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Note

Synthesis of substituted septanosyl-1,2,3-triazoles

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Abstract—A carbohydrate-based oxepine, derived from 2-deoxy-D-*arabino*-hexopyranose, was used to prepare a family of septanosyl-1,2,3-triazoles in four steps. DMDO mediated epoxidation of the oxepine followed by trapping of the intermediate 1,2-anhydroseptanose by sodium azide gave the β-substituted glycosyl azide. The septanosyl azide was then reacted with a number of alkynes under thermal Huisgen or copper(I) mediated reaction conditions. Hydrogenolysis of benzyl protecting groups gave substituted septanosyl-1,2,3-triazoles. The new septanose-based structures were then evaluated as potential glycosidase inhibitors.

Keywords: Septanose carbohydrates; Glycosidase; Triazole

A comprehensive list of protein–carbohydrate interactions includes mono-, oligo-, and polysaccharides bound by lectins (as ligands) and also by carbohydrate processing enzymes such glycosyltransferases and glycosidases (as substrates). Such interactions are integral to a number of biological processes such as cell–cell communication,[1] synthesis of cell-wall polysaccharides,[2] protein folding,[3] and glycoprotein synthesis.[4] Our group has become interested in evaluating the potential for unnatural, ring expanded carbohydrates to participate in protein–carbohydrate interactions with natural proteins. These investigations should deepen the understanding of the role molecular topology plays in protein–carbohydrate interactions generally. Specifically, we are interested in correlating the conformational preferences of septanose carbohydrates with their ability to be bound by lectins and carbohydrate processing enzymes.

We recently reported on the binding of methyl septanosides by the model plant lectin Concanavalin A (ConA).[5] In contrast to its preference for alpha over beta configured pyranosides, ConA bound methyl β-D-*glycero*-D-septanosides in preference to methyl α-D-*glycero*-D-septanosides. Our earlier conformational analysis of these monosaccharides[6] showed that: (i) both the alpha and beta configured methyl septanosides took up conformations that resembled the bound conformation of the natural ligands, and; (ii) the methyl septanoside structures were stable. That is, they populated one unique conformation as a large (>90) percent of the Boltzmann distribution of conformers. Overall, the investigation suggested septanose carbohydrates could serve as ligands for a variety of natural proteins.

As an extension of that original investigation of protein–septanose interactions, we wanted to know if septanoses could inhibit glycosidase enzymes. This exploration would inform the fundamental protein–septanose interaction question and could also serve as a starting point for the development of a new class of inhibitors. Some recent investigations served to motivate our efforts. For example, *para*-nitrophenyl septanosides were shown to be substrates for natural glycosidases.[7] Also, a number of groups have reported on the glycosidase inhibitory activity of polyhydroxylated azepanes.[8–10]

Here we report the synthesis of a family of septanosyl 1,2,3-triazoles from a carbohydrate-based oxepine. The synthetic strategy borrowed from previous reports of pyranosyl triazoles,[11,12] which have themselves been shown to be glycosidase inhibitors.[12] Septanosyl 1,2,3-triazoles and the known azepane glycosidase inhibitors share a polyhydroxylated seven-membered ring

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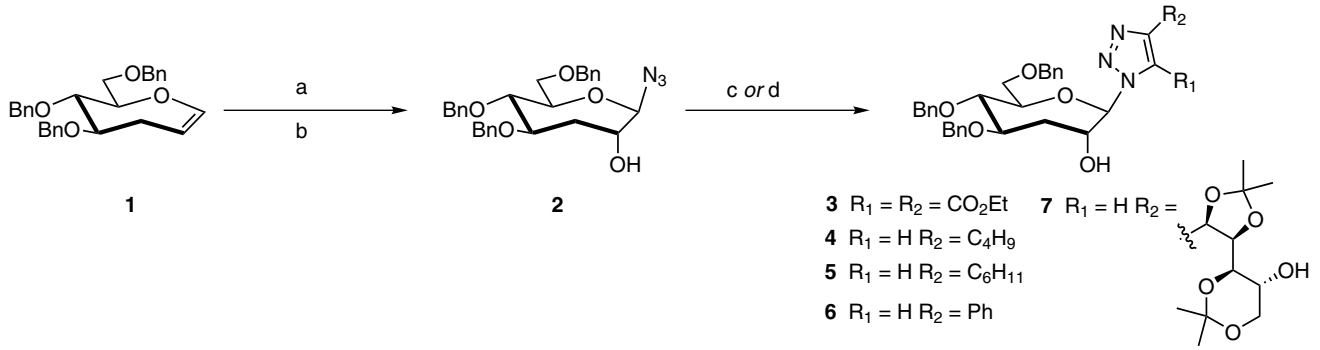
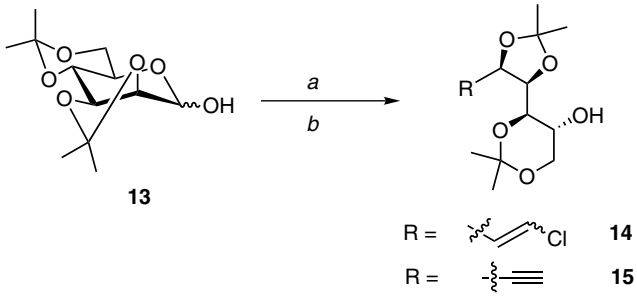


Scheme 1. Reagents and conditions: (a) DMDO, CH_2Cl_2, 0 °C; (b) NaN_3, DMF/H_2O, rt, 22%, two steps; (c) diethyl acetylene dicarboxylate, toluene, 110 °C, 70%; (d) alkyne, $Cu(OAc)_2$, sodium ascorbate, *t*-BuOH/H_2O, rt, 52–70%.

structure, with the addition of a basic nitrogen found only in the azepanes. Based on our familiarity with the low energy conformations of the related methyl septanosides, we wanted address the issue of flexibility that has been argued to be operative with the polyhydroxylated azepane glycosidase inhibitors.

Oxepine **1**[13] served as the starting material for the synthesis of the septanosyl 1,2,3-triazoles (Scheme 1). Epoxidation of **1** provided a 1,2-anhydroseptanose, which was not isolated, but carried directly onto the next step in the synthesis. Attack on the epoxide using tetrabutylammonium azide in methylene chloride[14] was sluggish with approximately 8–10% yield after 48 h at room temperature. Switching to sodium azide under reported conditions[15] gave septanosyl azide **2** in 22% over two steps. The low yield for this process is ascribed to the low solubility of sodium azide in the mixed DMF/H_2O solvent where water may also compete as a nucleophile. Consistent with the earlier preparation of methyl 3-deoxy-β-D-*glycero*-D-guloseptanoside from oxepine **1**,[5] azide **2** was assigned as being in the beta anomeric configuration, arising from S_N2 attack on the α-1,2-anhydroseptanose. The glycosyl azide was then reacted with alkynes under two separate types of reaction conditions to form protected triazoles. Huisgen dipolar cycloaddition[16,17] of **2** with diethyl acetylene dicarboxylate in refluxing toluene provided triazole **3** in 69% yield.

The other triazoles were prepared by reaction of azide **2** with terminal alkynes using the Cu(I) mediated addition reaction.[18,19] Reaction of **2** with commercially available 1-hexyne, cyclohexylacetylene, or phenylacetylene provided triazoles **4**, **5**, and **6** in 65%, 70%, and 65% yields, respectively. The regiochemistry of these adducts was confirmed by COSY and HMBC spectroscopy on the hexyne adduct **4**. An alkyne prepared by halovinylation and elimination of 2,3:4,6-di-*O*-isoproylidene-D-mannopyranose was also used in the addition reaction (Scheme 2).[20] Addition under the Cu(I) conditions with this new alkyne provided the corresponding triazole in 52% yield. Hydrogenolysis of the benzyl protecting groups of **3**–**7** provided the deprotected septanosyl 1,2,3-triazoles (>95%) **8**–**12** (Fig. 1). After hydrogenolysis of **7**, it was noted that one of the acetonide protecting groups was removed over the course of the reaction. The regiochemistry of this deprotection was rationalized in terms of the distinct ^{13}C chemical shift of the two (five-membered ring vs six-membered ring) acetonides,[21] and HMBC analysis of **12**.



Scheme 2. Reagents and conditions: (a) $ClCH_2PPh_3$, *n*-BuLi, HMPA, THF, 0 °C to rt, 61%; (b) *n*-BuLi, THF, 3 h, 68%.

Each of the triazoles **8**–**12** was then evaluated for activity against a battery of glycosidases. Standard UV-based assays measured inhibition by the triazoles on the activity of α-glucosidase (*Saccharomyces cerevisiae*), β-glucosidase (almonds), α-galactosidase (green coffee beans), β-galactosidase (*Aspergillus oryzae*), α-mannosidase (*Canavalia ensiformis*), β-mannosidase (snail acetone powder), or β-*N*-acetylglucosaminidase (*C. ensiformis*) on their corresponding *para*-nitrophenyl glycosides.[22] No inhibition of activity was noted under the assay conditions up to a concentration of 1 mM of **8**–**12**. Our current efforts are aimed at further evaluation of the potential activity of the septanosyl triazoles and the identification of inhibitors that include a septanose as a structural feature. The lack of activity in the molecules reported here prevents a substantive analysis on the importance of any alleged flexibility in seven-membered ring glycosidase inhibitors. New results will be reported in due course.

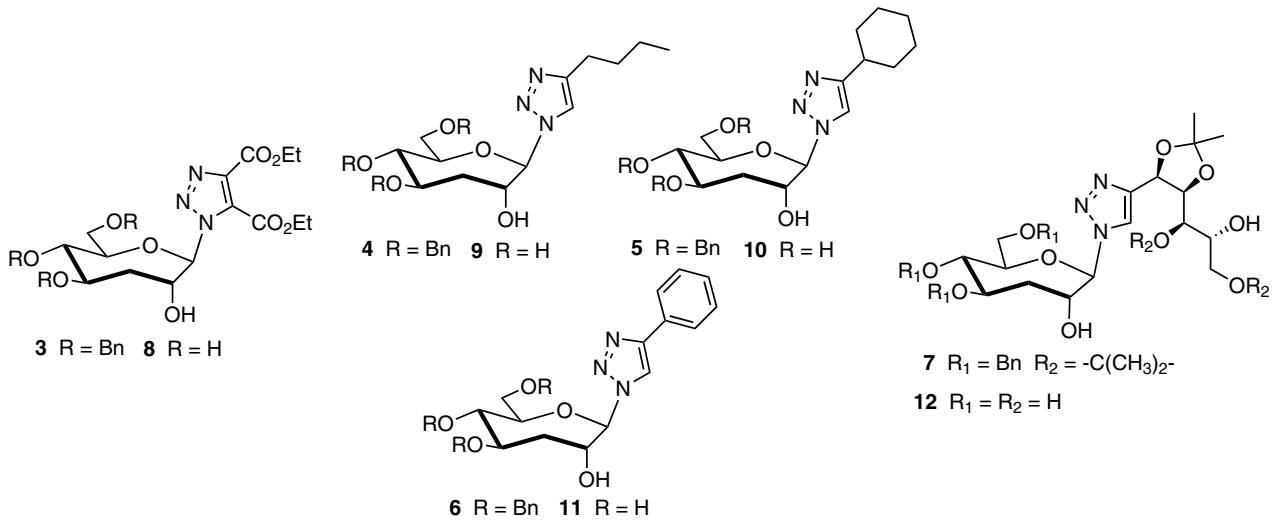


Figure 1.

1. Experimental

1.1. General methods

Unless stated otherwise, all reactions were conducted at room temperature (rt) under nitrogen atmosphere. DMDO was generated as described.[23] Reactions were monitored by TLC (silica gel, 60 Å, F_{254}, 250 μm). Visualization was conducted either under UV light or by charring with 2.5% *p*-anisaldehyde in H_2SO_4, acetic acid, and ethanol solution. Preparative chromatography was conducted on silica gel (60 Å, 32–63 μm). Melting points are uncorrected. Optical rotations were measured at 22 ± 2 °C. ^{1}H NMR spectra were collected at 300 or 400 MHz with chemical shifts referenced to $(CH_3)_4Si$ (δ_H 0.00 ppm), $CHCl_3$ (δ_H 7.27 ppm), or CD3OD (δ_H 3.31 ppm). ^{13}C NMR were collected at 75 or 100 MHz and referenced to $CDCl_3$ (δ_C 77.2 ppm) or CD_3OD (δ_C 49.0 ppm).

1.2. 1,6-Anhydro-4,5,7-tri-*O*-benzyl-2,3-dideoxy-D-*gluco*-sept-1-enitol (1)

1,6-Anhydro-4,5,7-tri-*O*-benzyl-2,3-dideoxy-D-gluco-sept-1-enitol (**1**) was synthesized by the route previously reported.[13] $R_f = 0.59$ (1:3, EtOAc–hexanes); $[\alpha]_D$ +14.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.44–7.19 (m, 15H), 6.50 (dd, 1H, $J = 6.4$, 1.1 Hz), 4.73 (d, 1H, $J = 12.2$ Hz), 4.68–4.59 (m, 4H), 4.56 (d, 1H, $J = 2.8$ Hz), 4.40 (d, 1H, $J = 11.2$ Hz), 4.15–4.11 (m, 1H), 3.79–3.69 (m, 4H), 2.65 (ddd, 1H, $J = 17.1$, 3.5, 1.8 Hz), 2.39 (ddd, 1H, $J = 16.9$, 13.6, 6.8 Hz); ^{13}C NMR 100 MHz ($CDCl_3$): δ 148.6, 138.7, 138.0, 128.6, 128.5, 128.2, 128.0 (2), 127.9, 127.8, 127.7, 103.3, 82.6, 79.6, 78.2, 77.7, 73.5, 72.9, 71.1, 70.7, 25.7; FABMS *m*/*z* calcd for $[M+H]^+$: 431.2222. Found: 431.2206.

1.3. 4,5,6-Tri-*O*-benzyl-3-deoxy-β-D-*glycero*-D-*gulo*-septanosyl azide (2)

Oxepine **1** (0.130 g, 0.302 mmol) was dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in dry CH_2Cl_2 (5 mL). The solution was cooled in an ice bath to 0 °C and a DMDO solution (0.38 mL, 0.24 M) was added dropwise. The mixture was stirred at 0 °C for 30 min and the solvent was removed under reduced pressure. The residue was dissolved in DMF (3 mL) and NaN_3 (0.573 g, 6.04 mmol) in water (2 mL) was added. After 4 h, water (5 mL) was added to the solution and it was extracted with ethyl acetate (EtOAc, 2 × 15 mL). The organic layers were dried (Na_2SO_4) and solvent was removed under reduced pressure. The material was purified by column chromatography, using 1:3 EtOAc–hexanes as eluent to give a clear and colorless oil (0.120 g, 22%). $R_f = 0.51$ (1:3, EtOAc–hexanes); $[\alpha]_D$ −2.90 (*c* 1.2, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.36–7.15 (m, 15H), 4.67–4.47 (m, 6H), 4.32 (d, 1H, $J = 11.39$ Hz), 3.8–3.78 (m 3H), 3.65–3.57 (m, 3H), 2.23 (ddd, 1H, $J = 14.7$, 7.5, 3.6 Hz) 1.90 (dd, 1H, $J = 14.6$, 9.6 Hz); ^{13}C NMR 100 MHz ($CDCl_3$): δ 138.4, 138.3, 137.9, 128.7 (2), 128.6, 128.1 (2), 128.0 (2), 127.9, 97.2, 82.1, 80.1, 75.9, 73.7, 72.9, 71.5, 71.4, 70.1, 32.1; ESIMS *m*/*z* calcd for $[M+Na]^+$: 512.2156. Found: 512.2170.

1.4. 1-(4′,5′,6′-Tri-*O*-benzyl-3′-deoxy-β-D-*glycero*-D-*gulo*-septanosyl)-[1,2,3]-trizaole-4,5-dicarboxylic acid diethyl ester (3)

Azide **2** (0.032 g, 0.065 mmol) was dried via azeotropic distillation from toluene (3 × 5 mL) under reduced pressure and dissolved in dry toluene (5 mL). To the

solution, diethyl acetylene dicarboxylate (0.011 mL, 0.065 mmol) was added dropwise and the mixture was heated to 110 °C for 24 h and then cooled to rt. The reaction mixture was concentrated under reduced pressure and the material was purified by column chromatography, using 1:1 EtOAc–hexanes as eluent to give a clear and colorless oil (0.030 g, 70%). $R_f = 0.11$ (1:3, EtOAc–hexanes); $[\alpha]_D$ −46.7 (*c* 2.9, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.37–7.21 (m, 15H), 5.93 (d, 1H, $J = 8.80$ Hz), 5.10–5.06 (m, 1H), 4.69 (d, 1H, $J = 12.1$ Hz), 4.58 (dd, 2H, $J = 12.3$, 2.7 Hz), 4.47–4.18 (m, 8H), 4.07 (dd, 1H, $J = 11.0$, 4.8 Hz), 3.98 (dd, 1H, $J = 5.7$, 5.7 Hz), 3.8 (dd, 1H, $J = 6.0$, 6.0 Hz), 3.60–3.57 (m, 2H), 2.83 (d, 1H, $J = 4.4$ Hz), 2.47 (ddd, 1H, $J = 14.8$, 7.5, 4.4 Hz), 2.21 (dd, 1H, $J = 14.6$, 9.2 Hz), 1.42 (t, 3H, $J = 7.1$, 7.1 Hz), 1.34 (t, 3H, $J = 7.1$, 7.1 Hz) ; ^{13}C NMR 100 MHz ($CDCl_3$): δ 138.9 (2), 138.4, 138.3, 128.6 (2), 128.4, 128.3, 128.2, 128.0, 127.9 (2), 127.7 (2), 108.3, 79.8, 79.7, 79.3, 75.8, 74.7 (2), 74.3, 73.9, 73.8, 70.2, 56.2.

1.5. Procedure for preparation of triazoles 4–7

Azide **2** (1.00 mmol) and the appropriate alkyne (1.00 mmol) were dissolved in a solution of water and *t*-BuOH (1:1) such that the azide was at a concentration of 0.5 M (2–3 mL). To this solution was added sodium ascorbate (0.40 mmol) and $Cu(OAc)_2$ (0.20 mmol). The reaction was allowed to stir at rt overnight. After, water (20 mL) was added to dilute the solution and the mixture was then extracted with CH_2Cl_2 (3×20 mL). The organic layer was washed with satd $NaHCO_3$ and aq NaCl and then dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and purified by flash column chromatography (1:1, EtOAc–hexanes).

1.6. 4-Butyl-1-(4′,5′,6′-tri-*O*-benzyl-3′-deoxy-β-D-*glycero*-D-*gluco*-septanosyl)-1,2,3-trizaole (4)

Triazole **4** was isolated in 65% as a clear syrup. $R_f = 0.65$ (1:1, EtOAc–hexanes); $[\alpha]_D$ +26.5 (*c* 6.2, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.60–7.21 (m, 16H), 5.46 (d, 1H, $J = 8.19$ Hz), 4.75–4.66 (m, 2H), 4.57 (dd, 4H, $J = 8.19$, 9.28 Hz), 4.40 (t, 1H, $J = 12.90$ Hz), 3.99 (dd, 2H, $J = 9.67$, 5.70 Hz), 3.85 (s, 1H), 3.69 (dd, 1H, $J = 10.80$, 3.16 Hz), 3.61 (dd, 2H, $J = 11.32$, 5.64 Hz), 2.71 (t, 2H, $J = 7.72$ Hz), 2.46 (ddd, 1H, $J = 14.53$, 7.80, 3.86 Hz), 2.20 (dd, 1H, $J = 14.69$, 9.08 Hz), 1.65 (ddd, 2H, $J = 14.76$, 7.42, 7.42 Hz), 1.42 (ddd, 2H, $J = 14.74$, 7.33, 7.33 Hz), 0.97 (t, 3H, $J = 7.32$ Hz); ^{13}C NMR 100 MHz ($CDCl_3$): δ 138.1 (2), 137.7, 128.6, 128.5 (2), 128.1, 128.0, 127.9, 127.8, 120.4, 94.6, 82.5, 80.3, 75.8, 73.4, 72.9, 71.3, 71.2, 68.9, 32.7, 31.5, 25.3, 22.3, 13.9; ESIMS *m*/*z* calcd for $[M+Na]^+$: 594.2938. Found: 594.2945.

1.7. 4-Cyclohexyl-1-(4′,5′,6′-tri-*O*-benzyl-3′-deoxy-β-D-*glycero*-D-*gluco*-septanosyl)-1,2,3-trizaole (5)

Triazole **5** was isolated in 70% yield as a clear syrup. $R_f = 0.72$ (1:1, EtOAc–hexanes); $[\alpha]_D$ +26.7 (*c* 4.8, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.58–7.21 (m, 16H), 5.43 (d, 1H, $J = 8.24$ Hz), 4.69 (ddd, 2H, $J = 15.74$, 9.61, 7.03 Hz), 4.58 (dd, 3H, $J = 12.52$, 4.48 Hz), 4.52 (d, 1H, $J = 11.84$ Hz), 4.37 (d, 1H, $J = 11.40$ Hz), 3.98 (dd, 2H, $J = 7.74$, 4.05 Hz), 3.69 (dd, 2H, $J = 10.20$, 2.60 Hz), 3.60 (ddd, 2H, $J = 16.37$, 6.55, 4.39 Hz), 2.76 (s, 1H), 2.46 (ddd, 1H, $J = 14.63$, 7.78, 3.88 Hz), 2.19 (dd, 1H, $J = 14.76$, 9.20 Hz), 2.04 (d, 2H, $J = 9.20$ Hz), 1.79 (dd, 3H, $J = 25.75$, 12.14 Hz), 1.51–1.26 (m, 5H); ^{13}C NMR 100 MHz ($CDCl_3$): δ 138.1, 137.7, 128.6 (3), 128.1, 128.0, 127.9, 127.8, 119.3, 94.7, 82.6, 80.4, 75.7, 73.4, 72.9, 71.3, 68.9, 35.3, 32.9, 32.6, 26.2, 26.1; ESIMS *m*/*z* calcd for $[M+Na]^+$: 620.3095. Found: 620.3103.

1.8. 4-Phenyl-1-(4′,5′,6′-tri-*O*-benzyl-3′-deoxy-β-D-*glycero*-D-*gluco*-septanosyl)-1,2,3-trizaole (6)

Triazole **6** was isolated in 65% yield as a clear syrup. $R_f = 0.63$ (1:1, EtOAc–hexanes); $[\alpha]_D$ +39.8 (*c* 4.7, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.06 (d, 1H, $J = 21.72$ Hz), 7.73 (d, 2H, $J = 6.16$ Hz), 7.42–7.24 (m, 18H), 5.53 (d, 1H, $J = 8.32$ Hz), 4.75 (d, 2H, $J = 12.08$ Hz), 4.62 (dd, 2H, $J = 11.66$, 3.98 Hz), 4.56 (dd, 2H, $J = 22.45$, 10.52 Hz), 4.39 (d, 1H, $J = 11.36$ Hz), 4.04–4.03 (m, 2H), 3.72 (dd, 2H, $J = 10.33$, 2.99 Hz), 3.63 (dd, 2H, $J = 14.94$, 6.02 Hz), 2.50 (ddd, 1H, $J = 14.46$, 7.80, 4.00 Hz), 2.36 (dd, 1H, $J = 14.78$, 9.02 Hz); ^{13}C NMR 100 MHz ($CDCl_3$): δ 147.7, 138.2, 138.1, 137.7, 130.3, 128.9, 128.6 (2), 128.3, 128.1, 128.0 (2), 127.9 (2), 125.8, 119.5, 94.9, 82.8, 80.4, 75.8, 73.5, 73.0, 71.4, 71.3, 69.0, 32.8; ES *m*/*z* calcd for $[M+Na]^+$: 614.2625. Found: 614.2614.

1.9. 4-(2,3:4,6-Di-*O*-isopropylidene-mannosyl)-1-(4,5,6-tri-*O*-benzyl-3-deoxy-β-D-*glycero*-D-glucoseptanosyl)-1,2,3-trizaole (7)

Triazole **7** was isolated in 52% yield as a white solid. $[\alpha]_D$ +18.4 (*c* 4.0, $CHCl_3$); ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.93 (s, 1H), 7.35–7.19 (m, 15H), 5.56 (s, 1H), 5.46 (d, 1H, $J = 9.24$ Hz), 4.75 (s, 1H), 4.68 (d, 1H, $J = 11.95$ Hz), 4.59 (d, 2H, $J = 13.36$ Hz), 4.51 (dd, 2H, $J = 15.47$, 11.58 Hz), 4.15 (dd, 1H, $J = 14.20$, 7.12 Hz), 3.97 (s, 2H), 3.87–3.81 (m, 2H), 3.60 (t, 2H, $J = 10.28$ Hz), 3.54 (dd, 2H, $J = 18.79$, 8.70 Hz), 3.30 (s, 1H), 2.45 (d, 1H, $J = 16.27$, 7.18 Hz), 1.60 (d, 4H, $J = 10.20$ Hz), 1.49 (s, 3H), 1.27 (t, 4H, $J = 10.06$), 1.00 (s, 2H); ^{13}C NMR 100 MHz ($CDCl_3$): δ 138.2, 138.0, 137.6, 128.7, 128.2, 128.0 (2), 109.7, 98.5, 94.8,

82.9, 82.8, 80.0, 76.5, 76.0, 73.4, 73.0, 72.3, 71.4, 71.2, 69.1, 65.0, 63.7, 32.8, 28.6, 26.8, 25.9, 18.6.

1.10. 1-Chloro-3,4:5,7-di-*O*-isopropylidene-1,2-dideoxy-D-*manno*-hept-1-enitol (14)

A solution of chloromethyltriphenylphosphonium chloride (15.4 mmol) in 10 mL dry THF was cooled to 0 °C. To this solution was added *n*-BuLi (9.60 mL, 15.4 mmol) and HMPA (2.67 mL, 15.4 mmol) dropwise. After 10 min, a solution of 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranose[24] (1.00 g, 3.8 mmol) in dry THF (10 mL) was added. The reaction was allowed to come to rt with stirring overnight. After, excess base was quenched by the addition of satd NH_4Cl (100 mL). The mixture was concentrated and the residue extracted with CH_2Cl_2 (3×40 mL). The organic layer was dried with Na_2SO_4 and concentrated. Purification by column chromatography (1:4, EtOAc–hexanes) led to the *trans* and *cis* vinyl chlorides **14** (0.66 g) in 61% combined yield. The vinyl chlorides were routinely used as the mixture of trans and cis isomers in the subsequent reaction.

1.11. *trans*-1-Chloro-3,4:5,7-di-*O*-isopropylidene-1,2-dideoxy-D-*manno*-hept-1-enitol (14-*trans*)

$[\alpha]_D$ −0.5 (*c* 4.5, $CHCl_3$); ^1H NMR 400 MHz ($CDCl_3$): δ 6.35 (d, 1H, $J = 13.36$ Hz), 6.24 (dd, 1H, $J = 8.28$, 13.32 Hz), 4.71 (t, 1H, $J = 7.76$ Hz), 4.39 (dd, 1H, $J = 7.30$, 1.34 Hz), 4.12 (dd, 1H, $J = 10.73$, 8.40 Hz), 4.00 (d, 2H, $J = 5.36$), 3.45 (d, 1H, $J = 6.99$ Hz), 2.18 (s, 1H), 1.52–1.36 (m, 12H); ^{13}C NMR 100 MHz ($CDCl_3$): δ 130.0, 123.5, 109.6, 76.9, 76.7, 76.3, 70.7, 67.4, 27.0, 26.9, 25.4, 24.6.

1.12. *cis*-1-Chloro-3,4:5,7-di-*O*-isopropylidene-1,2-dideoxy-D-*manno*-hept-1-enitol (14-*cis*)

$[\alpha]_D$ −100.4 (*c* 2.3, $CHCl_3$); ^1H NMR 400 MHz ($CDCl_3$): δ 6.21 (dd, 1H, $J = 7.28$, 1.28 Hz), 6.09 (t, 1H, $J = 7.12$ Hz), 5.26 (m, 1H), 4.59 (dd, 1H, $J = 23.86$, 7.34 Hz), 4.13 (dd, 1H, $J = 14.22$, 7.06 Hz), 3.91 (m, 1H), 3.62 (dd, 1H, $J = 12.76$, 11.00 Hz), 3.44 (dd, 1H, $J = 22.49$, 7.99 Hz), 2.37 (s, 1H), 1.56–1.33 (m, 12H); ^{13}C NMR 100 MHz ($CDCl_3$): δ 129.8, 121.2, 109.6, 98.8, 76.3, 75.2, 73.7, 65.0, 63.2, 28.6, 26.6, 26.0, 19.4.

1.13. 3,4:5,7-Di-*O*-isopropylidene-1,2-dideoxy-D-*manno*-hept-1-ynitol (15)

A solution of the vinyl chlorides **14** (0.230 g, 0.80 mmol) was dissolved in dry THF (3 mL) and cooled to −78 °C. To this solution was added *n*-BuLi (2.88 mL, 4.6 mmol) dropwise. After 3 h the reaction mixture was quenched by the addition of satd aq NH_4Cl (50 mL). The mixture was concentrated and the residue extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried with Na_2SO_4 and concentrated. Purification by flash column chromatography (1:2 to 1:1, EtOAc–hexanes) gave the alkyne **15** (0.137 g) in 68% yield. ^1H NMR 300 MHz ($CDCl_3$): δ 4.87 (dd, 1H, $J = 6.33$, 2.13 Hz), 4.31 (dd, 1H, $J = 6.29$, 3.29 Hz), 3.87–3.75 (m, 3H), 3.59 (dd, 1H, $J = 10.53$, 8.34 Hz), 2.92 (s, 1H), 1.48 (d, 6H, $J = 17.11$), 1.33 (d, 6H, $J = 16.11$ Hz); ^{13}C NMR 100 MHz ($CDCl_3$): δ 110.4, 98.6, 79.3, 76.3, 76.1, 73.2, 67.2, 64.8, 63.5, 28.2, 26.5, 26.0, 19.1.

1.14. General hydrogenolysis procedure

10% Pd/C (0.005–0.010 g) was added to a solution of the protected triazole **3**–**7** (0.05 mmol) in CH_3OH (6 mL). The reaction was placed under an H_2 atmosphere via a balloon and the mixture was stirred for 4 h at rt. The balloon was removed from the flask and the mixture was filtered through a short pad of Celite. The Celite was washed with additional CH_3OH (4×5 mL). The solvent was removed from the combined filtrates by rotary evaporation under reduced pressure to give the deprotected triazoles **8**–**12** in the yields indicated.

1.15. 1-(3′-Deoxy-β-D-*glycero*-D-*gluco*-septanosyl)-1,2,3-trizaole-4,5-dicarboxylic acid diethyl ester (8)

The product was isolated as a clear, colorless oil (100%). ^1H NMR 400 MHz (CD_3OD): δ 5.93 (d, 1H, $J = 8.1$ Hz), 5.05 (dd, 1H, $J = 8.49$, 4.5 Hz), 4.51 (dd, 2H, $J = 14.3$, 7.1 Hz), 4.44 (dd, 2H, $J = 14.3$, 7.2 Hz), 4.03 (dd, 1H, $J = 8.7$, 8.7 Hz), 3.83 (dd, 1H, $J = 11.9$, 2.2 Hz), 3.76 (m, 1H), 3.62 (dd, 1H $J = 11.9$, 6.34 Hz), 3.38 (m, 1H), 2.30 (ddd, 1H, $J = 14.7$, 10.1, 4.7 Hz), 2.09 (dd, 1H, $J = 4.6$, 3.3 Hz), 1.43 (dd, 6H, $J = 15.3$, 7.2 Hz); ^{13}C NMR 100 MHz (CD_3OD): δ 161.5, 159.9, 141.1, 132.5, 94.8, 87.7, 76.3, 70.9, 68.8, 64.4, 64.1, 63.1, 39.3, 14.5, 14.3; ES *m*/*z* $[M+Na]^+$ calcd 412.1327, found 412.1315.

1.16. 4-Butyl-1-(3′-deoxy-β-D-*glycero*-D-*gluco*-septanosyl)-1,2,3-trizaole (9)

The product was isolated as a white solid (99%). Mp = 159–161 °C; $[\alpha]_D$ +20.6 (*c* 3.3, CH_3OH); ^1H NMR 300 MHz (CD_3OD): δ 7.93 (s, 1H), 5.59 (d, 1H, $J = 7.77$ Hz), 4.59 (ddd, 1H, $J = 8.08$, 4.25, 4.25 Hz), 4.03 (t, 1H, $J = 8.00$ Hz), 3.85 (dd, 1H, $J = 11.75$, 2.21 Hz), 3.74 (dd, 1H, $J = 7.65$, 2.32 Hz), 3.63 (dd, 1H, $J = 11.77$, 6.36 Hz), 3.42 (dd, 1H, $J = 8.86$, 7.46 Hz), 3.33 (dd, 1H, $J = 3.13$, 1.54 Hz), 2.72 (t, 2H, $J = 7.76$ Hz), 2.26 (ddd, 1H, $J = 14.47$, 9.98, 4.41 Hz), 2.09 (ddd, 1H, $J = 14.54$, 4.95, 1.35 Hz), 1.68 (ddd,

2H, $J = 15.17$, 7.56, 7.56 Hz), 1.42 (dq, 2H, $J = 22.31$, 7.36 Hz), 0.97 (t, 3H, $J = 7.32$ Hz); ^{13}C NMR 100 MHz (CD_3OD): δ 149.3, 130.9, 122.3, 95.6, 86.8, 76.5, 71.3, 70.3, 64.3, 38.9, 32.8, 26.1, 23.4, 14.2; ES m/z $[M+Na]^+$ calcd 324.1530, found 324.1539.

1.17. 4-Cyclohexyl-1-(3′-deoxy-β-D-*glycero*-D-*gluco*-septanosyl)-1,2,3-trizaole (10)

The product **10** was isolated as a slightly yellow glass (99%). $[\alpha]_D$ +22.0 (*c* 2.6, CH_3OH); ^{1}H NMR 400 MHz (CD_3OD): δ 7.92 (s, 1H), 5.60 (d, 1H, $J = 7.72$ Hz), 4.60 (dt, 1H, $J = 7.80$, 4.20 Hz), 4.04 (t, 1H, $J = 8.32$ Hz), 3.86 (d, 1H, $J = 10.24$ Hz), 3.75 (t, 1H, $J = 6.66$ Hz), 3.64 (dd, 1H, $J = 11.76$, 6.32 Hz), 3.44 (t, 1H, $J = 8.14$ Hz), 3.35 (d, 1H, $J = 15.25$ Hz), 2.76 (s, 1H), 2.27 (ddd, 1H, $J = 14.26$, 10.05, 4.13 Hz), 2.12–2.05 (m, 2H), 1.93–2.86 (m, 3H), 1.59–1.40 (m, 5H); ^{13}C NMR 100 MHz (CD_3OD): δ 154.5, 121.0, 95.6, 86.9, 76.4, 71.3, 70.3, 64.3, 38.9, 36.7, 34.2 (2), 27.4, 27.2; ES m/z $[M+Na]^+$ calcd 350.1686, found 350.1690.

1.18. 4-Phenyl-1-(3′-deoxy-β-D-*glycero*-D-*gluco*-septanosyl)-1,2,3-trizaole (11)

The product was isolated as a whitish solid (98%). Mp = 204–207 °C (decomp.); $[\alpha]_D$ +1.0 (*c* 2.6, CH_3OH); ^{1}H NMR 300 MHz (CD_3OD): δ 8.53 (s, 1H), 7.86–7.24 (m, 5H), 5.69 (d, 1H, $J = 7.86$ Hz), 4.67 (ddd, 1H, $J = 8.11$, 4.28, 4.28 Hz), 4.06 (t, 1H, $J = 8.43$ Hz), 3.88 (dd, 1H, $J = 11.78$, 2.30 Hz), 3.79 (ddd, 1H, $J = 8.80$, 6.39, 2.38 Hz), 3.65 (ddd, 1H, $J = 11.47$, 5.57, 5.57 Hz), 3.45 (t, 1H, $J = 8.12$ Hz), 2.31 (ddd, 1H, $J = 14.44$, 9.97, 4.40 Hz), 2.13 (dd, 1H, $J = 14.54$, 5.06); ^{13}C NMR 100 MHz (CD_3OD): δ 149.0, 131.8, 130.1, 129.6, 126.9, 121.4, 95.8, 87.0, 76.5, 71.3, 70.3, 64.4, 38.9; ES m/z $[M+Na]^+$ calcd 344.1217, found 344.1218.

1.19. 4-(2,3-*O*-Isopropylidene-mannpyranosyl)-1-(3-deoxy-β-D-*glycero*-D-*gluco*-septanosyl)-1,2,3-trizaole (12)

The product was isolated as a whitish solid (99%). $[\alpha]_D$ +16.9 (*c* 2.3, CH_3OH); ^{1}H NMR 400 MHz (CD_3OD): δ 7.62 (s, 1H), 5.11 (d, 1H, $J = 10.41$ Hz), 4.97 (d, 1H, $J = 9.56$ Hz), 4.18 (dd, 1H, $J = 9.56$, 4.09 Hz), 4.17–4.04 (m, 1H), 3.60–2.86 (m, 9H), 1.76 (ddd, 1H, $J = 19.27$, 13.06, 5.89 Hz), 1.58 (dd, 1H, $J = 19.46$, 6.49 Hz), 1.09 (s, 3H), 0.96 (s, 3H); ^{13}C NMR 100 MHz (CD_3OD): δ 147.3, 124.5, 109.9, 95.7, 86.9, 78.7, 76.3, 73.9, 73.5, 71.2, 70.2, 64.5, 64.2, 38.6, 28.0, 25.0; ES m/z $[M+Na]^+$ calcd 458.1745, found 458.1746.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.03.026.

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