Strategies for Stereocontrol at C1 or C2 in Syntheses of α-Glucosaminides

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Abstract. The C1 and C2 stereocenters of α-glucosaminides can be prepared by establishing the stereocenters in either order. For the former, a C2-azido glucosyl donor is prepared first, and the restraining effect of a 4,6-O-benzylidene ring is used to induce α-coupling. For the latter, the C1 linkage is prepared first by use of an *n*-pentenyl-manno-1,2-orthoester donor which ensures (a) clean α-coupling and (b) a convenient C2-ester. The C2-ester is replaced with a triflate leaving group, and nucleophilic displacement is effected by use of a hypervalent silicon azide.

INTRODUCTION

2-Amino-2-deoxy-α-D-glucopyranosides (α-glucosaminides), for example **1**, are components of a wide variety of biologically important oligosaccharides, including the amino glycoside (aminocyclitol) antibiotics[1] and glycosylphosphatidylinositols (GPIs).[2]

Members of the former class[1] have been in clinical use for over fifty years, while the latter have recently entered into prominence following the first structure assignment in 1988.[2]

The burgeoning interest[3] in the latter class of oligosaccharides stems from their occurrence in a wide range of health-related disorders including African sleeping sickness,[4] Chagas' disease (or American sleeping sickness),[5] malaria,[6] paroxysmal nocturnal hemoglobinuria,[7] and transmissible spongiform encephalopathies[8] such as Mad Cow disease.

The ready availability of glucosamine, by acid hydrolysis of crustacean shells,[9] provides what should be a ready starting material for preparation of α-glucosaminides. The highly reactive amino group must be protected, but the nature of the amine protecting group is of paramount importance. N-Acyl protection, e.g., **2**, while convenient, may cause problems during glycosidation, owing to participation of the acyl group in the reaction at the anomeric center. Thus, with primary alcohol acceptors, trans-1,2-glycosides may be obtained.[10] However, with more hindered secondary alcohol acceptors, neighboring group participation intervenes, leading to oxazolines, **3**, as major products.[11] The use of phthalimide for amine protection, introduced by Lemieux and coworkers[12] in order to avoid oxazoline formation, leads to excellent production of trans-1,2-glycosides.

In order to meet the challenge of cis-1,2-α-anomeric selectivity, Paulsen and co-workers introduced the use of donors with a C2 azido functionality, e.g., **4**, as the "latent amine".[13] Since neighboring group participation is not a factor, α-glycosidation should be facilitated. On the basis of this precedent, a ready route to 2-azido hexopyranose donors was developed by Lemieux and Ratcliffe[14] as one of a series of preparative procedures based on electrophilic addition to glycals,[15] **5**→**6** (Scheme 1).

Traditionally, the azide serves as a convenient latent amine, **8**→**9**,[16] as indicated in Scheme 2. However, recent work in Vasella's laboratory has provided an elegant method for the reverse process, **9**→**8** by treating an amine with trifluoromethanesulphonyl (triflyl) azide (Scheme 2).[17] The azido group can therefore now be properly regarded as a "protecting group" for the amine,[18] as well as a latent form thereof.

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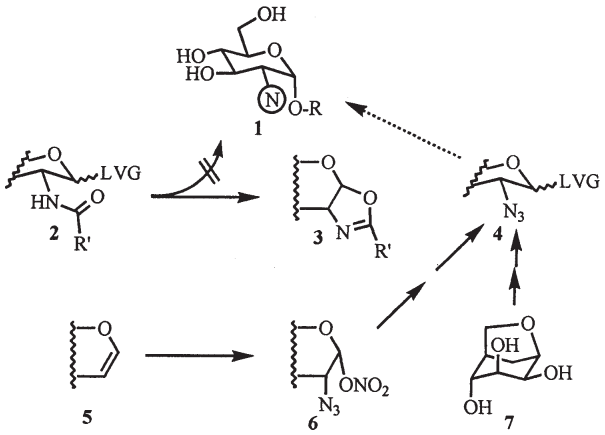
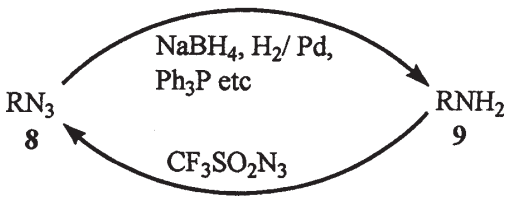


Scheme 1



Scheme 2

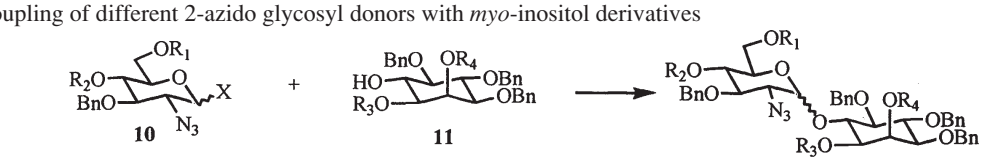
The glucosamine/inositol domain may be regarded as the "warhead"[19] of GPIs in view of the fact that several key biological[20] and biosynthetic[21] events are controlled from this pseudo-disaccharide motif. For synthetic approaches, 2-azido-2-deoxy glucosyl donors have been the preferred choice, in our[22] and other[23] laboratories, for coupling to inositol acceptors. Although the classic route of Paulsen et al.[24] for preparation of such donors from 1,6 anhydromannose has served well, the strategy of Vasella et al. (Scheme 2) opened the way for use of suitably protected amine precursors, as first illustrated by Konradsson and coworkers.[25] Similarly, the readily cleaved pent-4-enoyl[26] and tetrachlorophthaloyl (TCP)[27] protecting groups developed in our laboratory, have greatly simplified routes to azido donors such as **10a**.[28]

However, the results in Table 1 make it clear that 2-azido groups do not ensure α-glucoside formation. Thus, our efforts using donor **10a**[28] with acceptor **11a**[29] failed to give either the desired pseudo-disaccharide **12a**(α) or its anomer **12a**(β) (Table 1, entry i). The corresponding glycosyl bromide **10b** and trichloroacetimidate **10c** (prepared from **10a** by standard procedures)[30] also failed to couple with **11a** in ways that combined good yields with good α-selectivity as (Table 1, entries ii to v).

By contrast, good results were obtained with the benzylidenated derivative **10d** (Table 1, entry vi). This is of mechanistic significance in view of the poor results obtained with the related donor **10a** (See Table 1, entry i vs entry vi). It is clear that the conformational restraint imposed by the benzylidene ring of **10d** leads to acceptable coupling, in contrast to the conformationally mobile analogue **10a.** On the basis of trasition state modeling in our laboratory, we have advanced the use of cyclic acetal protecting groups for torsional control of coupling reactions.[31] Recently, elegant studies by Crich and coworkers[32] have validated our findings.

However, slower reaction times for many acetalated donors have been predicted theoretically,[31] and observed experimentally,[33] in our model studies, and this was borne out by the experiment summarized in entry

Table 1. Coupling of different 2-azido glycosyl donors with *myo*-inositol derivatives



a X = OPent, R_1 = Bn, R_2 = Ac
b X = α-Br, R_1 = Bn, R_2 = Ac
c X = O-C(NH)-CCl_3, R_1 = Bn, R_2=Ac
d X = OPent, R_1, R_2 = CHPh

a R_3 = All, R_4 = Bn; **b** R_3, R_4 =

entry	donor	acceptor	reaction conditions	yield	product ratio (12a/12b)
i	10a	11a	NIS/TESOTf/CH2Cl2	poor yield and selectivity	
ii	10b	11a	AgOTf/Et2O	60	(1:2.5)
iii	10b	11a	AgClO4/Et2O	50	(1:1)
iv	10c	11a	TESOTf/CH2Cl2	74	(1:9)
v	10c	11a	TfOH/CH2Cl2	80	(1:1)
vi	10d	11b	NBS/CH2Cl2/7 days	59	(1:0)

vi. Thus, the good yield notwithstanding, the 7-day reaction time was a strong disincentive.

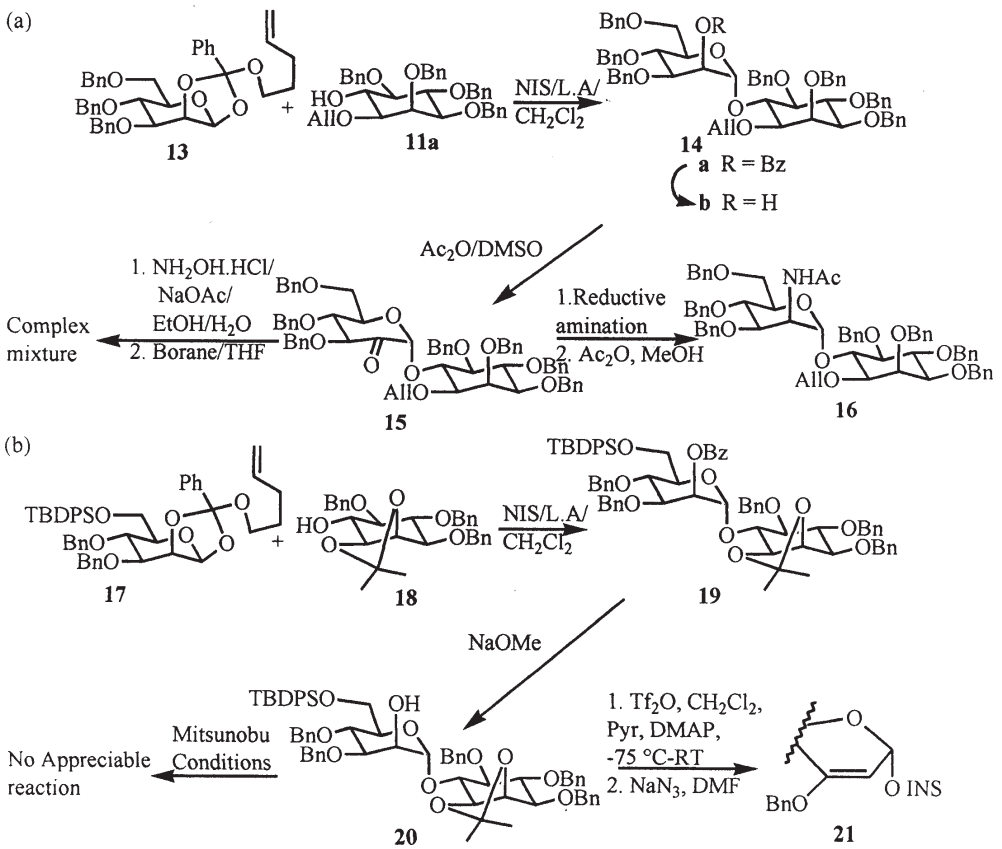
The sequence in the traditional strategy outlined in Scheme 1 is (a) to prepare the C2-azido donor (e.g., **4),** and then (b) carry out the (hopefully) α-coupling to give **1**. The alternative of carrying out the α-coupling *before* azide installation, could be advantageous in view of the ease of obtaining α-mannosides. In this context, we have found that *n*-pentenyl-1,2-orthoesters (NPOEs) are excellent donors; and the fact that the products are conveniently acylated at C2 enhances their attractiveness.[34]

Indeed coupling NPOE **13**[35] with acceptor **11a** afforded disaccharide **14a** in good yield. Conversion into ketone **15** proceeded smoothly (Scheme 3a); however, attempts to apply the Lemieux–Gunner strategy for α-glucosaminide formation involving oximation followed by borane reduction[36] led to decomposition. On the other hand, reductive amination of **15** under standard conditions[37] proceeded in excellent yield, but gave the manno-product **16** rather than the desired gluco-isomer.

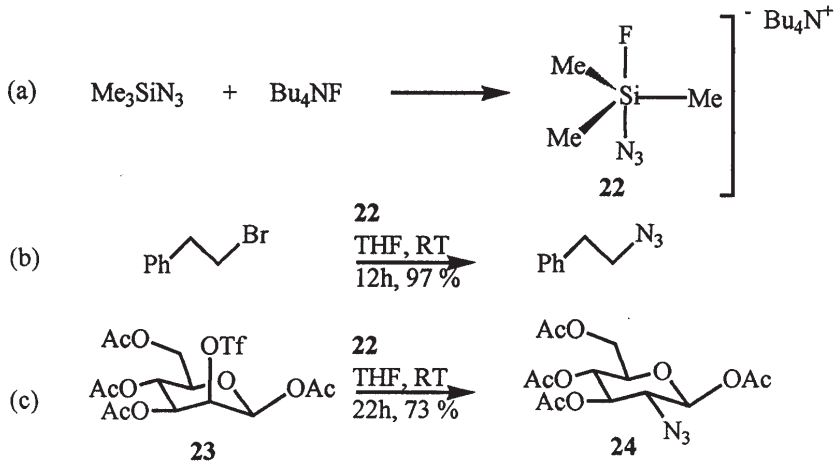
Nucleophilic displacement at C2 of sugars is traditionally problematic;[38] but it was hoped that modern methods might facilitate the process. Accordingly, coupling of NPOE **17** and the acetonide **18** afforded the pseudo-disaccharide **19**. The material was saponified to give **20**, which was subjected to a variety of Mitsunobu displacement conditions.[39] The results were uniformly unavailing. Binkley and coworkers have demonstrated the advantage of C2-triflates in displacement reactions;[40] but with the triflate from **20**, β-elimination to give hex-2-enopyranosides such as **21** (Scheme 3b) was the major reaction.

In light of the last result, we were struck by a report from DeShong's laboratory on the use of hypervalent silicon derivatives in nucleophilic displacements[41] (Scheme 4a). Particularly impressive was the virtually quantitative azide displacement of phenethyl bromide with reagent **22** (Scheme 4b) in a setting where β-elimination was highly favored. The result in Scheme 4c enhanced our enthusiasm even though, being a β-mannoside, substrate **23** would be a better candidate[38] for the observed displacement to **24** than the α-anomers of interest to us.

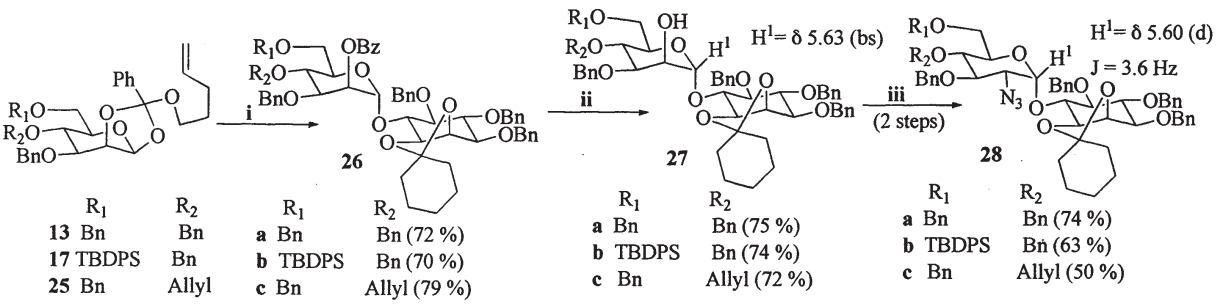
The two examples in Scheme 5 show that success with this strategy is possible. Thus the α-linked pseudo-disaccharides **26 (a, b,** and **c)** have been prepared in



Scheme 3



Scheme 4



Reaction Conditions: **i**. **11b** (1.3 equiv.), NIS (1.3 equiv.), BF_3. OEt_2(0.3 equiv.), 0°C, 20- 30 min.; **ii**. (a) Tf_2O, DMAP, Pyr, CH_2Cl_2, -75 °C- RT, 3 h. **iii**. $TMSN_3$ (1.5 equiv.), TBAF(1.5 equiv.), THF, 65 °C, 14-24 h.

Scheme 5

very good yields, and saponification led to alcohols **27** (**a**, **b**, and **c**, respectively). The corresponding triflates were stable enough to withstand column chromatography; however, normally the crude materials were directly subjected to the displacement. Scheme 5 shows that the yields for the two steps were moderate to good.

In summary, the C2 and C1 stereocenters of α-glucosaminides can be cleanly established by first installing either the C1 or C2 functionality. For the former, the restraining effect of a 4,6-*O*-benzylidene ring operating in a C2-azido donor, can be used to induce α-coupling. For the latter, a manno-1,2-orthoester donor (a) ensures clean α-coupling and (b) provides a convenient C2-ester, ready to be replaced with a triflate leaving group for displacement with DeShong's hypervalent silicon azide.

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EXPERIMENTAL

General Methods

Solvents of commercial anhydrous grade have been used. All reactions were conducted under an inert argon atmosphere. TLC plates (Riedel-de Haen, coated with silica gel 60 F 254) were detected by UV. Silica gel (Spectrum SIL 58, 230-400 mesh, grade 60) was used for column chromatography. All NMR spectra were recorded at 25 °C at 400/300 MHz (^{1}H) or 100/75 MHz (^{13}C), and chemical shifts are reported relative to internal TMS. Accurate mass measurements were made using FAB at 10 K resolution.

1-O-*Allyl-2,3,4,5-tetra*-O-*benzyl-6*-O-*(2*-O-*benzoyl-3,4,6-tri*-O-*benzyl-α-D-mannopyranosyl)-D*-myo-*inositol (**14a**)*. A mixture of donor **13** (208 mg, 0.335 mmol) and acceptor **11a** (150 mg, 0.258 mmol) was dried by azeotropic distillation with toluene, kept under vacuum overnight, and then dissolved in dry CH_2Cl_2 (3 mL). *N*-Iodosuccinimide (76 mg, 0.335 mmol) was added to the solution; after stirring for 3 min, TBDMSOTf (18 mL, 0.077 mmol) was added. The reaction was quenched after 20 min with 10% aq sodium thiosulfate and saturated sodium bicarbonate (1:1), and extracted with CH_2Cl_2. The organic layer was separated, dried, and the solvent was removed under reduced pressure. The crude residue on flash column chromatography (1:4 EtOAc–Hexane) afforded **14a** (225 mg, 0.20 mmol, 78%) as colorless semisolid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07–8.04 (d, 2H, Ar-H), 7.52–7.06 (m, 38H, Ar-H), 5.95–5.85 (m, 1H), 5.71–5.70 (dd, *J*=2, 2.4 Hz, 1H), 5.64–5.63 (d, *J*=1.6 Hz, 1H), 5.24–5.09 (m, 2H), 4.97–4.46 (m, 14H), 4.31–4.25 (m, 2H), 4.15–3.98 (m, 7H), 3.45–3.33 (m, 3H), 3.27–3.24 (dd, *J*=9.6, 2 Hz, 1H).

^{13}C NMR: δ 165.52, 138.94, 138.74, 138.60, 138.18, 134.29, 132.86, 130.02, 129.91, 128.34, 128.25, 128.18, 128.12, 128.06, 128.02, 127.94, 127.83, 127.68, 127.60, 127.41, 127.34, 127.17, 117.55, 98.20, 81.90, 81.60, 81.39, 80.79, 78.15, 75.81, 75.56, 74.99, 74.34, 73.87, 73.17, 73.05, 72.63, 71.36, 71.23, 69.02, 68.49.

1-O-*Allyl-2,3,4,5-tetra*-O-*benzyl-6*-O-*(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-D*-myo-*inositol (**14b**)*. The benzoate **14a** (210 mg, 0.187 mmol) was dissolved in CH_2Cl_2/MeOH (1 mL/4mL) solvent mixture and NaOMe (4.5 mg, 0.187 mmol) was added. The reaction mixture was stirred for 14 h and the solvent was evaporated off. The residue on flash column chromatography (1:3 EtOAc–Hexane) afforded the alcohol **14b** (180 mg, 0.18 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.06 (m, 35H, ArH), 5.89–5.79 (m, 1H), 5.505–5.501 (d, *J*=1.6Hz, 1H), 5.29–5.16 (m, 2H), 4.94–4.39 (m, 14H), 4.25–4.21 (m, 2H), 4.12–3.83 (m, 8H), 3.37–3.24 (m, 3H), 3.18–3.15 (dd, *J*=10, 2 Hz, 1H), 2.40 (d, 1H, -OH).

^{13}C NMR: δ 138.86, 138.74, 138.59, 138.24, 134.24, 128.37, 128.27, 128.16, 128.07, 127.98, 127.87, 127.70, 127.63, 127.49, 127.41, 127.33, 127.27, 127.16, 117.15, 100.11, 81.97, 81.72, 81.35, 80.83, 80.12, 76.30, 75.79, 75.46, 74.78, 74.17, 73.90, 73.25, 72.90, 72.67, 71.83, 70.90, 70.83, 68.65, 68.15.

FABMS *m*/*z*: 1013 (MH^+), 1145 ($M+CS^+$).

1-O-*Allyl-2,3,4,5-tetra*-O-*benzyl-6*-O-*(2-Acetamido-3,4,6-tri*-O-*benzyl-α-D-mannopyranosyl)-D*-myo-*inositol (**16**)*. The alcohol **14b** (50 mg, 0.048 mmol) was dissolved in 5 mL solvent mixture DMSO/Ac_2O (2:1) and stirred for 16 h (complete conversion, by TLC). The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with H_2O (3 × 10 mL). The aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was separated, dried, and the solvent evaporated off. The ketone **15** was dried under high vaccuum. $NaBH_3CN$ (3 mg, 0.048 mmol) and NH_4OAc (37 mg, 0.48 mmol) were added and the mixture dissolved in methanol (2 mL). After stirring for 3 h the reaction mixture was quenched with drops of water. The solvent was evaporated off and the residue on flash column chromatography (4:1 EtOAc–Hexane) afforded the amine. It was redissolved in MeOH (2.5 mL) and added Ac_2O (0.5 mL). After stirring for 14 h the solvent was evaporated off and the residue on flash column chromatography (2:3 EtOAc–Hexane) afforded the mannosamino derivative **16** (24 mg, 0.023 mmol, 47% [overall yield]) as the major product.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 - 7.03 (m, ArH), 5.97–5.88 (m, 2H), 5.46 (bs, 1H), 5.25–5.15 (m, 2H), 4.96–4.31 (m, 14H), 4.21–3.96 (m, 8H), 3.71–3.66 (t, *J*=9.6 Hz, 1H), 3.38–3.35 (dd, *J*=10, 2 Hz, 1H), 3.34–3.29 (t, *J*=9.6 Hz, 1H), 3.24–3.20 (m, 3H), 1.96 (s, 3H).

FABMS: *m*/*z* 1054.4 (MH^+)

1,2-O-*Isopropylidine-3,4,5-tri*-O-*benzyl-6*-O-*(2*-O-*benzoyl-3,4-di*-O-*benzyl-6*-O-*[t-butyldiphenylsilyl]-α-D-mannopyranosyl)-D*-myo-*inositol (**19**)*. A mixture of donor **17** (142 mg, 0.18 mmol) and acceptor **18** (70 mg, 0.14 mmol) was dried by azeotropic distillation with toluene, kept under vaccuum overnight, and then dissolved in dry CH_2Cl_2 (3 mL). *N*-Iodosuccinimide (42 mg, 0.18 mmol) was added to the solution; after stirring for 3 min, BF_3OEt_2 (5 μL, 0.04 mmol) was added. The reaction was quenched after 30 min with 10% aq sodium thiosulfate and saturated sodium bicarbonate (1:1), and extracted with CH_2Cl_2. The organic layer was separated, dried, and the solvent removed under reduced pressure. The crude residue on flash column chromatography (1:4 EtOAc–Hexane) afforded **19** (70 mg, 0.06 mmol, 43%) [89% yield based on recovered acceptor **18** (36 mg, 0.073 mmol)].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17–8.14 (m, Ar-H, 2H), 7.75–6.86 (m, Ar-H, 38H), 5.75–5.73 (dd, *J*=3.2, 2 Hz, 1H), 5.563–5.559 (d, *J*=1.6 Hz, 1H), 4.96–4.51 (m, 10H), 4.33–4.28 (t, *J*=9.6 Hz, 1H), 4.20–3.75 (m, 8H), 3.67–3.64 (dd, *J*=3.6, 8.8 Hz, 1H), 3.28–3.23 (t, *J*=9.6 Hz, 1H), 1.51 (s, 3H), 1.32 (s, 3H), 1.098 (s, 9H).

FABMS: *m*/*z* 1173.4 (M^+-1).

1,2-O-*Isopropylidine-3,4,5-tri*-O-*benzyl-6*-O-*(3,4-di*-O-*benzyl-6*-O-*[t-butyldiphenylsilyl]-α-D-mannopyranosyl)-D*-myo-*inositol (**20**)*. The benzoate **19** (30 mg, 0.025 mmol) was dissolved in CH_2Cl_2/MeOH (1 mL/2mL) solvent mixture and NaOMe (2 mg, 0.025 mmol) was added. The reaction mixture was stirred for 4 days and the solvent was removed. The residue on flash column chromatography (1:4 EtOAc–Hexane) afforded the alcohol **20** (26 mg, 0.024 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69–6.91 (m, ArH, 35H), 5.563–5.559 (d, *J*=1.6 Hz, 1H), 4.90–4.59 (m, 10H), 4.19–4.17 (dd, *J*=4.8, 4.4 Hz, 1H), 4.08–3.95 (m, 5H), 3.90–3.83 (m, 2H), 3.748–3.743 (d, *J*=2 Hz, 2H), 3.66–3.63 (dd, *J*=3.6, 8.8 Hz, 1H), 3.26–3.21 (t, *J*=8.8 Hz, 1H), 2.354–2.344 (d, 1H, -OH), 1.56 (s, 3H), 1.33 (s, 3H), 1.02 (s, 9H).

^{13}C NMR: δ 138.82, 138.53, 138.13, 137.97, 137.82, 135.85, 135.60, 133.75, 133.26, 129.42, 128.44, 128.38, 128.31, 128.13, 128.03, 127.92, 127.88, 127.82, 127.72, 127.58, 127.48, 127.34, 127.29, 110.06, 97.25, 80.91, 80.65, 79.67, 79.46, 76.87, 76.49, 75.65, 75.31, 75.03, 74.60, 74.03, 73.22, 72.17, 71.81, 68.65, 62.91, 27.85, 26.84, 25.96, 19.26.

FABMS: *m*/*z* 1069.5 (M^+-1).

1,2-O-*Cyclohexylidine-3,4,5-tri*-O-*benzyl-6*-O-*(2*-O-*benzoyl-3,4,6-tri*-O-*benzyl-α-D-mannopyranosyl)-D*-myo-*inositol (**26a**)*. A mixture of donor **13** (305 mg, 0.49 mmol) and acceptor **11b** (200 mg, 0.377 mmol) was dried by azeotropic distillation with toluene, kept under vaccuum overnight, and then dissolved in dry CH_2Cl_2 (3 mL). *N*-Iodosuccinimide (110 mg, 0.049 mmol) was added to the solution; after stirring for 3 min, BF_3OEt_2 (14.1 μL, 0.113 mmol) was added. The reaction was quenched after 20 min with 10% aq sodium thiosulfate and saturated sodium bicarbonate (1:1), and extracted with CH_2Cl_2. The organic layer was separated, dried, and the solvent removed under reduced pressure. The crude residue on flash column chromatography (1:5 EtOAc–Hexane) afforded **26a** (289 mg, 0.27 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09–8.07 (m, 2H, ArH), 7.53–7.01 (m, 33H, Ar-H), 5.72–5.70 (dd, *J*=2, 2.4 Hz, 1H), 5.536–5.531 (d, *J*=2 Hz, 1H), 4.89–4.39 (m, 12H), 4.27–4.06 (m, 6H), 3.91–3.87 (t, *J*=8 Hz, 1H), 3.76–3.69 (m, 2H), 3.59–3.56 (m, 1H), 3.35–3.30 (dd, *J*=8.4, 8 Hz, 1H), 1.77–1.33 (m, 10H).

FABMS: *m*/*z* 1065.4 (M^+-1).

1,2-O-*Cyclohexylidine-3,4,5-tri*-O-*benzyl-6*-O-*(3,4,6-tri*-O-*benzyl-α-D-mannopyranosyl)-D*-myo-*inositol (**27a**)*. The benzoate **26a** (289 mg, 0.27 mmol) was dissolved in CH_2Cl_2/MeOH (2mL/6mL) solvent mixture, and NaOMe (150 mg, excess) was added. The reaction mixture was stirred for 24 h and the solvent was evaporated off. The residue on flash column chromatography (1:4 EtOAc–Hexane) afforded **27a** (195 mg, 0.20 mmol, 75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.20 (m, 30H, ArH), 5.53 (bs, 1H), 4.84–4.33 (m, 12H), 4.25–4.21 (m, 1H), 4.11–3.85 (m, 7H), 3.69–3.44 (m, 3H), 3.30–3.24(dd, *J*=8.1 Hz, 10.2 Hz, 1H). 2.30 (bs, 1H, OH), 1.78–1.26 (m, 10H).

^{13}C NMR: d 138.75, 138.43, 138.33, 138.17, 138.88, 128.38, 128.28, 128.12, 127.89, 127.83, 127.54, 127.41, 127.31, 110.77, 97.42, 80.88, 80.75, 79.59, 78.71, 77.23, 76.81, 75.38, 74.84, 74.16, 73.99, 73.06, 72.96, 71.70, 70.76, 68.53, 37.13, 35.06, 24.91, 23.85, 23.56.

1,2-O-*Cyclohexylidine-3,4,5-tri*-O-*benzyl-6*-O-*(2-azido-3,4,6-tri*-O-*benzyl-α-D-glucopyranosyl)-D*-myo-*inositol (**28a**)*. The alcohol **27a** (45 mg, 0.046 mmol) was dissolved in 3 mL CH_2Cl_2 and cooled to –78 °C. Pyridine (0.3 mL) and DMAP (catalytic) was added to the reaction mixture followed by Tf_2O (79 mL, 0.46 mmol). The temperature was allowed to rise gradually to room temperature and the reaction mixture was stirred for 24 h. The solvent was evaporated off and the residue on flash column chromatography (1:4 EtOAc–Hexane) afforded the triflate (51 mg, 0.046 mmol) in almost quantitative yield. The triflate (24 mg, 0.022 mmol) was dissolved in dry THF (2 mL), and $TMSN_3$ (7.4 mL, 0.055 mmol) and TBAF (44 mL of 1M solution in THF) were added. The reaction mixture was stirred at 70 °C for 24 h. The solvent was evaporated off and the residue on flash column chromatography (1:5 EtOAc–Hexane) afforded the azide **28a** (16 mg, 0.016 mmol, 74%) as the major product. [The R_f value of the azide was the same as the triflate.] The side product due to elimination was not characterized due to the decomposition after isolation.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.02 (m, 30H, Ar-H), 5.617–5.604 (d, *J*=3.9Hz, 1H), 4.89–4.318 (m, 12H), 4.29–4.27 (t, *J*=5.1, 3.6 Hz, 1H), 4.20–4.16 (t, *J*=6.6 Hz, 1H), 4.12–3.90 (m, 4H), 3.80–3.70 (m, 2H), 3.49–3.36 (m, 4H), 1.77–1.24 (m, 10H).

IR (KBr, film): 2104.7 cm^{-1}.

FABMS: *m*/*z* 988 (MH^+).

1,2-O-*Cyclohexylidine-3,4,5-tri*-O-*benzyl-6*-O-*(2*-O-*benzoyl-3,4-di*-O-*benzyl-6*-O*[*t*-butyldiphenylsilyl]-α-D-mannopyranosyl)-D*-myo-*inositol (**26b**)*. The acceptor **11b** (100 mg, 0.18 mmol) and glycosyl donor **17** (200 mg, 0.25 mmol) were together taken up in a small quantity of toluene, azeotroped to remove traces of water and then placed under high vaccuum overnight. The mixture was dissolved in dry CH_2Cl_2 (3 mL) under argon atmosphere. *N*-Iodosuccinimide (58.5mg, 0.26 mmol) was added to the solution; after stirring for 3 min, BF_3OEt_2 (7.5 μL, 0.06mmol) was added. The reaction was quenched after 40 min with 10% aq sodium thiosulphate and saturated sodium bicarbonate (1:1), and extracted with CH_2Cl_2. The organic layer was separated, dried, and the solvent removed under reduced pressure. The crude residue on flash column chromatography (1:10 EtOAc–Hexane) afforded **26b** (118 mg, 70 %) as a colorless paste [yield is based on recovered acceptor **11b** (25 mg, 0.047 mmol)].

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17–8.14 (d, ArH, 2H), 7. 74–7.72 (d, ArH, 2H), 7.67–7.64 (d, ArH, 2H), 7.53–7.50 (t, 1H, ArH), 7.41–6.85 (m, 33H, ArH), 5.75–5.73 (t, *J*=2.1 Hz, 1H), 5.60 (bs, 1H), 4.95–4.50 (m, 10H), 4.31–4.24 (t, *J*=9.6 Hz, 1H), 4.22–4.19 (t, *J*=4.5 Hz, 1H), 4.11–3.96 (m, 3H), 3.87–3.73 (m, 3H), 3.68–3.64 (dd, J_1, J_2=4.2, 9.3 Hz), 3.28–3.22 (t, *J*=9.6 Hz, 1H), 1.76–1.72 (m, 2H), 1.60–1.55 (m, 6H), 1.35–1.33 (m, 2H), 1.08 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.77(OCOPh), 139.00, 138.59, 138.20, 138.08, 137.74, 135.87, 135.63, 133.69, 133.29, 133.00, 130.07, 129.52, 129.42, 128.39, 128.36, 128.32, 128.11, 127.98, 127.88, 127.82, 127.73, 127.64, 127.55, 127.48, 127.36, 127.20, 110.82, 96.20, 80.82, 80.70, 78.81, 77.89, 77.20, 75.71, 75.27, 75.15, 74.09, 74.03, 73.07, 72.38, 71.33, 69.21, 62.85, 37.42, 35.10, 26.85, 24.95, 23.82, 23.66, 19.37.

FABMS *m*/*z*: 1213 (M^+-1).

1,2-O-*Cyclohexylidine-3,4,5-tri*-O-*benzyl-6*-O-*(3,4-di*-O-*benzyl-6*-O-*[*t*-butyldiphenylsilyl]-α-D-mannopyranosyl)-D*-myo-*inositol (**27b**)*. The disaccharide **26b** (75 mg, 0.06 mmol) was dissolved in CH_2Cl_2/MeOH (1 mL/3 mL) solvent mixture and NaOMe (9.7 mg, 0.18 mmol) was added to it and stirred at RT under argon atmosphere. The solvent was evaporated off after 24 h and the residue on flash column chromatography [1:4 EtOAc–Hexane] afforded **27b** (50 mg, 0.045 mmol, 74%) as a colorless paste.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.62 (m, 4H, ArH), 7.41–6.90 (m, 31H, ArH), 5.60 (bs, 1H, H-1), 4.89–4.55 (m, 10H), 4.21–4.18 (t, 1H, *J*=3.6 Hz), 4.09–3.83 (m, 8H), 3.74 (bs, 1H), 3.67–3.62 (dd, J_1, J_2=3.9, 9.0 Hz, 1H), 3.26–3.19 (t, 1H, *J*=9.6 Hz), 2.36–2.35 (d, 1H, *J*=3.6 Hz), 1.82–1.78 (m, 2H), 1.64–1.54 (m, 6H), 1.39–1.36 (m, 2H), 1.01 (s, 9H).

FABMS *m*/*z*: 1109 (M^+-1).

1,2-O-*Cyclohexylidine-3,4,5-tri*-O-*benzyl-6*-O-*(2-azido-3,4-di*-O-*benzyl-6*-O-*[*t*-butyldiphenylsilyl]-*α*-D-glucopyranosyl)-D*-myo-*inositol (**28b**)*. The alcohol **27b** (35 mg, 0.031 mmol) was dissolved in 2 mL CH_2Cl_2 and cooled to –78 °C. Pyridine (0.5 mL) and DMAP (catalytic) was added to the reaction mixture, followed by Tf_2O (53 µL, 0.315 mmol). The temperature was allowed to rise gradually to room temperature and the reaction mixture was stirred for 24 h. The solvent was evaporated off and the residue on flash column chromatography [1:4 EtOAc–Hexane] afforded the triflate (38 mg) in almost quantitative yield. The triflate (20 mg, 0.016 mmol) was dissolved in dry THF (2 mL) and was added $TMSN_3$ (3.37 µL, 0.025 mmol) and TBAF (25 µL of 1M solution in THF). The reaction mixture was stirred at 70 °C for 16 h. The solvent was evaporated off, and the residue on flash column chromatography (1:10 EtOAc–Hexane) afforded the azide **28b** (12 mg, 0.01 mmol, 63%) as the major product. [The R_f value of the azide was the same as the triflate.] The side product due to elimination was not characterized due to the decomposition after isolation.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.59 (m, 5H, ArH) 7.42–7.26 (m, 28H, ArH), 7.20–7.17 (d, 2H, ArH), 7.12–7.01 (m, 3H, ArH), 6.93–6.88 (t, 2H, ArH), 5.68–5.67 (d, 1H, *J*=3.6 Hz), 4.88–4.61 (m, 10H), 4.23–4.20 (t, 1H, *J*=4.5 Hz), 4.16–4.12 (t, 1H, 5.1 Hz), 4.05–3.94 (m, 3H), 3.89–3.79 (m, 2H), 3.69–3.58 (m, 3H), 3.41–3.31 (m, 2H), 1.78–1.58 (m, 3H), 1.55–1.09 (7H), 1.01 (s, 9H).

IR (KBr, film) : 2106 cm^{-1}.

FABMS: *m*/*z* 1134 (M^+ –1).

1,2-O-*Cyclohexylidine-3,4,5-tri*-O-*benzyl-6*-O-*(4*-O-*allyl-2*-O-*benzoyl-3,6-di*-O-*benzyl-α-D-mannopyranosyl)-D*-myo-*inositol (**26c**). A mixture of* donor **25** (543 mg, 0.79 mmol) and acceptor **11b** (322 mg, 0.609 mmol) was dried by azeotropic distillation with toluene, kept under vaccuum overnight, and then dissolved in dry CH_2Cl_2 (5 mL). *N*-iodosuccinimide (180 mg, 0.79 mmol) was added to the solution; after stirring for 3 min, BF_3OEt_2 (22.7 µL, 0.182 mmol) was added. The reaction was quenched after 20 min with 10% aq sodium thiosulfate and saturated sodium bicarbonate (1:1), and extracted with CH_2Cl_2. The organic layer was separated, dried, and the solvent removed under reduced pressure. The crude residue on flash column chromatography (1:4 EtOAc–Hexane) afforded **26c** (490 mg, 0.48 mmol, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–8.04 (m, 2H, Ar-H), 7.55–7.13 (m, 28H, ArH), 5.92–5.78 (m, 1H), 5.673–5.658 (t, *J*=2.4 Hz, 1H), 5.502–5.495 (d, *J*=2.1 Hz, 1H), 5.17–5.05 (m, 2H), 4.83–4.40 (m, 10H), 4.36–4.23 (m, 2H), 4.12–3.53 (m, 10H), 3.35–3.29 (t, *J*=8.7 Hz, 1H), 1.76–1.25 (m, 10H).

1,2-O-*Cyclohexylidine-3,4,5-tri*-O-*benzyl-6*-O-*(4*-O-*allyl-3,6-di*-O-*benzyl-a-D-mannopyranosyl)-D*-myo-*inositol (**27c**)*. The benzoate **26c** (400 mg, 0.39 mmol) was dissolved in CH_2Cl_2/MeOH (3mL/9mL) solvent mixture and NaOMe (131 mg, 2.4 mmol) was added. The reaction mixture was stirred for 14 h and the solvent was removed under reduced pressure. The residue on flash column chromatography (1:3 EtOAc–Hexane) afforded the alcohol **27c** (260 mg, 0.28 mmol, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 –7.23 (m, 25H, ArH), 5.87–5.76 (m, 1H), 5.49 (s, 1H), 5.20–5.06 (m, 2H), 4.80–4.34 (m, 10H), 4.30–4.42 (m, 2H), 4.09–3.65 (m, 9H), 3.55–3.42 (m, 2H), 3.31–3.25 (t, *J*=8.7 Hz, 1H), 2.39 (s, 1H, -OH), 1.78–1.25 (m, 10H).

FABMS: *m*/*z* 911.4 (M^+-1).

1,2-O-*Cyclohexylidine-3,4,5-tri*-O-*benzyl-6*-O-*(2-azido-4*-O-*allyl-3,6-di*-O-*benzyl-a-D-glucopyranosyl)-D*-myo-*inositol (**28c**)*. The alcohol **27c** (500 mg, 0.55 mmol) was dissolved in 9 mL CH_2Cl_2 and cooled to –78 °C. Pyridine (3 mL) and DMAP (34 mg, 0.27 mmol) were added to the reaction mixture, followed by Tf_2O (599 µL, 2.75 mmol). The temperature was allowed to rise gradually to room temperature, and the reaction mixture was stirred for 24 h. The solvent was evaporated off and the residue on flash column chromatography [1:4 EtOAc–Hexane] afforded the triflate (570 mg, 0.55 mmol) in almost quantitative yield. The triflate (526 mg, 0.5 mmol) was dissolved in dry THF (2 mL) and was added $TMSN_3$ (101.2 µL, 0.75 mmol) and TBAF (750 µL of 1M solution in THF). The reaction mixture was stirred at 70 °C for 24 h. The solvent was evaporated off and the residue on flash column chromatography (1:5 EtOAc–Hexane) afforded the azide **28c** (235 mg, 0.25 mmol, 50%) as the major product. [The R_f value of the azide was the same as the triflate.] The side product due to elimination was not characterized due to the decomposition after isolation.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.24 (m, 25H, ArH), 5.86–5.74 (m, 1H), 5.587–5.575 (d, *J*=3.6Hz, 1H), 5.17–5.08 (m, 2H), 4.87–4.31 (m, 10H), 4.27–3.85 (m, 8H), 3.73–3.69 (dd, *J*=3.9, 8.1 Hz, 1H), 3.63–3.57 (t, *J*=9.6 Hz, 1H), 3.43–3.32 (m, 4H), 1.74–1.25 (m, 10H).

IR (KBr, film): 2104 cm^{-1}

FABMS: *m*/*z* 938 (MH^+)

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