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Synthesis of trehalose-based compounds and their inhibitory activities against *Mycobacterium smegmatis*

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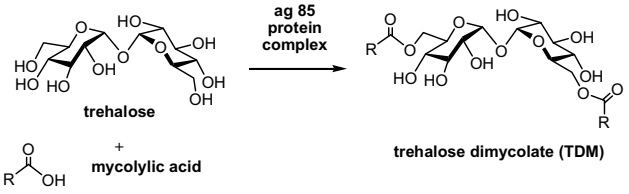
Abstract—The synthesis of a library of trehalose-based compounds has been accomplished, and their activities against *Mycobacterium smegmatis* have been determined. A preliminary structure–activity relationship (SAR) is reported. Despite not having a potent lead, one of the trehalose derivatives displays strong activity when applied with isoniazid (INH), which is known to have low sterilizing activity. The bacteriocidal nature of our compounds against *Mycobacterium* may be significant for the development of new therapies against tuberculosis.

1. Introduction

Tuberculosis (TB) is still the leading cause of death from a single infectious agent.[1,2] Once curable, the emergence of multi-drug resistant variants of *M. tuberculosis* (MDR-TB) have challenged normal therapeutic practices and increased mortality rates worldwide.[3] The high lipophilicity of the bacterial cell wall of *Mycobacterium*, which lowers the permeability of antitubercular agents and contributes to significant drug resistance, imposes great challenges in developing new drugs against TB.[4–6]

Fortunately, a potential target for the development of new antitubercular drugs has been revealed. Recent advances in the studies of the lipid envelope of TB have uncovered a unique structural component, 6,6′-dimycolyltrehalose (TDM), which forms the outmost layer of the bacterial cell wall of TB.[5,6] Three homologous proteins (ag85 A, B, and C), which possess mycolyltransferase activity, are responsible for the biosynthesis of TDM (Scheme 1).[7,8] Damage to the cellwall, due to the inhibition of ag85, has been shown to increase the efficacy of various antibiotics.[7,9] Therefore, ag85 represents a desirable target for the development of new antitubercular agents. More importantly, ag85 is a new target, and resistance related to ag85 modification has not been observed so far.



Scheme 1.

Inhibitors derived from trehalose that mimic the scaffold of TDM have been reported with modest to excellent activity against TB.[10] Based on the proposed mechanism of action of ag85, we designed and synthesized a second generation of trehalose-based antitubercular agents.[11] These agents contain a characteristic feature of long hydrocarbon chains and functionalities that may serve as acyltransferase inhibitors to target ag85 protein complex. Herein, we wish to report the synthesis and preliminary antibacterial studies of these trehalose-based compounds against *M. smegmatis*, a nonpathogenic surrogate of *M. tuberculosis*.

Keywords: Tuberculosis; Trehalose; Ag85 protein complex.
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2. Results

Our designed compounds are shown in Figure 1. These molecules contain a trehalose core with mono- or di-substituted hydrocarbon chains, varying in chain length, at the C-4 or C-6 position. Amide and urea linkages that are commonly found in the designs of inhibitors against proteases, esterases, and peptidases are employed as the linkages for attaching these hydrocarbon chains. A preliminary goal is to identify optimal functionalities and chain length. For compounds like **YH023** the amide linkage is constructed in a 'reversed' fashion compared to the linkage found in TDM.

Synthesis of trehalose-based compounds with an ether linkage starts from the known compounds, **1**,[11] **4**,[11] and **6**,[12] bearing free either 4-OH or 6-OH groups (Scheme 2). The hydrocarbon chains are attached via alkylation using the corresponding alkyl halide. By controlling the number of equivalents of alkyl halide, mono- and di-substituted alkyl trehalose derivatives can be obtained in one pot. Hydrogenation using $Pd(OH)_2/C$ as a catalyst yields the final products.

Synthesis of trehalose-based compounds bearing an amide linkage with the *C*-terminal on the trehalose begins from **6** (Scheme 3). After Swern oxidation,[13] the resulting aldehyde is divided into two parts for separate routes. In one branch, the aldehyde is further oxidized into the carboxylic acid, which is then coupled with alkyl amine and L-alanine ethyl ester using $(COCl)_2$ and EDC, respectively. Hydrogenation using $Pd(OH)_2/C$ as a catalyst gives the final amides. In the other route, treatment of the aldehyde with methyl diethylphosphonoacetate provides **14** with a two-carbon extension at C-6 (Scheme 4). Transamidation[14] of **14** using $AlMe_3$ and the corresponding amines or hydrazine, followed by hydrogenation, yields the desired trehalose-based derivatives with a reversed amide linkage, with respect to the corresponding ester linkage found in TDM.

Synthesis of trehalose-based compounds bearing an amide linkage with the *N*-terminal on the trehalose and urea linkage also begins from **6** (Scheme 5). The 6-amino groups are installed via triflation and azide substitution, followed by a Staudinger reaction. Treatment of the amine, **26**, with triphosgene yields an isocyanide, which is then reacted with octyl amine to generate the urea adduct. In another route, compound **26** is coupled with decanoyl chloride, leading to the desired compound with an amide linkage. Both of the benzyl-protected

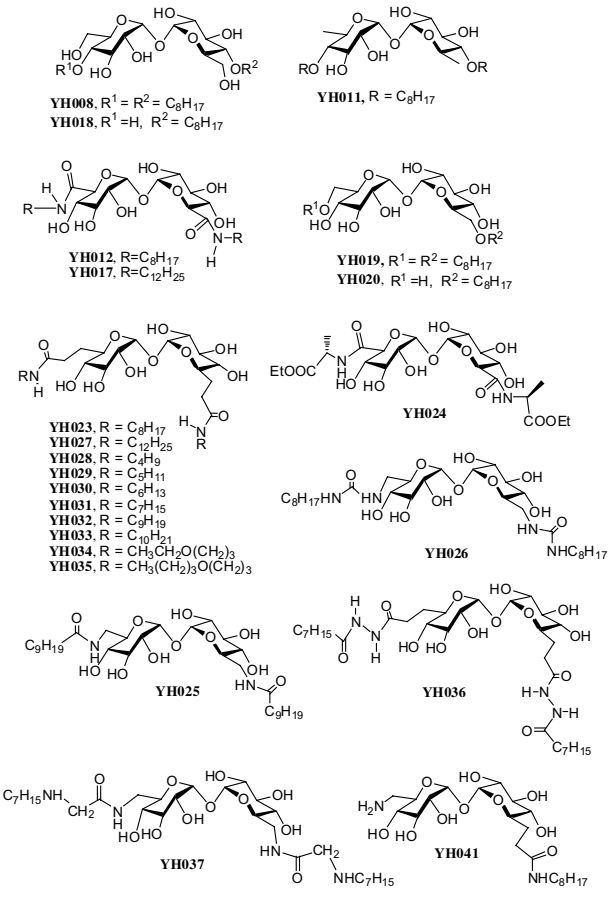
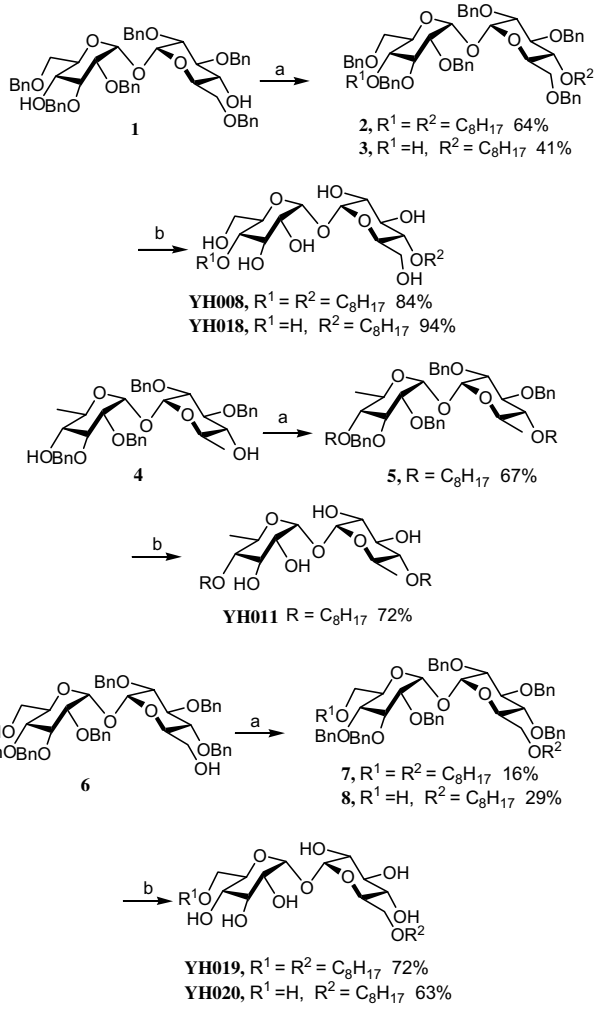
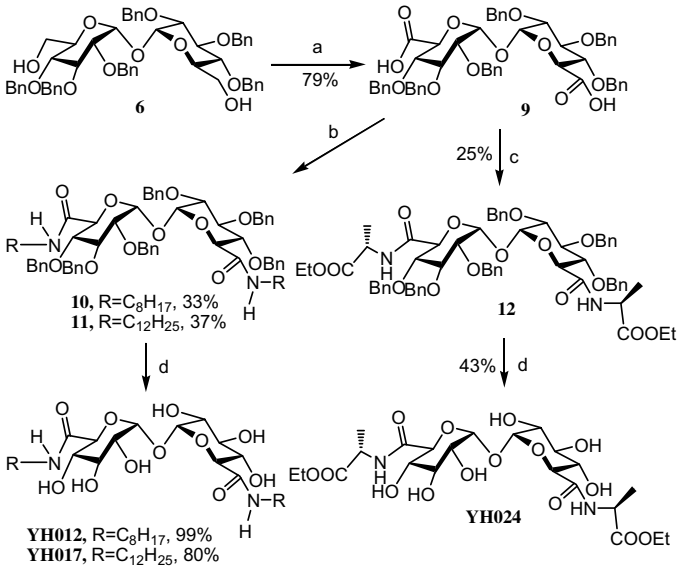


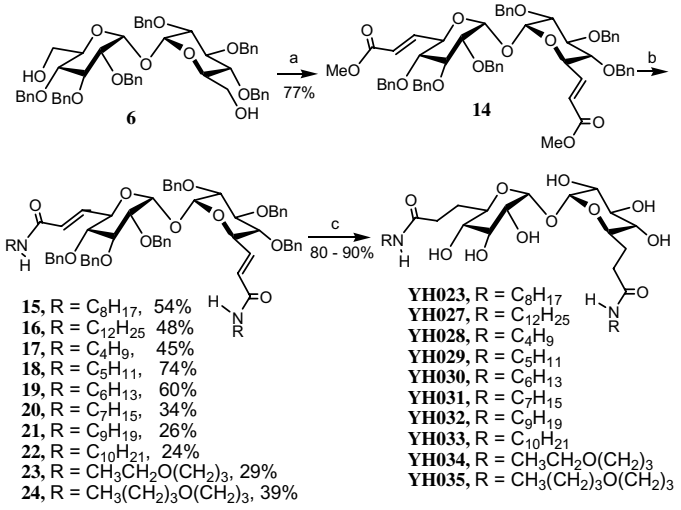
Figure 1. Structure of the second generation inhibitors.



Scheme 2. Reagents: (a) $C_8H_{17}Br$, NaH, TBAI, THF; (b) H_2, $Pd(OH)_2/C$, MeOH.



Scheme 3. Reagents: (a) (1) $(COCl)_2$, DMSO, DIPEA, (2) $NaClO_2$, H_2O_2; (b) (1) $(COCl)_2$, (2) $C_8H_{17}NH_2$ or $C_{12}H_{25}NH_2$; (c) L-alanine ethylester, EDC, pyr.; (d) H_2, $Pd(OH)_2/C$, MeOH.

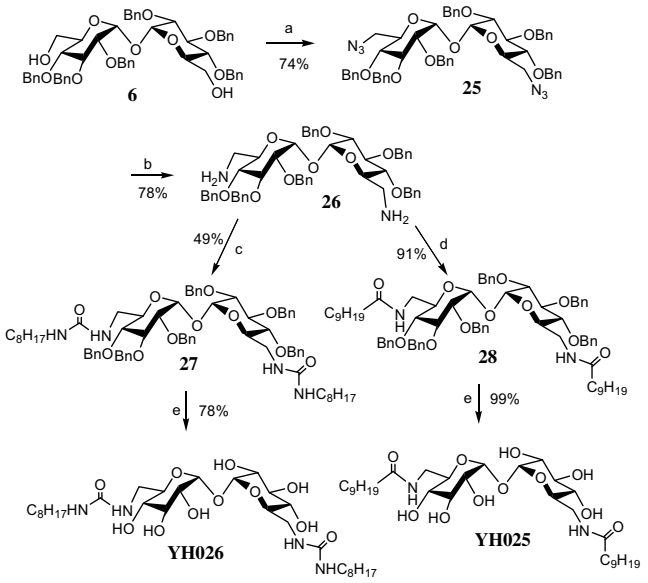


Scheme 4. Reagents: (a) (1) $(COCl)_2$, DMSO, DIPEA, (2) $MeOC(O)CH_2P(O)(OEt)_2$, NaH, THF; (b) alkyl amines, $AlMe_3$, CH_2Cl_2; (c) H_2, $Pd(OH)_2/C$, MeOH.

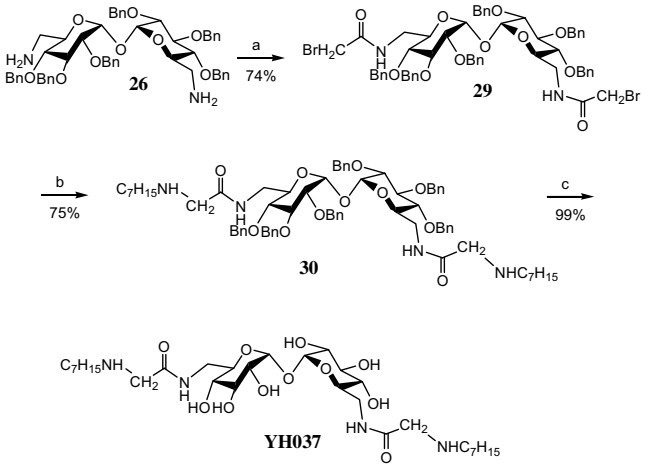
compounds are subjected to hydrogenation to furnish the final products. In an effort to increase the solubility of trehalose derivatives in aqueous media, we synthesized **YH037** with the expectation that the additional NH group would improve the solubility (Scheme 6). Coupling of **26** with bromoacetic acid affords **29**. Nucleophilic addition of **29** with heptylamine gives **30**, which is converted into **YH037** via hydrogenation.

We also designed **YH036** with a diacylhydrazine functionality with the expectation that the added –CONH– group will increase both antibacterial activity and solubility (Scheme 7). **YH036** is synthesized from **14** through hydrolysis, coupling with octanoic hydrazide, and hydrogenation. We also constructed a trehalose derivative, **YH041** with a mono-hydrocarbon chain (Scheme 8). Starting from a known compound **33**, one of the *O*-6 benzyl groups is selectively removed using Ac_2O, TMSOTf followed by base hydrolysis. Azido substitution at the *O*-6 position provided **35**, which is converted to **36** with the same conditions. The final product, **YH041** is synthesized from the identical procedures for the preparation of **YH023**. **YH041** is found to be soluble in water.

After completion of the synthesis, the trehalose derivatives are assayed against *M. smegmatis* (ATCC 14468), using isoniazid (INH) as the positive control.[15] Since *M. tuberculosis* is pathogenic and not easily manipulated experimentally, *M. smegmatis* is typically used to investigate issues related to the biology and pathogenesis of the former. Although associated with disease,



Scheme 5. Reagents: (a) (1) Tf_2O, pyr., CH_2Cl_2, (2) NaN_3, DMF; (b) PMe_3, THF, NaOH; (c) triphosgene, Et_3N, $C_8H_{17}NH_2$; (d) $C_9H_{19}COCl$, CH_2Cl_2; (e) H_2, $Pd(OH)_2/C$, MeOH.



Scheme 6. Reagents: (a) $BrCH_2CO_2H$, DMF; DIC; (b) $C_7H_{15}NH_2$, Cs_2CO_3, DMF; (c) H_2, Pd/C, MeOH.

Table 1. Inhibition zones of trehalose derivatives against *M. smegmatis*

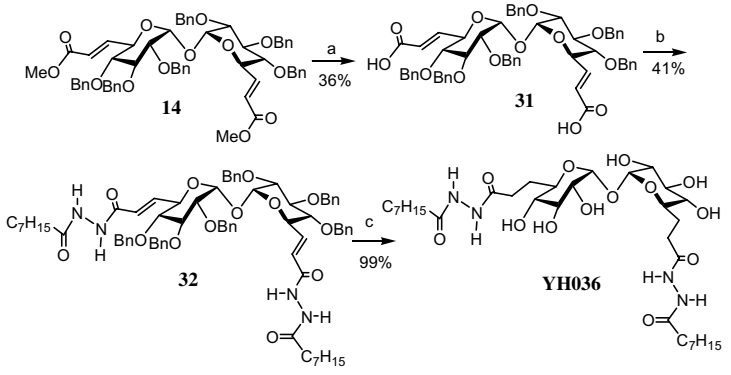
Compound[a]	Inhibition zone (mm)
INH	18
YH008	6
YH011	Inactive
YH012	10
YH017	6
YH018	5
YH019	11
YH020	Inactive
YH023	20
YH024	5
YH025	10
YH026	8
YH027	Inactive
YH028	Inactive
YH029	Inactive
YH030	Inactive
YH031	8
YH032	11
YH033	6
YH034	Inactive
YH035	Inactive
YH036	12
YH037	19
YH041	Inactive

[a] Concentration used: INH: 0.25 mg/mL, trehalose derivatives: 10 mg/mL.

M. smegmatis is not deemed an important human pathogen.[16] It is more amenable to experimentation since unlike *M. tuberculosis* it is a fast grower and genetically more tractable.[17] Most importantly, *M. smegmatis* shares several clinically important properties that characterize *M. tuberculosis*, including similar resistance to certain macrolide drugs.[18] Due to the poor solubility of our trehalose derivatives, DMSO/water solutions were used for the diffusion assay. The antibacterial activity of the trehalose derivatives is evaluated by the standard diffusion assay. The inhibition zones are summarized in Table 1.[19]

3. Discussion

The attempts to determine standard MIC values in liquid broth were hampered by the poor water-solubility.



Scheme 7. Reagents: (a) $LiOH–H_2O$, THF, H_2O; (b) $H_2NNHC(O)C_7H_{15}$; (c) H_2, $Pd(OH)_2/C$, MeOH.

Nevertheless, the MIC for the most active compound, **YH023** is estimated to be >256 μM. We have also derived the structure–activity relationship of the trehalose derivatives:

1. Compounds with di-hydrocarbon chain have similar or better activities than compounds with mono-hydrocarbon chain.[20]
2. The activity trends among functionalities:

   reversed acyl ≈ α-alkylaminoacetyl > acyl ≈ urea > ether > compounds without hydrocarbon chain

3. The optimal chain length is around C_8 or C_9.
4. Incorporation of oxygen atoms within the long hydrocarbon chain cannot be tolerated.

Despite significant progress, the mechanism of INH action is not fully understood. It is generally proposed that INH is a prodrug that can be rapidly transported into actively growing bacteria then activated via the action of catalase/peroxidase.[21] Several enzymes have been reported as the targets of activated INH, including enzymes for the biosynthesis of mycolic acid,[22] catalase/peroxidase involved in the activation of INH,[23] and alkyl hydroperoxide reductase.[24] While highly active against *M. tuberculosis*, INH is noted for its rapid sterilizing activity but lack of effectiveness during TB relapse.[25] The later leads to the requirement for long-term INH chemotherapy, and, hence, the increased chance of treatment failure. Unlike INH, the trehalose-based compound with reversed acyl linkage, **YH023**, is bacteriocidal.

INH has been found to induce the over-expression of ag85 protein complex,[26] and transient high-level resistance in *M. tuberculosis*.[27] On the other hand, it has been reasoned that the trehalose derivatives can act as inhibitors of ag85 protein complex.[10] Therefore, we evaluate the synergistic or additive effect between INH and the lead compound **YH023**. When INH and **YH023** were combined and employed together, we observed that the growth inhibitory zones of *M. smegmatis* were slightly larger than with INH alone at the same concentrations. Furthermore, with the **YH023**–INH combination, no return of growth was observed over a period of 2 weeks in the initially inhibited zones (Fig. 2). In contrast, significant growth occurred in the inhibitory zones with INH alone. This result suggests that **YH023** is synergistic with INH against *M. smegmatis*. This finding is potentially significant in shortening the timeline of TB treatment, leading to higher rates of success and lower cost in the battle against this disease.

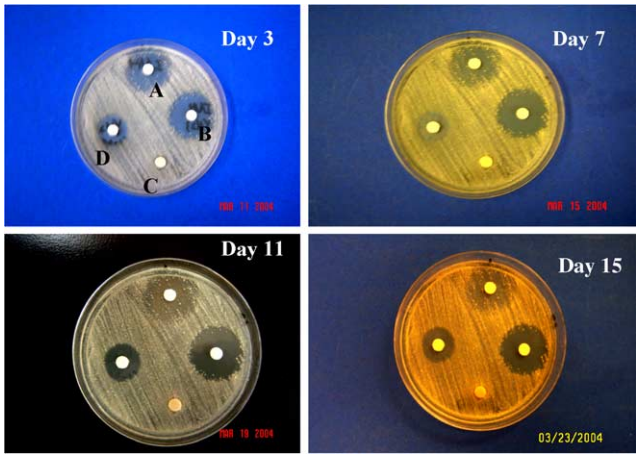
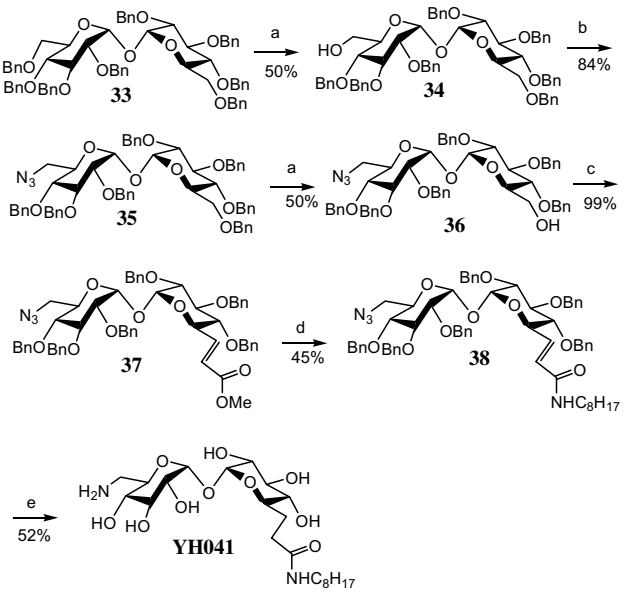


Figure 2. Assay of **YH023** and INH against *M. smegmatis* in water/DMSO solution. A: INH (250 μg/mL); B: INH (250 μg/mL) + **YH023** (10 mg/mL); C: DMSO; D: **YH023** (10 mg/mL).



Scheme 8. Reagents: (a) (1) Ac_2O, TMSOTf, (2) NaOMe, MeOH; (b) (1) Tf_2O, CH_2Cl_2, pry., (2) NaN_3, DMF; (c) (1) $(COCl)_2$, DMSO, DIPEA, (2) $MeOC(O)CH_2P(O)(OEt)_2$, NaH, THF; (d) $C_8H_{17}NH_2$, $AlMe_3$, CH_2Cl_2; (e) H_2, $Pd(OH)_2/C$, MeOH.

4. Conclusion

In summary, we have produced a new class of anti-TB compounds that may target the ag85 protein complex, which is a new target for the development of anti-TB agents. The observation that our compounds are bacteriocidal against *Mycobacterium* suggests that they may be developed to address resistance problems common to the use of current anti-TB drugs. We are currently synthesizing trehalose derivatives with the goal of increasing their solubility in aqueous media and the antibacterial activity of these compounds.

5. Experimental

Proton magnetic resonance spectra were recorded using a Jeol 270 or Bruker 400 spectrometers. Chemical shifts were reported as parts per million (ppm) downfield from tetramethylsilane in δ unit, and coupling constants were given in cycles per second (Hz). Splitting patterns were designed as s, singlet; d, doublet; t, triplet; q, quartet;

m, multiplet. ^{13}C spectra were obtained using the Jeol 270 spectrometer at 68 MHz, and were reported in ppm with center line of the triplet at 77.0 ppm for chloroform-*d*. Routine ^{13}C NMR spectra were fully decoupled by broad-band waltz decoupling. All NMR spectra were recorded at ambient temperature unless otherwise noted. Low-resolution fast-atom bombardment (LRFAB) and high-resolution fast-atom bombardment (HRFAB) were provided by the Mass Spectrometry Facilities, University of California, Riverside.

Chemical reagents and starting materials were purchased from Aldrich Chemical Co. or Acros Chemical Co. and were used without purification unless otherwise noted. Dichloromethane was distilled over CaH_2. Tetrahydrofuran, triethylamine, diisopropylethylamine dried and stored with activated 4 Å molecular sieves under nitrogen. Pyridine was dried over CaH_2 and kept under nitrogen.

5.1. 2,2′,3,3′,6,6′-Hexa-*O*-benzyl-4,4′-di-*O*-octyl-α-D-trehalose (2)

To a solution of **1** (0.10 g, 0.11 mmol) dissolved in 3 mL of anhydrous THF at 0 °C, TBAI (0.02 g, catalytic amount), NaH (0.02 g, 0.72 mmol), and 1-octyl bromide (0.063 mL, 0.36 mmol) were added. The reaction was stirred for 12 h, allowing the temperature to be warmed up to room temperature. After completion of the reaction, the reaction was quenched with few drops of MeOH. After removal of solvent, the crude product was diluted with Et_2O. The organic solution was washed with 1 N $HCl_{(aq)}$, water, saturated $NaHCO_{3(aq)}$, and brine, then dried over $Na_2SO_{4(s)}$. After removal of the solvent followed by purification with a gradient column chromatography (hexane–EtOAc = 100:0 to 60:40), the product was obtained as white powder (0.08 g, 0.07 mmol, 64%). ^1H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 5.20 (d, $J = 3.3$ Hz, 2H, H-1), 4.95 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.85 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.67 (s, 4H, PhCH_2O), 4.55 (d, $J = 11.8$ Hz, 2H, PhCH_2O), 4.40 (d, $J = 11.8$ Hz, 2H, PhCH_2O), 4.05–4.10 (m, 2H), 3.93 (t, $J = 9.6$ Hz, 2H), 3.70–3.82 (m, 2H), 3.30–3.60 (m, 10H), 1.10–1.60 (m, 24H), 0.87 (t, $J = 6.9$ Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 139.1 (s), 138.4 (s), 138.0 (s), 128.4 (s), 128.0 (s), 127.7 (s), 127.5 (s), 94.6 (s, C-1), 81.8 (s), 79.4 (s), 77.8 (s), 75.6 (s), 73.5 (s), 73.3 (s), 72.8 (s), 70.8 (s), 68.3 (s), 32.0 (s), 30.7 (s), 29.7 (s), 29.4 (s), 26.3 (s), 22.8 (s), 14.2 (s); MALDI Calcd for $C_{70}H_{90}O_{11}Na$ ($[M+Na]^+$) 1129.6375; measure 1129.6412.

5.2. 2,2′,3,3′,6,6′-Hexa-*O*-benzyl-4-*O*-octyl-α-D-trehalose (3)

To a solution of **1** (0.15 g, 0.17 mmol) dissolved in 3 mL of THF at 0 °C, TBAI (0.01 g, catalytic amount), NaH (0.012 g, 0.51 mmol), and 1-octyl bromide (0.050 mL, 0.26 mmol) were added. The reaction was stirred for 12 h, allowing the temperature to be warmed up to room temperature. After completion of the reaction, the reaction was quenched with few drops of MeOH. After removal of solvent, the crude product was diluted with Et_2O. The organic solution was washed with 1 N $HCl_{(aq)}$, water, saturated $NaHCO_{3(aq)}$, and brine, then dried over $Na_2SO_{4(s)}$. After removal of the solvent followed by purification with a gradient column chromatography (hexane–EtOAc = 100:0 to 60:40), the product was obtained as white powder (0.070 g, 0.070 mmol, 41%). ^1H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 5.23 (d, $J = 3.6$ Hz, 1H, H-1), 5.20 (d, $J = 3.6$ Hz, 1H, H-1′), 5.02 (d, $J = 11.2$ Hz, 1H, PhCH_2O), 4.95 (d, $J = 10.9$ Hz, 1H, PhCH_2O), 4.83 (d, $J = 10.9$ Hz, 1H, PhCH_2O), 4.80 (d, $J = 11.6$ Hz, 1H, PhCH_2O), 4.70 (d, $J = 11.9$ Hz, 1H, PhCH_2O), 4.66 (s, 2H, PhCH_2O), 4.64 (d, $J = 11.9$ Hz, 1H, PhCH_2O), 4.4–4.6 (m, 4H), 4.1–4.2 (m, 2H), 3.9–4.0 (m, 2H), 3.7–3.8 (m, 2H), 3.3–3.6 (m, 2H), 1.00–2.00 (m, 12H), 0.89 (t, $J = 6.3$ Hz, 3H, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 139.0 (s), 138.9 (s), 138.3 (s), 138.2 (s), 138.0 (s), 137.9 (s), 128.6 (s), 128.4 (s), 128.1 (s), 128.0 (s), 127.9 (s), 127.7 (s), 127.7 (s), 127.6 (s), 127.6 (s), 127.5 (s), 94.5 (s, C-1), 94.3 (s, C-1′), 81.8 (s), 81.1 (s), 79.2 (s), 79.1 (s), 77.8 (s), 75.6 (s), 75.3 (s), 73.7 (s), 73.6 (s), 73.3 (s), 72.9 (s), 72.5 (s), 70.9 (s, 2C), 70.6 (s), 69.3 (s), 68.3 (s), 32.0 (s), 30.6 (s), 29.6 (s), 29.4 (s), 26.3 (s), 22.8 (s), 14.2 (s); MALDI Calcd for $C_{62}H_{74}O_{11}Na$ ($[M+Na]^+$) 1017.5123; measure 1017.5125.

General procedure for hydrogenation: The starting material was added with catalytic amount of $Pd(OH)_2/C$ (20% Degussa type) or Pd/C (10%) and 5 mL of degassed MeOH or MeOH–EtOAc (1:1). After being further degassed, the reaction mixture was stirred at room temperature under atmospheric H_2 pressure. After being stirred for 1 day, the reaction mixture was filtered through Celite. The residue was washed with MeOH, and the combined solution was concentrated, affording pure final product.

5.3. 4,4′-Di-*O*-octyl-α-D-trehalose (YH008)

Please refer to the general procedure for hydrogenation. ^1H NMR (270 MHz, CD_3OD) δ 4.82 (d, $J = 3.3$ Hz, 2H, H-1), 3.30–4.00 (m, 12H), 3.22 (dd, $J = 9.8$ Hz, $J = 3.3$ Hz, 2H, H-2), 3.04 (t, $J = 9.8$ Hz, 2H, H-4), 1.00–1.60 (m, 24H), 0.87 (t, $J = 6.9$ Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, CD_3OD) δ 93.7 (s, C-1), 78.4 (s), 73.2 (s), 72.3 (s), 72.2 (s), 71.8 (s), 60.8 (s), 31.8 (s), 30.5 (s), 29.5 (s), 29.3 (s), 26.2 (s), 22.7 (s), 14.5 (s); LRFAB *m/e* 589 ($[M+Na]^+$); HRFAB Calcd for $C_{28}H_{54}O_{11}Na$ ($[M+Na]^+$) *m/e* 589.3564; measure *m/e* 589.3540.

5.4. 4-*O*-Octyl-α-D-trehalose (YH018)

Please refer to the general procedure for hydrogenation. ^1H NMR (270 MHz, CD_3OD) δ 5.09 (d, $J = 3.3$ Hz, 1H, H-1), 5.08 (d, $J = 3.3$ Hz, 1H, H-1′), 3.00–4.00 (m, 14H), 1.00–2.00 (m, 12H), 0.88 (t, $J = 5.9$ Hz, 3H, CH_2CH_3); ^{13}C NMR (68 Hz, CD_3OD) δ 93.7 (s, C-1), 93.6 (s, C-1′), 78.3 (s), 73.3 (s), 73.2 (s), 72.6 (s), 72.4 (s), 72.1 (s), 71.9 (s), 71.6 (s), 70.6 (s), 61.3 (s), 60.8 (s), 31.7 (s), 30.1 (s), 29.3 (s), 29.1 (s), 25.9 (s), 23.4 (s), 13.1 (s); LRFAB *m/e* 477 ($[M+Na]^+$); HRFAB Calcd for

$C_{20}H_{38}O_{11}Na$ ($[M+Na]^+$) *m/e* 477.2312; measure *m/e* 477.2305.

5.5. 2,2′,3,3′-Tetra-*O*-benzyl-4,4′-di-*O*-octyl-6,6′-dideoxy-α-D-trehalose (5)

To a solution of **4** (0.10 g, 0.15 mmol) dissolved in 3 mL of anhydrous THF at 0 °C, TBAI (0.020 g, catalytic amount), NaH (0.023 g, 0.96 mmol), and 1-octyl bromide (0.080 mL, 0.48 mmol) were added. The reaction was stirred for 12 h, allowing the temperature to be warmed up to room temperature. After completion of the reaction, the reaction was quenched with few drops of MeOH. After removal of solvent, the crude product was diluted with Et_2O. The organic solution was washed with 1 N $HCl_{(aq)}$, water, saturated $NaHCO_{3(aq)}$, and brine, then dried over $Na_2SO_{4(s)}$. After removal of the solvent followed by purification with a gradient column chromatography (hexane–EtOAc = 100:0 to 60:40), the product was obtained as white powder (0.090 g, 0.10 mmol, 67%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 20H), 5.09 (d, J = 3.6 Hz, 2H, H-1), 4.96 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.85 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.70 (s, 4H, PhCH_2O), 4.06–4.20 (m, 2H), 3.93 (t, J = 9.2 Hz, 2H), 3.83 (dt, J = 9.2 Hz, J = 6.6 Hz, 2H), 3.50–3.61 (m, 2H), 3.51 (dd, J = 9.2 Hz, J = 3.6 Hz, 2H, H-2), 2.93 (t, J = 9.2 Hz, 2H), 1.20–1.65 (m, 24H), 1.14 (d, J = 6.6 Hz, 6H, H-6), 0.89 (t, J = 6.3 Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 139.1 (s), 138.4 (s), 128.4 (s), 128.0 (s), 127.6 (s), 94.2 (s, C-1), 84.4 (s), 81.4 (s), 79.8 (s), 75.7 (s), 73.6 (s), 72.8 (s), 67.4 (s), 32.0 (s), 30.6 (s), 29.6 (s), 29.4 (s), 26.3 (s), 22.8 (s), 17.9 (s), 14.2 (s); MALDI Calcd for $C_{56}H_{78}O_9Na$ ($[M+Na]^+$) 917.5538; measure 917.5559.

5.6. 4,4′-Di-*O*-octyl-6,6′-dideoxy-α-D-trehalose (YH011)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 4.93 (d, J = 4.0 Hz, 2H, H-1), 3.82–3.93 (m, 4H), 3.79 (t, J = 9.2 Hz, 2H, H-3), 3.56 (dt, J = 9.2 Hz, J = 6.6 Hz, 2H, H-5), 3.42 (dd, J = 9.2 Hz, J = 4.0 Hz, 2H, H-2), 2.79 (t, J = 9.2 Hz, 2H, H-4), 1.10–1.60 (m, 24H), 1.20 (d, J = 6.6 Hz, 6H, H-6), 0.89 (t, J = 6.3 Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, CD_3OD) δ 93.7 (s, C-1), 84.7 (s), 73.2 (s), 72.7 (s), 72.4 (s), 66.9 (s), 31.7 (s), 30.1 (s), 29.3 (s), 29.1 (s), 25.9 (s), 22.4 (s), 17.0 (s), 13.1 (s); LRFAB *m/e* 557 ($[M+Na]^+$); HRFAB Calcd for $C_{28}H_{54}O_9Na$ ($[M+Na]^+$) *m/e* 557.3666; measure *m/e* 557.3652.

5.7. 2,2′,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-di-*O*-octyl-α-D-trehalose (7) and 2,2′,3,3′,4,4′-hexa-*O*-benzyl-6-*O*-octyl-α-D-trehalose (8)

To a solution of **6** (0.46 g, 0.52 mmol) in anhydrous DMF (5 mL), NaH (0.03 g, 1.04 mmol) was slowly added followed by a catalytic amount of TBAI and octyl bromide (0.14 mL, 0.78 mmol). The reaction was stirred overnight at room temperature. After complete consumption of the starting material, analyzed by TLC (hexane–EtOAc = 65:35), the reaction was quenched by addition of a few drops of H_2O. The solvent was then removed and the crude residue was purified by column chromatography. Pure products **7** and **8** were collected (0.09 g, 0.08 mmol, 16% and 0.15 g, 0.15 mmol, 29%, respectively).

5.8. 2,2′,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-di-*O*-octyl-α-D-trehalose (7)

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.3–7.4 (m, 30H), 5.21 (d, J = 3.6 Hz, H-1, 2H), 4.99 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.86 (d, J = 10.9 Hz, 4H, PhCH_2O), 4.68 (s, 4H, PhCH_2O), 4.59 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.15 (d, J = 10.2 Hz, 2H), 4.03 (dd, J = 9.6 Hz, J = 9.2 Hz, 2H), 3.68 (dd, J = 9.9 Hz, J = 9.2 Hz, 2H), 3.58 (dd, J = 9.6 Hz, J = 3.6 Hz, 2H), 3.2–3.5 (m, 8H), 1.5–1.6 (m, 4H), 1.2–1.3 (m, 20H), 0.86 (t, J = 6.9 Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 139.0 (s), 138.7 (s), 138.6 (s), 128.5 (s), 128.42 (s), 128.41 (s), 128.0(s), 127.96 (s), 127.8 (s), 127.6 (s), 94.6 (s, C-1), 81.9 (s), 79.5 (s), 77.8 (s), 75.7 (s), 75.2 (s), 72.7 (s), 71.9 (s), 70.7 (s), 69.0 (s), 31.9 (s), 29.7 (s), 29.6 (s), 29.3 (s), 26.3 (s), 22.7 (s), 14.2 (s); MALDI Calcd for $C_{70}H_{90}O_{11}Na$ ($[M+Na]^+$) *m/e* 1129.6375; measure *m/e* 1129.6340.

5.9. 2,2′,3,3′,4,4′-Hexa-*O*-benzyl-6-*O*-octyl-α-D-trehalose (8)

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.3–7.4 (m, 30H), 5.21 (d, J = 3.9 Hz, 1H), 5.19 (d, J = 3.9 Hz, 1H), 5.02 (d, J = 10.9 Hz, 1H, PhCH_2O), 5.01 (d, J = 10.9 Hz, 1H, PhCH_2O), 4.91 (s, 2H, PhCH_2O), 4.87 (s, 2H, PhCH_2O), 4.6–4.7 (m, 6H, PhCH_2O), 4.0–4.2 (m, 4H), 3.70 (t, J = 10.8 Hz, 1H), 3.2–3.6 (m, 9H), 1.55–1.57 (m, 2H), 1.2–1.3 (m, 10H), 0.88 (t, J = 5.8 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.98 (s), 138.92 (s), 138.6 (s), 138.4 (s), 138.23 (s), 138.21 (s), 128.6 (s), 128.5 (s), 128.2 (s), 128.0 (s), 127.8 (s), 127.6 (s), 94.4 (s, C-1), 94.2 (s, C-1′), 81.9 (s), 81.7 (s), 79.6 (s), 79.5 (s), 77.9 (s), 77.4 (s), 75.7 (s, 2 carbons), 75.2 (s, 2 carbons), 73.0 (s), 72.9 (s), 71.9 (s), 71.3 (s), 70.8 (s), 69.0 (s), 61.6 (s), 31.9 (s), 29.7 (s), 29.6 (s), 29.3 (s), 26.3 (s), 22.8 (s), 14.2 (s); MALDI Calcd for $C_{62}H_{74}O_{11}Na$ ($[M+Na]^+$) 1017.5123; measure 1017.5094.

5.10. 6,6′-Di-*O*-octyl-α-D-trehalose (YH019)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 5.08 (d, J = 3.6, 2H, H-1), 3.89–3.93 (m, 2H), 3.7–3.8 (m, 2H), 3.6–3.7 (m, 4H), 3.4–3.6 (m, 4H), 3.2–3.3 (m, 4H), 1.5–1.6 (m, 4H), 1.2–1.3 (m, 20H), 0.89 (t, J = 6.9 Hz, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 93.7 (s, C-1), 73.3 (s), 71.8 (s), 71.4 (s), 71.3 (s), 70.8 (s), 69.8 (s), 31.7 (s), 29.4 (s), 29.3 (s), 29.1 (s), 25.9 (s), 22.4 (s), 13.1 (s); LRFAB *m/e* 589 ($[M+Na]^+$); HRFAB Calcd for $C_{28}H_{54}O_{11}Na$ ($[M+Na]^+$) *m/e* 589.3564; measure *m/e* 589.3564.

5.11. 6-*O*-Octyl-α-D-trehalose (YH020)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 5.10 (d, J = 3.6 Hz, 1H, H-1), 5.09 (d, J = 3.6 Hz, 1H, H-1′), 3.88–3.93 (m, 1H), 3.75–3.82 (m, 3H), 3.6–3.7 (m, 2H), 3.4–3.6 (m, 4H),

3.3–3.4 (m, 4H), 1.5–1.6 (m, 2H), 1.30 (m, 10H), 0.89 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (68 MHz, CD_3OD) δ 93.74 (s, C-1), 93.66 (s, C-1′), 73.3 (s), 73.2 (s), 72.5 (s), 71.9 (s), 71.8 (s), 71.4 (s), 71.3 (s), 70.8 (s), 70.6 (s), 69.8 (s), 61.3 (s), 31.7 (s), 29.4 (s), 29.3 (s), 29.1 (s), 25.9 (s), 22.4 (s), 13.1 (s); LRFAB *m/e* ([M+Na]$^+$); HRFAB Calcd for $C_{20}H_{38}O_{11}Na$ ([M+Na]$^+$) *m/e* 477.2312; measure *m/e* 477.2318.

5.12. 2,2′,3,3′,4,4′-Hexa-*O*-benzyl-α-D-trehalopyranuronic acid (9)

To a solution of $(COCl)_2$ (1.46 mL, 17.0 mmol) in 10 mL anhydrous CH_2Cl_2 at −78 °C, anhydrous DMSO (2.43 mL, 34.2 mmol) was added and the resulting solution was stirred for 15 min, allowing the temperature to be warmed up to −65 °C. To the reaction flask, a solution of **6** (5.0 g, 5.7 mmol) in 5 mL CH_2Cl_2 was added. The reaction mixture was stirred for 0.5 h allowing the temperature to be warmed up to −45 °C. To this solution, anhydrous Et_3N (9.50 mL, 68.4 mmol) was added, and the reaction was allowed to be warmed up to −10–0 °C in 0.5 h. After completion of the reaction, the reaction mixture quenched with 1 N HCl and diluted with Et_2O. The combined organic layers were washed with pH 7 buffer (three times), brine, and dried over Na_2SO_4. After removal of solvent, the crude product, dialdehyde, (4.70 g, 5.35 mmol, 94%) was obtained as viscous oil, and used without further purification. To this solution of dialdehyde (0.5 g, 0.57 mmol) in 5 mL H_2O–CH_3CN (1:4) solution at 0 °C, NaH_2PO_4 (0.03 g, 0.6%), 30% H_2O_2 (0.14 mL, 1.26 mmol), and $NaClO_2$ (0.16 g, 17.1 mmol) were added. The reaction mixture was stirred for 12 h, allowing the temperature to be warmed up to room temperature. After the completion of the reaction, the reaction was quenched with 0.1 g $NaHSO_3$. The organic layer from the reaction was filtered through a SPE column packed with silica gel. The residue was washed with MeOH. After removal of solvent, the product (0.41 g, 0.45 mmol, 79%) was afforded as pale yellowish viscous oil, and used without further purification. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 5.17 (d, $J = 3.3$ Hz, 2H, H-1), 5.03 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.90 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.83 (d, $J = 10.6$ Hz, 2H, PhCH_2O), 4.60–4.75 (m, 8H), 4.08 (t, $J = 9.6$ Hz, 2H, H-3), 3.77 (t, $J = 9.6$ Hz, 2H, H-4), 3.60 (dd, $J = 9.6$ Hz, $J = 3.3$ Hz, 2H, H-2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 174.6 (s, *C*OOH), 138.5 (s), 137.5 (s), 137.5 (s), 128.6 (s), 128.4 (s), 128.2 (s), 126.0 (s), 127.8 (s), 95.0 (s, C-1), 81.1 (s), 79.3 (s), 78.1 (s), 75.9 (s), 75.5 (s), 73.4 (s), 70.4 (s); LRFAB *m/e* 933 ([M+Na]$^+$); HRFAB Calcd for $C_{54}H_{54}O_{13}Na$ ([M+Na]$^+$) *m/e* 933.3462; measure *m/e* 933.3499.

5.13. Bis(2,3,4,-tri-*O*-benzyl-*N*-octyl-α-D-glucopyranosyluronamide)ether (10)

To a solution of **9** (0.1 g, 0.11 mmol) in anhydrous CH_2Cl_2 (10 mL) and DMF (0.02 mL) at room temperature, $(COCl)_2$ (0.024 mL, 0.28 mmol) was added. The reaction was stirred for 1 h. After removal of solvents, the residue was redissolved in CH_2Cl_2 and added with octyl amine (0.073 mL, 0.44 mmol) at 0 °C. The reaction was stirred for 12 h, allowing the temperature to be warmed up to room temperature. After removal of the solvent followed by purification with a gradient column chromatography (hexane–EtOAc = 75:25 to 25:75), the product was obtained as a pale yellowish oil (0.04 g, 0.036 mmol, 33%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 5.30 (t, $J = 5.6$ Hz, 2H, CON*H*), 5.13 (d, $J = 3.3$ Hz, 2H, H-1), 4.96 (d, $J = 11.2$ Hz, 2H, PhCH_2O), 4.90 (d, $J = 11.2$ Hz, 2H, PhCH_2O), 4.77 (d, $J = 12.2$ Hz, 2H, PhCH_2O), 4.76 (d, $J = 10.2$ Hz, 2H, PhCH_2O), 4.65 (d, $J = 12.2$ Hz, 2H, PhCH_2O), 4.54 (d, $J = 10.2$ Hz, 2H, PhCH_2O), 4.31 (d, $J = 9.6$ Hz, 2H, H-5), 4.05 (t, $J = 9.6$ Hz, 2H, H-3), 3.69 (t, $J = 9.6$ Hz, 2H, H-4), 3.62 (dd, $J = 9.6$ Hz, $J = 3.3$ Hz, 2H, H-2), 2.9–3.0 (m, 4H, CONHCH_2), 1.00–2.00 (m, 24H), 0.86 (t, $J = 6.6$ Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.5 (s, *C*ONH), 138.5 (s), 138.2 (s), 138.0 (s), 128.7 (s), 128.5 (s), 128.4 (s), 128.2 (s), 128.0 (s), 127.8 (s), 127.7 (s), 127.0 (s), 94.8 (s, C-1), 81.4 (s), 80.3 (s), 78.7 (s), 75.8 (s), 75.4 (s), 73.1 (s), 71.6 (s), 39.8 (s), 31.9 (s), 29.33 (s), 29.27 (s), 29.21 (s), 27.0 (s), 22.7 (s), 14.2 (s); MALDI Calcd for $C_{70}H_{88}N_2O_{11}Na$ ([M+Na]$^+$) 1155.6280; measure 1155.6236.

5.14. Bis(*N*-octyl-α-D-glucopyranosyluronamide)ether (YH012)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 5.13 (d, $J = 3.0$ Hz, 2H, H-1), 4.26 (d, $J = 9.9$ Hz, 2H, H-5), 3.79 (t, $J = 9.9$ Hz, 2H, H-3), 3.55 (dd, $J = 9.9$ Hz, $J = 3.0$ Hz, 2H, H-2), 3.48 (t, $J = 9.9$ Hz, 2H, H-4), 3.20 (t, $J = 6.6$ Hz, 4H, CONHCH_2), 1.20–1.60 (m, 24H), 0.89 (t, $J = 5.3$ Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, CD_3OD) δ 171.2 (s, *C*ONH), 95.2 (s, C-1), 72.7 (s), 72.6 (s), 71.2 (s, 2C), 39.0 (s), 31.7 (s), 29.1 (s), 29.0 (s, 2 carbons), 26.6 (s), 22.4 (s), 13.1 (s); LRFAB *m/e* 615 ([M+Na]$^+$); HRFAB Calcd for $C_{28}H_{52}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 615.3469; measure *m/e* 615.3505.

5.15. Bis(2,3,4,-tri-*O*-benzyl-*N*-dodectyl-α-D-glucopyranosyluronamide)ether (11)

Please refer to the procedure for the preparation of **10**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 5.31 (t, $J = 5.9$ Hz, 2H, CON*H*), 5.13 (d, $J = 3.6$ Hz, 2H, H-1), 5.00 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.92 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.78 (d, $J = 12.2$ Hz, 2H, PhCH_2O), 4.78 (d, $J = 10.2$ Hz, 2H, PhCH_2O), 4.65 (d, $J = 12.2$ Hz, 2H, PhCH_2O), 4.54 (d, $J = 10.2$ Hz, 2H, PhCH_2O), 4.30 (d, $J = 9.9$ Hz, 2H, H-5), 4.05 (t, $J = 9.2$ Hz, 2H, H-3), 3.68 (t, $J = 9.2$ Hz, 2H, H-4), 3.61 (dd, $J = 9.2$ Hz, $J = 3.6$ Hz, 2H, H-2), 2.8–3.0 (m, 4H, CONHCH_2), 1.00–2.00 (m, 40H), 0.87 (t, $J = 6.6$ Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.5 (s, *C*ONH), 138.5 (s), 138.2 (s), 138.0 (s), 128.7 (s), 128.5 (s), 128.2 (s), 128.0 (s), 127.8 (s), 127.7 (s), 127.0 (s), 94.8 (s, C-1), 81.4 (s), 80.3 (s), 78.7 (s), 75.8 (s), 75.4 (s), 73.0 (s), 71.6 (s), 39.8 (s), 32.0 (s), 29.8 (s, 2 carbons), 29.7 (s), 29.6 (s), 29.4 (s), 29.3 (s, 2 carbons), 27.0 (s), 22.8 (s), 14.2 (s); MALDI Calcd for

$C_{78}H_{104}N_2O_{11}Na$ ($[M+Na]^+$) *m/e* 1267.7532; measure *m/e* 1267.7590.

5.16. Bis(*N*-dodectyl-α-D-glucopyranosyluronamide)ether (YH017)

Please refer to the general procedure for hydrogenation. ^1H NMR (270 MHz, CD_3OD) δ 5.14 (d, $J = 3.6$ Hz, 2H, H-1), 4.27 (d, $J = 9.9$ Hz, 2H, H-5), 2.80–3.80 (m, 10H), 1.10–1.80 (m, 40H), 0.92 (t, $J = 6.9$ Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, CD_3OD) δ 168.0 (s, *C*ONH), 95.0 (s, C-1), 72.7 (s), 72.5 (s), 71.2 (s, 2 carbons), 38.9 (s), 31.7 (s), 29.42 (s, 2 carbons), 29.40 (s, 2 carbons), 29.1 (s, 2 carbons), 29.0 (s), 26.6 (s), 22.4 (s), 13.1 (s); LRFAB *m/e* 727 ($[M+Na]^+$); HRFAB Calcd for $C_{36}H_{68}N_2O_{11}Na$ ($[M+Na]^+$) *m/e* 727.4721; measure *m/e* 727.4720.

5.17. Bis(2,3,4,-tri-*O*-benzyl-*N*-((*R*)-1-ethoxycarbonylethyl)-α-D-glucopyranosyluronamide)ether (12)

To a solution of **9** (1.0 g, 1.10 mmol) in pyridine, ethyl L-alanine ester HCl (0.55 g, 4.0 mmol) and EDC·HCl (0.76 g, 4.0 mmol) were added. The reaction was stirred for 12 h at 50 °C. After completion of the reaction, the reaction mixture was diluted with EtOAc. The combined organic solution was washed with 1 N $HCl_{(aq)}$, water, saturated $NaHCO_{3(aq)}$, and brine, then dried over $Na_2SO_{4(s)}$. After removal of the solvent, followed by purification with a gradient column chromatography (hexane–EtOAc = 75:25 to 25:75), the product was obtained as a yellowish viscous oil (0.3 g, 0.27 mmol, 25%). ^1H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 6.53 (d, $J = 6.9$ Hz, 2H, CON*H*), 5.10 (d, $J = 3.6$ Hz, 2H, H-1), 4.99 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.89 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.80 (d, $J = 10.2$ Hz, 2H, PhCH_2O), 4.70 (d, $J = 10.2$ Hz, 2H, PhCH_2O), 4.68 (s, 4H, PhCH_2O), 4.54 (d, $J = 9.9$ Hz, 2H, H-5), 4.42 (dt, $J = 6.9$ Hz, $J = 7.2$ Hz, 2H, COC*H*(CH_3)NH), 4.13 (q, $J = 6.9$ Hz, 4H, CH_3CH_2OOC), 4.05 (t, $J = 9.9$ Hz, 2H, H-3), 3.66 (t, $J = 9.9$ Hz, 2H, H-4), 3.56 (dd, $J = 9.9$ Hz, $J = 3.6$ Hz, 2H, H-2), 1.23 (d, $J = 7.2$ Hz, 6H, COCH(CH_3)NH), 1.18 (t, $J = 6.9$ Hz, 6H, CH_3CH_2-OOC); ^{13}C NMR (68 MHz, $CDCl_3$) δ 172.5 (s, *C*$OOCH_2CH_3$), 168.5 (s, *C*ONH), 138.6 (s), 138.0 (s), 137.9 (s), 128.6 (s), 128.4 (s), 128.0 (s), 127.9 (s), 127.8 (s), 127.7 (s), 95.4 (s, C-1), 81.4 (s), 80.2 (s), 78.1 (s), 75.8 (s), 75.4 (s), 73.0 (s), 71.1 (s), 61.5 (s), 48.1 (s), 18.1 (s), 14.2 (s); MALDI Calcd for $C_{64}H_{72}N_2O_{15}Na$ ($[M+Na]^+$) *m/e* 1131.4825; measure *m/e* 1131.4779.

5.18. Bis(*N*-((*R*)-1-ethoxycarbonylethyl)-α-D-glucopyranosyluronamide)ether (YH024)

Please refer to the general procedure for hydrogenation. ^1H NMR (270 MHz, CD_3OD) δ 5.17 (d, $J = 3.3$ Hz, 2H, H-1), 4.45 (q, $J = 7.2$ Hz, 2H, CONHC*H*(CH_3)), 4.35 (d, $J = 9.9$ Hz, 2H, H-5), 4.20 (q, J = 6.9 Hz, 4H, CH_3CH_2OOC), 3.80 (t, $J = 9.9$ Hz, 2H, H-3), 3.52 (dd, $J = 9.9$ Hz, $J = 3.3$ Hz, 2H, H-2), 3.49 (t, $J = 9.9$ Hz, 2H, H-4), 1.23 (d, $J = 7.2$ Hz, 6H, COCH(CH_3)NH), 1.18 (t, $J = 6.9$ Hz, 6H, CH_3CH_2OOC); ^{13}C NMR (68 MHz, CD_3OD) δ 172.7 (s, *C*$OOCH_2CH_3$), 170.9 (s, *C*ONH), 95.1 (s, C-1), 72.6 (s), 72.5 (s), 71.2 (s), 71.1 (s), 61.2 (s), 16.2 (s), 13.1 (s); LRFAB *m/e* 591 ($[M+Na]^+$); HRFAB Calcd for $C_{22}H_{36}N_2O_{15}Na$ ($[M+Na]^+$) *m/e* 591.2013; measure *m/e* 591.2002.

5.19. Bis(methyl (6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-α-D-*gluco*-oct-6-enopyranosyluronate)ether (14)

The dialdehyde was prepared according to the procedure described in the preparation of **9**. To a solution of methyl diethylphosphonoacetate (0.38 g, 1.8 mmol) in anhydrous THF at 0 °C, NaH (0.044 g, 1.8 mmol) was added. After being stirred for 1 h, a solution of dialdehyde (0.50 g, 0.57 mmol) was added. The reaction was stirred for another 12 h. After completion of the reaction, saturated $NH_4Cl_{(aq)}$ and Et_2O were added. The combined organic solution was washed with brine and dried over $Na_2SO_{4(s)}$. After removal of the solvents, followed by purification with a gradient column chromatography (hexane–EtOAc = 100:0 to 60:40), the product was obtained as a pale yellowish oil (0.46 g, 0.46 mmol, 82%). ^1H NMR (270 MHz, $CDCl_3$) δ 7.1–7.5 (m, 30H), 6.95 (dd, $J = 15.5$ Hz, $J = 4.3$ Hz, 2H, COCH=C*H*), 6.00 (dd, $J = 15.5$ Hz, $J = 2.0$ Hz, 2H, COC*H*=CH), 5.09 (d, $J = 3.6$ Hz, 2H, H-1), 5.00 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.87 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.78 (d, $J = 10.6$ Hz, 2H, PhCH_2O), 4.40–4.77 (m, 8H), 4.03 (t, $J = 9.6$ Hz, 2H, H-3), 3.74 (s, 6H, COOCH_3), 3.50 (dd, $J = 9.6$ Hz, $J = 3.6$ Hz, 2H, H-2), 3.21 (t, $J = 9.6$ Hz, 2H, H-4); ^{13}C NMR (68 MHz, $CDCl_3$) δ 166.7 (s, *C*OCH=CH), 144.6 (s, COCH=*C*H), 138.7 (s), 137.8 (s), 137.6 (s), 128.6 (s), 128.5 (s), 128.4 (s), 128.3 (s), 127.9 (s), 127.8 (s), 127.7 (s), 121.1 (s, CO*C*H=CH), 94.3 (s, C-1), 82.0 (s), 81.6 (s), 79.1 (s), 75.9 (s), 75.6 (s), 73.2 (s), 69.9 (s), 51.7 (s); MALDI Calcd for $C_{60}H_{62}O_{13}Na$ ($[M+Na]^+$) *m/e* 1013.4083; measure *m/e* 1013.4150.

General procedure for transamidation: The procedure was modified from the reported procedure of Ref. 14. To a solution of alkylamine in freshly distilled anhydrous CH_2Cl_2 (1 mL), $Al(Me)_3$ (1 equiv, from a 2.0 M solution in toluene) was slowly added. After being stirred for 0.5 h, a solution of **14** (0.17 equiv) dissolved in freshly distilled anhydrous CH_2Cl_2 (1 mL) was added. The mixture was stirred overnight at room temperature. After completion of the reaction (analyzed by TLC, eluted with hexane–EtOAc (1:3) solution), the reaction was quenched by the slow addition of 1 N HCl, then diluted with EtOAc. The combined organic solution was washed with 1 N HCl, H_2O, $NaHCO_3$, and brine then dried over $Na_2SO_{4(s)}$. After removal of the solvents, followed by purification with a gradient column chromatography (hexane–EtOAc = 90:10 to 20:80), the product was obtained as a pale yellowish oil.

5.20. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-octyl-α-D-*gluco*-oct-6-enopyranuronamide)ether (15)

Please refer to the general procedure for transamidation. ^1H NMR (270 MHz, $CDCl_3$) δ 7.3–7.4 (m, 30H), 6.78 (dd, $J = 5.9$ Hz, $J = 15.2$ Hz, 2H), 5.56 (d, $J = 15.2$ Hz, 2H), 5.16 (d, $J = 3.6$ Hz, 2H, H-1), 5.11 (t, $J = 5.9$ Hz, 2H, C(O)N*H*), 5.01 (d, $J = 10.9$ Hz, 2H, PhCH_2O),

4.92 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.78 (d, $J = 10.6$ Hz, 2H, PhCH_2O), 4.6–4.7 (m, 6H), 4.52 (d, $J = 10.6$ Hz, 2H, PhCH_2O), 4.07 (dd, $J = 9.2$ Hz, $J = 9.2$ Hz, 2H), 3.57 (dd, $J = 3.6$ Hz, $J = 9.6$ Hz, 2H, H-2), 3.27 (m, 6H), 1.2–1.5 (m, 24H), 0.87 (t, $J = 6.4$ Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.0 (s), 139.4 (s), 138.7 (s), 138.5 (s), 137.9 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.8 (s), 127.44 (s), 127.38 (s), 125.3 (s), 93.9 (s, C-1), 82.2 (s), 81.5 (s), 79.6 (s), 75.9 (s), 75.6 (s), 73.0 (s), 70.7 (s), 39.6 (s), 31.9 (s), 29.8 (s), 29.4 (s), 29.3 (s), 27.1 (s), 22.8 (s), 14.2 (s); MALDI Calcd for $C_{74}H_{92}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 1207.6593; measure *m/e* 1207.6593.

5.21. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-dodecyl-α-D-*gluco*-oct-6-enopyranuro-namide)ether (16)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.3 (m, 30H), 6.77 (dd, $J = 5.9$ Hz, $J = 15.2$ Hz, 2H), 5.55 (d, $J = 15.2$ Hz, 2H), 5.14 (d, $J = 3.3$ Hz, 2H, H-1), 5.12 (t, 2H, C(O)N*H*), 5.00 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.91 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.77 (d, $J = 10.6$ Hz, 2H, PhCH_2O), 4.6–4.7 (m, 6H), 4.51 (d, $J = 10.2$ Hz, 2H, PhCH_2O), 4.07 (dd, $J = 9.2$ Hz, $J = 9.2$ Hz, 2H), 3.56 (dd, $J = 3.3$ Hz, $J = 9.6$ Hz, 2H, H-2), 3.2–3.3 (m, 6H), 1.2–1.5 (m, 40H), 0.87 (t, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.0 (s), 139.3 (s), 138.7 (s), 138.4 (s), 137.9 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.7 (s), 127.4 (s), 125.3 (s), 93.9 (s, C-1), 82.2 (s), 81.5 (s), 79.6 (s), 75.9 (s), 75.6 (s), 72.9 (s), 70.6 (s), 39.6 (s), 32.0 (s, 2 carbons), 31.0 (s), 29.7 (s, 3 carbons), 29.4 (s, 2 carbons), 27.1 (s), 22.8 (s), 14.2 (s). LRFAB $C_{82}H_{108}N_2O_{11}K$ ([M+K]$^+$) *m/e* 1336.

5.22. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-butyl-α-D-*gluco*-oct-6-enopyranuronamide)ether (17)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.4 (m, 30H), 6.81 (dd, $J = 5.9$ Hz, $J = 15.2$ Hz, 2H), 5.61 (d, $J = 15.2$ Hz, 2H), 5.27 (t, $J = 5.9$ Hz, 2H, C(O)N*H*), 5.16 (d, $J = 3.3$ Hz, 2H, H-1), 5.01 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.92 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.78 (d, $J = 10.5$ Hz, 2H, PhCH_2O), 4.73 (d, $J = 12.2$ Hz, 2H, PhCH_2O), 4.6 (m, 2H), 4.64 (d, $J = 12.2$ Hz, 2H, PhCH_2O), 4.53 (d, $J = 10.5$ Hz, 2H, PhCH_2O), 4.09 (dd, $J = 9.6$ Hz, $J = 9.6$ Hz, 2H), 3.58 (dd, $J = 3.3$ Hz, $J = 9.9$ Hz, 2H, H-2), 3.2–3.3 (m, 6H), 1.2–1.5 (m, 8H), 0.93 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.1 (s), 139.3 (s), 138.7 (s), 138.4 (s), 138.0 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.7 (s), 127.5 (s), 127.4 (s), 125.3 (s), 93.9 (s, C-1), 82.2 (s), 81.5 (s), 79.6 (s), 75.9 (s), 75.6 (s), 73.0 (s), 70.6 (s), 39.3 (s), 31.8 (s), 20.2 (s), 13.9 (s); MALDI Calcd for $C_{66}H_{76}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 1095.5341; measure *m/e* 1095.5322.

5.23. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-pentyl-α-D-*gluco*-oct-6-enopyranuronamide)ether (18)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.4 (m, 30H), 6.79 (dd, $J = 5.9$ Hz, $J = 15.2$ Hz, 2H), 5.59 (d, $J = 15.2$ Hz, 2H), 5.18 (t, $J = 5.9$ Hz, 2H, C(O)N*H*), 5.16 (d, $J = 3.0$ Hz, 2H, H-1), 5.01(d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.92 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.78 (d, $J = 12.2$ Hz, 2H, PhCH_2O), 4.6–4.7 (m, 6H), 4.52 (d, $J = 10.5$ Hz, 2H, PhCH_2O), 4.08 (m, 2H), 3.56 (dd, $J = 9.6$ Hz, $J = 5.9$ Hz, 2H, H-2), 3.2–3.3 (m, 6H), 1.5 (m, 4H), 1.2–1.3 (m, 8H), 0.91 (t, $J = 5.3$ Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.0 (s), 139.4 (s), 138.7 (s), 138.4 (s), 137.9 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.7 (s), 127.4 (s), 125.3 (s), 93.92 (s, C-1), 82.2 (s), 81.5 (s), 79.6 (s), 75.9 (s), 75.6 (s), 73.0 (s), 70.6 (s), 39.6 (s), 29.4 (s), 29.2 (s), 22.5 (s), 14.1 (s); MALDI Calcd for $C_{68}H_{80}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 1123.5654; measure *m/e* 1123.5667.

5.24. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-hexyl-α-D-*gluco*-oct-6-enopyranuronamide)ether (19)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.4 (m, 30H), 6.78 (dd, $J = 5.9$ Hz, $J = 15.2$ Hz, 2H), 5.56 (d, $J = 15.2$ Hz, 2H), 5.15 (d, $J = 3.3$ Hz, 2H, H-1), 5.13 (t, $J = 5.9$ Hz, 2H, C(O)N*H*), 5.00 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.91 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.77 (d, $J = 10.6$ Hz, 2H, PhCH_2O), 4.6–4.7 (m, 6H), 4.51 (d, $J = 10.5$ Hz, 2H, PhCH_2O), 4.07 (dd, $J = 9.2$ Hz, $J = 9.2$ Hz, 2H), 3.55 (dd, $J = 3.3$ Hz, $J = 9.6$ Hz, 2H, H-2), 3.2–3.3 (m, 6H), 1.4–1.5 (m, 4H), 1.2–1.3 (m, 12H), 0.87 (t, $J = 6.6$ Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.0 (s), 139.4 (s), 138.7 (s), 138.4 (s), 137.9 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.7 (s), 127.4 (s), 125.3 (s), 93.9 (s, C-1), 82.2 (s), 81.5 (s), 79.6 (s), 75.9 (s), 75.6 (s), 72.9 (s), 70.6 (s), 39.6 (s), 31.6 (s), 29.7 (s), 26.0 (s), 22.7 (s), 14.1 (s); MALDI Calcd for $C_{70}H_{84}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 1151.5967; measure *m/e* 1151.5970.

5.25. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-heptyl-α-D-*gluco*-oct-6-enopyranuronamide)ether (20)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.1–7.5 (m, 30H), 6.80 (dd, $J = 5.9$ Hz, $J = 15.2$ Hz, 2H), 5.58 (d, $J = 15.2$ Hz, 2H), 5.16 (d, $J = 3.3$ Hz, 2H, H-1), 5.01 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.92 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.79 (d, $J = 10.6$ Hz, 2H, PhCH_2O), 4.6–4.7 (m, 6H), 4.53 (d, $J = 10.6$ Hz, 2H, PhCH_2O), 4.09 (dd, $J = 9.2$ Hz, $J = 9.2$ Hz, 2H), 3.57 (dd, $J = 3.6$ Hz, $J = 9.6$ Hz, 2H, H-2), 3.2–3.3 (m, 6H), 1.5–1.6 (m, 4H), 1.2–1.4 (m, 16H), 0.90 (t, $J = 6.9$ Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.0 (s), 139.4 (s), 138.7 (s), 138.5 (s), 138.0 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.8 (s), 127.4 (s), 125.3 (s), 93.9 (s, C-1), 82.2 (s), 81.5 (s), 79.6 (s), 75.9 (s), 75.6 (s), 73.0 (s), 70.6 (s), 39.6 (s), 31.9 (s), 29.8 (s), 29.1 (s), 27.0 (s), 22.7 (s), 14.2 (s); MALDI Calcd for $C_{72}H_{88}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 1179.6280; measure *m/e* 1179.6240.

5.26. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-nonyl-α-D-*gluco*-oct-6-enopyranuronamide)ether (21)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.3–7.4 (m, 30H), 6.80 (dd, $J = 5.9$ Hz, $J = 15.2$ Hz, 2H), 5.58 (d, $J = 15.2$ Hz, 2H), 5.16 (d, $J = 3.3$ Hz, 2H, H-1), 5.15 (m, 2H, C(O)N*H*), 5.00 (d, $J = 10.9$ Hz, 2H, PhCH_2O), 4.92 (d,

J = 10.9 Hz, 2H, PhCH_2O), 4.78 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.6–4.7 (m, 6H), 4.52 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.09 (dd, J = 9.2 Hz, J = 9.2 Hz, 2H), 3.57 (dd, J = 3.3 Hz, J = 9.6 Hz, 2H, H-2), 3.2–3.3 (m, 6H), 1.2–1.5 (m, 28H), 0.89 (t, J = 7.3 Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.0 (s), 139.4 (s), 138.7 (s), 138.4 (s), 137.9 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.8 (s), 127.44 (s), 127.40 (s), 125.3 (s), 93.93 (s, C-1), 82.2 (s), 81.5 (s), 79.6 (s), 75.9 (s), 75.6 (s), 73.0 (s), 70.6 (s), 39.6 (s), 32.0 (s), 29.8 (s), 29.6 (s), 29.5 (s), 29.4 (s), 27.1 (s), 22.8 (s), 14.2 (s); MALDI Calcd for $C_{76}H_{96}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 1235.6906; measure *m/e* 1235.6970.

5.27. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-decyl-α-D-*gluco*-oct-6-enopyranuronamide)ether (22)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.3 (m, 30H), 6.79 (dd, J = 5.9 Hz, J = 15.2 Hz, 2H), 5.57 (d, J = 15.2 Hz, 2H), 5.15 (d, J = 3.3 Hz, 2H, H-1), 5.14 (m, 2H, C(O)N*H*), 5.01 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.92 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.78 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.6–4.7 (m, 6H), 4.52 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.07 (dd, J = 9.2 Hz, J = 9.2 Hz, 2H), 3.57 (dd, J = 3.3 Hz, J = 9.6 Hz, 2H, H-2), 3.2–3.3 (m, 6H), 1.2–1.5 (m, 32H), 0.89 (t, J = 6.4 Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.0 (s), 139.4 (s), 138.7 (s), 138.4 (s), 137.9 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.7 (s), 127.4 (s), 125.3 (s), 93.9 (s, C-1), 82.2 (s), 81.5 (s), 79.6 (s), 75.9 (s), 75.6 (s), 73.0 (s), 70.6 (s), 39.6 (s), 32.0 (s), 29.8 (s), 29.7 (s, 2 carbons), 29.44 (s), 29.42 (s), 27.1 (s), 22.8 (s), 14.2 (s); MALDI Calcd for $C_{78}H_{100}N_2O_{11}$-Na ([M+Na]$^+$) *m/e* 1263.7219; measure *m/e* 1263.7253.

5.28. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-(3-ethoxypropyl)-α-D-*gluco*-oct-6-enopyranuronamide)ether (23)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.3 (m, 30H), 6.83 (dd, J = 5.6 Hz, J = 15.2 Hz, 2H), 5.79 (t, J = 4.9 Hz, 2H, C(O)N*H*), 5.69 (d, J = 15.2 Hz, 2H), 5.15 (d, J = 3.3 Hz, 2H, H-1), 5.00 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.90 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.77 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.6–4.7 (m, 6H), 4.53 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.07 (dd, J = 9.6 Hz, J = 9.6 Hz, 2H), 3.54 (dd, J = 3.3 Hz, J = 9.6 Hz, 2H, H-2), 3.4–3.5 (m, 12H), 3.24 (dd, J = 9.6 Hz, J = 9.6 Hz, 2H), 1.79 (m, 4H), 1.17 (t, J = 7.1 Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.1 (s, *C*(O)NH), 139.5 (s), 138.7 (s), 138.2 (s), 137.9 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.7 (s), 127.6 (s), 125.0 (s), 94.0 (s, C-1), 82.3 (s), 81.5 (s), 79.4 (s), 75.9 (s), 75.6 (s), 73.0 (s), 70.5 (s), 69.3 (s), 66.5 (s), 38.1 (s), 29.4 (s), 15.3 (s); MALDI Calcd for $C_{68}H_{80}N_2O_{13}Na$ ([M+Na]$^+$) *m/e* 1155.5553; measure *m/e* 1155.5618.

5.29. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-*N*-(3-butoxypropyl)-α-D-*gluco*-oct-6-enopyranuronamide)ether (24)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.3–7.4 (m, 30H), 6.86 (m, 2H), 5.7–5.8 (m, 4H), 5.12 (d, J = 3.9 Hz, 2H, H-1), 4.99 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.92 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.5–4.8 (m, 10H), 4.08 (m, 2H), 3.2–3.6 (m, 16H), 1.2–1.4 (m, 12H), 0.90 (t, J = 7.3 Hz, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.1 (s, *C*(O)NH), 139.5 (s), 138.7 (s), 138.2 (s), 137.9 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.7 (s), 127.6 (s), 124.9 (s), 94.1 (s, C-1), 82.3 (s), 81.5 (s), 79.4 (s), 75.9 (s), 75.6 (s), 73.1 (s), 71.1 (s), 70.5 (s), 69.6 (s), 38.2 (s), 31.9 (s), 29.3 (s), 19.5 (s), 14.1 (s); MALDI Calcd for $C_{72}H_{88}N_2O_{13}Na$ ([M+Na]$^+$) *m/e* 1211.6179; measure *m/e* 1211.6192.

5.30. Bis(*N*-octyl-α-D-*gluco*-octopyranuronamide)ether (YH023)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 5.00 (d, J = 3.0 Hz, 2H, H-1), 3.7–3.9 (m, 4H), 3.46 (dd, J = 9.6 Hz, J = 3.0 Hz, 2H, H-2), 3.0–3.2 (m, 4H), 3.09 (dd, J = 8.9 Hz, J = 9.2 Hz, 4H), 2.4–2.6 (m, 8H), 1.3–2.0 (m, 24H), 0.89 (t, J = 7.6 Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, CD_3OD) δ 174.8 (s, *C*ONH), 94.0 (s, C-1), 74.4 (s), 73.2 (s), 72.1 (s), 71.0 (s), 39.2 (s), 32.1 (s), 31.7 (s), 31.6 (s), 29.1 (s), 28.9 (s), 27.8 (s), 26.8 (s), 22.4 (s), 13.2 (s); LRFAB *m/e* 671 ([M+Na]$^+$); HRFAB Calcd for $C_{32}H_{60}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 671.4095; measure *m/e* 671.4121.

5.31. Bis(*N*-dodectyl-α-D-*gluco*-octopyranuronamide)-ether (YH027)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 5.00 (d, J = 3.6 Hz, 2H, H-1), 3.7–3.8 (m, 4H), 3.46 (dd, J = 9.6 Hz, J = 3.6 Hz, 2H), 3.0–3.2 (m, 6H), 2.2–2.4 (m, 4H), 2.1–2.2 (m, 4H), 1.6–1.7 (m, 4H), 1.4–1.5 (m, 4H), 1.28–1.30 (m, 32H), 0.86–0.91 (m, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 174.8 (s), 93.9 (s, C-1), 74.4 (s), 73.2 (s), 72.1 (s), 71.0 (s), 39.1 (s), 32.1 (s), 31.8 (s), 29.4 (s, 3 carbons), 29.2 (s, 3 carbons), 29.1 (s), 27.7 (s), 26.8 (s), 22.4 (s), 13.1 (s); LRFAB *m/e* 784 ([M+Na]$^+$); HRFAB Calcd for $C_{40}H_{76}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 783.5347; measure *m/e* 783.5364.

5.32. Bis(*N*-butyl-α-D-*gluco*-octopyranuronamide)ether (YH028)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 4.99 (d, J = 3.6 Hz, 2H, H-1), 3.7–3.8 (m, 4H), 3.45 (m, 2H), 3.31 (d, J = 10.8 Hz, 2H), 3.17 (t, J = 6.3 Hz, 2H), 3.07 (t, J = 9.3 Hz, 2H), 2.2–2.4 (m, 4H), 2.1–2.2 (m, 4H), 1.3–1.7 (m, 8H), 0.92 (t, J = 8.1 Hz, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 175.2 (s), 94.1 (s, C-1), 74.4 (s), 73.2 (s), 72.1 (s), 70.9 (s), 39.2 (s), 31.9 (s), 31.0 (s), 27.8 (s), 19.8 (s), 12.8 (s); LRFAB *m/e* 559 ([M+Na]$^+$); HRFAB Calcd for $C_{24}H_{44}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 559.2843; measure *m/e* 559.2845.

5.33. Bis(*N*-pentyl-α-D-*gluco*-octopyranuronamide)ether (YH029)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 4.96 (d, 2H, H-1

protons obscured by water peak), 3.7–3.8 (m, 4H), 3.47 (d, $J = 6.9$ Hz, 2H), 3.2–3.3 (m, 4H), 3.08 (t, $J = 9.2$ Hz, 2H), 2.4–2.5 (m, 4H), 2.2 (m, 4H), 1.5 (m, 4H), 1.3 (m, 8H), 0.9 (m, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 175.6 (s), 94.3 (s, C-1), 74.3 (s), 73.1 (s), 72.1 (s), 70.9 (s), 39.8 (s), 31.7 (s), 28.9 (s), 28.5 (s), 27.8 (s), 22.1 (s), 13.1 (s); LRFAB *m/e* 587 ($[M+Na]^+$); HRFAB Calcd for $C_{26}H_{48}N_2O_{11}Na$ ($[M+Na]^+$) *m/e* 587.3156; measure *m/e* 587.3155.

5.34. Bis(*N*-hexyl-α-D-*gluco*-octopyranuronamide)ether (YH030)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 4.99 (d, $J = 3.6$ Hz, 2H, H-1), 3.7–3.8 (m, 4H), 3.46 (dd, $J = 9.6$ Hz, $J = 3.6$ Hz, 2H), 3.3–3.4 (m, 2H), 3.13 (t, $J = 6.9$ Hz, 2H), 3.06 (dd, $J = 9.2$ Hz, $J = 9.2$ Hz, 2H), 2.1–2.4 (m, 8H), 1.6–1.7 (m, 4H), 1.4–1.5 (m, 4H), 1.2–1.3 (m, 8H), 0.9 (m, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 174.9 (s), 94.0 (s, C-1), 74.4 (s), 73.2 (s), 72.1 (s), 70.9 (s), 39.2 (s), 32.1 (s), 31.4 (s), 29.0 (s), 27.8 (s), 26.4 (s), 22.3 (s), 13.1 (s); LRFAB *m/e* 615 ($[M+Na]^+$); HRFAB Calcd for $C_{28}H_{52}N_2O_{11}Na$ ($[M+Na]^+$) *m/e* 615.3469; measure *m/e* 615.3473.

5.35. Bis(*N*-heptyl-α-D-*gluco*-octopyranuronamide)ether (YH031)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 4.98 (s, 2H, H-1), 3.7–3.8 (m, 4H), 3.46 (m, 2H), 3.29 (s, 2H), 3.0–3.2 (m, 4H), 2.1–2.4 (m, 8H), 1.5–1.7 (m, 8H), 1.3 (m, 12H), 0.9 (m, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 175.3 (s), 94.2 (s, C-1), 74.4 (s), 73.2 (s), 72.1 (s), 70.9 (s), 39.6 (s), 31.9 (s), 31.6 (s), 28.9 (s), 28.8 (s), 27.8 (s), 26.7 (s), 22.4 (s), 13.1 (s); MALDI Calcd for $C_{30}H_{56}N_2O_{11}Na$ ($[M+Na]^+$) *m/e* 643.3776; measure *m/e* 643.3758.

5.36. Bis(*N*-nonyl-α-D-*gluco*-octopyranuronamide)ether (YH032)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 4.93 (d, $J = 3.0$ Hz, 2H, H-1), 3.6–3.8 (m, 4H), 3.46 (m, 2H), 3.1–3.3 (m, 6H), 2.1–2.5 (m, 8H), 1.2–1.7 (m, 28H), 0.9 (m, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 175.6 (s), 94.3 (s, C-1), 74.4 (s), 73.2 (s), 72.1 (s), 70.9 (s), 39.9 (s), 39.8 (s), 31.7 (s), 29.4 (s), 29.1 (s, 2 carbons), 28.8 (s), 27.8 (s), 26.7 (s), 22.4 (s), 13.2 (s); MALDI Calcd for $C_{34}H_{64}N_2O_{11}Na$ ($[M+Na]^+$) *m/e* 699.4402; measure *m/e* 699.4372.

5.37. Bis(*N*-decyl-α-D-*gluco*-octopyranuronamide)ether (YH033)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 4.99 (s, 2H, H-1), 3.7–3.8 (m, 4H), 3.47 (m, 2H), 3.30 (s, 2H), 3.0–3.1 (m, 4H), 2.1–2.4 (m, 8H), 1.2–1.7 (m, 32H), 0.9 (m, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 175.0 (s), 94.1 (s, C-1), 74.4 (s), 73.2 (s), 72.1 (s), 71.0 (s), 39.4 (s), 32.0 (s), 31.8 (s), 29.4 (s, 2 carbons), 29.2 (s, 2 carbons), 29.0 (s), 27.8 (s), 26.8 (s), 22.4 (s), 13.2 (s); MALDI Calcd for $C_{36}H_{68}N_2O_{11}Na$ ($[M+Na]^+$) *m/e* 727.4715; measure *m/e* 727.4726.

5.38. Bis(*N*-(3-ethoxypropyl)-α-D-*gluco*-octopyranuronamide)ether (YH034)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 4.99 (d, $J = 3.9$ Hz, 2H, H-1), 3.7–3.8 (m, 4H), 3.4–3.5 (m, 8H), 3.2–3.3 (m, 6H), 3.06 (dd, $J = 8.9$ Hz, $J = 8.9$ Hz, 2H), 2.1–2.4 (m, 8H), 1.7–1.8 (m, 4H), 1.16 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 175.0 (s), 94.0 (s, C-1), 74.4 (s), 73.2 (s), 72.0 (s), 70.9 (s), 67.9 (s), 66.0 (s), 36.6 (s), 32.0 (s), 29.2 (s), 27.7 (s), 14.2 (s); MALDI Calcd for $C_{26}H_{48}N_2O_{13}Na$ ($[M+Na]^+$) *m/e* 619.3049; measure *m/e* 619.3064.

5.39. Bis(*N*-(3-butoxypropyl)-α-D-*gluco*-octopyranuronamide)ether (YH035)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 5.00 (d, $J = 4.0$ Hz, 2H, H-1), 3.7–3.8 (m, 4H), 3.4–3.5 (m, 8H), 3.29–3.34 (m, 4H), 3.23 (t, $J = 6.9$ Hz, 2H), 3.07 (dd, $J = 9.6$ Hz, $J = 8.9$ Hz, 2H), 2.1–2.4 (m, 8H), 1.7–1.8 (m, 4H), 1.5–1.6 (m, 4H), 1.3–1.4 (m, 4H), 0.92 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 174.79 (s, *C*(O)NH), 94.0 (s, C-1), 74.5 (s), 73.2 (s), 72.1 (s), 70.9 (s), 70.5 (s), 68.2 (s), 36.6 (s), 32.1 (s), 31.6 (s), 29.2 (s), 27.8 (s), 19.1 (s), 13.0 (s); MALDI Calcd for $C_{30}H_{56}N_2O_{13}Na$ ($[M+Na]^+$) *m/e* 675.3675; measure *m/e* 675.3702.

5.40. 6,6′-Diazido-2,2′,3,3′,4,4′-hexa-*O*-benzyl-6,6′-dideoxy-α-D-trehalose (25)

To a solution of **6** (1.0 g, 1.1 mmol) in anhydrous CH_2Cl_2 (10 mL) and pyridine (0.26 mL, 3.2 mmol) at 0 °C, Tf_2O (0.46 mL, 2.7 mmol) was slowly added. After completion of the reaction (ca. 30 min), the reaction mixture was diluted with CH_2Cl_2. The combined organic layers were washed with water, saturated $NaHCO_{3(aq)}$, and brine, then dried over $Na_2SO_{4(s)}$. After removal of solvent, the triflated crude product was dissolved in DMF (10 mL), and added with excess NaN_3. The reaction was stirred for 12 h. After removal of DMF, EtOAc was added, and the resulting cloudy yellowish solution was filtered through Celite. After removal of solvents followed by a gradient column chromatography (hexane–EtOAc = 90:10 to 65:35), the product was afforded as a pale yellowish oil (0.78 g, 0.84 mmol, 74%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 5.26 (d, $J = 3.6$ Hz, 2H, H-1), 5.03 (d, $J = 10.8$ Hz, 2H, PhCH_2O), 4.93 (d, $J = 10.0$ Hz, 2H, PhCH_2O), 4.90 (d, $J = 10.8$ Hz, 2H, PhCH_2O), 4.77 (d, $J = 12.0$ Hz, 2H, PhCH_2O), 4.74 (d, $J = 12.0$ Hz, 2H, PhCH_2O), 4.62 (d, $J = 10.0$ Hz, 2H, PhCH_2O), 4.21 (dt, $J = 9.6$ Hz, $J = 2.8$ Hz, 2H, H-5), 4.08 (t, $J = 9.6$ Hz, 2H, H-3), 3.65 (dd, $J = 9.6$ Hz, $J = 3.6$ Hz, 2H, H-2), 3.55 (t, $J = 9.6$ Hz, 2H, H-4), 3.23 (dd, $J = 13.2$ Hz, $J = 2.8$ Hz, 2H, H-6), 3.20 (dd, $J = 13.2$ Hz, $J = 2.8$ Hz, 2H, H-6′); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.8 (s), 138.2 (s), 138.0 (s), 128.6 (s), 128.1 (s), 128.0 (s), 127.8 (s), 127.8

(s), 127.7 (s), 127.5 (s), 94.1 (s, C-1), 81.6 (s), 79.7 (s), 78.5 (s), 75.7 (s), 75.3 (s), 73.2 (s), 70.7 (s), 51.2 (s); MALDI Calcd for $C_{54}H_{56}N_6O_9Na$ ($[M+Na]^+$) *m/e* 955.4001; measure *m/e* 955.3980.

5.41. 6,6′-Diamino-2,2′,3,3′,4,4′-hexa-*O*-benzyl-6,6′-dideoxy-α-D-trehalose (26)

To a solution of **25** (0.78 g, 0.84 mmol) in THF, 0.1 M NaOH (0.5 mL) and 1 M PMe_3 (2.7 mL, 2.7 mmol) were added. The reaction mixture was stirred at 50 °C for 3 h. Lots of bubbling was observed at the beginning. The reaction was monitored with TLC till completion. After removal of the solvent followed by purification with a gradient column chromatography (hexane–EtOAc–MeOH = 60:40:0 to 35:35:30), the product was afforded as a yellowish viscous oil (0.56 g, 0.64 mmol, 76%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 5.20 (s, br, 2H, H-1), 5.00 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.87 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.85 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.50–4.80 (m, 6H, PhCH_2O), 2.50–4.30 (m, 12H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.7 (s), 138.2 (s), 138.2 (s), 128.6 (s), 128.5 (s), 128.1 (s), 127.9 (s), 127.4 (s), 127.3 (s), 127.2 (s), 93.2 (s, C-1), 81.7 (s), 79.7 (s), 78.6 (s), 77.3 (s), 75.6 (s), 74.9 (s), 73.3 (s), 50.6 (s); LRFAB *m/e* 881 ($[M+H]^+$); HRFAB Calcd for $C_{54}H_{61}N_2O_9$ ($[M+H]^+$) *m/e* 881.4377; measure *m/e* 881.4418.

5.42. 6,6′-Dioctylcarbamoylamino-2,2′,3,3′,4,4′-hexa-*O*-benzyl-6,6′-dideoxy-α-D-trehalose (27)

To a solution of **26** (0.20 g, 0.22 mmol) dissolved in 5 mL of CH_2Cl_2 at −78 °C, triphosgene (0.044 g, 0.15 mmol) and Et_3N (0.13 mL, 0.91 mmol) were added. The reaction was allowed to warm up to room temperature. After being stirred for another 5 min, the reaction mixture was cooled to 0 °C, and was added with *n*-octyl amine (0.075 g, 0.46 mmol). The reaction was stirred for 12 h, allowing the temperature to be warmed up to room temperature. After the completion of the reaction, water was added to quench the reaction followed by EtOAc dilution. The combined organic solution was washed with 1 N $HCl_{(aq)}$, water, saturated $NaHCO_{3(aq)}$, and brine, then dried over $Na_2SO_{4(s)}$. After removal of the solvent followed by purification with a gradient column chromatography (hexane–EtOAc = 75:25 to 20:80), the product was afforded as a viscous yellowish oil (0.13 g, 0.11 mmol, 49%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 5.14 (d, J = 3.0 Hz, 2H, H-1), 5.00 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.87 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.85 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.65 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.65 (s, 4H, PhCH_2O), 4.03–4.16 (m, 6H), 3.50 (dd, J = 9.2 Hz, J = 3.0 Hz, 2H, H-2), 3.40 (t, J = 9.2 Hz, 4H), 3.0–3.2 (m, 8H), 1.10–1.50 (m, 24H), 0.87 (t, J = 5.9 Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 158.4 (s, NH*C*ONH), 138.7 (s), 138.2 (s), 138.1 (s), 128.6 (s), 128.5 (s), 128.0 (s), 127.8 (s), 127.7 (s), 127.5 (s), 93.1 (s, C-1), 81.5 (s), 79.5 (s), 78.8 (s), 75.6 (s), 75.1 (s), 72.9 (s), 70.6 (s), 41.2 (s), 40.5 (s), 31.9 (s), 30.3 (s), 29.4 (s), 29.4 (s), 27.0 (s), 22.7 (s), 14.2 (s); MALDI Calcd for $C_{72}H_{94}N_4O_{11}Na$ ($[M+Na]^+$) *m/e* 1213.6811; measure *m/e* 1213.6889.

5.43. 6,6′-Dioctylcarbamoylamino-6,6′-dideoxy-α-D-trehalose (YH026)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 5.05 (d, J = 3.3 Hz, 2H, H-1), 3.8–3.9 (m, 2H), 3.78 (t, J = 9.2 Hz, 2H, H-3), 3.4–3.5 (m, 6H), 3.1–3.3 (m, 6H), 1.1–1.5 (m, 24H), 0.89 (t, J = 6.9 Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, CD_3OD) δ 160.0 (s, NH*C*ONH), 94.2 (s, C-1), 72.8 (s), 72.0 (s), 71.6 (s), 71.2 (s), 40.8 (s), 39.9 (s), 31.7 (s), 29.9 (s), 29.2 (s), 29.1 (s), 26.7 (s), 22.4 (s), 13.1 (s); LRFAB *m/e* 673 ($[M+Na]^+$); HRFAB Calcd for $C_{30}H_{58}N_4O_{11}Na$ ($[M+Na]^+$) *m/e* 673.4000; measure *m/e* 673.4015.

5.44. 6,6′-Dideoxy-6,6′-didecylamino-2,2′,3,3′,4,4′-hexa-*O*-benzyl-α-D-trehalose (28)

To a solution of **26** (0.1 g, 0.11 mmol) dissolved in CH_2Cl_2 and Et_3N (0.040 mL, 0.28 mmol) at 0 °C, decanoyl chloride (0.050 mL, 0.28 mmol) was added slowly. The reaction was stirred for 12 h, allowing the temperature to be warmed up to room temperature. After completion of the reaction, the reaction was quenched with water and diluted with EtOAc. The combined organic solution was washed with 1 N $HCl_{(aq)}$, water, saturated $NaHCO_{3(aq)}$, and brine, then dried over $Na_2SO_{4(s)}$. After removal of the solvent, followed by purification with a gradient column chromatography (hexane–EtOAc = 75:25 to 25:75), the product was afforded as a viscous yellowish oil (0.12 g, 0.1 mmol, 89%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10–7.50 (m, 30H), 5.36 (d, br, J = 5.3 Hz, 2H, CON*H*), 5.08 (d, J = 3.6 Hz, 2H, H-1), 5.00 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.90 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.85 (d, J = 10.2 Hz, 2H, PhCH_2O), 4.74 (d, J = 12.2 Hz, 2H, PhCH_2O), 4.65 (d, J = 12.2 Hz, 2H, PhCH_2O), 4.62 (d, J = 10.2 Hz, 2H, PhCH_2O), 4.0–4.2 (m, 4H), 3.84 (td, J = 9.6 Hz, J = 3.3 Hz, 2H, H-5), 3.51 (dd, J = 9.6 Hz, J = 3.3 Hz, 2H, H-2), 3.32 (t, J = 9.6 Hz, 2H, H-4), 3.06 (dd, J = 13.9 Hz, J = 3.3 Hz, 2H, H-6), 2.00 (t, J = 7.9 Hz, 4H, CH_2CONH), 1.1–1.6 (m, 28H), 0.89 (t, J = 5.9 Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.0 (s, *C*ONH), 138.6 (s), 138.1 (s), 138.0 (s), 128.6 (s), 128.5 (s), 128.0 (s), 127.9 (s), 127.8 (s), 127.4 (s), 94.0 (s, C-1), 81.6 (s), 79.4 (s), 78.8 (s), 75.8 (s), 75.4 (s), 73.2 (s), 69.7 (s), 39.3 (s), 36.9 (s), 32.0 (s), 29.6 (s), 29.45 (s, 2 carbons), 29.37 (s), 25.8 (s), 22.8 (s), 14.2 (s); MALDI Calcd for $C_{74}H_{96}N_2O_{11}Na$ ($[M+Na]^+$) *m/e* 1211.6906; measure *m/e* 1211.6946.

5.45. 6,6′-Dideoxy-6,6′-didecylamino-α-D-trehalose (YH025)

Please refer to the general procedure for hydrogenation ^{1}H NMR (270 MHz, CD_3OD) δ 5.04 (d, J = 3.9 Hz, 2H, H-1), 3.8–3.9 (m, 2H), 3.76 (t, J = 9.2 Hz, 2H, H-3), 3.4–3.5 (m, 6H), 3.13 (t, J = 9.2 Hz, 2H, H-4), 2.22 (t, J = 7.3 Hz, 4H, CH_2CONH), 1.1–1.6 (m, 28H), 0.89 (t, J = 6.9 Hz, 6H, CH_2CH_3); ^{13}C NMR (68 MHz, CD_3OD) δ 175.8 (s, *C*ONH), 94.2 (s, C-1), 72.8 (s), 72.0 (s), 71.8 (s), 70.7 (s), 40.1 (s), 35.7 (s), 31.7 (s), 29.3 (s), 29.2 (s), 29.1 (s), 29.0 (s), 25.8 (s), 22.4 (s), 12.3 (s); LRFAB

m/e 671 ([M+Na]$^+$); HRFAB Calcd for $C_{32}H_{60}N_2O_{11}Na$ ([M+Na]$^+$) *m/e* 671.4095; measure *m/e* 671.4067.

5.46. 6,6′-Dideoxy-6,6′-di(monobromoacetyl)amino-2,2′,3,3′,4,4′-hexa-*O*-benzyl-α-D-trehalose (29)

To a solution of **26** (0.32 g, 0.36 mmol) in anhydrous DMF (3 mL), bromoacetic acid (7.2 mL of 1 M solution in DMF), and diisopropylcarboimide (1.3 mL) were added. The reaction mixture was stirred at room temperature for 4 h. After complete consumption of the starting material (monitored by TLC, EtOAc–hexanes = 50:50), the reaction mixture was concentrated, and the residue was diluted with EtOAc, followed by washing with 1 N HCl, saturated $NaHCO_3$ solution (three times), brine then dried over Na_2SO_4. After removal of the solvent followed by a gradient column chromatography (hexanes–EtOAc = 80:20 to 20:80), the product was afforded as a yellowish oil (0.30 g, 0.27 mmol, 74%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.4 (m, 30H), 5.17 (d, J = 3.3 Hz, 2H, H-1), 5.02 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.90 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.89 (d, J = 10.2 Hz, 2H, PhCH_2O), 4.79 (d, J = 11.9 Hz, 2H, PhCH_2O), 4.69 (d, J = 11.9 Hz, 2H, PhCH_2O), 4.63 (d, J = 10.2 Hz, 2H, PhCH_2O), 4.0–4.1 (m, 4H, H4, H-5), 3.76 (d, J = 13.5 Hz, 2H, CH_2Br), 3.69 (d, J = 13.5 Hz, 2H, CH_2Br), 3.6–3.7 (m, 2H, H-6), 3.58 (dd, J = 9.6 Hz, J = 3.3 Hz, 2H, H-2), 3.34 (dd, J = 6.6 Hz, J = 9.2 Hz, 2H, H-3), 3.19 (d, J = 13.9 Hz, 2H, H-6); ^{13}C NMR (68 MHz, $CDCl_3$) δ 165.6 (s), 138.5 (s), 138.0 (s), 137.9 (s), 128.6 (s), 128.56 (s), 128.5 (s), 128.1 (s), 127.9 (s), 127.8 (s), 127.4 (s), 93.6 (s, C-1), 81.6 (s), 79.6 (s), 78.8 (s), 75.8 (s), 75.4 (s), 73.4 (s), 69.6 (s), 40.2 (s), 29.3 (s); MALDI Calcd for $C_{58}H_{62}Br_2N_2O_{11}Na$ ([M+Na]$^+$) 1143.2613; measure 1143.2642.

5.47. 6,6′-Dideoxy-6,6′-di(monoheptaminoacetyl)amino-2,2′,3,3′,4,4′-hexa-*O*-benzyl-α-D-trehalose (30)

To a solution of **29** (0.15 g, 0.13 mmol) in anhydrous DMF (5 mL), heptamine (0.0 mL, 0.32 mmol), and Cs_2CO_3 (0.10 g, 0.32 mmol) were added. The reaction mixture was stirred overnight at room temperature. The reaction can be monitored by TLC. The product has a R_f of 0 when eluted with EtOAc–MeOH (9:1) solution and a R_f of 0.3 when eluted with *i*-PrOH–1 M NH_4OH (8:1) solution. After completion of the reaction, the reaction mixture was concentrated and loaded to a short column (5 cm in height) packed with TLC silica gel on top of Celite. The column was eluted with a series of solutions as following: CH_2Cl_2, CH_2Cl_2–EtOAc, EtOAc, EtOAc–MeOH. The fractions containing desired product were analyzed by TLC and collected. The product was afforded as white solid (0.12 g, 0.11 mmol, 75%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.4 (m, 30H), 5.14 (d, J = 3.6 Hz, 2H, H-1), 4.97 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.87 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.83 (d, J = 10.2 Hz, 2H, PhCH_2O), 4.71 (d, J = 11.9 Hz, 2H, PhCH_2O), 4.65 (d, J = 11.9 Hz, 2H, PhCH_2O), 4.63 (d, J = 10.2 Hz, 2H, PhCH_2O), 4.13 (m, 2H, H-6), 4.06(dd, J = 9.9 Hz, J = 9.6 Hz, 2H, H-3), 3.8–3.9 (m, 2H, H-5), 3.50 (dd, J = 3.6 Hz, J = 9.9 Hz, 2H, H-2), 3.30 (dd, J = 9.6 Hz, J = 9.2 Hz, 2H, H-4), 3.09 (m, 2H, H-6), 2.51 (dd, J = 6.3 Hz, J = 5.9 Hz, 4H, H-1′), 1.40 (m, 4H, H-2′), 1.26 (m, 20H), 0.87 (m, 6H, H-7′); ^{13}C NMR (68 MHz, $CDCl_3$) δ 171.6 (s), 138.76 (s), 138.2 (s), 137.9 (s), 128.5 (s), 128.0 (s), 127.9 (s), 127.8 (s), 127.7, 93.8 (s, C-1), 81.6 (s), 79.6 (s), 78.6 (s), 75.8 (s), 75.4 (s), 73.1 (s), 69.8 (s), 52.5 (s), 50.3 (s), 38.8 (s), 31.9 (s), 30.1 (s), 29.3 (s), 27.2 (s), 22.7 (s), 14.2 (s); MALDI Calcd for $C_{72}H_{95}N_4O_{11}$ ([M+H]$^+$) 1191.6992; measure 1191.7062.

5.48. 6,6′-Dideoxy-6,6′-di(monoheptaminoacetyl)amino-α-D-trehalose (YH037)

Please refer to the general procedure for hydrogenation. Using Pd/C as catalyst instead of $Pd(OH)_2$/C. ^{1}H NMR (270 MHz, CD_3OD) δ 5.07 (d, J = 3.6 Hz, 2H, H-1), 3.92 (m, 2H), 3.7–3.8 (m, 4H), 3.49 (dd, J = 3.6 Hz, J = 9.9 Hz, 2H, H-2), 3.3–3.4 (m, 2H), 3.16 (dd, J = 9.6 Hz, J = 9.2 Hz, 2H), 3.02 (m, 4H), 1.70 (s, 4H), 1.3–1.4 (m, 20H), 0.90 (m, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 165.6 (s), 95.0 (s), 73.0 (s), 71.9 (s, 2 carbons), 70.7 (s), 58.3 (s), 41.1 (s), 40.3 (s), 31.4 (s), 28.5 (s), 26.2 (s), 25.9 (s), 22.3 (s), 13.1 (s); MALDI Calcd for $C_{30}H_{59}N_4O_{11}$ ([M+H]$^+$) 651.4175; measure 651.4176.

5.49. Bis((6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-α-D-*gluco*-oct-6-enopyranosyluronate)ether (31)

A solution of **14** (0.20 g, 0.21 mmol) and LiOH–H_2O (0.03 g, 0.71 mmol) in THF/H_2O (6 mL/2 mL) was stirred at room temperature for 2 days. After completion of the reaction (monitored by TLC, EtOAc–hexane = 3:1), Dowex 50W (H^+ form) resin was added, and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through Celite. After removal of the solvents, the crude product was purified with a gradient column chromatography (hexane–EtOAc to EtOAc–MeOH = 60:40 to 90:10). The purified product was obtained as white solid (0.070 g, 0.080 mmol, 36%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.4 (m, 30H), 7.09 (dd, J = 15.8 Hz, J = 3.0 Hz, 2H, H-6), 6.03 (d, J = 15.8 Hz, 2H, H-7), 5.13 (s, 2H, H-1), 5.03 (d, J = 10.5 Hz, 2H, PhCH_2O), 4.92 (d, J = 10.8 Hz, 2H, PhCH_2O), 4.83 (d, J = 10.5 Hz, 2H, PhCH_2O), 4.6–4.8 (m, 8H, PhCH_2O, H-5), 4.08 (dd, J = 8.8 Hz, J = 9.3 Hz, 2H, H-3), 3.55 (d, J = 8.8 Hz, 2H, H-2), 3.26 (dd, J = 9.3 Hz, J = 9.3 Hz, 2H, H-4); ^{13}C NMR (68 MHz, $CDCl_3$) δ 171.7 (s, *C*OOH), 147.1 (s), 138.6 (s), 137.7 (s), 137.6 (s), 128.7 (s), 128.6 (s), 128.5 (s), 128.2 (s), 128.0 (s), 127.8 (s), 120.7 (s), 94.4 (s, C1), 81.8 (s), 81.7 (s), 79.2 (s), 75.9 (s), 75.7 (s), 73.4 (s), 69.9 (s); MALDI Calcd for $C_{58}H_{58}O_{13}Na$ ([M+Na]$^+$) 985.3770; measure 985.3798.

5.50. Bis(octanoyl (6*E*)-2,3,4,-tri-*O*-benzyl-6,7-dideoxy-α-D-*gluco*-oct-6-enopyranosyluronoylhydrazine)ether (32)

To a solution of **31** (0.15 g, 0.16 mmol) in anhydrous DMF (5 mL), octanoic hydrazine (0.10 g, 85% purity, 0.49 mmol), and EDC (0.10 g, 0.52 mmol) were added. The reaction mixture was stirred overnight at room temperature. After the complete consumption of starting

material (monitored by TLC, EtOAc–hexanes = 3:1), the reaction mixture was concentrated and the residue was diluted with CH_2Cl_2. To this mixture, $NaHCO_{3(s)}$ and $Na_2CO_{3(s)}$ were added. After being stirred for 1 h, the reaction mixture was filtered through Celite. After removal of the solvents followed by a gradient column chromatography (hexanes–EtOAc = 80:20 to 20:80), the product was afforded as white solid (0.080 g, 0.070 mmol, 41%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.46 (d, J = 4.9 Hz, 2H), 10.06 (s, 2H), 7.2–7.4 (m, 30H), 6.96 (dd, J = 15.5 Hz, J = 5.3 Hz, 2H, H-6), 6.00 (d, J = 15.5 Hz, 2H, H-7), 5.28 (d, J = 3.0 Hz, 2H, H-1), 4.93 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.83 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.5–4.7 (m, 8H, H5, PhCH_2O), 4.43 (d, J = 10.6 Hz, 2H, PhCH_2O), 4.04 (dd, J = 10.2 Hz, J = 9.2Hz, 2H, H-4), 3.47 (dd, J = 3.0 Hz, J = 9.6 Hz, 2H, H-2), 3.19 (dd, J = 9.6 Hz, J = 9.2 Hz, 2H, H-3), 2.36 (dd, J = 7.3 Hz, J = 7.6 Hz, 4H), 1.2–1.3 (m, 20H), 0.88 (m, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.8 (s), 160.4 (s), 141.4 (s, C6), 138.7 (s), 138.0 (s), 137.8 (s), 128.6 (s), 127.6 (s), 127.3 (s), 128.3 (s), 128.0 (s), 127.8 (s), 127.7 (s), 127.6 (s), 127.3 (s), 121.6 (s, C7), 95.1 (s, C-1), 82.0 (s), 81.3 (s), 80.0 (s), 75.6 (s), 75.2 (s), 72.8 (s), 70.7 (s), 34.0 (s), 31.8 (s), 29.3 (s), 29.1 (s), 25.7 (s), 22.7 (s), 14.2 (s); MALDI Calcd for $C_{74}H_{90}N_4O_{13}Na$ ([M+Na]$^+$) 1265.6397; measure 1265.6365.

5.51. Bis(octanoyl (α-D-*gluco*-oct-pyranosyluronoylhydrazine)ether (YH036)

Please refer to the general procedure for hydrogenation. ^{1}H NMR (270 MHz, CD_3OD) δ 5.04 (d, J = 3.3 Hz, 2H, H-1), 3.78 (m, 2H, H-5), 3.73 (dd, J = 9.6 Hz, J = 8.9 Hz, 2H, H-4), 3.48 (dd, J = 3.6 Hz, J = 9.2 Hz, 2H, H-2), 3.08 (dd, J = 8.9 Hz, J = 9.2 Hz, 2H, H-3), 2.7–2.8 (m, 4H), 2.24 (dd, J = 7.2 Hz, J = 7.2 Hz, 4H), 1.64 (m, 4H), 1.31 (m, 20H), 0.89 (m, 6H); ^{13}C NMR (68 MHz, CD_3OD) δ 173.9 (s), 173.6 (s), 94.1 (s), 74.5 (s), 73.1 (s), 72.0 (s), 70.7 (s), 33.5 (s), 31.6 (s), 29.6 (s), 28.9 (s), 28.8 (s), 27.1 (s), 25.3 (s), 22.4 (s), 13.1 (s); MALDI Calcd for $C_{32}H_{58}N_4O_{13}Na$ ([M+Na]$^+$) 729.3893; measure 729.3930.

5.52. 2,2′,3,3′,4,4′,6-Hepta-*O*-benzyl-α-D-trehalose (34)

To a solution of **33** (1.30 g, 1.2 mmol) in anhydrous CH_2Cl_2 (20 mL) and Ac_2O (0.15 mL, 1.6 mmol) at −78 °C, TMSOTf (0.31 mL, 1.6 mmol) was slowly added. The reaction was stirred for 9 h, allowing the temperature to be warmed up to room temperature. A solution of NaOMe (3 mL, 2 M in MeOH) was added. After being stirred for 0.5 h, Amberlite IR 120 (H^+ form) was added. The reaction mixture was filtered and concentrated. After purification with a gradient column chromatography (hexane–EtOAc = 75:25 to 25:75), the product was afforded as a clear oil (0.59 g, 0.61 mmol, 50%) along with the recovered **33** (0.31 g, 0.29 mmol, 24%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.1–7.4 (m, 35H), 5.21 (d, J = 3.0 Hz, 1H, H-1), 5.20 (d, J = 3.3 Hz, 1H, H-1′), 5.01 (d, J = 10.9 Hz, 2H, PhCH_2O), 4.7–4.9 (m, 8H, PhCH_2O), 4.66 (d, J = 11.2 Hz, 1H, PhCH_2O), 4.56 (d, J = 12.2 Hz, 1H, PhCH_2O), 4.48 (d, J = 10.9 Hz, 1H, PhCH_2O), 4.40 (d, J = 11.9 Hz, 1H, PhCH_2O), 4.0–4.2 (m, 3H), 3.69 (dd, J = 9.9 Hz, J = 9.2 Hz, 1H), 3.5–3.6 (m, 7H), 3.39 (d, J = 10.6 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.96 (s), 138.90 (s), 138.44 (s), 138.35 (s), 138.25 (s), 138.21 (s), 137.9 (s), 128.56 (s), 128.47 (s), 128.44 (s), 128.2 (s), 128.08 (s), 128.06 (s), 127.98 (s), 127.78 (s), 127.72 (s), 127.62 (s), 127.5 (s), 94.4 (s), 94.2 (s), 81.89 (s), 81.68 (s), 79.64 (s), 79.45 (s), 77.8 (s), 77.45 (s), 75.70 (s, 2 carbons), 75.16 (s, 2 carbons), 73.61 (s), 73.0 (s), 72.92 (s), 71.3 (s), 70.8 (s), 68.3 (s), 61.6 (s); MALDI Calcd for $C_{61}H_{64}O_{11}Na$ ([M+Na]$^+$) 995.4341; measure 995.4300.

5.53. 6′-Azido-2,2′,3,3′,4,4′,6-hepta-*O*-benzyl-6,6′-dideoxy-α-D-trehalose (35)

To a solution of **34** (0.53 g, 0.55 mmol) in anhydrous pyridine (10 mL), TsCl (1.2 g, 6.5 mmol) was added. After being stirred for 3 h, the reaction was quenched by addition of water. The reaction mixture was diluted with EtOAc, and washed with 1 N HCl (three times), water, saturated $NaHCO_3$ solution, brine then dried over Na_2SO_4. After removal of the solvent, the crude product was redissolved in DMF (10 mL), and added with excess NaN_3 (ca. 0.5 g). The reaction mixture was stirred at 100 °C for 5 h then was concentrated. The brownish solid was added with EtOAc and filtered through Celite. After removal of the solvents, followed by purification with a gradient column chromatography (hexane–EtOAc = 75:25 to 25:75), the product was afforded as a clear oil (0.46 g, 0.46 mmol, 84%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.1–7.4 (m, 35H), 5.22 (d, J = 3.6 Hz, 2H, H-1, H-1′), 5.00 (d, J = 10.9 Hz, 1H, PhCH_2O), 4.99 (d, J = 10.9 Hz, 1H, PhCH_2O), 4.7–4.9 (m, 8H, PhCH_2O), 4.57 (d, J = 11.2 Hz, 1H, PhCH_2O), 4.55 (d, J = 12.2 Hz, 1H, PhCH_2O), 4.47 (d, J = 10.6 Hz, 1H, PhCH_2O), 4.39 (d, J = 11.9 Hz, 1H, PhCH_2O), 3.9–4.2 (m, 5H), 3.69 (dd, J = 9.9 Hz, J = 9.2 Hz, 1H), 3.4–3.6 (m, 5H), 3.18 (d, J = 3.3 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.91 (s), 138.75 (s), 138.40 (s), 138.24 (s), 138.15 (s, 2 carbons), 137.90 (s), 128.54 (s), 128.47 (s), 128.43 (s), 128.06 (s), 127.95 (s), 127.77 (s), 127.70 (s), 127.63 (s), 127.53 (s), 127.44 (s), 94.6 (s), 94.1 (s), 81.9 (s), 81.5 (s), 79.6 (s), 79.5 (s), 78.4 (s), 77.8 (s), 75.7 (s, 2 carbons), 75.25 (s), 75.17 (s), 73.6 (s), 73.1 (s), 72.9 (s), 70.9 (s), 70.4 (s), 68.2 (s), 51.2 (s); MALDI Calcd for $C_{61}H_{63}N_3O_{10}Na$ ([M+Na]$^+$) 1020.4406; measure 1020.4357.

5.54. 6′-Azido-2,2′,3,3′,4,4′-hexa-*O*-benzyl-6′-deoxy-α-D-trehalose (36)

Please refer to the procedure for the preparation of **34**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.1–7.4 (m, 30H), 5.18 (d, J = 3.0 Hz, 1H, H-1), 5.17 (d, J = 3.3 Hz, 1H, H-1′), 5.01 (d, J = 11.2 Hz, 1H, PhCH_2O), 5.00 (d, J = 10.9 Hz, 1H, PhCH_2O), 4.7–4.9 (m, 8H, PhCH_2O), 4.65 (d, J = 11.2 Hz, 1H, PhCH_2O), 4.57 (d, J = 10.9 Hz, 1H, PhCH_2O), 3.9–4.2 (m, 5H), 3.5–3.6 (m, 6H), 3.18 (d, J = 3.3 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 138.8 (s), 138.7 (s), 138.28 (s), 138.16 (s, 2 carbons), 138.03 (s), 128.55 (s), 128.50 (s), 128.18 (s), 128.04

(s), 127.94 (s), 127.75 (s), 127.68 (s), 127.57 (s), 127.51 (s), 94.2 (s), 94.0 (s), 81.7 (s), 81.5 (s), 79.6 (s, 2 carbons), 78.4 (s), 77.5 (s), 75.7 (s, 2 carbons), 75.3 (s), 75.2 (s), 73.17 (s), 73.09 (s), 71.4 (s), 70.5 (s), 61.6 (s), 51.2 (s); MALDI Calcd for $C_{54}H_{57}N_3O_{10}Na$ ($[M+Na]^+$) 930.3936; measure 930.3934.

5.55. 6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-trehalose methyl (6*E*)-2′,3′,4′-tri-*O*-benzyl-6′,7′-dideoxy-α-D-*gluco*-oct-6-enopyranosyluronate)ether (37)

To a solution of $(COCl)_2$ (29 μL, 0.33 mmol) in 5 mL anhydrous CH_2Cl_2 at −78 °C, anhydrous DMSO (47 μL, 0.66 mmol) was added and the resulting solution was stirred for 15 min, allowing the temperature to be warmed up to −65 °C. To the reaction flask, a solution of **36** (0.15 g, 0.17 mmol) in 5 mL CH_2Cl_2 was added. The reaction mixture was stirred for 0.5 h allowing the temperature to be warmed up to −45 °C. To this solution, anhydrous DIPEA (0.23 mL, 1.32 mmol) was added, and the reaction was allowed to be warmed up to −10–0 °C in 0.5 h. After completion of the reaction, the reaction mixture quenched with 1 N HCl and diluted with CH_2Cl_2. The organic layer was washed with pH 7 buffer (three times), brine, and dried over Na_2SO_4. After removal of the solvents, the product, aldehyde, was used for the next step without further purification. To a solution of methyl diethylphosphonoacetate (50 μL, 0.27 mmol) in THF (5 mL) at 0 °C, NaH (0.011 g, 0.27 mmol) was added. After being stirred for 1 h, the aldehyde from first step was added. The reaction was stirred for another 12 h. After completion of the reaction, 50 μL MeOH was added to quench the reaction. After removal of the solvents, the residue was dissolved in EtOAc, and washed with brine then dried over $Na_2SO_{4(s)}$. After removal of the solvent, followed by purification with a gradient column chromatography (hexane–EtOAc = 90:10 to 50:50), the product was obtained as a pale yellowish oil (0.16 g, 0.17 mmol, 99%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.3–7.4 (m, 30H), 6.94 (dd, J = 15.8 Hz, J = 4.3 Hz, 1H), 6.01 (dd, J = 15.8 Hz, J = 1.6 Hz, 1H), 5.20 (d, J = 3.6 Hz, 1H, H-1), 5.10 (d, J = 3.6 Hz, 1H, H-1), 4.5–5.1 (m, 13H), 3.9–4.1 (m, 4H), 3.75 (s, 3H, $COOCH_3$), 3.4–3.6 (m, 3H), 3.2–3.3 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (s), 144.7 (s), 138.9 (s), 138.8 (s), 138.3 (s), 138.2 (s), 137.9 (s), 137.8 (s), 129.1 (s), 128.9 (s), 128.63 (s), 128.58 (s), 128.49 (s), 128.2 (s), 128.1 (s), 127.9 (s), 127.85 (s), 127.6 (s), 121.3 (s), 94.4 (s), 94.3 (s, C-1), 82.2 (s), 81.74 (s), 81.66 (s), 79.6 (s, 2 carbons), 78.5 (s), 75.9 (s), 75.8 (s), 75.7 (s), 75.4 (s), 73.3 (s, 2 carbons), 70.7 (s), 70.1 (s), 51.8 (s), 51.3 (s); MALDI Calcd for $C_{57}H_{59}N_3O_{11}Na$ ($[M+Na]^+$) 984.4042; measure 984.3991.

5.56. 6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-trehalose ((6*E*)-2′,3′,4′-tri-*O*-benzyl-6′,7′-dideoxy-*N*-octyl-α-D-*gluco*-oct-6-enopyranosyluronamide)ether (38)

Please refer to the general procedure for transamidation. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.2–7.3 (m, 30H), 6.77 (dd, J = 15.2 Hz, J = 5.6 Hz, 1H), 5.55 (dd, J = 15.2 Hz, J = 1.3 Hz, 1H), 5.18 (d, J = 3.6 Hz, 1H, H-1), 5.14 (d, J = 3.6 Hz, 1H, H-1), 4.8–5.0 (m, 4H), 4.5–4.7 (m, 9H), 3.9–4.1 (m, 4H), 3.5–3.6 (m, 3H), 3.2–3.3 (m, 4H), 1.48 (dd, J = 6.9 Hz, J = 6.9 Hz, 2H), 1.2–1.3 (m, 10H), 0.87 (dd, J = 6.9 Hz, J = 6.9 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.9 (s), 149.1 (s), 139.4 (s), 138.7 (s, 2 carbons), 138.3 (s), 138.1 (s), 137.9 (s), 128.5 (s), 128.4 (s), 128.0 (s), 127.7 (s), 127.5 (s), 127.4 (s), 125.1 (s), 94.1 (s, C-1), 93.9 (s), 82.2 (s), 81.5 (s, 2 carbons), 79.7 (s), 79.3 (s), 78.4 (s), 75.8 (s), 75.7 (s), 75.6 (s), 75.3 (s), 73.2 (s), 72.9 (s), 70.6 (s), 70.5 (s), 51.1 (s), 39.6 (s), 31.9 (s), 29.7 (s), 29.4 (s), 29.3 (s), 27.0 (s), 22.7 (s), 14.2 (s); MALDI Calcd for $C_{64}H_{74}N_4O_{10}Na$ ($[M+Na]^+$) 1081.5297; measure 1081.5306.

5.57. 6-Amino-6-deoxy-α-D-trehalose (*N*-octyl-α-D-*gluco*-octopyranosyluronamide)ether (YH041)

Please refer to the general procedure for hydrogenation ^{1}H NMR (400 MHz, D_2O) δ 5.13 (d, J = 3.6 Hz, 1H, H-1), 5.09 (d, J = 3.8 Hz, 1H, H-1), 3.6–4.0 (m, 5H), 3.1–3.3 (m, 5H), 2.2–2.4 (m, 2H), 2.10 (m, 1H), 1.71 (m, 1H), 1.44 (m, 2H), 1.23 (m, 12H), 0.81 (m, 3H); ^{13}C NMR (100 MHz, D_2O) δ 175.1 (s), 94.0 (s), 93.8 (s), 73.6 (s), 72.7 (s), 72.4 (s), 71.8 (s), 71.6 (s), 71.5 (s), 71.0 (s), 68.4 (s), 40.8 (s), 39.7 (s), 32.3 (s), 31.3 (s), 28.6 (s, 2 carbons), 28.5 (s), 27.3 (s), 26.3 (s), 22.3 (s), 13.7 (s); MALDI Calcd for $C_{22}H_{42}N_2O_{10}Na$ ($[M+Na]^+$) 517.2732; measure 517.2749.

5.58. Procedure for disk assay of antimicrobial activity

Disk diffusion assays were modified from methods outlined by the National Committee on Clinical Laboratory Standards.[15] *M. smegmatis* (ATCC 14468) was inoculated in LB (Lennox) broth, and the resulting solution was incubated at 37 °C for 2 days then was transferred into the LB (Lennox) agar plate by swab. Aliquots (20 μL) of solutions of INH (250 μg/mL) and trehalose derivatives (10 mg/mL) were applied to the disks. The plate was incubated at 37 °C for 2–3 days. The diameter of the zone of inhibition is measured, to the nearest whole millimeter.

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References and notes

1. Bloom, B. R.; Murray, C. J. L. *Science* **1992**, *257*, 1055–1064.
2. Manabe, Y. C.; Bishai, W. R. *Nature Med.* **2000**, *6*, 1327–1329.
3. (a) Russell, D. G. *Mol. Cell Biol.* **2001**, *2*, 1–9; (b) Viskum, K.; Kok-Jensen, A. *Int. J. Tuberc. Lung Dis.* **1997**, *1*, 299–301; (c) Dye, C.; Williams, B. G.; Espinal, M. A.; Raviglione, M. C. *Science* **2002**, *295*, 2042–2046.

4. (a) Blanchard, J. S. *Ann. Rev. Biochem.* **1996**, *65*, 215–239; (b) Jarlier, V.; Nikaido, H. *FEMS Microbiol. Lett.* **1994**, *123*, 11–18.
5. Chatterjee, D. *Curr. Opin. Chem. Biol.* **1997**, *1*, 579–588.
6. Tonge, P. J. *Nature Struct. Biol.* **2000**, *7*, 94–96.
7. Belisle, J. T.; Vissa, V. D.; Sievert, T.; Takayama, K.; Brennan, P. J.; Besra, G. S. *Science* **1997**, *276*, 1420–1422.
8. Ronning, D. R.; Klabunde, T.; Besra, G. S.; Vissa, V. D.; Belisle, J. T.; Sacchettini, J. C. *Nature Struct. Biol.* **2000**, *7*, 141–146.
9. Mizuguchi, Y.; Udou, T.; Yamada, T. *Microbiol. Immunol.* **1983**, *27*, 425–431.
10. Rose, J. D.; Maddry, J. A.; Comber, R. N.; Suling, W. J.; Wilson, L. N.; Reynolds, R. C. *Carbohydr. Res.* **2002**, *337*, 105–120.
11. We have reported the synthesis of seven 1st generation trehalose derivatives but no activity against *M. smegmatis* was found. Please see: Chang, C.-W. T.; Hui, Y. *Org. Lett.* **2002**, *4*, 2245–2248.
12. Gilbertson, S. R.; Chang, C.-W. T. *J. Org. Chem.* **1995**, *60*, 6226–6228.
13. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
14. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174.
15. *Methods for Dilution Antimicrobial Susceptibility Testing for Bacteria that Grow Aerobically*. Approved standard M7-A5, and *Performance Standards for Antimicrobial Disk Susceptibility Tests*. Approved standard M2-A7, National Committee for Clinical Laboratory Standards, Wayne, PA.
16. Pierre-Audigier, C.; Jouanguy, E.; Lamhamedi, S.; Altare, F.; Rauzier, J.; Vincent, V.; Canioni, D.; Emile, J. F.; Fischer, A.; Blanche, S.; Gaillard, J. L.; Casanova, J. L. *Clin. Infect. Dis.* **1997**, *24*, 982–984.
17. Springer, B.; Kidan, Y. G.; Prammananan, T.; Ellrott, K.; Böttger, E. C.; Sander, P. *Antimicrob. Agents Chemother.* **2001**, *45*, 2877–2884.
18. Nash, K. A. *Antimicrob. Agents Chemother.* **2003**, *47*, 3053–3060.
19. Despite the structural similarities, our compounds are much less active than those reported in Ref. 10. One of the reasons may be the difference in the strains of *Mycobacterium* that were used for antibacterial assay. We are currently synthesizing the lead compound reported in Ref. 10 for testing against *M. smegmatis*.
20. Similar observation has been reported. Please refer to Ref. 10.
21. Johnsson, K.; Schultz, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 7425–7426.
22. Dessen, A.; Quemard, A.; Blanchard, J. S.; Jacobs, W. R.; Sacchettini, J. C. *Science* **1995**, *267*, 1638–1641.
23. (a) Zhang, Y.; Garbe, T.; Young, D. *Mol. Microbiol.* **1993**, *8*, 521–524; (b) Zhang, Y.; Young, D. B. *Trends Microbiol.* **1993**, *1*, 109–113.
24. Deretic, V.; Philipp, W.; Dhandayuthapani, S.; Mudd, M. H.; Curcic, R.; Garbe, T.; Heym, B.; Via, L. E.; Cole, S. T. *Mol. Microbiol.* **1995**, *17*, 889–900.
25. (a) Wallis, R. S.; Phillips, M.; Johnson, J. L.; Teixeira, L.; Rocha, L. M. M. C.; Maciel, E.; Rose, L.; Wells, C.; Palaci, M.; Dietze, R.; Eisenach, K.; Ellner, J. J. *Antimicrob. Agents Chemother.* **2001**, *45*, 1302–1304; (b) Mitchison, D. A. *Tubercle* **1985**, *66*, 219–225.
26. Garbe, T. R.; Hibler, N. S.; Deretic, V. *Antimicrob. Agents Chemother.* **1996**, *40*, 1754–1756.
27. Viveiros, M.; Portugal, I.; Bettencourt, R.; Victor, T. C.; Jordaan, A. M.; Leandro, C.; Ordway, D.; Amaral, L. *Antimicrob. Agents Chemother.* **2002**, *46*, 2804–2810.