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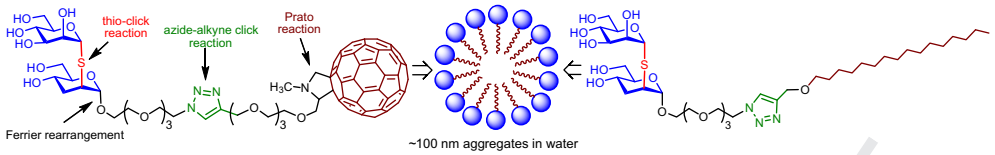
Graphical abstract

Rapid synthesis of self-assembling 1,2-thiomannobioside glycoconjugates as potential multivalent ligands of mannose-binding lectins pp xxx–xxx

Magdolna Csávás *, Tamás Demeter, Mihály Herczeg, István Timári, Katalin E. Kövér, Pál Herczegh, Anikó Borbás *



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Tetrahedron Letters xxx (2014) xxx–xxx

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Rapid synthesis of self-assembling 1,2-thiomannobioside glycoconjugates as potential multivalent ligands of mannose-binding lectins

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ARTICLE INFO

Article history:
Received 19 August 2014
Revised 2 October 2014
Accepted 16 October 2014
Available online xxxx

Dedicated to Professor Sándor Antus on the occasion of his 70th birthday

Keywords:
Ferrier glycoside
Photoinduced thiol-addition
Amphiphilic
Glycomimetic
Multivalent

ABSTRACT

Among the pathogen-associated carbohydrate patterns, the Man(α1→2)Man α disaccharide motif is of particular interest because its multivalent derivatives are considered as potential antiviral or antibacterial agents through interaction with mannose-binding lectins. We present a straightforward synthesis of amphiphilic compounds containing a hydrolytically stable *S*-linked 1,2-mannobioside residue, a tetraethylene glycol linker to ensure water solubility and various lipophilic carriers such as a hexadecyl chain and two pyrrolidinofullerene derivatives. According to a dynamic light scattering study, the obtained amphiphiles form nanoscale aggregates in water producing multivalent presentation of the thiomannobioside residue.

Mannose-binding lectins expressed on the surface of human dendritic cells (DCs) play key roles in the infection processes of various pathogens. For example, the C-type lectin receptor DC-SIGN (dendritic cell specific ICAM-3 grabbing non-integrin) specifically recognizes highly mannosylated structures of bacterial and viral glycoconjugates and functions as an entry receptor for several viruses such as HIV or Ebola by binding to their high-mannose-containing envelope glycoproteins.[1] The design and synthesis of carbohydrate ligands which might inhibit the pathogen entry by preferential binding to this receptor is of significant importance.

Multimeric presentation of the terminally exposed motif of the high-mannose structure, the monosaccharide Man α and the disaccharide Man(α 1→2)Man α, is considered to be an adequate strategy to interact with mannose-binding lectins with high affinity.[2] Indeed, it has been demonstrated by several groups that multiple copies of mannose, oligomannoside and its glycomimetics were able to block DC-SIGN.[3–7] However, mannose is not specific enough for in vivo applications, while the development of oligosaccharide-containing multivalent derivatives as potential therapeutics is hampered by both the demanding synthesis and the low chemical stability of oligosaccharides against enzymatic hydrolysis.[8,9]

Recently, we reported a simple and efficient synthesis of a thio-linked mimic of the disaccharide Man(α 1→2)Man α via photoinduced hydrothiolation of a 2,3-unsaturated glucoside.[10] By exploitation of this hydrothiolation approach, we envisaged the rapid assembly of amphiphiles composed of a hydrolytically stable *S*-linked mannobioside head, a hydrophilic linker to ensure water solubility and various lipophilic carriers, example fullerene. We assumed that these conjugates might display enhanced metabolic stability due to the interglycosidic thio-linkage and would form aggregates in water providing multivalent presentation of the sugar residue. Schaeffer and co-workers have shown recently that dynamic micelles of mannoside glycolipids displayed high affinity interactions with DC-SIGN and inhibited HIV-1 *trans*-infection more efficiently than multivalent polymers.[7] Here, we present the synthesis and aggregating properties of 1,2-thiomannobioside glycoconjugates containing different lipophilic residues.

Commercially available 3,4,6-tri-*O*-acetyl-d-glucal (**1**) was subjected to Ferrier rearrangement[11] with tetraethylene glycol

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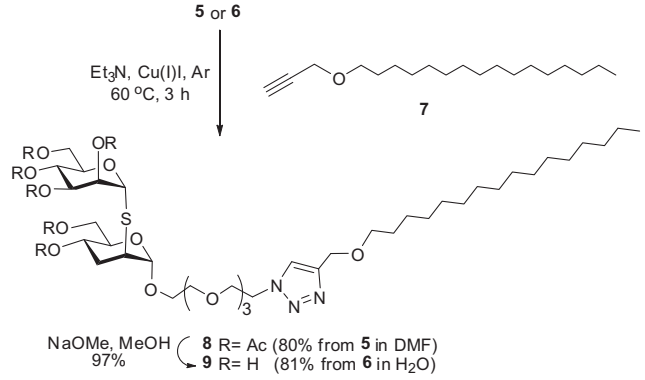
http://dx.doi.org/10.1016/j.tetlet.2014.10.104
0040-4039/

monotosylate[12] to afford the spacer-armed Ferrier glycoside **2** in 95% yield as an anomeric mixture (α/β, 85:15) as determined by ^{1}H NMR spectroscopic analysis. Addition of 2,3,4,6-tetra-*O*-acetyl-1-thio-α-d-mannopyranose (**3**)[13] to enoside **2** in toluene by irradiation at λ_{max} 365 nm in the presence of 2,2-dimethoxy-2-phenylacetophenone (DPAP) as a cleavage-type photoinitiator[14] provided exclusively the axially linked thio-mannobioside mimic **4** in 71% yield. Replacement of the tosyloxy group by azide resulted in compound **5**, deacetylation of which by using the Zemplén method afforded the mannobioside derivative **6** in 96% yield. Both latter compounds were ready to be conjugated to lipophilic carrier molecules bearing a terminal alkyne moiety (Scheme 1).

Initially, the Cu(I)-catalyzed azide–alkyne cycloaddition reaction[15] of the acetyl protected derivative **5** with hexadecyl propargyl ether (**7**) was carried out in DMF to obtain compound **8** (Scheme 2).

At room temperature, only 50% conversion of **5** was observed after 16 h. Repeating the experiment at 60 °C, the click reaction went to completion after 3 h, providing the coupled product in 80% yield. Zemplén deacetylation of **8** afforded the first mannobioside-containing amphiphile **9** in 97% yield. This compound was also prepared directly via click reaction between **6** and **7**. The 1,3-dipolar cycloaddition proceeded readily in water to afford **9** in 81% yield.[16]

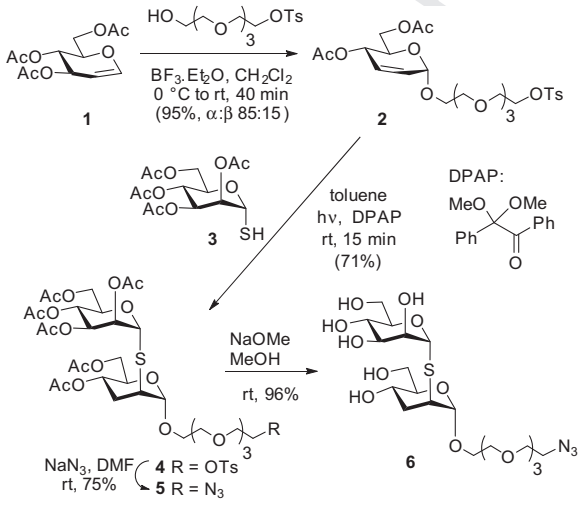
It has been shown by Rojo and co-workers that globular glycofullerenes with multimeric presentation of mannoses were able to inhibit a DC-SIGN dependent viral infection.[5] It is also known that fullerene derivatives can form self-assembled supramolecular nanostructures in water.[17] Hence, we intended to conjugate our mannobioside mimic to C60 fullerene. However, water solubility of glycofullerenes substituted with one or two sugar residues is quite limited.[18] Therefore, we chose as a carrier, our recently developed pyrrolidinofullerene derivative **10**, equipped with four tetraethyleneglycol chains for improving water solubility, and a propargyl ether residue allowing its functionalization with bioactive compounds via a 1,3-dipolar cycloaddition reaction.[19] Compound **10** has been successfully applied for the synthesis of a self-assembled sialodisaccharide conjugate which exhibited neuraminidase inhibitory activity in a micromolar range.[20] To avoid a deprotection procedure on the fullerene-sugar hybrid, the free mannobioside derivative **6** was reacted with **10** in water under copper(I)-catalysis with heating at 60 °C. The azide–alkyne cycloaddition reaction proceeded readily and the desired product **11** was isolated in good yields (Scheme 3).



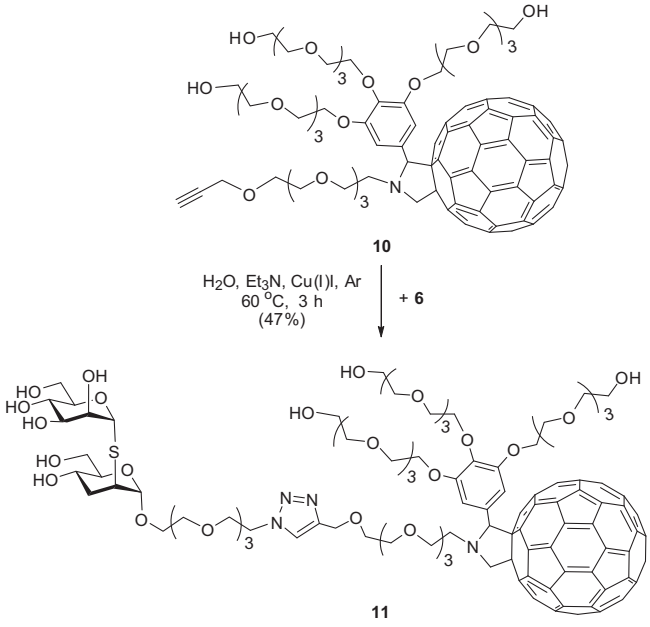
Scheme 2. Cu(I)-catalyzed azide–alkyne click reactions in DMF and water for the synthesis of mannobioside-hexadecanol conjugate **9**.

As we were determined to develop easy access to mannobioside-containing amphiphiles, besides **10** which was quite demanding to synthesize, the much simpler fullerene derivative **14** was also designed as a lipophilic carrier. Similar to the synthesis of **10**,[19] derivatization of the fullerene molecule was accomplished by the versatile Prato reaction,[21] which is a 1,3-dipolar cycloaddition of an azomethine ylide generated by the thermal reaction of an *N*-alkyl glycine with an aldehyde. In this case, triethylene glycol carbonylmethyl ether propargyl ether **12**[22] was used as the aldehyde partner, reaction of which with *N*-methyl glycine (**13**) and fullerene afforded the pyrrolidine derivative **14** bearing a tetraethylene glycol chain with a terminal alkyne moiety ready for the subsequent click reaction with the azide partner. The free mannobioside derivative **6** was subjected to a 1,3-dipolar cycloaddition reaction with **14**, that went to completion providing readily the third mannobioside-containing amphiphile **15** (Scheme 4). It is worth mentioning, however, that **15** was less soluble in polar solvents compared to **11**.

The cluster formation properties of the obtained mannobioside amphiphiles were studied by dynamic light scattering. According to these studies, compounds **9** (Fig. 1), **11** and **15** form 10–300 nm

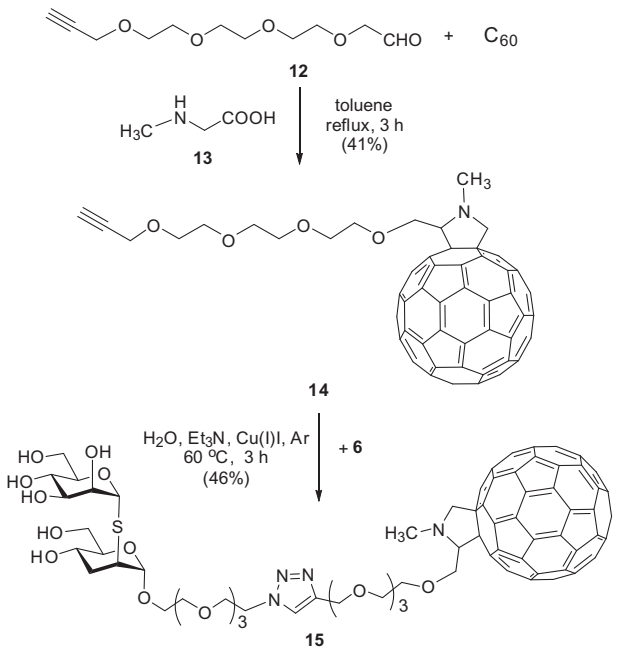


Scheme 1. Synthesis of the spacer-armed mannobioside mimics **5** and **6** via Ferrier rearrangement and subsequent radical thiol addition.



Scheme 3. Conjugation of mannobioside mimic **6** with the water soluble fullerene derivative **10**.

Please cite this article in press as: Csávás, M.; et al. *Tetrahedron Lett.* (2014), http://dx.doi.org/10.1016/j.tetlet.2014.10.104



Scheme 4. Functionalization of C60 fullerene via the Prato reaction and its conjugation with the mannobioside mimic **6**.

sized aggregates in water with a bimodal distribution. The effective diameter of these clusters was 108 nm for **9**, 66 nm for **11**, and 133 nm for **15** (see Supporting information).

In conclusion, we have demonstrated that Ferrier rearrangement combined with radical hydrothiolation is a simple and highly efficient approach to produce spacer-armed and hydrolytically stable 1,2-mannobioside mimics on a large scale.[23] The azide-functionalized disaccharides, both in protected and unprotected forms, could be conjugated to propargyl-containing lipophilic carriers. The obtained amphiphiles (**9**, **11** and **15**) form nanoscale aggregates in water and therefore can function as multivalent ligands. Investigation of the binding affinity of the derivatives toward mannose-binding lectins and the preparation of further multivalent oligomannosides are underway.

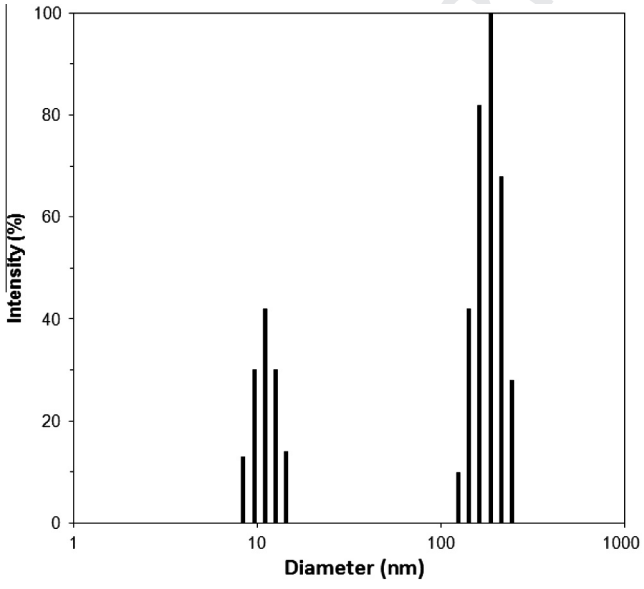


Figure 1. Size distribution of aggregates of compound **9** in water.

Acknowledgments

This study was supported by the TÁMOP 4.2.4.A/2-11-1-2012-0001 Project (National Excellence Program). The project is co-financed by the European Union and the European Social Fund. Financial support from the Hungarian Research Fund (OTKA K 109208 and K 105459) is also acknowledged. The authors wish to thank Erzsébet Rőth for her dedicated technical assistance and Dr. Sándor Kéki for the dynamic light scattering measurements.

Supplementary data

Supplementary data (experimental section, Dynamic Light Scattering (DLS) experiments, spectral data for compounds **9**, **11**, and **15** and ^{1}H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.104.

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16. This result is in accordance with the findings of Sharpless[15a] that click reactions often proceed readily in hot water, to give a single product, even when one or more of the reactants, as well as the product, appear to be insoluble in this medium.
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23. Analytical data:
Compound **2**: $[\alpha]_D^{24}$ +46.89 (*c* 8.77, $CHCl_3$); R_f 0.53 (9:1 CH_2Cl_2-acetone); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.79 (d, 2H, *J* = 8.2 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 5.87 (s, 2H), 5.32 (d, 1H, *J* = 9.6 Hz), 5.08 (s, 1H), 4.37–3.79 (m, 18H), 3.80–3.44 (m, 1H), 2.45 (s, 3H), 2.09 (d, 6H, *J* = 4.3 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.5, 170.1 (2C, 2 × C=O), 144.6, 132.9 (2C, 2 × C_q arom), 129.6, 127.8 (4C, arom), 128.9, 127.6 (2C, C-2, C-3), 94.4 (C-1), 70.5, 70.4, 70.3, 70.2, 69.1, 68.5, 67.6 (8C, 8 × OCH_2), 66.7, 65.1 (2C, C-4, C-5), 62.8 (C-6), 21.4, 20.8, 20.6 (3C, 3 × CH_3). MALDI-TOF (positive ion): *m*/*z* calcd for $C_{25}H_{36}NaO_{12}S$ $[M+Na]^+$ 583.18. Found: 583.21.
Compound **4**: $[\alpha]_D^{24}$ +36.43 (*c* 2.91, $CHCl_3$); R_f 0.30 (92:8 CH_2Cl_2-acetone); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.81 (d, 2H, *J* = 8.2 Hz), 7.36 (d, 2H, *J* = 7.9 Hz), 5.38 (s, 1H), 5.36–5.17 (m, 4H), 5.10–4.95 (m, 1H), 4.86 (s, 1H), 4.47–3.50 (m, 23H), 3.25 (s, 1H), 2.46 (s, 3H), 2.33–1.88 (m, 18H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.8, 170.5, 169.8, 169.7 (6C, 6 × C=O), 144.8, 132.9 (2C, 2 × C_q arom), 129.8, 127.9 (4C, arom), 98.7 (C-1), 82.6 (C-1′), 76.8, 70.8, 70.7, 70.6, 70.5, 70.1, 69.3, 69.2, 68.8, 68.6, 66.9, 66.1, 64.7 (skeleton carbons and OCH_2), 62.9, 62.2 (2C, C-6, C-6′), 44.7 (C-2), 29.2 (C-3), 21.6, 21.0, 20.8, 20.7, 20.6 (7C, 7 × CH_3). MALDI-TOF (positive ion): *m*/*z* calcd for $C_{39}H_{56}NaO_{21}S$ $[M+Na]^+$ 947.27 Found: 948.36.
Compound **5**: ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 5.51–5.26 (m, 4H), 5.13 (dt, 1H, J_1 = 15.8 Hz, J_2 = 7.8 Hz), 4.95 (s, 1H), 4.52–4.43 (m, 1H), 4.42–4.15 (m, 5H), 4.08 (ddd, 1H, J_1 = 9.7 Hz, J_2 = 4.8 Hz, J_3 = 2.6 Hz), 3.91 (ddd, 1H, J_1 = 9.5 Hz, J_2 = 4.0 Hz), 3.84–3.66 (m, 12H), 3.53–3.44 (m, 2H), 3.34 (s, 1H), 2.37–2.28 (m, 2H), 2.29–1.97 (m, 18 H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.7, 170.4, 169.7, 169.6, 169.5 (6C, C=O), 98.7 (C-1), 82.3 (C-1′), 70.8, 70.6, 70.5, 70.0, 69.9, 69.2, 68.7, 66.8, 66.1, 64.7, 62.8, 62.2, 50.5 (skeleton carbons and OCH_2), 44.6 (C-2), 29.1 (C-3), 20.9, 20.8, 20.7, 20.6, 20.5 (6C, 6 × $AcCH_3$). MALDI-TOF (positive ion): *m*/*z* calcd for $C_{32}H_{49}N_3NaO_{18}S$ $[M+Na]^+$ 818.26. Found: 818.38.
Compound **6**: $[\alpha]_D^{24}$ +118.41 (*c* 8.97, MeOH); R_f 0.48 (8:2 CH_2Cl_2-MeOH); ^1H NMR (MeOH-d_4, 400 MHz): δ (ppm) 5.31 (s, 1H), 4.90 (s, 1H), 3.96–3.60 (m, 29H), 3.39–3.25 (m, 2H), 2.99 (s, 1H), 2.86 (s, 1H), 2.19–1.99 (m, 2H); ^{13}C NMR (MeOH-d_4, 100 MHz) δ (ppm) 100.4 (C-1), 87.4 (C-1′), 75.5, 75.2, 73.6, 73.2, 71.7, 71.6, 71.5, 71.1, 69.0, 67.7, 63.9, 63.2, 62.9 (skeleton carbons and OCH_2), 63.1, 62.8 (2C, C-6, C-6′), 51.8 (1C, CH_2N_3), 47.0 (C-2), 34.2 (C-3). MALDI-TOF (positive ion): *m*/*z* calcd for $C_{20}H_{37}N_3NaO_{12}S$ $[M+Na]^+$ 566.20. Found: 566.24.
Compound **8**: $[\alpha]_D^{24}$ + 88.30 (*c* 0.49, $CHCl_3$); R_f 0.23 (1:2 *n*-hexane–EtOAc); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.71 (s, 1H), 5.38–5.21 (m, 4H), 5.03 (d, 1H, *J* = 9.6 Hz), 4.86 (s, 1H), 4.61 (s, 2H), 4.54 (t, 2H, *J* = 5.0 Hz), 4.40–4.36 (m, 1H), 4.28 (dd, 1H, J_1 = 12.3 Hz, J_2 = 5.2 Hz), 4.22–4.09 (m, 4H), 3.99–3.96 (m, 1H), 3.88 (t, 2H, *J* = 5.0 Hz), 3.83–3.79 (m, 1H), 3.67–3.62 (m, 12H), 3.51 (t, 2H, *J* = 6.7 Hz), 3.24 (s, 1H), 2.96 (s, 2H), 2.89 (s, 2H), 2.24–1.97 (m, 20H), 1.58 (dd, 2H, J_1 = 13.8 Hz, J_2 = 6.8 Hz), 1.26 (s, 20H), 0.88 (t, 3H, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.7, 170.4, 169.7, 169.6, 169.5 (6C, 6× C=O), 145.2 (1C, HC=*C*), 123.4 (1C, *H*C=C), 98.7 (C-1), 82.3 (C-1′), 70.8, 70.7, 70.5, 70.4, 70.1, 69.4, 69.2, 68.8, 66.8, 66.1, 64.7, 64.2, 62.8, 62.2, 50.1 (skeleton carbons and OCH_2), 44.6 (C-2), 31.8 (C-3), 29.6, 29.4, 29.2, 26.0, 22.6 (14C, 14× CH_2), 20.9, 20.8, 20.7, 20.6, 20.5 (6C, 6 × $AcCH_3$), 14.0 (1C, CH_3). MALDI-TOF (positive ion): *m*/*z* calcd for $C_{51}H_{85}N_3NaO_{19}S$ $[M+Na]^+$ 1098.54. Found: 1098.65.
Compound **9**: $[\alpha]_D^{24}$ +79.57 (*c* 0.93, MeOH); R_f 0.50 (8:2 CH_2Cl_2-MeOH). MALDI-TOF (positive ion): *m*/*z* calcd for $C_{39}H_{73}N_3NaO_{13}S$ $[M+Na]^+$ 846.48. Found: 846.40.
Compound **14**: ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.32 (s, 1H, *H*CO), 4.87 (d, *J* = 9.4 Hz, 1H), 4.67–4.53 (m, 1H), 4.51–4.33 (m, 1H), 4.33–4.07 (m, 3H), 3.86–3.57 (m, 11H), 3.06 (s, 3H), 1.64 (s, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 146.9-135.5 (C_{60}), 75.5, 74.3, 71.7, 71.5, 68.9, 57.9, 39.9. MALDI-TOF (positive ion): *m*/*z* calcd for $C_{73}H_{23}NNaO_4$ $[M+Na]^+$ 1000.15. Found: 1000.16.