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Note

Synthetic studies on dendritic glycoclusters: a convergent palladium-catalyzed strategy

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Abstract

A facile Pd-catalyzed strategy by which multiantennary glycoclusters and sugar dendrons can be readily assembled in one-step is described. © 2001 Elsevier Science Ltd. All rights reserved.

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Carbohydrate–protein interactions are responsible for several cell–cell and host–pathogen interactions.[1] These interactions, however, are very weak and hence, as a compensatory measure, nature adopts the multiple binding strategy. Thus, in many biological phenomena, carbohydrates and their recognition domains are organized as supramolecular clusters that are held together by co-operative binding forces.[2] However, little is known on the nature of these forces, a detailed understanding of which may lead to effective designs of glycoprotein inhibitors and other carbohydrate-based therapeutic agents.[2,3] Dendritic glycoclusters can play a major role towards these ends. Dendrimers having peripheral saccharide units can be constructed in varying shapes, sizes and carbohydrate content, and their binding studies with proteins may provide insight into the topography of the binding sites and their directional properties. In view of these, in recent years, much attention has been paid towards synthesis of multivalent dendritic glycoclusters (glycodendrimers).[4] Since dendrimer synthesis requires multiple coupling reactions to be carried out in one step, Pd-catalyzed reactions, in view of their high atom efficiencies, appeared ideally suited for this purpose. We now present here a facile synthetic strategy by which multiantennary glycoclusters can be rapidly assembled in a convergent way using the Pd-catalyzed reactions, our disclosure being prompted by a recent report on the synthesis of some carbohydrate dimers using the Sonogashira-type coupling reactions.[5]

In this study, we have used the readily available D-glucose-derived β-propargyl glycoside (**1**)[6] as the antennary saccharide ligand. A threefold Pd-catalyzed reaction of **1** with 1,3,5-tribromobenzene (**2**) under a Sonogashira-coupling protocol without the use of CuI ($Pd(dba)_2$, $4PPh_3$, Et_3N, DMF, 60 °C) smoothly gave rise to the centrally planar triantennary glycocluster **3** in 70% isolated yield after silica-gel chromatography (Scheme

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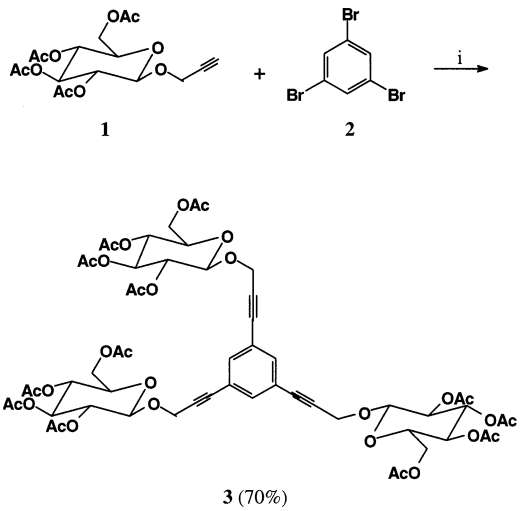
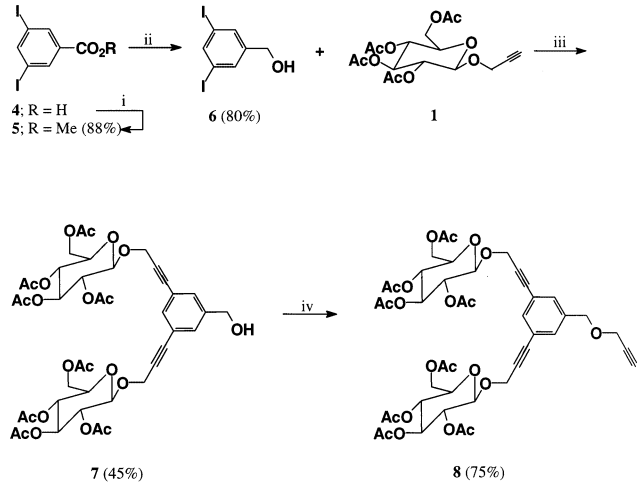
1). This coupling reaction was best carried out in the absence of CuI, a co-catalyst routinely used in Pd-catalyzed coupling reactions of terminal acetylenes, which otherwise led to considerable dimerization[5a] of the propargyl glycoside **1**, resulting in complex product mixtures. The glycocluster **3** was produced with complete retention of the starting β-saccharide configuration (δ 4.82, $J_{1,2}$ 7.8 Hz in **3**), attesting to the mild and neutral conditions employed for its synthesis.



Scheme 1. (i) 10% $Pd(dba)_2$, 40% PPh_3, DMF, Et_3N, 60–70 °C.

We then turned our attention towards synthesis of an appropriate dendron for the convergent assembly of higher generation glycoclusters. Thus, 3,5-diiodobenzoic acid (**4**) was first converted to the corresponding benzyl alcohol **6** through conventional esterification, followed by $LiAlH_4$ reduction (Scheme 2). A twofold Pd-catalyzed coupling of **6** with **1**, under the same copper-less coupling conditions described above, gave rise to the diantennary benzyl alcohol **7** in 45% yield. It was then converted to the propargyl ether dendron **8** (75%), which may be used for coupling with the tritopic core **2** to produce a second-generation glycocluster.

We also present here an example by which multivalent glycoclusters can be rapidly assembled via a multiple Heck reaction strategy. For this purpose, we have used the saccharide acrylate ester **10**, derived from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**9**), as the



Scheme 2. (i) MeOH, concd H_2SO_4; (ii) $LiAlH_4$, THF 0 °C; (iii) 10% $Pd(dba)_2$, 40% PPh_3, DMF, Et_3N, 60 °C; (iv) propargyl bromide, NaH, THF.

Heck olefin component (Scheme 3). A fourfold Heck reaction of **10** with the centrally tetrahedral tetratopic core tetra(*p*-iodophenyl)methane (**11**)[7] under Jefferey's phase-transfer catalyzed conditions ($Pd(OAc)_2$, Bu_4NBr, $NaHCO_3$, DMF, 80 °C) then smoothly gave rise to the topologically interesting three-dimensional glycocluster **12** in 60% isolated yield.

In summary, we have shown a facile Pd-catalyzed strategy by which multivalent glycoclusters and sugar dendrons can be rapidly assembled in one step. The methodology is particularly attractive since it can lead to rigid and yet topologically different multivalent glycoclusters through appropriate choice of the aromatic cores (cf. **3** vs. **12**). Based on this strategy, synthesis of higher generation glycoclusters is currently in progress.

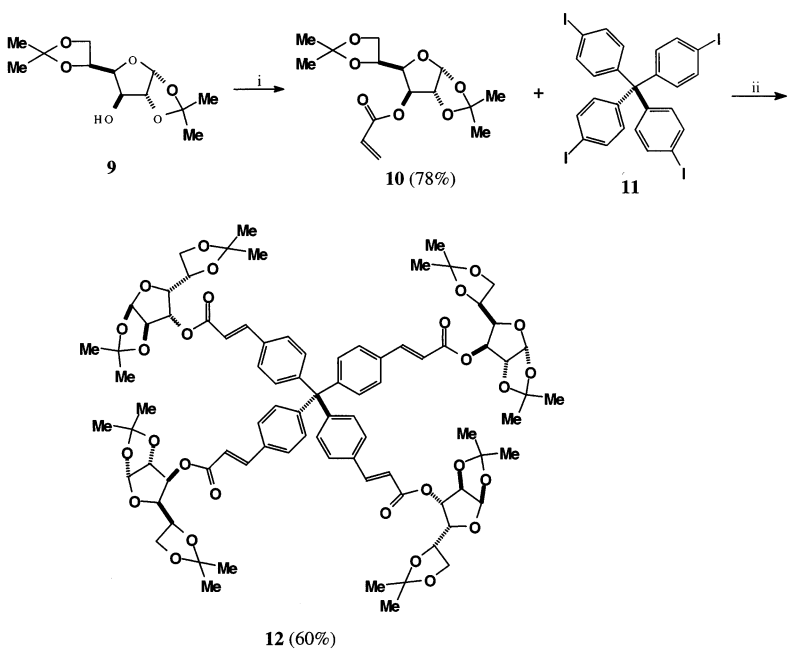
1. Experimental

General methods.—All melting points are uncorrected. IR spectra were taken in a Perkin–Elmer R-297 spectrometer. NMR spectra were recorded in $CDCl_3$ solutions on a Bruker Avance-300 (300 MHz) instrument and are reported in the δ scale, ppm downfield from tetramethylsilane as the internal standard. Optical rotations were measured on a JASCO DIP-360 automatic polarimeter. Elemental analyses were carried out at the Indian

Association for the Cultivation of Science. The β-propargyl glycoside **1**,[6], 3,5-diiodobenzyl alcohol (**6**),[8] 3-*O*-acryloyl-1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose (**10**)[9] and tetra(4-iodophenyl)methane (**11**)[7] were prepared following the cited literature procedures. All reactions were carried out using dried distilled solvents under a N_2 atmosphere. The Pd-catalyzed coupling reactions were carried out in solutions that were degassed thoroughly with N_2. Reactions were monitored by thin-layer chromatography (TLC) on glass plates precoated with Silica Gel G (Tara Chemicals). Components were visualized by staining with iodine or heating on a hot plate after spraying with aq H_2SO_4. Petroleum ether refers to the fraction boiling at 60–80 °C range.

*1,3,5-Tri[1′-*O*-(2″,3″,4″,6″-tetra-*O*-acetyl-β-*D*-glucofuranosyl)prop-3′-ynyl]benzene* (**3**).—$Pd(dba)_2$ (6 mg, 0.01 mmol) was added to a degassed solution of 1,3,5-tribromobenzene (**2**) (0.02 g, 0.067 mmol), the propargyl glycoside **1** (0.121 g, 0.301 mmol) and PPh_3 (0.01 g, 0.04 mmol) in a mixture of DMF (2 mL) and Et_3N (2 mL). The mixture was heated at 70 °C for 30 h. It was then concentrated under reduced pressure, diluted with water and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel (3:2 EtOAc–petroleum ether) to give **3** (0.06 g, 70%): mp 108–110 °C; $[\alpha]_D^{20}$ −38.2° (*c* 1.1, $CHCl_3$). IR: 3010, 1750, 1360, 1210, 1035 cm^{-1}. ^1H NMR: δ 2.01 (s, 9 H), 2.03 (s, 9 H), 2.05 (s, 9 H), 2.09 (s, 9 H), 3.76 (ddd, 3 H, *J* 9.3, 4.3, 2.4 Hz), 4.17 (dd, 3 H, *J* 12.3, 2.1 Hz), 4.29 (dd, 3 H, *J* 12.3, 4.5 Hz), 4.59 (s, 6 H), 4.82 (d, 3 H, *J* 7.8 Hz), 5.04 (dd, 3 H, *J* 9.3, 8.1 Hz), 5.09–5.15 (m, 3 H), 5.23–5.29 (m, 3 H), 7.47 (s, 3 H). Anal. Calcd for $C_{57}H_{66}O_{30}$: C, 55.64; H, 5.36. Found: C, 56.14; H, 5.02.

*3,5-Bis[1′-*O*-(2″,3″,4″,6″-tetra-*O*-acetyl-β-*D*-glucofuranosyl)prop-3′-ynyl]benzyl alcohol* (**7**).—$Pd(dba)_2$ (8 mg, 0.013 mmol) was added to a degassed solution of 3,5-diiodo benzyl alcohol (**6**) (0.024 g, 0.066 mmol), the propargyl glycoside **1** (0.08 g, 0.2 mmol) and PPh_3 (0.01 g, 0.04 mmol) in a mixture of DMF (2 mL) and Et_3N (2 mL). The mixture was heated at 60 °C for 30 h. It was then concentrated under reduced pressure, diluted with water and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC over silica gel (70:30 EtOAc–petroleum ether) to give **7** (0.027 g, 45%): $[\alpha]_D^{20}$



Scheme 3. (i) CH_2=CHCOCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C–rt; (ii) 40% $Pd(OAc)_2$, Bu_4NBr, $NaHCO_3$, DMF, 80° C.

−26.1° (*c* 1, $CHCl_3$). IR: 3010, 1755, 1365, 1215, 1035 cm^{-1}; ^1H NMR: δ 2.01 (s, 6 H), 2.03 (s, 6 H), 2.05 (s, 6 H), 2.08 (s, 6 H), 3.73–3.80 (m, 2 H), 4.17 (dd, 2 H, *J* 12.3, 2.1 Hz), 4.29 (dd, 2 H, *J* 12.3, 4.5 Hz), 4.59 (s, 4 H), 4.69 (s, 2 H), 4.83 (d, 2 H, *J* 7.9 Hz), 5.04 (t, 2 H, *J* 9.3 Hz), 5.12 (t, 2 H, *J* 9.6 Hz), 5.26 (t, 2 H, *J* 9.3 Hz), 7.43 (s, 3 H). Anal. Calcd for $C_{41}H_{46}O_{21}$: C, 56.32; H, 5.26. Found: C, 55.89; H, 5.11.

*3,5-Bis[1′-*O*-(2″,3″,4″,6″-tetra-*O*-acetyl-β-*D*-glucofuranosyl)prop-3′-ynyl]benzylprop-2-yn-1-ol* (**8**).—NaH (50% dispersion in mineral oil, 4 mg, 0.08 mmol) was added to a stirred solution of **7** (0.05 g, 0.055 mmol) in THF (2 mL) at 0 °C. After 15 min, a solution of propargyl bromide (0.014 g, 0.11 mmol) in THF (1 mL) was added. The reaction mixture was stirred at ambient temperature for 24 h. It was then diluted with CH_2Cl_2 (5 mL) and washed with water, and the organic layer was dried over Na_2SO_4. Evaporation of solvent under reduced pressure, followed by preparative TLC on silica gel (60:40 EtOAc–petroleum ether), gave **8** (0.038 g, 75%): mp 65–66 °C; $[\alpha]_D^{20}$ −20.7° (*c* 1.2, $CHCl_3$). IR: 2890, 1750, 1365, 1220, 1040 cm^{-1}. ^1H NMR: δ 2.01 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 2.08 (s, 3 H), 2.09 (s, 3 H), 2.10 (s, 3 H), 2.12 (s, 3 H), 2.13 (s, 3 H), 3.66–3.71 (m, 1 H), 3.74–3.79 (m, 1 H), 3.84 (t, 1 H, *J* 9.2 Hz), 4.10–4.33 (m, 6 H), 4.57 (s, 2 H), 4.59 (s, 2 H), 4.74 (d, 1 H, *J* 7.9 Hz), 4.82 (d, 1 H, *J* 7.9 Hz), 4.90–5.20 (m, 7 H), 5.26 (t, 1 H, *J* 9.3 Hz), 7.40 (s, 2 H), 7.45 (s, 1 H). Anal. Calcd for $C_{44}H_{48}O_{21}$: C, 57.92; H, 5.26. Found: C, 57.66; H, 5.04.

*Tetra[4-(1′,2′,5′,6′-di-*O*-isopropylidene-α-*D*-glucofuran-3-oxycarbonylethenyl)phenyl] methane* (**12**).—$Pd(OAc)_2$ (1.0 mg, 0.004 mmol) was added to a degassed solution of tetra(4-iodophenyl)methane (**11**) (0.012 g, 0.014 mmol), the sugar acrylate **10** (0.028 g, 0.087 mmol), KOAc (0.014 g, 0.145 mmol) and Bu_4NBr (0.02 g, 0.058 mmol) in DMF (3 mL). The reaction mixture was heated at 80 °C for 12 h. It was then concentrated under reduced pressure, diluted with water, and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel (60:40 petroleum ether–EtOAc) to give **12** (0.014 g, 60%): mp 212–214 °C; $[\alpha]_D^{20}$ −42.3° (*c* 1.2, $CHCl_3$). IR: 2980, 1710, 1630, 1200, 1150, 1060, 1015 cm^{-1}. ^1H NMR: δ 1.30 (s, 12 H), 1.31 (s, 12 H), 1.41(s, 12 H), 1.54 (s, 12 H), 4.07 (br s, 8 H), 4.28 (br s, 8 H), 4.56 (d, 4 H, *J* 3.5 Hz), 5.39 (br s, 4 H), 5.91 (d, 4 H, *J* 3.5 Hz), 6.40 (d, 4 H, *J* 15.9 Hz), 7.25 (d, 8 H, *J* 8.2 Hz), 7.45 (d, 8 H, *J* 8.2 Hz), 7.68 (d, 4 H, *J* 15.9 Hz). Anal. Calcd for $C_{85}H_{100}O_{28}$: C, 65.05; H, 6.41. Found: C, 64.87; H, 6.15.

Acknowledgements

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