Synthesis and glycosidation of building blocks of D-altrosamine

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Presented herein is a streamlined synthesis of building blocks of a rare sugar D-altrosamine. Also investigated was the glycosylation of different glycosyl acceptors with differentially protected altrosamine donors. High facial stereoselectivity was achieved with 3-O-picoloyl donors and reactive glycosyl acceptors via the H-bond-mediated aglycone delivery (HAD) pathway. In contrast, glycosidations of the altrosamine donor equipped with the 3-O-benzoyl group were poorly stereoselective.

KEYWORDS
glycosylation, synthesis, sugars, glycan, oligosaccharides

Introduction

Due to significant progress in recent years, many glycans can now be obtained by using chemical methods and automated platforms (Panza et al., 2018). However, the availability of selectively protected sugar building blocks remains scarce, which hampers the scientific progress in the area of carbohydrate synthesis. Despite general improvements in the application of protecting group strategies in the mainstream carbohydrate research (Polyakova et al., 2015; Jager and Minnaard, 2016; Ágoston et al., 2016; Kulkarni et al., 2018; Volbeda et al., 2019; Wang and Demchenko, 2019), building blocks for the introduction of uncommon (rare or unnatural) sugars remain largely underdeveloped or not available at all (Emmadi and Kulkarni, 2014; Sanapala and Kulkarni, 2016a; Sanapala and Kulkarni, 2016b; Behera and Kulkarni, 2018; Wang et al., 2020).

Early reports for the synthesis of rare sugar D-altrose relied on the degradation of heptuloses (Ritchmyer et al., 1939) or modification of fructose (Araujo et al., 2012) among others. The synthesis of D-altrosamine could be achieved from 2,3-anhydroaltrose that was obtained from D-glucose precursors via a multi-step protocol (Vega-Perez et al., 1995; Nilsson and Norberg, 2000; Chiu et al., 2007; Shrestha et al., 2022). These building blocks have previously been used as synthons to access derivatized rare sugars. Nevertheless, altrosamine remains prohibitively expensive to be used as the starting material both for laboratory and industrial applications. Reported herein is a streamlined and scalable procedure for the synthesis of D-altrosamine building blocks. Also investigated was the first glycosidation of altrosamine donors with standard glycosyl acceptors.
Results and discussion

Previously, we developed methods to obtain mannosamine building blocks from methyl 4,6-O-benzylidene-α-D-glucopyranoside 1 (Alex et al., 2020a; Alex et al., 2020b). High regioselectivity of sulfonation of diol 1 with triflic anhydride at C-2 (Knapp et al., 1990) was the key to success in obtaining 2-azido-2-deoxy-D-mannopyranoside 2 (Scheme 1A). This reaction proceeded via a stereospecific nucleophilic displacement at C-2 with sodium azide in DMF (A) (Knapp et al., 1992). Compound 2 was then subjected to sequential acetolysis and a leaving group introduction to afford thioglycoside 3. The latter was protected to afford 3-OH derivative 4, which was then picoloylated to afford donor 5 or benzyolated to afford donor 6. These donors were then used for stereoselective introduction of mannosides.

However, the synthesis of 5 and 6 remained somewhat tedious and required a lengthy and multi-step process to arrive at the desired compounds. In an effort to streamline the approach, we attempted to carry out the synthesis from thioglycoside 7 (Takeo et al., 1993) instead of the previously employed methyl glycoside 1. All efforts to sulfonate thioglycoside 7 at position C-2 have failed, regardless of whether this reaction was performed in the presence of dibutyl tin oxide or not (Scheme 1B). Sulfonation was consistently directed to the C-3 position, and the subsequent nucleophilic displacement resulted in a cascade reaction with the
anticipated pathway (B). Presumably, first, 2,3-cyclization would occur, and the resulting 2,3-epoxide (Walvoort et al., 2011) would then open upon the nucleophilic attack by N3 to afford D-altro-configured amino sugar 8. This discovery led to a straightforward one-pot protocol for the synthesis of this rare sugar series and derivatives thereof. To elaborate upon this finding, we protected the 3-OH derivative 8 with picoloyl or benzoyl groups to afford glycosyl donors 9 and 10 in good yields of 95 and 91%, respectively (Scheme 1B).

We have previously reported that picolinyl or picoloyl (Pico) protecting groups at remote C-3, C-4, or C-6 positions of pyranose sugars can provide high facial syn-stereoselectivity in glycosylations (Yasomanee and Demchenko, 2012). This is due to the H-bond-mediated aglycone delivery (HAD) reaction pathway (Mannino et al., 2021). For the HAD reaction to take place, the Pico nitrogen of the glycosyl donor has to establish a hydrogen bond with the hydroxyl group of the glycosyl acceptor. Upon activation of the glycosyl donor, the glycosyl acceptor forms the glycosidic bond, which is syn with respect to the Pico substituent.

As previously proposed by our group (Alex et al., 2020a; Alex and Demchenko, 2021; Alex et al., 2021), the mannosamine donor equipped with the 3-O-Pico group will favor formation of the β-linked mannoside, as shown
TABLE 1 Glycosidation of donors 9 and 10 with glycosyl acceptors 11–14.

| Entry | D + A | Product: yield, stereoselectivity |
|-------|-------|----------------------------------|
| 1     | 9 + 11| ![Image of product 15-22](image) |
| 2     | 10 + 11| ![Image of product 15-22](image) |
| 3     | 9 + 12| ![Image of product 15-22](image) |
| 4     | 10 + 12| ![Image of product 15-22](image) |
| 5     | 9 + 13| ![Image of product 15-22](image) |

(Continued on following page)
In Scheme 2. In the case of 3-O-benzyolated (3-Bz) mannosamine donor, excellent α-stereoselectivity was obtained. This result was explained by the occurrence of a remote participation of the 3-O-benzoyl group. Our expectations for glycosyl donors of the D-altrosamine series were opposed to those observed with D-manno donors. This is because of the orientation of the substituent at C-3. Thus, we anticipated that 3-Pico donors will provide preferential α-altro stereoselectivity whereas 3-Bz donor will be β-altro stereoselective due to the remote participation effect (Scheme 2).

We hypothesized that the remote 3-O-Pico group in donor 9 will act as an H-bond acceptor for the incoming nucleophile (hydroxyl group of the glycosyl acceptor). As a result, the formation of α-altrosides was anticipated. With that, we set up a series of glycosylations with common sugar acceptors 11–14 (Ranade et al., 2010), as shown in Table 1. When glycosyl donor 9 was coupled with 6-OH acceptor 11 in the presence of NIS/TfOH in 1,2-dichloroethane (1,2-DCE), the expected disaccharide 15 was obtained in 98% and complete α-altro stereoselectivity (entry 1). Since the HAD reaction pathway is absent in 3-Bz donor 10, an opposing stereoselectivity was anticipated. However, the reaction between 3-Bz donor 10 and acceptor 11 yielded the corresponding disaccharide 16 in a high yield of 98%, albeit with modest stereoselectivity with α-anomer still favored (α/β = 3.0/1, entry 2). Both reactions were completed in 1 h. This result implies that the participation of the 3-Bz group seen for mannosides, (Crich et al., 2000) mannosamine glycosides, (Alex et al., 2020a; Alex et al., 2020b; Alex and Demchenko, 2020).

Table 1 (Continued) Glycosidation of donors 9 and 10 with glycosyl acceptors 11–14.

| Entry | D + A | Product: yield, stereoselectivity |
|-------|-------|----------------------------------|
| 6     | 10+13 | 20: 80%, α/β = 2.5/1            |
| 7     | 9+14  | 21: 65%, α/β > 25/1             |
| 8     | 10+14 | 22: 66%, α/β = 1.5/1            |
When the reaction of 4-OH glycosyl acceptor 12 was conducted with glycosyl donor 9 under the promotion of NIS/TFOH, disaccharide 17 was obtained in 71% yield, albeit with poor stereoselectivity \((\alpha/\beta = 1.7/1, \text{entry 3})\). When 3-Bz donor 10 was glycosidated with acceptor 12, disaccharide 18 was obtained in 84% yield with no stereoselectivity \((\alpha/\beta = 1.0/1, \text{entry 4})\). A very similar trend was achieved in the reaction of 3-OH acceptor 13 with glycosyl donors 9 and 10. The corresponding disaccharides 19 and 20 were achieved in good yields of 63–80% but with modest stereoselectivity in both cases \((\alpha/\beta = 2.2–2.5/1, \text{entries 5–6})\). When glycosyl donor 9 was glycosidated with 2-OH acceptor 14, disaccharide 21 was isolated in a good yield of 65% and with complete \(\alpha\)-altro selectivity \((\text{entry 7})\). The reaction between 3-Bz glycosyl donor 10 and glycosyl acceptor 14 produced the corresponding disaccharide 22 in 66% yield, albeit with poor stereoselectivity \((\alpha/\beta = 1.5/1, \text{entry 2})\). All glycosylations of secondary acceptors 12–14 were completed in 2 h. These results confirm the general trend previously seen in some HAD reactions wherein poorly nucleophilic acceptors provided lower stereoselectivity.

To confirm the stereoselectivity observed, we removed 3-ester groups from disaccharides 15 and 16 (Scheme 3). The comparison of the NMR data on the resulting disaccharide 23 ultimately confirmed the preferential \(\alpha\)-altrosamine configuration of disaccharides obtained with 3-Bz donor 10. In conclusion, a useful method for the synthesis of building blocks of D-altro-configured sugars is practically ineffective in case of D-altro-configured sugars.

**Synthesis of glycosyl donors 9 and 10**

Ethyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-\(\alpha\)-D-altropyranoside (8): lutidine (4.80 ml, 41.6 mmol), and Bu₂SnO (0.10 g, 0.41 mmol) were added to a stirring solution of ethyl 4,6-O-benzylidene-1-thio-\(\alpha\)-D-glucopyranoside (7, Takeo et al., 1993) 2.60 g, 8.32 mmol) in \(\text{CH}_2\text{Cl}_2\) (30 ml) under argon at room temperature. The resulting mixture was cooled to 0°C; Tf₂O (4.90 ml, 29.1 mmol) was added dropwise. The mixture was then stirred for 1 h at 0°C. The reaction mixture was then diluted with \(\text{CH}_2\text{Cl}_2\) (250 ml) and washed with \(\text{H}_2\text{O}\) (5 × 50 ml). The organic phase was separated, dried with \(\text{Na}_2\text{SO}_4\) concentrated under reduced pressure, and dried in vacuo.

**Experiment**

In general, the reactions were performed using commercial reagents. The ACS grade solvents used for reactions were purified and dried in accordance with the standard procedures. Column chromatography was performed on silica gel 60 (70–230 mesh), and reactions were monitored by TLC on Kiesel gel 60 F254. The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. The solvents were removed under reduced pressure at \(<40^\circ\text{C}\). \(\text{ClCH}_2\text{CH}_2\text{Cl}\) (1,2-DCE) was distilled from CaH₂ directly prior to application. Anhydrous DMF was used. Molecular sieves (4 Å), used for reactions, were crushed and activated in vacuo at 390°C during 8 h in the first instance and then for 2–3 h at 390°C directly prior to application. Optical rotations were measured by using a ’Jasco P-2000’ polarimeter. \(^1\text{H}\) NMR spectra were recorded in \(\text{CDCl}_3\) at 400 MHz, and \(^13\text{C}\) NMR spectra were recorded in \(\text{CDCl}_3\) at 100 or 175 MHz. The \(^1\text{H}\) NMR chemical shifts are referenced to tetramethyl silane (TMS, \(\delta_{\text{H}} = 0 \text{ ppm}\)) or \(\text{CDCl}_3\) (\(\delta_{\text{H}} = 7.26 \text{ ppm}\)) for \(^1\text{H}\) NMR spectra for solutions in \(\text{CDCl}_3\). The \(^13\text{C}\) NMR chemical shifts are referenced to the central signal of \(\text{CDCl}_3\) (\(\delta_{\text{C}} = 77.00 \text{ ppm}\)) for solutions in \(\text{CDCl}_3\). Compound purity or compound ratios were accessed or calculated by comparing the integration intensities of the relevant signals in their \(^1\text{H}\) NMR spectra. Accurate mass spectrometry determinations were performed using the Agilent 6230 ESI-TOF LC/MS mass spectrometer.

**Synthesis of glycosyl donors 9 and 10**

Ethyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-\(\alpha\)-D-altropyranoside (8): lutidine (4.80 ml, 41.6 mmol), and Bu₂SnO (0.10 g, 0.41 mmol) were added to a stirring solution of ethyl 4,6-O-benzylidene-1-thio-\(\alpha\)-D-glucopyranoside (7, Takeo et al., 1993) 2.60 g, 8.32 mmol) in \(\text{CH}_2\text{Cl}_2\) (30 ml) under argon at room temperature. The resulting mixture was cooled to 0°C; Tf₂O (4.90 ml, 29.1 mmol) was added dropwise. The mixture was then stirred for 1 h at 0°C. The reaction mixture was then diluted with \(\text{CH}_2\text{Cl}_2\) (250 ml) and washed with \(\text{H}_2\text{O}\) (5 × 50 ml). The organic phase was separated, dried with \(\text{Na}_2\text{SO}_4\) concentrated under reduced pressure, and dried in vacuo.
and HRMS [M + Na]+ calcd for C_{13}H_{15}N_{2}O_{5}Na 360.0994; found 360.0995.

Ethyl 2-azido-4,6-O-benzylidene-2-deoxy-3-O-picoloyl-1-thio-a-D-altropyranoside (9): picolinic acid (0.39 g, 3.2 mmol), EDC (0.61 g, 3.2 mmol), and DMAP (51 mg, 0.42 mmol) were added to a solution of compound 8 (0.71 g, 2.1 mmol) in dry CH₂Cl₂ (10 ml), and the resulting mixture was stirred under argon for 3 h at room temperature. After that, the reaction mixture was diluted with CH₂Cl₂ (20 ml) and washed with water (10 ml), sat. aq. NaHCO₃ (10 ml), and water (2 × 10 ml). The organic phase was separated, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to afford the title compound as a white amorphous solid in 95% yield (1.32 g, 2.98 mmol).

Analytical data for 9: R₂ = 0.50 (ethyl acetate/hexane, 1/1, v/v); [α]D²⁰ +57.4 (c = 1.0, CHCl₃); 1H NMR (400 MHz, CDCl₃): δ 8.82 (dd, 1H, aromatic), 8.36 (d, 1H, J = 7.8 Hz, aromatic), 7.88 (m, 1H, aromatic), 7.30–7.55 (m, 6H, aromatic), 5.64 (s, 1H, >C=Ph), 5.59 (dd, 1H, J₅,₆a = 3.2 Hz, H-3), 5.30 (s, 1H, H-1), 4.75 (m, 1H, J₅,₆b = 5.2, J₆a₆b = 10.1 Hz, H-5), 4.33 (dd, 1H, J₁₆,₆b = 10.5 Hz, H-6a), 4.22 (d, 1H, J₁,₁₆ = 4.0 Hz, H-2), 4.14 (dd, 1H, J₅,₁₆ = 9.8 Hz, H-4), 3.86 (dd, 1H, H-6b), 2.69 (m, 2H, S CH₂), and 1.31 (3H, S CH₂CH₃) ppm; 13C NMR (100 MHz, CDCl₃): δ 163.3, 150.4, 147.2, 137.1, 136.9, 129.1, 128.3 (x2), 127.1, 126.1 (x2), 125.9, 102.1, 82.5, 74.3, 68.9, 68.5, 62.4, 60.0, 27.2, and 15.1 ppm; and HRMS [M + H]+ calcd for C₂₁H₂₃N₄O₅S 443.1395; found 443.1384.

Synthesis of disaccharides 15–22

General procedure for glycosylation in the presence of NIS/TIOH: a mixture of glycosyl donor (0.11 mmol), glycosyl acceptor (0.09 mmol), and freshly activated molecular sieves (4 Å, 100 mg) in 1,2-DCE (2.0 ml) was stirred under argon for 1 h at room temperature. The mixture was then cooled to −30°C, N-iodosuccinimide (NIS, 0.22 mmol) and trifluoromethanesulfonic acid (TIOH, 2.0 µl, 0.02 mmol) were added, and the resulting mixture was allowed to warm to ambient temperature and stirred for 1–2 h at room temperature. After that, the solids were filtered off and washed successively with CH₂Cl₂. The combined filtrate (30–40 ml) was washed with water (10 ml), 10% sodium thiosulfate (Na₂SO₄, 10 ml), and water (2 × 10 ml). The organic phase was separated, dried with Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (acetone–toluene gradient elution) to afford corresponding disaccharide derivatives. Anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of the relevant signals in 1H NMR spectra.

Methyl 6-O-(2-azido-4,6-O-benzylidene-2-deoxy-3-O-picoloyl-a-D-altropyranosyl)-2,3,4-tri-O-benzyl-D-glucopyranoside (15): the title compound was obtained as an off-white amorphous solid from glycosyl donor 9 and acceptor 11 in 98% yield. Analytical data for 15: R₂ = 0.40 (ethyl acetate/toluene, 3/7, v/v); [α]D²⁰ +42.5 (c 1.0, CHCl₃); 1H NMR (400 MHz, CDCl₃): δ 8.64 (dd, 1H, aromatic), 8.04 (dd, 1H, aromatic), 7.50–7.00 (m, 2H, aromatic), 5.61 (s, 1H, >C=Ph), 5.51 (dd, 1H, J₁,₁₆ = 3.0 Hz, H-3), 4.95 (d, 1H, CH₂Ph), 4.92 (s, 1H, H-1'), 4.69–4.84 (m, 3H, 3 x CH₂Ph), 4.58 (d, 1H, CH₂Ph), 4.46 (m, 2H, H-5', CH₂Ph), 4.45 (d, 1H, J₁,₁₆ = 3.5 Hz, H-1), 4.23 (d, 1H, J₁₅,₁₆ = 2.8 Hz, H-2'), 4.20 (dd, 1H, J₁₆,₁₆a = 10.4 Hz, H-6a), 4.09 (dd, 1H, J₁₆,₁₆b = 9.7 Hz, H-4), 4.01 (dd, 1H, J₁₆,₁₆b = 11.4 Hz, H-6a), 3.91 (dd, 1H, J₁₆,₁₆a = 9.3 Hz, H-3), 3.77 (dd, 1H, H-6b'), 3.71–3.67 (m, 1H, H-5), 3.63 (dd, 1H, H-6b), 3.48 (dd, 1H, J₁₆,₁₆a = 9.5 Hz, H-4), 3.27 (dd, 1H, J₁₆,₁₆a = 9.3 Hz, H-3), and 3.22 (3H, CH₃) ppm; 13C NMR (100 MHz, CDCl₃): δ 164.2, 150.4, 147.4, 138.7, 138.2, 138.1, 137.0, 136.9, 128.5 (x2), 128.4 (x2), 128.3 (x2), 128.2 (x4), 128.0 (x2), 127.9, 127.7 (x2), 127.5 (x2), 126.9, 126.1 (x2), 125.2, 102.1, 98.9, 98.0, 81.7, 80.1, 75.7, 74.8, 73.8, 73.4 (x2), 69.8, 69.0, 68.9, 67.2, 60.1, 59.3, and 55.2 ppm; and HRMS [M + Na]+ calcd for C₃₀H₃₁N₄O₁₁Na 867.3238; found 867.3212.

Methyl 6-O-(2-azido-3-O-benzyl-4,6-O-benzylidene-2-deoxy-a-D-altropyranosyl)-2,3,4-tri-O-benzyl-a-D-glucopyranoside (16): the title compound was obtained as an off-white sticky semi-solid from glycosyl donor 10 and acceptor 11 in 98% yield (α/β = 3.0/1). Selected analytical data for a 16: R₂ = 0.40 (ethyl acetate/toluene, 3/7, v/v); [α]D²⁰ +42.5 (c 1.0, CHCl₃); 1H NMR (400 MHz, CDCl₃): δ 8.11–7.98 (m, 3H, aromatic),...
7.49 (m, 1H, aromatic), 7.43–7.09 (m, 21H, aromatic), 5.62 (s, 1H, >C=CHPh), 5.39 (dd, 1H, J_{α,β} = 3.1 Hz, H-3'), 4.91 (s, 1H, H-1'), 4.76–4.71 (m, 4H, H-5', 3 x C=CHPh), 4.66–4.54 (m, 4H, H-6'a, 3 x C=CHPh), 4.41 (dd, 1H, J_{α,β} = 3.5 Hz, H-1'), 4.24 (dd, 1H, J_{α,β} = 3.1 Hz, H-2'), 4.07 (dd, 1H, J_{α,β} = 9.7 Hz, H-4'), 3.90 (dd, 1H, J_{α,β} = 9.2 Hz, H-3') (×2), 3.79 (m, 2H, H-3'b), 3.71–3.63 (m, 3H, H-3', 5, 6 b), 3.36–3.27 (m, 2H, H-2'), 4), and 3.14 (s, 3H, CH₃) ppm; and HRMS [M + H]^+ calcld for C_{48}H_{50}O_{11}N_{3} 844.3443; found 844.3440.

Methyl 3-O-(2-azido-4,6-O-benzylidene-2-deoxy-3-O-picoloyl-D-altropyranosyl)-2,4,6-tri-O-benzyl-D-gluco-1,6-pyranoside (17): the title compound was obtained as a white amorphous solid from glycosyl donor 9 and acceptor 12 in 71% yield (α/β = 1/7:1). Selected analytical data for α-17: R_f = 0.40 (ethyl acetate/toluene, 3/7, v/v); 1H NMR (400 MHz, CDCl₃): δ 165.9, 165.1, 138.7 (×2), 138.3, 138.1 (×2), 138.0, 137.1, 136.9, 133.7, 133.3, 129.8 (×2), 129.7, 129.6 (×2), 129.4, 129.2, 129.1, 129.0, 128.7, 128.6 (×2), 128.5 (×2), 128.4 (×4), 128.3 (×3), 128.2 (×3), 127.9 (×2), 127.8, 127.7, 127.6 (×6), 126.1 (×5), 120.3, 102.1, 99.1 (×2), 98.0, 97.9, 82.1, 81.7, 80.1, 79.8, 77.6, 77.1, 75.7, 74.9, 74.7, 74.0, 73.9, 73.5 (×2), 70.1, 69.7, 69.6, 69.1, 6.3, 68.9, 68.7, 68.5 (×2), 67.3, 64.7, 61.0, 60.1, 59.4, 55.2, and 55.1 ppm; and HRMS [M + H]^+ calcld for C_{48}H_{50}O_{11}N_{3} 844.3443; found 844.3440.
Analytical data for H-4, H-6, H-5: 1H NMR (100 MHz, CDCl3): δ 8.56 (dd, 1H, aromatic), 7.92 (d, 1H, aromatic), 7.46–6.97 (m, 2H, aromatic), 5.63 (s, 1H, >CHPh), 5.49 (dd, 1H, JFα = 3.1 Hz, H-3′), 4.95 (d, 1H, CHPh) 4.93 (s, 1H, H-1′), 4.83 (d, 1H, J1,2 = 3.4 Hz, H-1), 4.75–4.65 (m, 2H, JFβ = 5.4 Hz, H-5′, CHPh), 4.59 (d, 1H, CHPh), 4.52–4.38 (m, 3H, 3 × CHPh), 4.29 (dd, 1H, JFαβ = 10.4 Hz, H-6″a), 4.26 (d, 1H, J2,5 = 2.8 Hz, H-2′), 4.11 (dd, 1H, JFβα = 9.9 Hz, H-4′), 3.88 (dd, 1H, J1,2 = 9.6 Hz, H-2), 3.78 (dd, 1H, JFβ = 9.7 Hz, H-3), 3.76 (dd, 1H, J2,5 > 10.5 Hz, H-6″b), 3.71–3.60 (m, 4H, H-4, 5, 6a, 6b), and 3.29 (s, 3H, CH3) ppm; 13C NMR (100 MHz, CDCl3): δ 164.3, 149.5, 147.1, 137.9, 137.6, 137.4, 136.8, 136.2, 136.1, 135.9, 135.8, 135.7, 135.6, 135.5, 135.3, 135.2, 135.1, 135.0, 134.9, 134.8, 134.7, 134.6, 134.5, 134.4, 134.3, 134.2, 134.1, 134.0, 133.9, 133.8, 133.7, 133.6, 133.5, 133.4, 133.3, 133.2, 129.9, 129.8 (×4), 129.7, 129.6, 129.2 (×3), 128.7, 128.6, 128.5, 128.4 (×8), 128.3 (×6), 128.2 (×2), 128.0, 127.9 (×8), 127.8 (×3), 127.7 (×2), 127.6 (×2), 127.5, 126.3 (×2), 126.1 (×2), 126.0, 102.4, 102.2, 96.7, 96.6, 93.0, 92.5, 90.5, 77.8, 77.1, 75.5, 75.1, 75.0, 74.1, 74.0, 73.8, 73.5 (×2), 70.0, 69.5, 69.2, 69.1, 68.9 (×2), 68.4, 68.3, 65.0, 62.3, 60.5, 60.4, 60.3, 59.5, 59.3, and 54.9 ppm; and HRMS [M + Na]+ calcd for C41H45N3O10Na 867.3238; found 867.3212.

Methyl 6-O-(2-azido-3,6-O-benzylidene-2-deoxy-D-altropyranosyl)-3,4,6-tri-O-benzyl-D-glucopyranoside (22): the title compound was obtained as a yellowish sticky semi-solid from glycosyl donor 10 and acceptor 14 in 66% yield (αD = 1.5/1). Selected analytical data for 22: Ry = 0.60 (ethyl acetate/toluene, 1/4, v/v); 1H NMR (100 MHz, CDCl3): δ 8.01–7.93 (m, 2H, aromatic), 7.52–6.98 (m, 23H, aromatic), 5.61 (s, 1H, >CHPh), 5.39 (dd, 1H, JFα = 3.1 Hz, H-3′), 4.94 (s, 1H, H-1′), 4.87–4.84 (d, 1H, CHPh), 4.79 (d, 1H, J1,2 = 3.3 Hz, H-1), 4.68 (dd, 1H, JFβ = 4.7, JFβα = 10.4 Hz, H-5′), 4.60–4.28 (m, 5H, 5 × CHPh), 4.29 (d, 1H, JFαβ = 10.5 Hz, H-6″a), 4.25 (d, 1H, J2,5 = 2.7 Hz, H-2′), 4.09 (dd, 1H, JFβ = 9.8 Hz, H-4′), 3.84 (dd, 1H, J1,2 = 9.6 Hz, H-2), 3.81–3.75 (m, 2H, H-3, 6″b), 3.72–3.58 (m, 4H, H-4, 5, 6a, 6b), and 3.24 (s, 3H, CH3) ppm; 13C NMR (100 MHz, CDCl3): δ 166.5, 165.2, 158.3, 138.1, 138.1, 137.9, 137.8, 137.2, 136.9, 133.7, 133.5, 133.2, 129.9, 129.8 (×4), 129.7, 129.6, 129.2 (×3), 128.7, 128.6, 128.5, 128.4 (×8), 128.3 (×6), 128.2 (×2), 128.0, 127.9 (×8), 127.8 (×3), 127.7 (×2), 127.6 (×2), 127.5, 126.3 (×2), 126.1 (×2), 126.0, 102.4, 102.2, 96.7, 96.6, 93.0, 92.5, 90.5, 77.8, 77.1, 75.5, 75.1, 75.0, 74.1, 74.0, 73.8, 73.5 (×2), 70.0, 69.5, 69.2, 69.1, 68.9 (×2), 68.4, 68.3, 65.0, 62.3, 60.5, 60.4, 60.3, 59.5, 59.3, and 54.9 ppm; and HRMS [M + Na]+ calcd for C41H45N3O10Na 867.3238; found 867.3212.

From compound 16, a 11 N solution of sodium methoxide in MeOH was added to a solution of compound 15 (38 mg, 0.05 mmol) in MeOH (1.2 ml) until pH reached ~ 9, and the resulting mixture was kept for 1 h at room temperature. After that, the reaction mixture was neutralized with Dowex (H+); the resin was filtered off and washed successively with MeOH. The combined filtrate (~25 ml) was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate–hexane gradient elution) to afford the title compound as a white amorphous solid.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2022.945779/full#supplementary-material

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