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Synthesis of Calix[4]arene Appended Lactosylated G_1 and Galactosylated G_2 Generation Glycodendrimers using a 'CuAAC' Click Approach

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This manuscript is dedicated to (Late) Prof. Alan R. Katritzky for his contributions to benzotriazole chemistry.

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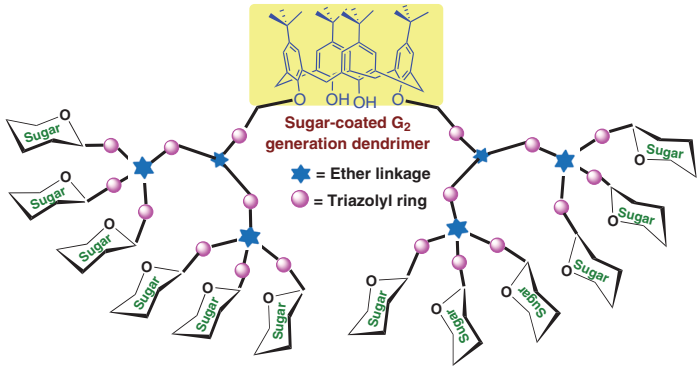

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Abstract A modular and highly reliable click approach is applied for the expeditious synthesis of lactose- and galactose-coated calixarene-cored G_1 and G_2 generation glycodendrimers, respectively. The developed calixarene glycodendrimers have been characterized by using extensive spectral analysis including NMR (^{1}H and ^{13}C), MS, IR, and SEC data.

Key words azide, alkyne, click reaction, calix[4]arene, macrocyclic, glycodendrimer, catalysis

Introduction

Calixarenes, a class of macrocyclic compounds, have unique three-dimensional architecture that is amenable to functional group transformation at both upper and lower rims. They serve as promising building blocks for a wide range of applications in organic synthesis.[1,2] In general, calixarenes have an array of notable applications as supramolecular scaffolds for molecular recognition, sensing, self-assembly, catalysis, as well as in drug discovery and development.[3,4] They exhibit features similar to those of cyclodextrin with respect to their host-guest behaviour. However, calixarene-based analogues are more diverse and adjustable than cyclodextrin. Catalysis and reactivity are the two important factors that influence the functional behaviour of host-guest chemistry.[5] These complexes are extremely valuable candidates for the effective detection and removal of heavy metal ions as well as for remediating nuclear waste from the environment.[6] A recent theoretical study has revealed the strong affinity of calixarene-derivatives towards Ni as compared to Cd and Cr metal.[7] Typically, the host chemistry of calixarene produces stable complexes with biomolecules that have extensive applications in supramolecular chemistry.[8] In addition, biomimetic compounds derived from calixarene are exceptionally useful in biotechnology,[9] such as biosensor and chemosensor technologies,[10] gene transport,[11] and platonic micelles.[12] In addition to biomimetics, such compounds have been well explored in the fields of catalysis[13] and chiral molecular recognition.[14] Dondoni and Marra demonstrated the synthesis of multiple triazolyl glycoconjugates anchored to calix[4]arene scaffolds *via* a modular click approach and explored their use in potential molecular recognition processes.[2] Microwave-assisted CuAAC coupled with a variety of claix[4]arene glycoconjugates having diverse conformations are found to bond effectively to lectins.[15] Several reports on the synthesis of various glycodendrimers using this orthogonal azide-alkyne coupling reaction have been published in recent years.[16] The most powerful and widely used tool for the regioselective synthesis of 1,4-disubstituted triazoles is the Cu(I)-catalyzed azide-alkyne coupling 'click reaction'.[17] The bio-isostere of the amide functional group is triazole, which can be generated *via* azide-alkyne coupling. The resulting triazole component has been widely studied as a useful pharmacophore in medicinal chemistry as well as being a suitable binding site for various metal ions in mo-

lecular sensing.[18] In addition to sensing, it has a diverse and growing impact on the development of efficient catalysts.[19,20] However, most biological recognition and propagation transduction processes associated with them are dependent on multivalent glycan–protein interactions, including surface sensing and adhesion by bacteria and viruses, drug effect or mechanisms, cellular interactions, cell cycle regulation and diversity, cancer cell aggregation, and metastatic spread.[21,22] Because of their ability to organise their size and sugar units at the periphery, glycodendrimers have received a lot of attention in the field of multivalent glycocluster architectures.[23] The flexibility of these macrocycles towards functionalization at the lower rim allows for the selective coordination of a wide range of metal ions. The group of Marradi reported an effective binding of alkali metal (Na^+ and K^+) at the lower calixarene rim that provides rigidity to the dendrimer structure, resulting in convergence of iminosugar in the cluster.[24] The resultant chiral dendrimerric cluster could be a promising candidate for enantioselective catalysis. However, the stability of complexes were highly influenced by the nature of solvent media and thus, in another similar study, the highest affinity of such receptors was further confirmed towards Na^+ through physicochemical parameters.[25] Several glyco-molecular architectures of similar shape have been shown to play an important role in a number of biological as well photophysical processes.[26–28]

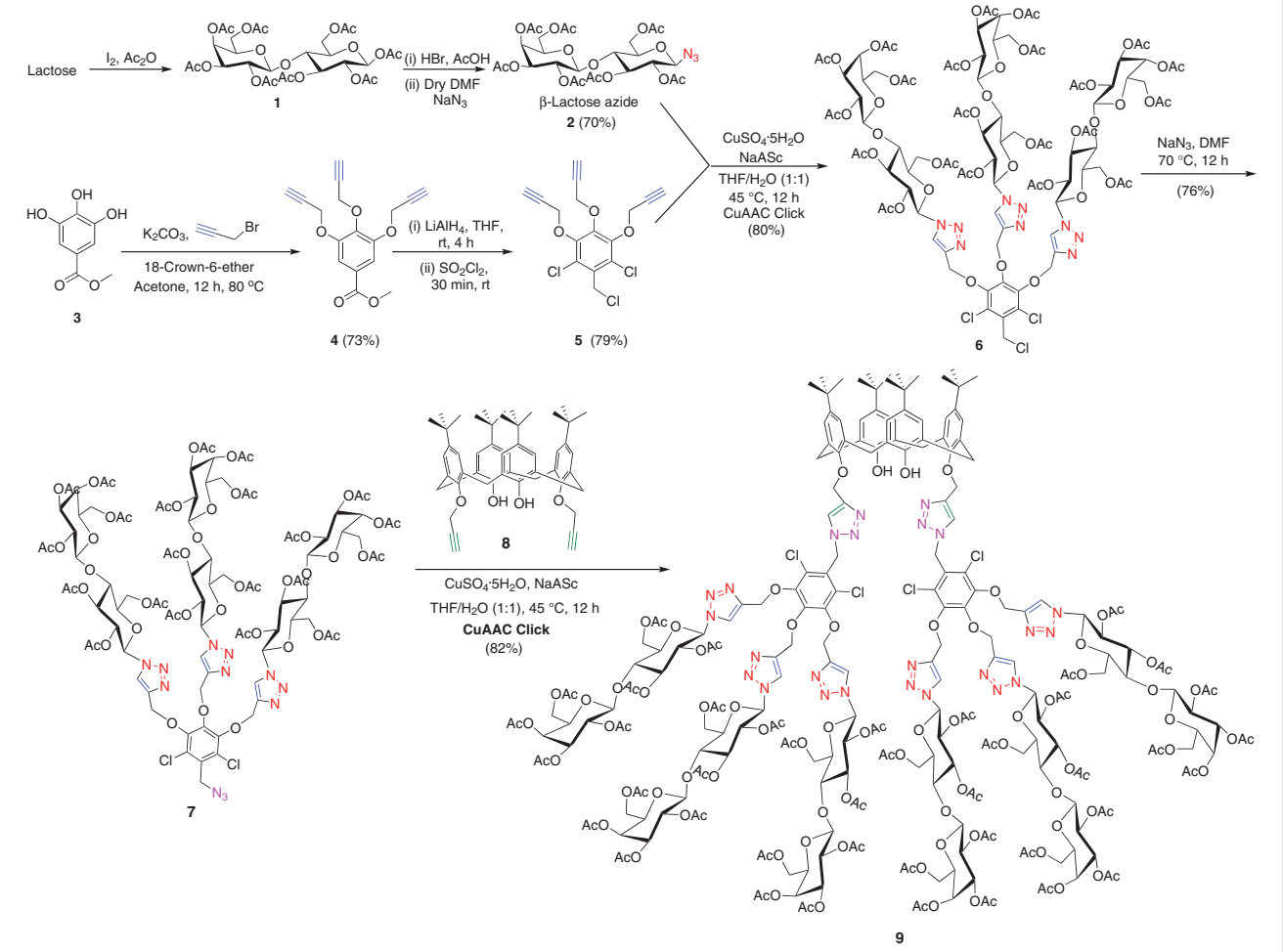
In a continuation of our work on glycodendrimers synthesis,[29] herein, we wish to report a click-mediated highly expedient synthesis of calix[4]arene-cored lactosylated G_1 and galactosylated G_2 generation glycodendrimers. The developed galactosylated dendritic architectures and dendrimers have been well characterised by extensive spectroscopic analysis including NMR (^1H and ^{13}C), IR, MS data and SEC analyses.

Results and Discussion

Our synthesis commenced with the synthesis of sugar-based azides for example, β-D-lactose azide (**2**) which was obtained from the respective sugar in two high-yielding steps under a standard protocol (Scheme 1).[16a] The first step involved the reaction of D-lactose with acetic anhydride in the presence of iodine to afford the acetylated lactose **1**. Subsequently, the resulting acetylated lactose **1** was treated with 33% HBr in acetic acid in anhydrous DCM and the bromo sugar thus obtained was then subjected to azidation reaction with NaN_3 in anhydrous DMF to furnish the desired lactose azide **2** in overall 70% yield. Alternatively, synthesis of targeted counterpart alkyne analogue, i.e., 1,3-dichloro-2-(chloromethyl)-4,5,6-tris(prop-2-yn-1-yloxy) (**5**), was achieved from gallic acid derived methyl 3,4,5-trihydroxybenzoate (**3**). Esterification of the carboxylic functionality of commercially available gallic acid in methanol under acidic medium afforded the desired compound **3**, which was submitted to propargylation using propargyl bromide with the assistance of K_2CO_3 and 18-crown-6 as co-catalyst to furnish 3,4,5-tris(prop-2-yn-1-yloxy)benzoate (**4**) in 73% yield. The desired alkynated compound **5** was obtained by reduction of **4** using lithium aluminium hydride (hydride ion transfer based reducing agent) in anhydrous THF at room temperature for 4 h followed by chlorination of the resulting alcohol using sulfuryl chloride (SO_2Cl_2) under neat conditions at room temperature for 30 minutes, in overall 79% yield. In a continuation, we move towards the synthesis of dendritic architecture **6** in 80% yield, by performing the CuAAC click reaction of β-lactose azide **2** with alkynyl compound **5** using a modular click protocol. Furthermore, we performed the azidation of dendritic architecture **6** in the presence of NaN_3 in anhydrous DMF at 70 °C, which afforded the glycosyl triazole based dendron **7** in 76% yield. In order to gain the target lactose-coated glycodendrimer **9**, we accomplished the click conjugation reaction of calix[4]arene-cored **8** with azido dendron **7** using $CuSO_4{\cdot}5H_2O$/NaASc in THF/water (1:1) at 45 °C for 12 h to furnish the G_1 generation lactose coated glycodendrimer **9** in 82% yield (Scheme 1). The synthesized G_1-generation glycodendrimer **9** was well characterized by extensive spectroscopic analysis such as NMR (^1H, ^{13}C NMR), IR, MS data, and size-exclusion chromatography (SEC) analysis.

Synthesis of Calix[4]arene Cored G_2 Generation Glycodendrimer 16

Synthesis of glycodendrimer **16** began with 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl azide **10**, which was derived from of D-galactose by sequential high-yielding steps involving acetylation and bromination followed by azidation in the presence of NaN_3 in anhydrous DMF for 6 h (Scheme 2). The reaction of galactose azide **10** with 1,3-dichloro-2-(chloromethyl)-4,5,6-tris(prop-2-yn-1-yloxy)benzene **5** was performed in the presence of $CuSO_4{\cdot}5H_2O$/NaASc in THF/water (1:1) at 45 °C for 12 h to give the desired glycodendron **11** in 80% yield. Azidation of the resulting triazole-appended dendron architecture **11** with NaN_3 in anhydrous DMF afforded the azido dendron **12** in 77% yield. In successive step towards the synthesis of the desired glycodendrimer **16**, 1-(bromomethyl)-3,5-bis(prop-2-yn-1-yloxy)benzene **13** underwent regioselective click conjugation with azido dendron **12** to afford the triazole-appended bromo analogue **14** in 85% yield. The latter compound was then subjected to azidation by reaction with sodium azide in anhydrous DMF, leading to the formation of azide functionalized G_2 generation dendron architecture **15** in 86% yield. In the final step, the G_2 generation glycodendrimer **16** was achieved in 79% yield *via* regioselective tri-



Scheme 1 Synthesis of calix[4]arene appended lactosylated G_1 generation glycodendrimers **9**. Yields reported after flash column chromatography (SiO_2).

azole forming reaction of azido dendron **15** with bis-propargyloxy-*p*-*tert*-butyl-calix[4]arene **8** in the presence of the optimized standard catalytic system [$CuSO_4{\cdot}5H_2O$/NaASc in THF/water (1:1) at 45 °C]. The dendrimer was purified by flash column chromatography (SiO_2). Characterization of the developed glycodendrimer **16** was supported by the disappearance of vibrational peaks of alkyne and azide in the IR spectra. The developed G_2 generation glycodendrimer **16** was well characterized by using extensive spectral analyses including NMR (^1H, ^{13}C) data. Size-exclusion chromatogram (SEC) of the synthesized glycodendrimer **9** and **16** is depicted in Figure 1. SEC of glycodendrimers **9** and **16** showed polydispersity (PDI) 1.08 (elution time 10.58 min) and 1.07 (elution time 10.46 min), respectively.

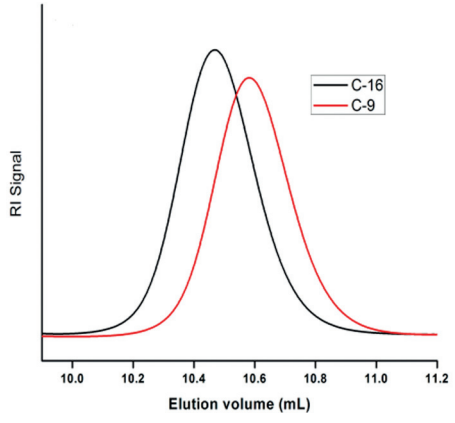
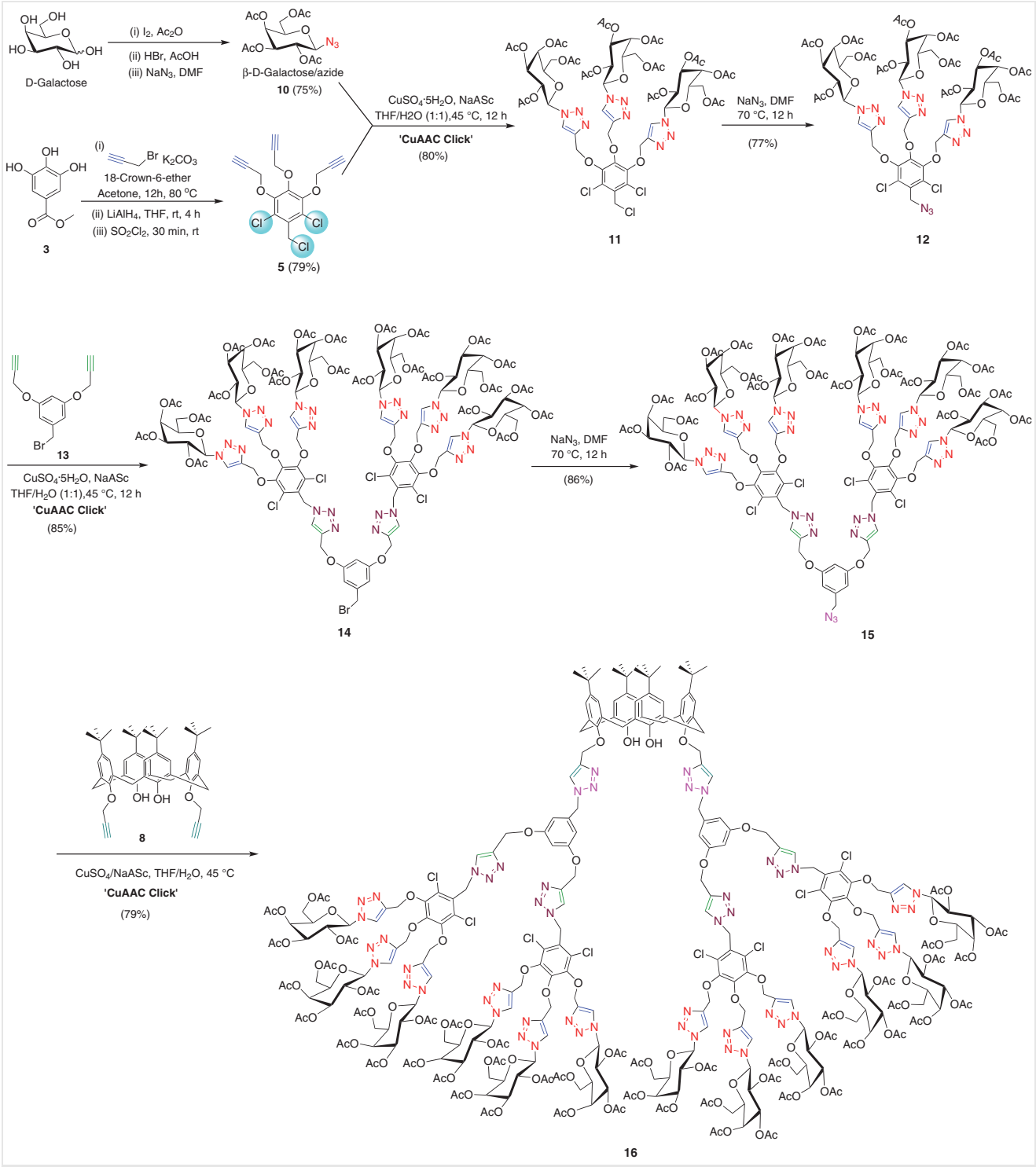


Figure 1 Size-exclusion chromatogram (SEC) diagrams of the synthesized glycodendrimers **9** and **16**



Scheme 2 Synthesis of calix[4]arene appended galactosylated G_2 generation glycodendrimer **16**. Yields reported after flash column chromatography (SiO_2).

Conclusions

In this report, we have explored regioselective Cu-catalyzed alkyne-azide cycloaddition reaction and developed calix[4]arene-appended glycodendrimers having lactose and galactose in G_1 and G_2 generation, respectively. The developed G_1 and G_2 generation glycodendrimers, which assembled well with a biocompatible triazolyl-glycosyl moiety at the periphery and macrocyclic calix[4]arene at the core, was characterized by standard spectroscopic analyses. The further applications of calix[4]arene-appended glycodendrimers in sensing and studies on the bioactivities and chemotherapeutic potential of the compounds are ongoing in our laboratory.

General Consideration

Pure analytical grade solvents and reagents were used in all reactions. 60 F-254 silica gel pre-coated on aluminium plates was used for thin-layer chromatography (TLC); a UV lamp (λ_{max} = 254 nm) or 5% H_2SO_4/CH_3OH solution (charring solution) was used to identify the sugar molecules. Alkynes were detected after heating the sample in an alkaline $KMnO_4$ solution. All the synthesized compounds were purified by using flash column chromatography (200–400 mesh silica gel). ^1H and ^{13}C NMR spectra of the compound were recorded, respectively, at 500 MHz and 125 MHz with a JEOL Delta spectrometer. Deuterated solvents were used for all NMR studies. Resonance multiplicities in the ^1H NMR spectra are described as: s (singlet), d (doublet), dd (double doublet), t (triplet), and m (multiplet), residual protic solvent of $CDCl_3$ is described as s (singlet) (^1H NMR, 7.26 ppm; ^{13}C NMR, 77.0 ppm). The IR spectra were recorded as Nujol mulls in a KBr pellet. Mass spectra were recorded with a SCIEX X500r Q-TOF, high-resolution mass spectrometer (HRMS).

Cu(I)-Catalyzed Azide-Alkyne Cycloaddition Reaction; General Procedure

$CuSO_4{\cdot}5H_2O$ (0.3 equiv per alkyne), sodium ascorbate (0.3 equiv per alkyne), and alkyne-possessing analogues and azides were agitated in a THF/water (1:1) solution at 45 °C for 12 h. The reaction was monitored with TLC and, after its completion, the reaction mixture was run through Celite and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (20 mL), saturated (aq. NH_4Cl 20–40 mL) and brine solution (5 mL). Under reduced pressure, the reaction mixture was concentrated to obtain a crude mass, which was purified by using column chromatography (SiO_2) to result in good yields of the desired triazoles in pure form.

Physical Data for the Developed Dendrons and Glycodendrimers

β-D-Lactosylated Azide 2

Per-*O*-acetylated-D-lactose **1** was prepared by dissolving D-lactose (5.0 g, 14.6 mmol) in ice-cold acetic anhydride (20 mL) followed by the addition of molecular iodine. The reaction mixture was stirred at room temperature for 6 h to obtain the desired product **1**. Per-*O*-acetylated-D-lactose (7.8 g, 11.4 mmol) was dissolved in anhydrous dichloromethane and HBr in 33% acetic acid (12 mL) was added gradually at 0 °C. The reaction mixture was stirred for 6 h at 0–5 °C. After completion of the reaction (as monitored by TLC), the desired product was diluted with dichloromethane (100 mL), extracted into the organic layer, and washed with $NaHCO_3$ solution (2 × 50 mL). The per-*O*-acetylated galactose bromide was obtained (6.1 g, 8.7 mmol) in pure form. The per-*O*-acetylated lactose bromide was dissolved in anhydrous dimethylformamide followed by addition of NaN_3 and the reaction mixture was stirred for 6 h at 80 °C. After completion the reaction (monitored by TLC), the mixture was worked up in ice-cold water and extracted in EtOAc. The organic layer was evaporated under reduced pressure, and the resulting product was purified using column chromatography (silica gel, 100–200 mesh) to afford lactose azide **2** as a yellow liquid.

Yield (4.06 g, 70%); R_f = 0.4 (EtOAc/*n*-hexane, 60%).

^1H NMR (500 MHz, $CDCl_3$): δ = 5.34 (d, *J* = 4.0 Hz, 1 H), 5.20 (t, *J* = 9.5 Hz, 1 H), 5.11–5.08 (m, 1 H), 4.96–4.93 (m, 1 H), 4.85 (t, *J* = 9.5 Hz, 1 H), 4.62 (d, *J* = 9.0 Hz, 1 H), 4.51–4.46 (m, 2 H), 4.13–4.09 (m, 3 H), 3.88–3.79 (m, 2 H), 3.71–3.68 (m, 1 H), 2.14 (d, *J* = 7.0 Hz, 6 H), 2.06–2.03 (m, 12 H), 1.96 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 170.2, 170.09, 170.03, 169.6, 169.4, 169.0, 101.0, 87.6, 75.7, 74.7, 72.5, 70.96, 70.91, 70.74, 69.0, 66.5, 61.7, 60.7, 60.3, 21.0, 20.78, 20.71, 20.6 and 20.4.

IR (KBr): 3479.64, 2942.76, 2121.03 and 1766.31 cm^{-1}.

Methyl 3,4,5-Tris(hydroxy)benzoate 3[16]

3,4,5-Tris(hydroxy)benzoic acid (6.0 g, 35.28 mmol) was dissolved in anhydrous methanol (60 mL), and a catalytic amount of concentrated H_2SO_4 (1.2 mL) was added dropwise under cooling. After complete addition of H_2SO_4, the reaction mixture was continuously stirred for 4 h. TLC was used to monitor the progress of the reaction. The resulting mixture was evaporated under reduced pressure and the resulting crude mass was worked up with EtOAc, washed with $NaHCO_3$ solution, and the organic layer was evaporated under reduced pressure. The crude mass was purified using column chromatography (silica gel, 100–200 mesh) to afford compound **3**.

Yield: 5.71 g (88%); white solid; R_f = 0.4 (EtOAc/*n*-hexane, 40%).

Methyl 3,4,5-Tris(prop-2-yn-1-yloxy)benzoate 4[16]

Compound methyl 3,4,5-tris(hydroxy)benzoate (2.8 g, 15.2 mmol) was dissolved in dried acetone (25 mL) in the presence of the co-catalyst 18-crown-6 (125 µL), followed by addition of K_2CO_3 (16.8 g, 121.6 mmol, 8 equiv) and propargyl bromide (9.2 mL, 121.6 mmol, 8 equiv) under argon. After complete addition, the reaction mixture was heated at reflux for 12 h. TLC indicated that the reaction was completed. The reaction mixture was extracted by using EtOAc and evaporated under reduced pressure The crude mass was purified using column chromatography (silica gel, 100–200 mesh) to afford compound **4** in pure form.

Yield: 3.3 g (73%); white solid; R_f = 0.5 (EtOAc/*n*-hexane, 15%).

1,3-Dichloro-2-(chloromethyl)-4,5,6-tris(prop-2-yn-1-yloxy)benzene 5[16]

Methyl 3,4,5-tris(prop-2-yn-1-yloxy)benzoate **4** (3.0 g, 10.05 mmol) was dissolved in anhydrous THF (30 mL), and $LiAlH_4$ (0.45 g, 11.8 mmol 1.2 equiv) was added at 0 °C under an inert atmosphere. The reaction was then stirred for 6–8 h. After the completion of reaction (monitored by TLC), the reaction was quenched with 5% aq. sodium hydroxide. The mixture was then filtered, extracted with EtOAc (2 × 50 mL), and washed with brine solution (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude mass was subjected to column chromatography to obtain the desired (3,4,5-tris(prop-2-yn-1-yloxy)phenyl)methanol in 84% yield.

The resulting alcohol (1.0 g, 12.70 mmol) was taken in a round-bottom flask followed by addition of sulfuryl chloride (SO_2Cl_2) in ice-cold condition and stirred for 30 min at room temperature. When the reaction completed (monitored by TLC), aq. NaOH was added at 0 °C to neutralize the reaction mixture. The mixture was extracted with EtOAc (2 × 50 mL), dried over anhydrous Na_2SO_4, and the organic layer was evaporation under reduced pressure to yield the crude mass, which was then purified using column chromatography to furnish the desired product **5** (1.04 g, 79%) as a white solid; R_f = 0.45 (EtOAc/hexane, 15%). The structural data of compound **5** were in close agreement with reported data.[16a]

Synthesis of the First Generation Lactosylated Dendritic Architecture 6

1,3-Dichloro-2-(chloromethyl)-4,5,6-tris(prop-2-yn-1yloxy)benzene (250 mg, 0.699 mmol) was added to β-D-lactopyranosyl azide **2** (3.35 g, 2.80 mmol, 4.0 equiv) in the presence of $CuSO_4{\cdot}5H_2O$ (513 mg, 2.09 mmol, 3.0 equiv), and sodium ascorbate (415 mg, 2.09 mmol, 3.0 equiv) in THF/water (1:1) solvent at 45 °C for 12 h (the reaction was monitored by TLC). After completion of reaction, the mixture was filtered with Celite by using sintered crucible. After workup with EtOAc, the organic layer was evaporated under reduced pressure to obtain the crude mass, which was subjected to column chromatography (SiO_2) to furnish the desired compound **6**.

Yield: 1.3 g (80%); white solid; R_f = 0.45 (EtOAc/*n*-hexane, 70%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 8.05 (s, 2 H), 5.89–5.86 (m, 3 H), 5.55–5.48 (m, 3 H), 5.44–5.39 (m, 3 H), 5.36 (d, *J* = 2.5 Hz, 3 H), 5.23 (s, 2 H), 5.20 (s, 4 H), 5.14–5.10 (m, 3 H), 5.01–4.97 (m, 3 H), 4.81 (s, 2 H), 4.60–4.56 (m, 3 H), 4.59 (d, *J* = 12.0 Hz, 3 H), 4.20–4.13 (m, 6 H), 4.10–3.92 (m, 12 H), 2.15 (s, 9 H), 2.07–2.05 (m, 45 H), 1.96 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5, 170.47, 170.41, 170.3, 170.2, 170.09, 170.04, 169.5, 169.1, 169.0, 147.8, 147.1, 143.7, 143.6, 130.0, 126.0, 123.7, 123.0, 101.0, 85.4, 75.8, 75.5, 72.66, 72.61, 70.8, 70.7, 70.6, 70.49, 70.42, 69.1, 69.0, 66.7, 66.5, 66.3, 61.9, 61.7, 60.7, 41.1, 20.7, 20.6, 20.5, 20.4, 20.19, 20.15.

Synthesis of Azide Functionalized Lactosylated Dendritic Architecture 7

Galactosylated dendritic architecture **6** (400 mg, 0.170 mmol) was dissolved in anhydrous DMF (3 mL) followed by the addition of NaN_3 (22.1 mg, 0.341 mmol, 2.0 equiv) in an inert atmosphere, and mixture was stirred at 70 °C for 12 h. After the completion of the reaction (monitored by TLC), the mixture was extracted with EtOAc in ice-cold water. The organic layer was dried under reduced pressure and obtained crude mass was subjected to column chromatography to give **7**.

Yield: 305 mg (76%); white solid; R_f = 0.45 (EtOAc/*n*-hexane, 70%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 8.03 (s, 2 H), 5.86 (d, *J* = 9.0 Hz, 3 H), 5.52–5.47 (m, 3 H), 5.42–5.38 (m, 3 H), 5.34 (s, 3 H), 5.22 (s, 2 H), 5.19 (s, 4 H), 5.12–5.08 (m, 3 H), 4.98–4.96 (m, 3 H), 4.59 (s, 2 H), 4.57–4.54 (m, 3 H), 4.48 (d, *J* = 12.0 Hz, 3 H), 4.18–3.91 (m, 18 H), 2.13 (s, 9 H), 2.03–2.00 (m, 45 H), 1.94 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4, 170.3, 170.28, 170.20, 170.0, 169.9, 169.5, 169.0, 168.5, 147.6, 147.0, 143.5, 142.8, 140.6, 128.0, 126.2, 123.7, 123.0, 100.9, 85.3, 75.7, 75.5, 70.8, 70.6, 68.9, 66.5, 61.8, 61.7, 60.6, 49.4, 20.66, 20.62, 20.5, 20.4, 20.1, 20.0.

IR (KBr): 3473.06, 3147.26, 2925.07, 2853.96, 2104.92, 1755.05 cm^{-1}.

Bispropargyloxy-*p*-*tert*-butylcalix[4]arene 8[4]

Synthesis of bispropargyloxy-*p*-*tert*-butylcalix[4]arene was carried out by dissolving *tert*-butyl calix[4]arene (1.7 g, 2.3 mmol) in anhydrous acetone(10 mL), followed by addition of base (K_2CO_3, 0.79 g, 5.75 mmol, 2.5 equiv) and propargyl bromide (0.43 mL, 5.75 mmol, 2.5 equiv) to the reaction mixture, which was then stirred overnight. The progress of reaction was monitored by TLC and, upon completion, the mixture was evaporated under reduced pressure. The obtained crude mass was subjected to column chromatography to give the final compound **8** (1.04 g, 55%) as a white solid.

Synthesis of Lactose-Coated Calix[4]arene Cored G_1 Generation Glycodendrimer 9

Synthesis of galactose coated G_1 generation glycodendrimer **9** was achieved by the reaction of synthesized lactose-coated dendron **7** (202 mg, 0.085 mmol, 2.5 equiv) with core unit **8** (25 mg, 0.034 mmol, 1.0 equiv) in the presence of $CuSO_4{\cdot}5H_2O$ (16.6 mg, 0.068 mmol, 2.0 equiv) and sodium ascorbate (13.4 mg, 0.067 mmol, 2.0 equiv) in THF/water (1:1) as a solvent for 12 h at room temperature. After the completion of the reaction (monitored by TLC), the mixture was filtered with a sintered funnel, washed with water (10 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure and the obtained crude mass was subjected to column chromatography to give the desired compound **9** in pure form. The lactose-coated glycodendrimer was characterised by NMR (^{1}H, ^{13}C), IR, MS and SEC analysis.

Yield: 382 mg (82%); light-yellow solid; R_f = 0.50 (MeOH/CH_2Cl_2, 4%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (s, 2 H), 8.34 (s, 4 H), 8.18 (s, 2 H), 6.85 (s, 2 H), 6.75 (s, 2 H), 6.68 (s, 2 H), 6.64 (s, 2 H), 6.56 (s, 2 H), 6.00–5.95 (m, 6 H), 5.77–5.73 (m, 3 H), 5.64 (t, *J* = 9.0 Hz, 3 H), 5.50–5.47 (m, 2 H), 5.42–5.39 (m, 4 H), 5.35 (s, 7 H), 5.30 (d, *J* = 10.5 Hz, 4 H), 5.17–5.10 (m, 6 H), 5.02–4.92 (m, 9 H), 4.87–4.79 (m, 4 H), 4.58–4.51 (m, 10 H), 4.34–4.29 (m, 4 H), 4.22–4.19 (m, 6 H), 4.12–4.07 (m, 25 H), 4.01–3.92 (m, 15 H), 3.15 (d, *J* = 13.5 Hz, 2 H), 2.97 (d, *J* = 12.0 Hz, 2 H), 2.15 (s, 18 H), 2.08–1.96 (m, 108 H), 1.24 (s, 18 H), 0.99 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 170.5, 170.2, 170.1, 170.0, 169.8, 169.5, 169.16, 169.10, 168.8, 150.0, 149.5, 148.8, 148.5, 147.1, 146.0, 143.9, 143.6, 141.4, 132.2, 131.7, 128.7, 127.6, 126.9, 126.7, 126.4, 125.7, 125.4, 125.2, 124.8, 124.6, 124.4, 123.9, 123.0, 119.0, 114.0, 100.9, 100.8, 85.7, 85.2, 76.4, 75.7, 75.6, 75.2, 72.8. 71.9, 71.0, 70.9, 70.8, 70.4, 70.2, 69.0, 68.9, 67.0, 66.7, 66.6, 66.3, 62.1, 61.8, 61.2, 60.4, 49.3, 33.7, 33.6, 33.4, 31.8, 31.3, 31.2, 30.6, 30.1, 20.7, 20.6, 20.4, 20.08, 20.00.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl Azide (10)[16a,27]

Per-*O*-acetylated-D-galactose 1 (4.0 g, 10.71 mmol) was dissolved in anhydrous dichloromethane and 33% HBr in acetic acid (20 mL) was gradually added at 0 °C. The reaction mixture was stirred for 4–6 h at 0–5 °C. After completion of the reaction (monitored by TLC), the mixture was diluted with DCM (100 mL) and washed with $NaHCO_3$ solution (2 × 50 mL). The per-*O*-acetylated galactose bromide was obtained by evaporating the separated organic layer under reduced pressure (3.8 g, 9.24 mmol). The per-*O*-acetylated galactose bromide was dissolved in anhydrous dimethylformamide followed by addition of NaN_3, and the reaction mixture was further stirred for 6 h at 80 °C. Upon completion of the reaction (monitored by the TLC), the reaction mixture was worked up in ice-cold water and EtOAc. The organic layer was evaporated under low pressure and the resulting product was purified using column chromatography (silica gel, 100–200 mesh) to afford 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl azide **2**.

Yield: 2.58 g (75%); white crystalline solid; R_f = 0.40 (EtOAc/*n*-hexane, 30%).

Synthesis of Galactosylated Dendritic Architecture 11[16a,27]

1,3-Dichloro-2-(chloromethyl)-4,5,6-tris(prop-2-yn-1 yloxy)benzene **5** (1.0 g, 2.79 mmol) was reacted with **β**-D-galactopyranosyl azide **2** (4.16 g, 11.14 mmol, 4.0 equiv) in the presence of $CuSO_4{\cdot}5H_2O$ (2.08 g, 8.37 mmol, 3.0 equiv), and sodium ascorbate (1.6 g, 8.37 mmol, 3 equiv) in THF/water (1:1) solvent system at 45 °C for 12 h. The reaction was monitor by TLC until the reaction was complete. The mixture was then filtered with Celite by using a sintered crucible. After workup of the mixture with EtOAc, the organic layer was evaporated under reduced pressure and the obtained crude mass was subjected to purification using flash column chromatography to afford the desired compound as a white solid. Yield (3.30 g, 80%); R_f = 0.4 (60% EtOAc/*n*-hexane). The physical data matched the reported data.[16a,27]

Synthesis of Azide Functionalized Galactosylated Dendritic Architecture 12[16a,27]

Galactosylated dendritic architecture **11** (3.0 g, 2.03 mmol) was dissolved in anhydrous DMF followed by addition of NaN_3 (264 mg, 4.06 mmol, 2.0 equiv) under an inert atmosphere, and mixture was stirred at 70 °C for 12 h. Upon completion of the reaction (monitored by TLC), the mixture was washed with ice-cold water and extracted with EtOAc (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The obtained crude mass was subjected to column chromatography to give **12** (2.3 g, 77%) as a white solid; R_f = 0.42 (EtOAc/*n*-hexane, 60%). The physical data matched closely with reported data.[16a,27]

Synthesis of 1-(Bromomethyl)-3,5-bis(prop-2-yn-1-yloxy)benzene Dendritic Architecture 13[16a,27]

Synthesis of 1-(bromomethyl)-3,5-bis(prop-2-yn-1-yloxy)benzene started from 3,5-dihydroxy benzoic acid, which was esterified in MeOH in the presence of a catalytic amount of conc. H_2SO_4 followed by propargylation, followed by reduction of the ester group to the alcohol to give the (3,5-bis(prop-2-yn-1-yloxy)phenyl)methanol. This compound was then dissolved in ice-cold anhydrous DCM followed by dropwise addition of PBr_3. The reaction mixture was stirred at room temperature overnight and progress of the reaction was monitored by TLC until its completion. The reaction was quenched with saturated solution of $NaHCO_3$ and the mixture was extracted with EtOAc. The obtained crude mass was subjected to column chromatography to give the desired compound **13** as a white solid. The spectral data of compound **13** was in close agreement with the reported standard.[16a,27]

Synthesis of Second-Generation Galactosylated Dendritic Architecture 14

The synthesized galactosylated dendritic architecture **12** (1.9 g, 1.23 mmol) was 'clicked' with the counterpart alkyne functionalized compound **13** (150 mg, 0.537 mmol) in the presence of $CuSO_4{\cdot}5H_2O$ (262.7 mg, 1.07 mmol, 3.0 equiv) and sodium ascorbate (212.7 mg, 1.07 mmol, 2.0 equiv) in THF/water (1:1) solvent system at 45 °C for 12 h. The reaction was monitored by TLC (EtOAc/*n*-hexane, 90%). The mixture was filtered with Celite, the organic layer was evaporated under reduced pressure, and the crude mass thus obtained was purified by column chromatography to afford a good yield of desired compound **14**.

Yield: 1.4 g (85%); white solid; R_f = 0.5 (EtOAc/*n*-hexane, 90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (s, 2 H), 8.10 (s, 4 H), 7.59 (s, 2 H), 6.65 (s, 2 H), 6.61 (s, 1 H), 5.90–5.86 (m, 6 H), 5.79 (d, *J* = 4.0 Hz, 4 H), 5.63–5.51 (m, 12 H), 5.32 (d, *J* = 5.5 Hz, 3 H), 5.29–5.22 (m, 15 H), 5.13 (s, 4 H), 4.38 (s, 2 H), 4.28–4.08 (m, 18 H), 2.22 (d, *J* = 12.0 Hz, 18 H), 2.01–1.98 (m, 36 H), 1.80 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 170.07, 170.0, 169.8, 169.7, 168.9, 159.4, 147.9, 147.5, 143.5, 143.3, 139.9, 126.7, 126.2, 123.3, 122.9, 122.8, 108.4, 102.0, 86.0, 73.8, 70.7, 67.8, 66.8, 66.4, 66.2, 61.9, 61.0, 60.9, 60.3, 49.4, 20.59, 20.56, 20.4, 20.1.

Synthesis of Second-Generation Azide-Functionalized Galactosylated Dendritic Architecture 15

Galactosylated second-generation dendron **14** (1.0 g, 0.307 mmol) was dissolved in anhydrous DMF followed by addition of sodium azide (39.9 mg, 0.614 mmol, 2.0 equiv) under argon (inert) atmosphere, and the mixture was stirred at 70 °C for 12 h. After the completion of the reaction (monitored by TLC), workup of the mixture was performed (washing with ice-cold water and extracted in EtOAc). The organic layer was dried under anhydrous Na_2SO_4, evaporated under reduced pressure, and the obtained crude mass was subjected to column chromatography to furnish the desired compound **15**.

Yield: 0.84 g (86%); white solid; R_f = 0.51 (EtOAc/*n*-hexane, 90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (s, 2 H), 8.10 (s, 4 H), 7.58 (s, 2 H), 6.63 (s, 1 H), 6.57 (d, *J* = 2.5 Hz, 2 H), 5.90–5.85 (m, 5 H), 5.78 (d, *J* = 4.0 Hz, 3 H), 5.62–5.50 (m, 12 H), 5.34–5.21 (m, 18 H), 5.12 (s, 4 H), 4.28–4.07 (m, 22 H), 2.20 (d, *J* = 12.0 Hz, 18 H), 2.00–1.97 (m, 36 H), 1.79 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.35, 170.32, 170.1, 170.0, 169.85, 169.83, 168.9, 159.7, 147.9, 147.5, 143.5, 143.4, 137.8, 126.8, 126.2, 123.3, 122.9, 122.8, 114.0, 107.4, 101.6, 86.0, 73.8, 70.8, 67.86, 67.82, 66.8, 66.3, 61.9, 61.04, 61.00, 54.5, 20.6, 20.4, 20.1.

IR (KBr): 3453.65, 2925.08, 2853.91, 2104.75, 1754.87 cm^{-1}.

Synthesis of Galactose Coated Calix[4]arene Cored G_2 Generation Glycodendrimer 16

Synthesis of galactose-coated G_2 generation glycodendrimer **16** was achieved by click reaction of second-generation galactosylated azido functionalized dendron **15** (442 mg, 0.137 mmol, 2.5 equiv) with core bis-propargyloxy-*p*-*tert*-butyl-calix[4]arene **8** (40 mg, 0.055 mmol, 1.0 equiv) in the presence of $CuSO_4{\cdot}5H_2O$ (67 mg, 0.274 mmol, 2.0 equiv) and sodium ascorbate (22 mg, 0.109 mmol, 2.0 equiv) in THF/water (1:1) as solvent system at 45 °C for 12 h. After completion of the reaction (monitored by TLC), the mixture was filtered with Celite using a sintered crucible, washed with water (10 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and the obtained crude mass was subjected to column chromatography to afford the desired galactose-coated G_2 generation glycodendrimers **16**. The structure of galactose-coated G_2 generation glycodendrimer **16** was characterised by ^{1}H NMR, ^{13}C NMR, MS, and SEC techniques.

Yield: 311 mg (79%); white solid; R_f = 0.50 (CH_3OH/CH_2Cl_2, 10%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.28 (s, 4 H), 8.12 (s, 8 H), 7.94 (s, 2 H), 7.62 (s, 4 H), 6.96 (s, 4 H), 6.77 (s, 4 H), 6.60 (s, 2 H), 6.55 (s, 4 H), 5.91–5.88 (m, 12 H), 5.75 (s, 8 H), 5.64–5.59 (m, 12 H), 5.54–5.52 (m, 13 H), 5.46 (s, 3 H), 5.33–5.24 (m, 38 H), 5.12 (s, 3 H), 5.05 (s, 7 H), 4.28–4.11 (m, 42 H), 3.20 (s, 2 H), 3.18 (s, 2 H), 2.21 (d, *J* = 13.5 Hz, 36 H), 2.01–1.98 (m, 72 H), 1.80 (d, *J* = 2.5 Hz, 36 H), 1.20 (s, 18 H), 0.94 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 170.07, 170.01, 169.7, 168.8, 159.8, 150.2, 149.4, 147.9, 147.4, 147.2, 144.3, 143.5, 143.2, 141.5, 132.6, 127.6, 126.7, 126.3, 125.6, 125.0, 123.8, 123.4, 123.2, 123.0, 107.2, 101.7, 86.0, 73.7, 70.8, 67.8, 66.8, 66.4, 66.2, 61.8, 61.04, 61.00, 49.3, 34.0, 33.8, 33.7, 31.5, 30.9, 22.2, 20.6, 20.5, 20.4, 20.1.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2063-4139. Copies of ^{1}H and ^{13}C NMR for all the developed compounds for this article are available.

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