Synthesis of clustered xenotransplantation antagonists using palladium-catalyzed cross-coupling of prop-2-ynyl α-D-galactopyranoside

Bingcan Liu and René Roy *

Department of Chemistry, Centre for Research in Biopharmaceuticals, University of Ottawa, Ottawa, ON, Canada K1N 6N5. Fax: +1 613 562 5170

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Hyperacute rejection of pig liver transplantation can be antagonized using high affinity anti α-galactoside epitopes (Galα1-3Galβ, Galili antigen). To this end, clusters containing the Galili antigen were synthesized using palladium cross-coupling reactions. Thus, benzyl 3-(*O*-α-D-galactopyranosyl)-β-D-galactopyranoside derivative **6** was prepared using perbenzylated thiophenyl β-D-galactopyranosyl donor **5** and benzyl 2,6-di-*O*-benzoyl-α-D-galactopyranosyl acceptor **3**. Aglycone interchange from benzyl to prop-2-ynyl disaccharide **8** was successively achieved by hydrogenolysis, peracetylation, regioselective anomeric de-*O*-acetylation, trichloroacetimidate activation, and finally coupling to propargyl alcohol with triflic acid. The resulting prop-2-ynyl disaccharide **8** was transformed in high yields (>85%) into dimer **10**, trimer **12**, and tetramer **17** using oxidative homocoupling (**10**) and palladium-catalyzed aryl iodide cross-coupling (**12**, **17**), respectively. Ester protecting group removal under transesterification conditions afforded fully deprotected α-Gal clusters.

Introduction

Galili antigens are cell surface carbohydrate motifs containing Galα1-3Galβ non-reducing ends responsible for hyperacute rejection following pig to human xenotransplantation.[1] As a result of organ donor shortage, pig's livers have been highly considered as a viable alternative since their size, availability, and low risk of viral transmission have been well established.[2] Unfortunately, most humans possess abundant anti α-Gal antibodies (1–2% IgG, 3–8% IgM) as a result of prior exposure to bacterial or viral infections.[3] Thus, within minutes to hours of surgery and in spite of immunosuppressive treatments, the transplanted organs are rapidly rejected by most recipients. To overcome this problem, a possible strategy has been to develop antagonizing anti α-Gal inhibitors by infusing large concentrations of synthetic α-Gal oligosaccharides or by using affinity columns to deplete the patient's serum of α-Gal antibodies.[4] Polymeric α-Gal epitopes have also been designed to increase the antagonizing activity of simple, low affinity oligosaccharides.[5,6]

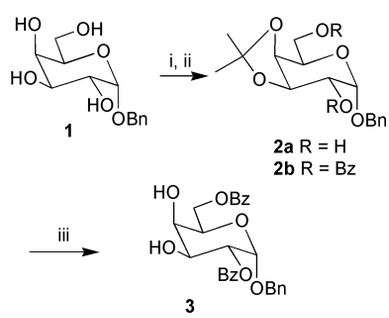
In the present study, the synthesis of various α-Gal clusters is described for the purpose of creating smaller size, high affinity anti-α-Gal antibody antagonists. Previous investigations by us[7] and others,[8] including the findings by Magnusson *et al.*[9] on nanomolar inhibition of bacterial receptors by galactobiose clusters, strongly support the concept of multivalent inhibitors.

Results and discussion

Synthesis of Galili epitope (Galα1-3Galβ-OR)

Recent investigations have shown that propynyl to aryl halide palladium-catalyzed cross-coupling of saccharides bearing these functionalities provided an efficient entry into glycoclusters having high affinity.[10] The rationale for rigid-linkers is based on the findings that conformationally restricted ligands are exposed to a lesser entropic loss during binding to their homologous receptors.[11] To reach this goal for the Galili antigen, we chose prop-2-ynyl disaccharide **8** from which dimer **10** could be obtained by oxidative homocoupling, while trimer **12** and tetramer **17** could be obtained by a Sonogashira cross-coupling between **8** and aryl iodides **11** and **16**, respectively.

Initial attempts to introduce the suitably protected prop-2-ynyl β-D-galactopyranoside as a glycosyl acceptor were met with some difficulties due to either incompatibility of the alkyne moieties toward glycosylating reagents such as *N*-iodosuccinimide–triflic acid† (NIS–TfOH) or to the lack of selective benzyl ether deprotection. Therefore a feasible strategy was designed in which the required prop-2-ynyl aglycone was introduced at the very end of the disaccharide synthesis. Thus, benzyl 2,6-di-*O*-benzoyl-α-D-galactopyranoside acceptor **3** was synthesized using an established protocol (Scheme 1). Starting



Scheme 1 *Reagents and conditions*: i) 2,2-dimethoxypropane, PTSA, rt, 5 h, 85%; ii) BzCl, pyridine, DMAP, rt, 2 h, 90%; iii) 60% AcOH, 80 °C, 5 h, 95%.

from the known[12] benzyl α-D-galactopyranoside **1**, 3,4-diol free galactosyl acceptor **3** was obtained by regioselective acetalation of **1** with 2,2-dimethoxypropane in the presence of toluene-*p*-sulfonic acid (PTSA) to provide the corresponding acetal **2a** in 85% yield. Treatment of the resulting diol **2a** with benzoyl chloride (pyridine, 4-(*N*,*N*-dimethylamino)pyridine (DMAP))

† The IUPAC name for triflic acid is trifluoromethanesulfonic acid.

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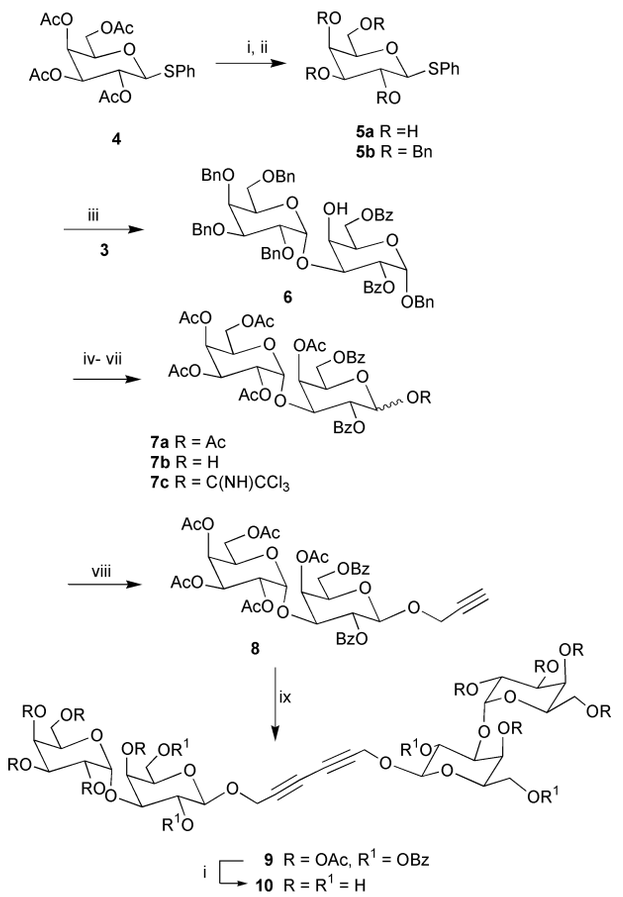
gave **2b** (90%). Acetal hydrolysis in hot 60% aqueous acetic acid (80 °C) afforded galactosyl acceptor **3** in 95% yield.

Perbenzylated phenyl β-D-thiogalactosyl donor **5b**[13] was prepared from known peracetylated β-D-galactopyranoside **4** (i) NaOMe, MeOH; ii) NaH, BnBr, DMF, 85%) obtained under phase transfer catalyzed conditions (PTC) previously developed in our group (Scheme 2).[14] Glycosidation of diol **3** with galactosyl donor **5b** using NIS–triflic acid as promoter gave disaccharide **6** as an α–β mixture (6 : 1, 76%) from which the pure α-anomer (δ H-1′ 4.84 ppm, $J_{1',2'}$ 3.8 Hz) could be isolated in 65% yield after careful column chromatography separation.

The desired prop-2-ynyl disaccharide **8** was then readily synthesized through a sequence of straightforward manipulations. Benzyl glycoside **6** was hydrogenolyzed (H_2, Pd-C, MeOH, 95%) and peracetylated using acetyl chloride to give **7a** (pyridine, DMAP, 90%). The anomeric mixture was then regioselectively de-*O*-acetylated using hydrazinium acetate to provide the reducing disaccharide **7b** that was transformed into trichloroacetimidate **7c** (Cl_3CCN, DBU, CH_2Cl_2, 90%). Finally, treatment of **7c** with propargyl‡ alcohol with triflic acid afforded β-galactoside **8** in 86% yield (δ H-1 4.90 ppm, $J_{1,2}$ 7.9 Hz).



Scheme 2 *Reagents and conditions*: i) NaOMe, MeOH, quant. (95% for **10**); ii) BnBr, NaH, DMF, rt, 2 h, 85%; iii) **3**, NIS, TfOH, CH_2Cl_2, 4 Å MS, −40 °C, 1 h, α–β (6 : 1), 76%; iv) H_2, Pd-C, MeOH, rt, 2 days, 95%; v) AcCl, pyridine, DMAP, rt, 4 h, 90%; vi) H_2NNH_2–HOAc, CH_2Cl_2, rt, 2 h, 75%; vii) Cl_3CCN, DBU, CH_2Cl_2, rt, 5 h, 90%; viii) propargyl alcohol, CH_2Cl_2, TfOH, 4 Å MS, rt, 4 h, 86%; ix) $(Ph_3P)_2PdCl_2$, CuI, DMF–TEA 1 : 1, rt, 3 h, 95%.

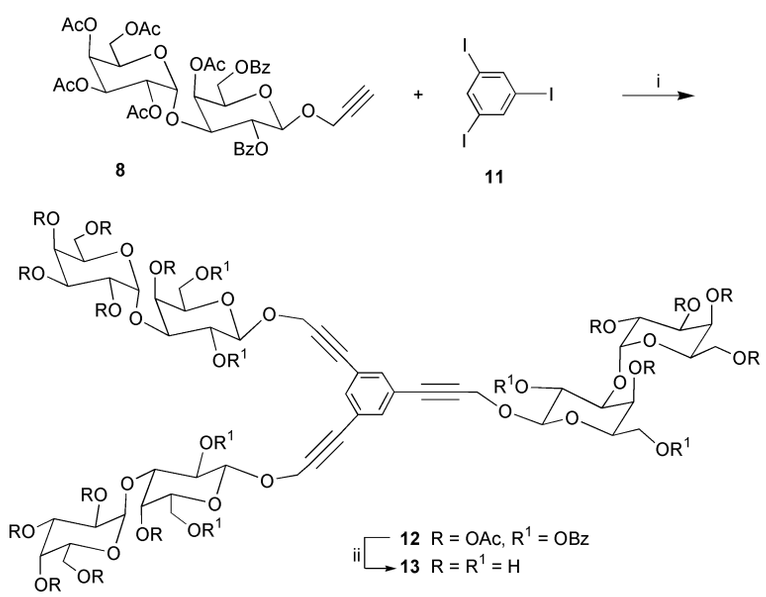
Synthesis of α-Gal containing clusters

In order to obtain Galili antigens as small rigid clusters that may have the potential to form stable cross-linked complexes with naturally occurring anti α-Gal antibodies, a series of palladium catalyzed transformations were then effected. The goal was to obtain di- to tetra-mers analogous to those previously prepared for galabiosides that have shown nanomolar inhibitory properties against various pathogens with carbohydrate binding lectins on their surfaces.[9]

Dimer **9** was successfully prepared from prop-2-ynyl glycoside **8** by oxidative homocoupling using palladium catalyzed conditions ($(Ph_3P)_2PdCl_2$, CuI, DMF–TEA (1 : 1), rt, 95%) (Scheme 2).[15] Interestingly, these conditions were found to be milder than the classical Glaser reaction[16] previously used by us in analogous circumstances.[17] Acetylenic dimer **9** was then subjected to Zemplèn transesterification (NaOMe, MeOH) to provide fully deprotected dimer **10** in 95% yield.

Trimer **13** was then obtained using a Sonogashira reaction[18] similar to the one recently described for the synthesis of mannoside clusters.[10,15] Thus, palladium catalysts such as $(PPh_3)_2PdCl_2$, $(PPh_3)_4Pd$ and $Pd_2(dba)_3$ were all successfully applied for the cross-coupling of prop-2-ynyl glycoside **8** and 1,3,5-triiodobenzene (**11**)[19] which provided trimer **12** with more or less analogous yields (85% with $(PPh_3)_2PdCl_2$) (Scheme 3). As previously observed,[15] it is noteworthy to mention that CuI is not essential for the successful cross-coupling in this reaction. In fact, without CuI, the coupling reaction proceeds under heating conditions (60 °C) while the reaction can function at room

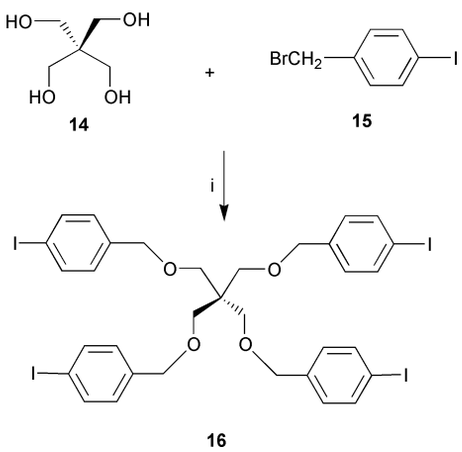
‡ The IUPAC name for propargyl is prop-2-ynyl.



Scheme 3 *Reagents and conditions*: i) $(Ph_3P)_2PdCl_2$, DMF–TEA 1 : 1, 60 °C, 5 h, 81%; ii) NaOMe, MeOH, 24 h, rt, 95%.

temperature in the presence of CuI, albeit in lower yields. However in the absence of CuI, the oxidative homodimerization of the alkynyl moiety is abolished. These observations are particularly important when the desired cross-coupling products and the homodimers are difficult to separate. Finally, trimer **12** was fully deprotected to its corresponding analog **13** using NaOMe in methanol (95%).

To provide sufficient inter-sugar distances required for efficient protein cross-linking, a tetrameric core was constructed using pentaerythritol (**14**) as a seed molecule. Tetra-*p*-iodobenzylated precursor **16** was prepared by a classical etherification procedure using *p*-iodobenzyl bromide **15**, tetrabutylammonium iodide, NaH, and DMF in moderate yield (47%) (Scheme 4). In spite of several efforts, the yield



Scheme 4 *Reagents and conditions*: i) NaH, TBAI, DMF, rt, 5 h, 47%.

could not be improved further. However, for reasons not yet fully understood, **14** is known to be reluctant to full derivatization under Williamson etherification. Moreover, *p*-iodobenzyl bromide is light sensitive and unstable in various solvents which may contribute to the low yield.

Using the cross-coupling conditions described above for the synthesis of trimer **12** without CuI, treatment of propynyl glycoside **8** with tetrakis *p*-iodobenzyl ether **16** ($(PPh_3)_2PdCl_2$), DMF-TEA (1 : 1), 60 °C, 5 h) afforded fully protected tetramer **17** (Scheme 5). Usual deprotection (NaOMe, MeOH) of all ester protecting groups in **17** gave tetramer **18** (95%).

In conclusion, efficient oxidative homocoupling or palladium catalyzed cross-coupling reactions of alkynyl glycosides with aryl iodides provided an efficient entry into novel "rigid-like" glycoclusters that may have the potential to inhibit various carbohydrate binding proteins (lectins and antibodies). Work is now in progress to evaluate the above series of clusters bearing the Galili epitope against human anti α-Gal antibodies.[1]

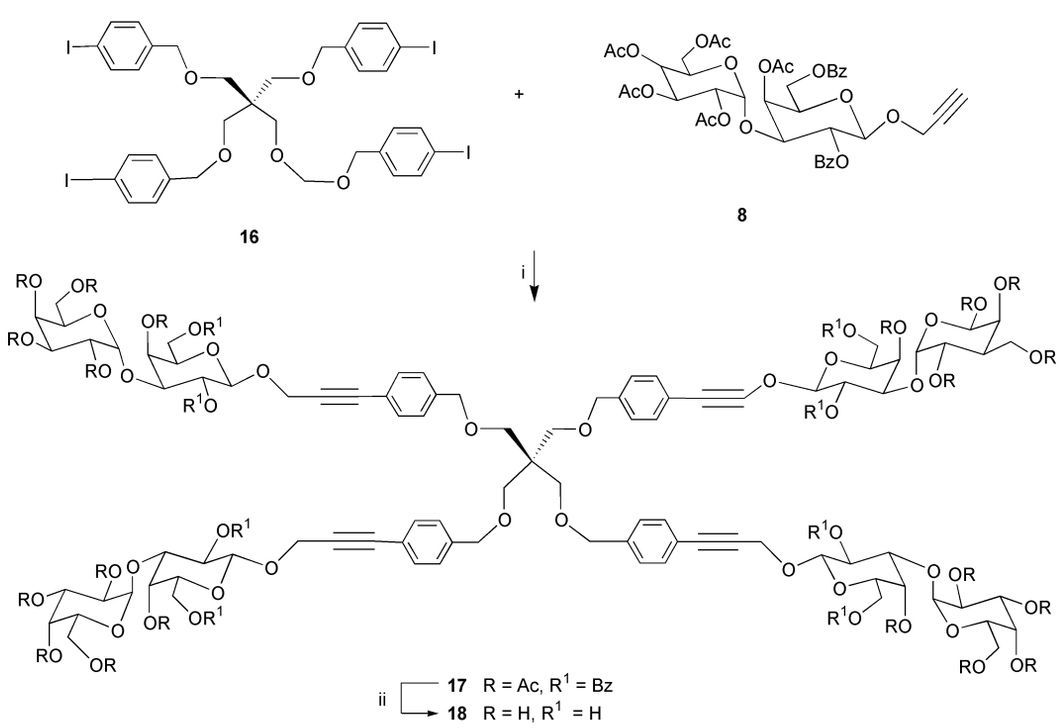
Experimental

General

Dichloromethane was stored over 4 Å MS after drying over P_2O_5 and distillation. Propargyl alcohol was from Fluka and *p*-iodobenzyl bromide was from KARL INDUSTRIES INC. All the other reagents were purchased from Aldrich. Thin layer chromatography was performed on Silica Gel F_{254} (Merck) precoated aluminium sheets and visualized with molybdenum solution and an UV lamp. Column chromatography was run on Ultra Pure Silica Gel (SILICYCLE). Elemental analyses were measured on a CE-2500 instrument. Melting points were determined on a Gallenkamp melting point apparatus without temperature correction. Optical rotations were measured on a PERKIN-ELMER 241 polarimeter and are given as 10^{-1} deg $cm^2\ g^{-1}$. All the NMR spectra (500 MHz for ^1H and 125.7 MHz for ^{13}C) were recorded on a Bruker AMX-500 spectrometer. The resonances were assigned based on ^1H, ^{13}C, ^1H–^1H COSY, DEPT, and HMQC experiments. Chemical shifts are referenced to $CDCH_3$ (δ_H 7.29 and δ_C 77.0 ppm). *J* values are given in Hz. ESI-MS analyses were carried out on a MICROMASS Quattro LC. FAB-MS spectra were recorded on KRATOS Concepts IIH with Cs^+ beam. MALDI-TOF MS was acquired on a PerSeptive Biosystems Elite-STR (Framingham, MA, USA).

Glycosyl acceptor 3

Benzyl 3,4-*O*-isopropylidene-α-D-galactopyranoside 2a. Benzyl α-D-galactopyranoside **1**[12] (246 mg, 1 mmol) was dissolved into acetone (5 ml) to which was added 2,2-dimethoxypropane (250



Scheme 5 *Reagents and conditions*: i) $(Ph_3P)_2PdCl_2$, DMF–TEA (1 : 1), 60 °C, 5 h, 85%; ii) NaOMe, MeOH, 24 h, rt, 95%.

μl, 2 mmol) and a catalytic amount of toluene-*p*-sulfonic acid. The mixture was stirred at room temperature for 5 h. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using ethyl acetate–hexane (1.5 : 1) to give **2a** as a thick liquid in 85% yield, $[\alpha]_D$ +110 (*c* 3.2, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.28–7.36 (5 H, m, aromatic), 4.99 (1 H, d, *J* = 3.8, H-1), 4.77 (1 H, d, *J* = 11.8, PhCH_2), 4.57 (1 H, d, *J* = 11.8, PhCH_2), 4.26 (1 H, t, *J* = 6.2, H-4), 4.21 (1 H, dd, *J* = 3.3, 7.2, H-3), 4.07–4.09 (1 H, m, H-5), 3.89 (1 H, dd, *J* = 6.3, 11.8, H-6a), 3.82 (1 H, dd, *J* = 3.8, 7.2, H-2), 3.77 (1 H, dd, *J* = 6.3, 11.8, H-6b), 1.48 (3 H, s, CH_3), 1.32 (3 H, s, CH_3); δ_C (125 MHz; $CDCl_3$) 137.0, 128.5, 128.1, 128.0 and 109.8 (aromatic), 96.9 (C-1), 76.1 (C-4), 73.9 (C-3), 69.4 (Ph*C*H_2), 69.3 (C-2), 68.4 (C-5), 62.7 (C-6), 27.5 and 25.8 (*C*H_3); *m*/*z* (FAB-MS) 349.2 (Found: [M + K^+]. $C_{16}H_{22}O_6$ requires [M + K^+] 349.1).

Benzyl 2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-α-D-galactopyranoside 2b. Compound **2a** (310 mg, 1 mmol) was dissolved into pyridine (5 ml) and a catalytic amount of DMAP (10 mg) was added followed by benzoyl chloride (280 μl, 2.2 mmol). The mixture was stirred at room temperature for 2 h. After removal of pyridine under reduced pressure, the residue was dissolved into 50 ml of ether which was washed with water (3 × 30 ml). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate–hexane (1 : 4) to provide **2b** as a liquid in 90% yield, $[\alpha]_D$ +90.2 (c 1, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.03–8.09 (4 H, m, aromatic), 7.55–7.59 (6 H, m, aromatic), 7.15–7.20 (5 H, m, aromatic), 5.20 (1 H, dd, *J* = 3.7, 7.9, H-2), 5.17 (1 H, d, *J* = 3.7, H-1), 4.77 (1 H, d, *J* = 12.3, PhCH_2), 4.67 (1 H, dd, *J* = 4.8, 11.8, H-6a), 4.63 (1 H, dd, *J* = 7.5, 11.8, H-6b), 4.50 (1 H, dd, *J* = 5.5, 7.9, H-3), 4.50 (1 H, d, *J* = 11.8, PhCH_2), 4.47–4.51 (1 H, m, H-5), 4.38 (1 H, dd, *J* = 2.6, 5.5, H-4), 1.56 (3 H, s, CH_3), 1.36 (3 H, s, CH_3); δ_C (125 MHz; $CDCl_3$) 166.3, 165.9 (Ph*C*O), 136.8, 133.1, 133.0, 130.0, 129.8, 129.7, 129.6, 128.4, 128.3, 128.2, 127.8, 127.5 and 110.1 (aromatic), 95.3 (C-1), 73.6 (C-2), 72.1 (C-4), 69.6 (Ph*C*H_2), 66.1 (C-3 and C-5), 64.0 (C-6), 27.9 and 26.3 (*C*H_3); *m*/*z* (FAB-MS) 557.0 (Found: [M + K^+]. $C_{30}H_{30}O_8$ requires [M + K^+] 557.0).

Benzyl 2,6-di-*O*-benzoyl-α-D-galactopyranoside 3. Benzyl 2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-α-D-galactopyranoside **2b** (518 mg, 1 mmol) was placed into a round-bottomed flask with 30 ml of 60% aqueous acetic acid. The mixture was heated and stirred at 80 °C for 5 h. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography using ethyl acetate–hexane (1.5 : 1) to yield **3** as a white solid in 95% yield, $[\alpha]_D$ +111.6 (*c* 1, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.02–8.11 (4 H, m, aromatic), 7.53–7.58 (2 H, m, aromatic), 7.39–7.46 (4 H, m, aromatic), 7.16–7.29 (5 H, m, aromatic), 5.33 (1 H, dd, *J* = 3.8, 10.2, H-2), 5.21 (1 H, d, *J* = 3.8, H-1), 4.72 (1 H, d, *J* = 12.2, PhCH_2), 4.66 (1 H, dd, *J* = 6.0, 11.4, H-6a), 4.52 (1 H, d, *J* = 12.2, PhCH_2), 4.50 (1 H, dd, *J* = 7.0, 11.4, H-6b), 4.27 (1 H, d, *J* = 1.4, H-5), 4.26 (1 H, dd, *J* = 3.6, 10.2, H-3), 4.10 (1 H, dd, *J* = 1.0, 3.6, H-4), 2.97 (2 H, br s, -OH); δ_C (125 MHz; $CDCl_3$) 166.9 and 166.6 (Ph*C*O_2), 137.0, 133.3, 133.2, 129.9, 129.6, 128.4, 128.3, 127.8 and 127.6 (aromatic), 95.7 (C-1), 72.1 (C-2), 69.6 (Ph*C*H_2), 69.5 (C-4), 68.4 and 68.2 (C-3 and C-5), 63.5 (C-6); *m*/*z* (ESI-MS) 496.0 (Found: [M + NH_4^+]. $C_{27}H_{30}NO_8$ requires [M + NH_4^+] 496.2).

α-Gal epitope 8

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside 5b. Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**4**)[14] (1 g, 2.27 mmol) was dissolved into 25 ml of methanol to which was added a catalytic amount of sodium methoxide. The solution was stirred overnight at room temperature. After neutralization of the reaction mixture with Amberlite (IR-120, H^+), the solution was filtered through a cotton plug. Methanol was evaporated under reduced pressure to provide **5a** in a quantitative yield and the product was used directly in the next step without further purification.

Compound **5a** was dissolved into 30 ml of DMF to which was added sodium hydride (440 mg, 11 mmol). After stirring at room temperature for 20 minutes, benzyl bromide (1.3 ml, 10.9 mmol) was added to the suspension during a period of 10 minutes. The mixture was further stirred at room temperature for 2 hours. Excess sodium hydride was destroyed with several drops of methanol. The solution was diluted with 100 ml of ether and washed with 3 × 100 ml of water. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate–hexane (1 : 10) to provide **5b** as a white solid with a mp 88.9 to 90.1 °C and a $[\alpha]_D$ 1 (*c* 1.0, $CHCl_3$), literature[13] mp 88–89 °C and a $[\alpha]_D$ 1 (*c* 1.0, $CHCl_3$).

Benzyl (2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→3)-2,6-di-*O*-benzoyl-α-D-galactopyranoside 6. Glycosyl donor **5b** (200 mg, 0.32 mmol) and glycosyl acceptor **3** (230 mg, 0.48 mmol) and 4 Å MS were put into a dry flask. After flushing the flask with dry nitrogen, 20 ml of dry CH_2Cl_2 was injected into it. The suspension was stirred for 30 min at −40 °C, then NIS (106.6 mg, 0.48 mmol) and a catalytic amount of triflic acid was added to the solution. One hour later, the mixture was neutralized with DIPEA and filtered over Celite. The filtrate was washed with diluted sodium thiosulfate solution and the organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated on a rotavapor. The residue was subjected to silica gel column chromatography using ethyl acetate–hexane (2 : 3) to afford **6** as a white foam in 65% yield, $[\alpha]_D$ +84.4 (*c* 1.8, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 8.08–8.11 (4 H, m, aromatic), 7.08–7.60 (31 H, m, aromatic), 5.45 (1 H, *J* = 3.8, 10.0, dd, H-2), 5.24 (1 H, d, *J* = 3.8, H-1), 4.88 (1 H, d, *J* = 11.5, PhCH_2), 4.84 (1 H, d, *J* = 3.8, H-1′), 4.82 (1 H, d, *J* = 11.5, PhCH_2), 4.70 (1 H, d, *J* = 12.5, PhCH_2), 4.69 (2 H, s, PhCH_2), 4.65 (1 H, d, *J* = 11.5, PhCH_2), 4.63 (1 H, dd, *J* = 6.3, 11.6, H-6a), 4.56 (1 H, dd, *J* = 7.6, 11.6, H-6b), 4.48 (1 H, d, *J* = 12.5, PhCH_2), 4.45 (1 H, d, *J* = 11.5, PhCH_2), 4.27 (1 H, t, *J* = 6.6, H-5), 4.25 (1 H, dd, *J* = 3.4, 10.0, H-3), 4.16 (1 H, d, *J* = 11.5, PhCH_2), 4.08 (1 H, d, *J* = 11.5, PhCH_2), 4.02 (1 H, dd, *J* = 3.8, 10.0, H-2′), 4.01 (1 H, m, H-4), 3.91–3.94 (2 H, m , H-3′, H-5′), 3.86 (1 H, br d, *J* = 1.5, H-4′), 3.47 (1 H, t, *J* = 8.6, H-6a′), 3.22 (1 H, dd, *J* = 5.5, 8.8, H-6b′); δ_C (125 MHz; $CDCl_3$), 166.3 and 165.8 (Ph*C*O_2), 138.6, 138.3, 137.9, 137.5, 137.0, 136.5, 135.5, 133.0, 131.3, 130.1, 129.8, 129.6, 129.4, 128.7, 128.5, 128,4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4 and 127.3 (aromatic), 96.1 (C-1), 95.4 (C-1′), 79.5 (C-3′ or C-5′), 75.6 (C-2′), 74.9 and 74.8 (Ph*C*H_2), 74.5 (C-3), 74.4 (C-4′), 73.2 and 72.6 (Ph*C*H_2), 69.8 (C-5′ or C-3′), 69.6 (C-2), 69.3 (Ph*C*H_2), 68.3 (C-6′), 67.8 (C-5), 66.2 (C-4), 64.5 (C-6); *m*/*z* (ESI-MS) 1018.1 (Found: [M + NH_4^+]. $C_{61}H_{64}NO_{13}$ requires [M + NH_4^+] 1018.4).

Prop-2-ynyl (2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranoside 8. To compound **6** (1 g, 1 mmol) dissolved in 30 ml of methanol was added a catalytic amount of 10% Pd/C and 2 drops of acetic acid. The suspension was subjected to hydrogenolysis at rt for 2 days. After the reaction was completed, the solution was filtered through a pad of Celite. After removal of methanol under reduced pressure, the dry residue was dissolved into 10 ml of pyridine to which was added acetyl chloride (0.52 ml, 6 mmol) and a catalytic amount of DMAP (10 mg) at 0 °C. The mixture was stirred at room temperature for 4 h. Pyridine was then removed under reduced pressure. The residue was dissolved

into 60 ml of ether and washed with water (3 × 40 ml). The organic layer was dried over anhydrous sodium sulfate. After removal of ether under reduced pressure, the residue was purified by silica gel column chromatography using ethyl acetate–hexane (1 : 1) to provide **7a** (α–β) as a white foam in 90% yield which was used in the next step without further purification.

Compound **7a** (800 mg, 1 mmol) was dissolved into 20 ml of dichloromethane to which was added hydrazinium acetate (135 mg, 1.5 mmol). The solution was stirred at room temperature for 2 h. After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography using ethyl acetate–hexane (1.5 : 1) to give **7b** as a white foam in 75% yield. Compound **7b** was obtained as an anomeric α–β mixture, which was used directly in the next step without further purification.

Compound **7b** (760 mg, 1 mmol), trichloroacetonitrile (0.15 ml, 1.5 mmol), and DBU (30 µl, 0.2 mmol) were added to 20 ml of dry dichloromethane. The solution was stirred at room temperature for 5 h. After removal of the solvent under reduced pressure, the residue was subjected to silica gel column chromatography using ethyl acetate–hexane (1 : 1) to give **7c** as a white foam in 90% yield. Compound **7c** existed as an α–β mixture (~10 : 1 ratio), which was used directly in the next step without further purification.

Crude trichloroacetimidate **7c** (200 mg, 0.22 mmol), propargyl alcohol (25.8 µl, 0.44 mmol) and 4 Å MS were added into 20 ml of dry dichloromethane. The mixture was stirred at room temperature for 30 minutes to which was added a catalytic amount of triflic acid. Four hours later the suspension was neutralized with DIPEA and filtered over Celite. After evaporation of the solvent, the residue was purified by silica gel column chromatography using ethyl acetate–hexane (1 : 1) to provide **8** as a white foam in 86% yield, $[\alpha]_D$ +117.0 (*c* 1, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.98–8.06 (4 H, m, aromatic), 7.53–7.57 (2 H, m, aromatic), 7.40–7.45 (4 H, m, aromatic), 5.52 (1 H, dd, *J* = 7.9, 10.1, H-2), 5.50 (1 H, br d, *J* = 2.4, H-4), 5.21 (1 H, br d, *J* ~3.5 Hz, H-1′), 5.19 (1 H, dd, *J* = 3.5, 10.5, H-2′), 5.03 (1 H, dd, *J* = 3.3, 10.5, H-3′), 4.91 (1 H, m, H-4′), 4.90 (1 H, d, *J* = 7.9, H-1), 4.53 (1 H, dd, *J* = 6.6, 11.3, H-6a), 4.41 (1 H, dd, *J* = 2.4, 16.1, CH_2-CCH), 4.34 (1 H, dd, *J* = 2.4, 16.1, CH_2-CCH), 4.32 (1 H, dd, *J* = 6.7, 11.3, H-6b), 4.10 (1 H, dd, *J* = 3.2, 10.1, H-3), 4.03 (1 H, m, H-5), 4.00 (1 H, m, H-5′), 3.80 (1 H, dd, *J* = 6.8, 12.1, H-6a′), 3.72 (1 H, dd, *J* = 6.6, 12.1, H-6b′), 3.45 (1 H, t, *J* = 3.4, acetylenic), 2.20, 2.04, 2.00, 1.89 and 1.86 (each 3 H, 5s, 5 CH_3CO_2); δ_C (125 MHz; $CDCl_3$) 170.2, 169.9, 169.8 and 169.3 (CH_3CO_2), 165.7 and 165.0 (PhCO_2), 133.4 (2), 129.7, 129.6, 129.3, 129.2, 128.5 and 128.4 (aromatic), 98.7 (C-1), 95.7 (C-1′), 78.2 and 75.3 (acetylenic), 73.7 (C-3), 71.1 (C-5), 69.8 (C-2), 67.6 (C-4′), 66.9 (C-3′ and C-5′), 66.5 (C-2′), 65.2 (C-4), 61.8 (C-6), 61.1 (C-6′), 55.9 (C-1″), 20.7, 20.5, 20.3 (3) (CH_3CO_2); *m*/*z* (FAB-MS) 837.2 (Found: [M + K^+]. $C_{39}H_{42}O_8$ requires [M + K^+] 837.2).

α-Gal homodimer 9

To a solution of compound **8** (79.8 mg, 0.1 mmol) in 5 ml of DMF–TEA (1 : 1) was added $Pd(PPh_3)_2Cl_2$ (3.6 mg, 5 mol%) and CuI (3.8 mg, 20 mol%). The solution was stirred under nitrogen at room temperature for 3 h. The solvent and TEA were evaporated under reduced pressure. The resulting mixture was purified by silica gel column chromatography using ethyl acetate–hexane (1.5 : 1) to provide compound **9** as a white foam in 95% yield, $[\alpha]_D$ +115.6 (*c* 1, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.98–8.00 (8 H, m, aromatic), 7.32–7.47 (12 H, m, aromatic), 5.49–5.53 (4 H, m, H-2, H-4), 5.19 (2 H, d, *J* < 1, H-1′), 5.18 (2 H, dd, *J* = 3.5, 10.5, H-2′), 5.02 (2 H, dd, *J* = 3.3, 10.5, H-3′), 4.90 (2 H, m, H-4′), 4.83 (2 H, d, *J* = 7.9, H-1), 4.54 (2 H, dd, *J* = 6.6, 11.3, H-6a), 4.46 (2 H, d, *J* = 16.1, H-1a″), 4.41 (2 H, d, *J* = 16.1, H-1b″), 4.30 (2 H, dd, *J* = 6.6, 11.3, H-6b), 4.11 (2 H, dd, *J* = 3.1, 10.1, H-3), 4.04 (2 H, t, *J* = 6.7, H-5), 3.96 (2 H, t, *J* = 7.1, H-5′), 3.77 (2 H, dd, *J* = 7.1, 11.1, H-6a′), 3.68 (2 H, dd, *J* = 6.6, 11.1, H-6b′), 2.19, 2.03, 2.00, 1.86 and 1.83 (each 6 H, 5s, 10 CH_3CO_2); δ_C (125 MHz; $CDCl_3$) 170.2, 169.9, 169.8, 169.7, 169.3 (CH_3CO_2), 166.0, 165.1 (PhCO_2), 133.5, 133.4, 129.7, 129.3, 129.1, 128.5, 128.4 and 128.1 (aromatic), 99.2 (C-1), 93.4 (C-1′), 74.3 (acetylenic), 73.7 (C-3), 71.2 (C-5), 70.3 (acetylenic), 69.8 (C-2), 67.6 (C-4′), 66.9 (C-3′ and C-5′), 66.5 (C-2′), 65.2 (C-4), 61.7 (C-6), 61.0 (C-6′), 56.5 (C-1″), 20.7, 20.5 and 20.4 (CH_3CO_2); *m*/*z* (FAB-HRMS) 1633.4570 (Found: [M + K^+]. $C_{78}H_{82}O_{36}$ requires [M + K^+] 1633.4223).

Fully deprotected α-Gal homodimer 10

α-Gal homodimer **9** (80 mg, 0.050 mmol) was dissolved into 30 ml of methanol. A catalytic amount of sodium methoxide was then added to the solution. The mixture was stirred at room temperature for 24 h. Sodium methoxide was neutralized with AMBERLITE IR-120 (H+). After careful filtration of the resin through a loose cotton plug, methanol was removed under reduced pressure. After evaporation of the methanol under reduced pressure, the dried residue was extracted with ether 3 × 10 ml to remove methyl benzoate to afford the deprotected glycocluster **10** as a white powder in 95% yield, $[\alpha]_D$ 0.0 (*c* 2.1, H_2O); δ_H (500 MHz; H_2O) 5.22 (2 H, d, *J* = 3.9, H-1′), 4.69 (2 H, d, *J* = 7.9, H-1), 4.65 (4 H, br s, H-1″), 4.25 (4 H, m, H-5 and H-5′), 4.08 (2 H, m, H-4′), 4.02 (2 H, dd, *J* = 3.4, 10.4, H-3′), 3.92 (2 H, dd, *J* = 3.9, 10.4, H-2′), 3.84–3.94 (6 H, m, H-3 and H-6 or H-3 and H-6′), 3.76–3.81 (6 H, m, H-4 and H-6 or H-4 and H-6′), 3.72 (2 H, dd, *J* = 7.9, 10.0, H-2); δ_C (125 MHz; D_2O) 100.6 (C-1), 94.8 (C-1′), 76.8 (C-3), 74.6 (C-2), 74.5 (acetylenic), 70.42 (C-5 or C-5′), 70.0 (acetylenic), 68.8 (C-3′), 68.7 (C-4′), 68.6 (C-4), 67.7 (C-2′), 64.3 (C-5 or C-5′), 60.5 and 60.4 (C-6 and C-6′), 56.5 (C-1″); *m*/*z* (FAB-MS) 797.1 (Found: [M + K^+]. $C_{30}H_{46}O_{22}$ requires [M + K^+] 797.2).

α-Gal trimer 12

To a solution of compound **8** (100 mg, 0.12 mmol) in 5 ml of DMF–TEA (1 : 1) was added $Pd(PPh_3)_2Cl_2$ (4.3 mg, 0.006 mmol (5 mol%)) and 1,3,5-triiodobenzene (**11**)[19] (15.8 mg, 0.035 mmol). The solution was stirred under nitrogen at 60 °C for 5 h. The solvent and TEA were evaporated under reduced pressure and the resulting mixture was purified by silica gel column chromatography using ethyl acetate–hexane (2 : 1) to provide compound **12** as a white foam in a yield of 85%, $[\alpha]_D$ +93.4 (*c* 1.8, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.98–8.00 (12 H, m, aromatic), 7.32–7.47 (18 H, m, aromatic), 5.53 (3 H, dd, *J* = 8.0, 10.0, H-2), 5.46 (3 H, d, *J* = 3.0, H-4), 5.19 (3 H, d, *J* < 1, H-1′), 5.18 (3 H, dd, *J* = 3.5, 10.5, H-2′), 5.04 (3 H, dd, *J* = 3.3, 10.5, H-3′), 4.91 (3 H, d, *J* = 8.0, H-1), 4.90 (3 H, m, H-4′), 4.60 (6 H, s, H-1″), 4.55 (3 H, dd, *J* = 6.4, 11.3, H-6a), 4.32 (3 H, dd, *J* = 6.6, 11.3, H-6b), 4.12 (3 H, dd, *J* = 3.1, 10.0, H-3), 4.04 (3 H, t, *J* = 6.7, H-5), 3.97 (3 H, t, *J* = 6.9, H-5′), 3.74 (3 H, dd, *J* = 7.1, 11.1, H-6a′), 3.68 (3 H, dd, *J* = 6.6, 11.1, H-6b′), 2.19, 2.03, 2.00, 1.86 and 1.72 (each 9 H, 5s, 15 CH_3CO_2); δ_C (125 MHz; $CDCl_3$) 170.2, 169.9, 169.8, 169.7 and 169.3 (CH_3CO_2), 166.0 and165.1 (PhCO_2), 134.7, 133.4, 133.3, 129.7, 129.6, 129.3, 129.1, 128.5, 128.4 and 122.1 (aromatic), 99.2 (C-1), 94.0 (C-1′), 85.4 and 84.5 (acetylenic), 73.9 (C-3), 71.1 (C-5), 70.1 (C-2), 67.6 (C-4′), 66.9 (C-3′), 66.5 (C-2′ and C-5′), 65.3 (C-4), 61.8 (C-6), 61.0 (C-6′), 56.5 (C-1″), 20.7, 20.6, 20.4 and 20.3 (CH_3CO_2); *m*/*z* (ESI-MS) 2485.1 (Found: [M + NH_4^+]. $C_{123}H_{130}NO_{54}$ requires [M + NH_4^+] 2484.7).

Fully deprotected α-Gal trimer 13

α-Gal trimer **12** (90 mg, 0.036 mmol) was dissolved into 30 ml of methanol. A catalytic amount of sodium methoxide was added to the solution. The mixture was stirred at room temperature for 24 h. Sodium methoxide was neutralized with AMBERLITE IR-120 (H+). After careful filtration of the

resin through a loose cotton plug, methanol was removed under reduced pressure. The dried residue was extracted with ether 3 × 10 ml to remove methyl benzoate to provide the fully deprotected glycocluster **13** as an off-white foam in 95% yield, $[\alpha]_D$ 0.0 (*c* 1.5, H_2O); δ_H (500 MHz; D_2O) 7.67 (3 H, s, aromatic), 5.23 (3 H, d, *J* = 3.8, H-1′), 4.79 (6 H, br s, H-1″), 4.75 (3 H, d, *J* = 7.9, H-1), 4.27 (6 H, m, H-5 and H-5′), 4.09 (3 H, m, H-4′), 4.04 (3 H, dd, *J* = 3.3, 10.4, H-3′), 3.94 (3 H, dd, *J* = 3.9, 10.4, H-2′), 3.76–3.89 (21 H, m, H-2, H-3, H-4, H-6 and H-6′); δ_C (125 MHz; D_2O) 134.4 and 122.2 (aromatic), 100.8 (C-1), 94.9 (C-1′), 85.2 and 84.6 (acetylenic), 76.9 (C-3), 74.6 (C-2 or C-4), 72.3 (C-5 or C-5′), 70.4 (C-3′), 68.9 and 68.7 (C-3′, C-4′ and C-4 or C-3′, C-4′ and C-2), 67.8 (C-2′), 64.4 (C-5 or C-5′), 60.5 (C-6 and C-6′), 56.7 (C-1″); *m*/*z* (ESI-MS) 1230.0 (Found: $[M + NH_4^+]$. $C_{51}H_{76}NO_{33}$ requires $[M + NH_4^+]$ 1230.4).

Pentaerythritol tetrakis(*p*-iodobenzyl) ether 16

Pentaerythritol (**14**) (27.2 mg, 0.2 mmol) was dissolved into 10 ml of dry DMF, then a catalytic amount of tetrabutylammonium iodide and 46 mg of NaH (0.96 mmol, 1.2 eq./OH) were added to the solution. After one hour, *p*-iodobenzyl bromide (**15**) (286 mg, 0.96 mmol) was added. The mixture was stirred at room temperature for 5 h. Excess NaH was slowly quenched with cold water. The solution was washed with 3 × 20 ml of ether and the organic phases were combined together and washed with 3 × 20 ml of water. After drying over anhydrous sodium sulfate the solvent was evaporated and the residue was carefully separated by silica gel column chromatography using hexane–ether (7 : 1) to give **16** as a white solid in 47% yield, mp 136–138 °C; δ_H (500 MHz; $CDCl_3$) 7.58 (8 H, d, *J* = 8.1, aromatic), 6.95 (8 H, d, *J* = 8.1, aromatic), 4.36 (8 H, s, PhCH_2), 3.45 (8 H, s, C(CH_2-)$_4$); δ_C (125 MHz; $CDCl_3$) 138.2, 137.3, 129.2 and 92.8 (aromatic), 72.5 (Ph*C*H_2), 69.1 (C(*C*H_2-)$_4$), 45.5 (*C*(CH$_2$-)$_4$); *m*/*z* (FAB-MS) 1001.2 (Found: $[M + H^+]$. $C_{33}H_{33}O_4$ requires $[M + H^+]$ 1001.0) (Anal. Calcd for $C_{33}H_{32}O_4I_4$: C, 39.63; H, 3.22. Found: C, 39.83; H, 3.19%).

α-Gal tetramer 17

To a solution of compound **8** (150 mg, 0.188 mmol) in 10 ml of DMF–TEA (1 : 1) were added $Pd(PPh_3)_2Cl_2$ (6.7 mg, 0.009 mmol (5 mol%)) and **16** (39.1 mg, 0.039 mmol). The solution was stirred under nitrogen at 60 °C for 5 h. The solvent and TEA were evaporated under reduced pressure. The resulting mixture was purified by silica gel column chromatography using ethyl acetate–hexane (2 : 1) to provide compound **17** as a white foam in 81% yield, $[\alpha]_D$ +97.5 (*c* 1, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 7.98–8.02 (16 H, m, aromatic), 7.40–7.55 (16 H, m, aromatic), 7.14–7.29 (20 H, m, aromatic), 5.54 (4 H, dd, *J* = 8.0, 10.1, H-2), 5.51 (4 H, d, *J* = 2.8, H-4), 5.20 (4 H, d, *J* < 1, H-1′), 5.18 (4 H, dd, *J* = 3.5, 10.4, H-2′), 5.03 (4 H, dd, *J* = 3.3, 10.4, H-3′), 4.90 (4 H, d, *J* = 8.0, H-1), 4.88 (4 H, m, H-4′), 4.58 (8 H, s, H-1″), 4.55 (4 H, dd, *J* = 6.4, 11.3, H-6a), 4.45 (8 H, s, PhCH_2), 4.32 (4 H, dd, *J* = 6.6, 11.3, H-6b), 4.10 (4 H, dd, *J* = 3.1, 10.1, H-3), 4.04 (4 H, t, *J* = 6.7, H-5), 3.96 (4 H, t, *J* = 6.5, H-5′), 3.73 (4 H, dd, *J* = 6.6, 11.2, H-6a′), 3.66 (4 H, dd, *J* = 6.6, 11.2, H-6b′), 3.56 (8 H, s, C(CH_2OR)$_4$), 2.20, 2.03, 1.99, 1.86 and 1.72 (each 12 H, 5s, 20 CH_3CO$_2$); δ_C (125 MHz; $CDCl_3$) 170.2, 169.9, 169.8, 169.7 and 169.3 (CH$_3$*C*O$_2$), 166.0, 165.0 (Ph*C*O$_2$), 139.5, 133.4, 133.3, 132.1, 132.0, 131.7, 129.7, 129.4, 129.3, 128.5, 128.4, 127.1, 127.0 and 121.1 (aromatic), 98.9 (C-1), 93.7 (C-1′), 86.7 and 83.5 (acetylenic), 73.7 (C-3), 72.8 (Ph*C*H$_2$), 71.0 (C-5), 70.0 (C-2), 69.5 (C(*C*H$_2$OR)$_4$), 67.6 (C-4′), 66.9 (C-3′), 66.5 (C-2′), 66.4 (C-5′), 65.1 (C-4), 61.7 (C-6), 61.2 (C-6′), 56.8 (C-1″), 45.7 (*C*(CH$_2$OR)$_4$), 20.7, 20.4 and 20.3 (*C*H$_3$CO$_2$); *m*/*z* (MALDI-TOF MS) 3706.55 (Found: $[M + Na^+]$. $C_{189}H_{196}O_{78}$ requires $[M + Na^+]$ 3706.68).

Fully deprotected α-Gal tetramer 18

α-Gal tetramer **17** (95 mg, 0.026 mmol) was dissolved into 40 ml of methanol to which a catalytic amount of sodium methoxide was added. The mixture was stirred at room temperature for 24 h. Sodium methoxide was neutralized with AMBERLITE IR-120 (H+). After careful filtration of the resin through a loose cotton plug, methanol was removed under reduced pressure, the dried residue was extracted with ether 3 × 10 ml to remove methyl benzoate to afford the deprotected glycocluster **18** as an off-white foam in 95% yield, $[\alpha]_D$ 0.0 (*c* 1.8, H_2O); δ_H (500 MHz; D_2O) 7.30 (8 H, br s, aryl), 6.98 (8 H, br s, aryl), 5.21 (4 H, br s, H-1′), 4.82 (8 H, s, PhCH_2 or H-1″), 4.63 (8 H, s, PhCH_2 or H-1″), 4.60 (4 H, br s, H-1), 4.23 (8 H, br s, H-5 and H-5′), 4.06 (4 H, br s, H-4′), 4.01 (4 H, br d, *J* = 10.8, H-3′), 3.93 (4 H, dd, *J* = 2.9, 10.1, H-2′), 3.77–3.83 (28 H, m, H-2, H-3, H-4, H-6 and H-6′), 3.42 (8 H, s, C(CH_2OR)$_4$); δ_C (125 MHz; D_2O) 138.5, 131.3, 126.8 and 120.6 (aromatic), 101.1 (C-1), 95.0 (C-1′), 85.2 and 84.5 (acetylenic), 77.2, 70.3, 68.9, 68.7, 67.8, 64.2, 60.5, 60.2, 56.6 (C-4, C-5, C-6, C-2′, C-3′, C-4′, C-5′, C-6′, Ph*C*H$_2$, C-1″); *m*/*z* (ESI-MS) 1022.2 (Found: $[M + 2NH_4^+]$. $C_{93}H_{132}N_2O_{48}$ requires $[M + 2NH_4^+]$, 1022.4).

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