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Synthesis of a *Mycobacterium tuberculosis* Tetra-acylated Sulfolipid Analogue and Characterization of the Chiral Acyl Chains Using Anisotropic NAD 2D-NMR Spectroscopy

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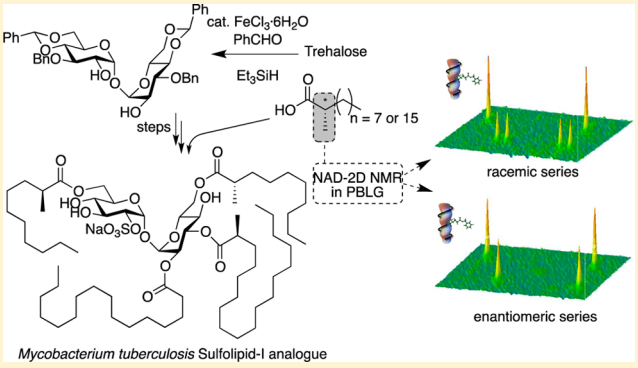
Supporting Information

ABSTRACT: Tetra-*O*-acylated sulfolipids are metabolites found in the cell wall of *Mycobacterium tuberculosis*, the causative agent of tuberculosis. Their role in pathogenesis remains, however, undefined. Here we describe a novel access to model tetra-*O*-acylated trehalose sulfate derivatives having simple acyl chains. The trehalose core was regioselectively protected using a tandem procedure with catalytic iron(III) chloride hexahydrate and further desymmetrized. Model chiral fatty acids, prepared by a zinc-mediated cross-coupling, were incorporated into the trehalose core. The enantiomeric excess of the chiral fatty acids has been measured by natural abundance deuterium (NAD) 2D-NMR spectroscopy in a polypeptide based chiral liquid crystal. The synthetic approach established for the model compounds can easily be developed for the preparation of other analogues and natural sulfolipids.



INTRODUCTION

Tuberculosis is still responsible for approximately two million deaths per year throughout the world, and especially in third world countries.[1,2] Sulfolipids **I** and **IV** are metabolites found in the cell wall of *Mycobacterium tuberculosis*, the bacteria responsible for this disease (Figure 1). Di-*O*-acylated sulfolipids **IV** (SL-IV)[3−6] were recently identified as new antigens able to control mycobacterium infection,[7−10] and tetra-*O*-acylated derivatives **I** (SL-I) are the most abundant sulfolipids found in the bacteria. These sulfolipids are *O*-acylated α,α-D-trehalose derivatives[11] bearing a sulfate moiety. More precisely, sulfolipid **I** are 2′-*O*-sulfate trehalose cores, functionalized by two hydroxyphthioceranoyl groups at the C-6 and C-6′ positions and esterified by a palmitic or stearic acid at the C-2 position and by a phthioceranoic acid at C-3. To the best of our knowledge, only one access to a tetra-*O*-acylated sulfolipid analogue starting from D-glucose was reported by Leigh and Bertozzi.[12] Herein we report our results for the synthesis of tetra-*O*-acylated sulfolipid **1** related to SL-I starting from C_2-symmetric α,α-D-trehalose[13] **2**. Our strategy is based on a tandem regioselective protection of α,α-D-trehalose followed by desymmetrization of this disaccharide.

RESULTS AND DISCUSSION

Synthesis of the Tetra-acylated Sulfolipid 1 and 16. We recently reported a tandem regioselective protection of carbohydrates with catalytic $Cu(OTf)_2$ or $FeCl_3{\cdot}6H_2O$ as Lewis acids.[14,15] The $FeCl_3{\cdot}6H_2O$-catalyzed tandem procedure applied to persilylated trehalose **3**, obtained after treatment of **2** with an excess of TMSCl in pyridine, provided symmetrical compound **4** in good yield,[15] in which the Lewis acid catalyzed two acetalizations and two regioselective reductive etherifications (Scheme 1). Nonsymmetrical mono-*O*-palmitoylated trehalose 7′, envisaged in a first approach as a key synthetic intermediate to the tetra-*O*-acylated sulfolipid, was provided directly by terminating this tandem procedure with a mono-*O*-acylation step with palmitoyl chloride. This gave however a complex reaction mixture from which mono-*O*-palmitoylated derivative 7′ was isolated in a 27% yield, separated from diol **4** (17% yield). To overcome the modest efficiency of this one-pot process, we chose the easy desymmetrization of diol **4** by mono-*O*-silylation with TBSOTf at a low temperature to give **5**

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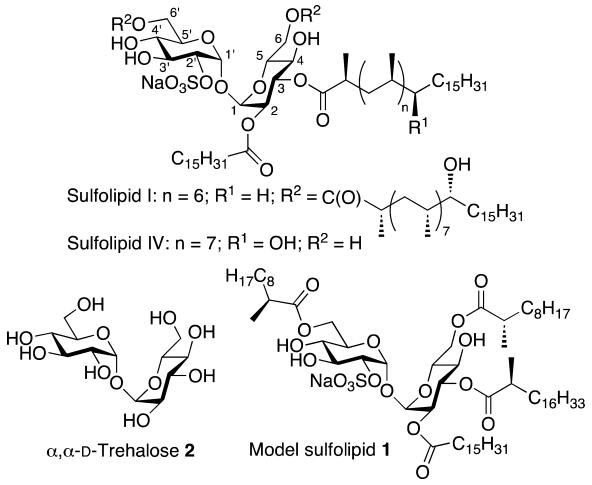


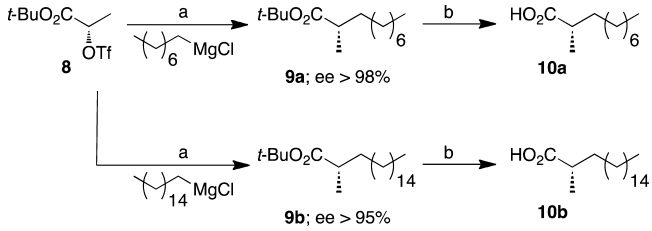
Figure 1. Structures of the major sulfolipids I and IV from *Mycobacterium tuberculosis* and model sulfolipid **1**.

in a 74% yield. During this step 3% of the starting material and 4% of the bis-*O*-silylated derivative were also isolated. The less hindered *O*-benzyl group was then regioselectively removed under catalytic hydrogen transfer conditions,[16] providing diol **6** in 65% yield. Small amounts of side products resulting from bis-3,3′-de-*O*-benzylation, mono-3′-de-*O*-benzylation, and hydrogenolysis of the 4,6-*O*-benzylidene acetals were detected by chromatography. Monoacylation using palmitic acid, DCC, and DMAP finally led selectively to compound **7** in 85% yield (Scheme 1).

Several approaches for the iterative syntheses of polydeoxypropionates have been developed.[17] For the rapid syntheses of the model enantiopure fatty acids **10a** and **10b**, we used the zinc-catalyzed enantiospecific cross-coupling strategy reported by Breit.[18,19] The Grignard reagents were easily coupled in high yields to methyl (L)-lactate triflate **8**, and chiral esters **9a**[18] and **9b**[20] obtained were quantitatively converted to carboxylic acids **10a** and **10b** by treatment with trifluoroacetic acid (Scheme 2).

The synthetic route to a tetra-*O*-acyled trehalose sulfate model was first tested with palmitic acid. The first acylation

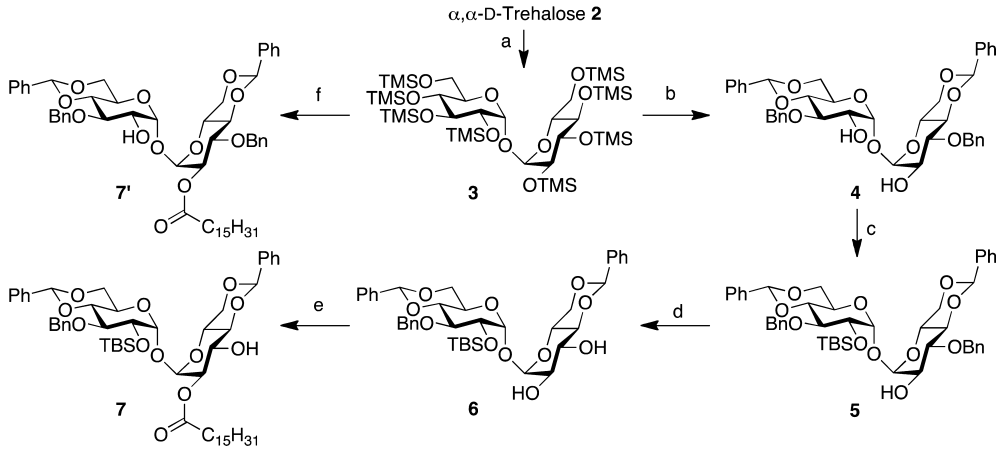
Scheme 2. Syntheses of Enantiopure 10a and 10b *via* a Zinc-Catalyzed Cross-Coupling[a]



[a]Reagents and conditions: (a) $C_8H_{17}MgCl$ or $C_{16}H_{33}MgCl$, 1.5 equiv; $ZnCl_2$, 15 mol %; THF; 0 °C to rt; overnight; **9a**: 98%, **9b**: 81%; (b) TFA, CH_2Cl_2; rt; 5 h; quantitative.

step with DCC and DMAP provided quantitatively bis-*O*-palmitate derivative **11a** (Scheme 3). The primary C-6 and C-6′ positions were selectively deprotected by regioselective reductive opening of the two 4,6-*O*-benzylidene acetals using $PhBCl_2$ in the presence of Et_3SiH,[21] affording diol **12a** in a 93% yield. Other known reductive conditions leading to the primary alcohol, such as BH_3·THF in the presence of $Cu(OTf)_2$, $AlCl_3$, or TMSOTf as Lewis acids, were tested on the di-*O*-acetate derivative of **4** as a model compound. These conditions led to complex mixtures, and only the use of $PhBCl_2/Et_3SiH$ was effective. Acylation of diol **12a** with excess palmitic acid gave tetra-*O*-palmitate derivative **13a** in a high yield (95%). Desilylation and sulfation by the SO_3·pyridine complex provided sulfate **15a** in 87% yield (two steps). Final deprotection by hydrogenolysis of the three *O*-benzyl groups of **15a** furnished model tetra-*O*-acylated sulfolipids **16** in 86% yields (Scheme 3). This optimized sequence of transformations was subsequently applied to acids **10a** and **10b**, with an expectation of a lower reactivity of these α-methylated carboxylic acids. We indeed noticed a lower efficiency with each step of the synthesis. Esterification of **7** with **10b** to ester **11b** (64% yield), regioselective reductive opening to diol **12b** (71% yield), and bis-esterification in the presence of an excess of **10a** led to **13a** (83% yield, Scheme 3). Finally, desilylation

Scheme 1. Preparation of Palmitoyled Trehalose Intermediate 7[a]



[a]Reagents and conditions: (a) TMSCl, 10 equiv; pyridine; 0 °C to rt; overnight; 96%; (b) PhCHO, 6 equiv; Et_3SiH, 2.2 equiv; $FeCl_3·6H_2O$, 5 mol %; CH_2Cl_2/CH_3CN: 4/1; 0 °C to rt, 3 h; 61%; (c) TBSOTf, 1.1 equiv; 2,6-lutidine, 2 equiv; CH_2Cl_2, −78 °C, 3.5 h; 74%; (d) HCO_2NH_4, 20 equiv; Pd/C, 10%; MeOH; 65 °C, 45 min; 65%; (e) $C_{15}H_{31}CO_2H$, 1.1 equiv; DCC, 1.5 equiv; DMAP, 1.7 equiv; CH_2Cl_2; rt, 4 h; 85%; (f) step b then $C_{15}H_{31}COCl$, 4 equiv; 50 °C overnight; 27%.

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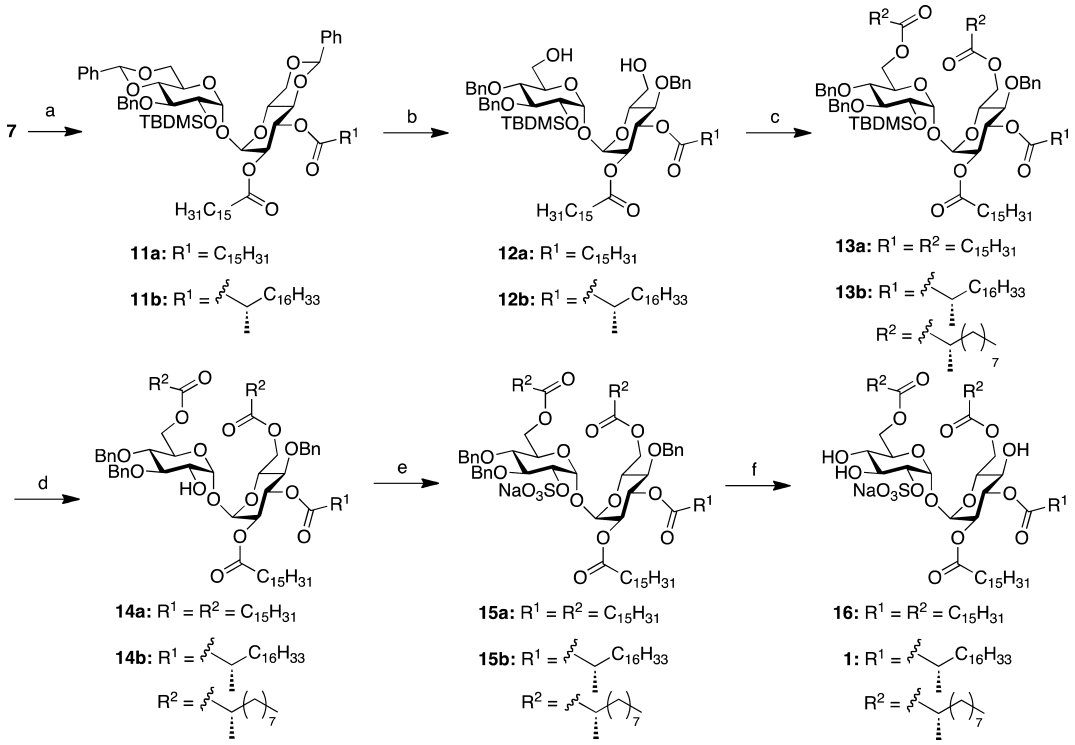
Scheme 3. Completion of the Synthesis of Model Sulfolipids[a]



[a]Reagents and conditions: (a) for **11a**: $C_{15}H_{31}CO_2H$, 1.3 equiv; DCC, 1.3 equiv; DMAP, 1.9 equiv; CH_2Cl_2; rt; 6 h; quantitative; for **11b**: **10b**, 1.1 equiv; DCC, 1.1 equiv; DMAP, 1.1 equiv; CH_2Cl_2; rt; 6 h; 64%; (b) $PhBCl_2$, 5 equiv; Et_3SiH, 10 equiv; CH_2Cl_2; −78 to −20 °C; 6.5 h; **12a**: 93%; **12b**: 71%; (c) for **13a**: $C_{15}H_{31}CO_2H$, 3 equiv; DCC, 2.5 equiv; DMAP, 1 equiv; CH_2Cl_2; rt; overnight; 95%; for **13b**: compound **10a**, 3.2 equiv; DCC, 3.2 equiv; DMAP, 3 equiv; CH_2Cl_2; rt; overnight; 83%; (d) TBAF, 2−3 equiv; THF; rt; 2 h; **14a**: 91%; **14b**: 85%; (e) [SO_3:pyridine], 5 equiv; pyridine; 90 °C; 2−3 h; then Amberlit IR120 Na; **15a**: 96%; **15b**: 93%; (f) H_2, 1 atm; Pd/C 5%; MeOH/CH_2Cl_2: 1/1; rt; 2h; **16**: 86%; **1**: 56%.

and sulfation (**15b** in a 79% yield) and deprotection provided model sulfolipid **1** in a 56% yield.

Anisotropic Natural Abundance Deuterium 2D-NMR Spectroscopy with Esters 9a and 9b. In order to determine the enantiomeric excess of chiral compounds **9a** and **9b**, and as a part of our work led by some of us on the spectral enantiodiscrimination of chiral compounds coupled with the analysis of the natural isotopic distribution of deuterium in fatty acids, we turned to the analytical potential of anisotropic NMR using polypeptide chiral liquid crystals (CLC) as enantiodiscriminating NMR solvents. Unlike isotropic solvents, all solute molecules dissolved in a liquid-crystalline media adopt an averaged orientational ordering. This ordering is generally different for two enantiomers when a CLC is used; hence it can be revealed by recording all magnetically active nuclei at a natural abundance level (^{1}H, ^{13}C, ^{2}H, ...).[22] As the enantiodiscrimination mechanisms mainly depend on molecular-shape recognition phenomena, no peculiar chemical groups of a chiral guest are requested to discriminate between enantiomers.[23,24] In contrast, the choice of order-sensitive NMR interaction, and thereby the associated nuclei, is important to optimize the magnitude of spectral discriminations. Among anisotropic interactions, the quadrupolar interaction associated to nuclei with $I > 1/2$ is the most sensitive one to molecular ordering differences.[23]

As the second isotope of hydrogen, deuterium ($I = 1$) is naturally present in all organic molecules and provides an efficient nuclear spy to reveal chiral discrimination. Although the average natural abundance of ^{2}H nuclei is equal to 1.55×10^{-2} % (Vienna Standard Mean Ocean Water value) compared to ^{1}H, routine (9.4 T) or higher field NMR spectrometers, equipped with classical or cryogenically cooled probes, allow recording natural abundance deuterium (NAD) NMR spectra in polypeptide CLC in about 15 h, with a satisfactory *S*/*N* ratio, thus achieving the determination of enantiomeric purity for a large range of chiral molecules. Combined with 2D-NMR experiments able to simplify the analysis of complex NAD spectra,[25] this approach was successfully applied for discriminating the *R*/*S* isomers of 3-methylhexane[23] or the enantioisotopomers[26] of saturated (prochiral) fatty acid methyl esters (FAME), such as methyl linoleate or methyl stearate.[27,28]

Considering its analytical potentials, this approach was used to evaluate the enantiopurity of **9a** and **9b** synthesized in enantioenriched series. Anisotropic NAD 2D-NMR spectra were recorded in the PBLG/pyridine chiral mesophase w(PBLG)/w(total) ≈ 23%); this system was shown to be a highly efficient CLC to discriminate enantiomers of weakly polar compounds such as FAME.[27,28] Although already described elsewhere, the basics of anisotropic NAD 2D-NMR spectroscopy, sample preparation, and tube compositions are given in the Supporting Information. Figure 2 shows a zoom of the tilted Q-COSY Fz 2D map of (*rac*)-**9a** centered on the signals of the methyl groups recorded at 92.1 MHz equipped with a 5-mm ^{2}H cryoprobe. The series of NAD 1D subspectra associated to the various ^{2}H sites of **9a** (and **9 b**) are reported in the Supporting Information.

For a given ^{2}H site, the presence of two quadrupolar doublets, denoted $\Delta\nu_Q(R \text{ or } S)$, centered around the same $\delta(^2H)$ indicated that the spectral discrimination at this particular site occurs. These kinds of spectral patterns were

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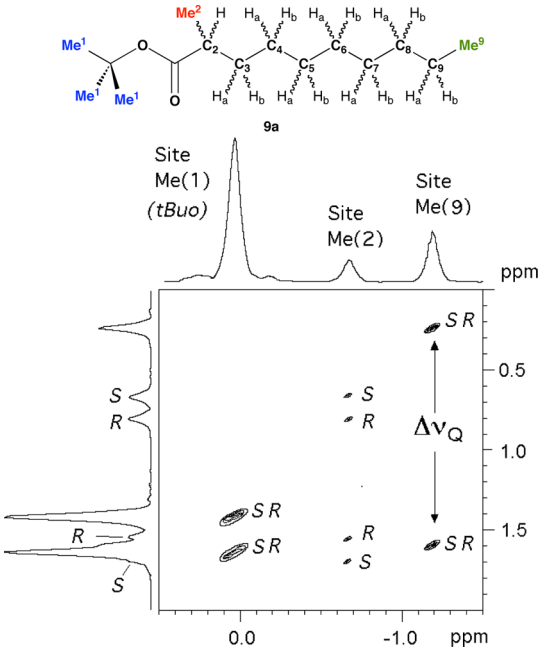

Figure 2. Expansion of the NAD tilted Q-COSY Fz 2D map of (*rac*)-**9a** (100 mg) recorded at 305 K in PBLG/pyridine (130 mg/365 mg) showing the methyl groups (Me^1, Me^2, and Me^9). The *R*/*S* assignment is based on the results obtained with an enantioenriched series (see text). The differences in peak intensity arise from the number of isotopomers contributing to the NAD signal (9 for Me^1, 3 for Me^2 and Me^9) and whether the enantiodiscrimination occurs or not (Me^2). The horizontal scale has no spectral meaning. The structure of **9a** is shown above, with the methylene and methyl group numbering used for the anisotropic NAD-NMR analysis.

typically observed on the 2D map of (*rac*)-**9a** at the methyl site 2 (see Figure 2), while no differentiation (a single doublet observed) occurred for the terminal methyl (Me^9) and the *t*-Bu methyl groups (Me^1). The absence of discrimination at these latter ^2H sites originates from different phenomena. For Me^9, the fast rotation of C−D directions in methyl combined with the complex conformational dynamic of the alkyl chain and the distance (≈ 10.4 Å) to the stereogenic center C-2 explains why this group is not a good spy in terms of chiral recognition mechanisms. In other words, for this specific position and from an orientational viewpoint, the molecule formally behaves as if it was of C_s symmetry on average instead of C_1 symmetry.[27,29] This qualitative interpretation is supported by three other experimental facts:[30] (i) the presence of two ^2H doublets at the CH_2 groups 8 and 9 when **9a** is dissolved in the CLC, while four doublets are expected for diastereotopic directions in methylene groups of a chiral flexible molecule; (ii) the presence of a single doublet for methylene groups 8 and 9 when the NAD spectra of **9a** is recorded in the achiral liquid crystal (PBG = 50% PBLG + 50% PBDG); (iii) the same number of ^2H doublets when the NAD spectrum of **9a** in enantiopure series (see below) is recorded in either the PBLG or PBG oriented system. For Me^1 of *t*-Bu, the distance to the C-2 remains reasonable (≈ 4.7 Å) and chiral discrimination might be expected. However the double rotation of C−D directions around the C−CH_3 and O−C(CH_3) axis leads also to a complex conformational dynamic that is incompatible with efficient enantiorecognition at these sites.

Finally it could be noted that compared to other ^2H sites (see the Supporting Information), the quadrupolar splittings measured on the methyl groups are generally among the smallest ones. This effect is due to the rotation of the methyl group around the C−CH_3 axis. Consequently, by calculating the average orientation, the order parameter associated to a methyl C−D bond appears equal to the order parameter of the C−C bond times $[3\cos^2(\pi - 2\theta_m) - 1]/2 = -1/3$, where θ_m is the so-called magic angle. The same phenomenon occurs for the three methyl groups of *t*-Bu, and hence the associated $\Delta\nu_Q$ is reduced again by a factor −1/3, leading to an averaged quadrupolar splitting of 26 Hz (absolute value).

Although other ^2H sites show enantiodiscriminations (C1, C2a,b), the Me^2 site is the most valuable position for a robust evaluation of the *e.e.*: (i) the *R*- and *S*-signals have baseline separation up to the peak's base; (ii) three isotopomers contribute to the NAD signal, thus increasing the *S*/*N* ratio by a factor of about 3 compared to other sites. Figure 3a and 3b

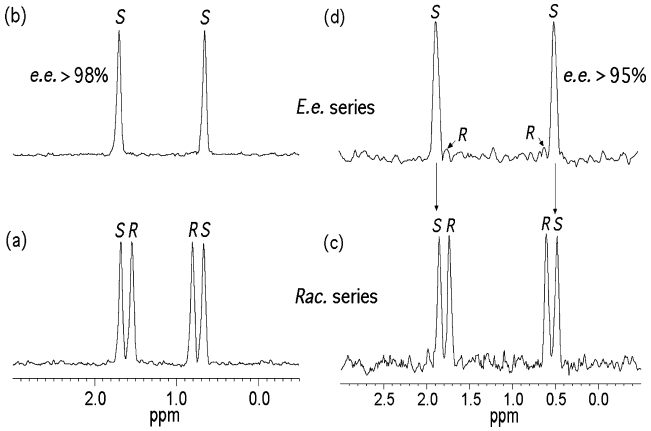

Figure 3. Comparison of NAD signals of Me^2 (columns extracted from the 2D maps) of (*R*/*S*)-**9a** and (*S*)-**9a** (left panel, a and b) and (*R*/*S*)-**9b** and (*S*)-**9b** (right panel, c and d). Spectra are plotted at the same vertical scale. The difference of *S*/*N* ratios between a/b and c/d spectra originates from the difference of MW of both solutes and the mass used (50 mg for **9b**).

report the NAD signals of Me^2 of **9a** obtained in the racemic series (a) and enantioenriched series (b). As seen a unique ^2H quadrupolar doublet is observed in Figure 3b. The total absence of visible ^2H signals (even on the 2D map) for the minor enantiomer (*R*) indicates that the enantiopurity of the mixture is at least over 98%. Taking into account the strategy to obtain an enantiopure chiral lipid, the remaining doublets correspond to the (*S*)-isomer. As both oriented samples containing (*rac*)-**9a** and (*S*)-**9a** were prepared with the same mass composition, the comparison of both NAD 1D-NMR subspectra allows assigning the *R*/*S* doublet recorded in the racemic mixture.

Anisotropic NMR methodology has been applied to determine the enantiopurity of **9b** (see Scheme 2) using the same NMR experimental conditions (except temperature: *T* = 315 K) and close to the sample compositions as those chosen for analyzing **9a**. Compared to **9a**, **9b** possesses eight additional methylene groups (namely an additional 16 inequivalent ^2H sites), both increasing its MW by ∼45%, and significantly complicating the analysis of their anisotropic NAD spectra, except for the methyl groups.[31] Not surprisingly, the orientational behaviors of the *t*-Bu methyl groups (Me^1), the methyl group bonded to the asymmetric carbon (Me^2), and the methyl group at the terminal position (Me^{17} for **9b**) in both chiral solutes are very similar in terms of the magnitude of $\Delta\nu_Q$. Only

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the NAD signals of methyl group 2 show two ^{2}H doublets, indicating that this ^{2}H site is spectrally enantiodiscriminated. Due to their molecular similarities, the absence of chiral discrimination of Me^1 and Me^{17} for **9b** originates for the same reasons described for **9a**.

The NAD signals of Me^2 obtained with (*rac*)-**9b** and (*S*)-**9b** in PBLG/pyridine are compared in Figure 3c and 3d. At first glance, a single doublet is observed in the enantioenriched mixture. A deeper examination of the NAD 1D subspectrum associated to Me^2 and the 2D maps[32] shows however a residual doublet weakly emerging from noise, corresponding to the minor *R*-isomer (see Figure S12 in the Supporting Information). Due to the very low *S*/*N* ratio, deconvolution of the NAD signals of the minor isomer was not possible, but we can safely estimate that the *e.e.* is over 95%.

CONCLUSION

This work highlights the usefulness of the $FeCl_3{\cdot}6H_2O$-mediated tandem regioselective protection of trehalose. We have achieved an efficient synthesis of model tetra-*O*-acylated sulfolipid **1** in 11 steps and in 4% overall yield starting from α,α-D-trehalose. Interestingly, enantiomeric excesses of monomethylated fatty acids were measured for the first time by NAD 2D-NMR spectroscopy in a polypeptide chiral liquid crystal. The analytical potential of this original approach and the quality of the first experimental NMR results obtained for **9a** and **9b** suggest that this tool should be efficient enough to analyze di- or trimethylated fatty acid esters. To access active compounds and natural metabolites from *Mycobacterium tuberculosis*, the syntheses of enantiopure polydeoxypropionates are currently in progress.

EXPERIMENTAL SECTION

General. All air sensitive reactions were carried out in oven-dried glassware under a slight positive pressure of argon. Dichloromethane, acetonitrile, methanol, and tetrahydrofuran were dried using a dry solvent station. TLC plates (Silica Gel 60 F_{254}) were visualized under UV (254 nm) and by staining in a 5% ethanolic sulfuric acid solution. Silica Gel 60 (40−63 μm) was used for column chromatography. Melting points are uncorrected. NMR spectra were recorded at 250, 300, or 360 MHz. Chemical shifts (in ppm) were determined relative to residual undeuterated solvent as an internal reference. Abbreviations of multiplicity were as follows: s (singlet), d (doublet), t (triplet), m (multiplet), b (broad). High-resolution mass spectra (positive or negative mode ESI) were performed with a tandem Q-TOF analyzer. For optical rotations, concentrations (*c*) are given in g/100 mL. Elemental analyses were obtained at the Service de Microanalyse of ICSN-CNRS (Gif-sur-Yvette).

Compounds **3** and **4** were synthetized according to reported procedures,[15] and analytical data were in agreement with those previously reported: **3**,[15,33] **4**.[15,34] Compounds **8** and **9a** were prepared according to the procedure reported by Breit,[18] and analytical data were in agreement with those reported.

3,3′-Di-*O*-benzyl-4,6;4′,6′-di-*O*-benzylidene-2′-*O*-*tert*-butyldimethylsilyl-α,α-D-trehalose (5). *tert*-Butyldimethylsilyl triflate (540 μL, 2.34 mmol, 1.0 equiv) was added slowly at −78 °C to a solution of compound **4** (1.63 g, 2.34 mmol) and 2,6-lutidine (550 μL, 4.72 mmol, 2.0 equiv) in dichloromethane (8.0 mL). The reaction mixture was stirred for 3 h at −78 °C and then warmed to room temperature for 1 h. Methanol (10 mL) was added and the resulted mixture was diluted with ethyl acetate and with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 9/1 to 7/3) to afford the expected compound **5** (1.40 g, 74%). White solid; mp 74−76 °C; $[\alpha]^{27}_D$ = +54 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.50−7.27 (m, 20H, H_{ar}), 5.58 (s, 1H, CH−Ph), 5.57 (s, 1H, CH−Ph), 5.22 (d, $J_{1',2'}$ = 4.0 Hz, 1H, $H_{1'}$), 5.05 (d, $J_{1,2}$ = 3.5 Hz, 1H, H_1), 5.01 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.96 (d, *J* = 11.2 Hz, 1H, CH_2−Ph), 4.79 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.76 (d, *J* = 11.2 Hz, 1H, CH_2−Ph), 4.32−4.23 (m, 2H, H_{6b}, $H_{6'b}$), 4.22−4.13 (m, 2H, $H_{5'}$, H_5), 3.98 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.2 Hz, 1H, $H_{3'}$), 3.92 (t, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, 1H, H_3), 3.82 (dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, 1H, H_2), 3.81−3.68 (m, 4H, $H_{2'}$, $H_{6'a}$, H_{6a}, $H_{4'}$), 3.67 (t, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, 1H, H_4), 0.96 (s, 9H, $SiC(CH_3)_3$), 0.12 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 138.7, 138.3, (C_q-Ar), 137.4, (2C, C_q−Ar), 128.9, 128.8, 128.4, 128.2, 128.1, 127.9, 127.8, 126.4, 126.2, 126.0 (20C, CH−Ar), 101.6 (CH−Ph), 101.2 (CH−Ph), 95.8 (C_1), 94.4 ($C_{1'}$), 82.5, 82.4 (C_4, $C_{4'}$), 78.6 (C_3), 78.1 ($C_{3'}$), 75.2 (CH_2−Ph), 74.8 (CH_2−Ph), 72.8 (C_2), 71.7 ($C_{2'}$), 69.0, 68.9 (C_6, $C_{6'}$), 63.3, 62.9 (C_5, $C_{5'}$), 26.0 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −4.3, −4.7 ($Si(CH_3)_2$). Anal. Calcd for $C_{46}H_{56}O_{11}Si$: C, 67.96; H, 6.94. Found: C, 67.99; H, 7.05. ESI HRMS for $C_{46}H_{56}O_{11}Si$ $[M+Na]^+$: Calcd 835.3484, Found 835.3453.

3′-*O*-Benzyl-4,6;4′,6′-di-*O*-benzylidene-2′-*O*-*tert*-butyldimethylsilyl-α,α-D-trehalose (6). A solution of compound **5** (398 mg, 0.490 mmol) in methanol (16 mL) containing $HCOONH_4$ (618 mg, 9.80 mmol, 20 equiv) and 10% Pd/C (50 wt %, 230 mg) was stirred at reflux for 45 min. After cooling to room temperature, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 90/10 then 80/20 then 75/25 then 70/30 then 60/40) to give the expected compound **6** (230 mg, 65%). White solid; mp 101−103 °C; $[\alpha]^{27}_D$ = +48 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.51−7.28 (m, 15H, H_{ar}), 5.57 (s, 1H, CH−Ph), 5.53 (s, 1H, CH−Ph), 5.22 (d, $J_{1,2}$ = 3.9 Hz, 1H, H_1), 5.08 (d, $J_{1',2'}$ = 3.9 Hz, 1H, $H_{1'}$), 4.95 (d, *J* = 11.1 Hz, 1H, CH_2−Ph), 4.77 (d, *J* = 11.1 Hz, 1H, CH_2−Ph), 4.31 (dd, $J_{5',6'b}$ = 4.8 Hz, $J_{6'a,6'b}$ = 10.2 Hz, 1H, $H_{6'b}$), 4.26 (dd, $J_{5,6b}$ = 4.8 Hz, $J_{6a,6b}$ = 10.2 Hz, 1H, H_{6b}), 4.16−4.06 (m, 2H, $H_{5'}$, H_5), 4.10 (t, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, 1H, H_3), 3.93 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.0 Hz, 1H, $H_{3'}$), 3.84 (dd, $J_{1',2'}$ = 3.9 Hz, $J_{2',3'}$ = 9.0 Hz, 1H, $H_{2'}$), 3.78−3.64 (m, 4H, H_2, $H_{4'}$, $H_{6'a}$, H_{6a}), 3.52 (t, $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz, 1H, H_4), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.12, 0.11 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 138.7, 137.3, 137.1 (3C, C_q−Ar), 129.3, 128.9, 128.3, 128.2, 128.1, 127.9, 127.4, 126.5, 126.0 (15C, CH−Ar), 102.3 (CH−Ph), 101.3 (CH−Ph), 95.3 ($C_{1'}$), 94.0 (C_1), 82.6 ($C_{4'}$), 81.2 (C_4), 78.5 ($C_{3'}$), 75.2 (CH_2−Ph), 72.7 ($C_{2'}$), 72.5 (C_2), 71.2 (C_3), 69.0, 68.9 (C_6, $C_{6'}$), 63.1, 63.0 (C_5, $C_{5'}$), 26.0 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −4.2, −4.7 ($Si(CH_3)_2$). Anal. Calcd for $C_{39}H_{50}O_{11}Si$: C, 64.80; H, 6.97. Found: C, 64.36; H, 7.13. ESI HRMS for $C_{39}H_{50}O_{11}Si$ $[M+Na]^+$: Calcd 745.3015, Found 745.2999.

3′-*O*-Benzyl-4,6;4′,6′-di-*O*-benzylidene-2′-*O*-*tert*-butyldimethylsilyl-2-*O*-palmitoyl-α,α-D-trehalose (7). To a solution of compound **6** (205 mg, 0.283 mmol) and palmitic acid (80 mg, 0.312 mmol, 1.1 equiv) in dichloromethane (10 mL) were added DCC (89.2 mg, 0.432 mmol, 1.5 equiv) and DMAP (53 mg, 0.432 mmol, 1.5 equiv). The mixture was stirred for 5 h at room temperature, filtered through Celite, and rinsed with ice-cold dichloromethane. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 95/5 then 90/10) to afford the expected compound **7** (224 mg, 82%). White solid; mp 89−91 °C; $[\alpha]^{27}_D$ = +48 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.52−7.28 (m, 15H, H_{ar}), 5.56 (s, 1H, CH−Ph), 5.54 (s, 1H, CH−Ph), 5.38 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 5.04 (d, $J_{1',2'}$ = 3.6 Hz, 1H, $H_{1'}$), 4.94 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.93 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.6 Hz, 1H, H_2), 4.77 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.34 (t, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, 1H, H_3), 4.20−4.12 (m, 3H, H_{6b}, $H_{6'b}$, H_5), 3.93 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.3 Hz, 1H, $H_{3'}$), 3.91 (m, 1H, $H_{5'}$), 3.81 (dd, $J_{1',2'}$ = 3.6 Hz, $J_{2',3'}$ = 9.3 Hz, 1H, $H_{2'}$), 3.76 (t, $J_{6,6'}$ = $J_{5,6}$ = 9.6 Hz, 1H, H_{6a}), 3.71 (t, $J_{6'a,6'b}$ = $J_{5',6'a}$ = 9.6 Hz, 1H, $H_{6'a}$), 3.66 (t, $J_{3',4'}$ = $J_{4',5'}$ = 9.3 Hz, 1H, $H_{4'}$), 3.61 (t, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, 1H, H_4), 2.48 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 1.26−1.19 (m, 24H), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.89 (t, *J* = 7.0 Hz, 3H, CH_3), 0.10 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 173.6 (C═O), 138.7, 137.4, 137.0 (C_q-Ar), 129.3,

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128.8, 128.3, 128.1, 128.0, 127.9, 127.4, 126.5, 126.0 (15C, CH−Ar), 102.4 (CH−Ph), 101.3 (CH−Ph), 95.3 ($C_{1'}$), 91.8 (C_1), 82.4 ($C_{4'}$), 81.6 (C_4), 78.6 ($C_{3'}$), 75.2 (CH_2−Ph), 72.9 (C_2), 72.6 ($C_{2'}$), 68.9, 68.8 (C_6 and $C_{6'}$), 68.5 (C_3), 63.2 ($C_{5'}$), 62.7 (C_5), 34.1 (CH_2), 31.9 (CH_2), 29.7, 29.6, 29.5, 29.4, 29.2, 29.1 (10C, CH_2), 26.0 ($SiC(CH_3)_3$), 24.7 (CH_2), 22.7 (CH_2), 18.1 ($SiC(CH_3)_3$), 14.1 (CH_3), −4.2, −4.8 ($Si(CH_3)_2$). Anal. Calcd for $C_{55}H_{80}O_{12}Si$: C, 68.72; H, 8.39. Found: C, 68.59; H, 8.61. ESI HRMS for $C_{55}H_{80}O_{12}Si$ $[M+Na]^+$: Calcd 983.5311, Found 983.5280.

3,3′-Di-*O*-benzyl-4,6;4′,6′-di-*O*-benzylidene-2-*O*-palmitoyl-α,α-D-trehalose (7′). To an ice-cold solution of the per-*O*-silylated α,α-D-trehalose **3** (100 mg, 0.109 mmol) and benzaldehyde (66 μL, 0.654 mmol, 6 equiv) in dichloromethane (200 μL) were added dropwise a solution of $FeCl_3$·$6H_2O$ in acetonitrile (50 μL of a 111 mM solution; 5 mol %) and triethylsilane (38 μL, 0.240 mmol, 2.2 equiv). The reaction was stirred for 3 h at room temperature. Palmitoyl chloride (133 μL, 0.136 mmol, 4 equiv) was then added. The solution was stirred overnight at 50 °C and treated with TBAF (700 μL, 1 M solution in THF). The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate: 90/10 to 50/50) to give the expected product 7′ as a colorless syrup (28 mg, 27%). $[\alpha]^{27}_D$ = +61 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.55−7.28 (m, 20H, H_{ar}), 5.63 (s, 1H, CH−Ph), 5.60 (s, 1H, CH−Ph), 5.37 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 5.17 (d, $J_{1',2'}$ = 3.6 Hz, 1H, $H_{1'}$), 5.06 (d, *J* = 11.5 Hz, 1H, CH_2−Ph), 5.01 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.7 Hz, 1H, H_2), 4.97 (d, *J* = 11.9 Hz, 1H, CH_2−Ph), 4.79 (d, *J* = 11.5 Hz, 1H, CH_2−Ph), 4.77 (d, *J* = 11.9 Hz, 1H, CH_2−Ph), 4.33 (dd, $J_{5,6b}$ = 4.5 Hz, $J_{6a,6b}$ = 10.0 Hz, 1H, H_{6b}), 4.26−4.16 (m, 2H, H_5, $H_{6'b}$), 4.12 (t, $J_{2,3}$ = $J_{3,4}$ = 9.7 Hz, 1H, H_3), 3.95 (m, 1H, $H_{5'}$), 3.94 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.4 Hz, 1H, $H_{3'}$), 3.82−3.67 (m, 5H, $H_{2'}$, H_{6a}, $H_{6'a}$, H_4, $H_{4'}$), 2.40 (t, *J* = 7.2 Hz, 2H, CH_2), 1.64 (m, 2H, CH_2), 1.42−1.12 (m, 24H, CH_2), 0.91 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 173.0 (C=O), 138.5, 138.3, 137.3 (4C, C_q−Ar), 128.9, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 127.5, 126.0, 125.9 (20C, CH−Ar), 101.2 (2C, CH−Ph), 95.1 ($C_{1'}$), 93.1 (C_1), 82.1, 81.9 (C_4, $C_{4'}$), 78.7 ($C_{3'}$), 76.3 (C_3), 75.0, 74.9 (CH_2−Ph), 72.4 (C_2), 71.5 ($C_{2'}$), 68.8 (2C, C_6, $C_{6'}$), 63.5 ($C_{5'}$), 63.0 (C_5), 34.1 (CH_2), 31.9 (CH_2), 29.7, 29.6, 29.5, 29.3, 29.2 (10C, CH_2), 24.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3). Anal. Calcd for $C_{56}H_{72}O_{12}$: C, 71.77, H, 7.74. Found: C, 71.33, H, 7.78. ESI HRMS for $C_{56}H_{72}O_{12}$ $[M+Na]^+$: Calcd 959.4916, Found 959.4884.

(*S*)-*tert*-Butyl 2-Methyloctadecanoate (9b). To a solution of compound **8** (1.22 g, 4.39 mmol) in dry THF (11 mL) under an argon atmosphere, were successively added at 0 °C a solution of anhydrous $ZnCl_2$ in dry THF (1 mL of a 0.65 M solution, 15 mol %) and $C_{16}H_{33}MgCl$[35] (6 mL of a 1.1 M solution, 1.5 equiv). The reaction mixture was stirred for 3 h at 0 °C and diluted with *n*-pentane. A saturated aqueous NH_4Cl solution was added, the aqueous layer was extracted with *n*-pentane, and the combined organic layers were carefully concentrated. The crude product was purified by silica gel chromatography (*n*-pentane/Et_2O: 50/1). The solvents were removed under atmospheric pressure to give the expected compound **9b** as a colorless oil (1.26 g, 81%) (*ee* > 95%, see above). $[\alpha]^{20}_D$ = +8 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.29 (m, 1H, CH), 1.65−1.55 (m, 1H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 1.35−1.20 (m, 29H, CH_2), 1.08 (d, *J* = 6.9 Hz, 3H, CH_3), 0.88 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 176.3 (C=O), 79.6 ($C(CH_3)_3$), 40.6 (CH), 33.9 (CH_2), 31.9, 29.7, 29.6, 29.5, 29.4, 28.1, 27.2, 22.7 (14C, CH_2), 28.1 ($C(CH_3)_3$), 17.1 (CH_3), 14.1 (CH_3). ESI HRMS for $C_{23}H_{46}NaO_2$ $[M+Na]^+$: Calcd 377.3390, Found 377.3359.

(*S*)-2-Methyldecanoic Acid (10a). To a solution of **9a** (312 mg, 1.29 mmol) in dichloromethane (10 mL) at room temperature was added dropwise TFA (1.54 g, 13.5 mmol, 10.5 equiv). The solution was stirred for 5 h at room temperature, and the mixture was evaporated to dryness. The residue was coevaporated with toluene and dichloromethane to afford the expected compound **10a**[36] (236 mg, 95%) as a yellow oil. $[\alpha]^{20}_D$ = +12 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.24 (bs, COOH), 2.47 (m, 1H, CH), 1.69 (m, 1H, CH_2), 1.45 (m, 1H, CH_2), 1.37−1.22 (m, 12H, CH_2), 1.18 (d, 3H, *J* = 6.9 Hz, CH_3), 0.88 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 182.2 (C=O), 39.3 (CH), 33.5, 31.9, 29.5, 29.4, 29.2, 27.1, 22.7 (CH_2), 16.8 (CH_3), 14.1 (CH_3); ESI HRMS for $C_{11}H_{21}O_2$ $[M-H]^-$: Calcd 185.1547, Found 185.1544.

(*S*)-2-Methyloctadecanoic Acid (10b). To a solution of **9b** (501 mg, 1.41 mmol) in dichloromethane (10 mL) at room temperature was added dropwise TFA (1.54 g, 13.4 mmol, 9.5 equiv). The solution was stirred for 5 h at room temperature, and the mixture was evaporated to dryness. The residue was coevaporated with toluene and dichloromethane to afford the expected compound **10b** (421 mg, 99%) as a white solid. $[\alpha]^{20}_D$ = +7 (*c* 1.0, $CHCl_3$); mp 49−51 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 10.96 (bs, COOH), 2.47 (m, 1H, CH), 1.68 (m, 1H, CH_2), 1.43 (m, 1H, CH_2), 1.37−1.21 (m, 28H, CH_2), 1.18 (d, 3H, *J* = 6.9 Hz, CH_3), 0.89 (t, 3H, *J* = 6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 182.2 (C=O), 39.2 (CH), 33.5, 31.9, 29.7, 29.6, 29.5, 29.4, 27.1, 22.7 (14C, CH_2), 16.8 (CH_3), 14.1 (CH_3); ESI HRMS for $C_{19}H_{37}O_2$ $[M-H]^-$: Calcd 297.2799, Found 297.2796.

3′-*O*-Benzyl-4,6;4′,6′-di-*O*-benzylidene-2′-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-palmitoyl-α,α-D-trehalose (11a). To a solution of the monoacylated derivative **7** (164 mg, 0.171 mmol) and palmitic acid (60 mg, 0.232 mmol, 1.4 equiv) in dichloromethane (6 mL) were added DCC (54 mg, 0.263 mmol, 1.5 equiv) and DMAP (31 mg, 0.254 mmol, 1.5 equiv). The reaction mixture was stirred overnight at room temperature, filtered through Celite, and rinsed with ice-cold dichloromethane. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 95/5 then 90/10 then 80/20). The expected compound **11a** (224 mg) was obtained quantitatively as a colorless syrup. $[\alpha]^{20}_D$ = +38 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.45−7.27 (m, 15H, H_{ar}), 5.75 (t, $J_{2,3}$ = $J_{3,4}$ = 9.7 Hz, 1H, H_3), 5.52 (s, 1H, CH−Ph), 5.50 (s, 1H, CH−Ph), 5.38 (d, $J_{1,2}$ = 4.0 Hz, 1H, H_1), 5.06 (dd, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 9.7 Hz, 1H, H_2), 5.05 (d, $J_{1',2'}$ = 3.6 Hz, 1H, $H_{1'}$), 4.96 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.81 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.31−4.23 (m, 2H, H_{6b}, H_5), 4.13 (dd, $J_{5',6'b}$ = 4.9 Hz, $J_{6'a,6'b}$ = 10.2 Hz, 1H, $H_{6'b}$), 4.01 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.0 Hz, 1H, $H_{3'}$), 3.91 (m, 1H, $H_{5'}$), 3.81 (dd, $J_{1',2'}$ = 3.6 Hz, $J_{2',3'}$ = 9.0 Hz, 1H, $H_{2'}$), 3.76−3.63 (m, 4H, H_{6a}, $H_{6'a}$, H_4, $H_{4'}$), 2.42−2.36 (m, 2H), 2.34−2.26 (m, 2H), 1.62−1.55 (m, 4H), 1.36−1.16 (m, 48H), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.90 (t, *J* = 7.2 Hz, 6H, CH_3), 0.10, 0.09 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 173.2, 172.5 (C=O), 138.9, 137.4, 137.1 (C_q−Ar), 129.0, 128.8, 128.1, 128.0, 127.3, 126.4, 126.1 (15C, CH−Ar), 102.0 (CH−Ph), 101.4 (CH−Ph), 95.7 ($C_{1'}$), 92.1 (C_1), 82.6 ($C_{4'}$), 79.6 (C_4), 78.5 ($C_{3'}$), 75.3 (CH_2−Ph), 72.7 ($C_{2'}$), 71.0 (C_2), 68.9, 68.8 (C_6, $C_{6'}$), 68.7 (C_3), 63.2, 63.0 ($C_{5'}$, C_5), 34.3, 34.1 (CH_2), 31.9 (2C, CH_2), 29.7, 29.5, 29.4, 29.3, 29.1, 29.0 (20C, CH_2), 26.0 ($SiC(CH_3)_3$), 25.1, 24.8 (CH_2), 22.7 (2C, CH_2), 18.2 ($SiC(CH_3)_3$), 14.1 (2C, CH_3), −4.3, −4.7 ($Si(CH_3)_2$). Anal. Calcd for $C_{71}H_{110}O_{13}Si$: C, 71.08; H, 9.24. Found: C, 71.04; H, 9.46. ESI HRMS for $C_{71}H_{110}O_{13}Si$ $[M+Na]^+$: Calcd 1221.7608, Found 1221.7543.

3′-*O*-Benzyl-4,6;4′,6′-di-*O*-benzylidene-2′-*O*-*tert*-butyldimethylsilyl-3-*O*-[(*S*)-2-methyloctadecanoyl]-2-*O*-palmitoyl-α,α-D-trehalose (11b). To a solution of compound **7** (389 mg, 0.405 mmol) and (*S*)-2-methyloctadecanoic acid **10b** (133 mg, 0.446 mmol, 1.1 equiv), in dichloromethane (17 mL) were added DCC (92 mg, 0.446 mmol, 1.1 equiv) and DMAP (54 mg, 0.446 mmol, 1.1 equiv). The reaction was stirred overnight at room temperature and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 90/10). The expected compound **11b** (322 mg, 64%) was obtained as a colorless syrup. $[\alpha]^{20}_D$ = +37(*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.46−7.28 (m, 15H, H_{ar}), 5.78 (t, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, 1H, H_3), 5.54 (s, 1H, CH−Ph), 5.52 (s, 1H, CH−Ph), 5.40 (d, $J_{1,2}$ = 3.9 Hz, 1H, H_1), 5.09 (dd, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H_2), 5.06 (d, $J_{1',2'}$ = 3.3 Hz, 1H, $H_{1'}$), 4.98 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.82 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.34−4.22 (m, 2H, H_{6b}, H_5), 4.14 (dd, $J_{5',6'b}$ = 4.5 Hz, $J_{6'a,6'b}$ = 10.2 Hz, 1H, $H_{6'b}$), 4.02 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.0 Hz, 1H, $H_{3'}$), 3.92 (m, 1H, $H_{5'}$), 3.82 (dd, $J_{1',2'}$ = 3.3 Hz, $J_{2',3'}$ = 9.0 Hz, 1H, $H_{2'}$), 3.78−3.61 (m, 4H, H_{6a}, $H_{6'a}$, H_4, $H_{4'}$), 2.51−2.30 (m, 3H), 1.67−1.54 (m, 3H), 1.46−1.14 (m, 53H), 1.12 (d, *J* = 7.2 Hz, 3H, CH_3), 0.95 (s, 9H, $SiC(CH_3)_3$), 0.91 (t, *J* = 7.2 Hz, 6H, CH_3), 0.10, 0.09 (2s, 6H,

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$Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 175.5, 173.2 (C═O), 138.8, 137.4, 137.0 (C_q–Ar), 128.9, 128.8, 128.1, 128.0, 127.3, 126.1, 126.0 (15C, CH–Ar), 101.8 (CH–Ph), 101.4 (CH–Ph), 95.6 ($C_{1'}$), 92.0 (C_1), 82.5 ($C_{4'}$), 79.6 (C_4), 78.5 ($C_{3'}$), 75.3 (CH_2–Ph), 72.7 ($C_{2'}$), 70.8 (C_2), 68.9, 68.8 (C_6, $C_{6'}$), 68.4 (C_3), 63.2 ($C_{5'}$), 62.9 (C_5), 39.9 (CH), 34.0, 33.7, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 27.3 (27C, CH_2), 26.0 ($SiC(CH_3)_3$), 24.7, 22.8 (CH_2), 18.2 ($SiC(CH_3)_3$), 17.3 (CH_3), 14.1 (2C, CH_3), −4.2, −4.6 ($Si(CH_3)_2$); ESI HRMS for $C_{74}H_{116}O_{13}Si$ $[M+Na]^+$: Calcd 1263.8077, Found 1263.8090.

3′,4,4′-Tri-*O*-benzyl-2′-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-palmitoyl-α,α-D-trehalose (12a). To a solution of compound **11a** (82 mg, 0.068 mmol) in dry dichloromethane (2.5 mL) containing 4 Å molecular sieves at −78 °C were added dichlorophenylborane (45 μL, 0.343 mmol, 5 equiv) and triethylsilane (110 μL, 0.689 mmol, 10 equiv). The mixture was stirred for 6 h at −78 °C and then warmed to −20 °C for 1 h. The reaction mixture was quenched with triethylamine (2.5 mL) and methanol (2.5 mL) and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 80/20 to 70/30) to afford the title compound **12a** (77 mg, 93%) as a colorless syrup. $[\alpha]^{20}_D$ = +65 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.39–7.19 (m, 15H, H_{ar}), 5.71 (t, $J_{2,3}$ = $J_{3,4}$ = 9.8 Hz, 1H, H_3), 5.27 (d, $J_{1,2}$ = 4.0 Hz, 1H, H_1), 4.97 (d, $J_{1',2'}$ = 3.5 Hz, 1H, $H_{1'}$), 4.97 (d, *J* = 11.7 Hz, 1H, CH_2–Ph), 4.90 (dd, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 9.8 Hz, 1H, H_2), 4.89 (d, *J* = 11.7 Hz, 1H, CH_2–Ph), 4.81 (d, *J* = 11.0 Hz, 1H, CH_2–Ph), 4.62 (m, 2H, CH_2–Ph), 4.59 (d, *J* = 11.0 Hz, 1H, CH_2–Ph), 4.09 (m, 1H, H_5), 3.94 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.5 Hz, 1H, $H_{3'}$), 3.82–3.60 (m, 7H, H_{6b}, H_{6a}, $H_{6'b}$, $H_{6'a}$, H_4, $H_{5'}$, $H_{2'}$), 3.52 (t, $J_{3',4'}$ = $J_{4',5'}$ = 9.5 Hz, 1H, $H_{4'}$), 2.29–2.15 (m, 4H, CH_2), 1.70–1.49 (m, 4H, CH_2), 1.40–1.10 (m, 48H, CH_2), 0.95–0.83 (m, 15H, $SiC(CH_3)_3$, $2CH_3$), 0.07, 0.06 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 173.2, 172.6 (C═O), 139.0, 138.2, 137.9 (C_q–Ar), 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.1 (15C, CH–Ar), 95.1 ($C_{1'}$), 91.6 (C_1), 81.5 ($C_{3'}$), 77.8 ($C_{4'}$), 75.5 (C_4), 75.3 (CH_2–Ph), 74.8 (CH_2–Ph), 74.4 (CH_2–Ph), 73.1 ($C_{5'}$), 71.7, 71.6 (C_3, $C_{2'}$), 71.1 (C_5), 70.8 (C_2), 61.7 ($C_{6'}$), 61.2 (C_6), 34.3, 34.1 (CH_2), 31.9 (2C, CH_2), 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1 (20C, CH_2), 26.0 ($SiC(CH_3)_3$), 24.9, 24.7 (CH_2), 22.7 (2C, CH_2), 18.0 ($SiC(CH_3)_3$), 14.1 (2C, CH_3), −4.2, −4.8 ($Si(CH_3)_2$); ESI HRMS for $C_{71}H_{114}O_{13}Si$ $[M+Na]^+$: Calcd 1225.7921, Found 1225.7860.

3′,4,4′-Tri-*O*-benzyl-2′-*O*-*tert*-butyldimethylsilyl-3-*O*-[(*S*)-2-methyloctadecanoyl]-2-*O*-palmitoyl-α,α-D-trehalose (12b). To a solution of compound **11b** (161 mg, 0.130 mmol) in dry dichloromethane (2 mL) containing 4 Å molecular sieves at −78 °C were added dichlorophenylborane (85 μL, 0.650 mmol, 5 equiv) and triethylsilane (207 μL, 1.30 mmol, 10 equiv). The mixture was stirred for 6 h at −78 °C and then warmed to −20 °C for 1 h. The reaction mixture was quenched with triethylamine (5 mL) and methanol (5 mL) and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 80/20 to 70/30) to afford the title compound **12b** (115 mg, 71%) as a colorless syrup. $[\alpha]^{20}_D$ = +68 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.41–7.22 (m, 15H, H_{ar}), 5.78 (t, $J_{2,3}$ = $J_{3,4}$ = 9.9 Hz, 1H, H_3), 5.37 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 5.03 (d, $J_{1',2'}$ = 3.0 Hz, 1H, $H_{1'}$), 5.01 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.96 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.9 Hz, 1H, H_2), 4.93 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.85 (d, *J* = 11.1 Hz, 1H, CH_2–Ph), 4.71 (s, 2H, CH_2–Ph), 4.63 (d, *J* = 11.1 Hz, 1H, CH_2–Ph), 4.14 (m, 1H, H_5), 3.98 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.1 Hz, 1H, $H_{3'}$), 3.85 (t, $J_{3,4}$ = $J_{4,5}$ = 9.9 Hz, 1H, H_4), 3.84–3.60 (m, 6H, H_{6b}, H_{6a}, $H_{6'b}$, $H_{6'a}$, $H_{5'}$, $H_{2'}$), 3.54 (t, $J_{4',3'}$ = $J_{4',5'}$ = 9.1 Hz, 1H, $H_{4'}$), 2.45–2.34 (m, 1H), 2.34–2.26 (m, 2H), 1.75–1.50 (m, 3H), 1.47–1.16 (m, 53H), 1.12 (d, *J* = 7.2 Hz, 3H, CH_3), 0.95–0.88 (m, 15H, $SiC(CH_3)_3$ and 2 CH_3), 0.11, 0.09 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 175.5, 173.3 (C═O), 138.9, 138.1, 137.9 (C_q–Ar), 128.2, 128.1, 127.7, 127.6, 127.5, 127.3, 127.2, 127.1 (15C, CH–Ar), 94.8 ($C_{1'}$), 91.2 (C_1), 81.5 ($C_{3'}$), 77.8 ($C_{4'}$), 75.5 (C_4), 75.3 (CH_2–Ph), 74.8 (CH_2–Ph), 74.3 (CH_2–Ph), 72.9 ($C_{2'}$), 71.9 ($C_{5'}$), 71.4 (C_3), 71.2 (C_5), 70.9 (C_2), 61.5 (C_6), 61.0 ($C_{6'}$), 39.5 (CH), 34.0, 33.7, 31.9, 29.7, 29.6, 29.5, 29.3, 27.2 (27C, CH_2), 25.9 ($SiC(CH_3)_3$), 24.5, 22.8 (CH_2), 17.9 ($SiC(CH_3)_3$), 16.6 (CH_3), 14.1 (2C, CH_3), −4.3, −4.8 ($Si(CH_3)_2$). ESI HRMS for $C_{74}H_{120}O_{13}Si$ $[M+Na]^+$: Calcd 1267.8390, Found 1267.8375.

3′,4,4′-Tri-*O*-benzyl-2′-*O*-*tert*-butyldimethylsilyl-2,3,6,6′-tetra-*O*-palmitoyl-α,α-D-trehalose (13a). To a solution of compound **12a** (33.0 mg, 0.027 mmol) and palmitic acid (21 mg, 0.081 mmol, 3.0 equiv) in dichloromethane (1.4 mL) were added DCC (14 mg, 0.068 mmol, 2.5 equiv) and DMAP (5.0 mg, 0.041 mmol, 1.5 equiv). The reaction mixture was stirred overnight at room temperature and then concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 95/5 then 90/10). The expected tetra-*O*-acylated derivative **13a** (43.7 mg, 95%) was obtained as a colorless syrup. $[\alpha]^{20}_D$ +47 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.37–7.15 (m, 15H, H_{ar}), 5.72 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 9.4 Hz, 1H, H_3), 5.24 (d, $J_{1,2}$ = 4.0 Hz, 1H, H_1), 5.01 (d, $J_{1',2'}$ = 3.2 Hz, 1H, $H_{1'}$), 5.00 (dd, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 10.2 Hz, 1H, H_2), 4.99 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.89 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.82 (d, *J* = 11.2 Hz, 1H, CH_2–Ph), 4.62 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.57 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.52 (d, *J* = 11.2 Hz, 1H, CH_2–Ph), 4.29–4.16 (m, 5H, H_5, H_{6b}, H_{6a}, $H_{6'b}$, $H_{6'a}$), 3.97 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.0 Hz, 1H, $H_{3'}$), 3.86 (m, 1H, $H_{5'}$), 3.75 (dd, $J_{1',2'}$ = 3.2 Hz, $J_{2',3'}$ = 9.0 Hz, 1H, $H_{2'}$), 3.70 (t, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, 1H, H_4), 3.44 (t, $J_{3',4'}$ = 9.0 Hz, $J_{4',5'}$ = 10.0 Hz, 1H, $H_{4'}$), 2.36–2.18 (m, 8H, CH_2), 1.68–1.52 (m, 8H, CH_2), 1.35–1.19 (m, 96H, CH_2), 0.93–0.88 (m, 21H, $SiC(CH_3)_3$, $4CH_2$), 0.09, 0.07 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 173.4, 173.3, 172.8, 172.5 (C═O), 138.8, 137.9, 137.5 (C_q–Ar), 128.4, 128.3, 128.2, 127.8, 127.7, 127.5, 127.2 (15C, CH–Ar), 94.5 ($C_{1'}$), 91.1 (C_1), 81.7 ($C_{3'}$), 78.1 ($C_{4'}$), 76.1 (C_4), 75.5 (CH_2–Ph), 74.9 (CH_2–Ph), 74.4 (CH_2–Ph), 73.0 ($C_{2'}$), 71.9 (C_3), 70.3 (C_2), 69.6 ($C_{5'}$), 68.9 (C_5), 62.7, 62.3 ($C_{6'}$, C_6), 34.3, 34.1, 34.0 (3C, CH_2), 31.9 (4C, CH_2), 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1 (40C, CH_2), 26.0 ($SiC(CH_3)_3$), 24.9, 24.8, 24.7 (4C, CH_2), 22.7 (4C, CH_2), 18.0 ($SiC(CH_3)_3$), 14.1 (4C, CH_3), −4.1, −4.8 ($Si(CH_3)_2$); ESI HRMS for $C_{103}H_{174}O_{15}Si$ $[M+Na]^+$: Calcd 1702.2514, Found 1702.2474.

3′,4,4′-Tri-*O*-benzyl-2′-*O*-*tert*-butyldimethylsilyl-3-*O*-[(*S*)-2-methyloctadecanoyl]-6,6′-di-*O*-[(*S*)-2-methyldecanoyl]-2-*O*-palmitoyl-α,α-D-trehalose (13b). To a solution of compound **12b** (100 mg, 0.080 mmol) and (*S*)-2-methyldecanoic acid **10a** (48 mg, 0.256 mmol, 3.2 equiv) in dichloromethane (1 mL) were added DCC (53 mg, 0.256 mmol, 3.2 equiv) and DMAP (29 mg, 0.240 mmol, 3 equiv). The reaction was stirred overnight at room temperature and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 90/10). The expected compound **13b** (105 mg, 83%) was obtained as a colorless syrup. $[\alpha]^{20}_D$ = +60 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.37–7.14 (m, 15H, H_{ar}), 5.75 (dd, $J_{2,3}$ = 10.1 Hz, $J_{3,4}$ = 9.4 Hz, 1H, H_3), 5.25 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 5.00 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10.1 Hz, 1H, H_2), 4.99 (d, $J_{1',2'}$ = 3.6 Hz, 1H, $H_{1'}$), 4.98 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.88 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.82 (d, *J* = 11.2 Hz, 1H, CH_2–Ph), 4.63 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.54 (d, *J* = 11.5 Hz, 1H, CH_2–Ph), 4.51 (d, *J* = 11.2 Hz, 1H, CH_2–Ph), 4.35–4.23 (m, 3H, H_5, H_{6b}, H_{6a}), 4.21–4.16 (m, 2H, $H_{6'b}$, $H_{6'a}$), 3.97 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.4 Hz, 1H, $H_{3'}$), 3.85 (m, 1H, $H_{5'}$), 3.73 (dd, $J_{1',2'}$ = 3.6 Hz, $J_{2',3'}$ = 9.4 Hz, 1H, $H_{2'}$), 3.72 (t, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, 1H, H_4), 3.45 (dd, $J_{3',4'}$ = 9.4 Hz, $J_{4',5'}$ = 9.0 Hz, 1H, $H_{4'}$), 2.53–2.43 (m, 2H), 2.35 (m, 1H), 2.27–2.22 (m, 2H,), 1.72–1.60 (m, 3H), 1.54–1.49 (m, 2H), 1.35–1.19 (m, 79H), 1.18 (d, *J* = 7.2 Hz, 3H, CH_3), 1.14 (d, *J* = 7.2 Hz, 3H, CH_3), 1.08 (d, *J* = 6.8 Hz, 3H, CH_3), 0.91–0.85 (m, 21H, $SiC(CH_3)$ and 4 CH_3), 0.09, 0.07 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 176.6, 176.5, 175.5, 172.7 (C═O), 138.8, 137.9, 137.5 (C_q-Ar), 128.4, 128.3, 128.2, 127.7, 127.6, 127.5, 127.2, 127.1, 127.0 (15C, CH–Ar), 94.3 ($C_{1'}$), 91.0 (C_1), 81.6 ($C_{3'}$), 78.3 ($C_{4'}$), 76.3 (C_4), 75.5 (CH_2–Ph), 75.0 (CH_2–Ph), 74.4 (CH_2–Ph), 73.0 ($C_{2'}$), 71.7 (C_3), 70.4 (C_2), 69.5 ($C_{5'}$), 68.9 (C_5), 62.6 ($C_{6'}$), 62.1 (C_6), 39.5, 39.4, 39.3 (CH), 34.2, 34.0, 33.8, 33.7, 31.9, 3.8, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 27.3, 27.2, (40C, CH_2), 26.0 ($SiC(CH_3)_3$), 24.6, 22.7, 22.6 (CH_2), 18.0 ($SiC(CH_3)_3$), 17.1, 17.0, 16.5 (CH_3), 14.1, 14.0 (4C, CH_3), −4.1, −4.8 ($Si(CH_3)_2$); ESI HRMS for $C_{96}H_{160}O_{15}Si$ $[M+Na]^+$: Calcd 1604.1419, Found 1604.1457.

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3′,4,4′-Tri-*O*-benzyl-2,3,6,6′-tetra-*O*-palmitoyl-α,α-D-trehalose (14a). To a solution of compound **13a** (72 mg, 0.043 mmol) in THF (1.0 mL) was added a 1 M solution of tetrabutylammonium fluoride in THF (130 μL, 0.130 mmol, 3 equiv). The reaction mixture was stirred for 1.5 h at room temperature, diluted with ethyl acetate, and hydrolyzed with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 90/10 then 80/20) to afford the expected compound **14a** (61 mg, 91%) as a colorless syrup. $[\alpha]^{20}_D$ = +63 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.41−7.24 (m, 15H, H_{ar}), 5.62 (t, $J_{2,3} = J_{3,4}$ = 9.5 Hz, 1H, H_3), 5.21 (d, $J_{1,2}$ = 3.9 Hz, 1H, H_1), 5.07 (d, $J_{1',2'}$ = 3.3 Hz, 1H, $H_{1'}$), 4.96 (dd, $J_{1,2}$ = 3.9 Hz, $J_{2,3}$ = 9.5 Hz, 1H, H_2), 4.93 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.87 (d, *J* = 10.8 Hz, 1H, CH_2−Ph), 4.86 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.59 (d, *J* = 10.8 Hz, 1H, CH_2−Ph), 4.59 (d, *J* = 10.8 Hz, 1H, CH_2−Ph), 4.53 (d, *J* = 10.8 Hz, 1H, CH_2−Ph), 4.34−4.14 (m, 5H, H_5, H_{6b}, H_{6a}, $H_{6'b}$, $H_{6'a}$), 3.90 (t, $J_{2',3'} = J_{3',4'}$ = 9.0 Hz, 1H, $H_{3'}$), 3.88 (m, 1H, $H_{5'}$), 3.66 (m, 1H, $H_{2'}$), 3.65 (t, $J_{3,4} = J_{4,5}$ = 9.5 Hz, 1H, H_4), 3.47 (t, $J_{3',4'} = J_{4',5'}$ = 9.0 Hz, 1H, $H_{4'}$), 2.35−2.21 (m, 8H, CH_2), 1.88 (d, *J* = 5.7 Hz, 1H, OH), 1.67−1.56 (m, 8H, CH_2), 1.30−1.20 (m, 96H, CH_2), 0.89 (t, *J* = 7.0 Hz, 12H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 173.4, 173.3, 172.7, 172.5 (C═O), 138.3, 137.7, 137.3 (C_q−Ar), 128.7, 128.5, 128.4, 128.1, 128.0, 127.9 (15C, CH−Ar), 94.3 ($C_{1'}$), 91.9 (C_1), 82.1 ($C_{3'}$), 77.7 ($C_{4'}$), 76.1 (C_4), 75.6 (CH_2−Ph), 75.0 (CH_2−Ph), 74.6 (CH_2−Ph), 71.9 ($C_{2'}$), 71.7 (C_3), 70.3 (C_2), 69.9 ($C_{5'}$), 69.0 (C_5), 62.5, 62.2 (C_6, $C_{6'}$), 34.4, 34.2, 34.1 (4C, CH_2), 31.9 (4C, CH_2), 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, (40C, CH_2), 24.9, 24.8 (4C, CH_2), 22.7 (4C, CH_2), 14.1 (4C, CH_3); ESI HRMS for $C_{97}H_{160}O_{15}$ $[M+Na]^+$: Calcd 1588.1649, Found 1588.1641.

3′,4,4′-Tri-*O*-benzyl-3-*O*-[(*S*)-2-methyloctadecanoyl]-6,6′-di-*O*-[(*S*)-2-methyldecanoyl]-2-*O*-palmitoyl-α,α-D-trehalose (14b). To a solution of compound **13b** (94 mg, 0.06 mmol) in THF (2 mL) was added a 1 M solution of tetrabutylammonium fluoride in THF (120 μL, 0.120 mmol, 2 equiv). The reaction mixture was stirred for 2 h at room temperature, diluted with ethyl acetate, and hydrolyzed with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 90/10 then 80/20) to afford the expected compound **14b** (74 mg, 85%) as a colorless syrup. $[\alpha]^{23}_D$ = +74 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.41−7.20 (m, 15H, H_{ar}), 5.65 (t, $J_{2,3} = J_{3,4}$ = 9.9 Hz, 1H, H_3), 5.23 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 5.09 (d, $J_{1',2'}$ = 3.6 Hz, 1H, $H_{1'}$), 4.98 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H_2), 4.92 (d, *J* = 11.1 Hz, 1H, CH_2−Ph), 4.88 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.85 (d, *J* = 11.1 Hz, 1H, CH_2−Ph), 4.62 (d, *J* = 10.5 Hz, 1H, CH_2−Ph), 4.59 (d, *J* = 11.0 Hz, 1H, CH_2−Ph), 4.52 (d, *J* = 10.5 Hz, 1H, CH_2−Ph), 4.37−4.14 (m, 5H, H_5, H_{6b}, H_{6a}, $H_{6'b}$, $H_{6'a}$), 3.91 (t, $J_{2',3'} = J_{3',4'}$ = 9.6 Hz, 1H, $H_{3'}$), 3.88 (m, 1H, $H_{5'}$), 3.70−3.62 (m, 2H, $H_{2'}$, H_4), 3.50 (t, $J_{3',4'} = J_{4',5'}$ = 9.6 Hz, 1H, $H_{4'}$), 2.54−2.35 (m, 3H), 2.27 (m, 2H), 1.89 (bs, 1H, OH), 1.74−1.49 (m, 5H), 1.49−1.09 (m, 88H), 0.92−0.85 (m, 12H, 4 CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 176.5, 176.4, 175.6, 172.7 (C═O), 138.2, 137.7, 137.2 (C_q−Ar), 128.7, 128.5, 128.2, 128.0, 127.9, 127.8 (15C, CH-Ar), 94.2 ($C_{1'}$), 91.8 (C_1), 82.0 ($C_{3'}$), 77.9 ($C_{4'}$), 76.3 (C_4), 75.7 (CH_2−Ph), 75.1 (CH_2−Ph), 74.6 (CH_2−Ph), 71.9 ($C_{2'}$), 71.4 (C_3), 70.5 (C_2), 70.0 ($C_{5'}$), 69.0 (C_5), 62.3, 62.2 (C_6, $C_{6'}$), 39.6, 39.5, 39.4 (CH), 34.0, 33.8, 33.7, 33.6, 31.9, 31.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 27.3, 27.2, 24.7, 22.7, 22.6 (43C, CH_2), 17.1, 17.0, 16.6 (CH_3), 14.1 (4 C, CH_3); ESI HRMS for $C_{90}H_{146}O_{15}$ $[M+Na]^+$: Calcd 1490.0554, Found 1490.0468.

Sodium 3′,4,4′-Tri-*O*-benzyl-2,3,6,6′-tetra-*O*-palmitoyl-2′-*O*-sulfate-α,α-D-trehalose (15a). To a solution of compound **14a** (21.9 mg, 0.014 mmol) in dry pyridine (0.3 mL) was added [SO_3:pyridine] (23 mg, 0.070 mmol, 5 equiv). The reaction mixture was stirred for 3 h at 90 °C and then cooled to room temperature. The reaction was quenched with methanol (1 mL) and stirred until the precipitate disappeared. The mixture was concentrated *in vacuo* and coevaporated with toluene and dichloromethane. The residue was subjected to flash chromatography on silica gel (CH_2Cl_2/MeOH: 90/10), and the product-containing fractions were passed through an Amberlite IR-120 column (Na^+ form) with the use of the same solvent system before to be concentrated. The expected *O*-sulfated compound **15a** (22.4 mg, 96%) was obtained as a colorless syrup. ^{1}H NMR ($CDCl_3$/CD_3OD: 2/1, 300 MHz) δ (ppm): 7.42−7.14 (m, 15H, H_{ar}), 5.60 (t, $J_{2,3} = J_{3,4}$ = 10.0 Hz, 1H, H_3), 5.46 (d, $J_{1',2'}$ = 3.6 Hz, 1H, $H_{1'}$), 5.17 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 5.11 (d, *J* = 10.2 Hz, 1H, CH_2−Ph), 4.91 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H_2), 4.82 (d, *J* = 11.1 Hz, 1H, CH_2−Ph), 4.70 (d, *J* = 10.2 Hz, 1H, CH_2−Ph), 4.55 (s, 2H, CH_2−Ph), 4.49 (d, *J* = 11.1 Hz, 1H, CH_2−Ph), 4.51−4.27 (m, 4H, H_{6b}, H_{6a}, H_5, $H_{2'}$), 4.13 (m, 2H, $H_{6'a}$, $H_{6'b}$), 4.04 (t, $J_{2',3'} = J_{3',4'}$ = 9.5 Hz, 1H, $H_{3'}$), 3.86 (m, 1H, $H_{5'}$), 3.72 (t, $J_{3,4} = J_{4,5}$ = 10.0 Hz, 1H, H_4), 3.43 (t, $J_{3',4'} = J_{4',5'}$ = 9.5 Hz, 1H, $H_{4'}$), 2.34−2.13 (m, 8H, CH_2), 1.66−1.46 (m, 8H, CH_2), 1.34−1.12 (m, 96H, CH_2), 0.84 (m, 12H, CH_3); ^{13}C NMR ($CDCl_3$/CD_3OD: 2/1, 75 MHz) δ (ppm): 174.0, 173.6, 172.7, 172.6 (C═O), 138.0, 137.5, 137.1 (C_q−Ar), 128.3, 128.0, 127.9, 127.7, 127.6, 127.4, 127.2 (15C, CH−Ar), 92.9 ($C_{1'}$), 91.8 (C_1), 79.5 ($C_{3'}$), 76.8, 76.7 ($C_{4'}$, $C_{2'}$), 75.3 (C_4), 75.2 (CH_2−Ph), 74.6 (CH_2−Ph), 74.0 (CH_2−Ph), 71.5 (C_3), 70.3 (C_2), 69.0 ($C_{5'}$), 68.4 (C_5), 62.5 ($C_{6'}$), 61.9 (C_6), 33.9, 33.7, 33.6 (4C, CH_2), 31.6 (4C, CH_2), 29.3, 29.2, 29.1, 29.0, 28.9, 28.8 (40C, CH_2), 24.6, 24.5 (4C, CH_2), 22.3 (4C, CH_2), 13.5 (4C, CH_3); ESI HRMS for $C_{97}H_{159}NaO_{18}S$ $[M-Na]^-$: Calcd 1644.1253, Found 1644.1158.

Sodium 3′,4,4′-Tri-*O*-benzyl-3-*O*-[(*S*)-2-methyloctadecanoyl]-6,6′-di-*O*-[(*S*)-2-methyldecanoyl]-2-*O*-palmitoyl-2′-*O*-sulfate-α,α-D-trehalose (15b). To a solution of the desilylated compound **14b** (55 mg, 0.038 mmol) in dry pyridine (1 mL) was added [SO_3:pyridine] (61 mg, 0.190 mmol, 5 equiv). The reaction mixture was stirred for 3 h at 90 °C and then cooled to room temperature. The reaction was quenched with methanol (1.0 mL) and stirred until the precipitate disappeared. The mixture was concentrated under vacuum and coevaporated with toluene and dichloromethane. The residue was subjected to flash chromatography on silica gel (CH_2Cl_2/MeOH: 90/10), and the product-containing fractions were passed through an Amberlite IR-120 column (Na^+ form) with the use of the same solvent system before being concentrated. The expected *O*-sulfated compound **15b** (55 mg, 93%) was obtained as a colorless syrup. $[\alpha]^{20}_D$ = +57 (*c* 0.9, $CHCl_3$/CH_3OH: 1/1); ^{1}H NMR ($CDCl_3$/CD_3OD: 3/2, 360 MHz) δ (ppm): 7.42−7.17 (m, 15H, H_{ar}), 5.64 (t, $J_{2,3} = J_{3,4}$ = 9.7 Hz, 1H, H_3), 5.50 (d, $J_{1',2'}$ = 3.0 Hz, 1H, $H_{1'}$), 5.21 (d, $J_{1,2}$ = 3.8 Hz, 1H, H_1), 5.12 (d, *J* = 10.4 Hz, 1H, CH_2−Ph), 4.94 (dd, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 9.7 Hz, 1H, H_2), 4.84 (d, *J* = 11.2 Hz, 1H, CH_2−Ph), 4.70 (d, *J* = 10.4 Hz, 1H, CH_2−Ph), 4.61−4.30 (m, 7H, CH_2−Ph (3H), $H_{2'}$, H_{6b}, H_5, H_{6a}), 4.19−4.16 (m, 2H, $H_{6'b}$, $H_{6'a}$), 4.06 (t, $J_{2',3'} = J_{3',4'}$ = 9.4 Hz, 1H, $H_{3'}$), 3.88 (m, 1H, $H_{5'}$), 3.75 (t, $J_{3,4} = J_{4,5}$ = 9.7 Hz, 1H, H_4), 3.48 (t, $J_{3',4'} = J_{4',5'}$ = 9.4 Hz, 1H, $H_{4'}$), 2.55−2.41 (m, 1H), 2.40−2.28 (m, 2H), 2.27−2.19 (m, 2H), 1.71−1.04 (m, 93H), 0.89−0.78 (m, 12H); ^{13}C NMR ($CDCl_3$/CD_3OD: 3/2, 90 MHz) δ (ppm): 177.8, 177.6, 176.5, 173.3 (C═O), 138.9, 138.3, 137.9 (C_q−Ar), 129.0, 128.7, 128.6, 128.2, 128.1, 128.0 (15C, CH−Ar), 93.5 ($C_{1'}$), 92.4 (C_1), 80.3 ($C_{3'}$), 77.7 ($C_{4'}$), 77.6 ($C_{2'}$), 76.4 (C_4), 75.9 (CH_2−Ph), 75.5 (CH_2−Ph), 74.7 (CH_2−Ph), 72.1 (C_3), 71.3 (C_2), 69.8 ($C_{5'}$), 69.2 (C_5), 63.2 ($C_{6'}$), 62.7 (C_6), 40.1, 40.0, 39.9 (CH), 34.4, 34.3, 34.2, 34.1, 32.3, 32.2, 30.1, 30.0, 29.9, 29.8, 29.7, 29.6, 27.7, 27.6, 27.5, 25.1, 23.0 (43C, CH_2), 17.4, 17.1, 16.8 (CH_3), 14.3 (4C, CH_3); ESI HRMS for $C_{90}H_{145}Na_2O_{18}S$ $[M+Na]^+$: Calcd 1591.9942, Found 1591.9963.

Sodium 2,3,6,6′-Tetra-*O*-palmitoyl-2′-*O*-sulfate-α,α-D-trehalose (16). To a solution of compound **15a** (20.7 mg, 0.012 mmol) in a 1/1 mixture of CH_2Cl_2/MeOH (1.0 mL) were added 32 mg of 5% Pd/C. The suspension was vigorously stirred under 1 atm of H_2 for 2 h. The resulted mixture was then filtered through Celite, rinsed with methanol, and concentrated under reduced pressure. The residue was subjected to flash chromatography (CH_2Cl_2/MeOH: 90/10 then 80/20), and the product-containing fractions were passed through an Amberlite IR-120 column (Na^+ form) with the use of the same solvent system before being concentrated. The expected sulfolipid **16** (15.0 mg, 86%) was obtained as a syrup. $[\alpha]^{24}_D$ = +39 (*c* 0.8, $CHCl_3$/

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CH_3OH: 50/50); ^1H NMR ($CDCl_3/CD_3OD$: 1/1, 250 MHz) δ (ppm): 5.15 (d, $J_{1',2'}$ = 3.6 Hz, 1H, $H_{1'}$), 5.14 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 9.9 Hz, 1H, H_3), 4.94 (d, $J_{1,2}$ = 3.7 Hz, 1H, H_1), 4.60 (dd, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 10.2 Hz, 1H, H_2), 4.09 (m, 2H, H_{6b}, H_{6a}), 4.04−3.86 (m, 4H, $H_{6'b}$, $H_{6'a}$, H_5, $H_{2'}$), 3.61 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.0 Hz, 1H, $H_{3'}$), 3.52 (m, 1H, $H_{5'}$), 3.33 (t, $J_{3,4}$ = $J_{4,5}$ = 9.9 Hz, 1H, H_4), 3.06 (t, $J_{3',4'}$ = $J_{4',5'}$ = 9.0 Hz, 1H, $H_{4'}$), 2.10−1.98 (m, 8H, CH_2), 1.35−1.24 (m, 8H, CH_2), 1.10−0.90 (m, 96H, CH_2), 0.57 (t, J = 6.8 Hz, 12H, CH_3); ^{13}C NMR ($CDCl_3/CD_3OD$: 1/1, 90 MHz) δ (ppm): 174.1, 173.8, 173.3, 172.4 (C═O), 91.6 ($C_{1'}$), 90.9 (C_1), 76.0 ($C_{2'}$), 71.9 (C_3), 71.2 ($C_{3'}$), 70.2 (2C, C_2, $C_{4'}$), 69.8 ($C_{5'}$), 69.4 (C_5), 68.0 (C_4), 63.1 ($C_{6'}$), 61.7 (C_6), 33.8, 33.6, 33.5, 33.4 (CH_2), 31.4 (4C, CH_2), 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.5 (40C, CH_2), 24.5, 24.4, 24.3 (4C, CH_2), 22.1 (4C, CH_2), 13.2 (4C, CH_3); ESI HRMS for $C_{76}H_{141}NaO_{18}S$ $[M+Na]^+$: Calcd 1419.9629, Found 1419.9536.

Sodium 3-*O*-[(*S*)-2-Methyloctadecanoyl]-6,6′-di-*O*-[(*S*)-2-methyldecanoyl]-2-*O*-palmitoyl-2′-*O*-sulfate-α,α-D-trehalose (1). To a solution of compound **15b** (43 mg, 0.027 mmol) in a 1/1 mixture of CH_2Cl_2/MeOH (2 mL) were added 66 mg of 5% Pd/C. The suspension was vigorously stirred under 1 atm of H_2 for 2 h. The resulted mixture was then filtered through Celite, rinsed with MeOH, and concentrated under reduced pressure. The residue was subjected to flash chromatography (dichloromethane/methanol: 90/10 then 80/20), and the product-containing fractions were passed through an Amberlite IR-120 column (Na^+ form) with the use of the same solvent system before being concentrated. The expected sulfolipid **1** (20 mg, 56%) was obtained as a syrup $[\alpha]^{24}_D$ = +57 (*c* 1.0, $CHCl_3/CH_3OH$: 1/1); ^1H NMR ($CDCl_3/CD_3OD$: 1/1, 360 MHz) δ (ppm): 5.42 (d, $J_{1',2'}$ = 3.6 Hz, 1H, $H_{1'}$), 5.41 (dd, $J_{2,3}$ = 10.1 Hz, $J_{3,4}$ = 9.7 Hz, 1H, H_3), 5.21 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 4.90 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10.1 Hz, 1H, H_2), 4.37 (m, 2H, H_{6b}, H_{6a}), 4.28 (m, 1H, H_5), 4.25−4.18 (m, 3H, $H_{6'b}$, $H_{6'a}$, $H_{2'}$), 3.91 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.0 Hz, 1H, $H_{3'}$), 3.81 (m, 1H, $H_{5'}$), 3.58 (t, $J_{3,4}$ = $J_{4,5}$ = 9.7 Hz, 1H, H_4), 5.36 (dd, $J_{3',4'}$ = 9.0, Hz, $J_{4',5'}$ = 9.7 Hz, 1H, $H_{4'}$), 2.53−2.39 (m, 3H), 2.32−2.24 (m, 2H), 1.69−1.49 (m, 5H), 1.44−1.04 (m, 88H), 0.85 (t, J = 7.0 Hz, 12H, CH_3); ^{13}C NMR ($CDCl_3/CD_3OD$: 1/1, 90 MHz) δ (ppm): 178.3, 178.0, 177.6, 173.4 (C═O), 92.6 ($C_{1'}$), 91.9 (C_1), 77.0 ($C_{2'}$), 72.7 (C_3), 72.2 ($C_{3'}$), 71.3 ($C_{4'}$), 71.2 (C_2), 70.7 ($C_{5'}$), 70.5 (C_5), 69.2 (C_4), 64.1 ($C_{6'}$), 62.7 (C_6), 40.2, 40.1, 40.0 ($CHCH_3$), 34.4, 34.3, 32.4, 30.3, 30.2, 30.1, 30.0, 29.9, 29.8, 27.8, 27.7, 25.2, 23.1 (43C, CH_2), 17.3, 17.2, 17.1 (3C, CH_3), 14.3 (4C, CH_3); ESI HRMS for $C_{69}H_{127}O_{18}S$ $[M-Na]^-$: Calcd 1275.8749, Found 1275.8764.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra for new compounds, details on anisotropic NAD NMR, composition of oriented sample, further NAD spectra, and extra discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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