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Value-added carbohydrate building blocks by regioselective *O*-alkylation of *C*-glucosyl compounds

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Abstract

Functionalized carbohydrates and especially functionalized *C*-glycosides are useful intermediates for the synthesis of complex carbohydrates of interest. In this paper, we describe the synthesis of *C*-azidopropylglucopyranosides and give a full account of their regioselective acylation and alkylation. Alkylation of these *C*-glucosyl compounds containing 1,2-*trans*-diol, namely 2- and 3-OH were first optimized with benzyl bromide. The reaction has then been extended to various electrophiles thus providing 3-*O*-substituted *C*-glucosyl compounds. These results are one of the first examples of regioselective alkylation with functionalized electrophiles on glycosyl compounds featuring a *trans*-vicinal diol. Furthermore, we describe some results obtained during regioselective deprotection of 4,6-*O*-benzylidene protecting group. This work opens the way to the synthesis of complex carbohydrate derivatives.

Keywords: *C*-glycoside; regioselective alkylation; 1,2-*trans*-diol

Highlights

Efficient synthesis of *C*-azidopropylglucopyranosides

Regioselective alkylation of *C*-glucopyranosides

Access to value-added *C*-glycosyl derivatives

1. Introduction

The development of efficient methods for the preparation of carbohydrate derivatives is a crucial point for the synthesis of oligosaccharides, glycoconjugates or glycomimetics [1-7]. In this context, the access to saccharide-based building blocks requires multi-step routes and the development of regioselective strategies continues to be a field of interest in synthetic carbohydrate chemistry. In particular, regioselective protection of carbohydrates is still a challenge for chemists as attested by the number of publications dealing with mechanistic aspects nowadays, such as the recent reviews from Moitessier *et al.* [4] and Taylor *et al.* [8]. Regioselective protection *via* alkylation offers an efficient way to conveniently access protected carbohydrate derivatives. For this purpose, many metal compounds and organic small molecules have been used, such as iron [9-11], boron [12], NaH with metal chloride, or copper derivatives (*e.g.* CuCl₂) [13-15] and other additives [4]. Organotin derivatives [16-23] have proved their efficiency and are still used today despite their toxicity [24, 25]. Typically, these methods were employed for methylation, allylation or benzylation of carbohydrates. Most of these approaches have been efficiently applied to carbohydrate derivatives containing 1,2-*cis*-diol units. For the 1,2-*trans*-diol found in glucopyranose derivatives for example, only a few works have described regioselective alkylations and they are generally limited to methylation and benzylation. Moreover, these alkylations on 1,2-*trans*-diols have usually provided poor regioselectivities [11, 13, 14, 21] except for particular substrates [13, 21, 23]. Hence, a regioselective synthetic plan applicable to *gluco* configured derivatives is a currently unmet need.

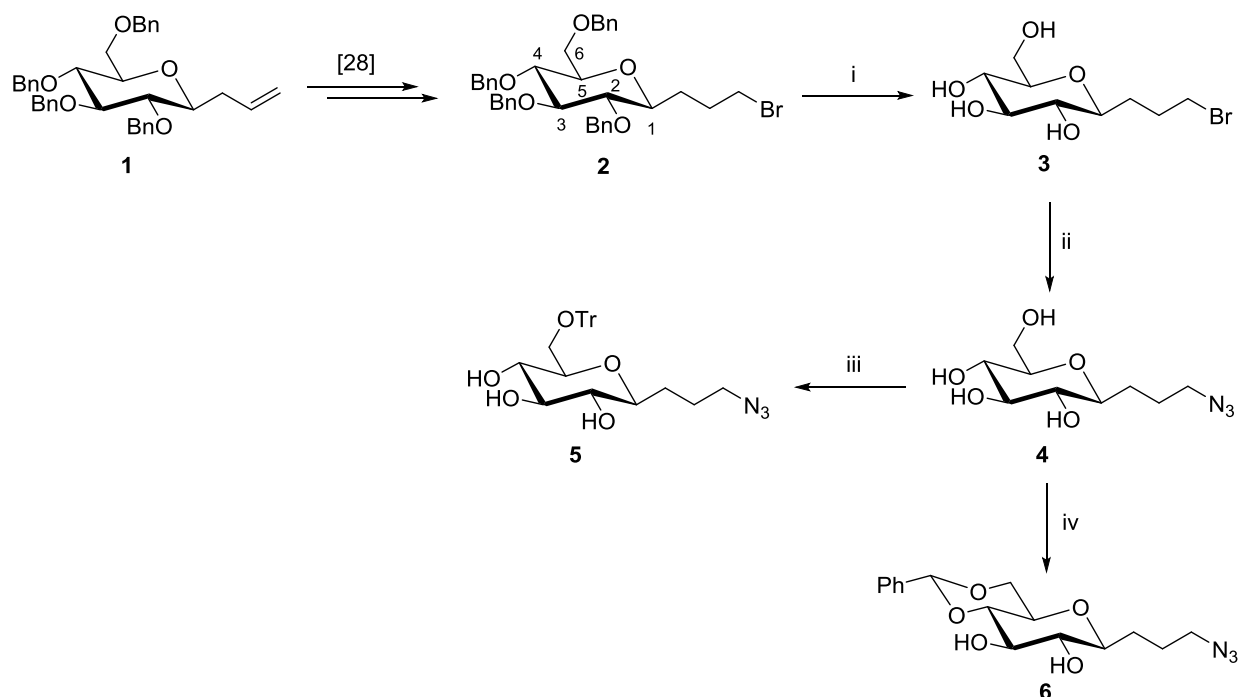
In the literature, most attention focuses on regioselective *O*-acylation or alkylation in order to protect carbohydrate derivatives in a regioselective manner. To go further with the preparation of complex carbohydrate intermediates, few publications have described regioselective alkylation with functional electrophiles. Lindhorst *et al.* have studied the alkylation of various carbohydrates with 3-bromopropyl phthalimide [26] and two papers from Saikam *et al.* and Eby *et al.* investigated reactions with allyl bromide [14, 27]. To the best of our knowledge, the only example dealing with 1,2-*trans*-diol was described in the publication by Eby *et al.* related to alkylation of differently protected glucopyranosides, however they reported poor regioselectivities. Therefore, highly regioselective alkylation with functional electrophiles is unprecedented on saccharides featuring a 1,2-*trans*-diol.

Our research focuses on synthetic routes to bioactive glycoconjugates, carbohydrate platforms and bioactive compounds based on *C*-glycosides [28-31]. Indeed, *C*-glycosyl compounds with

a robust C-C link at the anomeric position are known to be resistant to acidic and enzymatic hydrolyses and are thus stable *in vivo* [32-35]. In connection with these themes, we have developed the synthesis of value-added C-glycosyl building blocks *via* efficient regioselective functionalization. Particular attention is paid to the scope and limitations of regioselective *O*-alkylation of 1,2-*trans*-diol of C-glycosyl compounds with functional electrophiles. To the best of our knowledge, no similar example dealing with C-glycosides bearing functionalized arm at the anomeric position was documented. In this paper, we give a full account of regioselective functionalization of C-glycosyl compounds.

2. Results and discussion

We have recently optimized the synthesis and characterization of C-allylglucopyranoside [28] according to known methods [36-40]. Briefly, 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose [36, 37] was stereoselectively converted to the corresponding β -C-allylglucopyranoside **1** (Scheme 1) [38, 39]. The resulting alkene was treated with 9-BBN [28, 40] and the corresponding alcohol was converted to bromide derivative **2** (See SI) [28].

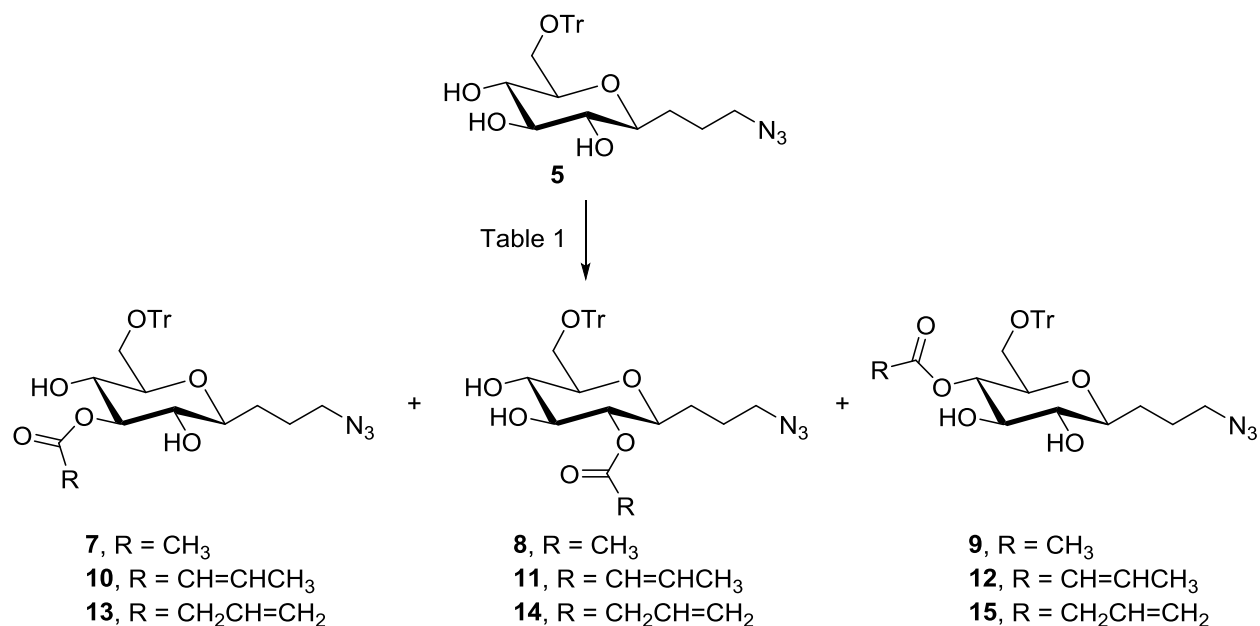


Scheme 1. Reagents and conditions: (i) Pd(OH)₂/C (20% w/w), THF/H₂O (5/1 v/v), H₂, 33 psi, 13 h, 95%; (ii) NaN₃, acetone/water (6/1 v/v), reflux, 12 h, 90%; (iii) TrCl, DABCO, CH₂Cl₂, 36 h, rt, 72%; (iv) PhCH(OMe)₂, I₂, acetonitrile, reflux, 12 h, 70%.

The removal of the benzyl ether protecting groups by hydrogenolysis required a meticulous optimization due to the presence of a bromide. Different parameters such as the nature of the solvent (dioxane, CH₂Cl₂/MeOH and THF/H₂O), the hydrogen pressure (30 to 50 psi), the nature and quantity of catalyst (Pd/C and Pd(OH)₂, 15 to 25% w/w) and the reaction time (4 h to 16 h) were screened in order to avoid the debromination side reaction. Catalytic hydrogenolysis under H₂ atmosphere (33 psi) with Pd(OH)₂/C (20% w/w) in a THF/H₂O (5/1 v/v) mixture during 13 h gave the best results. The fully deprotected derivative **3** was thus obtained in 95% yield and the formation of debrominated product was limited to 5%. An azide function, useful for late-stage functionalization *via* Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) [41], was introduced on the anomeric arm of the C-glycosyl intermediate **3**. Compound **3** was reacted with NaN₃ in an acetone/water (6/1 v/v) mixture at reflux during 12 h to afford **4** in 90% yield [42]. Two differently protected C-azidopropylglucopyranosides were then prepared.

For clarity, atom numbering is consistent with carbohydrate numbering (scheme 1, **2**) and did not correspond to IUPAC chemical name (specific nomenclature of C-glycosyl compounds). A first protection of 6-OH was performed by reaction with trityl chloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) in dichloromethane for 36 h at room temperature. As expected, the protection was regioselective and compound **5** was obtained in 72% yield. The 4- and 6-OH were also protected with a benzylidene acetal, opening a second route for further functionalization. Compound **4** was reacted in a sealed tube with benzaldehyde dimethyl acetal and a catalytic amount of I₂ in acetonitrile to afford **6** in 70% yield [43]. Compared to compound **5**, compound **6** only has two free hydroxyl groups, which is an advantage in case of regioselective functionalization.

We then planned to introduce a second functional arm by acylation or alkylation of remaining hydroxyl groups of compounds **5** and **6**. Initially, acylation of **5** was studied (Scheme 2).



Scheme 2. Acylation of **5**

It was documented that the presence of a sterically hindered group on 6-*O* oriented an acetylation on 3-OH for steric and electrical reasons [4, 44]. We postulated that **5** bearing a trityl group should react in the same way. Acetylation of **5** was performed as previously reported [44] using 0.7 equivalent of acetic anhydride (concentration of 1 mg/mL), K₂CO₃ and a catalytic amount of DMAP in chloroform at room temperature (table 1, entry 1). A weak conversion was observed due to the default in Ac₂O. As expected, the 3-OAc regioisomer **7** was predominantly obtained in 16% yield, **8** and **9** were also formed in low yields (approximately 5%). To improve the conversion rate, the amount of Ac₂O was increased to 1.1 equivalents and the concentration to 5 mg/mL (table 1, entry 2). In this case, a good conversion was achieved and 3-OAc regioisomer **7** was predominant (41% yield), **8** and **9** were recovered in 14 and 11% yield respectively. The regioselectivity was improved when the concentration of Ac₂O was decreased to 2.5 mg/mL (table 1, entry 3) allowing access to **7** in 38% yield, with compounds **8** and **9** still formed but in lower yields (compare entries 2 and 3). Given the difficulties to isolate with convenient purities the minor isomers **8** and **9** (close Rfs), the major isomer **7** was the only one obtained with excellent purity and thus fully characterized. Nevertheless, the identification of regioisomers was unambiguously established by assignment of ¹H and ¹³C signals together with 2D NMR spectroscopy.

To study the scope of regioselective acylation, the reaction with 3-butenic acid was next investigated. After introduction on the sugar building block, this alkene could be used for

further functionalization by thiol-ene coupling for example. To start with, a protocol using benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), *N,N*-diisopropylethylamine (DIEA) and 3-butenic acid in dichloromethane was carried out (table 1, entry 4). The conversion rate was moderate and unexpected compounds **10**, **11** and **12** were obtained resulting from the isomerization of the terminal double bond in a more stable substituted one [45]. The structures of compounds **10**, **11** and **12** were confirmed by ¹H NMR spectra thanks to characteristic multiplicities of (*E*)-disubstituted double bond moiety observed around 5.95 and 7.05 ppm with a coupling constant of 15.5 Hz. The reaction performed with isobutyl chloroformate (IBCF), triethylamine (TEA), a catalytic amount of 4-dimethylaminopyridine (4-DMAP) and 3-butenic acid in dichloromethane gave approximately the same result (table 1, entry 5). In both cases, we were pleased to note that the 3-*O*-substituted compound **10** was predominantly obtained in 38 and 31% yields respectively, both 2-*O*- and 4-*O*-acylated derivatives **11** and **12** were also obtained in low yields. Compound **12** was clearly identified on ¹H NMR spectrum, but was tedious to isolate with an acceptable purity. A protocol avoiding the use of amine was performed with *N,N'*-dicyclohexylcarbodiimide (DCC), a catalytic amount of 4-DMAP and 3-butenic acid in dichloromethane. This time no isomerization of the double bond occurred. Nevertheless, the reaction was not as efficient, giving **13** in 25% yield. The formation of **15** and **14** was limited, these isomers were identified on ¹H NMR spectrum of the crude reaction mixture, but could not be isolated. Non identified by-products were also detected explaining the moderate recovered yields.

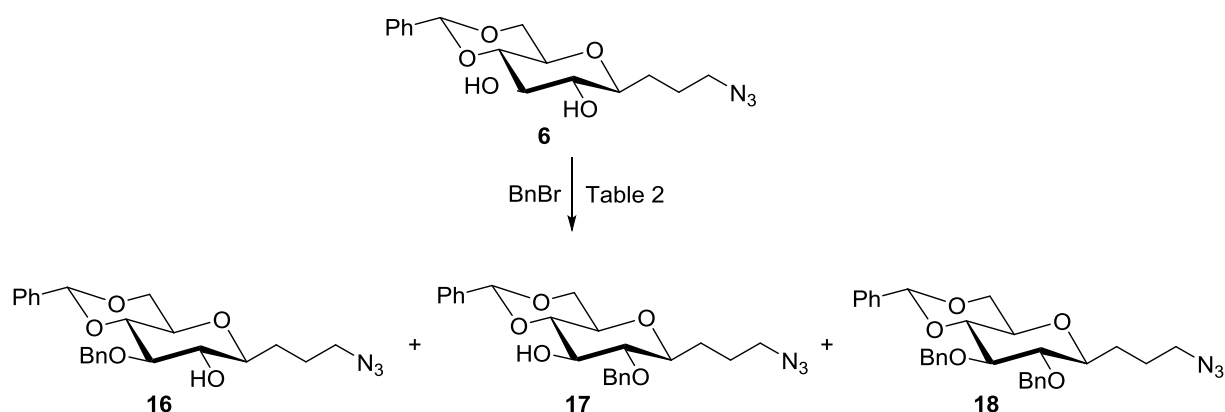
Table 1. Scope and limitation of **5** acylation

Entry	Reagent	Equiv. of reagent	Starting cpd (%) 5^e	<i>O</i> -substituted cpds (yield %)		
				3-<i>O^e</i>	2-<i>O^f</i>	4-<i>O^f</i>
1	Ac ₂ O ^a	0.7	54	7 (16)	8 (5)	9 (5)
2	Ac ₂ O ^a	1.1	12	7 (41)	8 (14)	9 (11)
3	Ac ₂ O ^a	1.1	31	7 (38)	8 (8)	9 (<5)
4	3-butenic acid ^b	1.2	37	10 (38)	11 (8) ^e	12 (<5)
5	3-butenic acid ^c	1.2	25	10 (31)	11 (10) ^e	12 (<5)
6	3-butenic acid ^d	1.2	10	13 (25)	14 (8)	15 (<5)

^a K₂CO₃, 4-DMAP cat, Ac₂O, CHCl₃; [Ac₂O] = 1mg/mL for entry 1; [Ac₂O] = 5mg/mL for entry 2; [Ac₂O] = 2.5mg/mL for entry 3. ^b PyBOP, DIEA, 3-butenic acid, CH₂Cl₂. ^c IBCF,

TEA, 4-DMAP cat., 3-butenic acid, CH₂Cl₂.^d DCC, 4-DMAP cat., 3-butenic acid, CH₂Cl₂/MeCN.^e isolated yield.^f estimated on ¹H NMR spectra.

These acylation reactions were regioselective, as previously described on other carbohydrate derivatives bearing a sterically hindered group on 6-*O*, and 3-*O*-substituted regioisomers were always predominantly obtained [4, 44]. However, in our case, the regioselectivity was not satisfactory. In order to develop tools compatible with biological applications displaying strong *in vivo* stability; we thus planned to explore other types of links, like ether for example. As attested by several studies, alkylations of carbohydrates with more than two free hydroxyls give complex mixtures of different regioisomers [16, 18]. For these reasons, alkylation reactions were investigated on 4,6-*O*-benzylidene derivative **6** which has only two unprotected hydroxyls. It is important to note that the regioselective alkylation of glycosides bearing a 1,2-*trans*-diol, *i.e.* 2-OH and 3-OH (Scheme 3) is challenging.



Scheme 3. Benzylation of **6** using different protocols.

At first, benzyl bromide (BnBr) was selected as model alkylating reagent and a phase-transfer procedure was explored (table 2, entry 1). This protocol is known to be poorly regioselective, but is widely used and gives excellent conversion rate [46-48]. Compound **6** was reacted with benzyl bromide, a catalytic amount of Bu₄NHSO₄ and an aqueous solution of NaOH in dichloromethane (protocol A). Not surprisingly, a poor regioselectivity was observed (table 2, entry 1) and alkylation reactions occurred at several positions, giving **16**, **17** and **18** in 19, 29 and 29% yields respectively after isolation by column chromatography. A second protocol using NaH and CuCl₂ in tetrahydrofuran with 4 equivalents of BnBr was carried out (table 2, entry 2) according to reported method [13]. Copper chelates of 4,6-*O*-benzylidene

glycopyranoside dianions are described to react regioselectively with alkylating agents giving predominantly 3-*O*-alkylation in good yields, even on 1,2-*trans*-diol [13- 15]. The carbohydrate dianions are postulated to be deactivated by the formation of the copper(II) salt, limiting the disubstitution. In our case, the reaction gave a mixture of starting compound **6**, mono- and disubstituted compounds in which 3-*O*-monobenzylated derivative **16** preponderated (51% yield, entry 2). Regioselective procedure for alkylation *via* formation of 2,3-*trans*-stannylidene acetal intermediate was then investigated. A recent, original and green procedure was carried out with a catalytic amount of Bu₂SnCl₂, TBABr and K₂CO₃ in acetonitrile [21, 22]. In our case, only modest conversion of compound **6** was observed and non-identified by-products were also detected despite optimizations (reaction time, equivalents of BnBr, temperature). Only 3-*O*-benzyl derivative **16** was obtained and isolated in a poor yield (5%, entry 3).

The classical one-pot procedure using bis-dibutyltin oxide was then investigated [18-20, 23, 49]. Bis-dibutyltin oxide has been used for a long time and its regioselective mechanism has been hypothesized to be controlled by complex stannylene structures (dimer or polymer) giving regioselective alkylation [4, 19]. Different protocols could be used but it has been reported that the use of additives such as tetrabutylammonium halides or fluoride salts increase the rate of alkylation reactions of organotin derivatives [18, 49-51]. Regioselective alkylation of diols is usually documented with catalytic amount of Bu₂SnO [16, 17]. However, it has been observed by Pei *et al.* [17] that benzylation of methyl 4,6-*O*-benzylidene- α -D-glucopyranoside requires a stoichiometric amount of dibutyltin oxide to predominantly form one regioisomer. They postulated that the dibutylstannylene acetal formed with catalytic amounts of Bu₂SnO cannot be regenerated with *trans*-diol, leading to poor regioselectivity. Following these observations, a solution of **6** and Bu₂SnO (1.2 equiv.) in toluene was refluxed during 2 h (entry 4). Infra-red spectrometry enabled monitoring of the disappearance of the absorption band of the hydroxyl groups and thus the stannylidene acetal intermediate formation. Dimethylformamide, BnBr (1.2 equiv.) and cesium fluoride (1.5 equiv.) were then added and the mixture was stirred at 90°C for 48 h. Regioselective 3-*O*-benzylation of **6** occurred and only regioisomer **16** was obtained in 33% yield. In these conditions, the conversion rate was about 60%, 39% of compound **6** being recovered. To improve the conversion rate, the amount of BnBr was increased (entries 5 and 6). With 2.5 equivalents of BnBr the conversion rate reached 80% and 3-*O*-Bn substituted compound **16** was isolated in 40% yield. The use of 4 equivalents of BnBr did not improve the conversion

and the yield of **16**. Taken together, these results suggested that the use of 2.5 equivalents of alkylating agent was the most efficient in terms of regioselectivity and yield.

Table 2. Scope and limitation of **6** benzylation

Entry	Protocol	BnBr (equiv.)	Starting cpd ^a (%)		Compounds ^a (yield %)	
			6	16	17	18
1	A	1.2	9	19	29	29
2	B	4	13	51	14	9
3	C	1.5	51	5	0	0
4	D	1.2	39	33	0	0
5	D	2.5	23	40	0	0
6	D	4	21	38	0	0

^a isolated yield; Protocol A: Bu₄NHSO₄, BnBr, NaOH, dichloromethane; Protocol B: NaH, dry THF then CuCl₂, BnBr; Protocol C: Bu₂SnCl₂, TBABr, K₂CO₃, BnBr, acetonitrile; Protocol D: Bu₂SnO, toluene, then dimethylformamide, BnBr, CsF.

Regioisomers **16**, **17** and **18** were purified by column chromatography on silica gel and their structures were established by 1D and 2D NMR spectroscopy. Some overlap of carbohydrate protons signal conducted us to further confirm these assignments and NOESY spectra of **16** and **17** were recorded (Fig. 1). The NOESY spectrum of the first eluted product showed several correlations of CH₂Bn with H-1, H-2 and H-3 and also with protons of the anomeric arm corroborating the structure of 2-*O*-benzyl derivative **17**. For the second eluted compound, a correlation between CH₂Bn and H-3 and H-4 confirmed the structure of 3-*O*-benzyl isomer **16**.

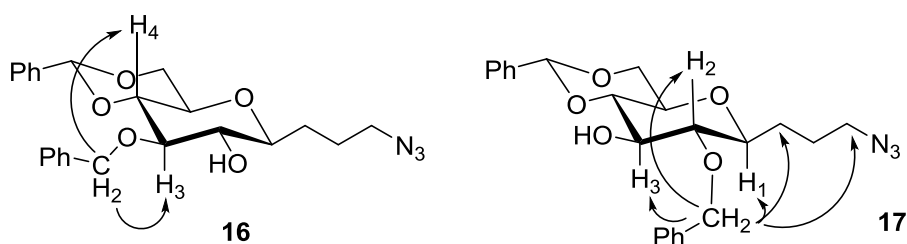


Figure 1. NOESY correlations in **16** and **17**.

This regioselective 3-*O*-alkylation is in accordance with the literature on *gluco* substrates [13, 21]. Particularly, the Bu₂SnO protocol (protocol D) was totally regioselective. These results provided a new example of regioselective benzylation of glucosyl compounds bearing 1,2-

trans-diol and were the first example with a *C*-glucosyl derivative. Indeed, most of regioselective 3-*O*-alkylations have been efficiently applied to carbohydrate bearing a 1,2-*cis*-diol composed of one axial hydroxyl and one equatorial hydroxyl, but they have rarely provided good regioselectivities for glucopyranose presenting 1,2-*trans*-diol, *i.e.* two equatorial hydroxy groups.

We next examined the scope and limitation of the regioselective 3-*O*-alkylation of compound **6** with various functional alkylating agents using Bu₂SnO (protocol D with 2.5 equivalents of alkylating agent, Fig. 2).

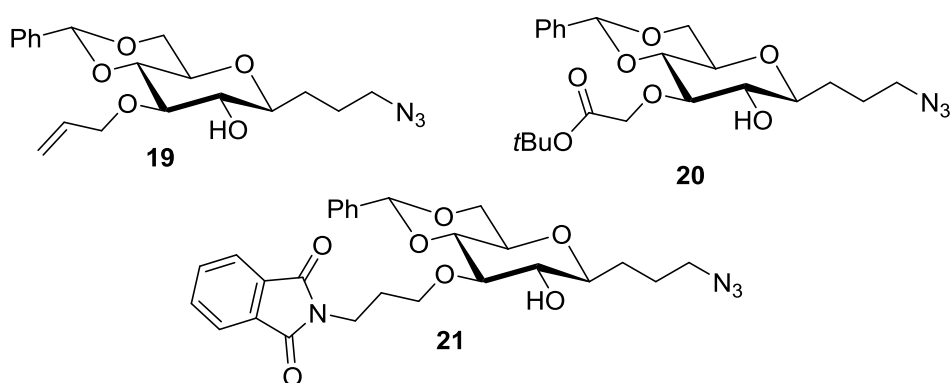
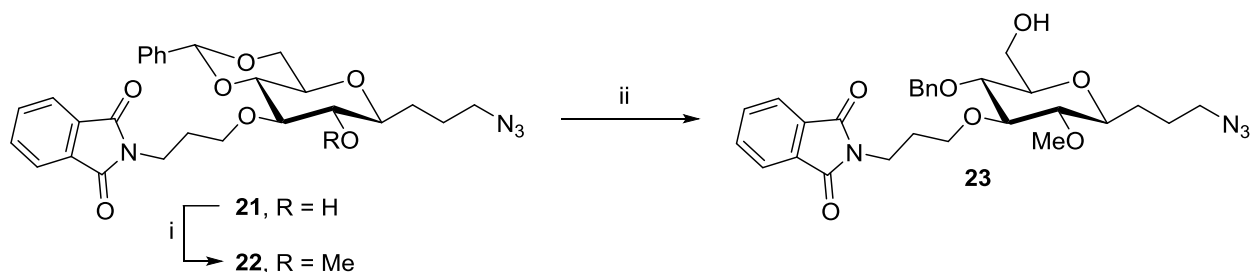


Figure 2. Structures of compounds **19-21**

Alkylation with allyl bromide carried out at 50°C gave 3-*O*-allyl derivative **19** in a good yield of 50%. Similarly to benzylation, the conversion was not complete and about 30% of starting material was recovered, even after careful optimization (temperature, reaction time). ¹H NMR presented no overlap of carbohydrate protons signal and thus structure of **19** was unambiguously confirmed by 1D and 2D spectroscopy. We then attempted alkylation with bromoacetic acid methyl ester, but the expected compound was not obtained. The conversion rate was poor and non-identified secondary products were formed. The analysis of the crude by mass spectrometry showed the presence of a *C*-glucosyl compound bearing a CH₂-COOH group (C₁₈H₂₃N₃O₇Na [M+Na]⁺: 416.1318). Assuming thus that methyl ester was too sensitive, we turned to bromoacetic acid ethyl ester, without success. Bromoacetic acid *tert*-butyl ester was finally tested and compound **20** was obtained in 32% yield. We then investigated another functional electrophile, 3-bromopropyl phthalimide, which was reacted with **6** and gave **21** in 31% yield, without byproducts formation and an estimated conversion rate of 59%. Regioselective 3-*O*-alkylation occurred for all functionalized electrophiles, no traces of 2-*O*-substituted or disubstituted compounds were observed. This result is one of the

first examples of regioselective alkylation on position 3 with functionalized electrophiles of glucosyl derivatives displaying a 1,2-*trans*-diol at position 2 and 3. Various chains were successfully introduced and the functional groups (allyl, phthalimide and *tert*-butyl ester) are prone to many synthetic transformations to provide a wide range of compounds of interest.



Scheme 4. Reagents and conditions: (i) NaH (1.8 equiv.), CH₃I (30 equiv.), DMF, 1 h, 0°C to rt, 77%; (ii) BH₃.THF (1M, 10 equiv.), TMSOTf (0.3 equiv.), dry CH₂Cl₂, 30 min., rt, 41%.

As an example, we investigated the reductive opening of the 4,6-*O*-benzylidene acetal of compound **21**. Beforehand, we managed to introduce an alkyl group on position 2. Compound **22** was obtained in 77% yield by reaction with NaH and MeI (Scheme 4), showing the reactivity of this hydroxyl with an alkylating agent. Numerous experimental conditions for regioselective reduction of 4,6-*O*-benzylidene acetal of pyranosides have been developed and described in the literature over the years [4, 52]. To obtain the 4-OBn, 6-OH compound, the highly regioselective method described by Daragics and Fügedi was selected [53]. The reaction was carried out on **22** using BH₃.THF as hydride donor in conjunction with TMSOTf. The 4-*O*-Bn compound **23** was obtained in 41% yield, along with the 4,6-OH diol **24** formed in 8% yield and 30% of starting material **22** (Scheme 4). The structure of **23** was unambiguously established by 1D and 2D NMR spectroscopy.

3. Conclusion

To conclude, we investigated the regioselective functionalization of *C*-glycosyl compounds in order to obtain high value added building blocks. In our hands, acylation reaction has proved to be more capricious than alkylation reaction. The regioselective alkylation of *C*-azidopropylglucopyranosides bearing 1,2-*trans*-diol was carefully optimized with benzyl bromide revealing that Bu₂SnO protocol was the most efficient. This strategy was successfully extended to functional electrophiles *i.e.* allyl bromide, 3-bromopropyl phthalimide and bromoacetic acid *tert*-butyl ester. The corresponding 3-*O*-substituted

carbohydrates were obtained in good to moderate yields depending on the reagent and these results are one of the first examples of regioselective alkylation with functional electrophiles on *trans*-vicinal diol. Furthermore, the regioselective reduction of 4,6-*O*-benzylidene was investigated on one compound. This work opens the way to the synthesis of complex carbohydrates derivatives and the diverse functional groups enable the coupling of various moieties for biological applications.

4. Experimental section

4.1. General information

Solvents and liquid reagents were purified and dried according to recommended procedures. Thin layer chromatography (TLC) analyses were performed using standard procedures on Kieselgel 60F254 plates (Merck, Kenilworth, NJ, USA). Compounds were visualized using UV light (254 nm) and a methanolic solution of sulfuric acid and charred. Column chromatography was performed on silica gel SI 60 (63-200 μm) (Merck). Melting points were determined with a Tottoli apparatus and are uncorrected. FTIR spectra were recorded on a Perkin-Elmer Spectrum 100 by using NaCl windows (film) or KBr pellets (cm^{-1}). Optical rotations were measured on an Anton-Paar MCP 300 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer DPX250 (250 MHz and 62.9 MHz respectively) or Avance III 400 (400 MHz and 100.6 MHz, respectively). For complete assignment of ^1H and ^{13}C signals, two-dimensional ^1H , ^1H COSY and ^1H , ^{13}C correlation spectra were recorded. Chemical shifts (δ) are given in parts per million relative to the solvent residual peak. For clarity, atom numbering resulting from the IUPAC naming of compounds (cf SI, fig S1) was used so atom numbering did not correspond to carbohydrate classical numbering. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, b = broad signal and app = apparent multiplicity. The given J values refer to apparent multiplicities and do not represent the true coupling constants. Mass and high resolution mass spectrometry spectra were recorded on a Bruker microTOFQ apparatus.

4.2. Chemistry

Compound **2** [28] was prepared according to previously described methods (see SI). Physico-chemical characterization of minor isomers **11**, **17**, **18** and **24** is described in the supporting information.

4.2.1 Synthesis of 4,8-anhydro-1-bromo-1,2,3-trideoxy-D-glycero-D-gulo-nonitol (3)

Compound **2** (5.0 g, 7.76 mmol) and Pd(OH)₂/C (1 g, 20 mol%) were added in THF/H₂O mixture (5/1 v/v, 110 mL). The reaction mixture was stirred under hydrogen atmosphere at 33 psi for 13 h (Paar apparatus). After completion of the reaction, the mixture was diluted with MeOH and the catalyst was filtered off through a Celite[®] pad. The filtrate was concentrated under reduced pressure to give **3** which was used without further purification.

Yield 95%; Oil; $[\alpha]_D^{25}$ -6.5 (*c* 0.1, CH₃OH); IR (film); ν 3306, 2924, 2872, 1636, 1406, 1370, 1314, 1258 cm⁻¹; ¹H NMR (400 MHz, D₂O): δ 1.53-1.65 (m, 1H, H-3a), 1.93-2.18 (m, 3H, H-3b and H-2), 3.24 (app t, 1H, $J_{5,4} = J_{5,6} = 9.5$ Hz, H-5), 3.33-3.44 (m, 3H, H-4, H-7 and H-8), 3.48 (app t, 1H, $J_{6,5} = J_{6,7} = 9.5$ Hz, H-6), 3.49 (app td, 2H, $J_{1,3a} = 7.0$ Hz, $J_{1,3b} = 1.0$ Hz, H-1), 3.71 (dd, 1H, $J_{9a,8} = 5.5$ Hz, $J_{9a,9b} = 12.0$ Hz, H-9a), 3.92 (dd, 1H, $J_{9b,8} = 2.0$ Hz, H-9b); ¹³C NMR (100.6 MHz, D₂O): δ 27.6 (C-2), 28.6 (C-3), 33.8 (C-1), 60.1 (C-9), 69.2 (C-7), 72.5 (C-5), 76.5 (C-8), 77.6 (C-6), 78.7 (C-4); HRMS (ESI): calcd for C₉H₁₇BrO₅Na [M+Na]⁺: 307.0157, found: 307.0153.

4.2.2. Synthesis of 4,8-anhydro-1-azido-1,2,3-trideoxy-D-glycero-D-gulo-nonitol (4)

To a solution of **3** (5.0 g, 20.2 mmol) in acetone/water mixture (6/1 v/v, 90 mL), NaN₃ (3.5 g, 2 equiv., 40.4 mmol) were added under argon. The mixture was stirred overnight at reflux. After evaporation under *vacuum*, the crude residue was purified by chromatography on silica gel (eluent: CH₂Cl₂/MeOH 90/10) to afford compound **4**.

Yield 90%; Oil; $[\alpha]_D^{25}$ -19.9 (*c* 0.07, CH₃OH); IR (film); ν 3350, 3232, 2086, 1597, 1355 cm⁻¹; ¹H NMR (400 MHz, CD₃OD): δ 1.49-1.59 (m, 1H, H-3a), 1.69-1.80 (m, 1H, H-2a), 1.86-1.96 (m, 1H, H-2b), 1.96-2.05 (m, 1H, H-3b), 3.13 (app t, 1H, $J_{5,4} = J_{5,6} = 9.0$ Hz, H-5), 3.20-3.30 (m, 2H, H-4 and H-8), 3.34 (app t, 1H, $J_{6,7} = J_{6,5} = 9.0$ Hz, H-7), 3.35-3.40 (m, 1H, H-6), 3.41 (t, 2H, $J_{1,2} = 7.5$ Hz, H-1), 3.71 (dd, 1H, $J_{9a,9b} = 12.0$ Hz, $J_{9a,8} = 5.5$ Hz, H-9a), 3.90 (dd, 1H, $J_{9b,8} = 2.5$ Hz, H-9b); ¹³C NMR (100.6 MHz, CD₃OD): δ 26.0 (C-2), 29.9 (C-3), 52.6 (C-1), 63.0 (C-9), 71.9 (C-7), 75.3 (C-5), 79.6 (C-6), 80.3 (C-8), 81.4 (C-4); HRMS (ESI): calcd for C₉H₁₇N₃BrO₅Na [M+Na]⁺: 270.1066, found: 270.1080.

4.2.3. 4,8-anhydro-1-azido-1,2,3-trideoxy-9-O-triphenylmethyl-D-glycero-D-gulo-nonitol (5)

To a solution of **4** (1.3g, 5.26 mmol) in dry CH₂Cl₂ (25 mL), was added, under argon at room temperature TrCl (4.4 g, 15.78 mmol, 3 equiv.) and DABCO (1.77 g, 15.78 mmol, 3 equiv.). The solution was stirred for 36 h at room temperature. The solution was diluted with CH₂Cl₂,

washed with an aqueous solution of HCl (0.5 N), an aqueous saturated solution of NaHCO₃ and brine. The organic layer was dried over MgSO₄, filtered and evaporated under *vacuum*. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc 60/40 to 0/100) to give **5**.

Yield 72%; White solid; mp 86-87°C (cyclohexane); $[\alpha]_D^{25}$ -15.2 (*c* 0.1, CH₃OH); IR (KBr); ν 3337, 2988, 2901, 2091, 1489, 1447, 1395, 1250 cm⁻¹; ¹H NMR (400 MHz, CD₃OD): δ 1.53-1.62 (m, 1H, H-3a), 1.76-1.86 (m, 1H, H-2a), 1.93-2.10 (m, 2H, H-2b and H-3b), 3.13 (app t, 1H, $J_{5,4} = J_{5,6} = 9.0$ Hz, H-5), 3.22-3.28 (m, 2H, H-9a and H-4), 3.31-3.37 (m, 2H, H-8 and H-6), 3.38-3.46 (m, 4H, H-1, H-9b and H-7), 7.23 (bt, 3H, $J = 7.5$ Hz, H_{Ar}), 7.30 (bt, 6H, $J = 7.5$ Hz, H_{Ar}), 7.51 (bd, 6H, $J = 7.5$ Hz, H_{Ar}); ¹³C NMR (100.6 MHz, CD₃OD): δ 26.4 (C-2), 30.1 (C-3), 52.6 (C-1), 65.2 (C-9), 72.3 (C-8), 75.5 (C-5), 80.0 (C-6), 80.3 (C-4), 80.6 (C-7), 87.6 (C_{Tr}), 127.9 (3C_{Ar}), 128.7 (6C_{Ar}), 129.9 (6C_{Ar}), 145.6 (3C_{qAr}); HRMS (ESI): calcd for C₂₈H₃₁N₃NaO₅ [M+Na]⁺: 512.2161, found: 512.2194.

4.2.4. 4,8-anhydro-1-azido-1,2,3-trideoxy-7,9-*O*-phenylmethylene-D-glycero-D-gulonitol (**6**)

To a solution of **4** (500 mg, 2.03 mmol) in acetonitrile (4 mL), was added at room temperature, benzaldehyde dimethyl acetal (395 μ L, 2.63 mmol, 1.3 equiv.) and I₂ (50 mg, 0.2 mmol, 0.1 equiv.) in a sealed tube. The solution was stirred for 13 h at 85°C. After evaporation under *vacuum*, the crude product was purified by column chromatography on silica gel (eluent: CH₂Cl₂/MeOH 100/0 to 80/20) to give **6**.

Yield: 70%; Colorless oil; $[\alpha]_D^{25}$ -19.5 (*c* 0.1, CHCl₃); IR (film); ν 3385, 2920, 2866, 2091, 1452, 1375, 1350 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.36-1.45 (m, 1H, H-3a), 1.55-1.66 (m, 1H, H-2a), 1.70-1.89 (m, 2H, H-3b, H-2b), 3.14-3.24 (m, 2H, H-4, H-5), 3.26 (t, 2H, $J_{1,2} = 7.0$ Hz, H-1), 3.27-3.35 (m, 1H, H-8), 3.37 (app t, 1H, $J_{6,7} = J_{6,5} = 9.0$ Hz, H-7), 3.57-3.66 (m, 3H, H-6, H-9a, OH), 4.00 (bs, 1H, OH), 4.26 (dd, 1H, $J_{9a,9b} = 10.0$ Hz, $J_{9b,8} = 4.5$ Hz, H-9b), 5.46 (s, 1H, H-10), 7.32-7.43 (m, 3H, H_{Ar}), 7.45-7.53 (m, 2H, H_{Ar}); ¹³C NMR (100.6 MHz, CDCl₃): δ 24.9 (C-2), 28.9 (C-3), 51.5 (C-1), 68.9 (C-9), 70.2 (C-8), 74.4 (C-5), 75.1 (C-6), 79.5 (C-4), 81.1 (C-7), 101.9 (C-10), 126.4 (2C_{Ar}), 128.4 (2C_{Ar}), 129.4 (C_{Ar}), 137.2 (C_{qAr}); HRMS (ESI): calcd for C₁₆H₂₂N₃O₅ [M+H]⁺: 336.1554, found: 336.1542.

4.2.5. Procedure for regioselective acetylation

To a solution of **5** (150 mg, 0.31 mmol) in chloroform (100 mL), was added, under argon at room temperature, K₂CO₃ (410 mg, 3.0 mmol, 9.6 equiv.), Ac₂O (33 μ L, 0.34 mmol, 1.1

equiv.) and 4-DMAP (1.89 mg, 0.016 mmol, 0.05 equiv.). The solution was stirred at room temperature for 13 h and was then diluted with water. The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated under *vacuum*. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc 90/10 to 50/50) to give **7**, **8** and **9**.

4.2.5.1. 6-acetate-4,8-anhydro-1-azido-1,2,3-trideoxy-9-O-triphenylmethyl-D-glycero-D-gulo-nonitol (**7**)

Yield: *vide supra*; Colorless oil; $[\alpha]_D^{25}$ -13.2 (*c* 0.1, MeOH); IR (film); ν 3370, 2922, 2853, 2091, 1738, 1651, 1595, 1489, 1449, 1371, 1225 cm⁻¹; ¹H NMR (400 MHz, CD₃OD): δ 1.54-1.63 (m, 1H, H-3a), 1.76-1.86 (m, 1H, H-2a), 1.91-2.09 (m, 2H, H-3b and H-2b), 2.12 (s, 3H, CH₃), 3.23 (dd, 1H, $J_{9a,9b}$ = 10.0 Hz, $J_{9a,8}$ = 5.5 Hz, H-9a), 3.26 (app t, 1H, $J_{5,6}$ = $J_{5,4}$ = 9.5 Hz, H-5), 3.33 (ddd, 1H, $J_{4,3a}$ = 7.5 Hz, $J_{4,3b}$ = 2.0 Hz, H-4), 3.40 (t, 2H, $J_{1,2}$ = 7.5 Hz, H-1), 3.41-3.45 (m, 1H, H-9b), 3.47 (ddd, 1H, $J_{8,7}$ = 9.5 Hz, $J_{8,9b}$ = 1.5 Hz, H-8), 3.52 (app t, 1H, $J_{7,6}$ = $J_{7,8}$ = 9.5 Hz, H-7), 4.90 (app t, 1H, H-6), 7.22 (t, 3H, J = 7.5 Hz, H_{Ar}), 7.28 (t, 6H, J = 7.5 Hz, H_{Ar}), 7.48-7.50 (m, 6H, H_{Ar}); ¹³C NMR (100.6 MHz, CD₃OD): δ 21.2 (CH₃), 26.3 (C-2), 30.0 (C-3), 52.6 (C-1), 64.8 (C-9), 70.4 (C-8), 73.7 (C-5), 80.3 (C-4), 80.5 (C-7), 81.2 (C-6), 87.6 (C_{qTr}), 128.0 (3C_{Ar}), 128.7 (6C_{Ar}), 129.9 (6C_{Ar}), 145.5 (3C_{qAr}), 172.9 (C=O); HRMS (ESI): calcd for C₃₀H₃₃N₃NaO₆ [M+Na]⁺: 554.2267, found: 554.2219.

4.2.6. Procedures for acylation

4.2.6.1. Protocol using PyBOP: To a solution of **5** (100 mg, 0.2 mmol) in CH₂Cl₂ (5 mL), was added dropwise under argon at room temperature 3-butenic acid (26 μ L, 0.3 mmol, 1.5 equiv.) and DIEA (105 μ L, 0.3 mmol, 3 equiv.). The solution was cooled at 0°C and PyBOP (188 mg, 0.36 mmol, 1.8 equiv.) was added dropwise. The solution was stirred for 48 h at room temperature, then an aqueous saturated solution of NH₄Cl was added. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and evaporated under *vacuum*. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc 90/10 to 50/50) to give **10**, **11** and **12**.

4.2.6.2. Protocol using IBCF: To a solution of 3-butenic acid (20 μ L, 0.24 mmol, 1.2 equiv.) in CH₂Cl₂ (5 mL) was added dropwise TEA (33 μ L, 0.24 mmol, 1.2 equiv.) under argon at 0°C, then IBCF (27 μ L, 0.24 mmol, 1.2 equiv.) was added and the solution was

stirred at 0°C for 1 h. A freshly prepared solution of **5** (100 mg, 0.2 mmol) and 4-DMAP (3 mg, 0.024 mmol, 0.12 equiv.) in CH₂Cl₂ (10 mL) was added dropwise under argon at 0°C. The solution was stirred at room temperature overnight. The organic layer was washed with an aqueous solution of NaHCO₃ (5%), an aqueous solution of citric acid (5%) and brine. The organic layer was dried over MgSO₄, filtered and evaporated under *vacuum*. The crude product was purified by column chromatography on silica gel previously neutralized with cyclohexane/Et₃N 95/5 (eluent: cyclohexane/EtOAc 90/10 to 60/40) to give **10**, **11** and **12**.

4.2.6.3. 4,8-anhydro-1-azido-6-[(2E)-2-butenate]-1,2,3-trideoxy-9-O-triphenylmethyl-D-glycero-D-gulo-nonitol (**10**)

Yield: *vide supra*; White solid; mp 70-71°C (cyclohexane); [α]_D²⁵ -11.3 (*c* 0.08, MeOH); IR (KBr); ν 3337, 2968, 2924, 2874, 2093, 1701, 1653, 1489, 1447, 1310, 1290 cm⁻¹; ¹H NMR (400 MHz, CD₃OD): δ 1.54-1.64 (m, 1H, H-3a), 1.79-1.86 (m, 1H, H-2a), 1.89 (dd, 3H, $J_{12,11}$ = 7.0 Hz, $J_{12,10}$ = 1.5 Hz, H-12), 1.94-2.09 (m, 2H, H-3b and H-2b), 3.23 (dd, 1H, $J_{9a,9b}$ = 10.0 Hz, $J_{9a,8}$ = 5.5 Hz, H-9a), 3.28 (app t, 1H, $J_{5,4}$ = $J_{5,6}$ = 9.5 Hz, H-5), 3.31-3.37 (m, 1H, H-4), 3.43 (t, 2H, $J_{1,2}$ = 7.0 Hz, H-1), 3.44-3.50 (m, 1H, H-8), 3.48 (dd, 1H, $J_{9b,8}$ = 1.5 Hz, H-9b), 3.52 (app t, 1H, $J_{7,6}$ = $J_{7,8}$ = 9.5 Hz, H-7), 4.95 (app t, 1H, H-6), 5.95 (dq, 1H, $J_{10,11}$ = 15.5 Hz, $J_{10,12}$ = 1.5 Hz, H-10), 7.03 (dq, 1H, $J_{11,12}$ = 7.0 Hz, H-11), 7.23 (bt, 3H, J = 7.5 Hz, H_{Ar}), 7.30 (bt, 6H, J = 7.5 Hz, H_{Ar}), 7.50 (bd, 6H, J = 7.5 Hz, H_{Ar}); ¹³C NMR (100.6 MHz, CD₃OD): δ 18.1 (C-12), 26.3 (C-2), 30.1 (C-3), 52.6 (C-1), 64.9 (C-9), 70.5 (C-8), 73.8 (C-5), 80.4 (C-4), 80.6 (C-7), 80.9 (C-6), 87.6 (C_{qTr}), 123.8 (C-10), 128.0 (3C_{Ar}), 128.7 (6C_{Ar}), 130.0 (6C_{Ar}), 145.5 (3C_{qAr}), 146.2 (C11), 168.2 (C=O); HRMS (ESI): calcd for C₃₂H₃₅N₃NaO₆ [M+Na]⁺: 580.2424, found: 580.2453.

4.2.6.4. Protocol using DCC: To a solution of **5** (100 mg, 0.2 mmol) in dichloromethane/acetonitrile mixture (1/1 v/v, 1 mL), was added dropwise under argon at room temperature 3-butenic acid (20 μ L, 0.24 mmol, 1.2 equiv.) and 4-DMAP (16 mg, 0.13 mmol, 0.65 equiv.). DCC (58 mg, 0.28 mmol, 1.4 equiv.) in CH₂Cl₂ (3 mL) was then added dropwise and the resulting solution was stirred for 24 h at room temperature. The solution was filtered and the organic layer was washed with water, an aqueous solution of HCl (1N) and water. The organic layer was further washed with a saturated aqueous solution of Na₂CO₃ and water. The organic layer was dried over MgSO₄, filtered and evaporated under *vacuum*. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc 90/10 to 50/50) to give **13**, **14** and **15**.

4.2.6.5 4,8-anhydro-1-azido-6-(3-butenate)-1,2,3-trideoxy-9-O-triphenylmethyl-D-glycero-D-gulo-nonitol (**13**)

Yield: *vide supra*; White solid; mp 47-48°C (cyclohexane); $[\alpha]_{\text{D}}^{25}$ -7.6 (*c* 0.18, MeOH); IR (KBr); ν 3401, 2970, 2922, 2093, 1699, 1651, 1489, 1447, 1373, 1290, 1242 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD): δ 1.55-1.66 (m, 1H, H-3a), 1.70-1.77 (m, 1H, H-2a), 1.83-1.92 (m, 1H, H-2b), 1.95-2.08 (m, 1H, H-3b), 3.21-3.26 (m, 3H, H-10 and H-9a), 3.27 (app t, 1H, $J_{5,4} = J_{5,6} = 9.0$ Hz, H-5), 3.31-3.36 (m, 1H, H-4), 3.44 (t, 2H, $J_{1,2} = 6.5$ Hz, H-1), 3.45-3.52 (m, 2H, H-9b and H-8), 3.52 (app t, 1H, $J_{7,6} = J_{7,8} = 9.5$ Hz, H-7), 4.93 (app t, 1H, $J_{6,5} = J_{6,7} = 9.0$ Hz, H-6), 5.17 (app dq, 1H, $J_{12a,11} = 10.0$ Hz, $J_{12a,12b} = J_{12a,10} = 1.5$ Hz, H-12a), 5.20 (app dq, 1H, $J_{12b,11} = 17.0$ Hz, $J_{12b,12a} = J_{12b,10} = 1.5$ Hz, H-12b), 5.94-6.04 (m, 1H, H-11), 7.24 (bt, 3H, $J = 7.0$ Hz, H_{Ar}), 7.31 (bt, 6H, $J = 7.0$ Hz, H_{Ar}), 7.51 (bd, 3H, $J = 7.0$ Hz, H_{Ar}); ^{13}C NMR (62.9 MHz, CD_3OD): δ 26.0 (C-2), 30.1 (C-3), 34.7 (C-10), 52.6 (C-1), 65.2 (C-9), 72.3 (C-8), 75.6 (C-5), 80.0 (C-7), 80.4 (C-4), 80.6 (C-6), 87.6 (C_{qTr}), 116.1 (C-12), 125.4 (C-11), 127.9 (3C_{Ar}), 128.6 (6C_{Ar}), 129.9 (6C_{Ar}), 145.6 (3C_{qAr}), 159.9 (C=O); HRMS (ESI): calcd for $\text{C}_{32}\text{H}_{35}\text{N}_3\text{NaO}_6$ $[\text{M}+\text{Na}]^+$: 580.2424, found: 580.2452.

4.2.7. Procedures for regioselective benzylation

4.2.7.1. Protocol A: To a solution of **6** (150 mg, 0.45 mmol) in CH_2Cl_2 (5 mL), was added dropwise, under argon at 0°C, Bu_4NHSO_4 (43 mg, 0.14 mmol, 0.3 equiv.) and benzyl bromide (52 μL , 0.54 mmol, 1.2 equiv.). Then, an aqueous solution of NaOH (80 mg in 0.65 mL of water) was added at room temperature. The solution was stirred for 35 h at 60°C. After evaporation under *vacuum*, the crude product was diluted in EtOAc. The organic layer was washed with an aqueous solution of HCl (1N), a saturated aqueous solution of Na_2CO_3 and water. The organic layer was dried over MgSO_4 , filtered and evaporated under *vacuum*. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc 95/5 to 50/50) to give **16**, **17** and **18**.

4.2.7.2. Protocol B: To a solution of **6** (150 mg, 0.45 mmol, 1 equiv.) in dry THF (15 mL) was added, under argon at 0°C, NaH in mineral oil (60%) (11 mg, 0.90 mmol, 2 equiv.). The formation of the disodium alcoholate was complete in 1 h at room temperature. Anhydrous copper(II) chloride (6 mg, 0.45 mmol, 1 equiv.) was added, affording a green solution. BnBr (215 μL , 1.8 mmol, 4.0 equiv.) was added and the reaction was refluxed for 24 h. The solution was cooled to room temperature, then water (6 mL) and a 50% aqueous NH_3 solution (6 mL)

were added to give a dark blue solution. The organic layer was separated and the aqueous layer extracted with EtOAc. The organic layer was dried over MgSO₄, filtered and evaporated under *vacuum*. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc 95/5 to 50/50) to give **16**, **17** and **18**.

4.2.7.3. Protocol C: To a solution of **6** (150 mg, 0.45 mmol) in dry acetonitrile (5 mL), was added under argon, Bu₂SnCl₂ (10 μL, 0.045 mmol, 0.1 equiv.), TBABr (14.5 mg, 0.045 mmol, 0.1 equiv.), K₂CO₃ (93 mg, 0.68 mmol, 1.5 equiv.) and BnBr (65 μL, 0.68 mmol, 1.2 equiv.). The solution was stirred for 72 h at 80 °C in a sealed tube. After evaporation under *vacuum*, the crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 95/5 to 50/50) to give **16**.

4.2.7.4. Protocol D: To a solution of **6** (150 mg, 0.45 mmol) in dry toluene (5 mL), was added under argon, dibutyltin oxide (130 mg, 0.68 mmol, 1.5 equiv.). The solution was stirred for 2 h at 110 °C with a Dean-Stark apparatus. After evaporation under *vacuum*, the product was diluted in 3 mL of dry DMF, then CsF (100 mg, 0.68 mmol, 1.5 equiv.) and benzyl bromide (95 μL, 1 mmol, 2.5 equiv.) were added under argon at room temperature. The solution was then stirred for 48 h at 90 °C. After evaporation under vacuum, the crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 95/5 to 50/50) to give **16**.

4.2.7.5. 4,8-anhydro-1-azido-6-O-benzyl-1,2,3-trideoxy-7,9-O-phenylmethylene-D-glycero-D-gulo-nonitol (16)

Yield: 33%; Gum; $[\alpha]_D^{25}$ -19.9 (*c* 0.1, CHCl₃); IR (film); ν 3443, 2922, 2868, 2091, 1497, 1452, 1368 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.48-1.57 (m, 1H, H-3a), 1.62-1.73 (m, 1H, H-2a), 1.77-1.87 (m, 1H, H-2b), 1.91-1.99 (m, 1H, H-3b), 3.29 (td, 2H, $J_{1,2} = 7.0$ Hz, $J_{1,3a} = 1.5$ Hz, H-1), 3.33-3.37 (m, 2H, H-4 and H-5), 3.45 (ddd, 1H, $J_{8,9a} = 10.0$ Hz, $J_{8,7} = 9.5$ Hz, $J_{8,9b} = 5.0$ Hz, H-8), 3.60 (app t, 1H, $J_{5,4} = J_{5,6} = 9.0$ Hz, H-6), 3.67 (app t, 1H, $J_{7,6} = J_{7,8} = 9.5$ Hz, H-7), 3.72 (app t, 1H, $J_{9a,9b} = J_{9a,8} = 10.0$ Hz, H-9a), 4.33 (dd, 1H, $J_{9b,9a} = 10.0$ Hz, $J_{9b,8} = 5.0$ Hz, H-9b), 4.71 (d, 1H, $J = 11.5$ Hz, CH₂Bn), 5.04 (d, 1H, $J = 11.5$ Hz, CH₂Bn), 5.58 (s, 1H, H-10), 7.35-7.40 (m, 8H, H_{Ar}), 7.49-7.52 (m, 2H, H_{Ar}); ¹³C NMR (100.6 MHz, CDCl₃): δ 25.0 (C-2), 29.2 (C-3), 51.6 (C-1), 69.1 (C-9), 70.6 (C-8), 73.7 (C-5), 74.7 (CH₂Bn), 79.6 (C-4), 82.4 (C-7 or C-6), 82.4 (C-6 or C-7), 101.3 (C-10), 126.1 (2C_{Ar}), 128.1 (C_{Ar}), 128.2

(2C_{Ar}), 128.4 (2C_{Ar}), 128.7 (2C_{Ar}), 129.1 (C_{Ar}), 137.5 (C_{qAr}), 138.4 (C_{qAr}); HRMS (ESI): calcd for C₂₃H₂₈N₃O₅ [M+H]⁺: 426.2023, found: 426.2018.

4.2.8. General procedure for regioselective alkylation with functionalized electrophiles

To a solution of **6** (150 mg, 0.4 mmol) in dry toluene (5 mL), was added under argon, dibutyltin oxide (130 mg, 0.68 mmol, 1.5 equiv.). The solution was stirred for 2 h at 110°C with a Dean-Stark apparatus. After evaporation under *vacuum*, the product was diluted in 3 mL of dry DMF, then CsF (100 mg, 0.68 mmol, 1.5 equiv.) and functionalized bromide (1 mmol, 2.5 equiv.) were added under argon at room temperature. The solution was then stirred for 48 h at 90°C (except for **19**, 50°C). After evaporation under *vacuum*, the crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 80/20 to 50/50).

4.2.8.1. 4,8-anhydro-1-azido-1,2,3-trideoxy-7,9-*O*-phenylmethylene-6-*O*-(2-propen-1-yl)-*D*-glycero-*D*-gulo-nonitol (**19**)

Yield: 53%; White solid; mp 50-52°C (diethyl ether); [α]_D²⁵ -27.6 (*c* 0.1, CHCl₃); IR (KBr); ν 3337, 2961, 2914, 2859, 2091, 1726, 1452, 1385, 1360, 1346 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.49-1.58 (m, 1H, H-3a), 1.64-1.74 (m, 1H, H-2b), 1.76-1.90 (m, 1H, H-2b), 1.94-2.02 (m, 1H, H-3b), 3.25 (td, 2H, $J_{1,2} = 7.0$ Hz, $J_{1,3a} = 1.5$ Hz, H-1), 3.33-3.38 (m, 2H, H-4 and H-5), 3.43 (ddd, 1H, $J_{8,9b} = 5.0$ Hz, $J_{8,7} = 9.0$ Hz, $J_{8,9a} = 10.0$ Hz, H-8), 3.52 (app t, 1H, $J_{6,7} = J_{6,5} = 9.0$ Hz, H-6), 3.59 (app t, 1H, $J_{7,8} = J_{7,6} = 9.0$ Hz, H-7), 3.70 (app t, 1H, $J_{9a,9b} = J_{9a,8} = 10.0$ Hz, H-9a), 4.20 (app ddt, 1H, $J_{11a,11b} = 12.5$ Hz, $J_{11a,12} = 6.5$ Hz, $J_{11a,13a} = J_{11a,13b} = 1.5$ Hz, H-11a), 4.31 (dd, 1H, $J_{9b,8} = 5.0$ Hz, H-9b), 4.50 (app ddt, 1H, $J_{11b,12} = 5.5$ Hz, $J_{11b,13a} = J_{11b,13b} = 1.5$ Hz, H-11b), 5.20 (b dddd, $J_{13a,12} = 10.5$ Hz, $J_{13a,13b} = 2.5$ Hz, H-13a), 5.29 (b dddd, $J_{13b,12} = 17.5$ Hz, H-13b), 5.54 (s, 1H, H-10), 5.90-6.00 (m, 1H, H-12), 7.35-7.40 (m, 8H, H_{Ar}), 7.46-7.50 (m, 2H, H_{Ar}); ¹³C NMR (100.6 MHz, CDCl₃): δ = 24.9 (C-2), 29.2 (C-3), 51.6 (C-1), 69.0 (C-9), 70.6 (C-8), 73.6 (C-11), 73.7 (C-5), 79.6 (C-4), 82.3 (C-7 or C-6), 82.3 (C-7 or C-6), 101.2 (C-10), 117.6 (C-13), 126.1 (2C_{Ar}), 128.4 (2C_{Ar}), 129.1 (C_{Ar}), 134.9 (C12), 137.5 (C_{qAr}); HRMS (ESI): calcd for C₁₉H₂₅NaN₃O₅ [M+Na]⁺: 398.1686, found: 398.1700.

4.2.8.2. 4,8-anhydro-1-azido-1,2,3-trideoxy-6-*O*-[2-(1,1-dimethylethoxy)-2-oxoethyl]-7,9-*O*-phenylmethylene-*D*-glycero-*D*-gulo-nonitol (**20**)

Yield: 32%; Colorless oil; $[\alpha]_D^{25}$ -39.5 (*c* 0.1; CHCl₃); IR (film); ν 3410, 2926, 2870, 2093, 1751, 1452, 1379 cm⁻¹; ¹H NMR (200 MHz, (CD₃)₂CO): δ 1.43 (s, 9H, 3CH₃), 1.52-1.65 (m, 1H, H-3a), 1.66-1.94 (m, 3H, H-2a, H-2b and H-3b), 2.82 (bs, 1H, OH), 3.42 (t, 2H, $J_{1,2}$ = 6.5 Hz, H-1), 3.53-3.63 (m, 1H, H-8), 3.65-3.85 (m, 3H, H-4, H-7 and H-9a), 3.97 (app t, 1H, $J_{5,4}$ = $J_{5,6}$ = 9.0 Hz, H-5), 4.17 (app t, 1H, $J_{6,7}$ = $J_{6,5}$ = 9.0 Hz, H-6), 4.30 (dd, 1H, $J_{9b,9a}$ = 10.0 Hz, $J_{9b,8}$ = 4.5 Hz, H-9b), 4.41 (d, 1H, $J_{11a-11b}$ = 17.5 Hz, H-11a), 4.56 (d, 1H, H-11b), 5.67 (s, 1H, H-10), 7.35-7.41 (m, 3H, H_{Ar}), 7.44-7.52 (m, 2H, H_{Ar}); ¹³C NMR (50 MHz, (CD₃)₂CO): δ 25.2 (C-2), 28.6 (C-3 and 3C_{CH3}), 51.9 (C-1), 66.1 (C-11), 69.1 (C-9), 71.6 (C-8), 75.8 (C-5), 77.7 (C-4), 79.4 (C-7), 79.9 (C-6), 82.5 (C_qtBu), 102.1 (C-10), 127.2 (2C_{Ar}), 128.9 (2C_{Ar}), 129.7 (C_{Ar}), 138.7 (C_qAr), 166.4 (C=O); HRMS (ESI): calcd for C₂₂H₃₁NaN₃O₇ [M+Na]⁺: 472.2060, found: 472.2047.

4.2.8.3. 4,8-anhydro-1-azido-1,2,3-trideoxy-6-*O*-[3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)propyl]-7,9-*O*-phenylmethylene-D-glycero-D-gulo-nonitol (21)

Yield: 31%; White solid; mp 50-52°C (ethanol); $[\alpha]_D^{25}$ -58.7 (*c* 0.1, CHCl₃); IR (KBr); ν 3505, 2924, 2868, 2093, 1769, 1701, 1466, 1439, 1395, 1369 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.50-1.60 (m, 1H, H3a), 1.64-1.75 (m, 1H, H2a), 1.77-2.08 (m, 4H, H2b, H12 and H3b), 3.30 (td, 2H, $J_{1,2}$ = 7.5 Hz, $J_{1,3a}$ = 2.5 Hz, H1), 3.32-3.42 (m, 4H, H5, H8, H4 and H6), 3.47-3.54 (m, 1H, H11a), 3.54 (app t, 1H, $J_{7,6}$ = $J_{7,8}$ = 9.0 Hz, H7), 3.68 (app t, 1H, $J_{9a,9b}$ = $J_{9a,8}$ = 10.5 Hz, H9a), 3.74 (dt, 1H, $J_{13a,13b}$ = 14.0 Hz, $J_{13a,12}$ = 5.0 Hz, H13a), 3.98-4.08 (m, 2H, H11b and H13b), 4.29 (dd, 1H, $J_{9b,8}$ = 4.5 Hz, H9b), 5.52 (s, 1H, H10), 7.29-7.35 (m, 3H, H_{Ar}), 7.40-7.43 (m, 2H, H_{Ar}), 7.67-7.72 (m, 2H, H_{Ar}), 7.80-7.85 (m, 2H, H_{Ar}); ¹³C NMR (100.6 MHz, CDCl₃): δ 25.0 (C2), 29.1 (C12), 29.2 (C3), 34.6 (C13), 51.6 (C1), 68.7 (C11), 69.0 (C9), 70.5 (C8), 73.6 (C5), 79.9 (C4), 82.4 (C7), 83.0 (C6), 101.1 (C10), 123.4 (2C_{Ar}), 126.0 (2C_{Ar}), 128.3 (2C_{Ar}), 129.0 (C_{Ar}), 132.1 (2C_qAr), 134.2 (2C_{Ar}), 137.5 (C_qAr), 169.0 (C=O); HRMS (ESI): calcd for C₂₇H₃₁N₄O₇ [M+H]⁺: 523.2187, found: 523.2187.

4.2.8.4. 4,8-anhydro-1-azido-1,2,3-trideoxy-6-*O*-[3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)propyl]-5-*O*-methyl-7,9-*O*-phenylmethylene-D-glycero-D-gulo-nonitol (22)

To a solution of **21** (300 mg, 0.576 mmol) in DMF (6 mL), was added dropwise, under argon at 0°C, NaH (60% w/w) (60 mg, 1.04 mmol, 1.8 equiv.) and CH₃I (1.20 mL, 1.728 mmol, 30 equiv.). The solution was stirred for 1 h at room temperature, was then diluted with MeOH and evaporated *under vacuum*. The residue was diluted in EtOAc and washed with an aqueous saturated solution of NaHCO₃ and with water. The solution was dried over MgSO₄, filtered

and evaporated *under vacuum*. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc: 95/5 to 60/40) to give **22**.

Yield: 77%; White Gum; $[\alpha]_D^{25}$ -45.7 (*c* 0.1, CHCl₃); IR (film); ν 2924, 2866, 2093, 1769, 1703, 1466, 1449, 1391, 1368, 1342, 1312, 1260 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.44-1.51 (m, 1H, H-3a), 1.59-1.68 (m, 1H, H-2a), 1.73-1.90 (m, 2H, H-3b and H-2b), 1.94-2.03 (m, 2H, H-12), 2.78 (bt, 1H, $J_{5,4} = J_{5,6} = 9.5$ Hz, H-5), 3.23 (app td, 1H, $J_{4,5} = J_{4,3a} = 9.5$ Hz, $J_{4,3b} = 2.0$ Hz, H-4), 3.29 (t, 2H, $J_{1,2} = 7.0$ Hz, H-1), 3.29-3.34 (m, 1H, H-8), 3.44-3.50 (m, 2H, H-6 and H-7), 3.57 (s, 3H, CH₃), 3.65 (app t, 1H, $J_{9a,9b} = J_{9a,8} = 10.0$ Hz, H-9a), 3.72 (ddd, 1H, $J_{11a,11b} = 12.0$ Hz, $J_{11a,12a} = 9.5$ Hz, $J_{11a,12b} = 5.5$ Hz, H-11a), 3.79-3.86 (m, 2H, H-13), 4.02 (ddd, 1H, $J_{11b,12a} = 7.0$ Hz, $J_{11b,12b} = 5.5$ Hz, H-11b), 4.28 (dd, 1H, $J_{9b,8} = 4.5$ Hz, H-9b), 5.53 (s, 1H, H-10), 7.28-7.33 (m, 3H, H_{Ar}), 7.41-7.45 (m, 2H, H_{Ar}), 7.64-7.69 (m, 2H, H_{Ar}), 7.76-7.80 (m, 2H, H_{Ar}); ¹³C NMR (100.6 MHz, CDCl₃): δ 25.3 (C-2), 29.2 (C-3 or C-12), 29.4 (C-12 or C-3), 35.8 (C-13), 51.6 (C-1), 61.5 (C_{CH3}), 69.1 (C-9), 70.2 (C-8), 70.3 (C-11), 79.5 (C-4), 82.5 (C-6 or C-7), 83.6 (C-5 and C-6 or C-7), 101.0 (C-10), 123.2 (2 C_{Ar}), 126.0 (2 C_{Ar}), 128.3 (2 C_{Ar}), 128.9 (C_{qAr}), 132.4 (2 C_{qAr}), 133.9 (2 C_{Ar}), 137.6 (C_{qAr}), 168.5 (2 C=O); HRMS (ESI): calcd for C₂₈H₃₂N₄NaO₇ [M+H]⁺: 559.2169, found: 559.2215.

4.2.9. Regioselective reduction of 4,6-*O*-benzylidene acetals of **22**

To a solution of **22** (50 mg, 0.093 mmol) in dry CH₂Cl₂ (1 mL), was added dropwise, under argon at room temperature, BH₃.THF (1M) (95 μ L, 0.93 mmol, 10 equiv.) and TMSOTf (5 μ L, 0.028 mmol, 0.3 equiv.). The solution was stirred for 30 minutes at room temperature, then 0.1 mL of Et₃N was added followed by careful addition of MeOH (1 mL). The solution was concentrated and the crude product was co-evaporated with MeOH. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc: 90/10 to 40/60) to give **23** and **24**.

4.2.9.1. 4,8-anhydro-1-azido-7-*O*-benzyl-1,2,3-trideoxy-6-*O*-[3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)propyl]-5-*O*-methyl-7,9-*O*-phenylmethylene-*D*-glycero-*D*-gulo-nonitol (**23**)

Yield: 41%; White Gum; $[\alpha]_D^{25}$ -9.9 (*c* 0.1, CHCl₃); IR (film); ν 3364, 2914, 2870, 2091, 1767, 1703, 1464, 1449, 1402, 1373, 1261 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.42-1.52 (m, 1H, H-3a), 1.60-1.70 (m, 1H, H-2a), 1.76-1.91 (m, 2H, H-3b and H-2b), 2.01 (app qt, 2H, $J_{12,11} = J_{12,13} = 7.0$ Hz, H-12), 2.79 (app t, 1H, $J_{5,4} = J_{5,6} = 9.5$ Hz, H-5), 3.14 (app td, 1H, $J_{4,5} = J_{4,3a} = 9.5$ Hz, $J_{4,3b} = 2.0$ Hz, H-4), 3.19-3.24 (m, 1H, H-8), 3.30 (t, 2H, $J_{1,2} = 6.5$ Hz, H-1),

3.33-3.37 (m, 2H, H-6 and H-7), 3.56 (s, 3H, CH₃), 3.61 (dd, 1H, $J_{9a,9b} = 12.0$ Hz, $J_{9a,8} = 4.5$ Hz, H-9a), 3.76-3.83 (m, 3H, H-13 and H-9b), 3.89 (bt, 2H, H-11), 4.61 (d, 1H, $J_{CH_2} = 11.0$ Hz, $\frac{1}{2}CH_2$), 4.82 (d, 1H, $\frac{1}{2}CH_2$), 7.23-7.29 (m, 1H, H_{Ar}), 7.29-7.33 (m, 4H, H_{Ar}), 7.69-7.73 (m, 2H, H_{Ar}), 7.81-7.86 (m, 2H, H_{Ar}); ¹³C NMR (100.6 MHz, CDCl₃): δ 25.3 (C-2), 29.1 (C-3), 29.8 (C-12), 35.9 (C-13), 51.6 (C-1), 61.1 (C_{CH3}), 62.4 (C-9), 71.1 (C-11), 75.0 (C_{CH2Bn}), 78.2 (C-6), 78.8 (C-4), 79.0 (C-8), 84.4 (C-5), 87.2 (C-7), 123.3 (2C_{Ar}), 128.0 (C_{Ar}), 128.1 (2C_{Ar}), 128.6 (2C_{Ar}), 132.3 (2C_{qAr}), 134.1 (2C_{Ar}), 138.2 (C_{qAr}), 168.5 (2C=O); HRMS (ESI): calcd for C₂₈H₃₄N₄NaO₇ [M+Na]⁺: 561.2320, found: 561.2341.

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