Lipase-Catalysed Selective Synthesis of Sucrose Mixed Diesters

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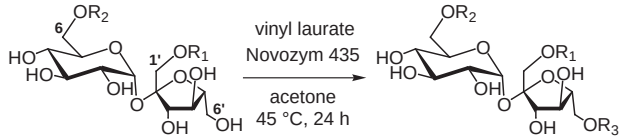
Received 25 July 2000; revised 20 November 2000

Abstract: The selectivity of the esterification of sucrose was studied in the case of lipase-catalysed reactions with activated and non-activated acyl donors. Using the lipase Novozym 435, sucrose fatty acid diesters and mixed fatty acid methacrylic acid diesters were obtained in high conversion and selectivity.

Key words: sucrose, lipase, enzymes, esterification, carbohydrates

During the course of our study of selective transformations of sucrose,[1] we have investigated the use of enzymes as catalysts for transesterifications.[2] Although the preparation of carbohydrate monoesters mediated by proteases or lipases is well documented, the application to the selective synthesis of mixed diesters has been less studied, in particular in the case of disaccharides. Lipases are active in solvents which are often not compatible with very polar substrates such as unprotected carbohydrates. The use of *tert*-butyl alcohol or acetone widens the scope of the method, although the hydrophobisation of the substrate is often necessary. For example, glycosides having an aglycon moiety apolar enough to provide solubility can be esterified in the presence of lipases.[3] In the case of sucrose, similar reactions were conducted after partial functionalisation by acetals or boronic esters.[4] Carrea et al. and Plou et al. mentioned that sucrose monoesters could undergo a second esterification although in moderate conversion or selectivity.[5] Having in hand a series of monosubstituted sucrose esters obtained either by protease-catalysed or base-catalysed transesterification, we were able to study in detail their second esterification with various carboxylic residues, with the goal of preparing selectively diesters having two different acyl residues, complementary to the Mistunobu type reactions which lead to homodiesters at positions 6 and 6'.[6]

The lipase Novozym 435 from *Candida antarctica*, immobilised on an acrylic resin, was chosen after a short qualitative comparison with porcine pancreatic lipase and Lipozym IM, based on the reaction of 1'-*O*-monolauryl sucrose (**1**) with vinyl laurate (5 equiv). Acetone as the solvent led to very selective reactions. In *tert*-butyl alcohol, the reaction was also very selective, but slightly more diesters were detected in this case. In acetone at 45 °C, 1',6'-di-*O*-lauryl sucrose (**2**) was obtained in 80% yield, together with the 6,1',6'-triester **3** (15%). Starting from the 6-*O*-lauryl-substituted sucrose ester **4** having a free OH-1', the reaction thus led to the 6,6'-diester **5** in 86% yield, with only trace amounts of the triester **3**, showing that the selectivity towards the position 6' of sucrose is very high for this enzyme. Among the two remaining primary OH-groups, OH-1' is less reactive compared to OH-6. This rather high selectivity for an acylation at OH-6' is complementary to the protease-catalysed reactions which exhibit a marked preference for an acylation at OH-1' (Scheme 1).



1 : R_1= $CO(CH_2)_{10}CH_3$; R_2=H

2 : R_2=H; R_1=R_3= $CO(CH_2)_{10}CH_3$

3 : R_1=R_2=R_3= $CO(CH_2)_{10}CH_3$

4 : R_1=H; R_2= $CO(CH_2)_{10}CH_3$

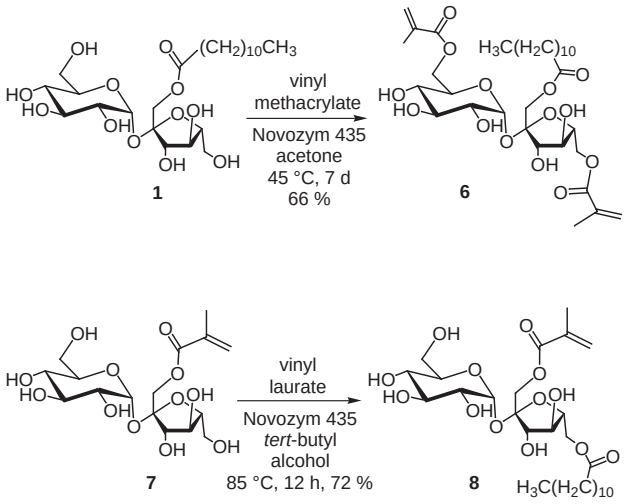
5 : R_1=H; R_2=R_3= $CO(CH_2)_{10}CH_3$

Scheme 1

In the case of a shorter and branched carboxylic residue such as vinyl methacrylate, the reaction is slower and less selective, a fact which prevents the isolation of the diesters. However, increasing the amount of enzyme and of acylating agent led to the clean preparation of the 6,6'-di-*O*-methacryloyl-1'-mono-*O*-lauryl sucrose (**6**). If a monomethacryloyl monolauryl sucrose mixed diester is desired, the alternative is to start from the sucrose 1'-*O*-monomethacryloyl ester **7** which is cleanly acylated at OH-6' in 72% yield by reaction with vinyl laurate in *tert*-butyl alcohol (because of insufficient solubility of this substrate in acetone) (Scheme 2).

The influence of the "leaving group" part of the acylating agent was then studied, in the case of the reaction of 1'-*O*-monolauryl sucrose with lauric acid, methyl laurate, and vinyl laurate. The results are depicted in the Figure. In acetone vinyl laurate led to faster reactions, a fair catalysis was observed with methyl laurate, and a small but not negligible one with lauric acid. In these two cases, the reaction was improved in the presence of 4 Å molecular sieves, although heating at 80 °C in *tert*-butyl alcohol was required for the reaction with lauric acid.

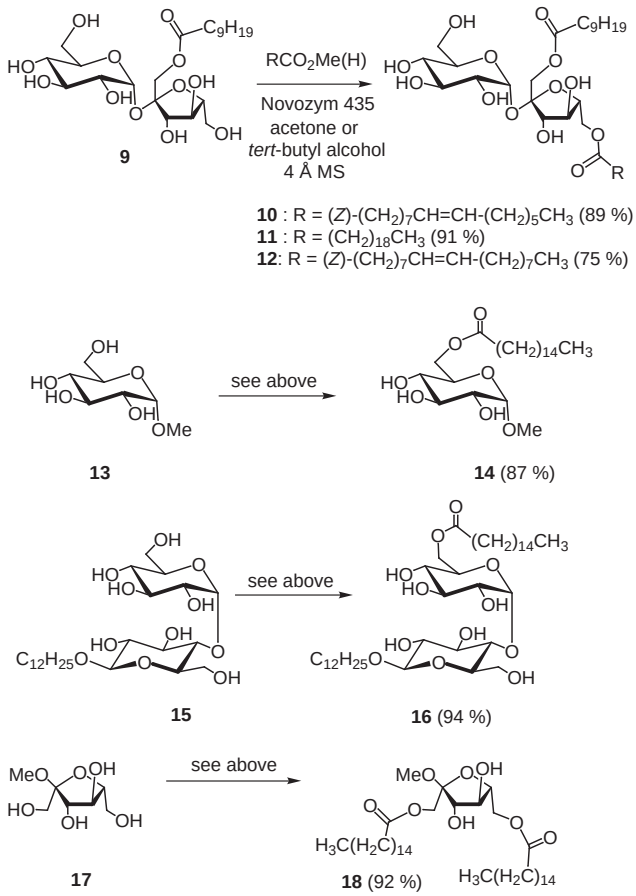
These observations were applied to the synthesis of sucrose esters having two different fatty acid residues. Starting from 1'-*O*-monodecanoyl sucrose (**9**), reaction in acetone with methyl palmitoleate [(*Z*)-hexadec-9-enoate] or methyl arachidate (eicosanoate) (5 equiv) led to the corresponding 1',6'-diesters **10** and **11** in 89% and 91%



Scheme 2

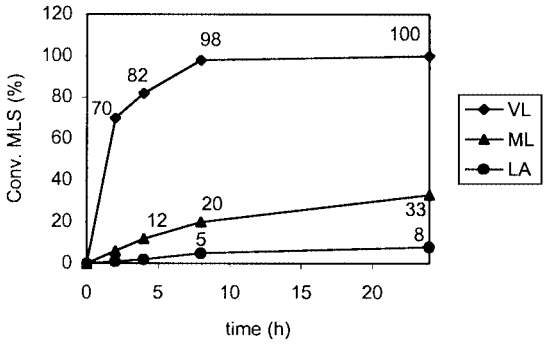
yield, respectively. Similarly, the reaction of **9** with oleic acid [(*Z*)-octadec-9-enoic acid] in *tert*-butyl alcohol at 80 °C led to the 6'-*O*-oleyl-1'-*O*-monodecanoyl diester (**12**) in 75% yield, with traces of the other regiosiomer at position 1',6 (Scheme 3).

The reaction could also be applied to other carbohydrates. Starting from methyl α-D-glucopyranoside (**13**) or β-dodecyl maltoside (**15**), the reaction with methyl palmitate (methyl hexadecanoate) led to derivatives **14** and **16** acylated at the primary OH-6 (of the terminal unit for the disaccharide) in 87% and 94% yield, respectively, confirming the accessibility of OH-6 of a glucopyranosyl moiety as in sucrose. However, methyl α-D-fructofuranoside (**17**), led to the 1,6-diester **18**, with intermediate monoesters formed at similar rates, preventing any selective monoesterification. This is in contrast with the reaction of 6-substituted sucrose derivatives, which also have both primary hydroxyl groups of the fructose moiety available (OH-1' and OH-6'), and which provide selectively esters at position 6', with no or very little reaction at OH-1' (Scheme 3).

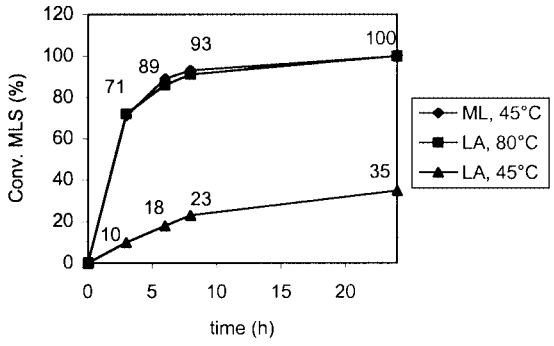


Scheme 3

In conclusion, we have shown that the immobilised lipase Novozym 435 promotes the selective esterification of monosubstituted sucrose esters in acetone or *tert*-butyl alcohol, in a very convenient manner, without protection-deprotection steps. The acylation takes place mostly at OH-6', on the fructose moiety, even when OH-1' is available, in contrast with the non-selective reactions on methyl fructoside. Long chain fatty acids are better substrates compared to shorter ones, giving faster and more selective



A. In acetone at 45 °C.



B. With 4 Å molecular sieves in acetone (45 °C) or *tert*-butyl alcohol (80 °C).

Figure Novozym 435-catalysed reaction of 1'-*O*-lauryl sucrose with vinyl laurate (VL), methyl laurate (ML) and lauric acid (LA) (5 equiv)

reactions. The carboxylic acids can be used directly as acylating agent but require higher reaction temperatures as well as the presence of molecular sieves. Methyl esters are also possible substrates. The combination of the OH-1' directed esterification mediated by proteases and this lipase catalysed OH-6' directed esterification is a straightforward route to sucrose mixed diesters. Using this sequence, sucrose methacryloyl-fatty esters and diesters having two different fatty residues were obtained in high yields and selectivity.

PPL (lipase from hog pancreas), vinyl laurate and methyl α-D-glucopyranoside were purchased from Fluka, acetone (99.9%), *tert*-butyl alcohol (99.5%), methyl arachidate, methyl palmitoleate, methyl palmitate and oleic acid were purchased from Aldrich, THF (99.7%) from SDS, n-dodecyl β-D-maltoside from Sigma, and sucrose from Béghin-Say. Novozym 435 (immobilised lipase from Candida antarctica) and Lipozyme IM (immobilised lipase from Mucor miehei) were gifts from Novo Nordisk. Molecular sieves 4 Å (Fluka) was crushed and dried at 400 °C for 8 h before use. Substituted sucrose derivatives **1** and **7** were prepared by Proteinase N catalysed transesterification,[2] as well as the 6-*O*-substituted ester **4**, obtained as side product by this method. Methyl α-D-fructofuranoside (**17**) was prepared by oxalic acid-catalysed reaction of fructose with MeOH.[7] NMR spectra were recorded at 300 MHz or 500 MHz (^{1}H) and 125 MHz or 75 MHz (^{13}C) on Bruker DRX 300 or DRX 500 spectrometers at the University Claude Bernard Lyon 1, in CD_3OD as solvent except for compound **18** ($CDCl_3$). TLC and flash chromatography were performed on silica gel 60 F_{254} plates (Merck). Optical rotations (Sodium D line) were measured at 20 °C with a Perkin-Elmer 241 digital polarimeter. Elemental analyses and high resolution FAB (+) mass spectra were performed by the Service central d'Analyse of the CNRS (Solaize).

Lipase-Catalysed Transesterification of Vinyl Esters with Carbohydrates; General Procedure

A mixture of the appropriate carbohydrate **1**, **4** or **7**, (0.12−0.48 mmol, 100 mg/mL), vinyl laurate (5 equiv) and Novozym 435 (used without any prior treatment, 100 mg/mL) was heated in acetone at 45 °C (or in *tert*-butyl alcohol at 85 °C for **7**) in a tube closed with a screw-cap and a teflon joint with magnetic stirring at 100 rpm. When TLC showed full consumption of the starting material, the suspension was filtered and the solids were washed with the solvent. The filtrate was then concentrated under reduced pressure and the residue was purified by flash-chromatography [CH_2Cl_2/MeOH/acetone/H_2O (78:10:10:2) for products **2** and **3**, CH_2Cl_2/MeOH (9:1) for products **5**, **6** and **8**]. In the case of the reaction of **1** with vinyl methacrylate, excess acylating agent (3 equiv) and enzyme (200 mg) were added after 2 d and the mixture was further stirred for 5 d. Compounds **2**, **3**, **5**, **6** and **8** were respectively obtained in the following amounts: 268, 65, 75, 167 and 140 mg.

Reaction of Crabohydrates with Other Acylating Agents; General Procedure

The carbohydrate **9**, **13**, **15** or **17** (0.12−0.51 mmol, 100 mg/mL), the methyl ester (or oleic acid for the synthesis of **12** from **9**) (5 equiv) and Novozym 435 (100 mg/mL) and 4 Å molecular sieves (500 mg/mL) were heated in acetone at 45 °C (for the synthesis of **10** and **11** from **9**) or in *tert*-butyl alcohol at 45 °C (for **14, 16, 18** from **13**, **15**, **17**) or at 80 °C (for **12** from **9**). Pure products were obtained after filtration, evaporation and flash-chromatography (CH_2Cl_2/MeOH, 9:1). Compounds **10**, **11**, **12**, **13**, **14**, **16** and **18** were respectively obtained in the following amounts: 130, 145, 70, 193, 138 and 320 mg.

2

$[\alpha]_D^{20}$ +40.0 (*c* = 1, MeOH).

^{1}H NMR (500 MHz): δ = 0.89−0.94 (m, 6 H, CH_3), 1.25−1.40 (m, 32 H, CH_2), 1.59−1.69 (m, 4 H, CH_2), 2.32−2.40 (m, 4 H, CH_2CO), 3.36 (t, *J* = 9.3 Hz, 1 H, H-4), 3.42 (dd, *J* = 9.9, 3.9 Hz, 1 H, H-2), 3.69 (t, *J* = 9.4 Hz, 1 H, H-3), 3.7 (dd, *J* = 12.4, 3.7 Hz, 1 H, H-6b), 3.82−3.86 (m, 2 H, H-5, H-6a), 3.90 (dt, *J* = 8.0, 3.1 Hz, 1 H, H-5'), 4.03 (t, *J* = 8.3 Hz, 1 H, H-4'), 4.08 (d, *J* = 8.5 Hz, 1 H, H-3'), 4.12 (d, *J* = 12.1 Hz, 1 H, H-1'b), 4.33 (dd, *J* = 11.8, 3.5 Hz, 1 H, H-6'b), 4.39 (d, *J* = 12.1 Hz, 1 H, H-1'a), 4.41 (dd, *J* = 11.8, 8.0 Hz, 1 H, H-6'a), 5.37 (d, *J* = 3.7 Hz, 1 H, H-1).

^{13}C NMR (125 MHz): δ = 13.5 (CH_3), 25.1 (CH_2), 22.8, 29.2−29.8, 32.1 (CH_2), 34.0 (CH_2), 61.5 (C-6), 62.5 (C-1'), 65.7 (C-6'), 70.5 (C-4), 72.1 (C-2), 73.3 (C-5), 73.7 (C-3), 75.1 (C-4'), 77.4 (C-3'), 79.8 (C-5'), 93.0 (C-1), 103.3 (C-2'), 174.4, 174.4 (C=O).

HRMS: *m*/*z* calcd for (M + Li): 713.4663. Found: 713.4645.

Anal. calcd for $C_{36}H_{66}O_{13}\bullet H_2O$: C, 59.6; H, 9.5; O, 30.9. Found: C, 59.8; H, 9.5; O, 31.1.

3

$[\alpha]_D^{20}$ +34.0 (*c* = 1, MeOH).

^{1}H NMR (500 MHz): δ = 0.89−0.96 (m, 9 H, CH_3), 1.26−1.40 (m, 48 H, CH_2), 1.59−1.69 (m, 6 H, CH_2), 2.32−2.44 (m, 6 H, CH_2), 3.27 (t, *J* = 9.4 Hz, 1 H, H-4), 3.43 (dd, *J* = 9.8, 4.0 Hz, 1 H, H-2), 3.69 (t, *J* = 9.7 Hz, 1 H, H-3), 3.86−3.93 (m, 1 H, H-5'), 4.04 (t, *J* = 8.3 Hz, 1 H, H-4'), 4.03−4.07 (m, 1 H, H-5), 4.09 (d, *J* = 8.6 Hz, 1 H, H-3'), 4.10−4.13 (m, 1 H, H-6b), 4.13 (d, *J* = 12.0 Hz, 1 H, H-1'b), 4.37 (d, *J* = 5.5 Hz, 2 H, H-6'a,b), 4.37 (d, *J* = 12.1 Hz, 1 H, H-1'a), 4.41 (dd, *J* = 11.8, 1.8 Hz, 1 H, H-6a), 5.35 (d, *J* = 3.8 Hz, 1 H, H-1).

^{13}C NMR (125 MHz): δ = 13.5 (CH_3), 25.1 (CH_2), 22.8, 29.2−29.8, 32.1 (CH_2), 34.0 (CH_2), 62.5 (C-1'), 64.2 (C-6), 65.7 (C-6'), 70.9 (C-4, C-5), 72.0 (C-2), 73.5 (C-3), 75.1 (C-4'), 77.4 (C-3'), 79.8 (C-5'), 92.8 (C-1), 103.2 (C-2'), 173.6, 174.1, 174.5 (C=O).

HRMS: m/z calcd for (M + Li): 895.6334. Found: 895.6333.

Anal. calcd for $C_{48}H_{88}O_{14}\bullet 0.4\ H_2O$: C, 64.3; H, 10.0; O, 25.7. Found: C, 64.4; H, 10.1; O, 25.8.

5

$[\alpha]_D^{20}$ +42.0 (*c* = 1, THF).

^{1}H NMR (500 MHz): δ = 0.85−1.00 (t, *J* = 7.0 Hz, 6 H, CH_3) 1.25−1.45 (m, 32 H, CH_2), 1.55−1.70 (m, 4 H, CH_2), 2.30−2.45 (m, 4 H, CH_2), 3.28 (t, *J* = 9.5 Hz, 1 H, H-4), 3.45 (dd, *J* = 9.7, 3.8 Hz, 1 H, H-2), 3.62 (d, *J* = 12.2 Hz, 1 H, H-1'b), 3.66 (d, *J* = 12.2 Hz, 1 H, H-1'a), 3.72 (t, *J* = 9.4 Hz, 1 H, H-3), 3.90−3.97 (m, 1 H, H-5'), 4.01 (t, *J* = 8.0 Hz, 1 H, H-4'), 4.05−4.10 (m, 1 H, H-5), 4.09 (d, *J* = 8.0 Hz, 1 H, H-3'), 4.14 (dd, *J* = 11.9, 6.0 Hz, 1 H, H-6b), 4.32−4.40 (m, 2 H, H-6'a,b), 4.45 (dd, *J* = 11.8, 2.1 Hz, 1 H, H-6a), 5.37 (d, *J* = 3.8 Hz, 1 H, H-1).

^{13}C NMR (125 MHz): δ = 13.3 (CH_3), 25.0 (CH_2), 22.6, 29.2−29.7, 32.0 (CH_2), 34.0 (CH_2), 63.3 (C-1'), 64.1 (C-6), 65.8 (C-6'), 70.1 (C-5, C-4), 72.3 (C-2), 73.9 (C-3), 76.1 (C-4'), 78.40 (C-3'), 79.9 (C-5'), 92.3 (C-1), 104.6 (C-2'), 174.2, 174.6 (C=O).

HRMS: *m*/*z* calcd for (M + Na): 729.4383. Found: 729.4401.

Anal. calcd for $C_{36}H_{66}O_{13}$: C, 61.1; H, 9.4; O, 29.4. Found: C, 61.1; H, 9.4; O, 29.2.

6

$[\alpha]_D^{20}$ +45.0 (*c* = 1, MeOH).

^{1}H NMR (500 MHz): δ = 0.91 (t, *J* = 9.0 Hz, 3 H, CH_3), 1.28−1.40 (m, 16 H, CH_2), 1.60−1.70 (m, 2 H, CH_2), 1.94, 1.96 (2 s, 6 H, CH_3), 2.39 (t, *J* = 7.1 Hz, 2 H, CH_2), 3.35 (t, *J* = 9.5 Hz, 1 H, H-4), 3.43 (dd, *J* = 9.8, 3.9 Hz, 1 H, H-2), 3.70 (t, *J* = 9.7 Hz, 1 H, H-3), 3.92−3.96 (m, 1 H, H-5'), 4.07 (t, *J* = 8.0 Hz, 1 H, H-4'), 4.08 (d, *J* = 8.0

Hz, 1 H, H-3'), 4.10−4.15 (m, 1 H, H-5), 4.18 (d, *J* = 12.0 Hz, 1 H, H-1'b), 4.31 (dd, *J* = 12.0, 5.1 Hz, 1 H, H-6b), 4.36 (dd, *J* = 11.9, 7.3 Hz, 1 H, H-6'b), 4.37 (d, *J* = 12.1 Hz, 1 H, H-1'a), 4.42 (dd, *J* = 11.9, 3.4 Hz, 1 H, H-6'a), 4.46 (dd, *J* = 12.0, 2.1, 1 H, H-6a), 5.39 (d, *J* = 3.8 Hz, 1 H, H-1), 5.64, 6.14 (2s, 4 H, $C=CH_2$).

^{13}C NMR (125 MHz): δ = 13.4 (CH_3), 17.5 (CH_3), 25.1 (CH_2), 22.7, 29.2−29.7, 32.1 (CH_2), 34.0 (CH_2), 62.8 (C-1'), 64.2 (C-6), 65.9 (C-6'), 70.8 (C-5), 71.0 (C-4), 72.0 (C-2), 73.6 (C-3), 75.3 (C-4'), 77.7 (C-3'), 79.8 (C-5'), 93.0 (C-1), 103.5 (C-2'), 125.5, 125.6 ($C=CH_2$), 136.5, 136.7 ($C=CH_2$), 167.5, 167.8, 173.7 (C=O).

HRMS: *m*/*z* calcd for (M + Li): 667.3517. Found 667.3526.

Anal. calcd for $C_{32}H_{52}O_{14}$•0.5 H_2O: C, 57.4; H, 7.9; O, 34.6. Found: C, 57.4; H, 8.1; O, 34.2.

8

$[\alpha]_D^{20}$ +46.0 (*c* = 1, MeOH).

^1H NMR (500 MHz): 0.91 (t, *J* = 9.0 Hz, 3 H, CH_3), 1.26−1.40 (m, 16 H, CH_2), 1.58−1.68 (m, 2 H, CH_2), 1.98 (s, 3 H, CH_3), 2.37 (t, *J* = 7.3 Hz, 2 H, CH_2), 3.36 (t, *J* = 9.0 Hz, 1 H, H-4), 3.43 (dd, *J* = 9.8, 3.8 Hz, 1 H, H-2), 3.70 (t, *J* = 8.9 Hz, 1 H, H-3), 3.73 (dd, *J* = 12.1, 5.3 Hz, 1 H, H-6b), 3.82−3.93 (m, 3 H, H-5, H-5', H-6a), 4.05 (t, *J* = 8.3 Hz, 1 H, H-4'), 4.11 (d, *J* = 8.5 Hz, 1 H, H-3'), 4.25 (d, *J* = 12.0 Hz, 1 H, H-1'b), 4.34 (dd, *J* = 11.8, 3.2 Hz, 1 H, H-6'b), 4.40 (d, *J* = 12.2 Hz, 1 H, H-1'a), 4.42 (dd, *J* = 11.8, 7.6 Hz, 1 H, H-6'a), 5.39 (d, *J* = 3.8 Hz, 1 H, H-1), 5.68, 6.17 (2 s, 2 H, $C=CH_2$).

^{13}C NMR (125 MHz): δ = 13.4 (CH_3), 17.5 (CH_3), 25.0 (CH_2), 22.7, 29.2−29.7, 32.1 (CH_2), 33.9 (CH_2), 61.5 (C-6), 63.1 (C-1'), 65.5 (C-6'), 70.6 (C-4), 72.1 (C-2), 73.3, 73.7 (C-5, C-3), 75.1 (C-4'), 77.6 (C-3'), 79.8 (C-5'), 93.0 (C-1), 103.3 (C-2'), 125.7 (C=CH), 136.5 (C=CH), 167.0, 174.5 (C=O).

HRMS: *m*/*z* calcd for (M + Li): 559.3255. Found: 559.3269.

Anal. calcd for $C_{28}H_{48}O_{13}$•1 H_2O: C, 55.1; H, 8.2. Found: C, 55.0; H, 7.9.

10

$[\alpha]_D^{20}$ +35.0 (*c* = 1, THF).

^1H NMR (500 MHz): δ = 0.82−0.97 (m, 6 H, CH_3), 1.20−1.43 (m, 28 H, CH_2), 1.50−1.70 (m, 4 H, CH_2), 1.97−2.11 (m, 4 H, CH_2), 2.25−2.42 (m, 4 H, CH_2), 3.36 (t, *J* = 9.2 Hz, 1 H, H-4), 3.42 (dd, *J* = 9.8, 3.8 Hz, 1 H, H-2), 3.69 (t, *J* = 9.3 Hz, 1 H, H-3), 3.73 (dd, *J* = 12.3, 3.7 Hz, 1 H, H-6b), 3.80−3.85 (m, 2 H, H-5, H-6a), 3.90 (dt, *J* = 7.9, 3.0 Hz, 1 H, H-5'), 4.03 (t, *J* = 8.3 Hz, 1 H, H-4'), 4.08 (d, *J* = 8.5 Hz, 1 H, H-3'), 4.12 (d, *J* = 12.0 Hz, 1 H, H-1'b), 4.33 (dd, *J* = 11.8, 3.5 Hz, 1 H, H-6'b), 4.39 (d, *J* = 12.0 Hz, 1 H, H-1'a), 4.41 (dd, *J* = 11.8, 7.9 Hz, 1 H, H-6'a), 5.32−5.43 (m, 3 H, H-1, HC=CH).

^{13}C NMR (125 MHz): δ = 13.6 (CH_3), 25.1 (CH_2), 27.1 (CH_2), 22.8, 29.2−29.8, 32.1 (CH_2), 34.0 (CH_2), 61.5 (C-6), 62.5 (C-1'), 65.7 (C-6'), 70.5 (C-4), 72.1 (C-2), 73.3 (C-5), 73.7 (C-3), 75.1 (C-4'), 77.4 (C-3'), 79.8 (C-5'), 93.0 (C-1), 103.3 (C-2'), 129.8, 129.9 (HC=CH), 173.6, 174.4 (C=O).

Anal. calcd for $C_{38}H_{68}O_{13}$: C, 62.3; H, 9.4. Found: C, 62.5; H, 9.5.

11

$[\alpha]_D^{20}$ +36.0 (*c* = 1, THF).

^1H NMR (300 MHz): δ = 0.82−0.97 (m, 6 H, CH_3), 1.18−1.44 (m, 44 H, CH_2), 1.53−1.72 (m, 4 H, CH_2), 2.28−2.46 (m, 4 H, CH_2), 3.32 (t, *J* = 9.2 Hz, 1 H, H4), 3.35 (dd, *J* = 9.8, 3.8 Hz, 1 H, H-2), 3.65 (t, *J* = 9.3 Hz, 1 H, H-3), 3.69 (dd, *J* = 12.3, 3.7 Hz, 1 H, H-6b), 3.78−3.87 (m, 2 H, H-5, H-6a), 3.89 (dt, *J* = 7.9, 3.0 Hz, 1 H, H-5'), 4.02 (t, *J* = 8.3 Hz, 1 H, H-4'), 4.06 (d, *J* = 8.5 Hz, 1 H, H-3'), 4.11 (d, *J* = 12.0 Hz, 1 H, H-1'b), 4.34 (dd, *J* = 11.8, 3.5 Hz, 1 H, H-6'b), 4.39 (d, *J* = 12.0 Hz, 1 H, H-1'a), 4.40 (dd, *J* = 11.8, 7.9 Hz, 1 H, H-6'a), 5.36 (d, *J* = 3.7 Hz, 1 H, H-1).

^{13}C NMR (75 MHz): δ = 13.5 (CH_3), 25.1 (CH_2), 22.8, 29.2−29.8, 32.1 (CH_2), 34.0 (CH_2), 61.5 (C-6), 62.5 (C-1'), 65.7 (C-6'), 70.5 (C-4), 72.1 (C-2), 73.3 (C-5), 73.7 (C-3), 75.1 (C-4'), 77.4 (C-3'), 79.8 (C-5'), 93.0 (C-1), 103.2 (C-2'), 173.6, 174.4 (C=O).

HRMS: *m*/*z* calcd for (M + Na): 813.5328. Found: 813.5340.

Anal. calcd for $C_{42}H_{78}O_{13}$: C, 63.8; H, 9.9; O, 26.3. Found: C, 63.8; H, 9.6; O, 26.4.

12

$[\alpha]_D^{20}$ +37.0 (*c* = 1, THF).

^1H NMR (300 MHz): δ = 0.86−0.96 (m, 6 H, CH_3), 1.20−1.42 (m, 32 H, CH_2), 1.57−1.72 (m, 4 H, CH_2), 1.99−2.12 (m, 4 H, CH_2), 2.31−2.40 (m, 4 H, CH_2), 3.36 (t, *J* = 9.2 Hz, 1 H, H-4), 3.42 (dd, *J* = 9.8, 3.8 Hz, 1 H, H-2), 3.69 (t, *J* = 9.3 Hz, 1 H, H-3), 3.73 (dd, *J* = 12.3, 3.7 Hz, 1 H, H-6b), 3.80−3.89 (m, 2 H, H-5, H-6a), 3.90 (dt, *J* = 7.9, 3.0 Hz, 1 H, H-5'), 4.03 (t, *J* = 8.3 Hz, 1 H, H-4'), 4.08 (d, *J* = 8.5 Hz, 1 H, H-3'), 4.12 (d, *J* = 12.0 Hz, 1 H, H-1'b), 4.33 (dd, *J* = 11.8, 3.5 Hz, 1 H, H-6'b), 4.39 (d, *J* = 12.0 Hz, 1 H, H-1'a), 4.41 (dd, *J* = 11.8, 7.9 Hz, 1 H, H-6'a), 5.36 (3, 3 H, H-1, HC=CH).

^{13}C NMR (75 MHz): δ = 13.5 (CH_3), 25.0 (CH_2), 27.2 (CH_2), 22.7, 29.2−29.9, 32.1, (CH_2), 34.0 (CH_2), 61.5 (C-6), 62.4 (C-1'), 65.7 (C-6'), 70.5 (C-4), 72.0 (C-2), 73.3 (C-5), 73.7 (C-3), 75.1 (C-4'), 77.4 (C-3'), 79.8 (C-5'), 93.0 (C-1), 103.2 (C-2'), 129.8, 129.9 (HC=CH), 173.6, 174.4 (C=O).

HRMS: *m*/*z* calcd for (M + Na): 783.4888. Found: 783.4870.

Anal. calcd for $C_{40}H_{72}O_{13}$•0.6 H_2O: C, 62.2; H, 9.6. Found: C, 62.2; H, 9.9.

14

$[\alpha]_D^{20}$ +70.0 (*c* = 1, THF).

^1H NMR (500 MHz): δ = 0.92 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.26−1.41 (m, 24 H, CH_2), 1.60−1.68 (m, 2 H, CH_2), 2.39 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.29 (t, *J* = 9.4 Hz, 1 H, H-4), 3.41 (s, 3 H, OCH_3), 3.39 (dd, *J* = 9.6, 3.8 Hz, 1 H, H-2), 3.63 (t, *J* = 9.2 Hz, 1 H, H-3), 3.70−3.75 (m, 1 H, H-5), 4.21 (dd, *J* = 11.8, 6.1 Hz, 1 H, H-6b), 4.41 (dd, *J* = 11.8, 2.2 Hz, 1 H, H-6a), 4.67 (d, *J* = 3.8 Hz, 1 H, H-1).

^{13}C NMR (125 MHz): δ = 13.3 (CH_3), 25.0 (CH_2), 22.6, 29.1−29.7, 32.0 (CH_2), 34.1 (CH_2), 64.6 (OCH_3), 63.8 (C-6), 70.2 (C-5), 71.0 (C-4), 72.6 (C-2), 74.1 (C-3), 100.3 (C-1), 174.4 (C=O).

HRMS: *m*/*z* calcd for (M + Na): 455.2986. Found: 455.2984.

Anal. calcd. for $C_{23}H_{44}O_7$: C, 63.9; H, 10.3. Found: C, 63.8; H, 10.5.

16

$[\alpha]_D^{20}$ +21.0 (*c* = 1, THF).

^1H NMR (500 MHz): δ = 0.92 (t, *J* = 7.0 Hz, 6 H, CH_3), 1.26−1.46 (m, 44 H, CH_2), 1.60−1.68 (m, 4 H, CH_2), 2.39 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.24 (t, *J* = 9.4 Hz, 1 H, H-2'), 3.28 (t, *J* = 9.4 Hz, 1 H, H-4), 3.37−3.41 (m, 1 H, H-5'), 3.47 (dd, *J* = 9.7, 3.8 Hz, 1 H, H-2), 3.51 (t, *J* = 9.1 Hz, 1 H, H-4'), 3.53−3.58 (m, 1 H, OCH_{2a}), 3.62 (t, *J* = 9.1 Hz, 1 H, H-3'), 3.62 (t, *J* = 9.3 Hz, 1 H, H-3), 3.82 (dd, *J* = 12.5, 5.1 Hz, 1 H, H-6'b), 3.88−3.94 (m, 3 H, H-6'a, OCH_{2a}, H-5), 4.17 (dd, *J* = 11.8, 6.8 Hz, 1 H, H-6b), 4.29 (d, *J* = 7.8 Hz, 1 H, H-1'), 4.42 (dd, *J* = 11.8, 2.0 Hz, 1 H, H-6a), 5.13 (d, *J* = 3.8 Hz, 1 H, H-1).

^{13}C NMR (125 MHz): δ = 13.5 (CH_3), 25.0 (CH_2), 22.8, 29.3− 29.9, 32.1 (CH_2), 34.0 (CH_2), 61.4 (C-6'), 64.0 (C-6), 70.0 (OCH_2), 70.6 (C-4), 71.3 (C-5), 73.1 (C-2), 73.6 (C-2'), 74.0 (C-3), 75.6 (C-5'), 76.8 (C-3'), 81.1 (C-4'), 102.1 (C-1), 103.3 (C-1'), 174.5 (C=O).

HRMS: *m*/*z* calcd for (M + Na): 771.5297. Found: 771.5234.

Anal. calcd for $C_{40}H_{76}O_{12}$•0.6 H_2O: C, 63.2; H, 10.3; O, 26.5. Found: C, 63.1; H, 10.4; O, 26.2.

18

$[\alpha]_D^{20}$ +31.0 (*c* = 1, THF).

^{1}H NMR (500 MHz): δ = 0.90 (t, *J* = 6.9 Hz, 6 H, CH_3), 1.21−1.39 (m, 26 H, CH_2, OH), 1.60−1.70 (m, 4 H, CH_2), 2.36 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.39 (t, *J* = 7.4 Hz, 2 H, CH_2), 3.37 (s, 3 H, OCH_3), 3.86 (s, 1 H, H-3), 3.98 (d, *J* = 1.9 Hz, 1 H, H-4), 4.16−4.20 (m, 1 H, H-5), 4.23−4.26 (m, 3 H, H-1b, H-6a,b), 4.42 (d, *J* = 12.8, 1 H, H-1a).

^{13}C NMR (125 MHz): δ = 14.5 (CH_3), 25.3 (CH_2), 23.1, 29.4−30.1, 32.3 (CH_2), 34.5 (CH_2), 49.2 (OCH_3), 58.3 (C-1), 64.6 (C-6), 79.1 (C-4), 79.7 (C-3), 85.4 (C-5), 109.3 (C-2), 173.9, 175.2 (C=O).

Anal. calcd for $C_{39}H_{74}O_8$: C, 69.8; H, 11.1. Found: C, 69.9; H, 11.2.

HRMS: *m*/*z* calcd for (M + Na): 693.5260. Found: 693.5281.

Acknowledgement

Financial support from Béghin-Say and CNRS is gratefully acknowledged. We thank Novo Nordisk for a gift of Novozym 435. We also thank M. Hervé Martin for the preparation of starting materials.

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Article Identifier:
1437-210X,E;2001,0,03,0458,0462,ftx,en;T00900SS.pdf