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Synthesis of galactose-mimicking 1*H*-(1,2,3-triazol-1-yl)-mannosides as selective galectin-3 and 9N inhibitors

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Abstract—1*H*-[1,2,3]-Triazol-1-yl mannosides have been synthesized as inhibitors for the β-galactoside-binding family of galectin proteins. Easier synthetic access to C1 in mannose, as compared to C3 in galactose, for attachment of affinity-enhancing triazoles rendered a synthetic advantage. The best mannose-derived inhibitor for galectin-9N, 4-benzylaminocarbonyl-1*H*-[1,2,3]-triazol-1-yl β-D-mannopyranoside, had a K_d value of 540 μM, which compares favorably with its galactoside counterpart ($K_d = 670$ μM) and with LacNAc ($K_d = 500$ μM).

Keywords: Galectin; Lectin; Triazole; Glycomimetic; Mannoside

1. Introduction

The galectin family contains about 15 mammalian intra- and extra-cellular β-galactoside-recognizing lectins with a correlation of expression and functional implication in inflammation and the aggressiveness and metastatic potential of cancer.[1–9] In several of these biological events glycoconjugate (i.e., galactose) binding is crucial, which makes the development of galectin inhibitors important. Our group has previously presented a number of low molecular weight ligands with high affinity for different galectins. However, many of the most promising inhibitors[10–12] are based on 3-azido-3-deoxy-β-D-galactose,[13] which is time consuming to synthesize. To circumvent this disadvantage, we[14] and Roy and co-workers[15] have presented alternative galactose-based inhibitors with easier synthetic access. An alternative strategy would be to use galactose-mimicking structures that even further simplify chemical synthesis of novel galectin inhibitors. Within this context, galactose and mannose have structural features in common in that the stereochemical relationship of the galactose axial O4 and equatorial O3 resembles the axial O2 and O1 of β-mannose. These similarities suggest possibilities to exploit β-mannoside-based galectin inhibitors, where easier access to the position C-1 in mannose as compared to C-3 in galactose gives advantages in using mannose-based ligands as galectin inhibitors. It is worthwhile to mention that the criteria of affinity for β-galactosides have been discussed as galectin-10 shows weak galactoside-binding activity and a few reports have instead suggested affinity for mannosides.[16,17]

Molecular and stereochemical mimicry are obviously established strategies with long history within medicinal and carbohydrate chemistry. The concept of glycomimicry typically implies stereochemical mimicry, be it through substitution of a monosaccharide moiety with another saccharide or with a non-saccharide structure. Within this context, prominent examples of successful substitution of protein-binding monosaccharides with other saccharides include α-D-mannoside derivatives[18–21] mimicking the α-L-fucose moiety of Lewis structures recognized by selectins and 2-acetamido-β-D-glucuronides[22–24] mimicking the sialic acid glycal transition-state analog of neuraminidases. In both these cases, the efficiencies of the mannoside- and glucuronide-based

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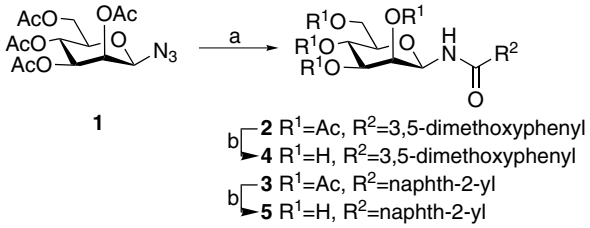
mimetics approach those of their respective parent fucose- and sialic acid glycal structures. A more recent study pointed to the use of mannose as a galactose-mimicking substrate for the retaining α-(1→4)-galactosyltransferase from *Neisseria meningitides*.[25]

Our previous findings that β-D-galactopyranosides substituted at C-3 with amide[10,11,13] or triazole[12] substituents gave affinity enhancement for varying galectins encouraged us to utilize these substituents for the derivatization of the anomeric position of β-mannoside. Syntheses of glycosyl triazoles have been reported,[15,26–28] as have their evaluation as carbonic anhydrase antagonists.[29] Computer modeling of amido and triazolyl β-mannosides with galectin-3 suggests favorable hydrogen-bond interaction between HO2 and Arg162 and his158, as observed for galactose HO4 in galectin-3 crystal structures. Furthermore, favorable interactions between the anomeric amide or triazolyl groups of the β-mannosides with Arg144, as seen for the corresponding galactose derivatives,[10] were indicated by the modeling results (Fig. 1). These results suggested that galactose-mimicking β-D-mannoside amides or triazoles may indeed be able to bind galectins with, in an optimal outcome, affinities approaching those of their galactoside counterparts. Herein we report the synthesis of amido and 1*H*-(1,2,3)-triazol-1-yl β-mannosides and their evaluation as galectin-1, 3, 7, 8N, and 9N inhibitors.

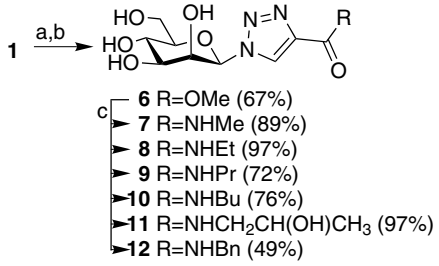
2. Results and discussion

2.1. Synthesis

Catalytic hydrogenation in ethanol over Pd/C of azide **1**,[30] followed by in situ acylation with an acid chloride and pyridine, gave the corresponding amides **2** and **3**. Zemplén transesterfication gave the final amides **4** and



Scheme 1. Synthesis of amides **4** and **5**. Reagents and conditions: (a) (i) Pd/C, H_2, EtOH (**4**) or THF (**5**), 200 psi, 75 min; (ii) acid chloride, CH_2Cl_2 (**4**) or THF (**5**), pyridine, over night; (b) MeOH, NaOMe.



Scheme 2. Synthesis of triazoles **7**–**12**. Reagents and conditions: (a) CuI, toluene, DIPEA, methyl propiolate, over night; (b) MeOH, NaOMe; (c) RNH_2 in MeOH or H_2O.

5 (Scheme 1). Copper(I)-catalyzed 1,3-dipolar cycloaddition[31–33] of **1** with methyl propiolate, followed by Zemplén transesterfication furnished the methyl ester **6**.[34] Treatment of the ester **6** with different amines afforded a panel of triazole amides **7**–**12** (Scheme 2).

2.2. Galectin binding

Evaluation of the amides **4** and **5** as inhibitors for galectin-1 and 3 were disappointing as no or very low affinity could be detected. The triazoles **7**–**12** showed no affinity

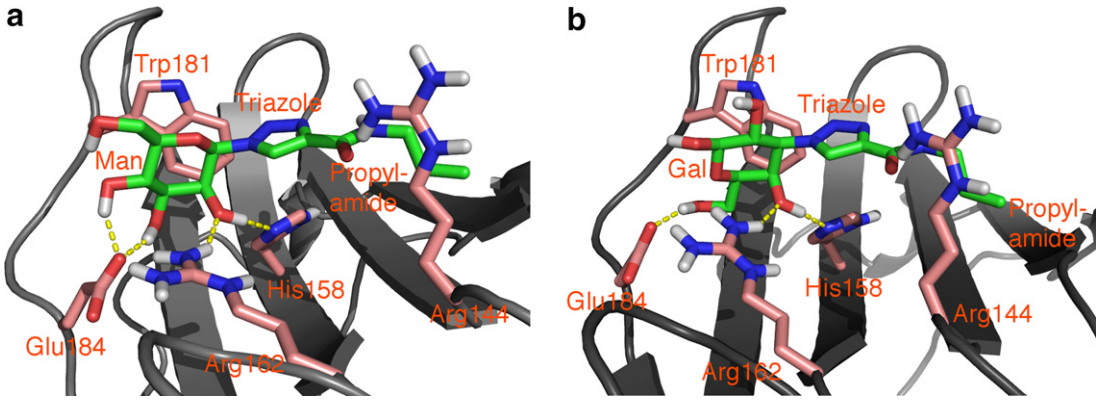


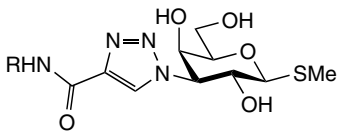
Figure 1. (a) Mannose and (b) galactose propylamide triazoles in modeled complexes with galectin-3. The hydrophobic surface of the saccharides stack onto Trp181, mannose HO2 and galactose HO4 are hydrogen bonded with Arg162 and His158, mannose HO3 and 4, and galactose HO6 are hydrogen bonded to Glu184, and the triazole moieties interact with Arg144.

for galectin-1 or 8N and only low affinity for galectin-7. However, a fortunate contrast to these observations was that inhibitors with good affinity for galectin-3 and 9N were found among the triazoles **7**–**12**. Computer modeling suggested that an extended binding groove of the CRD in galectin-3 could harbor a propylamide triazole **9**, whereas the methyl and ethyl analogue (**7** and **8**) were too small and the butyl analogue **10** was too large, which correlated well with the measured K_d values where **9** ($K_d = 1.4$ mM) had highest affinity for galectin-3 (Table 1). The racemic 2-hydroxy propyl analogue **11** ($K_d =$ 1.5 mM) showed affinity similar to **9**, whereas the benzyl amide **12** was the third best galectin-3 inhibitor. The corresponding galactose analogues (e.g., compare **12** with **15**[12]) were consistently better, which suggests that triazol-1-yl mannosides, although active, are not optimal mimetics of 3-(triazol-1-yl)-galactosides for galectin-3.

In case of galectin-9N, again the triazolyl amides **7**–**12** were efficient inhibitors, with **12** being the best. Indeed, the benzyl amide **12** displayed affinity for galectin-9N similar to that of methyl LacNAc and six times better than methyl β-D-galactoside. Furthermore, compound **12** compared favorably with the corresponding 3-triazolyl-galactose derivative **15**[12] showing that mannose-based mimics can indeed be at least as good galectin-9N inhibitors as the corresponding galactosides. The methyl and butyl triazoles **7** and **10** were somewhat less efficient than their galactose counterparts **13**[12] and **14**[12] as galectin-9N inhibitors. Hence, the benzyl moiety of **12** appears to provide an important affinity-enhancing interaction with this galectin. Furthermore, the benzylamide **12** displays excellent selectivity for galectin-9N over galectins-1, 7, and 8N and some selectivity over galectin-3. The selectivity is presumably a combined effect of the mannoside functioning well as a galactose mimic for galectin-9N and the amidotriazole moiety being clearly affinity-enhancing for this galectin. This result is important, as selective inhibitors are valuable tools for selective inhibition of one galectin in, for example, cell-based or in vivo assays.

Altogether, these results clearly demonstrate that properly designed β-D-mannosides can behave as galectin-9N-binding galactose mimetics. The concept of mimicry implies structural and functional mimicry, but not necessarily improved affinity compared to parent structures. Hence, successful mimicry is achieved when a simplified or more stable mimic is as efficient ligand as the parent structure. Improved affinity does typically not arise from the mimetic core itself, but rather from added functionalities or structures involved in beneficial interactions with the protein. This is the case in the present study, as indeed have been the case in previous studies with α-D-mannoside derivatives[18–21] mimicking the α-L-fucose moiety of Lewis structures recognized by selectins and mannose[25] mimicking galactose as a substrate for the *N. meningitides* α-(1→4)-galactosyltransferase. In these two studies, mannose itself was a poor binder and attached non-carbohydrate structures induced affinity-enhancements.

Table 1. K_d (μM) for galectin-1, 3, 7, 8N, and 9N with **4**–**5** and **7**–**15** as determined in a fluorescene polarization assay[35,36]

	Galectin				
	1	3	7	8N	9N
D-Mannose	>10,000	>10,000	>10,000	>10,000	>10,000
4	>10,000	>10,000	n.d.[a]	n.d.[a]	n.d.[a]
5	>10,000	≈8000	n.d.[a]	n.d.[a]	n.d.[a]
7	≈7000	≈8000	≈7000	>10,000	≈7000
8	≈6000	≈4000	≈4000	>10,000	2700 ± 140
9	≈8000	1400 ± 210[b]	≈3000	>10,000	1800 ± 410
10	>10,000	2100 ± 210	≈5000	>10,000	1900 ± 190
11	≈5000	1500 ± 330	≈5000	>10,000	1400 ± 390
12	>10,000	1900 ± 450	≈5000	>10,000	540 ± 250
Galactoside counterparts[12]					
					
13 (R = Me)	n.d.[a]	230	—[b]	>20,000	1300
14 (R = Bu)	n.d.[a]	120	1300	>20,000	650
15 (R = Bn)	n.d.[a]	110	2400	>20,000	670
Me β-D-gal[36]	10,000	4400	4800	5300	3300
Me β-LacNAc	70[37]	67[10]	490[37]	700[37]	500[37]

[a] Not determined.
[b] Standard deviation calculated from four experiments.

3. Conclusions

In conclusion, we have developed synthetically simple 1*H*-[1,2,3]-triazol-1-yl mannosides as inhibitors with selectivity for galectin-3 and 9N. For galectin-9N, the mannose-derived benzylamide triazole **12** compared favorable with its β-galactoside counterpart **15** evidencing that β-mannosides can be used as synthetically simple yet efficient galactose mimetica for this galectin. The fact that mannose effectively mimics galactose as a galectin-9N inhibitor suggests that mannose is indeed a suitable lead for further development of simplified high-affinity inhibitors of this galectin, which is in analogy with our use of the mM-binding galactose as a scaffold for the successful development of low nM inhibitors of galectin-3.[10,11]

4. Experimental

4.1. General methods

All commercial chemicals were used without further purification. Thin layer chromatography (TLC) was carried out on $60F_{254}$ Silica (Merck) and visualization was made by UV light followed by heating with aqueous sulfuric acid. Column chromatography (CC) was performed on silica (Amicon 35–70 μm, 60 Å). Reversed phase chromatography was performed on Waters Sep-Pack Vac 35cc C_{18}-5 g columns. NMR experiments were recorded with Bruker ARX 300 MHz or Bruker DRX 400 MHz spectrometers at ambient temperature. ^{1}H NMR assignments were derived from COSY experiments. Chemical shifts are given in ppm relative to TMS, using the solvent residual peaks of CD_2HOD at 3.31, HDO at 4.79, and $CHCl_3$ at 7.26. The optical rotations were measured with a Perkin–Elmer 341 polarimeter. HRMS (ESI) were recorded with a Micromass Q-TOF micro spectrometer. MALDI TOF MS were recorded with a Bruker Biflex III. Fluorescence polarization experiments and calculations were performed as described[35] and performed at 4 °C except for galectin-3 and 8N, which were done at ambient temperature. Concentrations and probes used for galectins-1, 3, 7, 8N, and 9N were as described.[35,36]

4.2. 2,3,4,6-Tetra-*O*-acetyl-1-deoxy-1-(3,5-dimethoxybenzamido)-β-D-mannopyranose 2

To a solution of 2,3,4,6-tetra-*O*-acetyl-1-azido-1-deoxy-β-D-mannopyranose **1** (31 mg, 84 μmol) in EtOH (3 mL) was added 10% Pd/C (28 mg) dissolved in EtOH (2 mL). The mixture was hydrogenated (H_2, 200 psi) for 60 min followed by addition of pyridine (540 μL) and slow addition of 3,5-dimethoxybenzoyl chloride (135 mg, 0.67 mmol), dissolved in THF (1 mL), under a nitrogen atmosphere. The reaction mixture was stirred over night, filtered through Celite, concentrated, and co-concentrated with toluene. Flash chromatography (heptane/EtOAc, 1:1) gave **2** (27 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (d, 2H, $J = 2.2$ Hz, Ar-H), 6.78 (br d, 1H, $J = 9.5$ Hz, NH), 6.60 (t, 1H, $J = 2.3$ Hz, Ar-H), 5.73 (br d, 1H, $J = 9.3$ Hz, H-1), 5.45 (dd, 1H, $J = 3.1$ Hz, $J = 1.1$ Hz, H-2), 5.29 (t, 1H, $J = 10.0$ Hz, H-4), 5.18 (dd, 1H, $J = 10.3$ Hz, $J = 3.3$ Hz, H-3), 4.33 (dd, 1H, $J = 12.5$ Hz, $J = 5.2$ Hz, H-6′), 4.12 (dd, 1H, $J = 12.6$ Hz, $J = 2.0$ Hz, H-6), 3.88–3.84 (m, 7H, H-5, OMe), 2.26 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.00 (s, 3H, OAc); MALDI MS *m*/*z* calcd for $[C_{23}H_{29}NO_{12}+Na]^+$: 534.159. Found: 534.541.

4.3. 2,3,4,6-Tetra-*O*-acetyl-1-deoxy-1-(2-naphthamido)-β-D-mannopyranose 3

To a solution of 2,3,4,6-tetra-*O*-acetyl-1-azido-1-deoxy-β-D-mannopyranoside **1** (37 mg, 100 mmol) in EtOH (2 mL) was added 10% Pd/C (30 mg) dissolved in THF (1 mL). The mixture was hydrogenated (H_2, 200 psi) for 75 min, followed by addition of pyridine (645 μL) and slow addition of a solution of 2-naphtoyl chloride (150 mg, 0.80 mmol) in THF (2 mL) under a nitrogen atmosphere. The reaction mixture was stirred over night, filtered through Celite, concentrated, and co-concentrated with toluene. Flash chromatography (heptane/EtOAc, 7:3–1:1) gave **3** (21 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (s, 1H, Ar-H), 7.93–7.84 (m, 3H, Ar-H), 7.75 (dd, 1H, $J = 8.5$ Hz, $J = 1.8$ Hz, Ar-H), 7.59–7.54 (m, 2H, Ar-H), 6.99 (br d, 1H, $J = 9.0$ Hz, NH), 5.82 (br d, 1H, $J = 9.2$ Hz, H-1), 5.51 (dd, 1H, $J = 3.2$ Hz, $J = 1.2$ Hz, H-2), 5.31 (t, 1H, $J = 10.0$ Hz, H-4), 5.21 (dd, 1H, $J = 10.1$ Hz, $J = 3.2$ Hz, H-3), 4.36 (dd, 1H, $J = 12.5$ Hz, $J = 5.1$ Hz, H-6′), 4.13 (dd, 1H, $J = 12.8$ Hz, $J = 2.4$ Hz, H-6), 3.89 (ddd, 1H, H-5), 2.29 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.00 (s, 3H, OAc).

4.4. 1-Deoxy-1-(3,5-dimethoxybenzamido)-β-D-mannopyranose 4

To **2** (27 mg, 53 μmol) dissolved in MeOH (4 mL) was added methanolic NaOMe (0.3 mL, 1 M). The reaction mixture was stirred over night and then neutralized with Duolite C436 resin, filtered, and concentrated. The residue was dissolved in H_2O and applied on to C-18 silica (5 g). Elution with a gradient of MeOH in H_2O and lyophilization gave **4** (18 mg, 99%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.00 (d, 2H, $J = 2.2$ Hz, Ar-H), 6.68 (t, 1H, $J = 2.3$ Hz, Ar-H), 5.38 (d, 1H, $J = 1.1$ Hz, H-1), 3.89 (dd, 1H, $J = 2.8$ Hz, $J = 1.2$ Hz, H-2), 3.88 (dd, 1H, $J = 11.9$ Hz, $J = 2.4$ Hz, H-6),

3.83–3.80 (m, 6H, OMe), 3.72 (dd, 1H $J = 11.9$ Hz, $J = 5.7$ Hz, H-6′), 3.62–3.58 (m, 2H), 3.37–3.35 (m, 1H, H-5); ESI MS *m*/*z* calcd for $[C_{15}H_{21}NO_8+Na]^+$: 366.1165. Found: 366.1155.

4.5. 1-Deoxy-1-(2-naphthamido)-β-D-mannopyranose 5

To **3** (21 mg, 42 μmol) dissolved in MeOH (4 mL) was added methanolic NaOMe (0.2 mL, 1 M). The reaction mixture was stirred over night and then neutralized with Duolite C436 resin, filtered, and concentrated under reduced pressure. The residue was dissolved in H_2O and applied on to C-18 silica (5 g). Elution with a gradient of MeOH in H_2O and lyophilization gave **5** (14 mg, 98%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.45–8.43 (m, 1H, Ar-H), 8.02–7.90 (m, 4H, Ar-H), 7.64–7.56 (m, 2H, Ar-H), 5.46 (d, 1H, $J = 1.1$ Hz, H-1), 3.96 (dd, 1H, $J = 2.8$ Hz, $J = 1.3$ Hz, H-2), 3.90 (dd, 1H, $J = 11.9$ Hz, $J = 2.3$ Hz, H-6), 3.74 (dd, 1H, $J = 11.9$ Hz, $J = 5.6$ Hz, H-6′), 3.65–3.63 (m, 2H), 3.43–3.38 (m, 1H, H-5); HRMS (ESI) *m*/*z* calcd for $[C_{17}H_{19}NO_6+Na]^+$: 356.1110. Found: 356.1095.

4.6. 1-Deoxy-1-[4-methoxycarbonyl-1*H*-(1,2,3)-triazol-1-yl]-β-D-mannopyranose 6

To **1** (1.1 g, 2.9 mmol) dissolved in toluene (30 mL) was added methylpropiolate (260 μL), *N*,*N*-diisopropylethylamine (495 μL) and CuI (0.5 g). The reaction mixture was stirred over night followed by concentration. Flash chromatography (heptane/EtOAc, 1:1) gave the acetylated intermediate (1.0 g, 75%), which was dissolved in MeOH (20 mL) and methanolic NaOMe (2 mL, 1 M) was added. The mixture was neutralized after 90 min with Duolite C436, filtrated, and concentrated. Flash chromatography gave **6** (0.5 g, 81%). $[\alpha]_D^{20}$ +15 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 8.76 (s, 1H, NCH), 6.12 (br s, 1H, H-1), 4.14 (br s, 1H, H-2), 3.96–3.92 (m, 4H, $-OCH_3$, H-6), 3.82–3.75 (m, 3H), 3.58–3.54 (m, 1H, H-5); HRMS (ESI) *m*/*z* calcd for $[C_{10}H_{15}N_3O_7+Na]^+$: 312.0808. Found: 312.0796.

4.7. 1-Deoxy-1-[4-methylaminocarbonyl-1*H*-(1,2,3)-triazol-1-yl]-β-D-mannopyranose 7

Compound **6** (108 mg, 0.37 mmol) was dissolved in $MeNH_2$ (2 mL, 40% in H_2O). The reaction mixture was stirred over night, and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 4:1) to give **7** (96 mg, 89%). $[\alpha]_D^{20}$ +15 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 8.61 (s, 1H, triazol-H), 6.09 (d, 1H, $J = 1.1$ Hz, H-1), 4.12 (br d, 1H, $J = 1.2$ Hz, H-2), 3.94 (dd, 1H, $J = 12.2$ Hz, $J = 2.1$ Hz, H-6), 3.81–3.71 (m, 3H), 3.59–3.53 (m, 1H, H-5), 2.93 (s, 3H, CH_3); HRMS (ESI) *m*/*z* calcd for $[C_{10}H_{16}N_4O_6+Na]^+$: 311.0968. Found: 311.0976.

4.8. 1-Deoxy-1-[4-ethylaminocarbonyl-1*H*-(1,2,3)-triazol-1-yl]-β-D-mannopyranose 8

Compound **6** (71 mg, 0.25 mmol) was dissolved in $EtNH_2$ (2 mL, 70% in H_2O). The reaction mixture was stirred over night and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 4:1) to give **8** (56 mg, 75%). $[\alpha]_D^{20}$ +15 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 8.62 (s, 1H, triazol-H), 6.09 (d, 1H, $J = 1.0$ Hz, H-1), 4.13 (br d, 1H, $J = 1.1$ Hz, H-2), 3.94 (dd, 1H, $J = 12.2$ Hz, $J = 2.1$ Hz, H-6), 3.81–3.71 (m, 3H), 3.58–3.54 (m, 1H, H-5), 3.42 (q, 2H, $J = 7.2$ Hz, CH_2), 1.22 (t, 3H, $J = 7.2$ Hz, CH_3). HRMS (ESI) *m*/*z* calcd for $[C_{11}H_{18}N_4O_6+Na]^+$: 325.1124. Found: 325.1126.

4.9. 1-Deoxy-1-[4-propylaminocarbonyl-1*H*-(1,2,3)-triazol-1-yl]-β-D-mannopyranose 9

To **6** (43 mg, 0.15 mmol) in MeOH (2 mL) was added propylamine (0.5 mL). The reaction mixture was stirred over night and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 4:1) to give **9** (34 mg, 72%). $[\alpha]_D^{20}$ +14 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, MeOD): δ 8.62 (s, 1H), 6.09 (d, 1H, $J = 1.1$ Hz, H-1), 4.12 (br d, 1H, $J = 1.1$ Hz, H-2), 3.94 (dd, 1H, $J = 12.2$ Hz, $J = 2.2$ Hz, H-6), 3.80–3.72 (m, 3H), 3.59–3.52 (m, 1H, H-5), 3.35 (br t, 3H, $J = 5.7$ Hz, CH_3), 1.71–1.59 (m, 2H, CH_2), 1.04–0.95 (m, 3H, CH_3). HRMS (ESI) *m*/*z* calcd for $[C_{12}H_{20}N_4O_6+Na]^+$: 339.1281. Found: 339.1276.

4.10. 1-[4-Butylaminocarbonyl-1*H*-(1,2,3)-triazol-1-yl]-1-deoxy-β-D-mannopyranose 10

To **6** (54 mg, 0.19 mmol) dissolved in water (2 mL) was added butylamine (0.5 mL). The reaction mixture was stirred over night, followed by heating to 60 °C, stirring for an additional 8 h, and concentration. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 4:1) to give **10** (47 mg, 76%). $[\alpha]_D^{20}$ +12 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, MeOD): δ 8.61 (s, 1H, H-triazole), 6.09 (d, 1H, $J = 1.2$ Hz, H-1), 4.12–4.11 (m, 1H, H-2), 3.94 (dd, 1H, $J = 12.2$ Hz, $J = 2.2$ Hz, H-6), 3.88–3.72 (m, 3H), 3.57–3.53 (m, 1H, H-5), 3.39 (t, 2H, $J = 7.1$ Hz, CH_2), 1.68–1.57 (m, 2H, CH_2), 1.48–1.36 (m, 2H, CH_2), 0.97 (m, 3H, $J = 7.6$ Hz, CH_3); HRMS (ESI) *m*/*z* calcd for $[C_{13}H_{22}N_4O_6+Na]^+$: 353.1437. Found: 353.1422.

4.11. 1-Deoxy-1-[4-(2-Hydroxypropyl)-aminocarbonyl-1*H*-(1,2,3)-triazol-1-yl]-β-D-mannopyranose 11

To **6** (67 mg, 0.23 mmol) dissolved in MeOH (5 mL) was added 1-amino-2-propanol (0.5 mL). The reaction mixture was stirred over night and concentrated. The resi-

due was purified by flash chromatography (CH_2Cl_2/MeOH, 4:1) to give **11** (75 mg, 97%). $[\alpha]_D^{20}$ +15 (*c* 0.5, MeOH); *R*/*S*-ratio about 3:1. ^{1}H NMR (400 MHz, MeOD): δ 8.63 (s, 1H, H-triazole), 6.09 (d, 1H, $J = 1.1$ Hz, H-1), 4.12 (br s, 1H, H-2) 3.99–3.92 (m, 2H, H-6, CH), 3.80–3.70 (m, 3H), 3.58–3.52 (m, 1H, H-5), 3.48 (dd, 1H, $J = 4.6$ Hz, $J = 1.8$ Hz, CH_2 *R* or *S*) 3.44 (dd, 1H $J = 4.6$ Hz, $J = 1.8$ Hz, CH_2 *R* or *S*), 1.20 (d, 3H, $J = 6.3$ Hz, CH_3), 3.48 (dd, 1H, $J = 1.8$ Hz, CH_2 *R* or *S*), 1.14 (d, 3H, $J = 6.2$ Hz, CH_3); HRMS (ESI) *m*/*z* calcd for $[C_{12}H_{20}N_4O_7+Na]^+$: 355.1230. Found: 355.1219.

4.12. 1-[4-Benzylaminocarbonyl-1*H*-(1,2,3)-triazol-1-yl]-1-deoxy-β-D-mannopyranose 12

To **6** (108 mg, 0.37 mmol) dissolved in H_2O (2 mL) was added benzylamine (2 mL). The reaction mixture was stirred over night and concentrated. The residue was dissolved in H_2O and applied on to C-18 silica (5 g). Elution with a gradient of MeOH in H_2O and lyophilization gave **12** (62 mg, 49%). $[\alpha]_D^{20}$ +16 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 8.65 (s, 1H, triazol-H), 7.37–7.21 (m, 5H, Ar-H), 6.09 (d, 1H, $J = 1.1$ Hz, H-1), 4.58 (s, 1H, Ar-CH_2), 4.12 (s, 1H, H-2), 3.94 (dd, 1H, $J = 12.2$ Hz, $J = 2.1$ Hz, H-6), 3.82–3.74 (m, 3H), 3.58–3.52 (m, 1H, H-5); HRMS (ESI) *m*/*z* calcd for $[C_{16}H_{20}N_4O_6+Na]^+$: 387.1281. Found: 387.1263.

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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.2007.03.012.

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