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Note

2-Allylphenyl glycosides as glycosyl donors for sugar coupling

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ABSTRACT

Glycosylations employing 2-allylphenyl glycoside, a new type of stable glycosyl donor, were optimized and explored with a variety of acceptors promoted by ICl/AgOTf. The utility of the protocol was further demonstrated with an efficient synthesis of the disaccharide fragment of bleomycins.

The ardent interests in glycobiology over the past few decades fueled increasing demands for well-defined sugar motifs accessible mainly through chemical synthesis.[1] Carbohydrate scaffolds in biological systems exhibit diverse roles in crucial physiological events such as fertilization,[2] immune response,[3] development,[4] and bacterial and viral infections.[5,6] In addition, the inherent asymmetry of sugar structures allowed them to serve as inexpensive chiral sources.[7,8] Oligosaccharide syntheses, however, have lagged far behind their nucleic acid and protein counterparts because of the highly functionalized and, in most cases, branched character of the emulated naturally occurring sugars. An integral part in the synthesis of an oligosaccharide is the formation of one or more glycosidic bonds using saccharide building blocks.[9] For over a century since Koenigs and Knorr[10] introduced the still widely used glycosyl halides into the chemist's armamentum, carbohydrate chemistry has evolved amidst the abundance of glycosyl donors which can be hand-picked to meet the constrains of the polymer assembly.[11] Glycosyl donors can be further categorized as stable- or unstable-type in relation to the lability of the leaving group on storage as well as the reagents applied in various chemical transformations. Consequently, several glycosylation promoters have been developed to match the distinct reactivities each donor manifests.[12]

Several leaving groups tolerate common protecting group manipulations and can be activated independently for coupling with an acceptor during sugar assembly. The most established donors under this premise are the 4-*n*-pentenyl glycosides (NPG), introduced by Fraser-Reid,[13,14] and thioglycosides.[15,16] Thioglycosides, although quite common, are coupled with the use of awful smelling thiols, which make their application driven by needs rather than choice. NPGs (e.g., compound **1**), on the other hand, rival thioglycosides in versatility and are environmentally friendly. Glycosylations involving NPGs are triggered by activation of the remote double bond by halonium ions (e.g., Br^+ or I^+).[17] It has been understood that such a reaction operates with the formation of the five-membered transition state **4** leading to the release of a halomethylfuran and an oxocarbenium ion (**5**), the actual reactive intermediate (Scheme 1). The intermediate **5**, when supplemented appropriately with a glycosyl acceptor, yields the desired saccharide **6** in either of two possible outcomes, the α- and β-isomers.

Aiming to bring diversity toward NPG-type glycosides, we previously demonstrated the ability of 2-allyloxyphenyl donors for glycosylation employing various acceptors in moderate to excellent yields.[18] Similarly, *gem*-dimethyl analogs of NPGs (i.e., compounds **2** and **3**) were recently examined by Andrade and co-workers[19] to probe the ring closure acceleration affected by steric buttressing. Continuing our efforts toward the exploration of NPG mimics for glycosylation, we focused on the development of a stable and viable glycosyl donor which can be accessed conveniently from cheap materials and should, in particular, involve readily available mild promoters for activation. In this regard, we wish to report the use of 2-allylphenyl glycosides (**7**) as novel donors for carbohydrate synthesis. We envisioned that the terminal double bond of **7** can, in principle, be activated by an appropriate promoter to yield the

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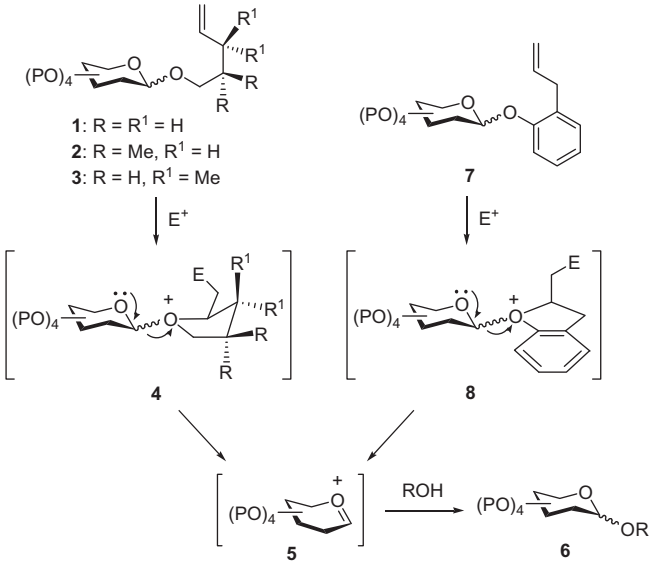
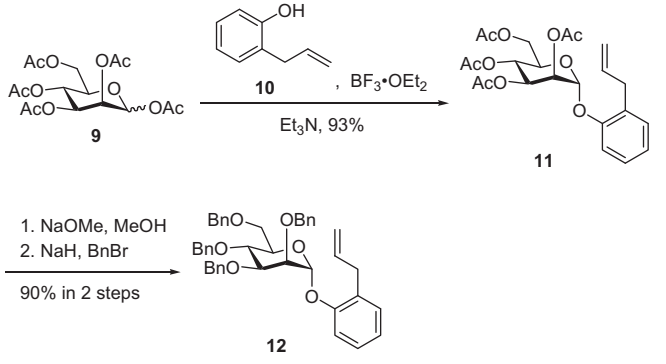


Scheme 1. An approach using NPG-type and 2-allylphenyl glycosides as glycosyl donors.

oxocarbenium ion **5** through the release of the 4-allylphenyl moiety as a benzofuran derivative via the transition state **8**. The positive charge in **8** is most likely stabilized through delocalization in the neighboring benzene ring. This should also be responsible for the facile generation of oxocarbenium ion **5** and the hereafter released benzofuran moiety would be inert and unlikely to dictate the future course of the glycosylation.

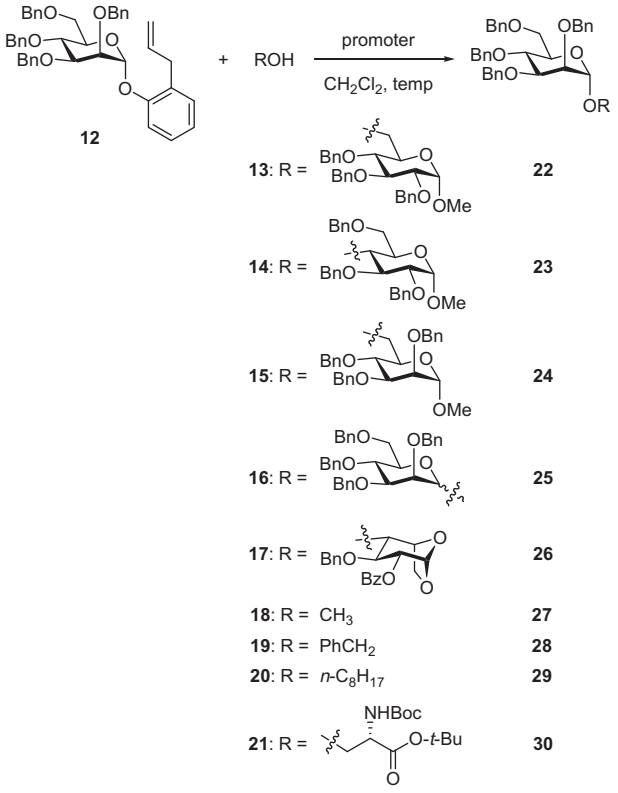
To test our hypothesis, D-mannose was selected as the model for our study and the synthesis of the respective 2-allyphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (**12**), is outlined in Scheme 2. Treatment of the per-O-acetylated mannoside **9**[20] with the cheap compound 2-allyl phenol (**10**) in the presence of $BF_3{\cdot}Et_2O$ delivered the corresponding α-glycoside **11** as a single isomer ($^3J_{1,2}$ = 1.8 Hz) in an excellent 93% yield. The required glycosyl donor **12** was accessed via deacetylation under Zemplén condition (NaOMe, MeOH) and subsequent per-O-benzylation of the ensuing tetraol with the NaH/BnBr reagent combination. As anticipated, compound **12** was found to be very stable toward air and moisture and can be conveniently stored for a few months with little precautions.

The feasibility of the allyphenyl mannoside **12** as donor for chemical glycosylation was first evaluated by its coupling with the glucopyranosyl alcohol **13** under the agency of some selected promoters (Table 1). Triethylsilyl triflate (TESOTf) in combination with *N*-iodosuccinimide (NIS) furnished the desired α-adduct **22**



Scheme 2. Preparation of the 2-allylphenyl mannopyranoside **12**.

Table 1
The results for coupling of the allyphenyl mannoside **12** with various alcohols



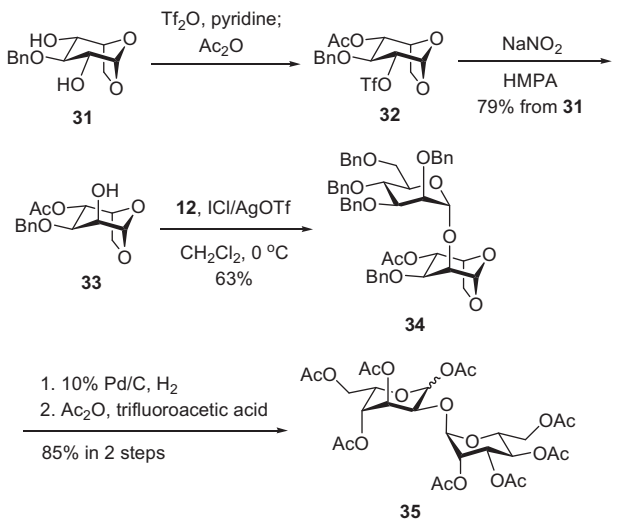
Entry	ROH	Promoter	Temp	Product	Yield (%)
1	**13**	NIS/TESOTf	rt	**22**	47
2	**13**	NIS/TMSOTf	rt	**22**	43
3	**13**	NIS/TfOH	rt	**22**	63
4	**13**	ICl/AgOTf	0 °C	**22**	74
5	**14**	ICl/AgOTf	0 °C	**23**	61
6	**15**	ICl/AgOTf	0 °C	**24**	65
7	**16**	ICl/AgOTf	0 °C	**25**	63
8	**17**	ICl/AgOTf	0 °C	**26**	63
9	**18**	ICl/AgOTf	0 °C	**27**	67
10	**19**	ICl/AgOTf	0 °C	**28**	89
11	**20**	ICl/AgOTf	0 °C	**29**	74
12	**21**	ICl/AgOTf	0 °C	**30**	53

as a single isomer ($^3J_{1',2'}$ = 2.2 Hz) in CH_2Cl_2 at room temperature in a modest 47% yield (entry 1). No increase in yield was observed when trimethylsilyl triflate (TMSOTf) was utilized as catalyst (entry 2). Fortunately, yield enhancement for compound **22** (63%) was observed with triflic acid (TfOH) and NIS reagent tandem (entry 3). The reduced yield observed with TESOTf and TMSOTf was probably the result of in situ silylation of the primary hydroxyl group of the acceptor, which not only formed the undesired product that was observed during the course of the reaction, but also limited the catalyst needed to drive the reaction forward. We noted that, under NIS/TfOH activation, the yield for the current donor is lower than that of the corresponding allyoxyphenyl mannoside the results of which were disclosed previously.[18] The switch to the ICl and silver triflate (AgOTf) combination proved favorable as the yield increased further to 74% even at ice-cold condition (entry 4). With an amicable promoter for activation of 2-allylphenyl glycosides, the scope of the reaction was extended to a range of monosaccharide acceptors (**14**–**17**) and other aglycones (**18**–**21**). Exclusive generation of α-mannosides (**23**–**30**) were observed with all the recruited alcohols in moderate to good yields. Notable herein is the generation of the α1→α1′-dimannoside **25** generated in a highly stereospecific fashion (entry 7). The protocol gains further

importance with the formation of the α1→6-linked mannoside **24** (entry 6), which is an essential constituent of glycosylphosphatidylinositol anchors associated with eukaryotes[21] and phosphatidylinositol D-mannosides present in the *Mycobacterium tuberculosis* cell wall.[22] It should be mentioned that when we carried out the activation of the disarmed mannoside **11** with ICl/AgOTf in the presence of alcohol **13**, the desired compound **22** was not isolated from the reaction mixture.

Further in pursuit of demonstrating the utility of our 2-allylphenyl donor toward the synthesis of biologically relevant scaffolds, we chose to prepare the sugar unit present in bleomycin. Bleomycin refers to a family of structurally related glycopeptides with antibiotic properties usually associated with *Streptomyces verticillus*.[23,24] They hold immense therapeutic value and are used effectively for the treatment of various types of cancers, mainly testicular cancer, lymphoma, and cancer of the head and neck. The carbohydrate moiety of bleomycin, comprised of a D-mannopyranose α1→2-linked to an L-gulopyranose, was found to play a pivotal role in the therapeutic ability of bleomycin by being involved in cell-surface recognition and closely associated with the metal-binding domain.[25] The efficient synthesis of the bleomycin carbohydrate fragment is depicted in Scheme 3. A highly regioselective triflation and acetylation of the 1,6-anhydro-L-idose **31**[26] in one pot generated the triflate **32**, which underwent nucleophilic substitution under the agency of $NaNO_2$ in hexamethylphosphoramide (HMPA) to afford the L-gulopyranosyl alcohol **33** in a 79% overall yield in three steps. With the required acceptor **33** in hand, glycosylation was pursued employing our 2-allylphenyl mannosyl donor **12** promoted by ICl/AgOTf in anhydrous CH_2Cl_2 at 0 °C. The α-linked disaccharide **34** was isolated in a 63% yield as a single isomer; 18% of the acceptor **33** that remained unreacted was recovered. Palladium-catalyzed debenzylation (10% Pd/C, H_2) of **34** followed by acetolysis with concomitant acetylation (Ac_2O, trifluoroacetic acid) supplied the peracetylated disaccharide **35** in an 85% yield (two steps). This disaccharide moiety was earlier utilized by Umezawa and co-workers for the successful synthesis of bleomycin A_2.[27]

In conclusion, we have presented a new type of stable glycosyl donor, which is readily accessible from inexpensive commercial sources and subsequently, glycosylations of various alcohols were also demonstrated. The relative ease of preparation, storage, and handling coupled with the inherent inertness of the 2-allylphenyl moiety to common manipulations associated with carbohydrates would enable them to be attractive donors in oligosaccharide assembly.



Scheme 3. Synthesis of the disaccharide moiety of bleomycins.

1. Experimental

1.1. General remarks

CH_2Cl_2 was purified and dried from a safe purification system filled with anhydrous Al_2O_3. All other reagents, obtained from commercial sources, were used without further purification. Flash column chromatography was carried out on Silica Gel 60 (230–400 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F254 (0.25 mm, E. Merck); detection was executed by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}$, and H_2SO_4 in water and subsequent heating on a hot plate. ^1H and ^{13}C NMR spectra were recorded using 400 MHz, 500, and 600 MHz spectrometers. Chemical shifts are in ppm from Me_4Si calibrated using the resonance of the residual proton and carbon of the deuterated solvent. Proton peak assignments were performed using 2D NMR techniques (^1H–^1H COSY, HMQC, and NOESY); the hydrogen multiplicity of carbon peaks was determined using DEPT experiments.

1.2. 2-Allylphenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (11)

$BF_3{\cdot}Et_2O$ (812 μL, 6.40 mmol) was added to a mixture of the pentaacetate **9** (1.00 g, 2.56 mmol), 2-allylphenol (**10**, 371 μL, 2.82 mmol), and Et_3N (179 μL, 1.28 mmol) in CH_2Cl_2 (1 mL) at 0 °C under N_2 atmosphere. The ice bath was removed and the mixture was kept stirring at room temperature for 36 h. The reaction mixture was neutralized with satd $NaHCO_{3(aq)}$ and then poured into a biphasic solution of EtOAc (30 mL) and H_2O (10 mL). The crude target material was extracted with EtOAc (2 × 15 mL), and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes = 1/2) to give compound **11** (1.11 g, 93%) as light yellow oil: $[\alpha]_D^{24}$ −76.3 (*c* 0.1, $CHCl_3$); IR (thin film): *ν* 3058, 2976, 2904, 1750, 1451, 1369, 1220, 1084, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.18–7.09 (m, 3H, Ar-H), 7.02–6.97 (m, 1H, Ar-H), 5.94 (ddt, 1H, *J* = 16.5, 10.0, 6.5 Hz, C*H*=CH_2), 5.54 (dd, 1H, *J* = 10.0, 3.4 Hz, H-3), 5.50 (d, 1H, *J* = 1.8 Hz, H-1), 5.43 (dd, 1H, *J* = 3.4, 1.8 Hz, H-2), 5.36 (t, 1H, *J* = 10.0 Hz, H-4), 5.12–5.02 (m, 2H, CH=CH_2), 4.26 (dd, 1H, *J* = 12.8, 6.0 Hz, H-6_a), 4.08–4.03 (m, 2H, H-5, H-6_b), 3.41 (d, 2H, *J* = 6.5 Hz, CH_2CH=CH_2), 2.17 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 170.6 (C), 170.1 (C), 170.0 (C), 169.9 (C), 153.7 (C), 136.7 (CH), 130.6 (CH), 129.4 (C), 127.6 (CH), 123.0 (CH), 116.0 (CH_2), 114.3 (CH), 95.9 (CH), 69.6 (CH), 69.4 (CH), 69.1 (CH), 66.0 (CH), 62.7 (CH_2), 34.9 (CH_2), 21.0 (CH_3 × 2), 20.8 (CH_3 × 2); HRMS (FAB): *m*/*z* Calcd for $C_{23}H_{29}O_{10}$ ($[M+H]^+$): 465.1761. Found: 465.1765; Anal. Calcd for $C_{23}H_{28}O_{10}$: C, 59.48; H, 6.08. Found: C, 59.85; H, 6.36.

1.3. 2-Allylphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (12)

NaOMe (24.3 mg, 0.45 mmol) was added to a solution of compound **11** (1.05 g, 2.26 mmol) in MeOH (10 mL) at room temperature under N_2 atmosphere. The mixture was stirred for 4 h and then neutralized with an acidic resin. After filtration, the filtrate was concentrated under reduced pressure. The vacuum-dried residue was dissolved in DMF (6.50 mL), and BnBr (1.28 mL, 10.9 mmol) was added at room temperature followed by addition of NaH (60% dispersion in mineral oil, 0.43 g, 10.9 mmol) at 0 °C. The temperature was gradually elevated to ambient level, and the mixture was kept stirring for 10 h. The reaction was quenched by addition of H_2O (20 mL) and the crude target material was extracted with EtOAc (3 × 20 mL). The combined organic layer was

washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes = 1/4) to give compound **12** (1.33 g, 90% in two steps) as a light yellow oil: $[\alpha]_D^{33}$ +60.2 (*c* 1.9, $CHCl_3$); IR (thin film): *v* 3030, 2904, 2867, 1600, 1492, 1451, 1229, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.23 (m, 18H, Ar-H), 7.19–7.10 (m, 5H, Ar-H), 6.94 (td, 1H, *J* = 7.4, 1.1 Hz, Ar-H), 5.83 (ddt, 1H, *J* = 17.0, 10.3, 6.6 Hz, C*H*=CH_2), 5.53 (d, 1H, *J* = 1.8 Hz, H-1), 4.98–4.91 (m, 2H, CH=CH_2), 4.92 (d, 1H, *J* = 10.8 Hz, CH_2Ph), 4.77 (s, 1H, CH_2Ph), 4.76 (s, 1H, CH_2Ph), 4.71 (d, 1H, *J* = 11.8 Hz, CH_2Ph), 4.66 (d, 1H, *J* = 11.8 Hz, CH_2Ph), 4.65 (d, 1H, *J* = 11.8 Hz, CH_2Ph), 4.54 (d, 1H, *J* = 10.8 Hz, CH_2Ph), 4.46 (d, 1H, *J* = 11.8 Hz, CH_2Ph), 4.15 (t, 1H, *J* = 9.5 Hz, H-4), 4.06 (dd, 1H, *J* = 9.5, 3.0 Hz, H-3), 3.87–3.82 (m, 2H, H-2, H-5), 3.79 (dd, 1H, *J* = 10.8, 4.5 Hz, H-6_a), 3.68 (dd, 1H, *J* = 10.8, 1.4 Hz, H-6_b), 3.24 (dd, 1H, *J* = 15.4, 6.6 Hz, CH_2CH=CH_2), 3.18 (dd, 1H, *J* = 15.4, 6.6 Hz, CH_2CH=CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.3 (C), 138.5 (C), 138.3 (C × 2), 138.1 (C), 136.7 (CH), 129.9 (CH), 128.9 (C), 128.41 (CH), 128.35 (CH), 128.29 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.74 (CH), 127.67 (CH), 127.5 (CH), 127.4 (CH), 122.2 (CH), 115.5 (CH_2), 114.6 (CH), 96.6 (CH), 79.5 (CH), 75.1 (CH_2), 74.9 (CH), 74.7 (CH), 73.3 (CH_2), 72.7 (CH_2), 72.6 (CH), 72.4 (CH_2), 69.0 (CH_2), 34.5 (CH_2); HRMS (FAB): *m*/*z* Calcd for $C_{43}H_{44}O_6$ ($[M]^+$): 656.3138. Found: 656.3130.

1.4. General procedure for glycosylation

ICl (1.2 equiv, 1 M solution in CH_2Cl_2) was added in a dropwise fashion to a premixed solution of compound **12** (80–100 mg, 1.2 equiv), acceptor (1 equiv), and AgOTf (1.26 equiv) in CH_2Cl_2 (20 mL/g of 12) under N_2 atmosphere at 0 °C. After the consumption of the respective alcohol as evident from TLC analysis (2–3 h), the mixture was diluted with 5% $Na_2S_2O_{3(aq)}$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to obtain the desired α-mannopyranosylated adducts.

1.4.1. (2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (25)

$[\alpha]_D^{28}$ +30.8 (*c* 3.5, $CHCl_3$); IR (thin film): *v* 3017, 2919, 2862, 1631, 1451, 1210, 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.20 (m, 20H, Ar-H), 5.21 (d, 1H, *J* = 1.8 Hz, H-1), 4.90 (d, 1H, *J* = 10.6 Hz, CH_2Ph), 4.67–4.64 (m, 3H, CH_2Ph), 4.56 (d, 1H, *J* = 11.0 Hz, CH_2Ph), 4.55 (s, 2H, CH_2Ph), 4.53 (d, 1H, *J* = 11.0 Hz, CH_2Ph), 3.99 (t, 1H, *J* = 9.6 Hz, H-4), 3.75–3.58 (m, 5H, H-2, H-3, H-4, H-5, H-6_a, H-6_b); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.48 (C), 138.47 (C), 138.4 (C), 138.1 (C), 128.6 (CH), 128.5 (CH), 128.46 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 93.5 (CH), 79.6 (CH), 75.4 (CH_2), 74.8 (CH), 74.2 (CH), 73.6 (CH_2), 72.8 (CH), 72.6 (CH_2), 72.2 (CH_2), 69.2 (CH_2); HRMS (FAB): *m*/*z* Calcd for $C_{68}H_{71}O_{11}$ ($[M+H]^+$): 1063.4996. Found: 1063.4991.

1.4.2. 1,6-Anhydro-2-*O*-benzoyl-3-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-β-L-idopyranose (26)

$[\alpha]_D^{28}$ +77.1 (*c* 0.8, $CHCl_3$); IR (thin film): *v* 3031, 2913, 2867, 1719, 1651, 1637, 1451, 1360, 1270, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.01 (dd, 2H, *J* = 7.9, 0.7 Hz, Bz-H), 7.59 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.45 (t, 2H, *J* = 7.4 Hz, Ar-H), 7.36–7.25 (m, 18H, Ar-H), 7.21–7.45 (m, 5H, Ar-H), 7.45–7.10 (m, 2H, Ar-H), 5.50 (d, 1H, *J* = 1.8 Hz, H-1′), 5.13 (d, 1H, *J* = 1.9 Hz, H-1), 5.03 (dd, 1H, *J* = 8.2, 1.8 Hz, H-2′), 4.86 (d, 1H, *J* = 10.8 Hz, CH_2Ph), 4.83 (t, 1H, *J* = 4.3 Hz, H-3), 4.67–4.54 (m, 8H, CH_2Ph), 4.50 (d, 1H, *J* = 10.8 Hz, CH_2Ph), 4.04 (d, 1H, *J* = 8.0 Hz, H-5), 3.94 (dd, 1H, *J* = 8.0, 4.3 Hz, H-4), 3.91–3.84 (m, 2H, H-3′, H-$6'_a$), 3.81 (dd, 1H, *J* = 9.0, 3.0 Hz, H-$6'_b$), 3.74–3.64 (m, 5H, H-6_a, H-6_b, H-2, H-4′, H-5′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.8 (C), 139.2 (C), 138.9 (C), 138.3 (C), 138.11 (C), 138.10 (C), 133.4 (CH), 130.0 (CH), 129.1 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 100.8 (CH), 99.3 (CH), 80.7 (CH), 79.6 (CH), 78.8 (CH), 76.7 (CH), 75.37 (CH_2), 75.3 (CH), 75.1 (CH), 74.8 (CH_2), 74.4 (CH), 73.6 (CH_2), 72.9 (CH), 72.8 (CH_2), 72.4 (CH_2), 69.5 (CH_2), 65.9 (CH_2); HRMS (FAB): *m*/*z* Calcd for $C_{54}H_{54}O_{11}$ ($[M]^+$): 901.3564. Found: 901.3578.

1.4.3. 3-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl)-*N*-*tert*-butoxycarbonyl-L-serine *tert*-butyl ester (30)

$[\alpha]_D^{28}$ +21.9 (*c* 3.9, $CHCl_3$); IR (thin film): *v* 3026, 2977, 2920, 1717, 1681, 1496, 1455, 1390, 1365, 1153, 1100, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.25 (m, 18H, Ar-H), 7.18–7.15 (m, 2H, Ar-H), 5.32 (d, 1H, *J* = 8.8 Hz, NH), 4.87 (d, 1H, *J* = 10.8 Hz, CH_2Ph), 4.83 (d, 1H, *J* = 1.8 Hz, H-1′), 4.74 (d, 1H, *J* = 12.4 Hz, CH_2Ph), 4.69 (d, 1H, *J* = 10.8 Hz, CH_2Ph), 4.68 (d, 1H, *J* = 12.4 Hz, CH_2Ph), 4.64 (d, 1H, *J* = 11.8 Hz, CH_2Ph), 4.60 (d, 1H, *J* = 11.8 Hz, CH_2Ph), 4.53 (d, 1H, *J* = 12.0 Hz, CH_2Ph), 4.51 (d, 1H, *J* = 10.8 Hz, CH_2Ph), 4.32 (d, 1H, *J* = 8.8 Hz, H-2), 4.03 (t, 1H, *J* = 9.6 Hz, H-4′), 3.85–3.69 (m, 7H, H-3_a, H-3_b, H-2′, H-3′, H-5′, H-$6'_a$, H-$6'_b$), 1.45 (s, 9H, CH_3 × 3), 1.39 (s, 9H, CH_3 × 3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 169.3 (C), 155.4 (C), 138.4 (C), 138.3 (C), 138.2 (C), 128.4 (CH), 128.34 (CH), 128.29 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.63 (CH), 127.62 (CH), 127.5 (CH), 99.0 (CH), 82.0 (CH), 79.9 (CH), 75.1 (CH_2), 74.7 (CH), 74.4 (CH), 73.4 (CH_2), 72.6 (CH_2), 72.3 (CH_2), 72.2 (CH), 69.2 (CH_2), 68.9 (CH_2), 54.3 (CH), 29.7 (C), 28.3 (CH_3), 28.0 (CH_3); HRMS (FAB): *m*/*z* Calcd for $C_{46}H_{58}O_{10}N$ ($[M+H]^+$): 784.4061. Found: 784.4066; Anal. Calcd for $C_{46}H_{57}O_{10}$: C, 70.48; H, 7.33. Found: C, 71.01; H, 7.30.

1.4.4. 4-*O*-Acetyl-1,6-anhydro-3-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-β-L-gulopyranose (34)

$[\alpha]_D^{23}$ −16.5 (*c* 0.9, $CHCl_3$); IR (thin film): *v* 2915, 2860, 1752, 1456, 1229, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36–7.20 (m, 23H, Ar-H), 7.15–7.13 (m, 2H, Ar-H), 5.51 (d, 1H, *J* = 2.4 Hz, H-1′), 5.15 (dd, 1H, *J* = 9.6, 4.0 Hz, H-4), 5.04 (d, 1H, *J* = 1.8 Hz, H-1), 4.85 (d, 1H, *J* = 10.8 Hz, CH_2Ph), 4.64 (d, 2H, *J* = 12.8 Hz, CH_2Ph), 4.59 (d, 1H, *J* = 11.6 Hz, CH_2Ph), 4.53–4.48 (m, 7H, CH_2Ph × 6, H-5), 3.99 (dd, 1H, *J* = 4.4, 2.4 Hz, H-2′), 3.94–3.92 (m, 3H, H-3′, H-$6'_a$, H-$6'_b$), 3.87 (d, 1H, *J* = 7.8 Hz, H-6_a), 3.83 (s, 1H, H-2), 3.76–3.69 (m, 2H, H-4′, H-5′), 3.71 (t, 1H, *J* = 9.6 Hz, H-3), 3.59 (dd, 1H, *J* = 7.7, 4.8 Hz, H-6_b), 2.04 (s, 3H, OAc); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9 (C), 138.5 (C), 138.3 (C × 2), 138.3 (C), 137.8 (C), 128.4 (CH), 128.3 (CH), 128.25 (CH), 128.16 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.55 (CH), 127.46 (CH), 127.41(CH), 100.8 (CH), 99.7 (CH), 79.8 (CH), 75.0 (CH_2), 74.8 (CH), 74.7 (CH), 74.5 (CH), 73.3 (CH_2), 72.5 (CH_2), 72.35 (CH_2), 72.26 (CH_2), 72.1 (CH), 71.9 (CH), 71.4 (CH), 69.3 (CH_2), 64.1 (CH_2), 21.0 (CH_3); HRMS (FAB): *m*/*z* Calcd for $C_{49}H_{52}O_{11}Na$ ($[M+H]^+$): 839.3407. Found: 839.3404.

1.5. 4-*O*-Acetyl-1,6-anhydro-3-*O*-benzyl-β-L-gulopyranose (33)

Triflic anhydride (Tf_2O, 0.18 mL, 1.07 mmol) was added to a solution of diol **31** (0.20 g, 0.79 mmol) in CH_2Cl_2 (2 mL) and pyridine (1.4 mL) at 0 °C. After 11 h, Ac_2O (0.22 mL, 2.38 mmol) was added to the reaction flask at room temperature, and the solution was stirred further for 2 h. The reaction was quenched with satd $NH_4Cl_{(aq)}$ (20 mL), and the crude target material was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to get the crude triflate derivative **32**. HMPA (2 mL) and $NaNO_2$ (0.55 g, 7.97 mmol) were added to the residue followed by stirring at room temperature for 12 h. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (2 × 10 mL). The organic solution was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (EtOAc/hexanes = 1/5) to furnish **33** (184 mg, 79%

from **31**) as a light yellow oil. $[\alpha]_D^{23}$ +33.5 (*c* 1.1, $CHCl_3$); IR (thin film): *v* 3413, 2922, 2881, 1742, 1409, 1212, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.36–7.31 (m, 2H, Ar-H), 7.31–7.26 (m, 3H, Ar-H), 5.47 (d, 1H, *J* = 2.42 Hz, H-1), 5.13 (ddd, 1H, *J* = 9.16, 4.44, 0.80 Hz, H-4), 4.65 (d, 1H, *J* = 11.94 Hz, CH_2Ph), 4.54 (d, 1H, *J* = 11.94 Hz, CH_2Ph), 4.51 (t, 1H, *J* = 4.44 Hz, H-5), 3.94 (dd, 1H, *J* = 4.73, 2.42 Hz, H-2), 3.88 (d, 1H, *J* = 7.77 Hz, H-6_a), 3.67 (dd, 1H, *J* = 4.73, 9.16 Hz, H-3), 3.62 (ddd, 1H, *J* = 7.77, 4.44, 0.80 Hz, H-6_b), 2.59 (br s, 1H, 2-OH), 2.01 (s, 1H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.4 (C), 137.1 (C), 128.5 (CH × 2), 128.1 (CH), 127.8 (CH × 2), 98.8 (CH), 86.8 (CH), 76.7 (CH), 75.4 (CH_2), 72.7 (CH), 72.6 (CH), 65.9 (CH_2), 20.6 (CH_3); HRMS (FAB): *m*/*z* Calcd for $C_{15}H_{18}O_6$ ($[M]^+$): 294.1103. Found: 294.1107.

1.6. 3,4,6-Tri-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-manno-pyranosyl)-L-gulopyranosyl acetate (35)

A solution of **34** (30 mg, 37 μmol) in a mixed solvent [EtOAc/MeOH (1/3), 4 mL] was hydrogenated under 50 psi pressure in the presence of 10% Pd/C (31 mg) at room temperature for 18 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give the crude debenzylated pentaol. To this crude compound was added Ac_2O (1 mL) and trifluoroacetic acid (0.1 mL), and the mixture was stirred at room temperature for 4 h. The reaction was quenched by MeOH (1 mL), and the resulting solution was kept stirring for 30 min. The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (EtOAc/hexanes = 1/1) to afford the expected product **35** (21 mg, 85%, α/β = 1/4). The NMR spectrum of compound **35** corroborated with the literature report.[28] ^1H NMR ($CDCl_3$, 600 MHz): δ 6.26 (d, 0.25H, *J* = 4.14 Hz), 5.86 (d, 1H, *J* = 8.40 Hz), 5.40 (t, 1.02H, *J* = 3.57 Hz), 5.29 (t, 0.30H, *J* = 3.66 Hz), 5.27–5.20 (m, 1.32H), 5.12 (dd, 1.05H, *J* = 10.02, 3.42 Hz), 5.08–5.03 (m, 1.87H), 4.99–4.91 (m, 2.43H), 4.50 (td, 0.26H, *J* = 6.84, 0.78 Hz), 4.33 (td, 1.03H, *J* = 12.99, 1.29 Hz), 4.29–4.21 (m, 0.69H), 4.21–4.15 (m, 1.88H), 4.15–4.09 (m, 1.78H), 4.09–4.02 (m, 2.50H), 3.99 (ddd, 0.31H, *J* = 10.07, 4.97, 2.33 Hz), 3.96 (dd, 1.03H, *J* = 8.43, 3.33 Hz), 2.16 (s, 0.86H), 2.15 (s, 3.00H), 2.14 (s, 0.96H), 2.12 (s, 3.08H), 2.11–2.10 (m, 6.47H), 2.094 (s, 1.01H), 2.087 (s, 2.85H), 2.08 (s, 1.08H), 2.03 (s, 0.82H), 2.035 (s, 0.88H), 2.029 (s, 0.84H), 2.02 (s, 3.01H), 2.00 (s, 3.07H), 1.94–1.92 (m, 3.70H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 170.5 (C), 170.4 (C), 169.9 (C), 169.8 (C), 169.7 (C), 169.52 (C), 169.50 (C), 169.47 (C), 169.42 (C), 169.24 (C), 169.21 (C), 168.6 (C), 95.8 (CH), 94.9 (CH), 90.6 (CH), 89.3 (CH), 71.3 (CH), 69.8 (CH), 69.6 (CH), 69.2 (CH), 68.7 (CH), 68.6 (CH), 68.5 (CH), 67.61 (CH), 67.58 (CH), 67.3 (CH), 65.8 (CH), 65.7 (CH), 65.51 (CH), 65.45 (CH), 65.3 (CH), 63.8 (CH), 62.2 (CH_2), 62.0 (CH_2), 61.6 (CH_2), 61.3 (CH_2), 20.80 (CH_3), 20.77 (CH_3), 20.70 (CH_3), 20.64 (CH_3), 20.60 (CH_3), 20.53 (CH_3).

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Supplementary data

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