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Facile synthesis of glycotope bioisosteres bearing β-D-galactoside moieties

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Abstract—To investigate the relationship between the structural features and binding effectiveness involved in multiple protein–carbohydrate interactions, glycoconjugate analogues of limited flexibility containing β-D-galactopyranoside moieties were synthesized in good yields using the Sonogashira reaction.

1. Introduction

Carbohydrate–protein interactions contribute to many important biological events such as cell adhesion, pathogenic infections, cell growth, and xenotransplantation.[1–3] Unfortunately, the intrinsic low affinity between monovalent carbohydrates and proteins discourages the applications of carbohydrates as therapeutic agents. To tackle this problem, a plethora of neoglycoconjugates[4–9] based on the 'multivalent effect'[10,11] have been synthesized and have shown remarkable increases in binding affinity. However, the multivalent interaction mechanism at the molecular level remains debatable. For instance, the length of the linkers,[8,9] the spatial arrangements of the sugar arrays, i.e. the relative geometry and orientation of the ligands, all may play significant roles in the binding process. It has been recognized that conformationally restricted or 'rigidified' domains[9,12] such as aryl cores or linkers in the synthetic ligands may compensate for the entropic loss accompanying binding.[10,13] If these structural concerns can be incorporated into the design of the synthetic glycoconjugates, it may help us to better refine our understanding of multiple carbohydrate–protein interactions. The aim of the present work is to investigate the syntheses of galactoside clusters having less flexible linkers than those frequently used for analogous purposes, such as oligoethylene glycol and hexamethylene diamine.[4]

Palladium-mediated organic synthesis has evolved into a very fast growing field during the last decades.[14] Among which the Sonogashira reaction,[15] based on the cross-coupling between vinyl or aryl halides and terminal alkynes using palladium(0) species offers a very efficient method for the construction of molecular rods and dendrimers with rigid structures.[16,17] The applications of the Sonogashira reaction toward the synthesis of rigid bivalent glycoclusters have been reported,[18–21] however, its usage for the synthesis of high-order glycoclusters was limited. In this respect, we report herein a facile method for the synthesis of glycocluster analogues with different geometry and rigid structures for the study of 'multivalent effect' and the molecular mechanism of carbohydrate–protein recognition. Herein, the important β-D-galactoside-containing glycotope bioisosteres, i.e. mimetics of multiantennary glycans, were synthesized since β-D-Gal is a key ligand involved in galectins known to mediate cell adhesion and tissue organization.[22,23]

2. Results and discussion

Traditionally, the Sonogashira reaction is carried out using CuI as a co-catalyst.[24] However, it was observed that in the presence of catalytic amount of CuI, the cross-coupling reaction also catalyzed the oxidative homocoupling of terminal alkynes at room temperature,[25–26] while the reaction did not proceed or proceeded very slowly without CuI. To explore the role of CuI in the Sonogashira reaction in carbohydrate chemistry, the reaction was performed at high temperature and it was found that in the absence of CuI the formation of homodimers was greatly inhibited or abolished.[19–21]

2.1. Syntheses of pentaerythritol-based cores

Due to its tetrahedral geometry pointing toward all directions, pentaerythritol (**1**) can provide a reasonable core structure to link multiple carbohydrates for the purpose of studying sugar–protein binding. Thus, pentaerythritol was chosen as the basic core for the preparation of fully iodobenzylated ethers. The rationale for the use of *para*-, *meta*- and *ortho*-iodobenzyl bromides **2**, **3** and **4** was based on the

Keywords: multivalent effect; glycoconjugates; Sonogashira reaction.

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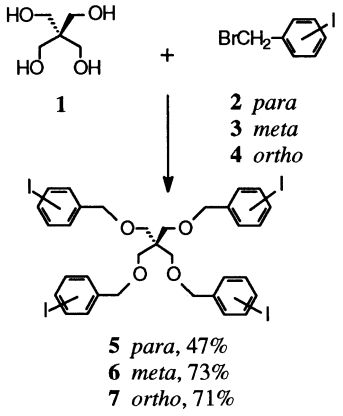


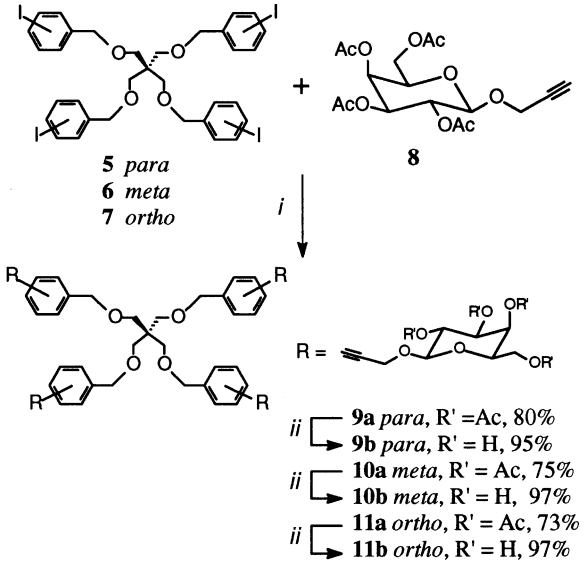
Scheme 1. *Reagents and conditions*: NaH, TBAI, DMF, rt, 5 h.

fact that after the Sonogashira reaction, the inter-sugar distances and relative orientation would be systematically varied which in turn would provide suitable models for the exploration of sugar–protein recognition, analogous to glycoforms seen in multi-antennary glycoproteins.

Treatment of pentaerythritol with NaH, iodobenzyl bromides (**3**, **4**), and a catalytic amount of tetrabutylammonium iodide in DMF, provided *meta*- and *ortho*-iodobenzyl precursors **6** and **7** in yields of 73 and 71%, respectively (Scheme 1). The yield for the formation of the *para*-derivative **5** was, however, moderate (47% yield).[27]

2.2. Syntheses of β-D-Gal-containing clusters

In this event, 2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **8**[28] was used in the synthesis. The preparation of the tetrameric glycoclusters was done using the Sonogashira reaction protocol described above without CuI. Treatment of **8** with iodobenzyl precusors **5**, **6** or **7** provided their corresponding tetrameric glycoclusters **9a**, **10a** and **11a** in good yields (Scheme 2). Fig. 1 shows the full structures of compounds **10**. Transesterification of **9a**, **10a** and **11a** under



Scheme 2. *Reagents and conditions:* (*i*) $(PPh_3)_2PdCl_2$, DMF/TEA (1:1), 60°C, 5 h; (*ii*) NaOMe, MeOH, 24 h.

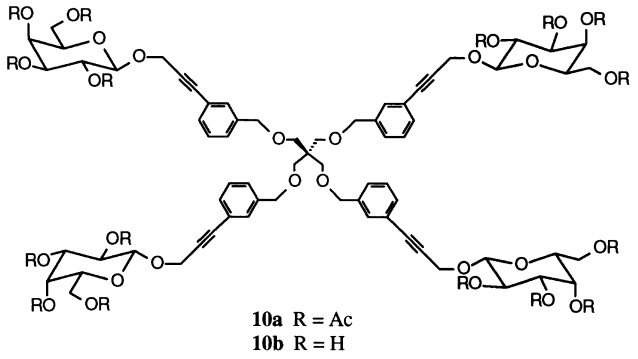
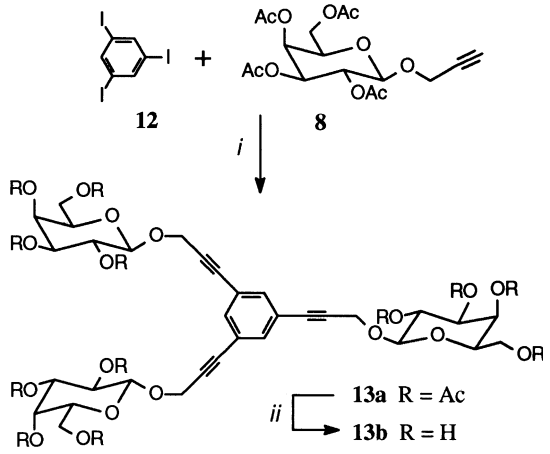


Figure 1. Structure of glycocluster **10**.

Zemplén conditions (NaOMe, MeOH) resulted in the fully deprotected glycoclusters **9b**, **10b** and **11b** in yields of 95, 97, and 97%, respectively.

The synthesis of the β-D-Gal trimer **13a** was carried out in the same manner (Scheme 3). The cross-coupling of 1,3,5-triiodobenzene **12**[29] with **8** provided a rigid structure, thus giving access to a good model for the study of the relationship between rigidity and binding behavior. Treatment of **12** with **8** catalyzed by $(PPh_3)_2PdCl_2$ in DMF and triethylamine provided **13a** in 85% yield. Full deprotection of **13a** with a catalytic amount of sodium methoxide in methanol as above generated **13b** in 95% yield.

In summary, we have reported a convenient route toward the synthesis of glycoclusters with different geometry and shapes for the investigation of multiple carbohydrate–protein interactions using the Sonogashira reaction in the absence of Cu(I) catalyst. Unfortunately, the present tetrameric galctoside clusters were found to be insufficiently water-soluble to justify further biological investigations. The lack of water solubility of **9b**–**11b** and **13b** is in strike contrast to previously described tetramers bearing the disaccharide Galα1-3Galβ-OR (Galili epitope)[27] in which the 'extra' α-galactoside residue obviously conferred the desired solubility (and specificity). Therefore, analogous clusters bearing lactose disaccharide (Galβ1-4Glcβ-OR, not α-Gal) would need to be further evaluated. Work is in progress to address this issue. Moreover, a recent report[30]



Scheme 3. *Reagents and conditions*: (*i*) $(PPh_3)_2PdCl_2$, DMF/TEA (1:1), 60°C, 85%, 5 h; (*ii*) NaOMe, MeOH, 24 h, 95%.

illustrated the preferred binding requirement of Galectin-1 toward lactose over single galactoside, thus supporting the need for the investigation.

3. Experimental

3.1. General methods and materials

Iodobenzyl bromides were from Karl Industries Inc. All the other chemicals were purchased from Aldrich Chemicals. Thin layer chromatography was performed on Silica Gel F_{254} (Merck) precoated aluminum sheets and visualized with molybdenum solution and/or UV detection. Column chromatography was run on Ultra Pure Silica Gel (Silicycle). Elemental analyses were measured on a CE-2500 Elemental Analyzer (Carlo Erba). Melting points were determined on a Gallenkamp melting point apparatus without temperature correction. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. All the NMR spectra (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) were recorded on an AMX500 spectrometer. The resonances were assigned based on ^{1}H, ^{1}C, ^{1}H–^{1}H COSY, DEPT, HMQC experiments. Chemical shifts were referenced to $CDCl_3$ (δ_H 7.29 and δ_C 77.0). FAB-MS spectra were recorded on Kratos Concepts IIH with Cs^+ beam and are not high resolution unless stated otherwise.

3.2. Pentaerythritol tetrakis (iodobenzyl) ethers 6 and 7

Pentaerythritol **1** (27.2 mg, 0.2 mmol) was dissolved into dry DMF (10 ml), to which were added a catalytic amount of tetrabutylammonium iodide (10 mg) and NaH (46 mg, 0.96 mmol). The mixture was stirred at room temperature for 30 min and then iodobenzyl bromide (**3** or **4**) (286 mg, 0.96 mmol) was added to it. The reaction was monitored by TLC and was completed in 4 h. Excess NaH was quenched with several drops of methanol. The mixture was diluted with 50 ml of water and then washed with 3×30 ml of ether. The combined organic layers were washed with 3×30 ml of water and dried over anhydrous sodium sulfate. After evaporating the solvent under reduced pressure, the residue was carefully separated by silica gel chromatography using hexane/ether (10:1). After removal of the solvent, a white solid was obtained. Tetrameric iodobenzyl ethers **6** and **7** were obtained in 73 and 75% yields, respectively.

3.2.1. Pentaerythritol tetrakis (*m*-iodobenzyl) ether (6). Mp 85–87°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 4H, aromatic), 7.56 (d, 4H, J=7.9 Hz, aromatic), 7.19 (d, 4H, J=7.7 Hz, aromatic), 7.05 (t, 4H, J=7.8 Hz, aromatic), 4.40 (s, 8H, PhCH_2), 3.49 (s, 8H, C(CH_2OR)$_4$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 136.4, 136.1, 130.0, 126.4 and 94.3 (aromatic), 72.3 (PhCH_2), 69.1 (C(*C*H_2OR)$_4$), 45.5 (*C*(CH$_2$OR)$_4$). Anal. calcd for $C_{33}H_{32}O_4I_4$: C, 39.64; H, 3.22, found: C, 39.74; H, 3.27. FAB-MS calcd for $C_{33}H_{32}O_4I_4K$ (M+K$^+$): 1038.8, found: 1038.8.

3.2.2. Pentaerythritol tetrakis (*o*-iodobenzyl) ether (7). Mp 109–111°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, 4H, J=7.9 Hz, aromatic), 7.35 (d, 4H, J=7.7 Hz, aromatic), 7.21 (t, 4H, J=7.7 Hz, aromatic), 6.91 (t, 4H, J=7.7 Hz, aromatic), 4.46 (s, 8H, PhCH_2), 3.70 (s, 8H, C(CH_2OR)$_4$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 138.8, 128.8, 128.5, 128.0 and 97.3 (aromatic), 77.0 (PhCH_2), 69.6 (C(*C*H_2OR)$_4$), 45.9 (*C*(CH$_2$OR)$_4$). Anal calcd for $C_{33}H_{32}O_4I_4$: C, 39.63; H, 3.22. Found: C, 39.77; H, 3.30). FAB-MS calcd for $C_{33}H_{32}O_4I_4K$ (M+K$^+$): 1038.8, found: 1038.7.

3.3. Preparation of 9a, 10a, 11a, and 13a using Sonogashira coupling reaction

Pentaerythritol tetrakis (*p*-iodobenzyl) ether **5**[27] (100 mg, 0.1 mmol) was dissolved into a mixture of DMF and TEA (20 ml, 1:1) to which were added $(PPh_3)_2PdCl_2$ (3.6 mg, 5 mol%) and 2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **8** (185 mg, 0.48 mmol). Under nitrogen, the solution was stirred at 60°C for 6 h. The solvent and triethylamine were removed under reduced pressure. The residue was purified by silica gel column chromatography using hexane/ethyl acetate (1:1.5) to afford **9a** as a white foam in 80% yield. Compound **10a** and **11a** were prepared in 75 and 73% yields, respectively, following the same procedure.

The same procedure was adopted for the cross-coupling between triiodobenzene **12** and 2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **8** to generate **13a** in 85% yield.

3.3.1. Compound 9a. $[\alpha]_D$=+95.2 (*c* 1.5, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, 8H, J=7.7 Hz, aromatic), 7.20 (d, 8H, J=7.7 Hz, aromatic), 5.38 (dd, 4H, J=1.0, 3.5 Hz, H-4), 5.24 (dd, 4H, J=8.0, 10.4 Hz, H-2), 5.05 (dd, 4H, J=3.5, 10.4 Hz, H-3), 4.77 (d, 4H, J=8.0 Hz, H-1), 4.58 (d, 8H, J=1.4 Hz, H-1′), 4.45 (s, 8H, PhCH_2), 4.08–4.21 (m, 8H, H-6), 3.95 (m, 4H, H-5), 3.55 (s, 8H, C(CH_2OR)$_4$), 2.14, 2.03, 2.02 and 1.97 (4s, 48H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1 and 169.5 (CH$_3$*C*O), 139.6, 131.7, 127.1 and 121.2 (aromatic), 99.0 (C-1), 86.9 and 83.5 (acetylenic), 72.9 (C-3), 70.9 (Ph*C*H$_2$), 70.8 (C-5), 69.6 (C(*C*H$_2$OR)$_4$), 68.7 (C-2), 67.0 (C-4), 61.2 (C-6), 56.9 (C-1′), 45.7 (*C*(CH$_2$OR)$_4$). Anal calcd for $C_{101}H_{116}O_{44}$: C, 59.52; H, 5.94, found: C, 59.87; H, 5.80). FAB-MS calcd for $C_{101}H_{116}O_{44}K$ (M+K$^+$): 2071.7, found: 2071.5.

3.3.2. Compound 10a. $[\alpha]_D$=+101.3 (*c* 1, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.31 (m, 8H, aromatic), 7.21–7.24 (m, 8H, aromatic), 5.37 (dd, 4H, J=1.0, 3.4 Hz, H-4), 5.21 (dd, 4H, J=8.0, 10.4 Hz, H-2), 5.03 (dd, 4H, J=3.4, 10.4 Hz, H-3), 4.75 (d, 4H, J=8.0 Hz, H-1), 4.55 (d, 8H, J=2.0 Hz, H-1′), 4.43 (s, 8H, PhCH_2), 4.07–4.18 (m, 8H, H-6), 3.91 (t, 4H, J=6.7 Hz, H-5), 3.52 (s, 8H, C(*C*H_2OR)$_4$), 2.12 (12H, s, CH_3CO), 2.00 (s, 24H, CH_3CO), 1.95 (s, 12H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 130.8, 130.4, 128.4, 127.7 and 122.1 (aromatic), 98.9 (C-1), 86.9 and 83.5 (acetylynic), 72.7 (C-3), 70.8 (Ph*C*H$_2$), 70.8 (C-5), 69.3 (C(*C*H$_2$OR)$_4$), 68.6 (C-2), 67.0 (C-4), 61.2 (C-6), 56.8 (C-1′), 45.6 (*C*(CH$_2$OR)$_4$). Anal calcd for $C_{101}H_{116}O_{44}$: C, 59.52; H, 5.94, found: C, 59.41; H, 5.79. HRMS-FAB calcd for $C_{101}H_{116}O_{44}K$ (M+K$^+$): 2071.6659, found: 2071.7598.

3.3.3. Compound 11a. $[\alpha]_D$=+97.0 (*c* 1.1, $CHCl_3$); ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.36–7.41 (m, 8H, aromatic), 7.14–7.20 (m, 8H, aromatic), 5.36 (bd, 4H, J=3.3 Hz, H-4), 5.21 (dd, 4H, J=8.0, 10.4 Hz, H-2), 5.03 (dd, 4H, J=3.4, 10.4 Hz, H-3), 4.75 (d, 4H, J=8.0 Hz, H-1), 4.64 (s, 8H, PhCH_2), 4.55 (s, 8H, H-1′), 4.07–4.17 (m, 8H, H-6), 3.91 (t, 4H, J=6.7 Hz, H-5), 3.69 (s, 8H, C(CH_2OR)$_4$), 2.12, 1.98, 1.96 and 1.94 (4s, 48H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 132.0, 128.8, 126.8, 126.5 and 119.7 (aromatic), 98.8 (C-1), 88.3 and 84.4 (acetylenic), 70.9 (PhCH_2 and C-3), 70.8 (C-5), 69.7 (C(CH$_2$OR)$_4$), 68.6 (C-2), 67.0 (C-4), 61.2 (C-6), 56.7 (C-1′), 45.8 (C(CH$_2$OR)$_4$). FAB-MS calcd for $C_{101}H_{116}O_{44}K$ (M+K$^+$): 2071.7, found: 2071.5.

3.3.4. 1,3,5-Tris [3′-*O*-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-galactopyranosyl)-prop-1′-enyl] benzene (13a). $[\alpha]_D$=+105.4 (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 3H, aromatic), 5.38 (dd, 3H, J=1.0, 3.4 Hz, H-4), 5.20 (dd, 3H, J=8.0, 10.5 Hz, H-2), 5.05 (dd, 3H, J=3.4, 10.5 Hz, H-3), 4.73 (d, 3H, J=8.0 Hz, H-1), 4.56 (d, 6H, J=3.2 Hz, H-1′), 4.09–4.12 (m, 6H, H-6), 3.94 (t, 3H, J=6.2 Hz, H-5), 2.13, 2.02, 2.01 and 1.99 (4s, 36H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7 (aromatic), 123.2 (aromatic), 99.0 (C-1), 85.2 and 84.8 (acetylenic), 70.8 (C-3 and C-5), 68.6 (C-2), 66.9 (C-4), 61.2 (C-6), 56.5 (C-1′). HRMS-FAB calcd for $C_{57}H_{66}O_{30}K$ (M+K$^+$): 1269.3276, found: 1269.3567 (M+K$^+$).

3.4. Preparation of 9b, 10b, 11b and 13b using Zemplén reaction

The fully protected glycocluster **9a** (50 mg, 0.025 mmol) was dissolved into methanol (20 ml), to which was added a catalytic amount of sodium methoxide. The solution was stirred at room temperature for 24 h. After neutralization of sodium methoxide with Amberlite IR-120 (H+), the solution was filtered through a cotton plug. Removal of methanol under reduced pressure afforded the fully deprotected cluster **9b** as a white foam in 95%.

Compounds **10b** and **11b** were generated in the same way in 97 and 97% yields, respectively. The same reaction was applied to compound **13a** to provide **13b** as a white foam in 95% yield.

3.4.1. Compound 9b. $[\alpha]_D$=+98.5 (c 1.5, DMSO); ^{1}H NMR (500 MHz, DMSO-d6) δ 7.38 (d, 8H, J=7.9 Hz, aromatic), 7.25 (d, 8H, J=7.9 Hz, aromatic), 4.61 (d, 4H, J=15.8 Hz, H-1a′), 4.49 (d, 4H, J=15.8 Hz, H-1b′), 4.44 (s, 8H, PhCH_2), 4.26 (d, 4H, J=6.8 Hz, H-1), 3.63 (bd, 4H, J=2.0 Hz, H-4), 3.52 (d, 8H, J=6.1 Hz, H-6), 3.45 (s, 8H, C(CH_2OR)$_4$), 3.36 (m, 4H, H-5), 3.32 (m, 4H, H-3), 3.30 (m, 4H, H-2); ^{13}C NMR (125 MHz, DMSO-d6) δ 139.4, 131.3, 127.4 and 120.9 (aromatic), 101.8 (C-1), 85.81 (acetylenic), 75.4 (C-5), 73.4 (C-2), 72.5 (PhCH_2), 70.4 (C-3), 69.0 (C(CH$_2$OR)$_4$), 68.2 (C-4), 60.5 (C-6), 55.6 (C-1′), 49.5 (C(CH$_2$OR)$_4$).). FAB-MS calcd for $C_{69}H_{84}O_{28}K$ (M+K$^+$): 1399.5, found: 1399.6.

3.4.2. Compound 10b. $[\alpha]_D$=+101.2 (c 1, DMSO); ^{1}H NMR (500 MHz, DMSO-d6) δ 7.26–7.34 (m, 16H, aromatic), 4.59 (d, 4H, J=15.6 Hz, H-1a′), 4.48 (dd, 4H, J=15.6 Hz, H-1b′), 4.43 (s, 8H, PhCH_2), 4.26 (d, 4H, J=7.0 Hz, H-1), 3.63 (bs, 4H, H-4), 3.51 (m, 8H, H-6), 3.44 (s, 8H, C(CH_2OR)$_4$), 3.30–3.36 (m, 12H, H-2, H-3 and H-5); ^{13}C NMR (125 MHz, DMSO-d6) δ 139.2, 130.4, 130.0, 128.7, 127.6 and 121.8 (aromatic), 101.8 (C-1), 85.9 and 85.4 (acetylenic), 75.4 (C-5), 73.4 and 70.4 (C-2 and C-3), 71.8 (PhCH$_2$), 68.8 (C(CH$_2$OR)$_4$), 68.2 (C-4), 60.5 (C-6), 55.2 (C-1′), 45.2 (C(CH$_2$OR)$_4$)). FAB-MS calcd for $C_{69}H_{84}O_{28}K$ (M+K$^+$): 1399.5, found: 1399.4.

3.4.3. Compound 11b. $[\alpha]_D$=+96.3 (c 1, DMSO); ^{1}H NMR (500 MHz, DMSO-d6) δ 7.23–7.42 (m, 16H, aromatic), 4.65 (m, 12H, PhCH_2 and H-1a′), 4.49 (d, 4H, J=15.8 Hz, H-1b′), 4.27 (d, 4H, J=6.7 Hz, H-1), 3.62 (bs, 4H, H-4), 3.59 (bs, 8H, C(CH_2OR)$_4$), 3.51 (m, 8H, H-6), 3.36 (m, 4H, H-5), 3.30 (m, 8H, H-2 and H-3); ^{13}C NMR (125 MHz, DMSO-d6) δ 140.4, 131.8, 128.8, 127.2, 126.8 and 119.9 (aromatic), 101.7 (C-1), 90.5 and 82.9 (acetylenic), 75.4 (C-5), 73.4 (C-2 or C-3), 70.4 (PhCH$_2$, C-2 or C-3), 69.3 (C(CH$_2$OR)$_4$), 68.1 (C-4), 60.5 (C-6), 55.6 (C-1′), 45.4 (C(CH$_2$OR)$_4$). FAB-MS calcd for $C_{69}H_{84}O_{28}K$ (M+K$^+$): 1399.5, found: 1399.4.

3.4.4. Compound 13b. $[\alpha]_D$=+92.4 (c 1.5, DMSO); ^{1}H NMR (500 MHz, DMSO-d6) δ 7.51 (s, 3H, aromatic), 4.60 (d, 3H, J=16.0 Hz, H-1a′), 4.50 (d, 3H, J=16.0 Hz, H-1b′), 4.27 (d, 3H, J=7.2 Hz, H-1), 3.62 (bs, 3H, H-4), 3.51 (d, 6H, J=6.1 Hz, H-6), 3.37 (t, 3H, J=6.0 Hz, H-5), 3.30–3.31 (m, 6H, H-2 and H-3); ^{13}C NMR (125 MHz, DMSO-d6) δ134.1 (aromatic), 123.3 (aromatic), 101.7 (C-1), 87.8, and 83.5 (acetylenic), 75.4 (C-5), 73.2 and 70.4 (C-2 and C-3), 68.2 (C-4), 60.5 (C-6), 55.4 (C-1′). FAB-MS calcd for $C_{33}H_{42}O_{18}K$ (M+K$^+$): 765.2, found: 765.3.

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