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Multicomponent Synthesis of Ugi-Type Ceramide Analogues and Neoglycolipids from Lipidic Isocyanides

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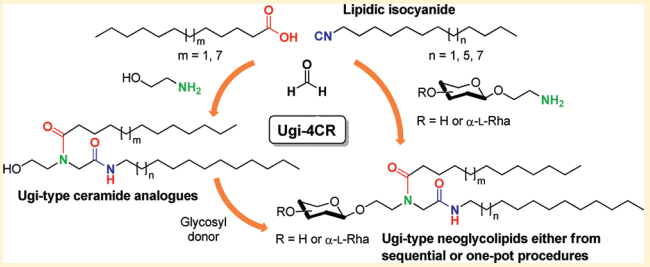
Supporting Information

ABSTRACT: Unique types of ceramide and glycolipid architectures were obtained by means of Ugi reactions incorporating lipidic isocyanides as surrogates of sphingolipids. The multicomponent nature of this approach allowed for a highly efficient assembly process, wherein two of the components provided the lipidic tails while a third one incorporated either the functionality suitable for the conjugation to sugar or the sugar moiety itself. Two dissimilar strategies were implemented: (i) the initial assembly of ceramide analogues followed by glycosylation to produce a glycolipid skeleton and (ii) the one-pot construction of glycolipid frameworks by condensation of lipidic isocyanides either with lipidic amines and oligosaccharidic acids or with fatty acids and oligosaccharidic amines. Whereas both approaches are amenable for accessing analogues of anticancer glycolipids, the latter one proved to have greater potential owing to its more straightforward and efficient character. Overall, the methodology developed shows great promise toward the massive (eventually combinatorial) production of neoglycolipids suitable for biological screening.



INTRODUCTION

Glycosphingolipids are important components of eukaryotic cell membranes, wherein their lipophilic portions are inserted into the bilayer leaving the hydrophilic moiety exposed toward the cell surface.[1] These molecules play crucial roles in various stages of the cell cycle, including proliferation, differentiation, adhesion, and apoptosis, etc.[1,2] They are also involved in signaling functions[3] and interaction in the cell surface with external agents such as toxins, viruses, and bacteria.[4] The interest on glycosphingolipids and their analogues has increased dramatically in the last years,[5] as some members of this family have proven success as anticancer agents[6] and in the prevention of microbial infections,[7] among other applications.[8]

The amphipathic structure of glycosphingolipids incorporates either mono- or oligosaccharide residues linked to a lipophilic ceramide unit by a glycosyl bond. The most common naturally occurring ceramide derives from sphingosine (i.e., C4−C5 *trans* double bond and D-*erythro* configuration), which is the hydrophobic portion of several cerebrosides and of tumor-associated antigens such as the ganglioside GM_3 (**1**, Figure 1). Other biologically relevant ceramides derive from phytosphingosine, which bears an additional hydroxyl group at C4 and is the aglycone of the immunostimulant α-galactosylceramide **2** (Figure 1).[9] The great potential of galactosylceramides as anticancer chemotherapeutics has prompted the design of various synthetic strategies[6b,10] as well as the performance of structure−activity relationship studies.[5c,6b,c,11,12] Hence, modifications at the galactosyl moiety,[5c,11]

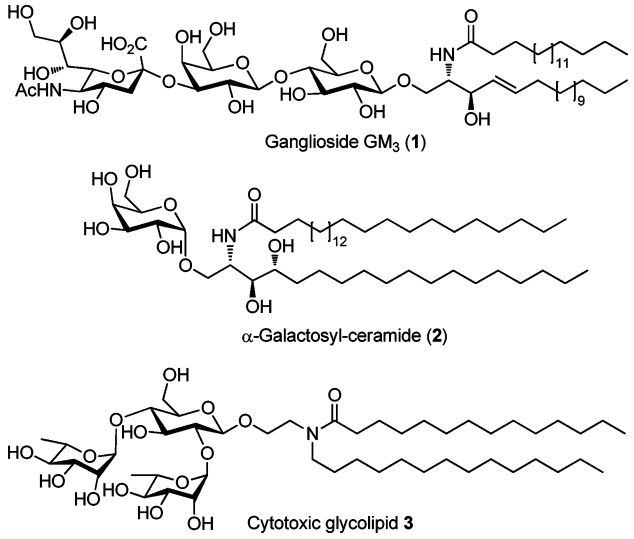


Figure 1. Glycolipids including natural and synthetic ceramides.

variation of the lipidic chain lengths,[12a−c] introduction of aromatic moieties,[12d,e] and isosteric replacement of the amide bond by a triazole unit[12f] are among the structural variations performed in this glycolipid platform.

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The design of glycolipids including non-natural ceramide scaffolds has also shown success in the pursuit of novel cytotoxic agents. For example, the trisaccharide β-chacotriose, commonly found in steroid saponins,[13] has been conjugated to double-lipidic scaffolds to produce a new type of cytotoxic glycolipids (e.g., compound **3**, Figure 1).[14]

Ceramides are not only structural components of glycosphingolipids, but they also regulate by themselves crucial biological processes such as cell cycle arrest, proliferation, differentiation, and apoptosis.[15] Because of the medicinal significance of ceramides and their sugar conjugates, extensive synthetic efforts toward these metabolites have been carried out in the past years.[16] Nevertheless, the utilization of multicomponent reactions (MCRs) either for the construction of ceramide-like skeletons or for their conjugation to carbohydrates has remained elusive so far, despite the huge number of applications that have been described for this type of procedure.[17] As glycosphingolipids incorporate three different components, i.e., a long-chain amino alcohol (e.g., sphingosine or phytosphingosine), a fatty acid, and a sugar moiety, we envisioned that this type of hybrid scaffold could be assembled in one pot by means of a multicomponent approach.

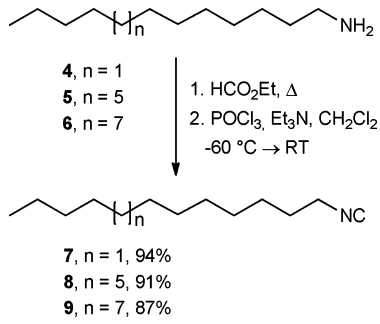
Herein we report on the one-pot synthesis of ceramide analogues and neoglycolipids by the Ugi four-component reaction (Ugi-4CR).[18] The multicomponent nature of this process enables the utilization of a unique assembly process, i.e., two of the components providing the lipidic tails while one or the two others incorporating either the functionality suitable for the conjugation to the carbohydrate or the sugar moiety itself. To prove the scope of this idea, two dissimilar strategies were implemented: (i) the construction of a double-lipidic chain framework analogous to ceramide followed by glycosylation with a glucosyl donor and (ii) the one-pot multicomponent assembly of varied hybrid carbohydrate/ceramide-like scaffolds from properly functionalized saccharidic and lipidic substrates. Additionally, we describe the synthesis of novel lipidic isocyanides, a unique class of compound that may be considered as surrogate either of fatty acids or of sphingolipids on the design of novel membrane active compounds.

RESULTS AND DISCUSSION

The Ugi-4CR is the one-pot condensation of a primary amine, an oxo compound (i.e., ketone or aldehyde), a carboxylic acid, and an isocyanide to produce an *N*-substituted dipeptide backbone.[18] Despite the great availability of fatty acids and long-chain aliphatic amines, we are not aware of the utilization of this MCR for the construction of double-lipidic-chain-based scaffolds resembling the ceramide skeleton. Moreover, lipidic aldehydes and isocyanides offer new prospects for the combinatorial synthesis of ceramide analogues, as they allow for the fast variation of each of the four different components upon the one-pot assembly of double-lipidic chain scaffolds by the Ugi-4CR. Whereas isocyanides featuring long aliphatic chains have been isolated from a variety of organisms,[18a,19] there is not much information regarding their properties and chemical behavior. Accordingly, we initially focused on the preparation as well as study of the reactivity and stability of lipidic isocyanides, which upon incorporation into a ceramide-like skeleton might be considered as mimics of fatty acids ubiquitous in cell membranes.

As shown in Scheme 1, *n*-dodecylamine (**4**), *n*-hexadecylamine (**5**), and *n*-octadecylamine (**6**) were subjected to formylation by refluxing in ethylformate, followed by

Scheme 1. Synthesis of Lipidic Isocyanides from Long-Chain Aliphatic Amines



phosphorylchloride-mediated dehydration[20] of the corresponding formamides to produce isocyanides **7**, **8**, and **9**, respectively, in excellent yields after flash column chromatography purification. These compounds are stable, pale yellow oils, whose smells are not as intense as for volatile aliphatic isocyanides such as the *t*-butyl, *n*-butyl, and cyclohexyl ones. In all procedures the isocyanide formation was confirmed by ^{13}C NMR analysis, wherein the typical triplets indicative of the isocyano functionality showed up. Interestingly, the highly lipophilic nature of these compounds provoked the lack of ionization in ESI-MS. The three lipidic isocyanides proved to be as reactive as other aliphatic isocyanides in comparative Ugi-4CRs (e.g., using propionic acid, butyraldehyde, and isopropylamine), albeit the solvent mixture MeOH/CH_2Cl_2 (3:1, v/v) was required because of their low solubility in pure MeOH.

Table 1 illustrates the implementation of the initial step of the first multicomponent strategy toward glycolipids, which encompasses the synthesis of ceramide analogues by means of the Ugi-4CR. Although lipidic aldehydes are known and readily available through a variety of methods, such prochiral aldehydes would lead to the formation of stereoisomers of difficult separation. Accordingly, paraformaldehyde was always employed as the oxo component, thus leaving the other Ugi-components for the incorporation of the two lipid chains and the functionality suitable for the conjugation to the carbohydrate moiety. As reports of Ugi-4CRs with such long-chain substrates are quite seldom, the initial efforts were directed to set up the experimental conditions as well as assessing the efficiency of such condensations between fatty acids and lipidic isocyanides of variable chain length.

As depicted in Table 1, ethanolamine was chosen as the amino component, thus providing the primary hydroxyl group required for the subsequent glycosylation of the resulting ceramide analogues. Thus, lauric acid (dodecanoic acid) was combined with isocyanide **7** to furnish the ceramide analogue **10**, which is endowed with two lipid chains of 12 carbon atoms each. Alternatively, the combination of stearic acid (octadecanoic acid) with isocyanides **8** and **9** afforded the ceramide analogues **11** and **12**, respectively, which differ only in the length of lipid chain attached to the secondary amide. The reaction yields did not drop significantly while increasing the chain length of the lipidic components, which is an important feature while looking for future applications in the production and biological screening of combinatorial libraries of ceramide analogues. It must be noticed that the substrate scope can be significantly expanded with the utilization of building blocks having further hydroxyl and olefin functionalities, which do not interfere in the normal course of the Ugi-4CR. Thus, not only a

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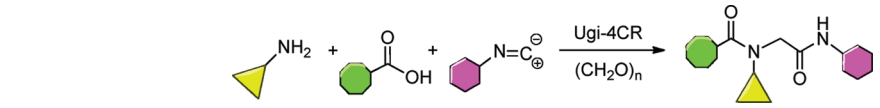
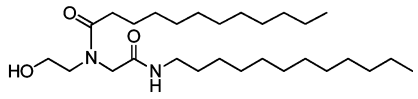
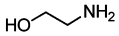
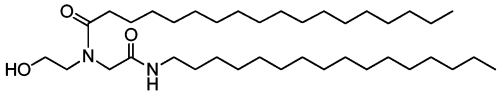
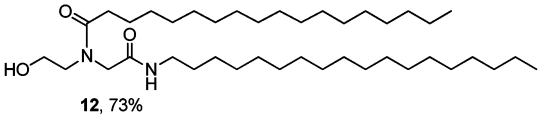
Table 1. Synthesis of Ceramide Analogues by the Ugi-4CR[a]



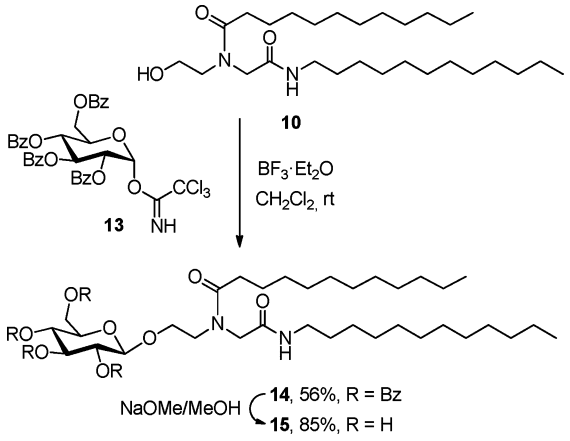
Amine	Acid	Isocyanide	Ugi-type Ceramide Analogue
	$C_{11}H_{23}COOH$	$C_{12}H_{25}NC$ (**7**)	 **10**, 81%
	$C_{17}H_{35}COOH$	$C_{16}H_{33}NC$ (**8**)	 **11**, 78%
	$C_{17}H_{35}COOH$	$C_{18}H_{37}NC$ (**9**)	 **12**, 73%

[a]All reactions were conducted in $MeOH/CH_2Cl_2$ (3:1, v/v) at room temperature using paraformaldehyde as the oxo component.

closer resemblance to the original ceramide skeleton can be achieved, but also a quite detailed structure–activity relationship study can be carried out through the tunable variation of the features influencing the interaction of these molecules with cell membranes. Indeed, the advantages of this one-pot approach are its efficiency and reproducibility, as well as the fact that several structural variations can be accomplished at once as a result of its multicomponent nature.

As proof of concept of the first proposal toward glycolipid, we turned to evaluate the scope of a traditional glycosylation protocol for a ceramide analogue prepared by means of the Ugi-4CR. As depicted in Scheme 2, compound **10** was

Scheme 2. Synthesis of a Neoglycolipid by Glycosylation of a Ceramide Analogue



subjected to glycosylation with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate **13**[21] to furnish conjugate **14** in 56% yield. Further global deprotection produced the neoglycolipid **15**, which can be considered as a new class of cerebroside mimetic. Whereas the sequential Ugi-4CR/glycosylation protocol toward glycolipids might ensure the levels of molecular diversity desired for a future implementation in combinatorial synthesis, the chemical efficiency of this two-step process is not as high as required for this application. Actually, the greatest limitation of this strategy is the fact that most glycosylation approaches proceed only in moderate yields[5a] when applied to ceramide and its analogues, likely because of the bulky character of these substrates. To overcome this limitation, we turned to the development of an alternative strategy comprising the construction of the whole glycolipid scaffold in one pot.

Previously, it was proven that the Ugi-4CR is a reliable and efficient method for the production of ceramide analogues from lipidic isocyanides and fatty acids. Accordingly, we envisioned that this process would allow for the incorporation not only of the two lipidic tails, but also the sugar moiety forming the glycolipid platform. To this end, the first step would be the functionalization of saccharidic building blocks with Ugi-reactive functional groups. Considering the success reported for the production of biologically active glycolipids derived from the β-chacotriosyl moiety[14] (i.e., 2,4-di-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranosyl; see compound **3**, Figure 1), we focused on the preparation of β-chacotriosyl building blocks suitably functionalized with Ugi-reactive groups for the construction of new glycolipid architectures. With this, we also aim to demonstrate that such bulky 2,4-branched oligosaccharides can be readily incorporated into complex hybrid architectures in one pot.[22]

Scheme 3 depicts the synthesis of β-chacotriosides functionalized with amino and carboxyl groups. To this end, the 2′-azidoethyl β-D-glucopyranoside **16**, prepared according to a reported procedure,[23] was subjected to deprotection under typical Zemplen conditions (NaOMe/MeOH) followed by selective pivaloylation[24] to furnish the 3,6-dipivaloylated β-D-glucosides **17** in 62% yield over two steps. Glucoside **17** was then subjected to double glycosylation with 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**18**)[25] according to the Schmidt's inverse procedure,[26] and subsequent palladium-catalyzed hydrogenation of the azido group to produce the 2′-aminoethyl β-chacotrioside **19** in 71% yield over two steps. Alternatively, the allyl β-chacotrioside **20**,[14] also prepared

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Scheme 3. Synthesis of β-Chacotriosides Functionalized with Amino and Carboxyl Groups

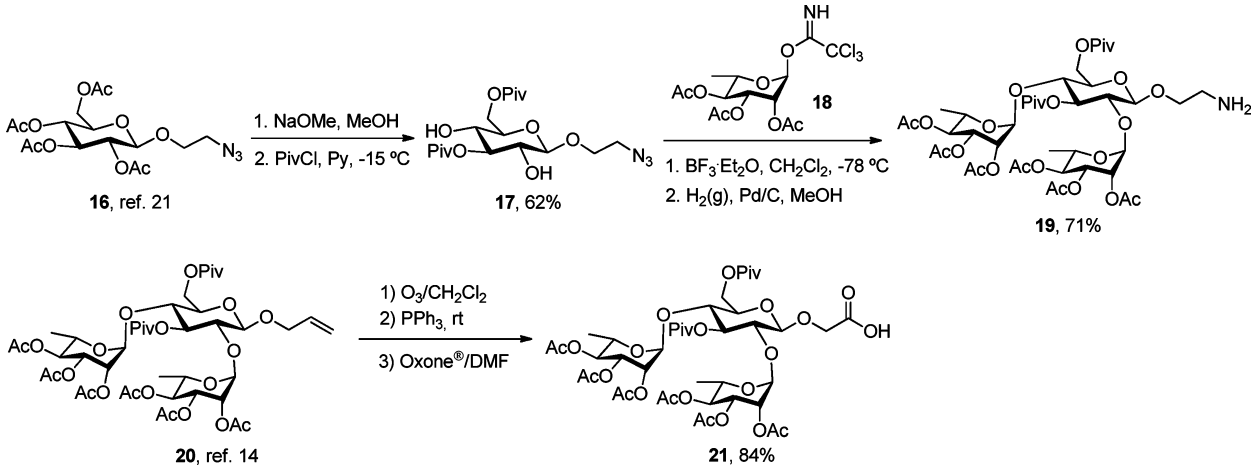

Table 2. One-Pot Multicomponent Synthesis of Neoglycolipids from Fatty Acids, Lipidic Isocyanides, and an Amino-Containing Oligosaccharide[a]

Amine	Acid	Isocyanide	Glycolipid
	$C_{11}H_{23}COOH$	$C_{12}H_{25}NC$ (**7**)	NaOH, THF/MeOH, 50 °C → **22**, 71%, R^1 = Piv, R^2 = Ac; **23**, 89%, $R^1 = R^2$ = H
19	$C_{11}H_{23}COOH$	$C_{18}H_{37}NC$ (**9**)	NaOH, THF/MeOH, 50 °C → **24**, 69%, R^1 = Piv, R^2 = Ac; **25**, 95%, $R^1 = R^2$ = H
	$C_{17}H_{35}COOH$	$C_{18}H_{37}NC$ (**9**)	NaOH, THF/MeOH, 50 °C → **26**, 73%, R^1 = Piv, R^2 = Ac; **27**, 93%, $R^1 = R^2$ = H

[a]All reactions were conducted in MeOH/CH_2Cl_2 (3:1, v/v) at room temperature using paraformaldehyde as the oxo component.

through 3,6-dipivaloylation of an allyl β-D-glucoside followed by glycosylation with the α-L-rhamnosyl donor **18**, was subjected to ozonolysis and subsequent oxidation with Oxone[27] to furnish the carboxymethyl β-chacotrioside **21** in 84% yield over two steps. With these functionalized sugars in hands, we turned to demonstrate the synthetic potential of the second Ugi-4CR-based strategy, which aims the incorporation of two lipidic chains and a large oligosaccharide moiety into a complex, glycolipid architecture, all over in a single step.

Table 2 shows the first three examples of this one-pot multicomponent approach that combines the 2′-aminoethyl β-chacotrioside **19** with lipidic isocyanides **7** and **9** as well as lauric and stearic acids, always utilizing paraformaldehyde as the oxo-component. Thus, conjugates **22**, **24**, and **26** were obtained in about 70% yield, which are remarkable results considering the great molecular complexity that is achieved in a single reaction step. Global deprotection of the β-chacotrioside/ceramide-like hybrids **22**, **24**, and **26** afforded the final neoglycolipids **23**, **25**, and **27**, respectively, in excellent overall yields. It must be noticed that compounds produced by this approach exhibit the same type of ceramide skeleton that those obtained by the former two-step protocol (e.g., compounds **15** and **23**). Indeed, the earlier preparation of functionalized glycosides to be subsequently reacted with the other two components by such multicomponent means shows more promise with regard to applications in combinatorial synthesis. This is not only due to the higher chemical efficiency of this second strategy, but also due to the greater structural diversity that can be accessed in one step with a process incorporating directly the three components into the final glycolipids.

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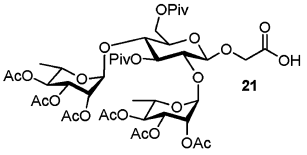
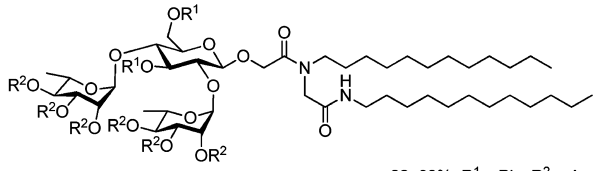
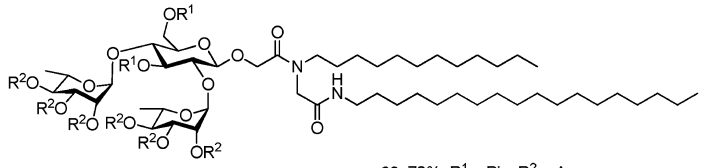
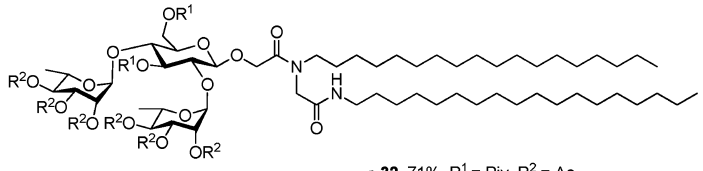
Table 3. One-Pot Multicomponent Synthesis of Neoglycolipids from Lipidic Isocyanides, Lipidic Amines, and a Carboxy-Containing Oligosaccharide[a]

Acid	Amine	Isocyanide	Glycolipid
 **21**	$C_{12}H_{25}NH_2$	$C_{12}H_{25}NC$ (**7**)	 NaOH, THF/MeOH, 50 °C → **28**, 68%, R^1 = Piv, R^2 = Ac; **29**, 93%, $R^1 = R^2$ = H
	$C_{12}H_{25}NH_2$	$C_{18}H_{37}NC$ (**9**)	 NaOH, THF/MeOH, 50 °C → **30**, 72%, R^1 = Piv, R^2 = Ac; **31**, 96%, $R^1 = R^2$ = H
	$C_{18}H_{37}NH_2$	$C_{18}H_{37}NC$ (**9**)	 NaOH, THF/MeOH, 50 °C → **32**, 71%, R^1 = Piv, R^2 = Ac; **33**, 92%, $R^1 = R^2$ = H

[a]All reactions were conducted in $MeOH/CH_2Cl_2$ (3:1, v/v) at room temperature using paraformaldehyde as the oxo component.

Table 3 illustrates three examples of alternative approach that combines carboxymethyl β-chacotrioside **21** with lipidic isocyanides and lipidic amines to produce the β-chacotrioside/ceramide-like hybrids **28**, **30**, and **32**. As before, the yields of these multicomponent procedures were as high as 70% yield, thus corroborating that large substrates such as 2,4-branched oligosaccharides can be incorporated into very complex glycolipid platforms in an efficient, reproducible manner. Global deprotection of glycosides **28**, **30**, and **32** led to the final neoglycolipids **29**, **31**, and **33**, respectively, in excellent overall yields. Analysis of Tables 2 and 3 shows that neoglycolipids **23**, **25**, and **27** are isomeric with **29**, **31**, and **33**, respectively, just differing in the positioning of the tertiary amide bond. This characteristic confirms the skeletal diversification that can be achieved only with minor changes in the component structures, as well as paves the way for the development of further one-pot approaches focused on the generation of higher levels of molecular diversity.

NMR analysis of the neoglycolipids demonstrates the occurrence of two conformers at room temperature, owing to the presence of a tertiary amide in the ceramide-like scaffolds. Thus, two different sets of signals appear in the ^{1}H NMR spectra for those protons of the methylenes nearby to the tertiary amides and those of the inner D-glucose units (see the Supporting Information). Also, duplicated signals of the amide bonds are observed in the ^{13}C NMR spectra, thereby confirming the presence of both the *cis* and the *trans* rotamers for the tertiary amide of each glycolipid. This is a typical feature of peptoid-type skeletons, wherein the *N*-alkylation of the amide bonds leads to similarly populated conformers derived from the s-*cis* and the s-*trans* configurations. Temperature-dependent NMR experiments were performed with glycolipid **26** to evaluate the possibility of fast interconversion at higher temperature between the two rotamers. These experiments showed that, e.g., at 30 °C there are two doublets corresponding to the anomeric proton of the inner β-D-glucoside, while at 70 °C both signals collapse into a single doublet (see the Supporting Information). The same effect takes place with other sets of duplicated signals such as the two protons of position 6 of the D-glucose and the methylenes nearby to the tertiary amide.

The occurrence of various conformations with similar energy for these glycolipids may comprise the generation, and therefore possibility of screening, of a larger conformational space compared to those accessible by methods producing only secondary-amide-based ceramide analogues. Finally, it must be mentioned that this method is not restricted to Ugi-type ceramide analogues derived from formaldehyde, as prochiral oxo-compounds can also be employed with similar success.

■ CONCLUSIONS

We have developed a multicomponent approach for the construction of double-lipidic scaffolds resembling bioactive ceramides and glycolipids. This is the first time that the Ugi-4CR is utilized for the synthesis of such lipid-based molecules, thus proving once more the tremendous potential of this reaction for the rapid creation of compounds resembling biologically relevant molecules. Lipidic isocyanides were initially produced from long-chain aliphatic amines and were next incorporated into ceramide-like skeletons, thus acting as mimics of sphingolipids. Two different multicomponent strategies were implemented: (i) the condensation of such isocyanides with fatty acids and a hydroxyl-containing amine to yield ceramide-like scaffolds, followed by their glycosylation to produce the glycolipid framework, and (ii) the one-pot construction of varied glycolipid skeletons by condensation of

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lipidic isocyanide either with lipidic amines and oligosaccharidic acids or with fatty acids and oligosaccharidic amines. The second approach proved greater success and higher efficiency owing to its more straightforward character and the possibility of accessing higher levels of molecular diversity in a single step. Nevertheless, both protocols show great promise toward the combinatorial production and biological screening of libraries of ceramide analogues and glycolipids. For example, considering that a tunable variation of the oligosaccharidic portion is quite compatible with the multicomponent nature of this approach, applications in the development of anticancer glycolipids analogous to galactosyl-ceramides and gangliosides are foreseeable.

EXPERIMENTAL SECTION

General Methods. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 500 MHz for ^{1}H and 100 and 125 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in parts per million relative to the residual solvent signals, and coupling constants (J) are reported in hertz. NMR peak assignments were accomplished by analysis of the ^{1}H−^{1}H COSY and HSQC data. High resolution ESI mass spectra were obtained from a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer, an RF-only hexapole ion guide, and an external electrospray ion source. Flash column chromatography was carried out using silica gel 60 (230−400 mesh), and analytical thin layer chromatography (TLC) was performed using silica gel aluminum sheets. Compounds **13**, **16**, **18**, and **20** were prepared according to refs 21, 23, 25, and 14, respectively. All commercially available chemicals were used without further purification. For compounds arising from the Ugi-4CR, the assigned signals belong to a mixture of conformers.

General Procedure for the Synthesis of the Lipidic Isocyanides. The lipidic amine (1 mmol) was dissolved in ethylformate (10 mL), and the resulting solution was stirred at reflux for 20 h. The volatiles were removed under reduced pressure to furnish the corresponding formamide. This crude product was dissolved in dry CH_2Cl_2 (5 mL), and the solution was cooled to −60 °C and treated with Et_3N (2 mL). A solution of $POCl_3$ (1 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise under nitrogen atmosphere, and the resulting reaction mixture was stirred at −60 °C for 2 h, then allowed to reach room temperature, and stirred for additional 4 h. The resulting suspension was poured into 20 mL of cold water, and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic phases were combined, washed with brine, and evaporated under reduced pressure to dryness. The resulting crude product was purified by flash column chromatography (*n*-hexane/EtOAc 10:1) to yield the pure isocyanide.

***n*-Dodecylisocyanide (7).** 94% yield. Pale yellow oil: R_f = 0.53 (*n*-hexane/EtOAc 10:1); IR (KBr, cm^{-1}) ν_{max} 2927, 2857, 2148, 1460; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.88 (t, 3H, J = 6.9 Hz, CH_3); 1.26−1.29 (m, 16H, 8 × CH_2); 1.42 (m, 2H, CH_2); 1.67 (m, 2H, CH_2); 3.37 (tt, 2H, J = 1.9/6.7 Hz, CH_2NC); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.0 (CH_3); 22.6, 26.3, 28.6, 29.1, 29.2, 29.3, 29.4, 29.5, 31.8 (CH_2); 41.5 (t, J = 6.4 Hz, CH_2NC); 155.6 (t, J = 6.0 Hz, NC). Anal. Calcd. for $C_{13}H_{25}N$: C, 79.9; H, 12.9; N, 7.2. Found: C, 79.8; H, 13.0; N, 7.3.

***n*-Hexadecylisocyanide (8).** 91% yield. Pale yellow oil: R_f = 0.46 (*n*-hexane/EtOAc 8:1); IR (KBr, cm^{-1}) ν_{max} 2925, 2856, 2147, 1461; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.87 (t, 3H, J = 6.8 Hz, CH_3); 1.25−1.29 (m, 24H, 12 × CH_2); 1.42 (m, 2H, CH_2); 1.67 (m, 2H, CH_2); 3.36 (tt, 2H, J = 1.9/6.6 Hz, CH_2NC); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.0 (CH_3); 22.6, 26.3, 28.7, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (CH_2); 41.5 (t, J = 6.4 Hz, CH_2NC); 155.6 (t, J = 5.5 Hz, NC). Anal. Calcd. for $C_{17}H_{33}N$: C, 81.2; H, 13.2; N, 5.6. Found: C, 81.1; H, 13.3; N, 5.5.

***n*-Octadecylisocyanide (9).** 87% yield. Pale yellow oil: R_f = 0.53 (*n*-hexane/EtOAc 8:1); IR (KBr, cm^{-1}) ν_{max} 2920, 2852, 2149, 1466; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.88 (t, 3H, J = 6.9 Hz, CH_3); 1.25−1.31 (m, 28H, 14 × CH_2); 1.42 (m, 2H, CH_2); 1.67 (m, 2H, CH_2); 3.37 (tt, 2H, J = 1.9/6.8 Hz, CH_2NC); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.1 (CH_3); 22.7, 26.3, 28.7, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9 (CH_2); 41.5 (t, J = 6.4 Hz, CH_2NC); 155.6 (t, J = 5.3 Hz, NC). Anal. Calcd. for $C_{19}H_{37}N$: C, 81.7; H, 13.3; N, 5.0. Found: C, 81.8; H, 13.1; N, 5.1.

General Procedure for the Ugi-4CR. A solution of the amine (1.0 mmol) and paraformaldehyde (1.0 mmol) in MeOH/CH_2Cl_2 (20 mL, 3:1, v/v) was stirred for 1 h at room temperature. The acid (1.0 mmol) and the isocyanide (1.0 mmol) were then added, and the reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure to dryness. The crude product was purified by flash column chromatography to afford the corresponding ceramide analogue or glycolipid.

Ceramide Analogue 10. 2-Amino-1-ethanol (40 μL, 0.66 mmol), paraformaldehyde (20 mg, 0.66 mmol), lauric acid (132 mg, 0.66 mmol), and *n*-dodecylisocyanide (129 mg, 0.66 mmol) were reacted in MeOH/CH_2Cl_2 (12 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 3:1) afforded the ceramide analogue **10** (250.6 mg, 81%) as a white solid: R_f = 0.30 (*n*-hexane/EtOAc 3:1); mp 75−77 °C; IR (KBr, cm^{-1}) ν_{max} 3353, 2925, 2851, 1641, 1558, 1155; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.81 (t, 6H, J = 6.7 Hz, 2 × CH_3); 1.20−1.34 (m, 35H); 1.49 (m, 2H, CH_2); 1.61 (m, 2H, CH_2); 2.23, 2.40 (2 × t, 2H, J = 7.6 Hz, CH_2); 3.21−3.28 (m, 2H, CH_2); 3.51, 3.62 (2 × t, 2H, J = 5.0 Hz, CH_2); 3.74, 3.80 (2 × m, 2H, CH_2); 3.87, 4.00 (2 × s, 2H, CH_2); 5.04, 6.35 (2 × m, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1 (CH_3); 22.6, 22.7, 25.0, 25.1, 26.9, 27.0, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 33.2, 33.4, 39.8, 39.9, 51.2, 51.6, 52.9, 53.8, 60.2, 60.3 (CH_2); 170.8, 174.7 (C═O); HRMS (ESI-FT-ICR) m/z 491.4190 [M + Na]$^+$; calcd. for $C_{28}H_{56}N_2O_3Na$ 491.4189.

Ceramide Analogue 11. 2-Amino-1-ethanol (40 μL, 0.66 mmol), paraformaldehyde (20 mg, 0.66 mmol), stearic acid (188 mg, 0.66 mmol), and *n*-hexadecylisocyanide (83 mg, 0.66 mmol) were reacted in MeOH/CH_2Cl_2 (6 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 3:1) afforded the ceramide analogue **11** (314 mg, 78%) as a white solid: R_f = 0.32 (*n*-hexane/EtOAc 3:1); mp 84−86 °C; IR (KBr, cm^{-1}) ν_{max} 3355, 2916, 2857, 1646, 1556, 1163; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.87 (t, 6H, J = 6.6 Hz, 2 × CH_3); 1.25−1.30 (m, 55H); 1.49 (m, 2H, CH_2); 1.61 (m, 2H, CH_2); 2.23, 2.32, 2.40 (3 × m, 2H, CH_2); 3.21−3.28 (m, 2H, CH_2); 3.51, 3.62 (2 × m, 2H, CH_2); 3.74, 3.80 (2 × m, 2H, CH_2); 3.87, 4.00 (2 × s, 2H, CH_2); 6.43, 6.81, 7.12 (3 × m, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1 (CH_3); 22.7, 24.8, 24.9, 25.0, 26.8, 26.9, 27.0, 27.1, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 33.2, 33.4, 34.2, 39.4, 39.8, 39.9, 51.2, 51.7, 53.0, 53.9, 54.4, 59.2, 60.4, 60.5, 61.8 (CH_2); 170.1, 170.8, 174.7 (C═O); HRMS (ESI-FT-ICR) m/z 609.5931 [M + H]$^+$; calcd. for $C_{38}H_{77}N_2O_3$ 609.5929.

Ceramide Analogue 12. 2-Amino-1-ethanol (25 μL, 0.41 mmol), paraformaldehyde (12 mg, 0.41 mmol), stearic acid (117 mg, 0.41 mmol), and *n*-octadecylisocyanide (115 mg, 0.41 mmol) were reacted in MeOH/CH_2Cl_2 (8 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 3:1) afforded the ceramide analogue **12** (191 mg, 73%) as a white solid: R_f = 0.32 (*n*-hexane/EtOAc 3:1); mp 91−93 °C; IR (KBr, cm^{-1}) ν_{max} 3357, 2916, 2849, 1648, 1148; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.88 (t, 6H, J = 7.1 Hz, 2 × CH_3); 1.22−1.31 (m, 59H); 1.50 (m, 2H, CH_2); 1.62 (m, 2H, CH_2); 2.24, 2.33, 2.40 (3 × m, 2H, CH_2); 3.22−3.29 (m, 2H, CH_2); 3.52, 3.62 (2 × m, 2H, CH_2); 3.75, 3.81 (2 × m, 2H, CH_2); 3.87, 4.00 (2 × s, 2H, CH_2); 6.25, 6.75, 6.99 (3 × m, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1 (CH_3); 22.7, 25.1, 26.9, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 33.2, 39.9, 51.7, 53.0, 60.5 (CH_2); 170.8, 174.7 (C═O); HRMS (ESI-FT-ICR) m/z 637.6242 [M + H]$^+$; calcd. for $C_{40}H_{81}N_2O_3$ 637.6242.

Glycolipid 14. The ceramide-like compound **10** (0.100 g, 0.21 mmol) and the glucosyl donor **13** (0.079 g, 0.106 mmol) were suspended in dry CH_2Cl_2 (2 mL) in the presence of 4 Å molecular sieves. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 2 h, and then BF_3·OEt_2 (27.3 μL, 0.22 mmol) was added. After stirring for 3 h, the reaction was quenched with aq 0.5

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M $NaHCO_3$ (2 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to dryness. The crude product was purified by flash column chromatography (*n*-hexane/EtOAc 1:1) to afford the glycolipid **14** (64 mg, 56%) as an amorphous solid: R_f = 0.35 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{20}$ +17.3 (*c* 5.2, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 2922, 2848, 2361, 1733, 1651, 1455, 1269, 1107, 1097, 1070; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.79 (t, 6H, *J* = 7.0 Hz, 2 × CH_3); 1.17 (m, 34H, 17 × CH_2); 1.31 (m, 2H, CH_2); 1.41 (m, 2H, CH_2); 1.85, 2.01 (2 × m, 2H, CH_2); 2.23 (t, 1H, *J* = 7.6 Hz); 3.02, 3.16 (2 × m, 2H, CH_2); 3.28, 3.44, 3.55, 3.65 (4 × m, 2H, CH_2); 3.72−3.78 (m, 2H, CH_2); 3.97 (m, 1H); 4.09 (m, 1H, H-5 Glc); 4.41 (m, 1H, H-6a Glc); 4.58 (m, 1H, H-6b Glc); 4.76, 4.78 (2 × d, 1H, *J* = 7.9 Hz, H-1 Glc); 5.43 (m, 1H, H-2 Glc); 5.60 (m, 1H, H-4 Glc); 5.84 (m, 1H, H-3 Glc); 6.04, 6.28 (2 × m, 1H, NH); 7.19 (m, 2H, Ar-H); 7.24−7.35 (m, 7H, Ar-H); 7.44 (m, 3H, Ar-H); 7.73 (m, 2H, Ar-H); 7.82−7.89 (m, 4H, Ar-H); 7.95 (m, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.5 (CH_3); 23.0, 25.2, 25.6, 27.2, 27.3, 29.7, 29.8, 29.9, 30.0, 30.1, 32.3, 33.3, 33.4, 39.8, 40.0, 47.6, 49.3, 51.4, 53.4 (CH_2); 56.5 (CH); 63.3, 67.4 (CH_2); 69.6, 70.0, 72.2, 72.6, 72.9, 73.1, 73.2, 99.7, 101.5, 101.6, 128.6, 128.7, 128.8 (CH); 128.9, 129.2, 129.4, 129.9 (C); 130.1, 130.2, 130.3, 133.5, 133.6, 133.7, 133.8, 133.9 (CH); 165.4, 165.6, 165.8, 166.0, 166.1, 166.5, 168.7, 169.8, 174.6, 174.9 (C═O); HRMS (ESI-FT-ICR) *m/z* 1069.5780 $[M + Na]^+$; calcd. for $C_{62}H_{82}N_2O_{12}Na$ 1069.5765.

Glycolipid 15. NaOMe was added to a solution of compound **14** (64 mg, 0.061 mmol) in THF/MeOH (4 mL, 1:1) until pH was set to 9−10. The reaction mixture was stirred overnight at room temperature, then neutralized with acid resin Dowex-50 (H^+), and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 9:1) to afford glycolipid **15** (33 mg, 85%) as a white solid: R_f = 0.30 (CH_2Cl_2/MeOH 9:1); mp 129−131 °C; $[\alpha]_D^{20}$−1.0 (*c* 5.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3428, 2918, 2855, 2361, 1638, 1544, 1468, 1078, 1047; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.88 (m, 6H, 2 × CH_3); 1.20−1.35 (m, 34H, 17 × CH_2); 1.62 (m, 2H, CH_2); 1.80 (m, 2H, CH_2); 2.56 (m, 2H, CH_2); 3.49 (m, 2H, CH_2); 3.86−4.65 (m, 12H); 4.86, 4.88 (2 × d, 1H, *J* = 7.6 Hz, H-1 Glc); 8.33, 8.63 (2 × m, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.7 (CH_3); 23.3, 26.0, 26.1, 27.7, 27.8, 30.0, 30.1, 30.2, 30.3, 30.4, 30.5, 30.6, 32.5, 33.7, 33.9, 40.2, 40.3, 48.3, 49.9, 51.0, 53.3, 63.0, 63.1, 68.5 (CH_2); 68.9, 71.9, 75.5, 75.6, 78.9, 79.0, 105.2, 105.3 (CH); 170.1, 170.3, 174.5, 174.6 (C═O); HRMS (ESI-FT-ICR) *m/z* 653.4722 $[M + Na]^+$; calcd. for $C_{34}H_{66}N_2O_8Na$ 653.4717.

2′-Azido-ethyl 3,6-Di-*O*-pivaloyl-β-D-glucopyranoside (17). NaOMe was added to a solution of compound **16** (2.94 g, 7.04 mmol) in CH_2Cl_2/MeOH (40 mL, 1:1, v/v) until pH was set to 9−10. The reaction mixture was stirred for 1 h at room temperature, then neutralized with acid resin Dowex-50 (H^+), and filtered. The filtrate was concentrated under reduced pressure, and the residue was dried in vacuo to furnish the deprotected β-D-glucoside. This product was dissolved in anhydrous pyridine (40 mL), and the solution was cooled to −15 °C and stirred under nitrogen atmosphere. Pivaloyl chloride (4.3 mL, 35.2 mmol) was added dropwise, and the reaction course was monitored by TLC. The stirring was continued at room temperature until the disappearance of the starting material. The mixture was then diluted with EtOAc (50 mL) and washed with dilute aq HCl, saturated aq $NaHCO_3$, and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by flash column chromatography (*n*-hexane/EtOAc 3:1) to afford **17** (1.73 g, 59%) as an amorphous solid: R_f = 0.31 (*n*-hexane/EtOAc 3:1); $[\alpha]_D^{20}$ +87.2 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3445, 2959, 2862, 2373, 2344, 2118, 1726, 1287, 1160, 1050; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.21, 1.24 (2 × s, 2 × 9H, 2 × $(CH_3)_3C$); 3.35 (m, 1H, H-2′a); 3.45−3.59 (m, 4H, H-2, H-4, H-5, H-2′b); 3.76 (m, 1H, H-1′a); 4.03 (m, 1H, H-1′b); 4.29 (dd, 1H, *J* = 5.8/12.0 Hz, H-6a); 4.40 (d, 1H, *J* = 7.7 Hz, H-1); 4.44 (dd, 1H, *J* = 2.4/12.0 Hz, H-6b); 4.89 (t, 1H, *J* = 9.2 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.0, 27.1 (CH_3); 38.9, 39.0 (C); 50.7, 63.1, 68.8 (CH_2); 69.7, 72.2, 74.5, 77.6, 103.0 (CH); 178.7, 180.2 (C═O); HRMS (ESI-FT-ICR) *m/z* 440.2021 $[M + Na]^+$ (calculated for $C_{18}H_{31}N_3O_8Na$ 440.2009).

2′-Amino-ethyl 2,4-Di-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-3,6-di-*O*-pivaloyl-β-D-glucopyranoside (19). $BF_3{\cdot}Et_2O$ (2.2 mL, 17.0 mmol) was added under nitrogen atmosphere to a stirring suspension of acceptor **17** (1.61 g, 3.86 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (20 mL) at −80 °C. After it was stirred for 1 h at this temperature, a solution of rhamnopyranosyl trichloroacetimidate **18** (5.22 g, 12.0 mmol) in CH_2Cl_2 (20 mL) was added, and the stirring was continued for 5 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (60 mL) and filtered through a pad of Celite. The filtrate was washed with saturated aq $NaHCO_3$ (30 mL) and brine (15 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was partially purified by flash column chromatography (*n*-hexane/EtOAc 3:2), yielding the crude trisaccharide as a white foam (4.02 g). This crude product was dissolved in MeOH (100 mL), and 5% Pd/C (81.8 mg, 0.039 mmol) was added. The reaction mixture was subjected successively to hydrogen atmosphere and vacuum and finally stirred under hydrogen atmosphere for 48 h, when TLC analysis revealed that all of the azide was consumed. The catalyst was removed by filtration over a pad of Celite, and the resulting solution was evaporated under reduced pressure. The crude product was purified by flash column chromatography ($CHCl_3$/MeOH 15:1) to afford the pure trisaccharide **19** (2.56 g, 71%) as a white solid: R_f = 0.30 ($CHCl_3$/MeOH 15:1); mp 96−97 °C; $[\alpha]_D^{20}$ +10.2 (*c* 1.6, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3425, 2980, 2941, 2881, 1752, 1371, 1247, 1228, 1146, 1080, 1046; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.14 (d, 3H, *J* = 6.3 Hz, CH_3 Rha); 1.16 (s, 9H, $(CH_3)_3C$); 1.17 (d, 3H, *J* = 6.3 Hz, CH_3 Rha′); 1.20 (s, 9H, $(CH_3)_3C$); 1.92, 1.95, 2.01, 2.02, 2.08, 2.09 (6 × s, 6 × 3H, 6 × CH_3CO); 2.23 (s, 2H, NH_2); 2.89 (s, 2H, H-2′); 3.57 (t, 1H, *J* = 7.6 Hz, H-2 Glc); 3.63 (m, 1H, H-1′a); 3.73 (m, 2H, H-4 Glc, H-5 Glc); 3.83−3.92 (m, 2H, H-1′b, H-5 Rha); 4.11 (m, 1H, H-5 Rha′); 4.21 (dd, 1H, *J* = 2.8/12.0 Hz, H-6a Glc); 4.48 (d, 1H, *J* = 7.0 Hz, H-1 Glc); 4.53 (d, 1H, *J* = 12.0 Hz, H-6b Glc); 4.84 (s, 1H, H-1 Rha); 4.86 (s, 1H, H-1 Rha′); 4.96−5.04 (m, 3H, H-2 Rha, H-4 Rha, H-4 Rha′); 5.13−5.19 (m, 3H, H-2 Rha′, H-3 Rha, H-3 Rha′); 5.24 (m, 1H, H-3 Glc); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 16.8, 16.9, 20.2, 20.3, 20.4, 20.5, 26.5, 26.8 (CH_3); 38.4, 38.5 (C); 41.4, 62.0 (CH_2); 66.5, 67.7, 68.4, 68.5, 69.3, 69.6, 70.2, 70.7 (CH); 71.6 (CH_2); 72.1, 74.5, 76.3, 77.4, 97.2, 97.3, 100.8 (CH); 169.1, 169.2, 169.3, 169.4, 169.5, 176.1, 177.5 (C═O); HRMS (ESI-FT-ICR) *m/z* 936.4066 $[M + H]^+$ (calculated for $C_{42}H_{66}NO_{22}$ 936.4076).

Carboxymethyl 2,4-Di-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-3,6-di-*O*-pivaloyl-β-D-glucopyranoside (21). Ozone was bubbled into a solution of the allyl trisaccharide **20** (2.33 g, 2.50 mmol) in CH_2Cl_2 (100 mL) for 5 min at −78 °C. The light-blue solution was then treated with PPh_3 (984 mg, 3.75 mmol), and the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The solvent was removed under reduced pressure, and the crude aldehyde was dissolved in DMF (25 mL) and teated with Oxone (1.54 g, 2.50 mmol). The reaction mixture was stirred for 8 h at room temperature, then diluted with EtOAc (50 mL), and washed with dilute aq HCl and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by flash column chromatography (EtOAc/MeOH 10:1) to afford acid **21** (2.01 g, 84%) as a white solid: R_f = 0.50 (EtOAc); mp 122−123 °C; $[\alpha]_D^{20}$ −65.0 (*c* 1.2, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3357, 2967, 2937, 2373, 1736, 1223, 1145, 1044; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.15 (d, 3H, *J* = 6.1 Hz, CH_3 Rha); 1.16 (d, 3H, *J* = 6.2 Hz, CH_3 Rha′); 1.18, 1.21 (2 × s, 2 × 9H, 2 × $(CH_3)_3C$); 1.95, 1.96, 2.02, 2.03 (4 × s, 4 × 3H, 4 × CH_3CO); 2.10 (s, 6H, 2 × CH_3CO); 3.65 (t, 1H, *J* = 7.3 Hz, H-2 Glc); 3.80 (m, 2H, H-4 Glc, H-5 Glc); 3.90 (m, 1H, H-5 Rha); 4.17−4.29 (m, 4H, H-5 Rha′, OCH_2, H-6a Glc); 4.49 (d, 1H, *J* = 11.9 Hz, H-6b Glc); 4.68 (d, 1H, *J* = 7.0 Hz, H-1 Glc); 4.85 (d, 1H, *J* = 1.7 Hz, H-1 Rha); 4.92 (s, 1H, H-1 Rha′); 4.97−5.07 (m, 3H, H-2 Rha, H-4 Rha, H-4 Rha′); 5.15−5.18 (m, 2H, H-2 Rha′, H-3 Rha); 5.23 (t, 1H, *J* = 7.7 Hz, H-3 Glc); 5.27 (dd, 1H, *J* = 4.0/9.7 Hz, H-3 Rha′); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 17.0, 17.2, 20.6, 20.7, 20.8, 26.9, 27.1 (CH_3); 38.8, 38.9 (C); 62.3, 66.4 (CH_2); 67.2, 68.0, 68.8, 69.1, 69.7, 70.0, 70.6, 70.9, 72.9, 74.6, 76.1, 77.6, 97.5, 97.6, 100.4 (CH); 169.7, 169.8, 169.9, 170.0, 170.1, 170.2, 176.6, 178.1 (C═O);

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HRMS (ESI-FT-ICR) m/z 973.3542 $[M + Na]^+$ (calculated for $C_{42}H_{62}O_{24}Na$ 973.3529).

Glycolipid 22. Chacotriose-based amine **19** (100 mg, 0.107 mmol), paraformaldehyde (3.2 mg, 0.107 mmol), lauric acid (21.4 mg, 0.107 mmol), and *n*-dodecylisocyanide (20.9 mg, 0.107 mmol) were reacted in MeOH/CH_2Cl_2 (12 mL, 3:1, v/v) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1 → 2:3) afforded the glycolipid **22** (102 mg, 71%) as an amorphous solid: R_f = 0.21 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{20}$ −67.1 (*c* 0.8, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3346, 2928, 2862, 2383, 1743, 1245, 1223, 1146, 1051; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.87 (t, 6H, J = 6.8 Hz, 2 × CH_3); 1.15 (m, 6H, CH_3 Rha, CH_3 Rha′); 1.18, 1.19 (2 × s, 9H, $(CH_3)_3C$); 1.21 (s, 9H, $(CH_3)_3C$); 1.23−1.31 (m, 34H, 17 × CH_2); 1.46 (m, 2H, CH_2); 1.60 (m, 2H, CH_2); 1.95 (m, 6H, 2 × CH_3CO); 2.03 (m, 6H, 2 × CH_3CO); 2.10 (m, 6H, 2 × CH_3CO); 2.22, 2.36 (2 × t, 2H, J = 7.5 Hz, CH_2); 3.21 (m, 2H, CH_2); 3.50 (m, 2H, CH_2); 3.62 (m, 1H); 3.69−3.78 (m, 3H); 3.85−3.93 (m, 3H); 3.99 (m, 2H); 4.22 (dd, 1H, J = 4.0/12.1 Hz, H-6a); 4.45 (t, 1H, J = 8.1 Hz, H-1 Glc); 4.56 (m, 1H, H-6b Glc); 4.82 (m, 2H, H-1 Rha, H-1 Rha′); 4.96−5.06 (m, 3H, H-4 Rha, H-4 Rha′, H-2 Rha); 5.11−5.29 (m, 4H, H-2 Rha′, H-3 Rha, H-3 Rha′, H-3 Glc); 6.35, 6.47 (2 × m, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.0, 17.2, 17.3, 17.4, 20.5, 20.6, 20.7, 20.8, 20.9 (CH_3); 22.6, 24.9, 25.3 (CH_2); 26.8, 27.1 (CH_3); 29.3, 29.4, 29.5, 29.6, 31.9, 32.9, 33.3 (CH_2); 38.8, 38.9 (*C*); 39.4, 39.6, 48.4, 48.5, 50.4, 53.2, 62.1, 66.8 (CH_2); 66.9, 68.0, 68.1, 68.8, 68.9, 69.7, 69.8, 69.9, 70.5, 70.6, 70.8, 70.9, 72.6, 72.7, 74.6, 74.8, 76.3, 76.5, 78.3, 78.4, 97.4, 97.7, 97.8, 101.3, 101.9 (*C*H); 168.4, 169.1, 169.5, 169.6, 169.7, 169.8, 169.9, 170.0, 174.2, 174.3, 176.4, 176.5, 177.7, 177.9 (*C*═O); HRMS (ESI-FT-ICR) m/z 1365.7642 $[M + Na]^+$ (calculated for $C_{68}H_{114}N_2O_{24}Na$ 1365.7659).

Glycolipid 23. An aqueous solution of NaOH (1.0 M, 0.5 mL) was added to a solution of glycolipid **22** (105 mg, 0.078 mmol) in THF/MeOH (3 mL, 1:1, v/v), and the reaction mixture was stirred at 50 °C overnight. The solution was then neutralized with acid resin Dowex-50 (H^+) and filtered to remove the resin. The filtrate was concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography (EtOAc/MeOH 4:1) to furnish the glycolipid **23** (64 mg, 89%) as a white solid: R_f = 0.44 ($CHCl_3$/MeOH 3:1); mp 184−185 °C; $[\alpha]_D^{20}$ +88.2 (*c* 1.2, MeOH); IR (KBr, cm^{-1}) ν_{max} 3358, 2924, 2855, 2372, 1635, 1055; ^1H NMR (400 MHz, pyridine-d_5) δ = 0.85 (m, 6H, 2 × CH_3); 1.17−1.32 (m, 36H, 18 × CH_2); 1.50−1.84 (m, 10H, CH_3 Rha, CH_3 Rha′, 2 × CH_2); 2.54 (m, 2H, CH_2); 3.37−3.56 (m, 3H, H-5 Rha, CH_2); 3.86−4.20 (m, 7H); 4.31 (m, 3H); 4.44−4.77 (m, 7H); 4.83 (m, 1H, H-1 Glc); 5.76 (m, 1H, H-1 Rha); 6.29, 6.35 (2 × s, 1H, H-1 Rha′); 8.43, 8.62 (2 × m, 1H, N*H*); ^{13}C NMR (100 MHz, pyridine-d_5) δ = 14.5, 18.7, 18.9 (CH_3); 23.2, 25.8, 25.9, 27.5, 27.6, 28.8, 28.9, 29.9, 30.0, 30.1, 30.3, 30.4, 30.5, 32.4, 33.4, 33.7, 40.0, 40.1, 48.4, 49.5, 50.5, 53.2, 56.4, 61.3, 61.4, 68.4, 68.8 (CH_2); 69.8, 69.9, 70.6, 72.6, 72.7, 72.8, 72.9, 74.0, 74.3, 74.4, 77.2, 77.7, 77.9, 78.4, 78.6, 78.8, 101.9, 102.3, 103.1, 103.2, 103.3 (*C*H); 169.7, 169.9, 174.4, 174.5 (*C*═O); HRMS (ESI-FT-ICR) m/z 945.5897 $[M + Na]^+$ (calculated for $C_{46}H_{86}N_2O_{16}Na$ 945.5875).

Glycolipid 24. Chacotriose-based amine **19** (100 mg, 0.107 mmol), paraformaldehyde (3.2 mg, 0.107 mmol), lauric acid (21.4 mg, 0.107 mmol), and *n*-octadecylisocyanide (29.9 mg, 0.107 mmol) were reacted in MeOH/CH_2Cl_2 (12 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1 → 2:3) afforded the glycolipid **24** (105.3 mg, 69%) as an amorphous solid: R_f = 0.24 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{20}$ −18.4 (*c* 0.85, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3419, 2927, 2862, 2108, 1653, 1222, 1145, 1045; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.88 (t, 6H, J = 7.1 Hz, 2 × CH_3); 1.16 (m, 6H, CH_3 Rha, CH_3 Rha′); 1.19, 1.20 (2 × s, 9H, $(CH_3)_3C$); 1.22 (s, 9H, $(CH_3)_3C$); 1.23−1.31 (m, 46H, 23 × CH_2); 1.48 (m, 2H, CH_2); 1.60 (m, 2H, CH_2); 1.95 (m, 6H, 2 × CH_3CO); 2.03 (m, 6H, 2 × CH_3CO); 2.11 (m, 6H, 2 × CH_3CO); 2.23 (t, 1H, J = 7.5 Hz); 2.37 (t, 1H, J = 7.4 Hz); 3.18, 3.26 (2 × m, 2H, CH_2); 3.48−3.56 (m, 2H); 3.62 (m, 1H); 3.67−3.79 (m, 3H); 3.86−3.94 (m, 3H); 3.98−4.04 (m, 2H); 4.23 (dd, 1H, J = 4.2/12.0 Hz, H-6a Glc); 4.45, 4.47 (2 × d, 1H, J = 7.3 Hz, H-1 Glc); 4.56 (m, 1H, H-6b Glc); 4.83, 4.85 (2 × d, 2H, J = 1.3 Hz, J = 1.9 Hz, H-1 Rha, H-1 Rha′); 4.97−5.05 (m, 2H, H-4 Rha, H-4 Rha′); 5.08 (m, 1H, H-2 Rha); 5.14 (m, 1H, H-2 Rha′); 5.18 (m, 2H, H-3 Rha, H-3 Rha′); 5.24 (m, 1H, H-3 Glc); 6.29, 6.43 (2 × m, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.1, 17.2, 17.3, 17.4, 20.6, 20.7, 20.8, 20.9 (CH_3); 22.7, 24.9, 25.3 (CH_2); 26.8 (CH_3); 26.9, 27.0 (CH_2); 27.1 (CH_3); 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.9 (CH_2); 38.8, 38.9 (*C*); 39.4, 39.6, 48.3, 48.4, 50.4, 53.2, 62.1, 66.8 (CH_2); 66.9, 68.0, 68.1, 68.7, 68.8, 69.7, 69.8, 69.9, 70.5, 70.6, 70.8, 70.9, 72.6, 72.7, 74.5, 74.7, 76.4, 76.5, 78.3, 78.4, 97.4, 97.7, 97.8, 101.3, 101.9 (*C*H); 169.2, 169.6, 169.7, 169.8, 169.9, 170.0, 174.2, 176.3, 176.4, 177.8, 177.9 (*C*═O); HRMS (ESI-FT-ICR) m/z 1449.8586 $[M + Na]^+$ (calculated for $C_{74}H_{126}N_2O_{24}Na$ 1449.8598).

Glycolipid 25. Compound **24** (93 mg, 0.065 mmol) was treated with NaOH (1.0 M, 0.5 mL) in THF/MeOH (3 mL, 1:1, v/v) according to the deprotection procedure described for the synthesis of **23**. Flash column chromatography purification ($CHCl_3$/MeOH 4:1) afforded the glycolipid **25** (62.2 mg, 95%) as a white solid: R_f = 0.47 ($CHCl_3$/MeOH 3:1); mp 188−189 °C; $[\alpha]_D^{20}$ +28.4 (*c* 1.20, MeOH); IR (KBr, cm^{-1}) ν_{max} 3345, 2923, 2851, 1624, 1060, 1041; ^1H NMR (400 MHz, pyridine-d_5) δ = 0.89 (m, 6H, 2 × CH_3); 1.23−1.35 (m, 48H, 24 × CH_2); 1.53−1.87 (m, 10H, CH_3 Rha, CH_3 Rha′, 2 × CH_2); 2.55 (m, 2H, CH_2); 3.40−3.59 (m, 3H, H-5 Rha, CH_2); 3.89−4.24 (m, 7H); 4.34 (m, 3H); 4.46−4.83 (m, 7H); 4.87 (m, 1H, H-1 Glc); 5.80 (m, 1H, H-1 Rha); 6.34, 6.40 (2 × s, 1H, H-1 Rha′); 8.43, 8.62 (2 × m, 1H, N*H*); ^{13}C NMR (100 MHz, pyridine-d_5) δ = 14.8, 18.9, 19.1 (CH_3); 23.4, 26.0, 26.1, 27.8, 27.9, 30.0, 30.1, 30.2, 30.3, 30.4, 30.5, 30.6, 30.7, 32.6, 33.7, 33.9, 40.2, 40.3, 48.7, 50.8, 53.4, 61.5, 61.6, 69.0 (CH_2); 70.1, 70.2, 70.9, 72.8, 72.9, 73.1, 74.3, 74.5, 74.6, 77.4, 77.9, 78.2, 78.6, 78.8, 78.9, 102.1, 103.3, 103.5 (*C*H); 169.9, 170.1, 174.6, 174.7 (*C*═O); HRMS (ESI-FT-ICR) m/z 1029.6829 $[M + Na]^+$ (calculated for $C_{52}H_{98}N_2O_{16}Na$ 1029.6814).

Glycolipid 26. Chacotriose-based amine **19** (100 mg, 0.107 mmol), paraformaldehyde (3.2 mg, 0.107 mmol), stearic acid (30.2 mg, 0.107 mmol), and *n*-octadecylisocyanide (29.6 mg, 0.107 mmol) were reacted in MeOH/CH_2Cl_2 (12 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded the glycolipid **26** (117 mg, 73%) as an amorphous solid: R_f = 0.29 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{20}$ −38.2 (*c* 0.90, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3372, 2925, 2855, 1752, 1245, 1223, 1145, 1046; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.87 (t, 6H, J = 7.1 Hz, 2 × CH_3); 1.15 (m, 6H, CH_3 Rha, CH_3 Rha′); 1.18, 1.19 (2 × s, 9H, $(CH_3)_3C$); 1.21 (s, 9H, $(CH_3)_3C$); 1.22−1.30 (m, 58H, 29 × CH_2); 1.47 (m, 2H, CH_2); 1.60 (m, 2H, CH_2); 1.95 (m, 6H, 2 × CH_3CO); 2.03 (m, 6H, 2 × CH_3CO); 2.11 (m, 6H, 2 × CH_3CO); 2.22 (t, 1H, J = 7.6 Hz); 2.36 (t, 1H, J = 7.5 Hz); 3.17, 3.25 (2 × m, 2H, CH_2); 3.47−3.54 (m, 2H); 3.62 (m, 1H); 3.67−3.78 (m, 3H); 3.84−3.94 (m, 3H); 3.97−4.03 (m, 2H); 4.22 (dd, 1H, J = 4.2/12.0 Hz, H-6a Glc); 4.44, 4.46 (2 × d, 1H, J = 7.3 Hz, H-1 Glc); 4.56 (m, 1H, H-6b Glc); 4.83 (m, 2H, H-1 Rha, H-1 Rha′); 4.97−5.04 (m, 2H, H-4 Rha, H-4 Rha′); 5.06 (m, 1H, H-2 Rha); 5.12 (m, 1H, H-2 Rha′); 5.17 (m, 2H, H-3 Rha, H-3 Rha′); 5.24 (m, 1H, H-3 Glc); 6.33, 6.46 (m, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.1, 17.1, 17.2, 17.3, 17.4, 20.5, 20.6, 20.7, 20.8 (CH_3); 22.6, 24.9, 25.3, 25.6 (CH_2); 26.8, 26.9, 27.0, 27.1 (CH_3); 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 32.9, 33.2 (CH_2); 38.8, 38.9 (*C*); 39.4, 39.6, 48.3, 48.4, 50.4, 62.0, 66.8 (CH_2); 66.9 (*C*H); 67.9 (CH_2); 68.0, 68.8, 68.9, 69.7, 69.9, 70.4, 70.5, 70.8, 70.9, 72.6, 72.7, 74.5, 74.8, 76.3, 76.5, 78.3, 78.4, 97.4, 97.7, 97.8, 101.3, 101.9 (*C*H); 169.5, 169.6, 169.7, 169.8, 169.9, 170.0, 174.2, 174.4, 177.7, 177.9 (*C*═O); HRMS (ESI-FT-ICR) m/z 1533.9546 $[M + Na]^+$ (calculated for $C_{80}H_{138}N_2O_{24}Na$ 1533.9537).

Glycolipid 27. Compound **26** (103.6 mg, 0.069 mmol) was treated with NaOH (1.0 M, 0.5 mL) in THF/MeOH (3 mL, 1:1, v/v) according to the procedure described for the synthesis of **23**. Flash column chromatography purification ($CHCl_3$/MeOH 4:1) afforded the glycolipid **27** (70 mg, 93%) as a white solid: R_f = 0.45 ($CHCl_3$/MeOH 3:1); mp 179−181 °C; $[\alpha]_D^{20}$ +49.1 (*c* 0.9, MeOH); IR (KBr, cm^{-1}) ν_{max} 3368, 2919, 2852, 2116, 1634, 1420, 1216, 1044; ^1H NMR (400 MHz, pyridine-d_5) δ = 0.89 (m, 6H, 2 × CH_3); 1.22−1.40 (m, 59H); 1.53−1.88 (m, 10H, CH_3 Rha, CH_3 Rha′, 2 × CH_2); 2.56 (m,

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2H, CH_2); 3.40−3.59 (m, 3H, H-5 Rha, CH_2); 3.89−4.25 (m, 7H); 4.34 (m, 3H); 4.46−4.80 (m, 8H); 4.87 (m, 1H, H-1 Glc); 5.80 (m, 1H, H-1 Rha); 6.34, 6.40 (2 × s, 1H, H-1 Rha′); 8.42, 8.61 (2 × m, 1H, N*H*); ^{13}C NMR (100 MHz, pyridine-d_5) δ = 14.7, 18.9, 19.1 (CH_3); 23.4, 26.0, 26.1, 27.8, 27.9, 30.0, 30.1, 30.2, 30.3, 30.4, 30.5, 30.6, 30.7, 32.6, 33.7, 33.9, 40.2, 40.3, 48.7, 49.7, 50.8, 53.5, 61.5, 61.6, 68.7, 69.1 (CH_2); 70.0, 70.2, 70.9, 72.8, 73.0, 73.1, 73.2, 74.3, 74.5, 74.6, 77.4, 77.9, 78.1, 78.2, 78.6, 78.9, 79.0, 102.1, 102.5, 103.3, 103.5 (CH); 169.8, 170.0, 174.6, 174.7 (C═O); HRMS (ESI-FT-ICR) *m*/*z* 1113.7749 $[M + Na]^+$ (calculated for $C_{58}H_{110}N_2O_{16}Na$ 1113.7753).

Glycolipid 28. *n*-Dodecylamine (40 mg, 0.216 mmol), paraformaldehyde (6.5 mg, 0.216 mmol), chacotriose-based acid **21** (205.4 mg, 0.216 mmol), and *n*-dodecylisocyanide (42.1 mg, 0.216 mmol) were reacted in MeOH/CH_2Cl_2 (18 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded the glycolipid **28** (197 mg, 68%) as an amorphous solid: R_f = 0.22 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{20}$ −54.8 (*c* 0.90, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3357, 2927, 2856, 1752, 1368, 1245, 1224, 1147, 1046; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.85−0.89 (m, 6H, 2 × CH_3); 1.13−1.18 (m, 15H, $(CH_3)_3C$, CH_3 Rha, CH_3 Rha′); 1.20−1.29 (m, 45H); 1.48, 1.59 (2 × m, 4H, 2 × CH_2); 1.96 (m, 6H, 2 × CH_3CO); 2.03 (m, 6H, 2 × CH_3CO); 2.10 (m, 6H, 2 × CH_3CO); 3.17, 3.29 (2 × m, 4H, 2 × CH_2); 3.52−4.50 (m, 11H, H-2 Glc, H-4 Glc, H-5 Glc, H-6a Glc, H-6b Glc, H-5 Rha, H-5 Rha′, 2 × CH_2); 4.56, 4.68 (2 × m, 1H, H-1 Glc); 4.81, 4.85, 4.89 (3 × m, 2H, H-1 Rha, H-1 Rha′); 4.98−5.08 (m, 3H, H-2 Rha, H-4 Rha′, H-4 Rha); 5.15−5.29 (m, 4H, H-2 Rha′, H-3 Rha, H-3 Rha′, H-3 Glc); 6.44, 6.50 (2 × m, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.1, 17.2, 20.5, 20.6, 20.7, 20.8, 20.9 (CH_3); 22.6 (CH_2); 26.8 (CH_3); 26.9 (CH_2); 27.2 (CH_3); 28.6, 29.2, 29.3, 29.4, 29.6, 31.9 (CH_2); 38.8, 38.9 (*C*); 39.5, 49.2, 51.2, 62.2, 66.6 (CH_2); 66.9, 67.1, 67.9, 68.1, 68.9, 69.7, 70.0, 70.4, 70.6, 70.8, 70.9, 72.3, 72.7, 75.0, 76.2, 77.8, 97.7, 97.8, 97.9, 98.1, 100.2 (CH); 168.8, 169.0, 169.5, 169.6, 169.8, 169.9, 175.8, 176.1, 176.5, 177.6 (C═O); HRMS (ESI-FT-ICR) *m*/*z* 1365.7672 $[M + Na]^+$ (calculated for $C_{68}H_{114}N_2O_{24}Na$ 1365.7659).

Glycolipid 29. Compound **28** (70 mg, 0.052 mmol) was treated with NaOH (1.0 M, 0.5 mL) in THF/MeOH (3 mL, 1:1, v/v) according to the procedure described for the synthesis of **23**. Flash column chromatography purification ($CHCl_3$/MeOH 4:1) afforded the glycolipid **29** (70 mg, 93%) as a white solid: R_f = 0.42 ($CHCl_3$/MeOH 3:1); mp 178−180 °C; $[\alpha]_D^{20}$ +64.8 (*c* 0.8, MeOH); IR (KBr, cm^{-1}) ν_{max} 3425, 2927, 2851, 2106, 1640, 1053; ^{1}H NMR (400 MHz, pyridine-d_5) δ = 0.87 (t, 6H, *J* = 6.9 Hz, 2 × CH_3); 1.24 (m, 36H, 18 × CH_2); 1.54−1.74 (m, 10H, CH_3 Rha, CH_3 Rha′, 2 × CH_2); 3.43−3.68 (m, 3H, H-5 Glc, CH_2); 3.74 (m, 1H); 4.02 (m, 1H, H-6a Glc); 4.12−4.53 (m, 9H); 4.61−4.86 (m, 8H); 4.87, 4.94 (2 × d, 1H, *J* = 7.6 Hz, H-1 Glc); 5.78, 5.84 (2 × s, 1H, H-1 Rha); 6.33, 6.40 (2 × s, 1H, H-1 Rha′); 8.44, 8.53 (2 × m, 1H, N*H*); ^{13}C NMR (100 MHz, pyridine-d_5) δ = 14.3, 18.4, 18.5, 18.6, 18.7 (CH_3); 22.9, 27.1, 27.4, 27.7, 29.0, 29.6, 29.7, 29.8, 29.9, 30.0, 30.1, 30.2, 32.1, 39.8, 39.9, 47.8, 49.4, 50.1, 51.2, 60.9, 61.2, 68.1, 69.3 (CH_2); 69.6, 69.7, 70.4, 72.3, 72.4, 72.5, 72.6, 72.7, 73.8, 74.3, 74.4, 77.0, 77.1, 77.4, 77.6, 77.7, 77.8, 78.3, 78.5, 101.8, 102.0, 102.2, 102.6, 102.8 (CH); 169.6, 169.7, 169.8, 169.9 (C═O); HRMS (ESI-FT-ICR) *m*/*z* 945.5891 $[M + Na]^+$ (calculated for $C_{46}H_{86}N_2O_{16}Na$ 945.5875).

Glycolipid 30. *n*-Dodecylamine (40 mg, 0.216 mmol), paraformaldehyde (6.5 mg, 0.216 mmol), chacotriose-based acid **21** (205.4 mg, 0.216 mmol) and *n*-octadecylisocyanide (60.3 mg, 0.216 mmol) were reacted in MeOH/CH_2Cl_2 (18 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded the glycolipid **30** (222 mg, 72%) as an amorphous solid: R_f = 0.24 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{20}$ −22.3 (*c* 0.80, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3436, 2104, 1657, 1646, 1640; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.87 (t, 6H, *J* = 6.8 Hz, 2 × CH_3); 1.13−1.18 (m, 15H, $(CH_3)_3C$, CH_3 Rha, CH_3 Rha′); 1.20−1.29 (m, 57H); 1.47, 1.59 (2 × m, 4H, 2 × CH_2); 1.95 (m, 6H, 2 × CH_3CO); 2.03 (m, 6H, 2 × CH_3CO); 2.11 (m, 6H, 2 × CH_3CO); 3.17 (m, 2H, CH_2); 3.30 (m, 2H, CH_2); 3.52−4.49 (m, 11H, H-2 Glc, H-4 Glc, H-5 Glc, H-6a Glc, H-6b Glc, H-5 Rha, H-5 Rha′, 2 × CH_2); 4.59, 4.68 (2 × m, 1H, H-1 Glc); 4.81, 4.85, 4.90 (3 × m, 2H, H-1 Rha, H-1 Rha′); 4.99−5.06 (m, 3H, H-2 Rha, H-4 Rha′, H-4 Rha); 5.15−5.29 (m, 4H, H-2 Rha′, H-3 Rha, H-3 Rha′, H-3 Glc); 6.44, 6.50 (2 × m, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.1, 17.2, 20.6, 20.7, 20.8, 20.9 (CH_3); 22.7 (CH_2); 26.8 (CH_3); 26.9 (CH_2); 27.2 (CH_3); 28.6, 29.2, 29.3, 29.4, 29.5, 29.6, 29.8, 31.9 (CH_2); 38.8, 38.9 (*C*); 39.5, 39.7, 49.2, 51.2, 62.2, 66.6 (CH_2); 66.9, 67.1, 67.9, 68.1, 68.7, 68.9, 69.7, 69.8, 69.9, 70.4, 70.5, 70.8, 70.9, 72.3, 72.7, 74.8, 74.9, 76.2, 76.4, 77.8, 78.2, 97.7, 97.8, 97.9, 98.1, 100.2, 100.5 (CH); 168.8, 169.0, 169.6, 169.7, 169.8, 169.9, 170.0, 176.5, 177.6 (C═O); HRMS (ESI-FT-ICR) *m*/*z* 1449.8656 $[M + Na]^+$ (calculated for $C_{74}H_{126}N_2O_{24}Na$ 1449.8598).

Glycolipid 31. Compound **30** (46 mg, 0.032 mmol) was treated with NaOH (1.0 M, 0.5 mL) in THF/MeOH (2 mL, 1:1, v/v) according to the procedure described for the synthesis of **23**. Flash column chromatography purification ($CHCl_3$/MeOH 3:1) afforded the glycolipid **31** (31 mg, 96%) as a white solid: R_f = 0.39 ($CHCl_3$/MeOH 4:1); mp 196−198 °C; $[\alpha]_D^{20}$ +38.1 (*c* 0.65, MeOH); IR (KBr, cm^{-1}) ν_{max} 3355, 2924, 2855, 1640, 1052; ^{1}H NMR (400 MHz, pyridine-d_5) δ = 0.87 (t, 6H, *J* = 6.8 Hz, 2 × CH_3); 1.26 (m, 45H); 1.54−1.78 (m, 10H, CH_3 Rha, CH_3 Rha′, 2 × CH_2); 3.41−3.66 (m, 5H, H-5 Glc, 2 × CH_2); 3.76 (m, 1H); 4.02 (m, 1H, H-6a Glc); 4.12−4.54 (m, 10H); 4.62−4.87 (m, 8H); 4.88, 4.94 (2 × d, 1H, *J* = 7.6 Hz, H-1 Glc); 5.78 (s, 1H, H-1 Rha); 6.34, 6.41 (2 × s, 1H, H-1 Rha′); 8.45, 8.55 (2 × m, 1H, N*H*); ^{13}C NMR (100 MHz, pyridine-d_5) δ = 14.3, 18.5, 18.7, 18.8 (CH_3); 23.0, 27.2, 27.4, 27.8, 29.1, 29.6, 29.7, 29.8, 29.9, 30.0, 30.1, 30.2, 30.3, 30.4, 32.1, 32.2, 39.8, 40.0, 49.4, 50.2, 51.3, 61.0, 61.2, 68.1, 69.4 (CH_2); 69.6, 69.7, 70.4, 72.3, 72.4, 72.5, 72.6, 72.7, 72.8, 73.9, 74.4, 77.1, 77.2, 77.4, 77.6, 77.7, 77.8, 78.3, 78.5, 101.8, 102.0, 102.7, 102.8 (CH); 169.6, 169.7, 169.8, 169.9 (C═O); HRMS (ESI-FT-ICR) *m*/*z* 1029.6836 $[M + Na]^+$ (calculated for $C_{52}H_{98}N_2O_{16}Na$ 1029.6814).

Glycolipid 32. *n*-Octadecylamine (62 mg, 0.230 mmol), paraformaldehyde (6.9 mg, 0.230 mmol), chacotriose-based acid **21** (218.7 mg, 0.230 mmol), and *n*-octadecylisocyanide (64.2 mg, 0.230 mmol) were reacted in MeOH/CH_2Cl_2 (24 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded the glycolipid **32** (247 mg, 71%) as an amorphous solid: R_f = 0.27 (*n*-hexane/EtOAc 1:1); $[\alpha]_D^{20}$ −31.5 (*c* 0.60, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 3687, 2926, 2859, 2372, 1716, 1555, 1221; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.88 (t, 6H, *J* = 6.9 Hz, 2 × CH_3); 1.14−1.23 (m, 24H, 2 × $(CH_3)_3C$, CH_3 Rha, CH_3 Rha′); 1.23−1.30 (m, 62H, 31 × CH_2); 1.47 (m, 2H, CH_2); 1.95, 1.97 (2 × s, 2 × 3H, 2 × CH_3CO); 2.03 (m, 6H, 2 × CH_3CO); 2.10, 2.11 (2 × s, 2 × 3H, 2 × CH_3CO); 3.17 (m, 2H, CH_2); 3.30 (m, 2H, CH_2); 3.52−4.55 (m, 11H, H-2 Glc, H-4 Glc, H-5 Glc, H-6a Glc, H-6b Glc, H-5 Rha, H-5 Rha′, 2 × CH_2); 4.59, 4.68 (2 × d, 1H, *J* = 7.2 Hz, H-1 Glc); 4.85 (d, 1H, *J* = 1.6 Hz, H-1 Rha); 4.90 (d, 1H, *J* = 1.3 Hz, H-1 Rha′); 4.99−5.08 (m, 3H, H-2 Rha, H-4 Rha′, H-4 Rha); 5.16−5.25 (m, 4H, H-2 Rha′, H-3 Rha, H-3 Rha′, H-3 Glc); 6.43, 6.50 (2 × m, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.1, 17.2, 20.6, 20.7, 20.8 (CH_3); 22.7 (CH_2); 26.8 (CH_3); 26.9 (CH_2); 27.2 (CH_3); 28.6, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (CH_2); 38.8, 38.9 (*C*); 39.3, 39.5, 51.2, 59.2, 62.2, 66.6 (CH_2); 66.9, 68.0, 68.7, 68.9, 69.7, 70.6, 71.0, 72.3, 75.0, 76.3, 77.8, 97.7, 97.9, 98.1, 100.1, 100.2, 100.5 (CH); 168.8, 169.0, 169.5, 169.6, 169.9, 170.0, 170.3, 176.4, 176.5, 177.6 (C═O); HRMS (ESI-FT-ICR) *m*/*z* 1533.9532 $[M + Na]^+$ (calculated for $C_{80}H_{138}N_2O_{24}Na$ 1533.9537).

Glycolipid 33. Compound **32** (106 mg, 0.070 mmol) was treated with NaOH (1.0 M, 0.5 mL) in THF/MeOH (3 mL, 1:1, v/v) according to the procedure described for the synthesis of **23**. Flash column chromatography purification ($CHCl_3$/MeOH 4:1) afforded the glycolipid **33** (70 mg, 92%) as a white solid: R_f = 0.53 ($CHCl_3$/MeOH 3:1); mp 181−183 °C; $[\alpha]_D^{20}$ +59.1 (*c* 0.95, MeOH); IR (KBr, cm^{-1}) ν_{max} 3369, 2914, 2855, 1640, 1054; ^{1}H NMR (400 MHz, pyridine-d_5) δ = 0.89 (t, 6H, *J* = 6.9 Hz, 2 × CH_3); 1.28 (m, 60H, 30 × CH_2); 1.56−1.80 (m, 10H, CH_3 Rha, CH_3 Rha′, 2 × CH_2); 3.42−3.68 (m, 5H, H-5 Glc, 2 × CH_2); 3.74 (m, 1H); 4.04 (m, 1H, H-6a Glc); 4.14−4.87 (m, 15H); 4.89, 4.96 (2 × d, 1H, *J* = 7.7 Hz, H-1 Glc); 5.79 (s, 1H, H-1 Rha); 6.35, 6.42 (2 × s, 1H, H-1 Rha′); 8.42, 8.51 (2 × m, 1H, N*H*); ^{13}C NMR (100 MHz, pyridine-d_5) δ = 14.6, 18.8, 19.1 (CH_3); 23.3, 27.5, 27.8, 28.1, 29.4, 30.0, 30.1, 30.2, 30.3, 30.4, 30.5,

30.6, 32.5, 40.2, 40.3, 48.2, 49.8, 50.6, 51.6, 61.4, 61.7, 68.5, 69.8 (CH_2); 69.9, 70.0, 70.8, 72.6, 72.7, 72.8, 72.9, 73.0, 73.1, 74.2, 74.8, 77.4, 77.5, 77.8, 77.9, 78.1, 78.2, 78.9, 79.0, 102.2, 102.4, 102.6, 103.0, 103.3 (CH); 169.6, 169.7, 169.8, 169.9 (*C*=O); HRMS (ESI-FT-ICR) *m/z* 1113.7775 $[M + Na]^+$ (calculated for $C_{58}H_{110}N_2O_{16}Na$ 1113.7753).

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of building blocks and final products. 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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■ DEDICATION

Dedicated to Professor Ludger Wessjohann on the occasion of his 50th birthday.

■ REFERENCES

(1) Hakomori, S. I. *Biochim. Biophys. Acta* **2008**, *1780*, 325−346.
(2) Tettamanti, G.; Bassi, R.; Viani, P.; Riboni, L. *Biochimie* **2003**, *85*, 423−437.
(3) Hakomori, S.-I. *Glycoconjugate J.* **2000**, *17*, 143−151.
(4) Varki, A. *Glycobiology* **1993**, *3*, 97−130.
(5) (a) Morales-Serna, J. A.; Boutureira, O.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Biomol. Chem.* **2008**, *6*, 443−446. (b) Wu, D.; Fujio, M.; Wong, C.-H. *Bioorg. Med. Chem.* **2008**, *16*, 1073−1083. (c) Savage, P. B.; Teyton, L.; Bendelac, A. *Chem. Soc. Rev.* **2006**, *35*, 771−779. (d) Tsuji, M. *Cell. Mol. Life Sci.* **2006**, *63*, 1889−1898. (e) Yamamura, T.; Miyamoto, K.; Illés, Z.; Pál, E.; Araki, M.; Miyake, S. *Curr. Top. Med. Chem.* **2004**, *4*, 561−567. (f) Miller-Podraza, H. *Chem. Rev.* **2000**, *100*, 4663−4682. (f) Morales-Serna, J. A.; Boutureira, O.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Carbohydr. Res.* **2007**, *342*, 1595−1612.
(6) (a) Radin, N. S. *Eur. J. Biochem.* **2001**, *268*, 193−204. (b) Hayakawa, Y.; Godfrey, D. I.; Smyth, M. J. *Curr. Med. Chem.* **2004**, *11*, 241−252. (c) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J. Med. Chem.* **1995**, *38*, 2176−2187.
(7) (a) Svensson, M.; Lindstedt, R.; Radin, N. S.; Svanborg, C. *Infect. Immun.* **1994**, *62*, 4404−4410. (b) Svensson, M.; Frendeus, B.; Butters, T.; Platt, F.; Dwek, D.; Svanborg, C. *Mol. Microbiol.* **2003**, *47*, 453−461.
(8) (a) Allende, M. L.; Proia, R. L. *Curr. Opin. Struct. Biol.* **2002**, *12*, 587−592. (b) Tagami, S.; Inokuchi, J.; Kabayama, K.; Yoshimura, H.; Kitamura, F.; Uemura, S.; Ogawa, C.; Ishii, A.; Saito, M.; Ohtsuka, Y.; Sakaue, S.; Igarashi, Y. *J. Biol. Chem.* **2002**, *277*, 3085−3092. (c) Ferrari, G.; Minozzi, M. C.; Zanellato, A. M.; Silvestrini, B. *Ann. N.Y. Acad. Sci.* **1998**, *845*, 263−273. (d) Svennerholm, L.; Brane, G.; Karlsson, I.; Lekman, A.; Ramstorm, I.; Wikkelso, C. *Dementia Geriatr. Cognit. Disord.* **2002**, *14*, 128−136. (e) Matsuoka, Y.; Saito, M.; LaFrancois, J.; Saito, M.; Gaynor, K.; Olm, V.; Wang, L.; Casey, E.; Lu, Y.; Shiratori, C.; Lemere, C.; Duff, K. *J. Neurosci.* **2003**, *23*, 29−33.
(9) (a) Vankar, Y. D.; Schmidt, R. R. *Chem. Soc. Rev.* **2000**, *29*, 201−216. (b) Natori, T.; Koezuka, Y.; Higa, T. *Tetrahedron Lett.* **1993**, *34*, 5591−5592.
(10) (a) Veerapen, N.; Brigl, M.; Garg, S.; Cerundolo, V.; Cox, L. R.; Brenner, M. B.; Besra, G. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4288−4291. (b) Michieletti, M.; Bracci, A.; Compostella, F.; De Libero, G.; Mori, L.; Fallarini, S.; Lombardi, G.; Panza, L. *J. Org. Chem.* **2008**, *73*, 9192−9195. (c) Lee, A.; Farrand, K. J.; Dickgreber, N.; Hayman, C. M.; Jürs, S.; Hermans, I. F.; Painter, G. F. *Carbohydr. Res.* **2006**, *341*, 2785−2798. (d) Plettenburg, O.; Bodmer-Narkevitch, V.; Wong, C.-H. *J. Org. Chem.* **2002**, *67*, 4559−4564. (e) Figueroa-Pérez, S.; Schmidt, R. R. *Carbohydr. Res.* **2000**, *328*, 95−102.
(11) (a) Jervis, P. J.; Cox, L. R.; Besra, G. S. *J. Org. Chem.* **2011**, *76*, 320−323. (b) Trappeniers, M.; Van Beneden, K.; Decruy, T.; Hillaert, U.; Linclau, B.; Elewaut, D.; Van Calenbergh, S. *J. Am. Chem. Soc.* **2008**, *130*, 16468−16469. (c) Liu, Y.; Goff, R. D.; Zhou, D.; Mattner, J.; Sullivan, B. A.; Khurana, A.; Cantu, C.; Ravkov, E. V.; Ibegbu, C. C.; Altman, J. D.; Teyton, L.; Bendelac, A.; Savage, P. B. *J. Immunol. Methods* **2006**, *312*, 34−39. (d) Xia, C.; Zhang, W.; Zhang, Y.; Woodward, R. L.; Wang, J.; Wang, P. G. *Tetrahedron* **2009**, *65*, 6390−6395. (e) Zhou, X. T.; Forestier, C.; Goff, R. D.; Li, C.; Teyton, L.; Bendelac, A.; Savage, P. B. *Org. Lett.* **2002**, *4*, 1267−1270. (f) Lacône, V.; Hunault, J.; Pipelier, M.; Blot, V.; Lecourt, T.; Rocher, J.; Turcot-Dubois, A.-L.; Marionneau, S.; Douillard, J.-Y.; Clément, M.; Le Pendu, J.; Bonneville, M.; Micouin, L.; Dubreuil, D. *J. Med. Chem.* **2009**, *52*, 4960−4963.
(12) (a) Veerapen, N.; Reddington, F.; Salio, M.; Cerundolo, V.; Besra, G. S. *Bioorg. Med. Chem.* **2011**, *19*, 221−228. (b) Goff, R. D.; Gao, Y.; Mattner, J.; Zhou, D.; Yin, N.; Cantu, C.; Teyton, L.; Bendelac, A.; Savage, P. B. *J. Am. Chem. Soc.* **2004**, *126*, 13602−13603. (c) Miyamoto, K.; Miyake, S.; Yamamura, T. *Nature* **2001**, *413*, 531−534. (d) Fujio, M.; Wu, D.; García-Navarro, R.; Ho, D. D.; Tsuji, M.; Wong, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 9022−9023. (e) Park, J.-J.; Lee, J. H.; Seo, K.-C.; Bricard, G.; Venkataswamy, M. M.; Porcelli, S. A.; Chung, S.-K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 814−818. (f) Lee, T.; Cho, M.; Ko, S.-Y.; Youn, H.-J.; Baek, D. J.; Cho, W.-J.; Kang, C.-Y.; Kim, S. *J. Med. Chem.* **2007**, *50*, 585−589. (g) Trappeniers, M.; Goormans, S.; Van Beneden, K.; Decruy, T.; Linclau, B.; Al-Shamkhani, A.; Elliott, T.; Ottensmeier, C.; Werner, J. M.; Elewaut, D.; Van Calenbergh, S. *ChemMedChem.* **2008**, *3*, 1061−1070. (h) Trappeniers, M.; Chofor, R.; Aspeslagh, S.; Li, Y.; Linclau, B.; Zajonc, D. M.; Elewaut, D.; Van Calenbergh, S. *Org. Lett.* **2010**, *12*, 2928−2931. (i) Hunault, J.; Diswall, M.; Frison, J. C.; Blot, V.; Rocher, J.; Marionneau-Lambot, S.; Oullier, T.; Douillard, J.-Y.; Guillarme, S.; Saluzzo, C.; Dujardin, G.; Jacquemin, D.; Graton, J.; Le Questel, J.-Y.; Evain, M.; Lebreton, J.; Dubreuil, D.; Le Pendu, J.; Pipelier, M. *J. Med. Chem.* **2012**, *55*, 1227−1241 and references cited therein.
(13) Pérez-Labrada, K.; Brouard, I.; Estévez, S.; Marrero, M. T.; Estévez, F.; Bermejo, J.; Rivera, D. G. *Bioorg. Med. Chem.* **2012**, *20*, 2690−2700 and references cited therein.
(14) Miyashita, H.; Ikeda, T.; Nohara, T. *Carbohydr. Res.* **2007**, *342*, 2182−2191.
(15) (a) Hannun, Y. A. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 139−150. (b) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532−1568. (b) Perry, D. K.; Hannun, Y. A. *Biochim. Biophys. Acta* **1998**, *1436*, 233−243. (c) Gómez-Muñoz, A. *Biochim. Biophys. Acta* **1998**, *1391*, 92−109. (d) Kolesnick, R. N.; Krönke, M. *Annu. Rev. Physiol.* **1998**, *60*, 643−665.
(16) (a) Kim, S.; Cho, M.; Lee, T.; Lee, S.; Min, H.-Y.; Lee, S. K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4584−4587. (b) de Jonghe, S.; Lamote, I.; Venkataraman, K.; Boldin, S. A.; Hillaert, U.; Rozenski, J.; Hendrix, C.; Busson, R.; de Keukeleire, D.; Van Calenbergh, S.; Futerman, A. H.; Herdewijn, P. *J. Org. Chem.* **2002**, *67*, 988−996. (c) Shikata, K.; Azuma, H.; Tachibana, T.; Ogino, K. *Tetrahedron* **2002**, *58*, 5803−5809. (d) Dagan, A.; Wang, C.; Fibach, E.; Gatt, S. *Biochim. Biophys. Acta* **2003**, *1633*, 161−169. (e) Macchia, M.; Bertini, S.; Fogli, S.; Giovannetti, E.; Minutolo, F.; Rapposelli, S.; Danesi, R. *Il Farmaco* **2003**, *58*, 205−211. (f) Chun, J.; Byun, H.-S.; Arthur, G.; Bittman, R. *J. Org. Chem.* **2003**, *68*, 355−359. (g) Azuma, H.; Takao, R.; Shikata, K.; Niiro, H.; Tachibana, T.; Ogino, K. *J. Med. Chem.* **2003**, *46*, 3445−3447. (h) Nakamura, Y.; Matsubara, R.; Kitagawa, H.; Kobayashi, S.; Kumagai, K. *J. Med. Chem.* **2003**, *46*, 3688−3695.

(i) Lu, X.; Arthur, G.; Bittman, R. *Org. Lett.* **2005**, *7*, 1645−1648. (j) Hillaert, U.; Van Calenbergh, S. *Org. Lett.* **2005**, *7*, 5769−5772. (k) Ha, H.-J.; Hong, M. C.; Ko, S. W.; Kim, Y. W.; Lee, W. K.; Park, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1880−1883. (l) Chang, Y.-T.; Choi, J.; Ding, S.; Prieschl, E. E.; Baumruker, T.; Lee, J.-M.; Chung, S.-K.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1856−1857.

(17) (a) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234−6246. (b) Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. *Chem. Rev.* **2009**, *109*, 796−814. (c) El Kaïm, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153−2171. (d) Hulme, C.; Dietrich, J. *Mol. Diversity* **2009**, *13*, 195−207. (e) Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324−331. (f) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (g) Zhu, J.; Bienyamé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. (h) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133−1144.

(18) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (b) Marcaccini, S.; Torroba, T. *Nat. Protoc.* **2007**, *2*, 632−639. (c) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrücker, C. *Angew. Chem.* **1959**, *71*, 386.

(19) Manzo, E.; Carbone, M.; Mollo, E.; Irace, C.; Di Pascale, A.; Li, Y.; Ciavatta, M. L.; Cimino, G.; Guo, Y.-W.; Gavagnin, M. *Org. Lett.* **2011**, *13*, 1897−1899.

(20) Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, 400−402.

(21) Fukase, K.; Winarno, H.; Kusumoto, S. *Chem. Express* **1993**, *8*, 409−412.

(22) For selected reports on the use of glycosides in Ugi-4CRs, see: (a) Brauch, S.; Gabriel, L.; Westermann, B. *Chem. Commun.* **2010**, *46*, 3387−3389. (b) Leyden, R.; VelascoTorrijos, T.; André, S.; Gouin, S.; Gabius, H. J.; Murphy, P. V. *J. Org. Chem.* **2009**, *74*, 9010−9026. (c) Westermann, B.; Döner, S. *Chem. Commun.* **2005**, 2116−2118. (d) Liu, L.; Li, C. P.; Cochran, S.; Ferro, V. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2221−2226. (e) Li, Y.; Zhang, X.; Chu, S.; Yu, K.; Guan, H. *Carbohydr. Res.* **2004**, *339*, 873−879. (f) Murphy, P. V.; Bradley, H.; Tosin, M.; Pitt, N.; Fitzpatrick, G. M.; Glass, W. K. *J. Org. Chem.* **2003**, *68*, 5692−5704. (g) Bradley, H.; Fitzpatrick, G.; Glass, W. K.; Kunz, H.; Murphy, P. V. *Org. Lett.* **2001**, *3*, 2629−2632. (h) Lockhoff, O. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3436−3439. (i) Sutherlin, D. P.; Stark, T. M.; Hughes, R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8350−8354. (j) Park, W. K. C.; Auer, M.; Jaksche, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 10150−10155.

(23) Hotha, S.; Kashyap, S. *J. Org. Chem.* **2006**, *71*, 364−367.

(24) Jiang, L.; Chan, T.-H. *J. Org. Chem.* **1998**, *63*, 6035−6038.

(25) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123.

(26) Schmidt, R. R.; Toepfer, A. *Tetrahedron Lett.* **1991**, *32*, 3353−3356.

(27) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031−1034.