp 165-166 °C; $[\alpha]_D$ + 113° (*c* 1.20, $CHCl_3$) Lit.[36] $[\alpha]_D$ + 111° (*c* 1.64, $CHCl_3$). **7c**; Rf 0.44 (heptane/EtOAc 1/1); mp 219-221 °C Lit.[35] mp 217-218 °C; $[\alpha]_D$ + 33° (*c* 1.04, $CHCl_3$) Lit.[36] $[\alpha]_D$ + 34° (*c* 1.10, $CHCl_3$).

3-*O*-Dodecanoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (8). Compound **1** (1.3 g, 5 mmol) and K_2CO_3 (495 mg, 3.58 mmol), Bu_4NBr (60 mg, 0.2 mmol) and methyl laurate (2.16 g, 10 mmol) were mixed in the flask, DMF (2 mL) added and irradiation maintained during 15 minutes (P: 150-15 W, T: 160 °C). After cooling, the reaction mixture was diluted with EtOAc, filtered through a pad of silica gel and the filtrate concentrated under vaccum. The residue was purified by flash chromatography (heptane/EtOAc 9/1) to give 3-*O*-dodecanoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**8**) as a colorless oil in 88% yield (1.95 g, 4.41 mmol). Rf 0.88 (heptane/EtOAc 1/1); $[\alpha]_D$ - 26° (*c* 0.967, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 0.9 [t, 3H, CH_3(12')], 1.25-1.6 [m, 30H, $4CH_3$ isopropylidenes and $9CH_2$(3'-11')], 2.4 [t, 2H, CH_2(2')], 4.0-4.2 (m, 4H, H-4, H-5, H-6a, H-6b), 4.5 (d, 1H, H-2), 5.3 (sl, 1H, $J_{2,3}$ < 1 Hz, $J_{3,4}$ = 1 Hz, H-3), 5.9 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2 (CH_3, C-12'), 25.4-26.8 ($4CH_3$ isopropylidenes), 22.8-25.0 and 29.2-34.4 [$10CH_2$, C(2'-11')], 67.4 (C-6), 72.5 (C-5), 75.9 (C-3), 80.0 (C-4), 83.5 (C-2), 105.2 (C-1), 109.4, 112.4 (C-7, C-8), 172.5 (C-1'). *Anal.* Calcd for $C_{24}H_{42}O_7$: C, 65.13; H, 9.57. Found: C, 65.35; H, 9.63.

Methyl 4,6-*O*-benzylidene-2,3-di-*O*-dodecanoyl-α-D-glucopyranoside (9a). Compound **3** (705 mg, 2.5 mmol) was mixed in the flask with K_2CO_3 (1.04 g, 7.5 mmol), Bu_4NBr (36 mg, 0.1 mmol) and methyl laurate (2.14 g, 10 mmol). DMF (2 mL) was added and irradiation maintained during 30 minutes (P: 150-15 W, T: 147 °C). After cooling, the reaction mixture was filtered through a pad of silica gel and the filtrate concentrated under vaccum. The residue was purified by flash chromatography (heptane/EtOAc 9/1 then 8/2 and 7.5/2.5) to give methyl 4,6-*O*-benzylidene-2,3-di-*O*-dodecanoyl-α-D-glucopyranoside (**9a**) in 77% yield (1.24

g, 1.92 mmol) and the monoesters **9b** (12%, 142 mg, 0.31 mmol) and **9c** (11%, 130 mg, 0.28 mmol). Rf 0.85 (heptane/EtOAc 1/1). Recrystallization from CH_2Cl_2/pentane; mp 68 °C; $[\alpha]_D$ + 35° (*c* 1.09, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 0.9 [t, 6H, CH_3(12') and CH_3(12")], 1.25 [m, 32H, 8CH_2(4'-11') and 8CH_2(4"-11")], 1.6 [m, 4H, CH_2(3') and CH_2(3")], 2.3 [m, 4H, CH_2(2') and CH_2(2")], 3.4 (s, 3H, OCH_3), 3.65 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 3.77 (t, 1H, $J_{5,6ax}$ = $J_{6ax,6eq}$ = 10 Hz), 3.93 (m, 1H, H-5), 4.3 (dd, 1H, $J_{5,6eq}$ = 4.6 Hz, $J_{6eq,6ax}$ = 10 Hz, H-6eq), 4.87 (m, 1H, H-2), 4.95 (m, 1H, H-1), 5.5 (s, 1H, H-7), 5.6 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H-3), 7.2-7.4 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2 (2CH_3, C-12' and C-12"), 22.8-34.4 [20CH_2, C(2'-11') and C(2"-11")], 55.5 (OCH_3), 62.5 (C-5), 68.7 (C-3), 69.0 (C-6), 71.5 (C-2), 79.5 (C-4), 97.8 (C-1), 101.6 (C-7), 126.2-129.1 (5CH, Ph), 137.1 (Cquat, Ph), 172.6, 173.3 (C-1' and C-1"). *Anal.* Calcd for $C_{28}H_{62}O_8$: C, 70.55; H, 9.66. Found: C, 70.13; H, 9.54.

Methyl 4,6-*O*-benzylidene-2-*O*-dodecanoyl-α-D-glucopyranoside (9b) and methyl 4,6-*O*-benzylidene-3-*O*-dodecanoyl-α-D-glucopyranoside (9c). Compound **3** (705 mg, 2.5 mmol) was mixed in the flask with K_2CO_3 (518 mg, 3.75 mmol), Bu_4NBr (32 mg, 0.1 mmol) and methyl laurate (802 mg, 3.75 mmol). DMF (2 mL) was added and irradiation maintained during 15 minutes (P: 150-15 W, T: 150 °C). After the same workup, the products were purified by column chromatography (heptane/EtOAc 9/1 then 8/2 and 7.5/2.5) to give 24% yield of **9a** (353 mg, 0.55 mmol) and 41% yield of the two monoesters: **9b** (26%, 308 mg, 0.67 mmol) and **9c** (15%, 176 mg, 0.40 mmol). All the products were recrystallized from CH_2Cl_2/pentane. **9b**; Rf 0.69 (heptane/EtOAc 1/1); mp 90-91 °C Lit.[37] mp 87-89 °C; $[\alpha]_D$ + 70° (*c* 1.175, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.9 [t, 3H, CH_3(12')], 1.25 [m, 16H, CH_2(4'-11')], 1.6 [t, 2H, CH_2(3')], 2.4 [t, 2H, CH_2(2')], 2.45 (d, 1H, OH), 3.4 (s, 3H, OCH_3), 3.55 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, H-4), 3.75 (t, 1H, $J_{6ax,6eq}$ = $J_{5,6ax}$ = 9.6 Hz, H-6ax), 3.85 (m, 1H, H-5), 4.17 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, H-3), 4.3 (dd, 1H, $J_{5,6eq}$ = 4.4 Hz, $J_{6eq,6ax}$ = 9.6 Hz, H-6eq), 4.78 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 4.95 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.55 (s, 1H, H-7), 7.2-7.5 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.2 (CH_3, C-12'), 22.8-34.3 [10CH_2, C(2'-11')], 55.5 (OCH_3), 62.1 (C-5), 68.9 (C-3), 69.0 (C-6), 73.6 (C-2), 81.5 (C-4), 97.8 (C-1), 102.2 (C-7), 126.4-129.4 (5CH, Ph), 137.3 (Cquat, Ph), 173.7 (C-1'). **9c**; Rf 0.49 (heptane/EtOAc 1/1); mp 123-126 °C Lit.[37] mp 115-117 °C; $[\alpha]_D$ + 66° (*c* 1.297, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.9 [t, 3H, CH_3(12')], 1.25 [m, 16H, CH_2(4'-11')], 1.6 [t, 2H, CH_2(3')], 2.3 (sl, 1H, OH), 2.4 [t, 2H, CH_2(2')], 3.45 (s, 3H, OCH_3), 3.57 (t, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 3.65 (m, 1H, H-2), 3.75 (t, 1H, $J_{5,6ax}$ = $J_{6ax,6eq}$ = 10 Hz, H-6ax), 3.85 (m, 1H, H-5), 4.3 (dd, 1H, $J_{5,6eq}$ = 4.6 Hz, $J_{6eq,6ax}$ = 10 Hz, H-6eq), 4.8 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.33 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, H-3), 5.48 (s, 1H, H-7), 7.25-7.5 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2 (CH_3, C-12'), 22.8-34.6 [10CH_2, C(2'-11')], 55.7 (OCH_3), 62.9 (C-5), 69.0 (C-6), 72.0 (C-2), 72.2 (C-3), 78.9 (C-4), 100.3 (C-1), 101.6 (C-7), 126.2-129.1 (5CH, Ph), 137.2 (Cquat, Ph), 174.1 (C-1').

Methyl 2,3-di-*O*-dodecanoyl-α-D-glucopyranoside (10a). Compound **9a** (2.88 g, 4.45 mmol) was dissolved in 110 mL of a solution of EtOH/CH_3COOH/H_2O 5/3/3. After 3 hours at 100 °C, the reaction mixture was concentrated under vaccum. The residue was purified by flash chromatography (heptane/EtOAc 1/1) to give methyl 2,3-di-*O*-dodecanoyl-α-D-glucopyranoside (**10a**) in 80% yield (1.98 g, 3.54 mmol). Rf 0.69 (EtOAc); recrystallized from pentane; mp 81-82 °C; $[\alpha]_D$ + 77° (*c* 1.065, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 0.95 [t, 6H, CH_3(12') and CH_3(12")], 0.9 [t, 3H, CH_3(12')], 1.15-1.4 [m, 32H, 8CH_2(4'-11') and 8CH_2(4"-11")], 1.5-1.65 [m, 4H, CH_2(3') and CH_2(3")], 2.1 (t, 1H, OH), 2.25-2.4 [m, 4H, CH_2(2') and CH_2(2")], 2.95 (d, 1H, OH), 3.4 (s, 3H, OCH_3), 3.65-3.75 (m, 2H, H-4, H-5), 3.75-3.95 (m, 2H, H-6eq, H-6ax), 4.85 (dd, 1H, H-2), 4.92 (d, 1H, $J_{1,2}$ = 2 Hz, H-1), 5.27 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 4.6 Hz, H-3); ^{13}C NMR

(62.9 MHz, $CDCl_3$): δ 14.2 ($2CH_3$, C-12' and C-12''), 22.8-34.5 [$20CH_2$, C(2'-11') and C(2''-11'')], 55.4 (OCH_3), 62.2 (C-6), 70.3 (C-5), 70.6 (C-2), 71.4 (C-4), 73.6 (C-3), 97.0 (C-1), 173.2, 175.1 (C-1' and C-1''). *Anal.* Calcd for $C_{31}H_{58}O_8$: C, 66.63; H, 10.46. Found: C, 66.52; H, 10.52.

Methyl 2-*O*-dodecanoyl-α-D-glucopyranoside (10b). Compound **9b** (982 mg, 2.11 mmol) was dissolved in 40 mL of a solution of EtOH/CH_3COOH/H_2O 1/1/1. After 2 hours at 100 °C, the reaction mixture was concentrated under vaccum. The residue was recrystallized from CH_2Cl_2/pentane to give methyl 2-*O*-dodecanoyl-α-D-glucopyranoside (**10b**) in 96% yield (764 mg, 2.03 mmol). Rf 0.37 (EtOAc); mp 70 °C Lit.[38] mp 67-69 °C; $[\alpha]_D$ + 109° (*c* 1.05, pyridine) Lit.[38] $[\alpha]_D$ + 108.1° (*c* 1.0, pyridine); ^1H NMR (250 MHz, $CDCl_3$): δ 0.9 [t, 3H, CH_3(12')], 1.25 [m, 16H, $8CH_2$(4'-11')], 1.6 [m, 2H, CH_2(3')], 2.4 [m, 2H, CH_2(2')], 3.35 (s, 3H, OCH_3), 3.57 (m, 1H, H-4), 3.65-3.75 (m, 1H, H-5), 3.75-3.95 (m, 3H, H-3, H-6eq, H-6ax), 4.7 (dd, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 4.85 (sl, 1H, $J_{1,2}$ = 3 Hz, H-1); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2 (CH_3, C-12'), 22.8-34.2 [$10CH_2$, C(2'-11')], 55.3 (OCH_3), 61.1 (C-6), 69.8 (C-5), 71.1 (C-4), 71.6 (C-3), 73.1 (C-2), 97.2 (C-1), 174.2 (C-1').

Methyl 3-*O*-dodecanoyl-α-D-glucopyranoside (10c). Compound **9c** (913 mg, 1.97 mmol) was dissolved in 40 mL of a solution of EtOH/CH_3COOH/H_2O 1/1/1. After 2 hours at 100 °C, the reaction mixture was concentrated under vaccum. The residue was recrystallized from CH_2Cl_2/pentane to give methyl 3-*O*-dodecanoyl-α-D-glucopyranoside (**10c**) in 94% yield (695 mg, 1.85 mmol). Rf 0.26 (EtOAc); mp 67-69 °C; $[\alpha]_D$ + 116° (*c* 1.017, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 0.9 [t, 3H, CH_3(12')], 1.3 [m, 16H, $8CH_2$(3'-11')], 1.6 [m, 2H, CH_2(3')], 2.0 (sl, 1H, OH), 2.35 (d, 1H, OH), 2.45 [t, 2H, CH_2(2')], 2.7 (sl, 1H, OH), 3.45 (s, 3H, OCH_3), 3.55-3.7 (m, 3H, H-4, H-5, H-2), 3.8-3.95 (m, 2H, H-6eq, H-6ax), 4.8 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.05 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9Hz, H-3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (CH_3, C-12'), 22.7-34.4 [$10CH_2$, C(2'-11')], 55.3 (OCH_3), 61.7 (C-6), 68.7 (C-5), 70.8 (C-2), 71.5 (C-4), 76.2 (C-3), 99.5 (C-1), 175.6 (C-1'). *Anal.* Calcd for $C_{19}H_{36}O_7$, 1/4 H_2O: C, 59.89; H, 9.66. Found: C, 60.01; H, 9.51.

1,4:3,6-Dianhydro-5-*O*-dodecanoyl-D-glucitol (11a) and 1,4:3,6-dianhydro-2-*O*-dodecanoyl-D-glucitol (11b). Dry isosorbide (**10**) (1.46 g, 10 mmol) was mixed in the flask with K_2CO_3 (967 mg, 7 mmol), Bu_4NBr (128 mg, 0.4 mmol) and methyl laurate (4.48 g, 20 mmol). DMF (2 mL) was added and irradiation maintained during 15 minutes (P: 20 W, T: 159 °C). After cooling, the reaction mixture was filtered through a pad of silica gel and the filtrate was concentrated under vaccum. The residue was purified by flash chromatography (heptane/EtOAc 8/2 then 7/3) to give first 1,4:3,6-dianhydro-2-*O*-dodecanoyl-D-glucitol (**11b**) (820 mg, 2.5 mmol) and then 1,4:3,6-dianhydro-5-*O*-dodecanoyl-D-glucitol (**11a**) (1.25 g, 3.81 mmol) in 63% total yield. **11a**; colorless oil; Rf 0.45 (heptane/EtOAc 1/1); $[\alpha]_D$ + 59° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 0.9 [t, 3H, CH_3(C-12')], 1.3 [sl, 16H, $8CH_2$(4'-11')], 1.6 [m, 2H, CH_2(3')], 2.35 [t, 2H, CH_2(2')], 2.8 (m, 1H, OH), 3.75 (dd, 1H, $J_{6a,6b}$ = 10 Hz, $J_{5,6b}$ = 5 Hz, H-6b), 3.9 (m, 3H, H-1a, H-1b, H-6a), 4.3 (s, 1H, $J_{1,2}$ < 1 Hz, H-2), 4.4 (d, 1H, $J_{2,3}$ < 1 Hz, H-3), 4.85 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 5 Hz, H-4), 5.15 (ddd, 1H, H-5); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (CH_3, C-12'), 22.7-34.1 ($10CH_2$, C-2' to C-11'), 70.4 (C-6), 74.0 (C-5), 75.5 (C-1), 76.2 (C-2), 80.4 (C-4), 88.3 (C-3), 173.4 (C-1'). *Anal.* Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.85; H, 9.99. **11b**; Rf 0.55 (heptane/EtOAc 1/1). White solid recrystallized from pentane; mp 79 °C Lit.[39] mp 73-74 °C (methanol, n-hexane); $[\alpha]_D$ + 44° (*c* 1.24, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 0.9 [t, 3H, CH_3(12')], 1.3 [sl, 16H, $8CH_2$(4'-11')], 1.6 [m, 2H, CH_2(3')], 2.3 [t, 2H, CH_2(2')], 2.65 (sl, 1H, OH), 3.55 (dd, 1H, $J_{5,6b}$ = 5.8 Hz, H-6b), 3.9 (dd, 1H, $J_{5,6a}$ = 6 Hz,

$J_{6a,6b}$ = 10 Hz, H-6a), 4.0 (d, 2H, $J_{1a,1b}$ = 2.8 Hz, H-1a, H-1b), 4.3 (ddd, 1H, H-5), 4.45 (d, 1H, $J_{2,3} < 1$ Hz, H-3), 4.6 (t, 1H, $J_{3,4} = J_{4,5}$ = 5 Hz, H-4), 5.23 (s, 1H, $J_{1,2} < 1$ Hz, H-2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (CH_3, C-12'), 22.7-34.2 ($10CH_2$, C-2' to C-11'), 72.4 (C-5), 73.6 (C-6), 73.7 (C-1), 78.2 (C-2), 82.0 (C-4), 85.8 (C-3), 172.8 (C-1'). *Anal.* Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.98; H, 9.72.

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