Synthesis of Deeper Calix-sugar–Based on the Sonogashira Reaction

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Abstract: The effective synthesis of tetrakis(mannopyranosyl) calix[4]arenes based in the cross-coupling Sonogashira reaction of propargyl α-D-mannopyranosyde and 25,26,27,28-tetrakis(4'-iodobenzyloxy)calix[4]arene is described.

Key words: alkynes, glycoclusters, carbohydrates, calixarenes, Pd-catalyzed reactions

The development of supramolecular chemistry has led to a growing interest in the design and synthesis of macrocyclic molecules containing intramolecular cavities.[1] In this regard, calix[n]arenes[2] have been used as building blocks for the synthesis of large host molecules with different supramolecular functions because they are readily accessible for chemical modification on both smaller (lower) and larger (upper) rims by attachment of a wide range of potential ligating groups. In particular, the synthesis of molecular receptors based on calixarenes have attracted some attention for their potential applications in the recognition of biologically active compounds (sugars,[3] aminoacids,[4] peptides,[5] nucleosides[6]) under physiological conditions. Calix-sugars[7] as well as calixresorcarene-sugars[8] have thus emerged as new medium-sized glycoconjugates. Remarkable features of those compounds are their polyhydroxylated and chiral nature. In addition, the incorporation of biorecognizable saccharide epitopes made of them potential molecular vectors for site-specific delivery of therapeutics.

As the host-guest properties of cavitands are dependent on the dimensions of their cavities, numerous synthetic attempts have been made to deepen the cavity, rigidify the structure, and functionalize the cavitand surface for further applications.[9] Up to the present, limited efforts have been conducted to enlarge the cavity of calix-sugar-based cavitands.[7i] Continuing our efforts in the design of multivalent glycoforms varying in molecular weights, shapes, valencies and geometries, we report in this paper the synthesis and biological activity of new calix-sugar with a deepened cavity constructed on the narrow rim using the Sonogashira reaction for the assembly of the sugar moieties onto the calixarene scaffolds.

As other synthetic-based calixarene receptors, calix-sugars have been generally prepared using the methodologies of classical organic synthesis. In the most of the cases, the grafting of the saccharides to the calixarene core have been performed by glycosidation[7a,b,e] or by formation of amide linkages.[7g,h,j] Other less used strategies include the formation of thiourea linkages,[7k] the Wittig olefination reaction,[7d] the Suzuki reaction[7i] and 1,3 dipolar cycloaddition reactions.[7l]

Considering the great utility of the Sonogashira reaction[10], we though that this coupling methodology could be also an adequate tool for grafting saccharides to calixarenes allowing also the simultaneous expanding of the cavity of carbohydrate-containing clusters. Recently, the Sonogoshira reaction has demonstrated its applicability in the carbohydrate field for the construction of related structures such as cyclic hydrils of 2,2'-bipyridine and acetylenosaccharides,[11a] "sugar-rods",[11b] α-Gal-containing clusters[11c] and acetyleno-linked adenosine dimers.[11d,e] Propargyl glycosides were thought to be adequate sugar building-blocks to perform Sonogashira coupling reaction owing to its easy accessibility. The synthetic strategy envisaged was based in the preliminary incorporation of an aryl iodide into a calixarene core by alkylation followed by Sonogashira cross-coupling of propargyl glycosides. Thus, calix[4]arenes **1** and **2** were reacted with commercially available *p*-iodobenzyl bromide using classical etherification conditions (NaH–DMF)[12] giving the corresponding iodoaryl derivatives **3** and **4** in high yield (97 and 84%, respectively). From these compounds, the tetrakis(mannopyranosyl) calix[4]arenes **6** and **7** were obtained[13] by the cross-coupling Sonogashira reaction with **5**[11b,14] using $(PPh_3)_4Pd$ as catalyst in the presence of a base (Et_3N or piperidine). When $(PPh_3)_2PdCl_2$ and a catalytic amount of CuI were used in these reactions a complex mixture of calixarene derivatives was formed together with the compound resulting of the oxidative homocoupling of the propargyl sugar derivative **5.**[15] In order to evaluate the biological activity of the obtained calix-sugars, compounds **6** and **7** were fully deprotected by standard Zemplen de-O-acetylation[16] to the corresponding free polyhydroxylated derivatives **8** and **9** (68 and 71% yield, respectively). The cross-linking properties of compound **8** toward the tetrameric plant lectin Concavalin A (Con A) were investigated by ELLA inhibition essays[17] using methyl α-D-mannopyranoside as a reference standard. Unfortunately, these essays showed that calix-sugar **8** has worse inhibitory properties in comparison with the reference. Similar essays could not be performed with compound **9** owing to its low solubility in water. The inclusion properties of these new calix-sugars will be the objective of future investigations.

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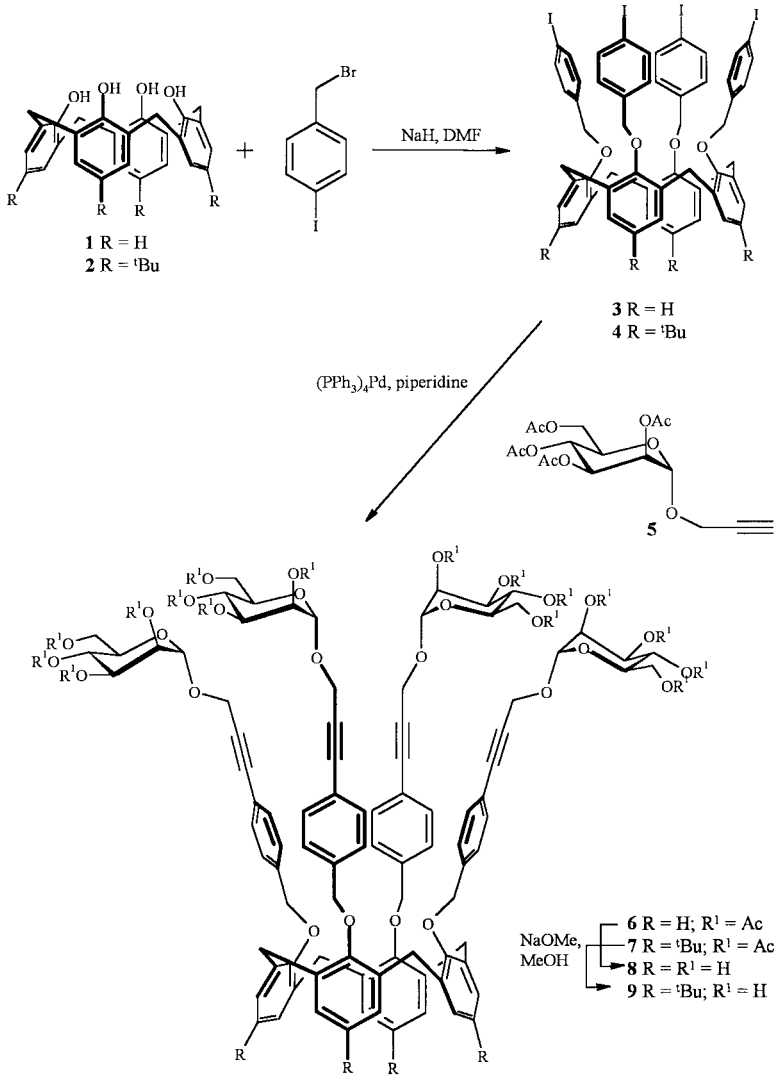

Scheme

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(12) **General procedure for the synthesis of iodoarylcalixarenes 3 and 4:** A suspension of the corresponding calix[4]arene (**1** or **2**) (0.23 mmol) and NaH (1.84 mmol) in DMF (10 mL) was kept at r.t. for 30 min. After this time *p*-iodobenzyl bromide (1.38 mmol) was added. The reaction mixture was then heated at 50 °C for 20 h. After cooling the excess of NaH was slowly quenched with cold methanol. Ether–toluene (3:1, 100 mL) was added and the resulting solution washed with water (3 × 21 mL). After drying over anhyd Na_2SO_4 the solvent was evaporated and the residue crystallized from MeOH giving **3** and **4**, respectively.

Physical data for compound **3: 25,26,27,28-tetrakis(4'-Iodo-benzyloxy)calix[4]arene** obtained as a solid (0.287 g, 97%): mp 80–82 ºC; IR (KBr): 1481, 1450, 1128, 1007, 806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)δ: 7.55 (d, 8 H, *J* = 8.2 Hz, C_6H_4I), 6.97 (d, 8 H, *J* = 8.2 Hz, C_6H_4I), 6.61–6.52 (m, 12 H, C_6H_3), 4.80 (s, 8 H, CH_2), 4.12, 2.97 (2 d, 8 H, *J* = 13.6 Hz, ArCH_2Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.2, 137.6, 137.4, 137.2, 135.1, 131.4, 129.7, 128.5, 122.6, 93.8, 75.8, 31.4; HRMS–FAB calcd for $C_{56}H_{44}I_4O_4$ + Na: 1310.9316 $(M + Na)^+$; found: 1310.9319.

Physical data for compound **4: 5,11,17,23-tetra-*tert*-Butyl-25,26,27,28-tetrakis(4'-iodo-benzyloxy)calix[4]arene** obtained as a solid (0.292 g, 84%): mp 212–214 ºC; IR (KBr): 1479, 1194, 1009 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.55, 6.97 (2 d, 16 H, *J* = 8.1 Hz, 4 C_6H_4 I), 6.75 (s, 8 H, Ar), 4.75 (s, 8 H, 4 CH_2O), 4.11, 2.91 (2 d, 8 H, *J* = 12.7 Hz, ArCH_2Ar), 1.08 (s, 36 H, 4 CMe_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.5, 145.0, 137.7, 133.6, 137.2, 131.4, 125.3, 93.6, 76.1, 33.9, 31.5, 31.4.; HRMS–FAB calcd for $C_{72}H_{76}I_4O_4$ + Na: 1535.1820 $(M + Na)^+$, found: 1535.1828.

(13) **General procedure for the synthesis of calix-sugars 6 and 7:** To a degassed solution of the corresponding 4-iodophenylcalixarene (**3** and **4**)(0.07 mmol)and the propargyl mannoside **5** (0.32 mmol) in anhyd piperidine (8 mL) was added $[Pd(PPh_3)_4]$ (0.007 mmol) and CuI. The solution was heated at 75 °C under an argon atmosphere for 30 min. The piperidine was removed by evaporation under vacuum. The residue was acetylated with Ac_2O–Pyridine (1:1, 10 mL). Conventional work-up gave a crude product, which was purified by column chromatography (silica gel, EtOAc–hexane 2:1) giving the calix-sugar **6** and **7**, respectively.

Physical data for **6: 25,26,27,28-tetrakis{4'-[1''-*O*-(2''',3''',4''',6'''-tetra-*O*-Acetyl-α-D-manno-pyranosyl)prop-3''-ynyl]benzyloxy}calix[4]arene** obtained as a solid (0.120 g, 74%): mp 100–103 °C; $[\alpha]_D$ +52 (*c* 0.5, $CHCl_3$); IR (KBr): 1749, 1369, 1224, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.27 (d, 8 H, *J* = 8.0 Hz, C_6H_4), 7.15 (d, 8 H, *J* = 8.0 Hz, C_6H_4), 6.51–6.15 (m, 12 H, C_6H_3), 5.31 (dd, 4 H, *J* = 10.1 and 3.3 Hz, H-3), 5.25 (t, 4 H, *J* = 10.0 Hz, H-4), 5.25 (d, 4 H, *J* = 3.3 Hz, H-2), 5.06 (s, 4 H, H-1), 4.85 (br s, 8 H, CH_2O), 4.43 (AB system, 8 H, *J* = 16.0 Hz, Δδ = 10.2 Hz; ArCH_2O), 4.24 (dd, 4 H, *J* = 12.1 and 4.8 Hz, H-6), 4.07–3.94 (m, 12 H, H-5,6', ArCH_2Ar), 2.78 (d, 4 H, *J* = 13.7 Hz, ArCH_2Ar), 2.08, 2.02, 1.97, 1.92 (4 s, 48 H, 16 MeCO); ^{13}C NMR (75 MHz, $CDCl_3$)δ: 170.0, 169.9, 169.8, 155.0, 138.3, 135.3, 131.7, 129.7, 128.4, 122.5, 121.5, 96.3, 87.2, 83.6, 75.9, 69.5, 69.1, 66.1, 62.4, 55.8, 31.4, 20.9, 20.8, 20.7; HRMS–FAB calcd for $C_{124}H_{128}O_{44}$ + Na: 2343.767 $(M + Na)^+$; found: 2343.765.

Physical data for **7: 5,11,17,23-tetra-*tert*-Butyl-25,26,27,28-tetrakis{4'-[1''-*O*-(2''',3''',4''',6'''-tetra-*O*-acetyl-α-D-mannopyranosyl)prop-3''-ynyl]benzyl-oxy}calix[4]arene** obtained as a solid (0.127 g, 71%): mp 127–129 °C;$[\alpha]_D$ +180 (*c* 1, chloroform); IR (KBr): 1753, 1485, 1367, 1223 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.32 (d, 8 H, *J* = 8.2 Hz, C_6H_4), 7.19 (d, 8 H, *J* = 8.2 Hz, C_6H_4), 6.66 (s, 8 H, Ar), 5.37 (dd, 4 H, *J* = 3.4 and 1.6 Hz, H-2), 5.30 (dd, 4 H, *J* = 10.1 and 3.4 Hz, H-3), 5.29 (t, 4 H, *J* = 9.7 Hz, H-4), 5.11 (d, 4 H, *J* = 1.6 Hz, H-1), 4.84 (s, 8 H, ArCH_2O), 4.52 (d, 4 H, *J* = 15.8 Hz, OCH_2), 4.49 (d, 4 H, *J* = 15.8 Hz, OCH_2), 4.29 (dd, 4 H, *J* = 12.1 and 4.8 Hz, H-6), 4.10 (dd, 4 H, *J* = 11.8 and 2.4 Hz, H-6'), 4.15–4.00 (m, 4 H, H-5), 3.98, 2.91 (2 d, 8 H, *J* = 12.7 Hz, ArCH_2Ar), 2.13, 2.07, 2.02, 1.97 (4 s, 48 H, 16 MeCO), 1.03 (s, 36 H, 4Me_3C); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 169.9, 169.8, 169.7, 152.2, 144.8, 138.9, 133.8, 121.4, 131.5, 129.7, 125.1, 96.2, 87.3, 83.4, 76.1, 69.5, 69.1, 69.0, 66.1, 55.7, 33.8, 31.5, 31.4, 20.9, 20.8, 20.7, 20.7; HRMS–FAB calcd for $C_{140}H_{160}O_{44}$ + Na: 2568.0180 $(M + Na)^+$, found: 2568.0177.

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(16) **Synthesis of fully deprotected calix-sugars 8 and 9:** Compounds **6** or **7** (0.1 mmol) was dissolved into methanol (30 mL) to which a catalytic amount of NaOMe was added.

The mixture was kept at r.t. for 12 h. NaOMe was neutralized with Amberlite IR-120 (H^+). The resine was filtered, washed with methanol and the solution evaporated under vacuum giving the corresponding hydroxylated derivatives **8** and **9**.

Physical Data for **8: 25,26,27,28-tetrakis{4'-[1''-(α-D-Mannopyranosyl)prop-3''-ynyl]benzyloxy}calix[4]arene** obtained as a solid (0.112 g, 68%): mp 147–150 °C (dec); $[\alpha]_D$ +22 (*c* 0.3, water); IR (KBr): 3400, 1570, 1450, 1059 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 7.36 (d, 4 H, *J* = 8.1 Hz, C_6H_4), 7.29 (d, 4 H, *J* = 8.1 Hz, C_6H_4), 6.58–6.44 (m, 12 H, C_6H_3), 4.91 (s, 8 H, ArCH_2), 4.85 (s, 4 H, H-1), 4.45 (AB system, 8 H, *J* = 16.1 Hz, Δδ = 21.8 Hz; CH_2 O), 4.05 (d, 4 H, *J* = 13.2 Hz, ArCH_2 Ar), 3.68–3.28 (m, 24 H, H-2, -3, -4, -5, -6 , -6'), 2.90 (d, 4 H, *J* = 13.4 Hz, ArCH_2Ar); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.2, 154.5, 137.9, 134.7, 131.5, 131.4, 129.7, 128.8, 127.9, 121.4, 98.3, 85.9, 85.3, 74.4, 70.9, 70.1, 66.8, 61.1, 53.6, 30.7; HRMS–FAB calcd for $C_{92}H_{96}O_{28}$ + Na: 1671.598 $(M + Na)^+$; found: 1671.606.

Physical Data for **9: 5,11,17,23-tetra-*tert*-Butyl-25,26,27,28-tetrakis{4'-[1''-O-(α-D-manno-pyranosyl)prop-3''-ynyl]benzyloxy}calix[4]arene** obtained as a solid (0.133 g, 71%): mp 190–195 °C (dec.) (from ether) ºC; IR (KBr): 3408, 1510, 1479, 1124, 1059 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 7.33 (AB system, 16 H, J = 8.2 Hz, Δ δ = 13.6 Hz, C_6H_4), 6.72 (s, 8 H, C_6H_2), 4.85
(br s, 12 H, CH_2O, H-1), 4.48 (AB system, 8 H, *J* = 16 Hz, PhCH_2), 4.05 (d, 4 H, *J* = 12.7 Hz, ArCH_2Ar), 3.70–3.29 (several m, 24 H, H-2, -3, -4, -5, -6, -6'), 2.85 (d, 4 H, *J* = 12.9 Hz, ArCH_2Ar), 1.00 (s, 36 H, $4Me_3C$); ^{13}C NMR (75 MHz, DMSO-d_6) δ:152.1, 143.9, 138.5, 133.3, 131.4, 129.6, 124.8, 121.2, 116.1, 98.4, 85.8, 85.5, 74.4, 70.9, 70.1, 66.9, 61.1, 53.7, 33.5, 31.1; HRMS–FAB calcd for $C_{108}H_{128}O_{28}$ + Na: 1895.8480 $(M + Na)^+$; found: 1895.3510.

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