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Synthesis of Maradolipid

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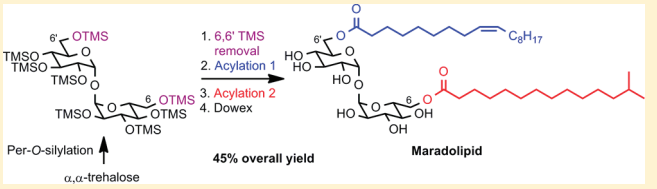
Supporting Information

ABSTRACT: The first synthesis of maradolipid, a unique dissymmetrically 6,6′-di-*O*-acylated trehalose glycolipid isolated from *C. elegans,* is accomplished in five steps starting from trehalose in 45% overall yield. The short synthesis relies on dissymmetrization of trehalose core via regioselective acylation of a 2,3,4,2′,3′,4′-hexa-*O*-TMS trehalose 6,6′-diol derivative as a key step.



Nematode *Caenorhabditis elegans* responds to extreme environmental stress by arresting its reproductive cycle and forming a highly stress resistant dauer larva. Very recently, it was discovered that during the transition from the reproductive larval stage to dauer larval stage, the worm synthesizes a novel class of 6,6′-di-*O*-acyltrehaloses, termed maradolipids.[1] The structure of the major component of maradolipids was assigned by using advanced 2D NMR spectroscopy as 6-*O*-(13-methylmyristoyl)-6′-*O*-oleoyltrehalose **1** (Figure 1).

Maradolipids are the first diacyltrehaloses found to be produced in animal kingdom. Intriguingly, they show striking structural resemblance with the glycolipid from *Mycobacterium tuberculosis* named cord factor (trehalose-6,6′-dimycolate, TDM), which is known to confer desiccation resistance to the bacteria by imparting stability to the lipid layer of the cell wall, and shows diverse immune activities.[2] In fact, such desiccation protection to membranes has also been observed for synthetic TDM analogues with symmetrical trehalose core linked to two simpler 15−18 carbon chains at 6,6′.[3] The structural similarity of maradolipids with TDM and their abundance (∼6% of the total dauer phospholipids) in dauer larvae are indicative of their putative biological functions. Although the dauer larvae formation pathway is well studied from biological perspectives, not much is known about the chemical changes that help the dauer larvae to resist and adapt the unfavorable environmental changes. The discovery of maradolipids is regarded as an important breakthrough, which may provide further clues in the pursuit of finding possible pathways of the stress associated chemical remodeling of cell. Toward understanding the molecular level details of the dauer resistance strategies and delineate the chemical pathway, structurally well-defined and chemically pure glycolipids are essential. However, the purified fractions of natural maradolipids show highly heterogeneous lipid composition. Thus, a short and efficient chemical synthesis of maradolipids is pivotal for obtaining pure glycolipids and their analogues in good purity and amounts for the structure−activity relationship studies. In this paper, we report the first total synthesis and structure confirmation of maradolipid **1**.

Maradolipid **1**, being a first example of a 6,6′-dissymmetrically substituted trehalose-based glycolipids, presents a challenge to synthetic chemists. Any route starting with commercially available α,α-trehalose **2** would essentially entail a differentiation of two primary alcohols as a key step. Regioselective protection of trehalose polyol has been the subject of intense research.[4−30] Synthesis of TDM analogues received immense attention, and procedures affording diesters[4−16] or monoesters[7−13] have been developed, both by nucleophilic displacement of 6,6′-dideoxy derivatives bearing sulfonates[5,13,15,16] or halides[4] at 6,6′positions and by acylations of 6,6′-diol of trehalose,[7−12,14] with its secondary hydroxyl groups protected as TMS[4−10] or benzyl[11−16] groups. Direct diacylations of unprotected trehalose using transesterification,[17] Mitsunobu conditions,[18,19] and tributylstannylation[20] are also reported. In addition, several protocols have been devised for selective protection of various hydroxyl groups to access more complex molecules containing dissymmetrically functionalized trehalose core.[21−30] Some of the routes, however, involve lengthy protection−deprotection steps affording mixtures of isomers, necessitating column chromatographic purification of the intermediates and resulting in poor overall efficiency.

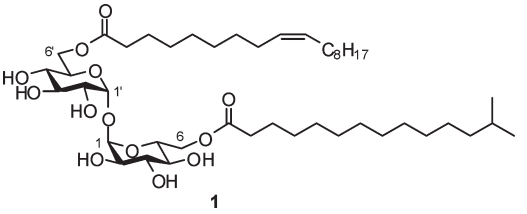


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Figure 1. Structure of maradolipid **1** from *C. elegans.*

In recent years, the trimethylsilyl group (TMS) has gained importance in carbohydrate synthesis, as evidenced by increasing number of publications involving this protection.[4−10,29−46] Hindsgaul first explored the use of TMS ethers in glycosylation reaction.[31,32] The unique reactivity of TMS protecting group is further endorsed by two seminal studies, Hung's TMSOTf

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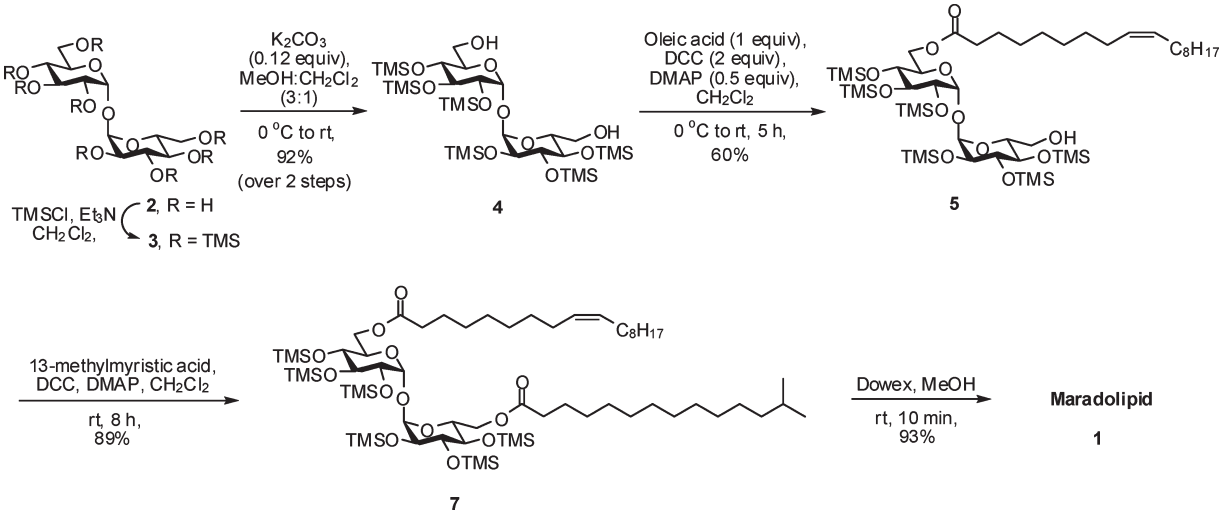
Scheme 1. Synthesis of Maradolipid 1



catalyzed one-pot protection of carbohydrate polyols[33−37] and Gervay-Hague's glycosyl iodide mediated one-pot stereoselective glycosylation protocols,[38−41] both involving per-*O*-silylated monosaccharides. Along with this, subsequent studies by Beau and co-workers first employing cat. $Cu(OTf)_2$ for one-pot protection of per-*O*-TMS monosaccharides[42] and recently extended to per-*O*-TMS trehalose using $FeCl_3 \cdot 6H_2O$,[30] speaks volumes about the stability of TMS groups under varied reaction conditions. We decided to use per-*O*-silylated trehalose **3** as a starting point for several reasons. TMS groups are easy to introduce; they improve the solubility of parent sugar in organic solvents and are fairly stable. More importantly, the primary TMS ethers could be hydrolyzed[4−10,43−45] or acetylated[46] selectively in the presence of secondary TMS ethers. Finally, global deprotection could be achieved instantly and cleanly under mild conditions without disturbing the double bonds.

It was envisaged that the known 2,3,4,2′,3′,4′-hexa-*O*-TMS trehalose 6,6′-diol[4,7] could be regioselectively monoacylated with oleic acid via a DCC-mediated coupling.[10] Sequential acylation using 13-methylmyristic acid followed by treatment with acidic resin would afford maradolipid **1**.

A short and efficient synthesis of maradolipid **1** is outlined in Scheme 1. Treatment of a suspension of anhydrous trehalose **2** in dichloromethane (CH_2Cl_2) with triethylamine (Et_3N) and trimethylsilyl chloride (TMSCl) afforded per-*O*-trimethylsilyl trehalose **3**. Employment of Et_3N as a base in place of pyridine[4,7,30] expedited the workup and evaporation. The crude compound **3**, which was free of any detectable impurities, was subjected to controlled alkaline hydrolysis using catalytic amount of potassium carbonate (K_2CO_3) in methanol/dichloromethane (3:1) solvent mixture to furnish the trehalose 6,6′-diol **4** in excellent yield (92% over two steps).[4] It should be noted that the use of dichloromethane as a cosolvent improved the solubility that allowed us to carry out the reaction with much lesser amount of methanol (∼1/10 volume) as compared to the original procedure, a feature which turned out to be useful for scale up operation. Regioselective acylation of the 6,6′-diol **4**, although reported in literature with a different set of carboxylic acids,[10] turned out to be notoriously difficult. Following the reported procedure, **4** was subjected to a DCC-mediated coupling with oleic acid. However, in our hands, the reaction proceeded sluggishly to afford the desired product in very low yields (12%). Use of EDCI[9,11] (3 equiv), as a coupling reagent, showed only marginal improvement as judged from the TLC analysis.

With these preliminary results, we decided to carry out a systematic study for selective acylation of 6,6′-diol **4**. The detailed reaction conditions including reagent equivalents, temperature, time, concentration, and product yields are presented in Table 1. First, toluene was added to an equimolar mixture of diol **4**, oleic acid, DCC, and catalytic amount of DMAP in the presence of 3 Å molecular sieves at 0 °C, and the reaction mixture was stirred at rt for 6 h and further heated to 60 °C for 12 h[10] to afford mono-oleate **5** (12%) along with the corresponding dioleate **6** (3%) and unreacted **4** (entry 1). The scenario could be improved (entry 2) by adding a premixed solution of oleic acid (1.15 equiv), DCC (3 equiv), and cat. DMAP to a solution of diol **4** and 3 Å MS in toluene at 0 °C, stirring the mixture at rt, and then heating it to 60 °C. This reaction offered mono-oleate **5** in a modest 34% yield along with the dioleate **6** (14%). Conducting the same reaction without molecular sieves did not show any significant effect on the yield (compare entries 2 and 3). Encouraged by these results, we changed the solvent to CH_2Cl_2 and conducted a series of reactions (entries 4−8) with increasing equivalents of reagents in CH_2Cl_2 at 0 °C to rt with overnight stirring. Among these, the best results were obtained when a combination of oleic acid (1.7 equiv), DCC (4 equiv), and DMAP (1 equiv) was used to furnish **5** (46%) as a major product along with minor **6** (16%) (entry 7). Prolonged stirring (∼2 d, entry 9) under these conditions offered marked improvements in yields of **5** (54%) and **6** (27%). In all cases, unused starting material **4** was recovered back. A characteristic feature of this reaction was its tendency to stall after a few hours. The observation that even after using 2 equiv of oleic acid only 23% of dioleate was formed (entry 8) encouraged us to try a reverse addition, wherein the diol solution was added to a premixed, well-stirred solution of oleic acid, DCC, and DMAP at 0 °C, and the stirring was continued for 5 h (entry 10). Gratifyingly, under the conditions, compound **5** was obtained in a satisfactory yield of 60% along with 17% of di and 14% recovered starting material. These conditions emerged as optimized conditions from our

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Table 1. Regioselective Acylation of 6,6′-Diol 4 with Oleic Acid

entry	acid (equiv)	DCC (equiv)	DMAP (equiv)	time (h)	solvent (mL/0.1 g)	*T* (°C)	Yield **5** (%)	Yield **6** (%)
1[a]	1	1	0.02	18	toluene (0.4)	0 to rt then 60	12	3
2[a]	1.15	3	0.16	36	toluene (0.4)	0 to rt then 60	34	14
3	1.15	3	0.16	28	toluene (1.2)	0 to rt then 60	35	12
4[a]	1	2.5	0.01	18	CH_2Cl_2 (1.2)	0 to rt	33	10
5	1.3	3.5	0.5	16	CH_2Cl_2 (1.7)	0 to rt	33	13
6	1.5	3.5	0.5	18	CH_2Cl_2 (1.7)	0 to rt	28	14
7	1.7	4	1	18	CH_2Cl_2 (3.0)	0 to rt	46	16
8	2	2	1	18	CH_2Cl_2 (3.0)	0 to rt	42	23
9	1.7	4	1	43	CH_2Cl_2 (3.0)	0 to rt	54	27
10	**1**	**2**	**0.5**	**5**	**CH_2Cl_2 (2.0)**	**0 to rt**	**60**	**17**
11	1	2	0.5	18	CH_2Cl_2 (2.3)	0 to rt	46	23

[a] 3 Å molecular sieves were used.

study. Running the same reaction for prolonged time (18 h, entry 11) resulted in an increase in the formation of di **6** (23%) and consequent decrease in the yield of **5** (46%). Compounds **4**, **5**, and **6** were well separated on TLC and easily purified by flash column chromatography. The secondary TMS ethers in **4**, **5**, and **6** are found to be stable to chromatographic purification conditions, and no special care is required.

With the mono-oleate **5** in hand, we proceeded further to complete the synthesis of **1** (Scheme 1). DCC-mediated coupling of alcohol **5** with readily accessible 13-methylmyristic acid[47] (13-methyltetradecanoic acid) furnished the requisite myristoyl derivative **7** (89%), which upon removal of TMS protecting groups using a brief treatment with Dowex 50WX8-200 ion-exchange resin in methanol cleanly afforded maradolipid **1** (93%). The spectral data of synthetic maradolipid **1** corroborated well with the reported one confirming its identity and structure (see the Supporting Information).[1]

In conclusion, we have completed first synthesis of maradolipid **1** starting from trehalose **2** in five steps and 45% overall yield. As per our knowledge, this is the first example of a dissymmetrically 6,6′-di-*O*-acylated trehalose derivative. Our synthesis capitalizes on the unique reactivity of TMS protecting groups. Regioselective acylation avoids lengthy protection-deprotection sequences improving the overall efficacy. All of the reactions are done either at rt or in ice bath and do not need any special apparatus. The short sequence may be executed in 3 d. The first synthesis of maradolipid has opened up a doorway to access pure maradolipids and related analogues to study their biological role in dauer larvae resistance as well as their immunological properties.

EXPERIMENTAL SECTION

General Methods. All reactions were conducted under a dry nitrogen atmosphere. Solvents (CH_2Cl_2 >99%, toluene >99%) were purchased in capped bottles and dried under CaH_2 or sodium. All other solvents and reagents were used without further purification. All glassware used was oven-dried before use. TLC was performed on precoated aluminum plates of silica gel 60 F254 (0.25 mm, E. Merck). Developed TLC plates were visualized under a short-wave UV lamp and by heating plates that were dipped in ammonium molybdate/cerium-(IV) sulfate solution. Silica gel column chromatography was performed using silica gel (100−200 and 230−400 mesh) and employed a solvent polarity correlated with TLC mobility. NMR experiments were conducted on 400 MHz instrument using $CDCl_3$ (D, 99.8%) or CD_3OD (D, 99.9%) as solvents. Chemical shifts are relative to the deuterated solvent peaks and are in parts per million (ppm). $^1H-^1H$ COSY was used to confirm proton assignments. Mass spectra were acquired in the ESI mode. Melting points were determined by capillary apparatus. Specific rotation experiments were measured at 589 nm (Na) and 25 °C unless otherwise mentioned. IR spectra were recorded on an FT-IR spectrometer using CsCl plates.

2,3,4,2′,3′,4′-Hexakis-*O*-(trimethylsilyl)-α,α-trehalose (4). Triethylamine (18.3 mL, 130.9 mmol) was added to a stirred suspension of trehalose (1.12 g, 3.27 mmol) in CH_2Cl_2 (15 mL). Reaction mixture was cooled to 0 °C, and trimethylsilyl chloride (4.87 mL, 39.26 mmol) was added to it. The solution was stirred at rt for 12 h. An additional 1.6 mL of trimethylsilyl chloride (13.08 mmol) was added at 0 °C, and the reaction was stirred for 4 h at rt. Solvents were evaporated on rotor, and the crude product was extracted in pet ether (50 mL × 5). The combined organic layer was dried on anhydrous sodium sulfate and concentrated in vacuo to obtain 2,3,4,6,2′,3′,4′6′-octakis-*O*-(trimethylsilyl)-α,α-trehalose **3** as a cream-colored solid (3.04 g). Compound **3** showed no impurity peaks in ^1H and ^{13}C NMR spectrum: $[\alpha]^{20}_D$ +111.0 (*c* 1, $CHCl_3$) [lit.[4] $[\alpha]^{20}_D$ +95.0 (*c* 1, $CHCl_3$)]; IR ($CHCl_3$) ν 2957, 1251, 1159, 1086, 1013, 906, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.91 (d, J = 3.1 Hz, 2H), 3.88 (t, J = 8.8 Hz, 2H), 3.80−3.77 (m, 2H), 3.71−3.64 (m, 4H), 3.42 (t, J = 9.3 Hz, 2H), 3.39 (dd, J = 3.1, 9.3 Hz, 2H), 0.14 (s, 18H), 0.13 (s, 18H), 0.11 (s, 18H), 0.09 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 94.5, 73.8, 73.4, 73.0, 71.9, 62.3, 1.3, 1.1, 0.3, −0.1; HRMS calcd for $C_{36}H_{86}O_{11}Si_8$ $[M + Na]^+$ 941.4222, found 941.4218.

To a cooled solution of compound **3** (3.04 g, 3.31 mmol) in MeOH and CH_2Cl_2 (19 mL, 3:1) at 0 °C was added K_2CO_3 (54 mg, 0.40 mmol), and the reaction was stirred for 15 min at 0 °C and then at rt for 1 h. Reaction was quenched by addition of acetic acid (0.7 mL). Solvents were evaporated in vacuo, and crude product was separated by column chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to afford compound **4** (2.38 g, 92%) as a white solid: $[\alpha]^{20}_D$ +120.4 (*c* 1, $CHCl_3$) [lit.[4] $[\alpha]^{20}_D$ +100 (*c* 1, $CHCl_3$)]; mp 114−115 °C [lit[4] 115−118 °C]; IR ν 3595, 3019, 2957, 1388, 1252, 1216, 1168, 1110, 1077, 1005, 965, 873, 845, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (d, J = 3.1 Hz, 2H, H-1, H-1′), 4.04 (t, J = 9.0 Hz, 2H, H-3, H-3′), 4.01 (dt, J = 3.1, 9.0 Hz, 2H, H-5, H-5′), 3.88−3.80 (m, 4H, H-6ab, H-6ab′), 3.63 (t, J = 9.0 Hz, 2H, H-4, H-4′), 3.57 (dd, J = 3.1, 9.0 Hz, 2H, H-2, H-2′), 1.97 (bt, 2H), 0.31 (s, 18H), 0.29 (s, 18H), 0.27 (s, 18H); ^{13}C NMR

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(100 MHz, $CDCl_3$): δ 94.8, 73.5, 73.2, 72.9, 71.5, 61.8, 1.2, 1.0, 0.3, 0.2; HRMS calcd for $C_{30}H_{70}O_{11}Si_6$ $[M + Na]^+$ 797.3432, found 797.3394.

6-*O*-Oleoyl-2,3,4,2′,3′,4′-hexakis-*O*-(trimethylsilyl)-α,α-trehalose (5). To a premixed, well-stirred solution of DCC (58 mg, 0.28 mmol), DMAP (9 mg, 0.07 mmol), and oleic acid (45 μL, 0.14 mmol) in CH_2Cl_2 (1 mL) was added a solution of **4** (105 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) at 0 °C in a slow, dropwise manner. The reaction mixture was gradually allowed to come to rt and stirred for 5 h. The reaction mixture was concentrated, and the crude product was purified by silica gel (230−400 mesh) column chromatography (1:9 ethyl acetate/petroleum ether, R_f = 0.3) of the residue to give pure compound **5** (84 mg, 60%) as a pale yellow liquid along with colorless liquid **6** (30 mg, 17%). **5**: $[\alpha]^{25}_D$ +81.5 (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν 3443, 2926, 2855, 1742, 1457, 1251, 1166, 1111, 1077, 1044, 1009, 965, 843, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.38−5.29 (m, 2H, CH═CH), 4.91 (t, *J* = 2.8 Hz, 1H, H-1), 4.90 (t, *J* = 2.8 Hz, 1H, H-1′), 4.29 (dd, *J* = 11.8, 1.2 Hz, 1H, H-6a), 4.06 (dd, *J* = 11.8, 4.5 Hz, 1H, H-6b), 4.02−3.99 (m, 1H, H-5), 3.91 (t, *J* = 9.0 Hz, 1H, H-3), 3.90 (t, *J* = 9.0 Hz, 1H, H-3′), 3.83 (td, *J* = 3.5, 6.6 Hz, 1H, H-5′), 3.69 (m, 2H, H-6a′, H-6b′), 3.48 (dd, *J* = 9.0, 2.4 Hz, 2H, H-4, H-4′), 3.45−3.41 (m, 2H, H-2, H-2′), 2.34 (dt, *J* = 7.5, 5.0 Hz, 2H), 2.05−1.98 (m, 4H), 1.76 (m, 1H, OH), 1.62 (m, 2H), 1.30−1.25 (m, 20H), 0.89−0.86 (m, 3H), 0.16 (s, 9H), 0.15 (s, 9H), 0.14 (s, 9H), 0.13 (s, 18H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 130.2, 129.9, 94.7, 94.5, 73.7, 73.5, 73.1, 72.9, 72.8, 72.1, 71.6, 70.9, 63.5, 61.8, 34.3, 32.1, 29.95, 29.90, 29.83, 29.80, 29.7, 29.5, 29.4, 29.3, 27.39, 27.35, 24.9, 22.9, 14.3, 1.2, 1.18, 1.1, 1.0, 0.3; HRMS calcd for $C_{48}H_{102}O_{12}Si_6$ $[M + Na]^+$ 1061.5885 found, 1061.5908.

6,6′-Di-*O*-oleoyl-2,3,4,2′,3′,4′-hexakis-*O*-(trimethylsilyl)-α,α-trehalose (6): $[\alpha]^{25}_D$ +71.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν 3020, 2856, 1733, 1252, 1215, 1168, 1111, 1078, 1044, 1008, 929, 897, 872, 847, 763, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.40−5.30 (m, 4H), 4.92 (d, *J* = 3.1 Hz, 2H), 4.28 (dd, *J* = 11.8, 1.8 Hz, 2H), 4.06 (dd, *J* = 11.8, 4.4 Hz, 2H), 4.02−3.98 (m, 2H), 3.91 (t, *J* = 9.0 Hz, 2H), 3.48 (t, *J* = 9.0 Hz, 2H), 3.44 (dd, *J* = 9.0, 3.1 Hz, 2H), 2.34 (dt, *J* = 7.5, 3.7 Hz, 4H), 2.08−1.98 (m, 8H), 1.70−1.59 (m, 4H), 1.30−1.26 (m, 40H), 0.89−0.86 (m, 6H), 0.15 (s, 18H), 0.14 (s, 18H), 0.13 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 130.2, 129.9, 94.6, 73.7, 72.8, 72.1, 70.9, 63.5, 34.3, 32.1, 29.95, 29.90, 29.84, 29.80, 29.7, 29.6, 29.5, 29.4, 29.3, 27.39, 27.35, 24.9, 22.9, 14.3, 1.2, 1.1, 0.4; HRMS calcd for $C_{66}H_{134}O_{13}Si_6$ $[M + H]^+$ 1303.8518, found 1303.8485.

13-Methyltetradecanoic Acid. 13-Methyltetradecanoic acid (13-methylmyristic acid) was prepared following a procedure reported by Foglia and Vail.[47] A Wittig olefination of isobuteraldehyde with a triphenylphosphonium iodide salt of 11-bromoundecanoate, followed by catalytic hydrogenation of the so-formed olefin and its concomitant hydrolysis afforded 13-methylmyristic acid in 47% overall yield: mp 51−51.7 °C (lit.[47] 51.5−52 °C); IR ($CHCl_3$) ν 3300 (br), 2925, 2854, 2254, 1965, 1708, 1466, 1412, 1384, 1288, 1096, 908, 733, 651, 544, 473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (t, *J* = 7.5 Hz, 2H), 1.63 (quin, *J* = 7.5 Hz, 2H), 1.51 (h, *J* = 6.6 Hz, 1H), 1.32−1.25 (m, 16H), 1.17−1.12 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 39.2, 34.3, 30.1, 29.9, 29.84, 29.79, 29.6, 29.4, 29.3, 28.2, 27.6, 24.9, 22.8; HRMS calcd for $C_{15}H_{30}O_2$ $[M + H]^+$ 243.2324, found 243.2319.

6-*O*-(13-Methyltetradecanoyl)-6′-*O*-oleoyl-2,3,4,2′,3′,4′-hexakis-*O*-(trimethylsilyl)-α,α-trehalose (7). A solution of compound **5** (105 mg, 0.10 mmol) in CH_2Cl_2 (2.5 mL) was added to a premixed, well-stirred solution of 13-methyltetradecanoic acid (49 mg, 0.20 mmol), DMAP (15 mg, 0.12 mmol), and DCC (90 mg, 0.41 mmol) in CH_2Cl_2 (1 mL) at rt. The reaction was allowed to stir for 8 h at rt. Solvents were evaporated in vacuo, and the crude product was purified by silica gel column chromatography (1:19 ethyl acetate/petroleum ether) to afford **7** as a colorless liquid (112 mg, 89%): $[\alpha]^{25}_D$ +72.9 (*c* 2, $CHCl_3$); IR ν 3021, 2927, 2855, 1737, 1461, 1252, 1216, 1167, 1078, 1007, 965, 872, 846, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36−5.33 (m, 2H, CH═CH), 4.92 (d, *J* = 3.1 Hz, 2H, H-1, H-1′), 4.28 (dd, *J* = 11.8, 1.8 Hz, 2H, H-6a, H-6a′), 4.06 (dd, *J* = 11.8, 4.4 Hz, 2H, H-6b, H-6b′), 4.02−3.98 (m, 2H, H-5, H-5′), 3.91 (t, *J* = 9.0 Hz, 2H, H-3, H-3′), 3.48 (t, *J* = 9.0 Hz, 2H, H-4, H-4′), 3.44 (dd, *J* = 3.2, 9.0 Hz, 2H, H-2, H-2′), 2.34 (dt, *J* = 3.6, 7.5 Hz, 4H), 2.02−1.98 (m, 4H), 1.68−1.61 (m, 4H), 1.51 (h, *J* = 6.5 Hz, 1H), 1.30−1.26 (m, 36H), 1.18−1.12 (m, 2H), 0.90−0.85 (m, 9H), 0.15 (s, 18H), 0.13 (s, 18H), 0.12 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.87, 173.84, 130.1, 129.9, 94.5, 73.7, 72.8, 72.1, 70.9, 63.5, 39.2, 34.3, 32.1, 30.1, 29.94, 29.88, 29.82, 29.79, 29.70, 29.6, 29.5, 29.4, 29.32, 29.30, 28.1, 27.6, 27.4, 27.3, 24.9, 22.8, 14.3, 1.2, 1.1, 0.3; HRMS calcd for $C_{63}H_{130}O_{13}Si_6$ $[M + Na]^+$ 1285.8025, found 1285.8010.

6-*O*-(13-Methyltetradecanoyl)-6′-*O*-oleoyl-α,α-trehalose/ Maradolipid (1).[1] Dowex-50WX8-200 ion-exchange resin (350 mg) was added to the solution of **7** (84 mg, 0.07 mmol) in methanol (20 mL) at rt and stirred for 15 min. Dowex was filtered using a sintered funnel and washed several times with methanol and concentrated to get a white crude product which was separated by column chromatography (1:19 ethyl acetate/methanol) to obtain a white solid (51 mg, 93%): $[\alpha]^{25}_D$ +70.7 (*c* 0.45, CH_3OH); IR ν 3399, 2926, 2854, 1739, 1459, 1033, 757 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 5.36−5.34 (m, 2H, CH═CH), 5.05 (d, *J* = 3.7 Hz, 2H, H-1, H-1′), 4.36 (dd, *J* = 11.9, 2.1 Hz, 2H, H-6a, H-6a′), 4.20 (dd, *J* = 11.9, 5.4 Hz, 2H, H-6b, H-6b′), 4.03−3.99 (m, 2H, H-5, H-5′), 3.78 (t, *J* = 9.5 Hz, 2H, H-3, H-3′), 3.47 (dd, *J* = 3.8, 9.5 Hz, 2H, H-2, H-2′), 3.35−3.30 (m, 2H, H-4, H-4′), 2.34 (t, *J* = 7.4 Hz, 4H), 2.04−2.01 (m, 4H), 1.64−1.60 (m, 4H), 1.53 (h, *J* = 6.6 Hz, 1H), 1.33−1.20 (m, 36H), 1.18−1.12 (m, 2H), 0.90−0.85 (m, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.6, 131.0, 130.9, 95.3, 74.6, 73.2, 72.0, 71.6, 64.5, 64.4, 40.4, 35.2, 33.2, 31.2, 30.96, 30.90, 30.87, 30.7, 30.6, 30.5, 30.4, 30.3, 29.3, 28.7, 28.3, 26.2, 23.8, 23.2, 14.6; HRMS calcd for $C_{45}H_{82}O_{13}$ $[M + Na]^+$ 853.5653, found 853.5674.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra for all compounds and $^1H-^1H$ COSY spectra for compounds **4**, **5**, **7**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Penkov, S.; Mende, F.; Zagoriy, V.; Erkut, C.; Martin, R.; Pässler, U.; Schuhmann, K.; Schwudke, D.; Gruner, M.; Mäntler, J.; Reichert-Müller, T.; Shevchenko, A.; Knölker, H.-J.; Kurzchalia, T. V. *Angew. Chem., Int. Ed.* **2010**, *49*, 9430–9435.

(2) Harland, C. W.; Rabuka, D.; Bertozzi, C. R.; Parthasarathy, R. *Biophys. J.* **2008**, *94*, 4718–4724 and references cited therein.

(3) Harland, C. W.; Botyanszki, Z.; Rabuka, D.; Bertozzi, C. R.; Parthasarathy, R. *Langmuir* **2009**, *25*, 5193–5198.

(4) Toubiana, R.; Das, B. C.; Defaye, J.; Mompon, B.; Toubiana, M.-J. *Carbohydr. Res.* **1975**, *44*, 308–312.

(5) Johnson, D. A.; Livesay, M. T. *J. Carbohydr. Chem.* **1998**, *17*, 969–974 and references cited therein.
(6) Rønnow, T. E. C. L.; Meldal, M.; Bock, K. *Carbohydr. Res.* **1994**, *260*, 323–328.
(7) Gensler, W. J.; Alam, I. *J. Org. Chem.* **1977**, *42*, 130–135.
(8) Gensler, W. J.; Chhatwal, V. K.; Alam, I.; Constantino, E.; Tarnowski, G. S.; Pimm, M. V.; Baldwin, R. W. *Cancer Immunol. Immunother.* **1980**, *9*, 101–109.
(9) Al Dulayymi, J. R.; Baird, M. S.; Maza-Iglesias, M.; Beken, S. V.; Grooten, J. *Tetrahedron Lett.* **2009**, *50*, 3702–3705.
(10) Datta, A. K.; Takayama, K.; Nashed, M. A.; Anderson, L. *Carbohydr. Res.* **1991**, *218*, 95–109 and references cited therein.
(11) Nishizawa, M.; Yamamoto, H.; Imagawa, H.; Barbier-Chassefière, V.; Petit, E.; Azuma, I.; Papy-Garcia, D. *J. Org. Chem.* **2007**, *72*, 1627–1633.
(12) Yoshimoto, K.; Wakamiya, T.; Nishikawa, Y. *Chem. Pharm. Bull.* **1982**, *30*, 1169–1174.
(13) Liav, A.; Goren, M. B. *Carbohydr. Res.* **1986**, *155*, 229–235.
(14) Nishizawa, M.; Minagawa, R.; Garcia, D. M.; Hatakeyama, S.; Yamada, H. *Tetrahedron Lett.* **1994**, *35*, 5891–5894.
(15) Liav, A.; Goren, M. B. *Carbohydr. Res.* **1980**, *81*, C1–C3.
(16) Liav, A.; Goren, M. B. *Chem. Phys. Lipids* **1980**, *27*, 345–352 and references cited therein.
(17) Toubiana, R.; Toubiana, M.-J. *Biochimie* **1973**, *55*, 575–578.
(18) Bottle, S.; Jenkins, I. D. *J. Chem. Soc., Chem. Commun.* **1984**, 385.
(19) Jenkins, I. D.; Goren, M. B. *Chem. Phys. Lipids* **1986**, *41*, 225–235.
(20) Gama, Y. *J. Jpn. Oil Chem. Soc.* **1995**, *44*, 671–673.
(21) Birch, G. G. *J. Chem. Soc.* **1966**, 1072–1074.
(22) Liav, A.; Goren, M. B. *Carbohydr. Res.* **1984**, *127*, 211–216.
(23) Vicent, C.; Martin-Lomas, M.; Penades, S. *Carbohydr. Res.* **1989**, *194*, 308–314.
(24) Wallace, P. A.; Minnikin, D. E. *J. Chem. Soc., Chem. Commun.* **1993**, 1292–1293.
(25) Baer, H. H.; Wu, X. *Carbohydr. Res.* **1993**, *238*, 215–230.
(26) Lin, F. L.; van Halbeek, H.; Bertozzi, C. R. *Carbohydr. Res.* **2007**, *342*, 2014–2030.
(27) Guiard, J.; Collmann, A.; Gilleron, M.; Mori, L.; De Libero, G.; Prandi, J.; Puzo, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 9734–9738.
(28) Patel, M. K.; Davis, B. G. *Org. Biomol. Chem.* **2010**, *8*, 4232–4235.
(29) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Fan, H.-F.; Pai, C.-L.; Yang, W.-C.; Lu, L.-D.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2360–2362.
(30) Bourdreux, Y.; Lemétais, A.; Urban, D.; Beau, J.-M. *Chem. Commun.* **2011**, *47*, 2146–2148.
(31) Uchiyama, T.; Hindsgaul, O. *Synlett* **1996**, 499–501.
(32) Uchiyama, T.; Hindsgaul, O. *J. Carbohydr. Chem.* **1998**, *17*, 1181–1190.
(33) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Chang, K.-L.; Hung, S.-C. *Nature* **2007**, *446*, 896–899.
(34) Wang, C.-C.; Kulkarni, S. S.; Lee, J.-C.; Luo, S.-Y.; Hung, S.-C. *Nat. Protoc.* **2008**, *3*, 97–113.
(35) Chang, K.-L.; Zulueta, M. M. L.; Lu, X.-A.; Zhong, Y.-Q.; Hung, S.-C. *J. Org. Chem.* **2010**, *75*, 7424–7427.
(36) Huang, T. Y.; Zueletta, M. M. L.; Hung, S.-C. *Org. Lett.* **2011**, *13*, 1506–1509.
(37) Hu, Y.-P.; Lin, S.-Y.; Huang, C.-Y.; Zulueta, M. M. L.; Liu, J.-Y.; Chang, W.; Hung, S.-C. *Nature Chem.* **2011**, *3*, 557–563.
(38) Du, W.; Kulkarni, S. S.; Gervay-Hague, J. *Chem. Commun.* **2007**, 2336–2338.
(39) Kulkarni, S. S.; Gervay-Hague, J. *Org. Lett.* **2008**, *10*, 4739–4742.
(40) Kulkarni, S. S. Gervay-Hague, J. In *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiley-VCH: New York, 2008; pp 59−93.
(41) Schombs, M.; Park, F. E.; Du, W.; Kulkarni, S. S.; Gervay-Hague, J. *J. Org. Chem.* **2010**, *75*, 4891–4898.
(42) Francais, A.; Urban, D.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662–8665.
(43) Hurst, D. T.; McInnes, A. G. *Can. J. Chem.* **1965**, *43*, 2004–2011.
(44) Fernández, C.; Nieto, O.; Rivas, E.; Montenegro, G.; Fontenla, J. A.; Fernández-Mayoralas, A. *Carbohydr. Res.* **2000**, *327*, 353–365.
(45) Jervis, P. J.; Cox, L. R.; Besra, G. S. *J. Org. Chem.* **2011**, *76*, 320–323.
(46) Witschi, M. A.; Gervay-Hague, J. *Org. Lett.* **2010**, *12*, 4312–4315.
(47) Foglia, T. A.; Vail, P. D. *Org. Prep. Proc. Int* **1993**, *25*, 209–213.