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Phase transfer agent assisted biphasic CuAAC reaction†

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A phase transfer agent assisted biphasic Cu(I) catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) reaction system was developed. A biphasic reaction medium consisting of water and an organic solvent ensures the dissolution of reagents and substrates. Tris(triazolylmethyl)amine ligands with an appropriate hydrophilic–lipophilic balance are able to extract copper from the aqueous phase to the organic phase, accelerating the CuAAC reaction rate. The present system is widely applicable to substrates with various functionalities, including a free amino group and especially to lipophilic substrates.

Introduction

While the traditional thermal azide–alkyne 1,3-dipolar cycloaddition reaction requires prolonged heating at elevated temperatures and results in mixtures of both 1,4- and 1,5-substituted triazole regioisomers,[1] the Cu(I) catalyzed version (CuAAC) provides only the 1,4-regioisomer under relatively mild conditions.[2] Since its discovery, CuAAC has emerged as the archetypical example of "click chemistry",[3] and has found widespread application in many areas such as drug discovery, material science, and bioconjugation.[4] This broad application was made possible in part by the advent of new reaction conditions that are more efficient and adaptable than the original CuAAC conditions.[5]

The original CuAAC conditions suggested by Sharpless use an *in situ* generated Cu(I) catalyst derived from the reaction of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate, and a mixture of water and *t*-BuOH.[2a] The general issues in the development of new CuAAC conditions are generating the effective Cu(I) catalyst and maintaining high levels of the catalytically active Cu(I) during the reaction. As a consequence, a wide range of Cu(I) sources have been introduced, and various Cu ligands were developed to prevent the formation of unreactive polynuclear Cu(I) acetylides and increase the thermodynamic stability of Cu(I).[5b,6,7] Alternatively, a variety of immobilized copper catalysts have been devised for heterogeneous or soluble polymer catalyst systems.[8]

Another important issue has been the different solubility preferences of the Cu(I) catalyst and substrates.[9] As one may notice, most of the copper salts have limited solubility in organic solvents[10] while the substrates of interest in organic synthesis generally have a high organic solubility. To solve this problem, the use of organic-soluble Cu(I) complexes has been suggested such as $(PPh_3)_3 \cdot CuBr$, $(EtO)_3P \cdot CuI$,[11a] bis-triazolylidene dicopper(I) complexes[11b] and $C_3H_7COOCu(PPh_3)_2$.[11c] Although these ligand chelated Cu(I) reagents exhibited better organic solubility and high reactivity, they possess some drawbacks. For example, phosphine based Cu(I) complexes have the intrinsic risk of the Staudinger reduction of azide.[5c] In some cases, these catalysts require harsh reaction conditions, such as elevated temperatures. In addition, the lengthy and complex procedures for catalysts preparation reduce the wide application of such catalysts.

Another way of solving the problem derived from the different solubility preferences is the careful choice of solvent systems.[5a] Most commonly, the reaction is performed in a mixture of water and water-miscible organic solvent, which facilitates solvation of hydrophobic substrates while still retaining the advantages of water. Organic solvents of intermediate polarity, such as THF, acetone, pyridine, CH_3CN, and DMSO, are often employed when partially organic soluble CuI or organic-soluble Cu complexes are used as a source of Cu(I). The two-phase solvent system composed of water and organic solvent was also reported to be effective to produce the triazole products with or without a ligand.[12] Although many solvent systems are available, finding the optimum solvent is still a case-to-case basis because there is no obvious correlation between which solvent is used and performance of the reaction.

Given our interest in developing reliable, general reaction conditions for CuAAC in organic synthesis, we sought to explore the possibility of applying the concept of phase transfer catalysis (PTC) as a solution for the different solubility preferences. PTC is an efficient and widely used method for promoting reactions between reaction partners that are present in two immiscible phases.[13] However, the concept of PTC has rarely been applied to CuAAC reactions,[14] and its potential use has not been sufficiently explored. One of the few investigations employing this concept is the utilization of β-cyclodextrin in

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water medium.[14a] Although this reaction system quickly provides the product by making a host–guest complex within the hydrophobic cyclodextrin cavity, there are some substrate limitations due to the capacity allowances of cyclodextrins.[15] Polyethylene glycol 400 (PEG-400) has been employed as a phase transferring agent in a one-pot multi-component CuAAC reaction in water medium.[14b,c] In this case, a large excess of PEG-400 was used as like a co-solvent.

Unlike the previous phase transfer CuAAC reactions in which substrates are delivered to the water medium, we employed an aqueous/organic two-phase solvent system and planned to transfer copper from the aqueous phase to the organic phase where the reaction occurs. We envisioned that the aqueous biphasic reaction system would be advantageous for a broad range of substrates and would be highly generalizable if the biphasic CuAAC reactions could be facilitated by a phase transfer agent. Herein, we report our studies on this subject and describe new CuAAC reaction conditions which are highly efficient, especially when a lipophilic substrate is involved.

Results and discussion

Our working hypothesis for the phase transfer agent assisted CuAAC reaction is shown in Fig. 1. The *in situ* generated Cu(I) catalyst produced by the reaction of Cu(II) and sodium ascorbate in aqueous phase would be ferried into the organic phase by a phase transfer agent as a complex form.[16] Similarly to other organic-soluble Cu(I) complexes, the relocated Cu(I) species would promote the CuAAC reactions in the organic phase. During the reaction process, Cu(I) can be inadvertently oxidized to Cu(II). In aqueous phase in which sodium ascorbate is dissolved, these oxidized Cu(II) species can revert back to the catalytically active Cu(I) species,[17] which are able to reenter the cycle with the help of the phase transfer agent.

In this phase transfer system, the phase transfer agents should be able to encapsulate Cu(I) in the aqueous phase or at the interface to deliver it to the organic phase. In addition, it is advantageous if they are able to be coordinated with Cu(I) during the reaction to enhance the rate of reaction and to protect the Cu(I) from oxidation.

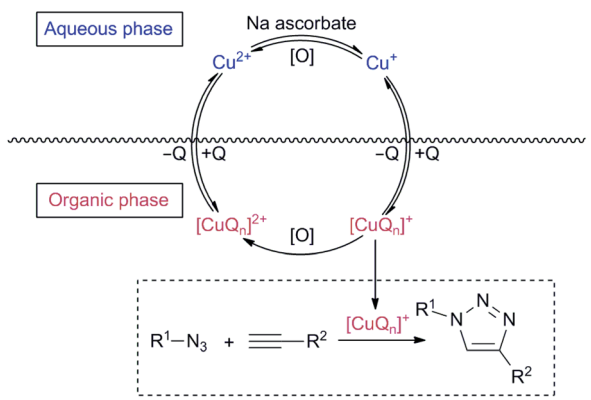


Fig. 1 Schematic representation of phase transfer agent assisted CuAAC reaction.

To identify phase transfer agents that fulfill the above conditions, we surveyed several types of ligands which have been devised to promote the Cu(I) catalyzed triazole formation. This effort resulted in the selection of tris(triazolylmethyl) amine ligands that are easily available and consist of several variants with different physicochemical properties.[7a,18] Four typical tris(triazolylmethyl)amine ligands (**1a–d**, Fig. 2) with different functional groups and log *P* values were chosen for the first step of the development. Benzyl azide (**2a**) and phenyl acetylene (**3a**) were chosen as a CuAAC reaction partners, and water soluble $CuSO_4 \cdot 5H_2O$ (0.5 mol%) and sodium ascorbate (1.5 mol%) were used to generate the Cu(I) *in situ*. A mixture of CH_2Cl_2–H_2O (1 : 1) was employed as a biphasic solvent system (Table 1).

When the reaction was performed without a ligand for 240 min (entry 1), most of the starting materials remained intact and the desired product was obtained in poor yield (20%). However, in the presence of TTTA (**1a**), the reaction was completed within 20 min with the formation of product in nearly quantitative yield (entry 2). TBTA (**1b**) increased the reaction rate such that the reaction was completed within 40 min (entry 3).[19] BTTAA (**1c**) was far less effective in accelerating the reaction (entry 4). The most hydrophilic ligand THPTA (**1d**) significantly retarded the reaction, resulting in only 3% product yield even after 240 min (entry 5).

To verify whether the observed reaction rates were related to the phase transfer activity of tris(triazolylmethyl)amine ligands, we used ICP-MS analysis to measure the copper content in the organic layer of the substrate-blank biphasic reaction system. As shown in Table 2, the copper content in the organic layer was very low (78 ppb) without any ligand (entry 1). In the presence of TTTA (**1a**, $C\log P = 1.1$), the copper content was increased approximately 900 times (entry 2). TBTA (**1b**, $C\log P = 2.7$) also resulted in an increase of copper content by approximately 500 times (entry 3). The more hydrophilic ligands **1c** and **1d** did not cause a significant increase in the copper content (entries 4 and 5). This result indicated that the tris(triazolylmethyl)-amine ligands with appropriate hydrophilic–lipophilic balances are able to extract copper from the aqueous phase to the organic phase, thereby accelerating the rate of the CuAAC reaction.

To understand the mechanism of copper transfer, we measured the partition ratio of TTTA (**1a**) between CH_2Cl_2 and H_2O by ^1H NMR analysis. To our surprise, although the calculated log *P* value for **1a** is 1.1, only a negligible amount of **1a** was resided in the aqueous layer while the overwhelming majority of

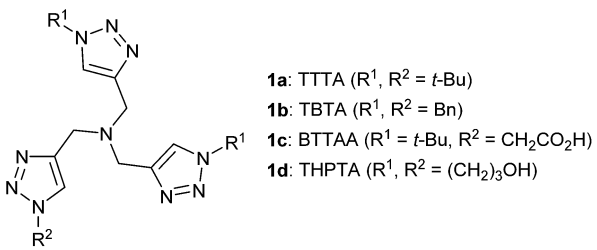
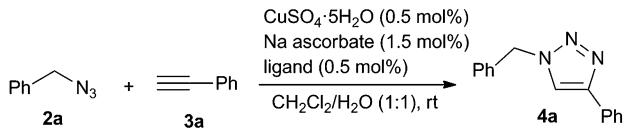


Fig. 2 Structures of tris(triazolylmethyl)amine ligands (**1a–d**).

Table 1 Effects of tris(triazolylmethyl)amine ligands on the CuAAC reaction[a]



Entry	Ligand	Time (min)	Yield[b] (%)
1	None	240	20
2	**1a**	20	100
3	**1b**	40	100
4	**1c**	240	47
5	**1d**	240	3

[a] Reaction conditions: **2a** (0.50 mmol), **3a** (0.55 mmol), $CuSO_4 \cdot 5H_2O$ (0.5 mol%), Na ascorbate (1.5 mol%), and ligand (0.5 mol%) in CH_2Cl_2–H_2O (1 : 1) (1 mL) at rt. [b] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Table 2 Effects of tris(triazolylmethyl)amine ligands on the Cu content in the CH_2Cl_2 layer[a]

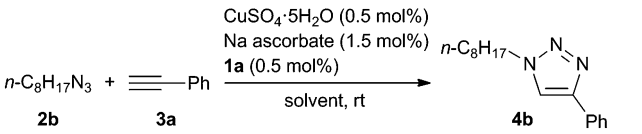
Entry	Ligand	*C* log *P*[b]	Cu content[c] (ppb)
1	None	—	78
2	**1a**	1.1	70 330
3	**1b**	2.7	39 475
4	**1c**	−0.37	125
5	**1d**	−3.7	128

[a] Conditions: $CuSO_4 \cdot 5H_2O$ (0.0025 mmol), Na ascorbate (0.0075 mmol), and ligand (0.0025 mmol) in CH_2Cl_2–H_2O (1 : 1) (1 mL) at rt for 30 min. [b] *C* log *P* values were calculated using ChemBioDraw Ultra 13.0. [c] Determined by ICP-MS analysis.

1a was detected in the CH_2Cl_2 layer. This result suggested that the complexation between **1a** and Cu(I) might occur mostly at or near the interface between CH_2Cl_2 and H_2O, and then this complex would move to the organic phase to promote the CuAAC reactions.[13c,20]

Toluene and $CHCl_3$ can also be used as the organic phase of the biphasic system (Table 3). The CuAAC reaction between the highly lipophilic alkyl azide **2b** and phenyl acetylene (**3a**) in biphasic $CHCl_3$–H_2O medium was completed in 25 min in the presence of **1a** (entry 1), and the reaction in toluene–H_2O was completed in 50 min (entry 2). Although the reaction in these solvent systems was slower than reactions performed in the CH_2Cl_2–H_2O solvent system (entry 3), the necessary reaction time was still short and the yield was very high. The corresponding reaction in the monophasic *t*-BuOH–H_2O solvent system was much less efficient and reached full conversion in 360 min (entry 4). When water was used as the only solvent, full conversion was not reached even after 360 min primarily because of the limited solubility of substrates (entry 5). The reaction in only CH_2Cl_2 solvent provided a trace amount of the product in 360 min because of the limited solubility of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate (entry 6).

Table 3 Effects of solvent systems on the CuAAC reaction[a]



Entry	Solvent	Time (min)	Yield[b] (%)
1	$CHCl_3$–H_2O (1 : 1)	25	100
2	Toluene–H_2O (1 : 1)	50	97
3	CH_2Cl_2–H_2O (1 : 1)	15	100
4	*t*-BuOH–H_2O (2 : 1)	360	99
5	H_2O	360	78
6	CH_2Cl_2	360	<1

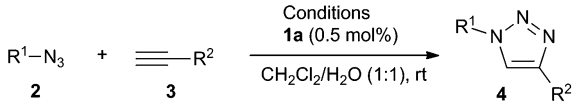
[a] Reaction conditions: **2b** (0.50 mmol), **3a** (0.55 mmol), $CuSO_4 \cdot 5H_2O$ (0.5 mol%), Na ascorbate (1.5 mol%), and **1a** (0.5 mol%) in solvent (1 mL) at rt. [b] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

The scope of applicability of the phase transfer agent assisted CuAAC reaction was explored with 0.5 mol% of TTTA (**1a**) in a biphasic CH_2Cl_2–H_2O medium containing $CuSO_4 \cdot 5H_2O$ and ascorbate (0.5 and 1.5 mol%, respectively; conditions (A)). First, we applied various types of azides to the reaction system. As shown in Table 4, the azide structure has no significant effect on the reaction rates. All of the reactions proceeded efficiently and were completed in less than 15 min, with excellent isolated yields (entries 1–5). However, the effects of alkyne structures on the reaction rates were significant. Alkynes with an ester group or a phenyl group proceeded efficiently, resulting in the corresponding triazole products within 20 min in excellent yields (entries 6 and 7). The *N*-Boc group at the propargylic position of the alkyne substrate did not affect the reaction rates (entry 8). Propargyl alcohols were also suitable for this reaction system, yielding product in less than 50 min (entries 9 and 10). The reaction of the *t*-butyl substituted alkyne was completed in 50 min (entry 11). However, the reaction of the *n*-hexyl or cyclohexyl substituted alkynes was not completed within the same time. These substrates required an increase in copper and sodium ascorbate loading (1.5 and 4.5 mol%, respectively; conditions (B)) for completion within 50 min (entries 12 and 13). The cycloadditions of propynoic acid also proceeded efficiently under these higher copper loading conditions (entry 14).

Noteworthy was the result obtained in the biphasic CuAAC reaction of propargyl amine (entry 15) because the CuAAC reaction generally fails or gives low yield in the presence of free amino groups as a consequence of the coordination between the Cu(I) ion and the amino group.[7a,21] Under higher reagent loading conditions, the triazole product **4q** was successfully obtained in 97% yield. In addition, the reactions between free amine containing azides **2h–j** and the phenyl acetylene (**3a**) proceeded efficiently in this reaction system (entries 16–18).

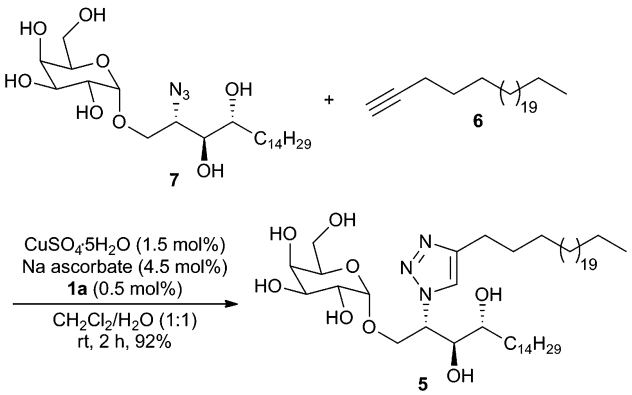
We demonstrated the utility and efficiency of the phase transfer agent assisted biphasic CuAAC reaction by applying it to the synthesis of an immunostimulant α-GalCer analog **5** (Scheme 1).[22] Because this synthesis required a highly lipophilic

Table 4 CuAAC reaction with various alkynes and azides using phase transfer agent[a]



Entry	R^1	R^2	Conditions[b]	Time (min)	4	Yield[c] (%)
1	Cyclohexyl (**2c**)	Ph (**3a**)	A	15	**4c**	97
2	$C_2H_5OCOCH_2$ (**2d**)	Ph (**3a**)	A	5	**4d**	98
3	*p*-$NO_2C_6H_4CH_2$ (**2e**)	Ph (**3a**)	A	10	**4e**	96
4	*p*-$BrC_6H_4CH_2$ (**2f**)	Ph (**3a**)	A	15	**4f**	96
5	*p*-$CH_3OC_6H_4CH_2$ (**2g**)	Ph (**3a**)	A	10	**4g**	99
6	$PhCH_2$ (**2a**)	$CO_2C_2H_5$ (**3b**)	A	15	**4h**	98
7	$PhCH_2$ (**2a**)	*p*-$CH_3OC_6H_4$ (**3c**)	A	20	**4i**	100
8	$PhCH_2$ (**2a**)	CH_2NHBoc (**3d**)	A	30	**4j**	95
9	$PhCH_2$ (**2a**)	CH_2OH (**3e**)	A	50	**4k**	99
10	$PhCH_2$ (**2a**)	Cyclohexane-1-ol (**3f**)	A	40	**4l**	95
11	$PhCH_2$ (**2a**)	*t*-Bu (**3g**)	A	50	**4m**	98
12	$PhCH_2$ (**2a**)	*n*-Hex (**3h**)	B	40	**4n**	98
13	$PhCH_2$ (**2a**)	Cyclohexyl (**3i**)	B	50	**4o**	100
14	$PhCH_2$ (**2a**)	CO_2H (**3j**)	B	20	**4p**	91
15	$PhCH_2$ (**2a**)	CH_2NH_2 (**3k**)	B	180	**4q**	97
16	$NH_2C_2H_4$ (**2h**)	Ph (**3a**)	B	20	**4r**	98
17	$NH_2C_6H_{12}$ (**2i**)	Ph (**3a**)	B	120	**4s**	93
18	$CH_3NHC_6H_{12}$ (**2j**)	Ph (**3a**)	B	50	**4t**	96

[a] Reaction conditions: **2** (0.50 mmol), **3** (0.55 mmol), **1a** (0.5 mol%), with conditions A or B in CH_2Cl_2–H_2O (1 : 1) (1 mL) at rt. [b] (A) $CuSO_4 \cdot 5H_2O$ (0.5 mol%), Na ascorbate (1.5 mol%). (B) $CuSO_4 \cdot 5H_2O$ (1.5 mol%), Na ascorbate (4.5 mol%). [c] Isolated yield.



Scheme 1 Efficient synthesis of α-GalCer analog **5** using the phase transfer agent assisted CuAAC reaction.

alkyne **6**, the CuAAC reaction of azide **7** with **6** under the conventional reaction system was not met with great success. For example, when the reaction was performed in monophasic *t*-BuOH–H_2O solvent system, the triazole product **5** was obtained in only 20% after 24 h even in the presence of TTTA (**1a**). However, under the presented biphasic system, we successfully obtained **5** in 92% yield in a short reaction time (2 h).

Conclusions

In summary, we have developed a phase transfer agent assisted biphasic CuAAC reaction system. A biphasic reaction media consisting of water and an organic solvent ensures a complete dissolution of reagents and substrates, thus broadening the scope of possible substrates. Among the tested tris(triazolylmethyl)amine Cu ligands, TTTA (**1a**) and TBTA (**1b**) afforded the expected phase transfer activity. The developed biphasic reaction system is highly efficient, especially when a lipophilic substrate is involved. The present system is widely applicable to substrates with various functionalities including a free amino group, making the CuAAC reaction more reliable.

Experimental

General considerations

All chemicals were reagent grade and used as purchased. The reactions were monitored with TLC analysis using silica gel 60 F-254 thin layer plates. Compounds on the TLC plates were sprayed with either potassium permanganate or phosphomolybdic acid and visualized under UV light. Flash column chromatography was conducted on silica gel 60 (230–400 mesh). Optical rotations were measured using a sodium lamp (D line 589.3 nm). Melting points were measured using an electrothermal capillary melting point apparatus and are uncorrected. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in δ units relative to the deuterated solvent. IR spectra were measured on a Fourier transform infrared spectrometer. High-resolution mass spectra (HRMS) were recorded using FAB. Inductively coupled plasma mass spectrometry (ICP-MS) analysis was performed for copper quantitation.

Preparation of the starting materials

Azides **2a–g** were synthesized according to procedures provided by Alvarez *et al.*[23] Azides **2h**,[24] **2i** and **2j**,[25] and alkyne **3d**[26] was also prepared according to the procedures in the literature. The NMR data were in agreement with those published for benzyl azide (**2a**),[23] 1-azidooctane (**2b**),[23] azidocyclohexane (**2c**),[23] ethyl 2-azidoacetate (**2d**),[27] 1-(azidomethyl)-4-nitrobenzene (**2e**),[28] 1-(azidomethyl)-4-bromobenzene (**2f**),[29] 1-(azidomethyl)-4-methoxybenzene (**2g**),[28] 2-azidoethan-1-amine (**2h**),[24] 6-azidohexan-1-amine (**2i**),[25] 6-azido-*N*-methylhexan-1-amine (**2j**)[25] and *tert*-butyl prop-2-ynylcarbamate (**3d**).[26]

Measurement of partition ratio of TTTA (1a) between CH_2Cl_2 and H_2O

In a vial fitted with a screw cap, TTTA (**1a**, 85.6 mg, 0.2 mmol) was dissolved in CH_2Cl_2–H_2O (1 : 1, 2 mL) and stirred at rt for 1 or 12 h. After phase separation, 0.5 mL of each layer was carefully sampled and the solvents were evaporated. The **1a** in each residue was measured by ^{1}H NMR in $CDCl_3$ using 1,1,2,2-tetrachloroethane as an internal standard. In the sample taken from the H_2O layer, no peak of **1a** was identified.

General procedure for CuAAC reactions

In a vial fitted with a screw cap, freshly prepared stock solutions of $CuSO_4 \cdot 5H_2O$ (50 μL, 50 mM stock solution in DDW, 0.5 mol%), TTTA (**1a**, 50 μL, 50 mM stock solution in CH_2Cl_2, 0.5 mol%), and sodium ascorbate (50 μL, 150 mM stock solution in DDW, 1.5 mol%) were added to a mixture of azide **2** (0.5 mmol, 1.0 equiv.) and acetylene **3** (0.55 mmol, 1.1 equiv.) in DDW (0.40 mL) and CH_2Cl_2 (0.45 mL). The reaction was allowed to proceed at rt and monitored by TLC. After total consumption of the starting azide, the reaction mixture was poured into saturated NH_4Cl aqueous solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL).

For the carboxylic acid containing compound **4p**, the mixture was acidified to pH 1 with 1 N HCl aqueous solution and extracted with CH_2Cl_2 (5 × 10 mL).

For the free amine containing compounds **4q** and **4r**, the reaction mixture was poured into 25% NH_4OH aqueous solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL).

The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. When required, the product was purified by flash column chromatography on silica gel.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (4a)

White solid (117.3 mg, 100%); m.p. 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.77 (m, 2H), 7.66 (s, 1H), 7.28–7.26 (m, 8H), 5.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 134.6, 130.4, 129.0 (2C), 128.7 (2C), 128.6, 128.0, 127.9 (2C), 125.5 (2C), 119.5, 54.0; IR (neat, cm^{-1}) ν_{max} 3141, 3027, 2976, 1468, 1449, 1361, 1222, 1140, 1073, 1044, 766, 727, 693; HRMS (FAB): calcd for $C_{15}H_{14}N_3$ $[M + H]^+$ 236.1188, found 236.1189.

1-Octyl-4-phenyl-1*H*-1,2,3-triazole (4b)

White solid (128.6 mg, 100%); m.p. 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.78 (m, 2H), 7.72 (s, 1H), 7.38–7.34 (m, 2H), 7.29–7.25 (m, 1H), 4.31 (t, J = 7.2 Hz, 2H), 1.91–1.84 (m, 2H), 1.28–1.21 (m, 10H), 0.83 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 130.6, 128.6 (2C), 127.9, 125.5 (2C), 119.4, 50.2, 31.5, 30.2, 28.9, 28.8, 26.3, 22.4, 13.9; IR (neat, cm^{-1}) ν_{max} 3120, 3092, 3064, 2954, 2917, 2849, 1484, 1463, 1356, 1215, 1190, 1078, 1051, 976, 839, 760, 693; HRMS (FAB): calcd for $C_{16}H_{24}N_3$ $[M + H]^+$ 258.1970, found 258.1976.

1-Cyclohexyl-4-phenyl-1*H*-1,2,3-triazole (4c)

White solid (110.2 mg, 97%); m.p. 107–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.78 (m, 2H), 7.75 (s, 1H), 7.37–7.33 (m, 2H), 7.27–7.23 (m, 1H), 4.39 (tt, J = 11.8, 3.7 Hz, 1H), 2.17–2.14 (m, 2H), 1.87–1.67 (m, 5H), 1.44–1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 130.7, 128.6 (2C), 127.7, 125.4 (2C), 117.3, 59.9, 33.3 (2C), 24.94 (2C), 24.89; IR (neat, cm^{-1}) ν_{max} 3126, 2936, 2854, 1480, 1452, 1374, 1223, 1054, 1000, 894, 826, 761, 691; HRMS (FAB): calcd for $C_{14}H_{18}N_3$ $[M + H]^+$ 228.1501, found 228.1503.

Ethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate (4d)

White solid (113.3 mg, 98%); m.p. 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.80–7.78 (m, 2H), 7.38–7.35 (m, 2H), 7.30–7.26 (m, 1H), 5.13 (s, 2H), 4.19 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 147.7, 130.2, 128.6 (2C), 127.9, 125.5 (2C), 121.1, 62.1, 50.6, 13.7; IR (neat, cm^{-1}) ν_{max} 3135, 2948, 1752, 1465, 1442, 1346, 1214, 1197, 1074, 1014, 763, 692; HRMS (FAB): calcd for $C_{12}H_{14}N_3O_2$ $[M + H]^+$ 232.1086, found 232.1087.

1-(4-Nitrobenzyl)-4-phenyl-1*H*-1,2,3-triazole (4e)

White solid (134.4 mg, 96%); m.p. 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.18 (m, 2H), 7.79–7.74 (m, 3H), 7.42–7.29 (m, 5H), 5.66 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 148.0, 141.7, 130.1, 128.9 (2C), 128.5 (2C), 128.4, 125.7 (2C), 124.3 (2C), 119.7, 53.1; IR (neat, cm^{-1}) ν_{max} 3127, 3083, 1606, 1517, 1347, 1222, 1077, 1045, 861, 803, 761, 729, 690; HRMS (FAB): calcd for $C_{15}H_{13}N_4O_2$ $[M + H]^+$ 281.1039, found 281.1034.

1-(4-Bromobenzyl)-4-phenyl-1*H*-1,2,3-triazole (4f)

White solid (150.4 mg, 96%); m.p. 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.76 (m, 2H), 7.66 (s, 1H), 7.48–7.45 (m, 2H), 7.39–7.37 (m, 2H), 7.31–7.27 (m, 1H), 7.14–7.12 (m, 2H), 5.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 133.7, 132.2 (2C), 130.3, 129.6 (2C), 128.8 (2C), 128.2, 125.6 (2C), 122.8, 119.5, 53.4; IR (neat, cm^{-1}) ν_{max} 3107, 3083, 1483, 1461, 1431, 1350, 1219, 1073, 1047, 1010, 799, 961, 687; HRMS (FAB): calcd for $C_{15}H_{13}BrN_3$ $[M + H]^+$ 314.0293, found 314.0292.

1-(4-Methoxybenzyl)-4-phenyl-1*H*-1,2,3-triazole (4g)

White solid (131.1 mg, 99%); m.p. 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.75 (m, 2H), 7.62 (s, 1H), 7.35

(t, J = 7.7 Hz, 2H), 7.28–7.21 (m, 3H), 6.86 (d, J = 8.6 Hz, 2H), 5.44 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 147.9, 130.5, 129.5 (2C), 128.6 (2C), 128.0, 126.6, 125.5 (2C), 119.3, 114.4 (2C), 55.2, 53.6; IR (neat, cm^{-1}) ν_{max} 3107, 3083, 1483, 1461, 1219, 1073, 1010, 816, 799, 761, 687; HRMS (FAB): calcd for $C_{16}H_{16}N_3O$ $[M + H]^+$ 266.1293, found 266.1291.

Ethyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate (4h)

White solid (113.3 mg, 98%); m.p. 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.25–7.17 (m, 5H), 5.48 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 140.1, 133.7, 128.9 (2C), 128.6, 127.9 (2C), 127.2, 60.8, 54.0, 13.9; IR (neat, cm^{-1}) ν_{max} 3126, 2983, 1715, 1539, 1368, 1226, 1044, 1022, 776, 716, 693; HRMS (FAB): calcd for $C_{12}H_{14}N_3O_2$ $[M + H]^+$ 232.1086, found 232.1088.

1-Benzyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (4i)

White solid (132.3 mg, 100%); m.p. 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.69 (m, 2H), 7.56 (s, 1H), 7.37–7.27 (m, 5H), 6.92–6.89 (m, 2H), 5.52 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 147.9, 134.7, 129.0 (2C), 128.6, 127.9 (2C), 126.9 (2C), 123.2, 118.7, 114.1 (2C), 55.2, 54.0; IR (neat, cm^{-1}) ν_{max} 3138, 3040, 2949, 2838, 2098, 1614, 1557, 1495, 1454, 1436, 1349, 1249, 1170, 1070, 1027, 973, 832, 794, 717; HRMS (FAB): calcd for $C_{16}H_{16}N_3O$ $[M + H]^+$ 266.1293, found 266.1286.

***tert*-Butyl((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)carbamate (4j)**

Light yellow solid (137.0 mg, 95%); m.p. 91–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.37–7.23 (m, 5H), 5.48 (s, 2H), 5.04 (brs, 1H, NH), 4.34 (d, J = 5.9 Hz, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 145.7, 134.5, 128.9 (2C), 128.5, 127.8 (2C), 121.7, 79.3, 53.9, 35.9, 28.2 (3C); IR (neat, cm^{-1}) ν_{max} 3405, 3111, 3063, 2978, 2954, 1688, 1515, 1454, 1268, 1169, 1123, 1054, 796, 717, 695; HRMS (FAB): calcd for $C_{15}H_{21}N_4O_2$ $[M + H]^+$ 289.1665, found 289.1666.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methanol (4k)

White solid (93.4 mg, 99%); m.p. 77–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.31–7.28 (m, 3H), 7.21–7.19 (m, 2H), 5.42 (s, 2H), 4.67 (s, 2H), 3.71 (brs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 134.4, 129.0 (2C), 128.6, 128.0 (2C), 121.8, 55.9, 54.0; IR (neat, cm^{-1}) ν_{max} 3252, 3140, 2934, 1457, 1222, 1129, 1036, 1012, 837, 788, 717, 691; HRMS (FAB): calcd for $C_{10}H_{12}N_3O$ $[M + H]^+$ 190.0980, found 190.0980.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)cyclohexan-1-ol (4l)

White solid (122.1 mg, 95%); m.p. 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.31–7.25 (3H), 7.19–7.17 (m, 2H), 5.40 (s, 2H), 3.05 (brs, 1H, OH), 1.91–1.25 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 134.6, 128.8 (2C), 128.4, 127.9 (2C), 119.5, 69.3, 53.8, 37.9 (2C), 25.2, 21.7 (2C); IR (neat, cm^{-1}) ν_{max} 3293, 2933, 2856, 1497, 1454, 1334, 1250, 1217, 1158, 1055, 979, 795, 727; HRMS (FAB): calcd for $C_{15}H_{20}N_3O$ $[M + H]^+$ 258.1606, found 258.1599.

1-Benzyl-4-(*tert*-butyl)-1*H*-1,2,3-triazole (4m)

White solid (105.1 mg, 98%); m.p. 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.24 (m, 3H), 7.19–7.17 (m, 2H), 7.15 (s, 1H), 5.39 (s, 2H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 134.9, 128.7 (2C), 128.2, 127.7 (2C), 118.3, 53.6, 30.5, 30.1 (3C); IR (neat, cm^{-1}) ν_{max} 3119, 2961, 2865, 1531, 1495, 1457, 1361, 1341, 1231, 1202, 1051, 821, 713, 673; HRMS (FAB): calcd for $C_{13}H_{18}N_3$ $[M + H]^+$ 216.1501, found 216.1498.

1-Benzyl-4-hexyl-1*H*-1,2,3-triazole (4n)

White solid (119.0 mg, 98%); m.p. 52–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 3H), 7.23–7.21 (m, 2H), 7.15 (s, 1H), 5.45 (s, 2H), 2.65 (t, J = 7.8 Hz, 2H), 1.64–1.56 (m, 2H), 1.34–1.25 (m, 6H), 0.83 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 134.9, 128.8 (2C), 128.3, 127.7 (2C), 120.4, 53.6, 31.3, 29.1, 28.7, 25.5, 22.3, 13.8; IR (neat, cm^{-1}) ν_{max} 3112, 3065, 2957, 2919, 2853, 1553, 1493, 1456, 1433, 1325, 1212, 1130, 1051, 1029, 856, 703, 691; HRMS (FAB): calcd for $C_{15}H_{22}N_3$ $[M + H]^+$ 244.1814, found 244.1816.

1-Benzyl-4-cyclohexyl-1*H*-1,2,3-triazole (4o)

White solid (120.4 mg, 100%); m.p. 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 3H), 7.24–7.22 (m, 2H), 7.12 (s, 1H), 5.46 (s, 2H), 2.72–2.71 (m, 1H), 2.01–1.99 (m, 2H), 1.77–1.66 (m, 3H), 1.37–1.29 (m, 4H), 1.22–1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 134.9, 128.8 (2C), 128.3, 127.8 (2C), 119.1, 53.7, 35.1, 32.8 (2C), 25.9 (2C), 25.8; IR (neat, cm^{-1}) ν_{max} 3121, 2925, 2851, 1540, 1495, 1450, 1264, 1208, 1128, 1049, 821, 754, 721, 699; HRMS (FAB): calcd for $C_{15}H_{20}N_3$ $[M + H]^+$ 242.1657, found 242.1660.

1-Benzyl-1*H*-1,2,3-triazole-4-carboxylic acid (4p)

White solid (92.1 mg, 91%); m.p. 184–185 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.92 (brs, 1H, CO_2H) 8.75 (s, 1H), 7.40–7.33 (m, 5H), 5.64 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 161.6, 140.1, 135.6, 128.9, 128.8 (2C), 128.2, 128.0 (2C), 53.0; IR (neat, cm^{-1}) ν_{max} 3115, 2556, 1681, 1540, 1495, 1425, 1232, 1049, 944, 895, 783, 714, 687; HRMS (FAB): calcd for $C_{10}H_{10}N_3O_2$ $[M + H]^+$ 204.0773, found 204.0767.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methanamine (4q)

White solid (91.2 mg, 97%); m.p. 106–109 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.92 (s, 1H), 7.39–7.30 (m, 5H), 5.56 (s, 2H), 3.75 (s, 2H), 2.31 (brs, 2H, NH_2); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 150.1, 136.2, 128.7 (2C), 128.0, 127.9 (2C), 121.8, 52.7, 37.2; IR (neat, cm^{-1}) ν_{max} 3345, 3137, 2917, 1604, 1494, 1454, 1328, 1212, 1124, 1050, 898, 802, 726, 693, 668; HRMS (FAB): calcd for $C_{10}H_{13}N_4$ $[M + H]^+$ 189.1140, found 189.1135.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1-amine (4r)

White solid (92.0 mg, 98%); m.p. 75–77 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.54 (s, 1H), 7.84 (d, J = 7.3 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 4.36 (t, J = 6.2 Hz, 2H), 3.02 (m, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 146.1, 130.9, 128.8 (2C),

127.7, 125.1 (2C), 121.6, 52.7, 41.7; IR (neat, cm^{-1}) ν_{max} 3338, 3125, 2952, 1461, 1217, 1075, 1039, 828, 760, 693; HRMS (FAB): calcd for $C_{10}H_{13}N_4$ $[M + H]^+$ 189.1140, found 189.1135.

6-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)hexan-1-amine (4s)

White solid (113.7 mg, 93%); m.p. 68–71 °C; ^1H NMR (400 MHz, C_5D_5N) δ 8.41 (s, 1H), 8.17 (d, $J = 7.4$ Hz, 2H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.33 (t, $J = 7.4$ Hz, 1H), 4.36 (t, $J = 7.1$ Hz, 2H), 2.65 (t, $J = 6.8$ Hz, 2H), 1.85–1.78 (m, 2H), 1.37–1.21 (m, 6H); ^{13}C NMR (100 MHz, C_5D_5N) δ 147.7, 132.0, 129.3 (2C), 128.2, 126.0 (2C), 121.0, 50.2, 42.1, 33.3, 30.4, 26.4 (2C); IR (neat, cm^{-1}) ν_{max} 3286, 3118, 3008, 2924, 2849, 1578, 1483, 1462, 1215, 1077, 838, 758, 692; HRMS (FAB): calcd for $C_{14}H_{21}N_4$ $[M + H]^+$ 245.1766, found 245.1768.

***N*-Methyl-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)hexan-1-amine (4t)**

White solid (124.1 mg, 96%); m.p. 58–60 °C; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.57 (s, 1H), 7.84 (d, $J = 7.5$ Hz, 2H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.32 (t, $J = 7.2$ Hz, 1H), 4.38 (t, $J = 7.0$ Hz, 2H), 2.39–2.38 (m, 2H), 2.23 (s, 3H), 1.89–1.82 (m, 2H), 1.38–1.26 (m, 6H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 146.2, 130.9, 128.8 (2C), 127.7, 125.0 (2C), 121.1, 51.4, 49.4, 36.1, 29.6, 29.0, 26.2, 25.8; IR (neat, cm^{-1}) ν_{max} 3297, 3118, 3091, 2925, 2850, 2787, 1462, 1439, 1357, 1215, 1077, 1051, 838, 759, 692; HRMS (FAB): calcd for $C_{15}H_{23}N_4$ $[M + H]^+$ 259.1923, found 259.1917.

Azide 7

Prepared according to the previously described procedure in which a glycosylation donor was changed to a galactosyl derivative.[30] TMSI (858 μL, 6.03 mmol) was added to a solution of 1,2,3,4,6-penta-*O*-trimethylsilyl-α-D-galactose[31] (3.26 g, 6.03 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The reaction mixture was stirred under N_2 atmosphere for 15 min before benzene (60 mL) was added. The solvent was removed under reduced pressure and the glycosyl iodide intermediate obtained was dissolved in CH_2Cl_2 (60 mL) and kept under N_2 atmosphere. In a separate flask, a mixture of activated 4 Å molecular sieves (1.50 g), *n*-Bu_4NI (4.47 g, 12.1 mmol), *i*-Pr_2NEt (1.58 mL, 9.05 mmol) and (2*S*,3*S*,4*R*)-2-azido-3,4-*O*-isopropylidene-1,3,4-octadecanetriol[32] (770 mg, 2.01 mmol) in CH_2Cl_2 (60 mL) was prepared and stirred under an argon atmosphere at rt for 15 min. The solution of glycosyl iodide in CH_2Cl_2 was then added drop-wise over 5 min and the resulting mixture was stirred overnight. After removal of the solvent under reduced pressure, Et_2O (60 mL) and H_2O (60 mL) were added and the phases were separated. The organic phase was concentrated under reduced pressure. MeOH (60 mL) and PTSA·H_2O (39.9 mg, 0.21 mmol) were added to the crude mixture and stirred at rt for 5 h. The reaction was quenched by the addition of $NaHCO_3$ (300 mg, 3.57 mmol), filtered, and then concentrated under reduced pressure. The crude mixture was purified by flash column chromatography ($CHCl_3$–MeOH, 6 : 1) to afford azide 7 (650 mg, 64%, α-anomer only) as a white solid. m.p. 195 °C (dec.); $[\alpha]_D^{25}$ +103.9 (*c* 0.3, $CHCl_3$–MeOH, 1 : 1); ^1H NMR (400 MHz, $CDCl_3$–CD_3OD, 2 : 1) δ 4.69 (d, $J = 3.5$ Hz, 1H), 3.90 (dd, $J = 10.8$ Hz, 3.2 Hz, 1H), 3.75–3.46 (m, 8H), 3.40–3.36 (m, 2H), 1.42–1.33 (m, 2H), 1.21–1.04 (m, 25H), 0.65 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD, 2 : 1) δ 99.2, 73.5, 71.6, 70.5, 69.8, 69.5, 68.4, 67.3, 61.4, 61.3, 31.8, 31.5, 29.33, 29.26, 29.21, 28.9, 25.4, 22.2, 13.5; IR (neat, cm^{-1}) ν_{max} 3325, 2917, 2851, 2100, 1569, 1469, 1262, 1137, 1065, 1023, 696, 763, 717; HRMS (FAB): calcd for $C_{24}H_{48}N_3O_8$ $[M + H]^+$ 506.3441, found 506.3438.

α-GalCer analog 5

In a vial fitted with a screw cap, freshly prepared stock solutions of $CuSO_4 \cdot 5H_2O$ (30 μL, 50 mM stock solution in DDW, 1.5 mol%), TTTA (**1a**, 10 μL, 50 mM stock solution in CH_2Cl_2, 0.5 mol%), and sodium ascorbate (30 μL, 150 mM stock solution in DDW, 4.5 mol%) were added to a mixture of 7 (50.5 mg, 0.1 mmol) and **6** (40 mg, 0.11 mmol) in DDW (0.44 mL) and CH_2Cl_2 (0.49 mL). The reaction was allowed to proceed at rt for 2 h. The crude reaction mixture was filtered and rinsed with Et_2O (10 mL) and DDW (10 mL). The resulting solid was dried *in vacuo* to afford **5** (78.6 mg, 92%) as a white solid. m.p. 166–168 °C; $[\alpha]_D^{25}$ +45.9 (*c* 0.3, pyridine); ^1H NMR (400 MHz, C_5D_5N) δ 8.28 (s, 1H), 7.07 (d, $J = 6.6$ Hz, 1H, NH), 6.70 (m, 1H, OH), 6.56 (m, 1H, OH), 6.51 (m, 1H, OH), 6.43 (d, $J = 6.3$ Hz, 1H, OH), 6.32 (m, 1H, OH), 5.97 (m, 1H, OH), 4.97 (dd, $J = 11.5$, 4.2 Hz, 1H), 4.69 (dd, $J = 11.3$, 6.8 Hz, 1H), 4.61 (m, 1H), 4.51–4.34 (m, 6H), 4.14 (m, 1H), 2.77 (t, $J = 7.7$ Hz, 2H), 2.16 (m, 1H), 1.81–1.58 (m, 6H), 1.31–1.25 (m, 63H), 0.86 (t, $J = 6.9$ Hz, 6H); ^{13}C NMR (100 MHz, C_5D_5N) δ 147.8, 122.1, 101.7, 76.7, 73.2, 72.2, 71.5, 71.0, 70.2, 67.4, 62.8, 62.7, 34.3, 32.1, 30.2, 30.00, 29.96, 29.89, 29.73, 29.62, 29.58, 26.3, 26.2, 22.9, 14.2; IR (neat, cm^{-1}) ν_{max} 3360, 2916, 2848, 1729, 1464, 1149, 1069, 1029, 794, 719; HRMS (FAB): calcd for $C_{50}H_{98}N_3O_8$ $[M + H]^+$ 868.7354, found 868.7348.

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