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Direct Synthesis of Maradolipids and Other Trehalose 6-Monoesters and 6,6'-Diesters

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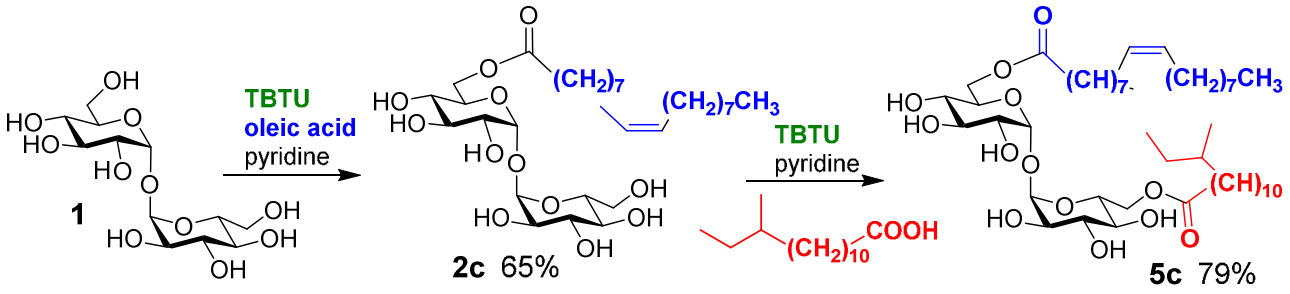

Abstract

It was shown that reaction of trehalose with one equivalent of a fatty acid in pyridine promoted by one equivalent of the uronium-based coupling agent 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) at room temperature gives a good yield of the primary ester accompanied by small amounts of the diprimary ester, using hexanoic, palmitic, and oleic acids as examples. Reactions using two equivalents of the fatty acids gave the symmetrical diesters. The monoesters were reacted with different fatty acids to give non-symmetric 6,6'-diesters in very good yields. Compounds synthesized include the most abundant component of the very complex maradolipid mixture, 6-*O*-(13-methyltetradecanoyl)-6'-*O*-oleoyltrehalose, and a component potentially present in this mixture, 6-*O*-(12-methyltetradecanoyl)-6'-*O*-oleoyltrehalose, a derivative of an ante fatty acid. The C5-C6 rotameric populations of 6-*O*-monoesters, symmetrical 6,6'-diesters, and 2,6,6'-triesters of fatty acids were calculated from the values of the H5-H6*R* and H5-H6*S* coupling constants and found to be similar to those found for glucose. The rotameric

populations of the monosubstituted glucose residues in the 2,6,6'-triesters was altered considerably to favor the *gt* rotamer, presumably because of attraction between the 2- and 6'-fatty acid chains.

Introduction

Primary monoesters and diesters of trehalose (see Figure 1) have been of interest since the recognition[1] that they were important components of the outer membranes of mycobacteria, in which the carboxylic acids are mycolic acids, complex long-chain β-hydroxy acids.[2] They are also of interest for many diverse biological activities.[2b,3] Recently, they have been identified as components of the outer membrane of dauer (enduring) larva of the well-known nematode, *caenorhabditis elegans*.[4] This form of larva appears when the nematode is exposed to extremely dry conditions and the altered membrane allows the nematode to survive extreme desiccation.[5] The mixture of fatty acids present in the outer membrane, the "maradolipids",[4] is extremely complex, with about 38% of the fatty acids being monomethyl branched fatty acids and about 16% containing cyclopropyl groups. The most abundant component is a nonsymmetric 6,6'-trehalose diester, 6-*O*-(13-methylmyristoyl)-6'-*O*-oleoyltrehalose.[4] The only monomethyl branched fatty acids that have been identified in *C. elegans* are branched next to the terminal carbon, that is, they are iso fatty acids.[4,6] Nevertheless, ante monomethyl branched fatty acids, that is, fatty acids branched on the carbon second from the terminal carbon are common in nature.[6b]

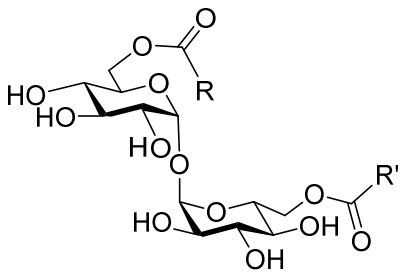

Figure 1. Trehalose 6,6'-diesters

There has been extensive effort directed at the synthesis of trehalose primary esters.[2b,7] Most authors have chosen to use protecting group strategies. One approach has been to use temporary

protection of the primary hydroxyls with trityl or *tert*-butyldimethylsilyl or *tert*-butyldiphenylsilyl groups before benzylation, removal of the primary protecting groups and acylation.[8] The discovery[9] that primary trimethylsilyl groups can be selectively removed by mild aqueous base has led to the extensive use of the 2,2',3,3',4,4'-hexa-*O*-trimethylsilyl derivative for acylation studies.[9-10] An alternative strategy has been to selectively convert the primary hydroxyls into leaving groups, either sulfonates[11] or halides,[9] before introducing acyl groups via S_N2 substitution with carboxylate salts.[8a,8b,10a] Trehalose has also been monoesterified at O-6 enzymically using a variety of vinyl fatty acid esters in dimethyl formamide by a protease from *Bacillus subtilis* in good yields.[12] Protecting-group-free strategies are inherently attractive but few have been disclosed to this point. Transesterification gave quite low yields.[3a,13] Tributylstannylation gave moderate yields only when the conditions using the toxic tributylstannyl ethers were carefully optimized.[14] Mitsunobu reactions are more attractive but again the yields are in the 50 to 60% range and the best solvent is toxic hexamethylphosphoramide.[15] This publication describes the protecting-group-free synthesis of 6-monoesters and 6,6'-diesters of trehalose using our primary-selective acylation procedure,[16] recently applied to the synthesis of a library of glycolipid antigens against Lyme disease.[17]

Results and Discussion

Synthesis. The conditions developed for the regioselective acylation of primary alcohols in the presence of secondary alcohols involved reaction of the diol or polyol with the carboxylic acid in *N*,*N*-dimethylformamide (DMF) with at least 2 equiv of diisopropylethylamine (DIEA) and 1.2 equiv of 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU).[16] Trehalose is relatively insoluble in DMF but it was found that pyridine was a good solvent for this reaction as it was for the selective acylation of galactose.[17] Reaction of trehalose (**1**) with a slight excess of the fatty acid at room temperature gave good yields (65-69%) of the

Scheme 1. Synthesis of trehalose 6-monoesters and 6,6'-diesters

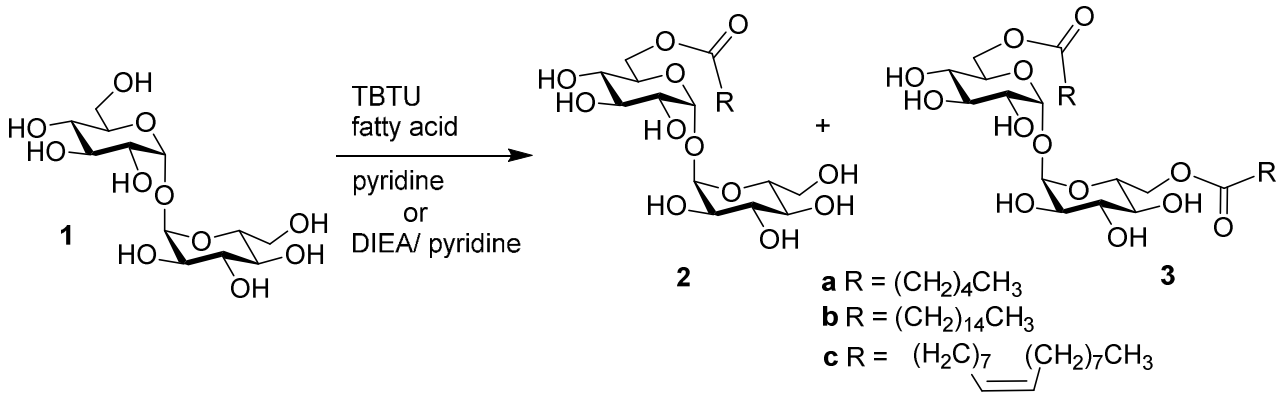

Table 1. Conditions and outcomes for the reactions of trehalose (1) with fatty acids

entry	fatty acid (equiv)	TBTU (equiv)	DIEA (equiv)	time (h)	temp	product, yield (%)	
						6-mono	**6,6'-di**
1	hexanoic (1.1)	1.1	2.1	36	rt	**2a**, 69	**3a**, 14
2	hexanoic (2.1)	2.1	2.1	36	rt	**2a**, 20	**3a**, 63
3	hexanoic (2.1)	2.1	0	36	rt	**2a**, 19	**3a**, 63
4	hexanoic (3.5)	3.5	3.5	48	rt	**2a**, 10	**3a**, 48[a]
5	palmitic (1.1)	1.1	0	72	rt	**2b**, 67	**3b**, 14
6	palmitic (1.1)	1.1	2.1	48	40 °C	**2b**, 37	**3b**, 32
7	palmitic (2.1)	2.1	0	72	rt	**2b**, 16	**3b**, 66
8	palmitic (2.2)	2.2	0	168	rt	**2b**, 18	**3b**, 69
9	oleic (1.1)	1.1	0	60	rt	**2c**, 65	**3c**, 15
10	oleic (2.1)	2.1	0	72	rt	**2c**, 18	**3c**, 66
11	oleic (2.2)	2.2	0	192	rt	**2c**, 22	**3c**, 70
12	oleic (3.5)	3.5	0	60	rt	**2c**, 19	**3c**, 66
13	oleic (5.0)	5.0	0	168	rt	**2c**, 0	**3c**, 48[a]

[a] Plus the 2,6,6'-triester (**4**) in the yield given in the experimental section.

6-*O*-monoacylated products as pictured in Scheme 1 and shown in entries 1, 5 and 9 of Table 1. Under these conditions, small amounts of the 6,6'-di-*O*-acylated products are also obtained, consistent with the first substitution having little effect on the reactivity of the second primary hydroxyl group. The long chains of the fatty acids cause these reactions to be considerably slower than the corresponding reactions with simple acids, such as benzoic acid, and longer reaction times are required to achieve complete reaction of the fatty acids. As noted in the reactions with galactose derivatives,[17] the added base is unnecessary if the solvent is pyridine (compare entries 1, 5, and 9 in

Table 1) consistent with the role of the base in the reactions of primary alcohols being to accept protons released from the initial reaction of the acid with the uronium salt (TBTU) and in the formation of the active ester on addition of the alcohol. Use of two or more equivalents of fatty acids gives reasonable yields of the 6,6'-di-*O*-acyl products (see entries 2, 3, 7, and 10 in Table 1). Neither increasing the relative amount of fatty acid beyond 2.1 equiv nor raising the reaction temperature improved the yields of the disubstituted products. Instead additional products were obtained of which the 2,6,6'-triester (**4**) (Figure 2) was the most prominent, isolated in 20% yield from the reaction of trehalose with 3.5 equiv of hexanoic acid for 48 h and in 40% yield from the reaction with 5 equiv of oleic acid for 168 h. No products of esterification on secondary oxygen atoms have previously been observed in reactions of this type with monosaccharides. Perhaps the hydroxyl group at O-2 of trehalose is more acidic than hydroxyls of monosaccharides because the anomeric oxygen is more electron withdrawing in a non-reducing disaccharide.

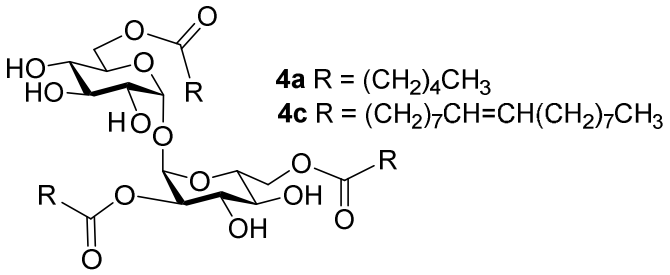

Figure 2. Structure of triester products

The most abundant component in the maradolipid mixture is 6-*O*-(13-methylmyristoyl)-6'-*O*-oleoyltrehalose (**5b**).[4] It was found that unsymmetrical derivatives of this type could be synthesized in good yields by reacting the monooleoyl derivative **2c** with 1.1 equiv of the fatty acid for extended reaction times at room temperature (see Scheme 2 and entries 4 and 6 of Table 2). Branched fatty acids such as 13-methylmyristic acid are available commercially from specialized

companies at great expense for the amounts necessary for synthetic purposes but here this acid was synthesized by the method of Foglia and Vail.[18] Compound **5b** has been synthesized previously in five-step routes using TMS ethers as temporary protecting groups.[10h,10i]

Scheme 2. Synthesis of nonsymmetric trehalose 6,6'-diesters

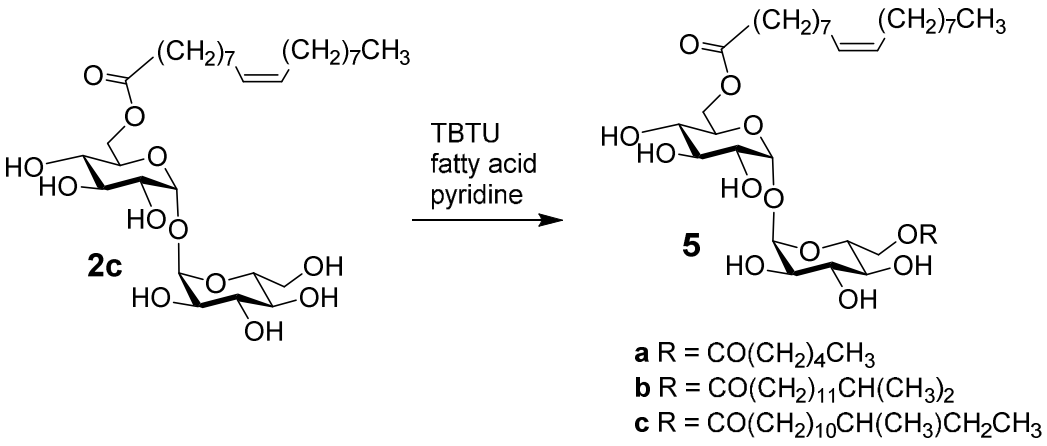

Table 2. Conditions and outcomes for the reactions of 6-*O*-oleoyltrehalose (2c) with fatty acids

entry	fatty acid (equiv)	TBTU (equiv)	time (h)	isolated yield (%)
1	hexanoic (1.1)	1.1	72	59[a]
2	13-methyltetradecanoic (1.1)	1.1	72	62[b]
3	13-methyltetradecanoic (1.1)	1.1	120	72[c]
4	13-methyltetradecanoic (1.1)	1.1	170	81
5	12-methyltetradecanoic (1.1)	1.1	72	54[d]
6	12-methyltetradecanoic (1.1)	1.1	170	79

[a]26% **2c** also isolated. [b]22% **2c** also isolated. [c]10% **2c** also isolated. [d]27% **2c** also isolated.

The ante derivative 6-*O*-(12-methyltetradecanoyl)-6'-*O*-oleoyltrehalose (**5c**) was prepared in the same way (see Scheme 2) from **2c** and 12-methylmyristic acid. This fatty acid was prepared in racemic form using a Wittig reaction of the Wittig reagent derived from 11-bromoundecanoic acid with 2-butanone followed by hydrogenation as previously.[19] Compound **5c** had never been synthesized previously and provides a sample for examining whether such compounds are part of the complex maradolipid mixture.

Conformational analysis. It was also of interest to determine whether the diverse biological activities of these compounds are influenced by alteration of the populations of the rotameric conformations adopted by the hydroxymethyl groups of trehalose caused by the interactions of the hydrophobic fatty acid alkyl groups. Trehalose itself adopts a conformation with both anomeric linkages adopting normal exo-anomeric conformations both in the solid-state[20] and in solution.[21] Hydroxymethyl rotameric populations have been discussed extensively[22] and have been determined carefully for glucose derivatives by making use of all H,H and C,H coupling constants of isotopically enriched derivatives (see Figure 3 for definition of rotamer names).[23] 4,6-Unsubstituted derivatives slightly prefer the *gt* conformer over the *gg* conformer with the *tg* conformer having a population of about 10% or slightly less.[22d,23] Barnett and Naidoo suggested that the preference for the *gt* conformer is due to direct and water-mediated hydrogen bonds between the O6 hydroxyl hydrogen and O5.[22c] In the solid state,[20] trehalose and its dihydrate are present in conformations where the two hydroxymethyl groups each adopt one of the two rotamers populated in solution, the *gg* and *gt* rotamers, giving rise to ^{13}C CP/MAS spectra with one signal for each of the 12 carbon atoms.[20a,24]

H5-H6 vicinal coupling constants were determined for the three monoesters (**2**), the three symmetrical diesters (**3**), and the two 2,6,6'-triesters (**4**) making the reasonable (all $\Delta\nu/J > 6$) assumption that the coupling patterns were first order. The values obtained are reported in Table 3.

The hydroxymethyl groups can adopt three conformers, termed the *gg*, *gt*, and *tg* rotamers, according to whether O5 and C4, respectively, are *gauche* or *trans* to O6 (see Figure 3). The

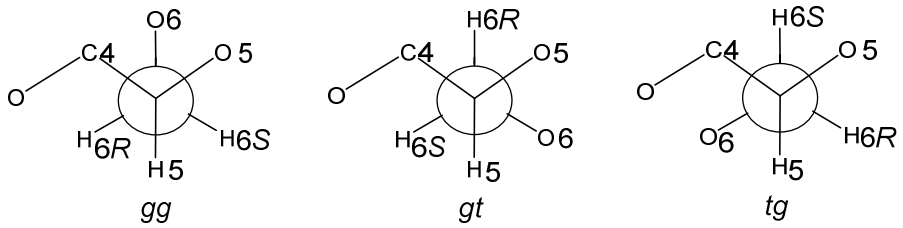

Figure 3. Newman projections from C5 to C6 illustrating the definitions of the three hydroxymethyl rotamers and atom labeling.

coupling constants were used to calculate rotameric populations using the values of the coupling constants for each rotamer calculated by Stennutz et al[23a] (see supporting information for the details). The percentage populations for each rotamer are listed in Table 4. The percentage populations for the monoesters and diesters are similar to those obtained for glucose previously[22d,23a] although the relative amounts of the *gg* rotamer appears to have increased slightly at the expense of the *gt* conformer. This is consistent with loss of the stabilizing effect for the *gt* rotamer of direct and hydroxylic solvent mediated hydrogen bonds between the O6 hydroxyl hydrogen and O5.[22c] Therefore, aggregation of the long lipophilic groups on O6 does not appear to influence the rotameric populations for the hydroxymethyl groups of these two classes of compounds significantly.

Table 3. Three-bond coupling constants observed for the C6 protons

Compound	$^3J_{5,6R}$ (Hz)	$^3J_{5,6S}$ (Hz)	$^3J_{5',6'R}$ (Hz)	$^3J_{5',6'S}$ (Hz)
2a	4.98	2.01	5.31	1.87
2b	5.08	2.00	5.53	2.04
2c	5.05	2.06	5.48	2.16
3a	5.20	2.11	5.20	2.11
3b	5.29	2.05	5.29	2.05
3c	5.28	2.11	5.28	2.11
4a	4.96	2.09	7.43	2.07
4c	4.87	2.07	7.90	1.89

Table 4. Percentage populations of rotamers

compound	% *gt* for C5C6 bond	% *gg* for C5C6 bond	% *tg* for C5C6 bond	% *gt* for C5'C6' bond	% *gg* for C5'C6' bond	% *tg* for C5'C6' bond
2a	43	50	6.6	48	47	5.0
2b	45	49	6.4	41	52	6.9
2c	44	49	7.1	48	44	8.4
3a	45	47	7.6	45	47	7.6
3b	47	47	6.9	47	47	6.9
3c	46	46	7.6	46	46	7.6
4a	43	50	7.4	70	23	6.6
4c	42	51	7.4	76	19	4.6

In contrast, for the 2,6,6'-triesters, the two sets of H5-H6 coupling constants were different; the set for the disubstituted glucose unit was similar to those observed for the mono and diesters but for the monosubstituted glucose residue, the $J_{5',6'R}$ value was between 2.2 and 2.7 Hz larger than those observed for all other residues. For this residue, the *gt* conformer was calculated to be more favored, to the extent of 70 and 76% of the rotamers for **4a** and **4c**, respectively, mostly at the expense of the *gg* conformer. This change probably is caused by intramolecular van der Waals interactions between the long chains of the 6'-ester and the 2-ester, favoring the rotamer where the C6' ester is turned toward the disubstituted glucose residue, as illustrated in Figure 4.

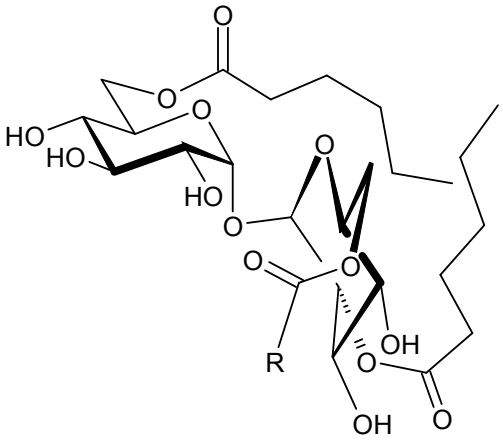

Figure 4. A conformation of **4a** (R = C_5H_{11}) illustrating how adopting the *gt* conformation for C5-C6 bond in the monosubstituted glucose ring allows van der Waals interactions between the long chains of the 6'-ester and the 2-ester

Conclusions

In summary, TBTU-promoted esterification of trehalose with one equivalent of fatty acids provides 6-*O*-monoesters in one step in good yields (~70%); two equivalents provides symmetrical 6,6'-diesters in fair yields. In comparison, enzymic esterification using a commercially available protease from *Bacillus subtilis* gave the monopalmitate **2b** in 84% yield but the monooleaoate **2c** in

55% yield using a quite long reaction time (12 days).[12] Other protecting-group-free chemical methods give monoesters in lower yields, of which, the Mitsunobu reaction is most efficient (47-61% yields).[15] The monoesters can be again monoesterified in the same way to provide non-symmetric 6,6'-*O*-diesters in two steps from trehalose in very good yields. Some of the diesters present in the complex mixture of maradolipids have been synthesized and the method allows expeditious synthesis of any desired structure.

Experimental Methods

General esterification procedures using TBTU

A. Use of trehalose (1). In an oven-dried round-bottomed flask equipped with a magnetic stir bar, a fatty acid (number of equiv given in Table 1) and TBTU (number of equiv given in Table 1) were dissolved in anhydrous pyridine (5 mL) and the resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. A solution of trehalose (amount used listed with the individual products) in dry pyridine (3 mL) was then injected into the reaction mixture via syringe and stirring was continued at the temperature and for the time given in Table 1. Pyridine was removed under vacuum and the resulting residue was purified using silica gel column chromatography with elution using a solvent gradient of 5 - 25% methanol in EtOAc - DCM (1:1).

B. Use of 6-*O*-oleoyl-α,α-trehalose (2c). In an oven-dried round-bottomed flask equipped with a magnetic stir bar, a fatty acid (1.1 equiv) and TBTU (1.1 equiv) were dissolved in anhydrous pyridine (5 mL) and the resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. A solution of 6-*O*-oleoyl-α,α-trehalose (**2c**) (amount used given with individual products) in dry pyridine (3 mL) was then injected into the reaction mixture via syringe and stirring was continued at rt for the time given in Table 2. Pyridine was removed under vacuum and the resulting residue was dissolved in EtOAc-THF (3:1, 20 mL). This solution was washed with saturated $NaHCO_3$ (2 x 3

mL), dried ($MgSO_4$), and concentrated to give a crude product which was purified using silica gel column chromatography with elution using a gradient of 5 - 25% methanol in EtOAc - DCM (1:1).

6-*O*-Hexanoyl-α,α-trehalose (2a). The title compound was synthesized using procedure A above with trehalose (1) (200 mg, 0.58 mmol) and hexanoic acid under conditions listed in Table 1, entry 1 and was obtained as a colorless solid (178 mg, 69% yield: R_F 0.20 [25% MeOH in EtOAc-DCM(1:1), v/v], mp 136 – 138 ^oC, lit[8g] mp 135-137 ^oC; ^1H NMR (CD_3OD) δ 0.91 (t, 3H, J = 7.0 Hz, Me), 1.28 - 1.36 (m, 4H, 2 x CH_2), 1.61 (m, 2H, CH_2CH_3), 2.33 (t, 2H, J = 7.5 Hz, CH_2CO), 3.34 - 3.38 (m, 2H, H-4, H-4'), 3.49 (dd, 2H, J = 3.9 Hz, 7.9 Hz, H-2, H-2'), 3.67 (dd, 1H, J = 5.2 Hz, 11.7 Hz, H-6'R), 3.79 - 3.83 (m, 4H, H-3, H-3', H-6', H-5'), 4.02 (ddd, 1H, $J_{4,5}$ = 10.1 Hz, $J_{5,6R}$ = 5.2 Hz, $J_{5,6S}$ = 2.1 Hz, H-5), 4.20 (dd, 1H, J = 5.2 Hz, 11.9 Hz, H-6R), 4.38 (dd, 1H, J = 2 Hz, 11.9 Hz, H-6S), 5.08 (d, 1H, J = 3.8 Hz, H-1'), 5.10 (d, 1H, J = 3.7 Hz, H-1); ^{13}C NMR δ 175.6 (C=O), 95.3, 95.2 (C-1, C-1'), 74.8, 74.6, 74.0, 73.33, (C-2, C-2', C-3, C-3'), 73.3, 72.0, 71.6 (C-4, C-4', C-5, C-5'), 64.5, 62.7 (C-6, C-6'), 35.1, 32.6, ($COCH_2$, $COCH_2CH_2$), 32.5, 26.0 (hexanoyl CH_2), 23.6 (CH_2CH_3), 14.4 (Me); HR ESI MS m/z calc for $C_{18}H_{32}NaO_{12}$: 463.1786; found: 463.1764.

In addition, some of compound **3a** (44 mg, 14% yield) was obtained.

6,6'-Di-*O*-hexanoyl-α,α-trehalose (3a). The title compound was synthesized using procedure A above with trehalose (200 mg, 0.58 mmol) and hexanoic acid under conditions listed in Table 1, entry 2 and was obtained as a colorless solid (198 mg, 63% yield): R_F 0.40 [20% MeOH in EtOAc-DCM(1:1), v/v], mp = 157 – 160 ^oC, lit[8g] mp 157.7-159.0 ^oC; ^1H NMR (CD_3OD) δ 0.91 (t, 6H, J = 6.0 Hz, 2 x Me), 1.30 - 1.37 (m, 8H, 4 x CH_2), 1.62 (m, 4H, CH_2CH_3), 2.34 (t, 4H, J = 7.0 Hz, CH_2CO), 3.33 (dd, 2H, J = 9.0 Hz, 10.0 Hz, H-4, H-4'), 3.47 (dd, 2H, J = 3.7 Hz, 9.7 Hz, H-2, H-2'), 3.77 (dd, 2H, J = 9.1 Hz, 9.6 Hz, H-3, H-3'), 4.01 (ddd, 2H, $J_{4,5}$ = 10.0 Hz, $J_{5,6R}$ = 5.2 Hz, $J_{5,6S}$ = 2.1 Hz, H-5, H-5'), 4.19 (dd, 2H, J = 5.2 Hz, 11.9 Hz, H-6R), 4.35 (dd, 2H, J = 2.1 Hz, 11.9 Hz, H-

6S), 5.03 (d, 2H, J = 3.7 Hz, H-1',H-1); ^{13}C NMR δ 175.5 (C=O), 95.3 (C-1, C-1'), 74.5, 73.1 (C-2, C-2', C-3, C-3'), 71.9, 71.5 (C-4, C-4', C-5, C-5'), 64.4 (C-6, C-6'), 35.0, 32.4 ($COCH_2$, $COCH_2CH_2$), 25.8 (hexanoyl CH_2), 23.4 (CH_2CH_3), 14.3 (Me); HR ESI MS m/z calc for $C_{24}H_{42}NaO_{13}$: 561.2518; found: 561.2517.

In addition, some of compound **2a** (49 mg, 20% yield) was obtained.

2,6,6'-Tri-*O*-hexanoyl-α,α-trehalose (4a). Following procedure A above using trehalose (325 mg, 0.95 mmol) with 3.5 equiv of hexanoic acid (385.8 mg) as in Table 1 entry 4, the reaction gave compounds **2a** (mg, 19% yield) and **3a** (mg, 48% yield) plus the title compound as a colorless syrup (119 mg, 20% yield): R_F 0.60 [5% MeOH in EtOAc-DCM(1:1), v/v]; ^{1}H NMR (CD_3OD) δ 0.91 (t, 9H, J = 6.0 Hz, 3 x Me), 1.30 - 1.39 (m, 12H, 6 x CH_2), 1.59-1.63 (m, 6H, CH_2CH_3), 1.95-2.45 (m, 6H, CH_2CO), 3.27 (dd, 1H, J = 9.0 Hz, 10.0 Hz, H-4'), 3.43 (dd, 1H, J = 9.1 Hz, 10.0 Hz, H-4), 3.47 (dd, 1H, J = 3.8 Hz, 9.8 Hz, H-2'), 3.69 (t, 1H, J = 9.0 Hz , H-3'), 3.77 (ddd, 1H, $J_{4',5'}$ = 9.6 Hz, $J_{5',6'R}$ = 7.2 Hz, $J_{5',6'S}$ = 2.0 Hz, H-5'), 3.99 (t, 1H, J = 9.1 Hz, H-3), 4.04 (ddd, 1H, $J_{4,5}$ = 7.0 Hz, $J_{5,6R}$ = 4.9 Hz, $J_{5,6S}$ = 2.0 Hz, H-5), 4.16 (dd, 1H, J = 7.0 Hz, 11.9 Hz, H-6'R), 4.23 (dd, 1H, J = 5.0 Hz, 12.0 Hz, H-6R), 4.29 (dd, 1H, J = 2.0 Hz, 11.8 Hz, H-6'S), 4.39 (dd, 1H, J = 2.0 Hz, 12.0 Hz, H-6S), 4.70 (dd, 1H, J = 3.6 Hz, 10.0 Hz, H-2), 5.02 (d, 1H, J = 3.7 Hz, H-1'), 5.18 (d, 1H, J = 3.6 Hz, H-1); ^{13}C NMR δ 175.52, 175.44, 174.8 (C=O), 95.3, 92.6 (C-1, C-1'), 74.8, 74.2, 73.0, 72.94 (C-2, C-2', C-3, C-3'),72.09, 72.04, 71.9, 71.6 (C-4, C-4', C-5, C-5'), 64.9, 64.2 (C-6, C-6'), 39.0, 35.1, 35.0, 34.96, 32.55, 32.52 ($COCH_2$, $COCH_2CH_2$), 25.9, 25.8, 25.76, 25.73, 25.66 (hexanoyl CH_2), 23.5 (CH_2CH_3), 14.5 (Me); HR ESI MS m/z calc for $C_{30}H_{52}NaO_{14}$: 659.3249; found: 659.3240.

6-*O*-Palmitoyl-α,α-trehalose (2b). The title compound was synthesized using procedure A above with trehalose (300 mg, 0.87 mmol) and palmitic acid under conditions listed in Table 1, entry 5 and

was obtained as a colorless solid (341 mg, 67% yield): R_F 0.33 [20% MeOH in EtOAc-DCM(1:1)], mp 156 – 159 ^oC, lit[12] mp 114- 116 ^oC.; ^1H NMR (CD_3OD) δ 0.90 (t, 3H, J = 6.0 Hz, Me), 1.29 - 1.37 (m, 24H, 12 x CH_2), 1.62 (m, 2H, CH_2CH_3), 2.34 (t, 2H, J = 7.2 Hz, CH_2CO), 3.30 - 3.33 (m, 2H, H-4, H-4'), 3.46, 3.47 (2 overlapping dd, 2H, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 9 Hz, H-2, H-2'), 3.67 (dd, 1H, J = 5.7 Hz, 12.1 Hz, H-6'R), 3.76 - 3.83 (m, 4H, H-3, H-3', H-6', H-5'), 4.01 (ddd, 1H, $J_{4,5}$ = 10.1 Hz, $J_{5,6R}$ = 5.1 Hz, $J_{5,6S}$ = 2.0 Hz, H-5), 4.19 (dd, 1H, J = 5.1 Hz, 11.9 Hz, H-6R), 4.35 (dd, 1H, J = 2.0 Hz, 11.9 Hz, H-6S), 5.07 (d, 1H, J = 3.7 Hz, H-1'), 5.10 (d, 1H, J = 3.7 Hz, H-1); ^{13}C NMR δ 175.6 (C=O), 95.4, 95.3 (C-1, C-1'), 74.8, 74.6, 74.1, 73.2, (C-2, C-2', C-3, C-3'), 73.4, 72.1, 71.6 (C-4, C-4', C-5, C-5'), 64.5, 62.8 (C-6, C-6'), 35.2, ($COCH_2$, $COCH_2CH_2$), 33.2, 30.9, 30.8, 30.6, 30.6, 30.4, 26.0 (palmitoyl CH_2), 23.9 (CH_2CH_3), 14.6 (Me); HR ESI MS m/z calc for $C_{28}H_{52}NaO_{12}$: 603.3351; found: 603.3335.

In addition, some of compound **3b** (71 mg, 14% yield) was obtained.

6,6'-Di-*O*-palmitoyl-α,α-trehalose (3b). The title compound was synthesized using procedure A above with trehalose (300 mg, 0.87 mmol) and palmitic acid under conditions listed in Table 1, entry 7 and was obtained as a gummy solid (480 mg, 66% yield): R_F 0.62 [20% MeOH in EtOAc-DCM(1:1), v/v] ; ^1H NMR (CD_3OD) δ 0.90 (t, 6H, J = 6.0 Hz, 2 x Me), 1.26 - 1.39 (m, 48H, 24 x CH_2), 1.61 (m, 4H, $\mathbf{CH_2}CH_3$), 2.34 (t, 4H, J = 7.2 Hz, CH_2CO), 3.30 - 3.34 (m, 2H, H-4, H-4'), 3.47 (dd, 2H, J = 3.7 Hz, 9.7 Hz, H-2, H-2'), 3.77 (t, 2H, J = 9.3 Hz, H-3, H-3'), 4.02 (ddd, 2H, $J_{4,5}$ = 10.0 Hz, $J_{5,6R}$ = 5.3 Hz, $J_{5,6S}$ = 2.1 Hz, H-5, H-5'), 4.19 (dd, 2H, J = 5.3 Hz, 11.9 Hz, H-6R, H-6'R), 4.35 (dd, 2H, J = 2.1 Hz, 11.9 Hz, H-6S, H-6'S), 5.04 (d, 2H, J = 3.7 Hz, H-1,H-1'); ^{13}C NMR δ 175.5 (C=O), 95.4 (C-1, C-1'), 74.7, 73.3 (C-2, C-2', C-3, C-3'), 72.1, 71.7 (C-4, C-4', C-5, C-5'), 64.6 (C-6, C-6'), 35.2, 33.2 ($COCH_2$, $COCH_2CH_2$), 30.96, 30.93, 30.8, 30.6, 30.6, 30.4, 26.2

(palmitoyl CH_2), 23.9 (CH_2CH_3), 14.6 (Me); HR ESI MS m/z calc for $C_{44}H_{82}NaO_{13}$: 841.5648; found: 841.5648.

In addition, some of compound **2b** (82 mg, 16% yield) was obtained.

6-*O*-Oleoyl-α,α-trehalose (2c). The title compound was synthesized using procedure A above with trehalose (300 mg, 0.87 mmol) and oleic acid under conditions listed in Table 1, entry 9 and was obtained as a colorless solid (346 mg, 65% yield): R_F 0.37 [20 % MeOH in EtOAc-DCM(1:1), v/v], mp become transparent at 120 – 130 °C, melted at 166 – 168 °C (lit[12] mp 165-167 °C) ; ^{1}H NMR (CD_3OD) δ 0.90 (t, 3H, J = 6.5 Hz, Me), 1.25 - 1.40 (m, 20H, 10 x CH_2), 1.45 - 1.61 (m, 2H, CH_2CH_3), 2.02 - 2.04 (m, 4H, 2 x CH_2CHCH), 2.34 (t, 2H, J = 7.0 Hz, CH_2CO), 3.30 - 3.32 (m, 2H, H-4, H-4'), 3.46, 3.47 (2 overlapping dd, 2H, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 8.8 Hz, $J_{1',2'}$ = 4.0 Hz, $J_{2',3'}$ = 9.2 Hz, H-2, H-2'), 3.67 (dd, 1H, J = 5.5 Hz, 12.1 Hz, H-6'R), 3.76 - 3.85 (m, 4H, H-3, H-3', H-6S', H-5'), 4.02 (ddd, 1H, $J_{4,5}$ = 10.1 Hz, $J_{5,6}$ = 5.1 Hz, $J_{5,6}$ = 2.1 Hz, H-5), 4.20 (dd, 1H, J = 5.1 Hz, 11.9 Hz, H-6R), 4.36 (dd, 1H, J = 2.1 Hz, 11.9 Hz, H-6S), 5.07 (d, 1H, J = 3.7 Hz, H-1'), 5.09 (d, 1H, J = 3.7 Hz, H-1), 5.35 (t, 2H, J = 4.8 Hz, CH=CH); ^{13}C NMR δ 175.4 (C=O), 130.9, 130.8 (CH=CH), 95.2, 95.1 (C-1, C-1'), 74.6, 74.4, 73.9, 73.19, 73.16, 71.91, 71.86, 71.4 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5'), 64.4, 62.6 (C-6, C-6'), 35.0, 33.1 ($COCH_2$, $COCH_2CH_2$), 30.8, 30.6, 30.5, 30.3, 30.2, 28.1, 26.0 (oleoyl CH_2), 23.7 (CH_2CH_3), 14.5 (Me); HR ESI MS m/z calc for $C_{30}H_{54}NaO_{12}$ 629.3507; found: 629.3527.

In addition, some of compound **3c** (115 mg, 15% yield) was obtained.

6,6'-Di-*O*-oleoyl-α,α-trehalose (3c). The title compound was synthesized using procedure A above with trehalose (150 mg, 0.43 mmol) and oleic acid under conditions listed in Table 1, entry 10 and was obtained as a gummy solid (260 mg, 66% yield): R_F 0.63 [20% MeOH in EtOAc-DCM(1:1), v/v]; ^{1}H NMR (CD_3OD) δ 0.94 (t, 6H, J = 6.5 Hz, 2 x Me), 1.32 - 1.45 (m, 40H, 20 x CH_2), 1.64 -

1.67 (m, 4H, CH_2CH_3), 2.05 - 2.07 (m, 8H, CH_2CHCH), 2.38 (t, 4H, J = 7.0 Hz, CH_2CO), 3.33 (dd, 2H, $J_{3,4}$ = 8.9 Hz, $J_{4,5}$ = 10.1 Hz, H-4, H-4'), 3.50 (dd, 2H, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.7 Hz, H-2, H-2'), 3.81 (dd, 2H, $J_{3,4}$ = 9.1 Hz, $J_{2,3}$ = 9.5 Hz, 2H, H-3, H-3'), 4.05 (ddd, 2H, $J_{4,5}$ = 10.1 Hz, $J_{5,6}$ = 5.1 Hz, $J_{5,6'}$ = 2.1 Hz, H-5, H-5'), 4.23 (dd, 2H, J = 5.1 Hz, 11.9 Hz, H-6R, H-6'R), 4.39 (dd, 2H, J = 2.1 Hz, 11.9 Hz, H-6S, H-6'S), 5.09 (d, 2H, J = 3.8 Hz, H-1',H-1), 5.35 (t, 4H, J = 4.8 Hz, 4H, CH=CH); ^{13}C NMR δ 175.5 (C=O), 131.1, 131.0 (CH=CH), 95.3, (C-1, C-1'), 74.7, 73.3, 72.1, 71.6 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5'), 64.6 (C-6, C-6'), 35.2, 33.2 ($COCH_2$, $COCH_2CH_2$), 31.0, 31.0, 30.8, 30.6, 30.5, 30.4, 28.3, 26.2 (oleoyl CH_2), 23.9 (CH_2CH_3), 14.6 (Me); HR ESI MS m/z calc for $C_{48}H_{86}NaO_{13}$: 893.5961; found: 893.5950.

In addition, some compound **2c** (48 mg, 18% yield) was obtained.

2,6,6'-Tri-O-oleoyl-α,α-trehalose (4c). The title compound was synthesized from trehalose (150 mg, 0.43 mmol) and 5 equiv of oleic acid (610 mg, 2.16 mmol) using procedure A under the conditions of Table 1 entry 13. Compound **3c** (mg, 48% yield) was obtained plus the title compound as a thick colorless syrup (198 mg, 40% yield): R_F 0.43 [1% MeOH in EtOAc-DCM(1:1), v/v]; ^{1}H NMR (CD_3OD) δ 0.90 (t, 9H, J = 6.5 Hz, 3 x Me), 1.19 - 1.35 (m, 60H, 30 x CH_2), 1.57-1.66 (m, 6H, CH_2CH_3), 1.99 - 2.07 (m, 12H, CH_2CHCH), 2.32-2.46 (m, 6H, CH_2CO), 3.24 (dd, 1H, J = 9.0 Hz, 10.0 Hz, H-4'), 3.44 (overlapped dd, 1H, H-4), 3.47 (dd, 1H, J = 3.8 Hz, 10.0 Hz, H-2'), 3.68 (t, 1H, J = 9.2 Hz, H-3'), 3.78 (ddd, 1H, $J_{4',5'}$ = 10.0 Hz, $J_{5',6'R}$ = 7.7 Hz, $J_{5',6'S}$ = 2.0 Hz, H-5'), 3.99 (t, 1H, J = 9.6 Hz, H-3), 4.07 (ddd, 1H, $J_{4,5}$ = 7.0 Hz, $J_{5,6R}$ = 4.5 Hz, $J_{5,6S}$ = 2.2 Hz, H-5), 4.15 (dd, 1H, J = 7.8 Hz, 11.7 Hz, H-6'R), 4.24 (dd, 1H, J = 5.0 Hz, 12.0 Hz, H-6R), 4.29 (dd, 1H, J = 1.9 Hz, 12.0 Hz, H-6'S), 4.39 (dd, 1H, J = 2.2 Hz, 12.0 Hz, H-6S), 4.70 (dd, 1H, J = 3.7 Hz, 10.0 Hz, H-2), 5.01 (d, 1H, J = 3.7 Hz, H-1'), 5.18 (d, 1H, J = 3.6 Hz, H-1), 5.33-5.36 (m, 6H, CH=CH); ^{13}C NMR δ 175.52, 175.38, 174.8 (C=O), 131.06, 131.02 (CH=CH), 95.3, 92.7 (C-1, C-1'), 74.9, 74.2, 73.0, 72.28 (C-2, C-2', C-3, C-3'),72.06, 72.00, 71.9, 71.6 (C-4, C-4', C-5, C-5'),

65.0, 64.2 (C-6, C-6'), 35.3, 35.1, 35.0 ($COCH_2$, $COCH_2CH2$), 33.2, 31.0, 30.8, 30.7, 30.6, 30.55, 30.47, 30.40. 28.3, 26.3, 26.2, 26.0 (oleoyl CH_2), 24.0 (CH_2CH_3), 14.7 (Me); HR ESI MS *m/z* calc for $C_{66}H_{118}NaO_{14}$ 1157.8414; found 1157.8451.

6-*O*-Hexanoyl-6'-*O*-oleoyl-α,α-trehalose (5a). The title compound was synthesized using procedure B above with 6-*O*-oleoyl-α,α-trehalose (**2c**) (100 mg, 0.17 mmol) and hexanoic acid (21 mg, 0.18 mmol) and was obtained as a gummy solid (69 mg, 59% yield): R_F 0.46 [20% MeOH in EtOAc-DCM(1:1), v/v]; ^{1}H NMR (CD_3OD) δ 0.89 – 0.93 (m, 6H, 2 x Me), 1.25 - 1.41 (m, 24H, 12 x CH_2), 1.61 - 1.64 (m, 4H, CH_2CH_3), 2.01 - 2.04 (m, 4H, CH_2CHCH), 2.34 (t, 4H, *J* = 7.3 Hz, CH_2CO), 3.32 - 3.35 (m, 2H, H-4, H-4'), 3.46 (dd, 2H, *J* = 3.8 Hz, 9.7 Hz, H-2, H2'), 3.77 (t, 2H, *J* = 9.3 Hz, H-3, H-3'), 3.99 - 4.03 (m, 2H, H-5, H-5'), 4.21 (dd, 2H, *J* = 5.4 Hz, 11.8 Hz, H-6R, H-6'R), 4.35 (dd, 2H, *J* = 2.0 Hz, 11.9 Hz, H-6S, H-6'S), 5.04 (d, 2H, *J* = 3.8 Hz, H-1',H-1), 5.35 (t, 2H, *J* = 4.8 Hz, CH=CH); ^{13}C NMR δ 175.62, 175.61 (C=O), 131.12, 130.97 (CH=CH), 95.4 (C-1, C-1'), 74.7, 73.3 (C-2, C-2', C-3, C-3'), 72.1, 71.6 (C-4, C-4', C-5, C-5'), 64.6 (C-6, C-6'), 35.2, 33.2 ($COCH_2$, $COCH_2CH_2$), 32.6, 30.99, 30.95, 30.8, 30.6, 30.5, 30.4, 30.3, 28.3, 26.2, 25.9 (CH_2), 23.9, 23.5 (CH_2CH_3), 14.6, 14.4 (Me); HR ESI MS m/z calc for $C_{36}H_{64}NaO_{13}$: 727.4239; found: 727.4216.

6-*O*-(13-Methyltetradecanoyl)-6'-*O*-oleoyl-α,α–trehalose (5b). The title compound was synthesized using procedure B above and the conditions in Table 2, entry 4 with 6-*O*-oleoyl-α,α–trehalose (150 mg, 0.24 mmol) and 13-methyltetradecanoic acid (66 mg, 0.27 mmol), prepared using a literature method.[18] A gummy solid (168 mg, 81% yield): R_F 0.51 [20% MeOH in EtOAc-DCM(1:1), v/v]; ^{1}H NMR (CD_3OD) δ 0.88 - 092 (m, 9H, 3 x Me), 1.06 - 1.12 (m, 2H, CH_2), 1.25 - 1.35 (m, 36H, 18 x CH_2), 1.53 (sept, 1H, *J* = 6.6 Hz, **CH**$(CH_3)_2$), 1.60 - 1.64 (m, 4H, **CH_2**CH_3), 2.01 - 2.05 (m, 4H, **CH_2**CHCH), 2.34 (t, 4H, *J* = 7.4 Hz, CH_2CO), 3.31 - 3.35 (m, 2H, H-4, H-4'),

3.43 (dd, 2H, *J* = 3.7 Hz, 9.8 Hz, H-2, H-2'), 3.78 (t, 2H, *J* = 9.5 Hz, H-3, H-3'), 3.99 - 4.03 (m, 2H, H-5, H-5'), 4.20 (dd, 2H, *J* = 5.3 Hz, 11.8 Hz, H-6R, H-6'R), 4.35 (dd, 2H, *J* = 1.7 Hz, 11.8 Hz, H-6S, H-6'S), 5.05 (d, 2H, *J* = 3.7 Hz, H-1, H-1'), 5.35 (t, 2H, *J* = 4.8 Hz, CH=CH); ^{13}C NMR δ 175.44, 175.41 (2 C=O), 130.9, 130.8 (CH=CH), 95.1 (C-1, C-1'), 74.5, 73.1 (C-2, C-2', C-3, C-3'), 71.9, 71.5 (C-4, C-4', C-5, C-5'), 64.4 (C-6, C-6'), 40.3 (CH), 35.1, 33.1 ($COCH_2$, $COCH_2CH_2$), 31.1, 30.9, 30.8, 30.8, 30.6, 30.5, 30.4, 30.3, 30.2, 29.2, 28.6, 28.2, 26.1 (CH_2), 23.8, 23.1 (CH_2CH_3), 14.9 (Me); HR ESI MS m/z calc for $C_{45}H_{82}NaO_{13}$: 853.5648; found: 853.5626.

6-*O*-(12-Methyltetradecanoyl)-6'-*O*-oleoyl-α,α-trehalose (5c). The title compound was synthesized using procedure B above under the conditions of Table 2, entry 6 with 6-*O*-oleoyl-α,α-trehalose (100 mg, 0.17 mmol) and 12-methyltetradecanoic acid (44 mg, 0.18 mmol) and was obtained as a gummy solid (108 mg, 79%): R_F 0.51 [20% MeOH in EtOAc-DCM(1:1), v/v]; ^{1}H NMR (DMSO) δ 0.80 - 0.90 (m, 9H, 3 x Me), 1.05 - 1.12 (m, 2H, CH_2), 1.16 -1.18 (m, 2H, CH_2), 1.20 - 1.35 (m, 37H, C*H*CH_2CH_3, 19 x CH_2), 1.48 - 1.51 (m, 2H, CH_2CH_3), 1.95 - 1.99 (m, 2H, C*H*$_2$CHCH), 2.26 (t, 4H, *J* = 7.0 Hz, CH_2CO), 3.10 - 3.14 (m, 2H, H-4, H-4'), 3.22 - 3.26 (m, 2H, H-2, H-2'), 3.52 - 3.57 (m, 2H, H-3, H-3'), 3.86 - 3.90 (m, 2H, H-5, H-5'), 4.02 (dd, 2H, *J* =5.7 Hz, 11.7 Hz, H-6R, H-6'R), 4.22 (m, 2H, H-6S, H-6'S), 4.70 (d, 2H, *J* = 5.5 Hz, OH), 4.82 (d, 2H, *J* =3.6 Hz, H-1,H-1'), 4.97 (d, 2H, *J* = 5.5 Hz, OH), 5.07 (d, 2H, *J* = 5.5 Hz, OH) 5.30 (t, 2H, *J* = 5 Hz, CH=CH); ^{13}C NMR δ 172.70, 172.68, (C=O), 129.6 (CH=CH), 93.3 (C-1, C-1'), 72.7, 71.4,71.3, 70.1, 70.0, 69.7 (C-2, C-2', C-3, C-3',C-4, C-4', C-5, C-5'), 63.1 (C-6, C-6'), 36.0, 33.8, 33.6, 31.3 ($COCH_2$, $COCH_2CH_2$), 29.4, 29.0, 28.9, 28.86, 28.74, 28.70, 28.6, 28.50, 28.46, 26.6, 26.5 (CH, CH_2), 24.3, 22.1 (CH_2CH_3), 13.9, 11.2 (Me); HR ESI MS m/z calc for $C_{45}H_{82}NaO_{13}$: 853.5648; found: 853.5620.

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Supporting Information Available General experimental procedures and ^{1}H and ^{13}C NMR spectra for all compounds prepared. This information is available free of charge via the Internet at http://pubs.acs.org.

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