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Florian Rouzier, Rosanne Sillé, Ophélie Montiège, Arnaud Tessier, Muriel Pipelier, et al.. Synthesis of Constrained C-Glycosyl Amino Acid Derivatives Involving 1,3-Dipolar Cycloaddition of Cyclic Nitron as Key Step. *European Journal of Organic Chemistry*, 2020, 2020 (43), pp.6673-6813. 10.1002/ejoc.202001162 . hal-03085851

**HAL Id: hal-03085851**

**<https://hal.science/hal-03085851>**

Submitted on 23 Dec 2020

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## Glycoconjugates

# Synthesis of Constrained C-Glycosyl Amino Acid Derivatives Involving 1,3-Dipolar Cycloaddition of Cyclic Nitron as Key Step

Florian Rouzier,<sup>[a]</sup> Rosanne Sillé,<sup>[a]</sup> Ophélie Montiège,<sup>[a]</sup> Arnaud Tessier,<sup>[b]</sup> Muriel Pipelier,<sup>[b]</sup> Gilles Dujardin,<sup>[a]</sup> Arnaud Martel,<sup>[a]</sup> Arnaud Nourry,<sup>\*[a]</sup> and Stéphane Guillarme<sup>\*[a]</sup>

**Abstract:** An efficient two-step strategy for the synthesis of constrained C-glycosyl amino acid derivatives from C-vinylglycosides involving a 1,3-dipolar cycloaddition using  $\iota$ -(-)-menthone-derived nitron as the key step is described. After optimization of 1,3-dipolar cycloaddition conditions, various C-vinylglycosides were tested leading exclusively to one dia-

stereoisomer of the corresponding cycloadduct in good to excellent yields. The total facial selectivity observed was also studied by DFT calculations. Original conformationally restricted C-glycosyl amino acid derivatives (8 examples) were isolated after simple cleavage of the chiral auxiliary.

## Introduction

Glycoconjugates such as glycoproteins and glycolipids are fundamental for many important biological processes including cell-cell, bacterium-cell, and virus-cell recognition, inflammation, signal transduction, fertilization, immune defense and they are major components of the outer surface of mammalian cells.<sup>[1]</sup> In glycoproteins, the carbohydrate part is generally covalently linked to the protein backbone through an oxygen atom (serine, threonine, tyrosine) or a nitrogen atom (asparagine). A glycosyl amino acid known as T<sub>N</sub> antigen ( $\alpha$ -D-GalNAc linked to Ser/Thr) has particularly attracted a great deal of interest since this antigen has been identified as tumor-associated carbohydrate antigens (TACA) which are highly expressed on tumor cells.<sup>[2]</sup> The incorporation of such a structure in an anti-cancer vaccine in order to stimulate the immune system to fight tumor cells became a therapeutic strategy. However, the main drawback of such carbohydrate-derived molecules is their low metabolic or chemical stability due to the hydrolytic lability of the glycosidic bond limiting their use as potential drug candidates.

It is now well established that the replacement of the anomeric oxygen (or nitrogen) atom of the glycosidic bond by a methylene group provide C-glycoside analogs as stable mim-

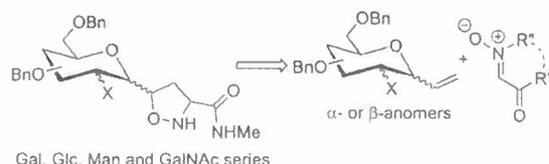
ics.<sup>[3]</sup> In that context, numerous research groups have focused their attention on the development of new methodologies to prepare C-glycosyl amino acids. These methods have already been reviewed<sup>[4]</sup> and most of them were focused on C-glycosyl serine. The latter can be synthesized involving, as a key step, SmI<sub>2</sub>-promoted C-glycosylation,<sup>[5]</sup> nucleophilic addition on carbohydrate derivative,<sup>[6]</sup> metathesis reaction,<sup>[7]</sup> Suzuki coupling<sup>[8]</sup> and Wittig-Horner<sup>[9]</sup> or Ramberg-Bäcklund<sup>[10]</sup> olefination. Construction of the amino acid moiety on a C-glycoside derivative has also been performed.<sup>[11]</sup> In the case of C-glycosyl threonine,<sup>[8,12]</sup> and C-glycosyl tyrosine,<sup>[8,13]</sup> only a few syntheses have been described.

In addition, the recognition of glycoproteins by the biological target is related to the presentation mode of the glycan part. In order to modulate the glycan presentation, the syntheses of constrained glycosyl amino acids have been reported. For example, Halcomb et al. prepared a conformationally constrained T<sub>N</sub> antigen by incorporating the side chain into a small ring<sup>[14]</sup> or the C $\alpha$  of the amino acid in a six-membered ring.<sup>[15]</sup> Dondoni et al. focused particularly on the synthesis of C-glycosyl amino acids with the amino acid side chains linked to the carbohydrate moiety via linkers such as triazole or isoxazole,<sup>[16]</sup> pyridine,<sup>[17]</sup> and tetrazole.<sup>[18]</sup> Avenozza and Peregrina demonstrated that their conformationally restricted T<sub>N</sub> antigen analogs were recognized by the SBL lectin (GalNAc specific lectin).<sup>[19]</sup> In addition, Nativi and Renaudet reported the first anti-cancer vaccine containing structurally constrained T<sub>N</sub> antigen analog which presented a robust and longlasting T<sub>N</sub>-specific antibodies response through a mechanism mediated by B cells leading to improved protection against cancer in mice.<sup>[20]</sup> Herein, we describe the synthesis of original constrained C-glycosyl amino acid derivatives in different series involving a 1,3-dipolar cycloaddition between a nitron<sup>[21]</sup> and C-vinylglycoside as key step (Scheme 1).

[a] Dr. F. Rouzier, R. Sillé, O. Montiège, Dr. G. Dujardin, Prof. Dr. A. Martel, Dr. A. Nourry, Dr. S. Guillarme  
Institut des Molécules et Matériaux du Mans, Le Mans Université and CNRS UMR 6283,  
Avenue O. Messiaen, 72085 Le Mans cedex 9, France  
E-mail: stephane.guillarme@univ-lemans.fr  
arnaud.nourry@univ-lemans.fr

[b] Dr. A. Tessier, Dr. M. Pipelier  
CEISAM, Université de Nantes and CNRS UMR 6220,  
2, rue de la Houssinière, 44322 Nantes cedex 3, France

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <https://doi.org/10.1002/ejoc.202001162>.

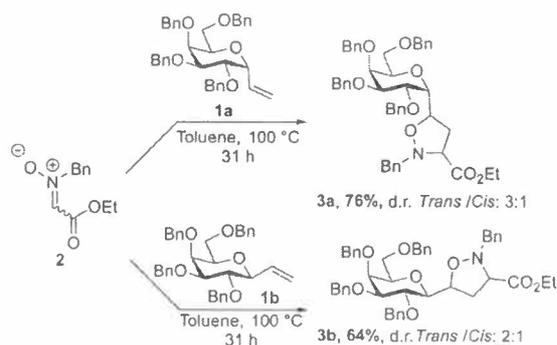


Scheme 1. General strategy for the synthesis of constrained C-glycosyl amino acid derivatives.

This kind of cycloaddition has already been performed between nitrones and carbohydrate-derived alkenes<sup>[22–24]</sup> as dipolarophiles but, to the best of our knowledge, the use of carbohydrate-containing a vinyl group in pseudo-anomeric position has not been described.<sup>[25]</sup>

## Results and Discussion

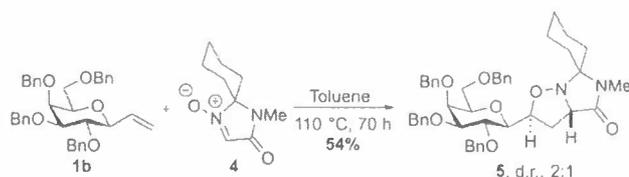
We recently reported an efficient synthesis of C-vinylglycoside in different series from the corresponding alkynes on gram scale.<sup>[26]</sup> The reactivity of such dipolarophiles towards the ethyl glyoxylate-derived nitronium **2** was first evaluated. The reaction between this nitronium and both  $\alpha$ - and  $\beta$ -anomers of C-vinylgalactoside **1a** and **1b** in toluene at 100 °C led to the expected adducts **3a** and **3b** as a mixture of isomers. Separation of isomers by chromatography on silica, although tough, led in both cases to two isolated diastereoisomers identified as a *trans* and a *cis* one, in a 3:1 ratio for the cycloadduct **3a** (76 % global yield) and in a 2:1 ratio for the cycloadduct **3b** (64 % global yield) (Scheme 2). This predominance of the *trans* adduct was confirmed by NOESY analyses of each isolated diastereoisomer in the two series (see Supporting Information). While *trans* diastereoisomers are undoubtedly formed via an *exo* approach (the less congested) to the *E* nitronium (the more reactive),<sup>[21]</sup> the *cis* diastereoisomers can result from either an *exo* approach to the *Z* nitronium or an *endo* approach to the *E* nitronium (or from both). In order to control the *cis/trans* selectivity, 1,3-dipolar cycloaddition was performed with the configurationally stable cyclic nitronium **4**.<sup>[28]</sup> The latter was prepared in three steps from methyl glycinate in 70 % overall yield (See supporting information).



Scheme 2. Reaction between nitronium **2** and C-vinylgalactoside **1a** and **1b**.

Heating of the cyclic nitronium with  $\beta$ -C-vinylgalactoside **1b** in toluene at 110 °C for 70 hours led to two cycloadducts **5** in 54 % yield in a 2:1 ratio (Scheme 3). The two compounds were

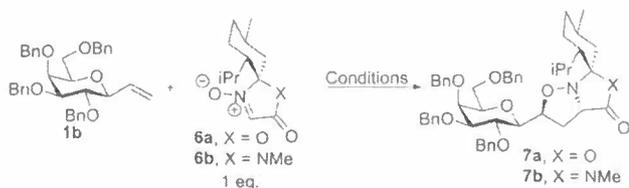
clearly identified as the two *trans* diastereoisomers from the NOESY spectra. The two *trans* isomers were derived from an *exo* approach but no facial discrimination was observed, showing that the chirality of the dipolarophile does not bring any selectivity.



Scheme 3. Reaction between nitronium **4** and C-vinylgalactoside **1b**.

To improve the facial selectivity, we focused our attention on chiral cyclic nitrones bearing a bulky group in order to mask one face of the dipole. The reactivity of the Katagiri's nitronium **6a**<sup>[29]</sup> with the  $\beta$ -C-vinylgalactoside **1b** was first evaluated. Whatever the activation mode (microwave or Lewis acid), the cycloaddition did not occur (Table 1, entries 1–2). Having in mind the reactivity of the chiral menthone-derived nitronium **6b** with C-, O-, and S-allyl glycosides reported by either Altenbach et al.<sup>[23]</sup> or Praly et al.,<sup>[30]</sup> we then performed the 1,3-dipolar cycloaddition with this dipole. The nitronium **6b** was prepared in two steps from L-menthone in a 27 % overall yield. As a first attempt, the procedure described by Altenbach et al.<sup>[23]</sup> i.e. heating of one equivalent of the nitronium **6b** with one equivalent of  $\beta$ -C-vinylgalactoside **1b** in toluene at reflux for 72 hours was reproduced, leading to the formation of only one diastereoisomer of cycloadduct **7b** in 36 % yield (entry 3). In our case, the reaction was incomplete after 72 hours. This can be explained by the use of a more hindered olefin compared with those involved by Altenbach. The NOESY analysis of the cycloadduct allowed clearly the identification of a *trans* diastereoisomer as a result of an *exo* approach.

Table 1. Optimization of the 1,3-dipolar cycloaddition of nitronium **6** with  $\beta$ -C-vinylgalactoside **1b**.



Entry	Nitronium	Conditions	Yield [%]
1	<b>6a</b>	CH <sub>3</sub> CN, 140 °C, $\mu$ -waves, 7 h	–
2	<b>6a</b>	BF <sub>3</sub> ·OEt <sub>2</sub> , CH <sub>3</sub> CN, 72 h, r.t.	–
3	<b>6b</b>	toluene, 110 °C, 0.1 M, 72 h	36
4	<b>6b</b>	<i>p</i> -xylene, 140 °C, 0.1 M, 30 h	27
5	<b>6b</b>	toluene, 140 °C, sealed tube, 0.1 M, 20 h	61
6	<b>6b</b>	toluene, 160 °C, sealed tube, 0.1 M, 16 h	66
7	<b>6b</b>	toluene, 180 °C, sealed tube, 0.1 M, 3 h	38
8	<b>6b</b>	toluene, 140 °C, $\mu$ -waves, 0.1 M, 7 h	69
9	<b>6b</b>	toluene, 160 °C, $\mu$ -waves, 0.1 M, 4 h	35
10	<b>6b</b>	toluene, 140 °C, $\mu$ -waves, 0.5 M, 2 h	75

Unfortunately, all attempts to obtain a crystalline structure of the unprotected cycloadduct,<sup>[31]</sup> in order to determine absolute configurations of the two new stereogenic centers, failed.

When the reaction was performed in *p*-xylene at 140 °C for 30 hours, increasing amounts of degradation products were observed and the same diastereoisomer was isolated in lower 27 % yield (entry 4). Reaction times could be reduced by heating the reaction mixture in a sealed tube at 140 °C or 160 °C and the yield was significantly improved to 66 % (entries 5–6). The same range of yield was observed when the reaction was performed at 140 °C under microwave activation but the reaction time was halved (entry 8). Whatever the activation mode, heating at a higher temperature has resulted in a drop in the yields (entries 7 and 9). Increase of the concentration of the reaction mixture (from 0.1 M to 0.5 M) allowed to isolate the cycloadduct in 75 % yield with only 2 hours of reaction time (entry 10). It is noteworthy that traces of nitrone **6b** were recovered along with the cycloadduct after purification since the two compounds had the same *R<sub>f</sub>*. Finally, the use of only 0.9 equivalent of nitrone **6b** under the optimal conditions (described in entry 10) furnished a pure cycloadduct without any trace of nitrone **6b** in 72 % yield.

The optimal conditions were then applied to different C-vinylglycosides. When the reaction was implemented for the  $\beta$ -anomers in glucose and mannose series, the corresponding cycloadducts **8** and **9** were isolated, after 2 hours of reaction, in excellent yields of 91 and 90 % respectively (Scheme 4). In the case of  $\alpha$ -anomers in galactose, glucose, and mannose series, a longer reaction time (6 hours) was required to complete the reaction and to access the corresponding cycloadducts **10–12** with good yields (Scheme 4). Both anomers of C-vinylgalactosamines were also subjected to the cycloaddition with nitrone **6b** leading to the cycloadduct **13** and **14** after 8 hours of reaction in 77 and 63 % yields respectively (Scheme 4). NOESY analyses of the cycloadducts showed that only one *trans* diastereoisomer was formed.

Among all cycloadducts, only cycloadduct **9** showed, on the <sup>1</sup>H NMR spectrum, three doublet signals at 0.78, 0.85, and 0.91 ppm as expected for the three corresponding CH<sub>3</sub> of the menthyl moiety. COSY NMR experiment allowed us to identify the two CH<sub>3</sub> of the isopropyl group which were located at 0.78 and 0.85 ppm (Figure 1). Furthermore, NOESY NMR spectrum highlighted a cross-peak between one CH<sub>3</sub> of the isopropyl group and H-3', thus indicating an *S* absolute configuration for the C-3' stereogenic center (Figure 1). As already mentioned, due to a *trans* relationship between H-1' and H-3', *S* absolute configuration could be assigned for the C-1' stereogenic center. This diastereoisomer could solely be obtained by an *exo* approach via the *Si* face of the nitrone. This total facial selectivity could be due to the strong discrimination imposed by the isopropyl group of the chiral auxiliary of the nitrone **6b**. The same stereoselectivity outcome was obtained compared to the one observed by Westerman<sup>[23]</sup> and Praly<sup>[30]</sup> groups with other dipolarophiles suggesting that the stereoselectivity is exclusively dependent on the stereochemistry of this nitrone.

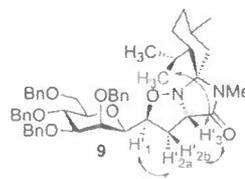
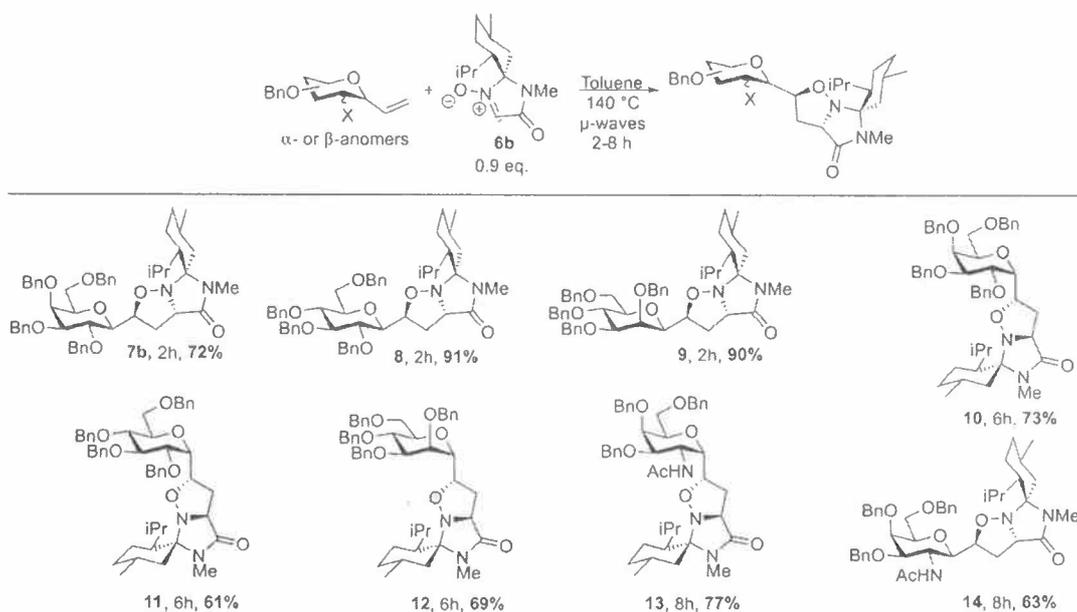


Figure 1. Main NOESY NMR cross-peaks of cycloadduct **9**.

In order to study the facial selectivity, DFT calculations were performed using Gaussian 09<sup>[32]</sup> at M06-2X/6-311+G(d,p) level.<sup>[33]</sup> The influence of the solvent (toluene) was studied using the SMD model.<sup>[34]</sup> With the aim of limiting the possible conformations and the calculation time, the study and the cal-

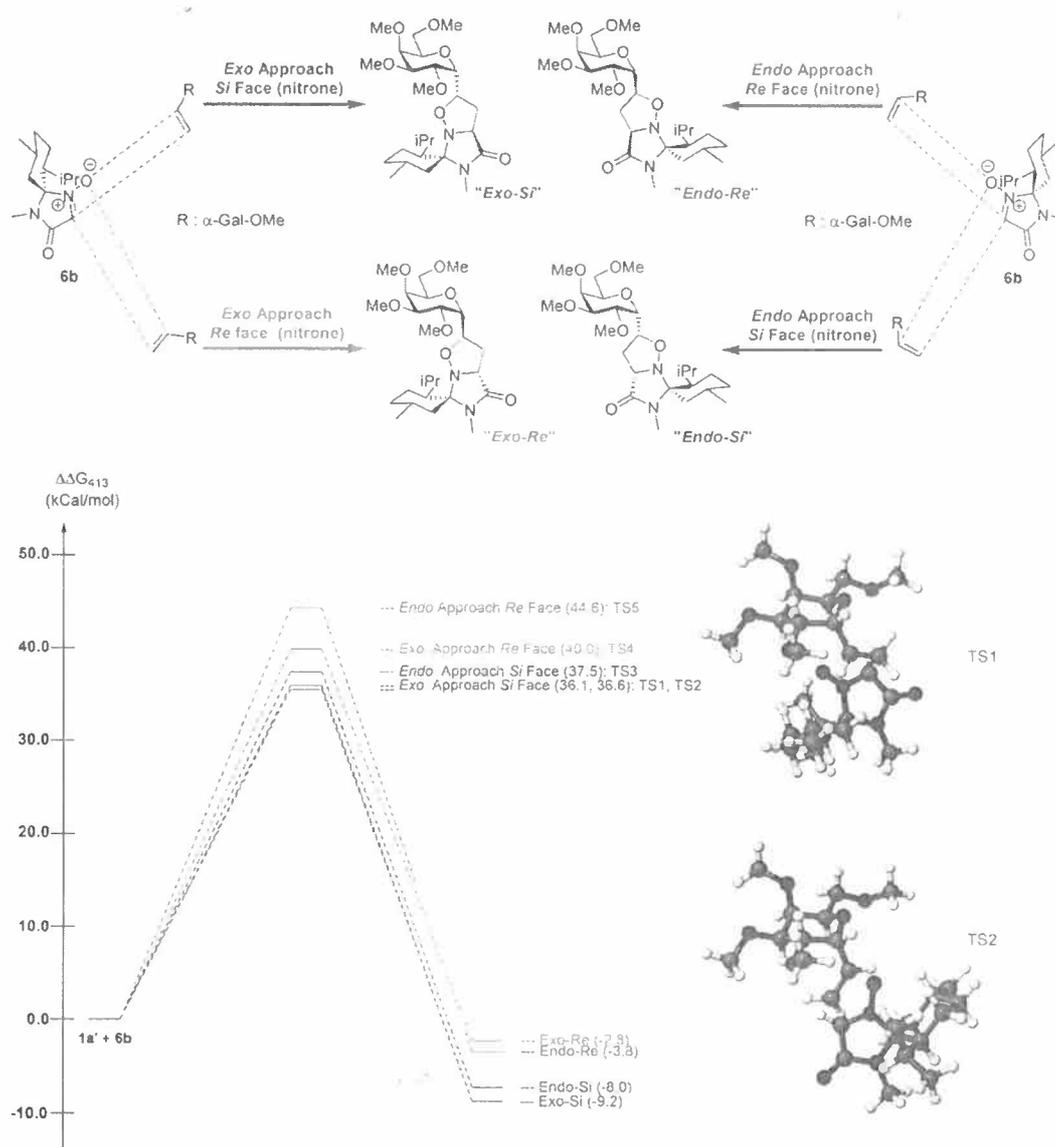


Scheme 4. 1,3-dipolar cycloaddition of nitrone **6b** with C-vinylglycosides in different series.

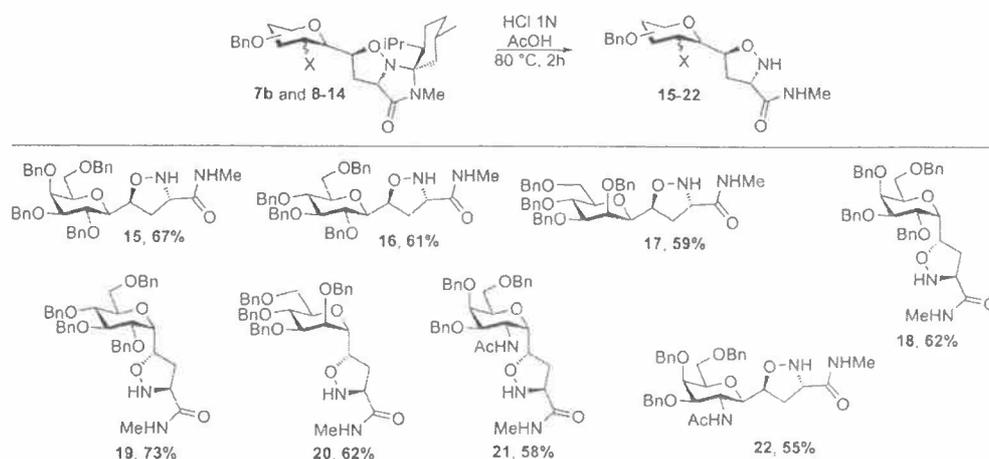
culations were carried out with the  $\alpha$ -C-vinylgalactoside for which the benzyl groups were replaced by methyl groups.<sup>[35]</sup> At the top of Scheme 5 are depicted the four cycloadducts that could be produced by the reaction of **1a'** and **6b** according to *exo/endo* approaches and *Si/Re* face of the nitron. The energy profile calculated for the four diastereoisomers (Scheme 5) describes the Gibbs free energy at 413K (reaction temperature, 140 °C). Five transition states were found during the study and the most favorable approach was the *exo* one from the *Si* face of the nitron (the less hindered). Indeed, the two lowest transition states observed for this approach (see Scheme 5) corresponded to a different orientation of the vinylic bond which benefits from a larger rotation degree than in the other three approaches. It is noteworthy that the contribution of the hindered face of the nitron can be considered as the major factor favoring the two approaches from the *Si* face of this nitron.

This total facial selectivity is therefore essentially due to the strong discrimination imposed by the isopropyl group of the chiral auxiliary of the nitron **6b**. These theoretical results are therefore in complete agreement with the experimental ones. Thus, taking into account that the stereoselectivity is only driven by the nitron, we assumed that all the cycloadducts (from all series) have been formed with the same stereoselectivity.

Finally, in order to complete our study, the cleavage of the chiral auxiliary was implemented on all cycloadducts. Treatment of cycloadduct **7b** with an aqueous hydrochloric acid solution in presence of acetic acid at 80 °C provided the constrained C-galactosyl amino acid derivative **15** in 67 % yield. The same procedure was applied to all the cycloadducts leading to the corresponding original constrained C-glycosyl amino acid derivatives **16–22** in moderate to good yields (Scheme 6).



Scheme 5. Different approaches of 1,3-dipolar cycloaddition of nitron **6b** with C-vinylgalactoside **1a'** and profiles of  $\Delta\Delta G_{\ddagger 13}$  (calculations performed at M06-2X/6-311+G(d,p) SMD (toluene) level).



Scheme 6. Access to constrained C-glycosyl amino acid derivatives.

## Conclusion

In summary, we described a two-step synthesis of original conformationally restricted C-glycosyl amino acid derivatives in different series involving 1,3-dipolar cycloaddition between L-(–)-menthone-derived nitron and C-vinylglycosides as key step. The 1,3-dipolar cycloaddition reaction was totally regio- and stereoselective leading to only one diastereoisomer in good to excellent yields whatever the dipolarophile. Based on both NMR experiments and DFT calculations, we showed that all the cycloadducts could solely be obtained by an *exo* approach via the *S<sub>i</sub>* face of the nitron with total facial discrimination. The cleavage of the chiral auxiliary allowed to access new constrained C-glycosyl amino acid- derivatives as interesting building blocks. Opening of the isoxazolidine ring and functionalization of the pseudo-anomeric position, offering the possibility to prepare different analogs of C-glycosyl serine, are currently ongoing.

## Experimental Section

All experiments were carried out under argon with anhydrous solvents in dried glassware. THF was dried with activated alumina on a dry station purchased from Innovative Technologies. Commercially available materials were used without further purification. Flash chromatography was performed on silica gel (40–63  $\mu\text{m}$  from Macherey-Nagel) using Reveleris X<sup>2</sup> Grace apparatus. Analytical TLCs were carried out on pre-coated silica gel 60 F254 from Macherey-Nagel. Optical rotations were measured using a Jasco P2000 at the sodium D line ( $\lambda = 589\text{ nm}$ ) with a 1-dm path length cell at 25  $^\circ\text{C}$ . Melting points were measured using Büchi B-545 apparatus. NMR spectra were recorded with a Bruker Avance 400. Chemical shifts are reported in ppm from TMS as the internal standard for the  $^1\text{H}$  NMR spectrum and from the residual peaks of the solvent ( $\text{CDCl}_3$ ) for  $^{13}\text{C}$  NMR spectrum. Structural assignments of the isolated compounds were based on  $^1\text{H}$ ,  $^{13}\text{C}$ , COSY, and HSQC NMR experiments (see Supporting Information for numbering of assignment). High-resolution mass spectroscopy was performed with a Bruker micro-TOF QIII mass spectrometer using ESI techniques.

**General Procedure for [3+2] Cycloaddition with Nitron 6b:** C-vinylglycoside (1 equiv.) and nitron (0.9 equiv.) were dissolved in toluene (3 mL, C = 0.5 M). The reaction mixture was stirred under

microwaves at 140  $^\circ\text{C}$  for 2–8 h then concentrated under reduced pressure.

**Cycloadduct (7b):** Following the general procedure (2 h),  $\beta$ -C-vinylgalactoside (304 mg, 0.553 mmol) afforded cycloadduct **7b** (273 mg, 0.35 mmol, 72 %) after purification by column chromatography (cyclohexane/EtOAc, 95:5 to 87:13). Colorless oil.  $R_f = 0.27$  (cyclohexane/EtOAc, 8:2).  $[\alpha]_D^{25} + 28.8$  (c 1.02,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>): Calculated for  $\text{C}_{49}\text{H}_{61}\text{N}_2\text{O}_7$  [ $\text{M} + \text{H}$ ]<sup>+</sup>:  $m/z = 789.4473$ , found 789.4442.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37–7.21 (m, 20H, ArH), 4.95 and 4.58 (AB syst,  $J = 11.3\text{ Hz}$ , 2H,  $\text{CH}_2\text{Ph}$ ), 4.92 and 4.53 (AB syst,  $J = 10.8\text{ Hz}$ , 2H,  $\text{CH}_2\text{Ph}$ ), 4.75 and 4.65 (AB syst,  $J = 11.7\text{ Hz}$ , 2H,  $\text{CH}_2\text{Ph}$ ), 4.47–4.40 (m, 2H,  $\text{CH}_2\text{Ph}$ ), 4.08–4.03 (m, 1H, H-1'), 4.01 (d,  $J = 2.5\text{ Hz}$ , 1H, H-4), 3.92 (d,  $J = 8.7\text{ Hz}$ , 1H, H-3'), 3.69 (d,  $J = 9.3\text{ Hz}$ , 1H, H-2), 3.63–3.50 (m, 5H, H-1, H-3, H-5, H-6), 2.70 (s, 3H,  $\text{NCH}_3$ ), 2.69–2.62 (m, 1H, H-2'), 2.45–2.39 (m, 1H, H-2'), 2.08–1.99 (m, 1H), 1.94–1.88 (m, 1H), 1.79–1.65 (m, 2H), 1.58–1.50 (m, 1H), 1.48–1.34 (m, 1H), 1.32–1.24 (m, 1H), 1.17 (t,  $J = 12.4\text{ Hz}$ , 1H), 0.86–0.78 (m, 10H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 173.3$  (C=O), 139.1 (C), 138.3 (C), 138.2 (C), 138.0 (C), 128.5 (3 CH), 128.2 (2 CH), 128.0 (CH), 127.8 (2 CH), 127.7 (CH), 127.6 (CH), 127.4 (2 CH), 89.7 (C), 84.9 (C3), 76.9 (C1 or C1'), 76.5 (C2 or C5), 76.4 (C2 or C5), 75.5 (CH<sub>2</sub>), 74.4 (CH<sub>2</sub>), 73.5 (CH<sub>2</sub>), 73.4 (C4), 72.1 (CH<sub>2</sub>), 68.2 (C6), 66.2 (C3'), 48.3 (CH), 40.5 (CH<sub>2</sub>), 34.8 (CH<sub>2</sub>), 32.6 (C2'), 29.4 (CH), 26.0 (CH<sub>3</sub>-N), 24.4 (CH), 24.2 (CH<sub>3</sub>), 22.4 (CH<sub>3</sub>), 22.2 (CH<sub>2</sub>), 18.4 (CH<sub>3</sub>).

**Cycloadduct (8):** Following the general procedure (2 h),  $\beta$ -C-vinylglucoside (373 mg, 0.68 mmol) afforded cycloadduct **8** (440 mg, 0.55 mmol, 91 %) after purification by column chromatography (cyclohexane/EtOAc, 95:5 to 87:13). Colorless oil.  $R_f = 0.28$  (cyclohexane/EtOAc, 8:2).  $[\alpha]_D^{25} + 31.1$  (c 0.99,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>): Calculated for  $\text{C}_{49}\text{H}_{61}\text{N}_2\text{O}_7$  [ $\text{M} + \text{H}$ ]<sup>+</sup>:  $m/z = 789.4473$ , found 789.4463.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.34–7.17 (m, 20H, ArH), 4.92 and 4.87 (AB syst,  $J = 10.9\text{ Hz}$ , 2H,  $\text{CH}_2\text{Ph}$ ), 4.87 and 4.56 (AB syst,  $J = 10.9\text{ Hz}$ , 2H,  $\text{CH}_2\text{Ph}$ ), 4.80 and 4.61 (AB syst,  $J = 10.8\text{ Hz}$ , 2H,  $\text{CH}_2\text{Ph}$ ), 4.60 and 4.52 (AB syst,  $J = 12.0\text{ Hz}$ , 2H,  $\text{CH}_2\text{Ph}$ ), 4.08–4.03 (m, 1H, H-1'), 3.94 (d,  $J = 8.5\text{ Hz}$ , 1H, H-3'), 3.76–3.63 (m, 4H, H-3, H-4, H-6), 3.57–3.52 (m, 1H, H-1), 3.44–3.39 (m, 1H, H-5), 3.39–3.33 (m, 1H, H-2), 2.71 (s, 3H,  $\text{NCH}_3$ ), 2.71–2.63 (m, 1H, H-2'), 2.48–2.42 (m, 1H, H-2'), 2.09–1.99 (m, 1H), 1.97–1.91 (m, 1H), 1.82–1.67 (m, 2H), 1.60–1.53 (m, 1H), 1.44–1.35 (m, 1H), 1.24–1.29 (m, 1H), 1.18 (t,  $J = 12.7\text{ Hz}$ , 1H), 0.93–0.79 (m, 10H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 173.3$  (C=O), 138.4 (C), 138.3 (C), 138.1 (C), 137.7 (C), 128.4 (2 CH), 128.3 (2 CH), 127.9 (3 CH), 127.7 (CH), 127.6 (3 CH), 127.5 (CH), 89.7 (C), 87.1 (C3 or C4), 79.6 (C2), 78.8 (C5), 78.1 (C3 or C4), 76.7 (C1 or C1'), 76.7 (C1 or C1'),

75.5 (CH<sub>2</sub>), 75.2 (CH<sub>2</sub>), 74.9 (CH<sub>2</sub>), 73.4 (CH<sub>2</sub>), 68.8 (C6), 66.0 (C3'), 48.2 (CH), 40.4 (CH<sub>2</sub>), 34.7 (CH<sub>2</sub>), 32.8 (C2'), 29.4 (CH), 25.9 (CH<sub>3</sub>-N), 24.4 (CH), 24.3 (CH<sub>3</sub>), 22.3 (CH<sub>3</sub>), 22.3 (CH<sub>2</sub>), 18.4 (CH<sub>3</sub>).

**Cycloadduct (9):** Following the general procedure (2 h),  $\beta$ -C-vinylmannoside (230 mg, 0.42 mmol) afforded cycloadduct **9** (253 mg, 0.32 mmol, 90 %) after purification by column chromatography (cyclohexane/EtOAc, 95:5 to 87:13). Colorless oil.  $R_f$  = 0.27 (cyclohexane/EtOAc, 8:2).  $[\alpha]_D^{25}$  + 19.5 (c 1.07, CHCl<sub>3</sub>). HRMS (ESI<sup>+</sup>): Calculated for C<sub>49</sub>H<sub>61</sub>N<sub>2</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z$  = 789.4473, found 789.4473. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.37–7.18 (m, 20H, ArH), 5.04 and 4.58 (AB syst,  $J$  = 11.4 Hz, 2H, CH<sub>2</sub>Ph), 4.86 and 4.56 (AB syst,  $J$  = 10.8 Hz, 2H, CH<sub>2</sub>Ph), 4.75 (s, 2H, CH<sub>2</sub>Ph), 4.61 and 4.52 (AB syst,  $J$  = 12.0 Hz, 2H, CH<sub>2</sub>Ph), 4.23–4.16 (m, 1H, H-1'), 4.00–3.97 (m, 1H, H-2), 3.94–3.88 (m, 2H, H-3', H-4), 3.77–3.65 (m, 2H, H-6), 3.60 (dd,  $J$  = 9.4, 2.7 Hz, 1H, H-3), 3.46–3.40 (m, 1H, H-5), 3.26 (dd,  $J$  = 8.6, 0.6 Hz, 1H, H-1), 2.83–2.76 (m, 1H, H-2'), 2.69 (s, 3H, N-CH<sub>3</sub>), 2.52–2.44 (m, 1H, H-2'), 2.09–2.03 (m, 1H), 2.00–1.90 (m, 1H), 1.88–1.80 (m, 1H), 1.68–1.59 (m, 2H), 1.48–1.40 (m, 1H), 1.38–1.33 (m, 1H), 1.18 (t,  $J$  = 12.3 Hz, 1H), 0.95–0.91 (m, 1H), 0.91 (d,  $J$  = 6.6 Hz, 3H, CH<sub>3</sub>), 0.85 (d,  $J$  = 6.6 Hz, 3H, CH<sub>3</sub>), 0.78 (d,  $J$  = 6.6 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  = 173.2 (C=O), 139.2 (C), 138.6 (2 C), 138.5 (C), 128.6 (CH), 128.4 (2 CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.8 (2 CH), 127.7 (CH), 127.6 (CH), 127.4 (2 CH), 88.7 (C), 84.5 (C3), 80.4 (C5), 79.2 (C1), 75.5 (C4), 75.3 (CH<sub>2</sub>), 75.3 (C2), 75.0 (CH<sub>2</sub>), 73.7 (CH<sub>2</sub>), 73.5 (C1'), 72.5 (CH<sub>2</sub>), 69.8 (C6), 65.6 (C3'), 48.2 (CH), 40.9 (CH<sub>2</sub>), 36.1 (C2'), 34.9 (CH<sub>2</sub>), 29.8 (CH), 26.0 (CH<sub>3</sub>-N), 24.5 (CH), 24.3 (CH<sub>3</sub>), 22.6 (CH<sub>2</sub>), 22.4 (CH<sub>3</sub>), 18.6 (CH<sub>3</sub>).

**Cycloadduct (10):** Following the general procedure (4 h),  $\alpha$ -C-vinylgalactoside (826 mg, 1.50 mmol) afforded cycloadduct **10** (790 mg, 1.00 mmol, 73 %) after purification by column chromatography (cyclohexane/EtOAc, 95:5 to 87:13). Colorless oil.  $R_f$  = 0.44 (cyclohexane/EtOAc, 6:4).  $[\alpha]_D^{25}$  + 42.3 (c 1.0, CHCl<sub>3</sub>). HRMS (ESI<sup>+</sup>): Calculated for C<sub>49</sub>H<sub>61</sub>N<sub>2</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z$  = 789.4473, found 789.4473. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.35–7.20 (m, 20H, ArH), 4.80 and 4.56 (AB syst,  $J$  = 11.7 Hz, 2H, CH<sub>2</sub>Ph), 4.72 and 4.65 (AB syst,  $J$  = 11.5 Hz, 2H, CH<sub>2</sub>Ph), 4.67 and 4.54 (AB syst,  $J$  = 11.5 Hz, 2H, CH<sub>2</sub>Ph), 4.54 and 4.43 (AB syst,  $J$  = 11.7, 2H, CH<sub>2</sub>Ph), 4.32–4.27 (m, 1H, H-5), 4.14–4.08 (m, 1H, H-1'), 4.07–3.91 (m, 5H, H-1, H-2, H-3, H-4, H-3'), 3.72–3.57 (m, 2H, H-6), 2.69 (s, 3H, N-CH<sub>3</sub>), 2.56–2.49 (m, 1H, H-2'), 2.49–2.39 (m, 1H, H-2'), 2.09–1.96 (m, 2H), 1.80–1.64 (m, 2H), 1.60–1.52 (m, 1H), 1.42–1.34 (m, 1H), 1.32–1.25 (m, 1H), 1.12 (t,  $J$  = 12.3 Hz, 1H), 0.92–0.79 (m, 10H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  = 172.8 (C=O), 138.6 (C), 138.5 (C), 138.2 (C), 138.0 (C), 128.3 (2 CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.6 (2 CH), 127.5 (CH), 127.4 (2 CH), 127.2 (CH), 89.9 (C), 76.7 (C1'), 76.0, 74.2, 74.1, 73.8, 73.8, 73.2, 72.9, 71.9, 68.5 (C6), 65.8 (C3'), 48.1 (CH), 40.0 (CH<sub>2</sub>), 34.8 (C2'), 34.6 (CH<sub>2</sub>), 29.6 (CH), 25.9 (CH<sub>3</sub>-N), 24.3 (CH), 24.1 (CH<sub>3</sub>), 22.3 (CH<sub>2</sub>), 22.1 (CH<sub>3</sub>), 18.3 (CH<sub>3</sub>).

**Cycloadduct (11):** Following the general procedure (4 h),  $\alpha$ -C-vinylglucoside (289 mg, 0.52 mmol) afforded cycloadduct **11** (228 mg, 0.28 mmol, 61 %) after purification by column chromatography (cyclohexane/EtOAc, 95:5 to 87:13). Colorless oil.  $R_f$  = 0.44 (cyclohexane/EtOAc, 6:4).  $[\alpha]_D^{25}$  + 48.4 (c 1.24, CHCl<sub>3</sub>). HRMS (ESI<sup>+</sup>): Calculated for C<sub>49</sub>H<sub>61</sub>N<sub>2</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z$  = 789.4473, found 789.4453. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.33–7.24 (m, 18H, ArH), 7.16–7.12 (m, 2H, ArH), 4.91 and 4.78 (AB syst,  $J$  = 10.8 Hz, 2H, CH<sub>2</sub>Ph), 4.81 and 4.49 (AB syst,  $J$  = 10.5 Hz, 2H, CH<sub>2</sub>Ph), 4.72 and 4.59 (AB syst,  $J$  = 11.6 Hz, 2H, CH<sub>2</sub>Ph), 4.61 and 4.47 (AB syst,  $J$  = 12.0 Hz, 2H, CH<sub>2</sub>Ph), 4.19–4.14 (m, 1H, H-1'), 4.11–4.06 (m, 1H, H-5), 3.98 (t,  $J$  = 9.2 Hz, 1H, H-3), 3.96–3.88 (m, 2H, H-1, H-3'), 3.83–3.78 (m, 1H, H-2), 3.67–3.64 (m, 2H, H-6), 3.61 (t,  $J$  = 9.2 Hz, 1H, H-4), 2.72 (s, 3H, N-CH<sub>3</sub>), 2.69–2.51 (m, 2H, H-2'), 2.16–2.01 (m, 2H), 1.80–1.67 (m, 2H), 1.59–1.50 (m,

1H), 1.43–1.35 (m, 1H), 1.33–1.25 (m, 1H), 1.15 (t,  $J$  = 12.3 Hz, 1H), 0.93–0.72 (m, 10H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  = 173.0 (C=O), 138.9 (C), 138.4 (C), 138.0 (C), 137.9 (C), 128.4 (2 CH), 128.3 (2 CH), 128.0 (CH), 127.9 (CH), 127.8 (2 CH), 127.6 (3 CH), 127.5 (CH), 89.9 (C), 83.7 (C3), 79.5 (C2), 78.1 (C4), 75.6 (CH<sub>2</sub>), 75.4 (C1'), 74.9 (CH<sub>2</sub>), 74.3 (C5), 74.0 (CH<sub>2</sub>), 73.5 (CH<sub>2</sub>), 72.9 (C1), 69.0 (C6), 66.0 (C3'), 48.2 (CH), 40.2 (CH<sub>2</sub>), 34.8 (C-2'), 34.6 (CH<sub>2</sub>), 29.3 (CH), 26.1 (CH<sub>3</sub>), 24.4 (CH), 24.1 (CH<sub>3</sub>), 22.5 (CH<sub>3</sub>), 22.1 (CH<sub>2</sub>), 18.3 (CH<sub>3</sub>).

**Cycloadduct (12):** Following the general procedure (4 h),  $\alpha$ -C-vinylmannoside (625 mg, 1.13 mmol) afforded cycloadduct **12** (561 mg, 0.71 mmol, 69 %) after purification by column chromatography (cyclohexane/EtOAc, 95:5 to 87:13). Colorless oil.  $R_f$  = 0.44 (cyclohexane/EtOAc, 6:4).  $[\alpha]_D^{25}$  + 39.5 (c 1.00, CHCl<sub>3</sub>). HRMS (ESI<sup>+</sup>): Calculated for C<sub>49</sub>H<sub>61</sub>N<sub>2</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z$  = 789.4473, found 789.4452. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.32–7.24 (m, 18H, ArH), 7.21–7.17 (m, 2H, ArH), 4.69–4.56 (m, 4H, CH<sub>2</sub>Ph), 4.55–4.49 (m, 4H, CH<sub>2</sub>Ph), 4.03–3.96 (m, 2H, H-1'), 3.94–3.87 (m, 3H, H-1, H-5, H-3'), 3.80–3.55 (m, 4H, H-2, H-3, H-6), 2.70 (s, 3H, N-CH<sub>3</sub>), 2.44–2.28 (m, 2H, H-2'), 2.15–2.05 (m, 1H), 1.95–1.88 (m, 1H), 1.80–1.66 (m, 2H), 1.58–1.51 (m, 1H), 1.41–1.24 (m, 2H), 1.19 (t,  $J$  = 12.4 Hz, 1H), 0.85–0.72 (m, 10H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  = 172.8 (C=O), 138.4 (C), 138.3 (C), 138.1 (C), 137.9 (C), 128.4 (2 CH), 128.3 (2 CH), 128.2 (CH), 127.8 (2 CH), 127.7 (3 CH), 127.6 (CH), 127.4 (CH), 89.6 (C), 77.9, 74.9, 74.8, 74.6, 74.3, 73.7, 73.4, 73.2, 72.4, 71.6, 69.2 (C6), 66.0 (C3'), 48.2 (CH), 40.6 (CH<sub>2</sub>), 34.6 (CH<sub>2</sub>), 29.3 (CH), 26.9 (CH), 26.1 (CH<sub>3</sub>-N), 24.3 (CH), 24.1 (CH<sub>3</sub>), 22.4 (CH<sub>3</sub>), 22.2 (CH<sub>3</sub>), 18.3 (CH<sub>3</sub>).

**Cycloadduct (13):** Following the general procedure (8 h),  $\alpha$ -C-vinyl-N-acetylgalactoside (565 mg, 1.13 mmol) afforded cycloadduct **13** (580 mg, 0.784 mmol, 77 %) after purification by column chromatography (cyclohexane/EtOAc, 5:5 to 2:8). White solid. M.p. 71.5–73 °C.  $R_f$  = 0.2 (cyclohexane/EtOAc, 3:7).  $[\alpha]_D^{25}$  + 22.6 (c 1.0, CHCl<sub>3</sub>). HRMS (ESI<sup>+</sup>): Calculated for C<sub>44</sub>H<sub>57</sub>N<sub>3</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z$  = 740.4269, found 740.4261. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.36–7.21 (m, 15H, ArH), 5.81 (d,  $J$  = 6.6 Hz, 1H, NH), 4.74 and 4.58 (AB syst,  $J$  = 11.8 Hz, 2H, CH<sub>2</sub>Ph), 4.57 and 4.51 (AB syst,  $J$  = 11.9 Hz, 2H, CH<sub>2</sub>Ph), 4.56 and 4.45 (AB syst,  $J$  = 11.9 Hz, 2H, CH<sub>2</sub>Ph), 4.35–4.30 (m, 1H, H-5), 4.21–4.13 (m, 2H, H-1, H-2), 4.05–3.98 (m, 2H, H-3, H-6), 3.93–3.89 (m, 1H, H-3'), 3.84–3.73 (m, 3H, H-1', H-4, H-6), 2.71 (s, 3H, N-CH<sub>3</sub>), 2.54–2.40 (m, 2H, H-2'), 2.01–1.88 (m, 2H), 1.90 (s, 3H, COCH<sub>3</sub>), 1.82–1.65 (m, 3H), 1.62–1.54 (m, 1H), 1.44–1.20 (m, 3H), 0.88–0.80 (m, 9H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  = 172.5 (C=O), 169.7 (C=O), 138.4 (C), 138.1 (C), 137.7 (C), 128.3 (3 CH), 127.7 (CH), 127.6 (3 CH), 127.5 (CH), 127.4 (CH), 89.9 (C), 77.6 (C1'), 75.5 (C5), 74.6 (C3), 73.1 (CH<sub>2</sub>), 72.8 (CH<sub>2</sub>), 71.9 (C4), 71.5 (CH<sub>2</sub>), 67.0 (C1), 66.1 (C6), 65.5 (C3'), 50.6 (C2), 48.1 (CH), 40.5 (CH<sub>2</sub>), 34.9 (C2'), 34.6 (CH<sub>2</sub>), 29.5 (CH), 26.0 (N-CH<sub>3</sub>), 24.3 (CH), 24.1 (CH<sub>3</sub>), 23.3 (COCH<sub>3</sub>), 22.6 (CH<sub>3</sub>), 22.1 (CH<sub>2</sub>), 18.3 (CH<sub>3</sub>).

**Cycloadduct (14):** Following the general procedure (8 h),  $\beta$ -C-vinyl-N-acetylgalactoside (462 mg, 0.921 mmol) afforded cycloadduct **14** (431 mg, 0.58 mmol, 63 %) after purification by column chromatography (cyclohexane/EtOAc, 5:5 to 3:7). Orange solid. M.p. 69.5–71.5 °C.  $R_f$  = 0.2 (cyclohexane/EtOAc, 3:7).  $[\alpha]_D^{25}$  + 40.1 (c 1.0, CHCl<sub>3</sub>). HRMS (ESI<sup>+</sup>): Calculated for C<sub>44</sub>H<sub>58</sub>N<sub>3</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z$  = 740.4269, found 740.4264. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.38–7.21 (m, 15H, ArH), 5.21 (d,  $J$  = 7.7 Hz, 1H, NH), 4.87 and 4.57 (AB syst,  $J$  = 11.6 Hz, 2H, CH<sub>2</sub>Ph), 4.66 and 4.41 (AB syst,  $J$  = 11.8 Hz, 2H, CH<sub>2</sub>Ph), 4.46 and 4.41 (AB syst,  $J$  = 11.8 Hz, 2H, CH<sub>2</sub>Ph), 4.01–3.97 (m, 1H, H-4), 3.95–3.84 (m, 3H, H-1', H-3', H-3), 3.84–3.75 (m, 1H, H-2), 3.73–3.67 (m, 1H, H-1), 3.57–3.52 (m, 3H, H-5, H-6), 2.68 (s, 3H, N-CH<sub>3</sub>), 2.71–2.64 (m, 1H, H-2'), 2.57–2.48 (m, 1H, H-2'), 1.98–1.89 (m, 2H), 1.86 (s, 3H, COCH<sub>3</sub>), 1.82–1.74 (m, 1H), 1.73–1.60 (m, 1H), 1.59–1.50 (m, 1H), 1.42–1.33 (m, 1H), 1.33–1.25 (m, 1H), 1.25–1.16 (m, 1H), 0.90–0.83

(m, 1H), 0.90 (d,  $J = 6.4$  Hz, 3H), 0.82 (d,  $J = 6.8$  Hz, 3H), 0.79 (d,  $J = 6.7$  Hz, 3H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 173.0$  (C=O), 170.3 (C=O), 138.6 (C), 138.0 (C), 137.9 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.0 (2 CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 89.3 (C), 79.4 (C1' or C3'), 78.1 (C1' or C3'), 77.2 (C1), 76.5 (C5), 74.3 (CH<sub>2</sub>), 73.5 (CH<sub>2</sub>), 72.3 (C4), 71.5 (CH<sub>2</sub>), 68.6 (C6), 65.5 (C3), 52.0 (C2), 48.2 (CH), 40.4 (CH<sub>2</sub>), 35.0 (C2'), 34.7 (CH<sub>2</sub>), 29.3 (CH), 26.0 (N-CH<sub>3</sub>), 24.4 (CH), 24.1 (CH<sub>3</sub>), 23.7 (COCH<sub>3</sub>), 22.6 (CH<sub>3</sub>), 22.2 (CH<sub>2</sub>), 18.4 (CH<sub>3</sub>).

**General Procedure for Cleavage of Chiral Auxiliary:** A solution of cycloadduct (**7b** and **8-14**) in AcOH (12.5 mL for 1 mmol) and aqueous 1 M HCl (2.5 mL for 1 mmol) was stirred at 80 °C for 2 h. The reaction mixture was diluted with EtOAc (30 mL) and a saturated aqueous NaHCO<sub>3</sub> solution (30 mL). Aqueous layer was extracted with EtOAc (30 mL) and organic layers were dried with MgSO<sub>4</sub>, and concentrated under reduced pressure to afford the crude product.

**N-Methyl-5-(2,3,4,6-tetra-O-benzyl- $\beta$ -D-galactopyranos-1-yl)-isoxazolidine-3-amide (15):** The crude product was purified by column chromatography (cyclohexane/EtOAc, 80:20 to 25:75) to provide compound **15** (218 mg, 0.33 mmol, 67 %). Colorless oil.  $R_f = 0.23$  (cyclohexane/EtOAc, 3:7).  $[\alpha]_D^{25} = -6.9$  (c 0.57,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>): Calculated for C<sub>39</sub>H<sub>45</sub>N<sub>2</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z = 653.3221$ , found 653.3210.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38–7.23 (m, 21H, ArH, NH), 6.10–6.08 (m, 1H, NH), 4.98–4.85 (m, 2H, CH<sub>2</sub>Ph), 4.78–4.62 (m, 2H, CH<sub>2</sub>Ph), 4.59–4.35 (m, 5H, CH<sub>2</sub>Ph, H-1'), 3.94–3.90 (m, 1H), 3.87–3.81 (m, 1H, H-3'), 3.65–3.54 (m, 4H), 3.51–3.40 (m, 2H), 2.79 (d,  $J = 4.9$  Hz, 3H, NCH<sub>3</sub>), 2.64–2.56 (m, 1H, H-2'), 2.42–2.34 (m, 1H, H-2').  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 172.5$  (C=O), 138.6 (C), 138.0 (C), 137.6 (2 C), 128.5 (CH), 128.4 (2 CH), 128.2 (2 CH), 128.0 (CH), 127.9 (2 CH), 127.8 (2 CH), 127.7 (CH), 127.4 (CH), 84.4, 82.3, 78.3, 76.3, 75.2 (CH<sub>2</sub>), 75.1, 74.4 (CH<sub>2</sub>), 73.4 (CH<sub>2</sub>), 72.2 (CH<sub>2</sub>), 68.8 (C6), 62.9 (C3'), 32.0 (C2'), 25.8 (CH<sub>3</sub>).

**N-Methyl-5-(2,3,4,6-tetra-O-benzyl- $\beta$ -D-glucopyranos-1-yl)-isoxazolidine-3-amide (16):** The crude product was purified by column chromatography (cyclohexane/EtOAc, 80:20 to 25:75) to provide compound **16** (94 mg, 0.14 mmol, 61 %). White solid. M.p. 156.5–158.1 °C.  $R_f = 0.23$  (cyclohexane/EtOAc, 3:7).  $[\alpha]_D^{25} = 3.2$  (c 0.95,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>): Calculated for C<sub>39</sub>H<sub>45</sub>N<sub>2</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z = 653.3221$ , found 653.3233.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.18 (m, 21H, NH, ArH), 6.17 (d,  $J = 5.0$  Hz, 1H, NH), 4.91 and 4.87 (AB syst.  $J = 10.9$  Hz, 2H, CH<sub>2</sub>Ph), 4.83 and 4.57 (AB syst.  $J = 11.0$  Hz, 2H, CH<sub>2</sub>Ph), 4.82 and 4.53 (AB syst.  $J = 10.8$  Hz, 2H, CH<sub>2</sub>Ph), 4.48 and 4.43 (AB syst.  $J = 12.1$  Hz, 2H, CH<sub>2</sub>Ph), 4.41–4.36 (m, 1H, H-1'), 3.85–3.79 (m, 1H, H-3'), 3.72–3.57 (m, 3H, H-1, H-3, H-6), 3.57–3.45 (m, 3H, H-4, H-5, H-6), 3.21 (t,  $J = 9.4$  Hz, 1H, H-2), 2.80 (d,  $J = 5.0$  Hz, 3H, N-CH<sub>3</sub>), 2.46–2.54 (m, 1H, H-2'), 2.32–2.40 (m, 1H, H-2').  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 172.4$  (C=O), 138.2 (C), 137.9 (2 C), 137.3 (C), 128.6 (CH), 128.5 (3 CH), 128.4 (CH), 128.2 (CH), 127.9 (2 CH), 127.8 (CH), 127.7 (2 CH), 127.6 (CH), 86.9 (C3), 82.0 (C1), 78.7 (C2), 78.3 (C4 or C5), 78.2 (C1'), 78.0 (C4 or C5), 75.5 (CH<sub>2</sub>), 75.1 (CH<sub>2</sub>), 75.0 (CH<sub>2</sub>), 73.2 (CH<sub>2</sub>), 69.1 (C6), 62.8 (C3'), 32.0 (C2'), 25.9 (CH<sub>3</sub>).

**N-Methyl-5-(2,3,4,6-tetra-O-benzyl- $\beta$ -D-mannopyranos-1-yl)-isoxazolidine-3-amide (17):** The crude product was purified by column chromatography (cyclohexane/EtOAc, 80:20 to 25:75) to provide compound **17** (210 mg, 0.32 mmol, 59 %). Colorless oil.  $R_f = 0.25$  (cyclohexane/EtOAc, 3:7).  $[\alpha]_D^{25} = 2.3$  (c 1.03,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>): Calculated for C<sub>39</sub>H<sub>45</sub>N<sub>2</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z = 653.3221$ , found 653.3232.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37–7.24 (m, 19H, ArH, NH), 7.22–7.18 (m, 2H, ArH), 6.09–5.86 (br s, 1H, NH), 4.93 and 4.63 (AB Syst.  $J = 11.3$  Hz, 2H, CH<sub>2</sub>Ph), 4.84 and 4.56 (AB syst.  $J = 10.8$  Hz, 2H, CH<sub>2</sub>Ph), 4.75 and 4.70 (AB syst.  $J = 11.8$  Hz, 2H, CH<sub>2</sub>Ph), 4.57 and 4.47 (AB syst.  $J = 12.0$  Hz, 2H, CH<sub>2</sub>Ph), 4.19–4.13 (m, 1H, H-1'),

3.92–3.90 (m, 1H, H-2), 3.86–3.81 (m, 2H, H-3', H-4), 3.72–3.67 (m, 1H, H-6), 3.65–3.56 (m, 2H, H-3, H-6), 3.50–3.45 (m, 1H, H-5), 3.43–3.40 (m, 1H, H-1), 2.92–2.84 (m, 1H, H-2'), 2.80 (d,  $J = 5.0$  Hz, 3H, N-CH<sub>3</sub>), 2.70–2.62 (m, 1H, H-2').  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 172.2$  (C=O), 138.1 (4 C), 128.4 (CH), 128.3 (3 CH), 128.2 (CH), 128.0 (2 CH), 127.7 (2 CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 84.5 (C3), 80.2 (C1), 79.5 (C1' and C5), 75.2 (CH<sub>2</sub>), 75.0 (C4), 74.4 (CH<sub>2</sub>), 74.4 (C2), 73.2 (CH<sub>2</sub>), 72.4 (CH<sub>2</sub>), 69.6 (C6), 62.6 (C3'), 34.8 (C2'), 25.8 (CH<sub>3</sub>).

**N-Methyl-5-(2,3,4,6-tetra-O-benzyl- $\alpha$ -D-galactopyranos-1-yl)-isoxazolidine-3-amide (18):** The crude product was purified by column chromatography (cyclohexane/EtOAc, 80:20 to 25:75) to provide compound **18** (809 mg, 1.24 mmol, 62 %). Colorless oil.  $R_f = 0.13$  (cyclohexane/EtOAc, 3:7).  $[\alpha]_D^{25} = +46.7$  (c 0.55,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>): Calculated for C<sub>39</sub>H<sub>44</sub>N<sub>2</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup>:  $m/z = 675.3041$ , found 675.3043.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.21 (m, 21H, ArH, NH), 4.73–4.46 (m, 8H, CH<sub>2</sub>Ph), 4.39–4.32 (m, 1H, H-1'), 4.31–4.25 (m, 1H, H-1), 4.02–3.96 (m, 1H), 3.91–3.64 (m, 5H), 3.61–3.50 (m, 1H, H-6), 2.80–2.74 (m, 3H, N-CH<sub>3</sub>), 2.70–2.60 (m, 1H, H-2'), 2.28–2.19 (m, 1H, H-2').  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.7 (C=O), 138.4 (C), 138.3 (C), 138.2 (C), 137.8 (C), 128.4 (3 CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.8 (2 CH), 127.7 (CH), 127.6 (2 CH), 127.5 (CH), 78.9 (C1'), 76.0 (CH), 74.7 (C1), 74.0 (CH), 73.3 (CH<sub>2</sub>), 73.2 (3 CH<sub>2</sub>), 72.9 (CH), 71.3 (CH), 68.0 (C6), 62.2 (C3'), 36.9 (C2'), 25.9 (CH<sub>3</sub>).

**N-Methyl-5-(2,3,4,6-tetra-O-benzyl- $\alpha$ -D-glucopyranos-1-yl)-isoxazolidine-3-amide (19):** The crude product was purified by column chromatography (cyclohexane/EtOAc, 80:20 to 25:75) to provide compound **19** (211 mg, 0.32 mmol, 73 %). Colorless oil.  $R_f = 0.13$  (cyclohexane/EtOAc, 3:7).  $[\alpha]_D^{25} = +34.2$  (c 1.04,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>): Calculated for C<sub>39</sub>H<sub>44</sub>N<sub>2</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup>:  $m/z = 675.3041$ , found 675.3041.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37–7.24 (m, 18H, ArH), 7.23–7.18 (m, 2H, ArH), 7.12 (br s, 1H, NH), 5.96 (br s, 1H, NH), 4.87 and 4.78 (AB syst.  $J = 10.8$  Hz, 2H, CH<sub>2</sub>Ph), 4.78 and 4.74 (AB syst.  $J = 11.8$  Hz, 2H, CH<sub>2</sub>Ph), 4.60 and 4.56 (AB syst.  $J = 12.0$  Hz, 2H, CH<sub>2</sub>Ph), 4.50–4.43 (m, 3H, CH<sub>2</sub>Ph, H-1'), 4.02–3.85 (m, 3H, H-2, H-4, H-3'), 3.81–3.75 (m, 2H, H-1, H-3), 3.68 (dd, 1H,  $J = 10.4$ , 2.3 Hz, H-6), 3.56 (dd, 1H,  $J = 10.4$ , 5.3 Hz, H-6), 3.55–3.51 (m, 1H, H-5), 3.43–3.40 (m, 1H, H-1), 2.80 (d,  $J = 5.0$  Hz, 3H, N-CH<sub>3</sub>), 2.79–2.70 (m, 1H, H-2'), 2.45–2.35 (m, 1H, H-2').  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.3 (C=O), 138.5 (C), 138.1 (C), 138.0 (C), 137.7 (C), 128.5 (CH), 128.4 (CH), 128.3 (2 CH), 128.0 (CH), 127.9 (CH), 127.8 (3 CH), 127.7 (2 CH), 127.6 (CH), 82.4 (C2), 78.8 (C1), 77.9 (C5), 76.5 (C1'), 75.1 (CH<sub>2</sub>), 74.7 (C4), 74.6 (CH<sub>2</sub>), 73.7 (CH<sub>2</sub>), 73.5 (CH<sub>2</sub>), 69.6 (C6), 62.2 (C3'), 36.9 (C2'), 26.0 (CH<sub>3</sub>).

**N-Methyl-5-(2,3,4,6-tetra-O-benzyl- $\alpha$ -D-mannopyranos-1-yl)-isoxazolidine-3-amide (20):** The crude product was purified by column chromatography (cyclohexane/AcOEt, 80:20 to 25:75) to provide compound **20** (297 mg, 0.45 mmol, 62 %). Colorless oil.  $R_f = 0.15$  (cyclohexane/EtOAc, 3:7).  $[\alpha]_D^{25} = +60.7$  (c 1.0,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>): Calculated for C<sub>39</sub>H<sub>45</sub>N<sub>2</sub>O<sub>7</sub> [M + H]<sup>+</sup>:  $m/z = 653.3221$ , found 653.3215.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.18 (m, 21H, NH, ArH), 7.637 (br s, 1H, NH), 4.58–4.42 (m, 7H, CH<sub>2</sub>Ph, H-1'), 4.40 and 4.34 (AB syst.  $J = 12.2$  Hz, 2H, CH<sub>2</sub>Ph), 4.13–4.08 (m, 1H, H-5), 4.03 (dd,  $J = 9.7$ , 2.8 Hz, 1H, H-3), 3.94–3.90 (m, 1H, H-3'), 3.82 (t,  $J = 2.8$  Hz, 1H, H-2), 3.77 (dd,  $J = 9.7$ , 0.8 Hz, 1H, H-4), 3.73 (dd, 1H,  $J = 10.1$ , 8.2 Hz, H-6), 3.55–3.49 (m, 2H, H-1, H-6), 2.84–2.77 (m, 1H, H-2'), 2.80 (d,  $J = 5.0$  Hz, 3H, N-CH<sub>3</sub>), 2.64–2.56 (m, 1H, H-2').  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ):  $\delta = 172.7$  (C=O), 137.9 (2 C), 137.8 (2 C), 128.4 (5 CH), 127.9 (3 CH), 127.8 (CH), 127.7 (2 CH), 127.5 (CH), 77.3 (C1'), 75.4 (C1), 74.9 (C5), 74.1 (C3), 73.6 (C2), 73.3 (CH<sub>2</sub>), 73.0 (C4), 72.8 (CH<sub>2</sub>), 72.3 (CH<sub>2</sub>), 71.4 (CH<sub>2</sub>), 68.3 (C6), 62.7 (C3'), 34.8 (C2'), 25.9 (CH<sub>3</sub>).

**N-Methyl-5-(2-acetamido-3,4,6-tri-O-benzyl- $\alpha$ -D-galactopyranos-1-yl)-isoxazolidine-3-amide (21):** The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 98:2 → 96:4) to provide compound **21** (268 mg, 0.444 mmol, 58 %). White solid. M.p. 73–6–75 °C. *R*<sub>f</sub> = 0.15 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5). [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 51.8 (c 0.75, CHCl<sub>3</sub>). HRMS (ESI<sup>+</sup>): Calculated for C<sub>34</sub>H<sub>42</sub>N<sub>3</sub>O<sub>7</sub> [M + H]<sup>+</sup>: *m/z* = 604.3017, found 604.2985. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.37–7.22 (m, 15H, ArH), 7.07 (br s, 1H, NHMe), 6.62 (br s, 1H, NHAc), 6.09 (br s, 1H, NH), 4.73 and 4.68 (AB syst. *J* = 11.8 Hz, 2H, CH<sub>2</sub>Ph), 4.55 and 4.47 (AB syst. *J* = 11.8 Hz, 2H, CH<sub>2</sub>Ph), 4.51 and 4.41 (AB syst. *J* = 12.0 Hz, 2H, CH<sub>2</sub>Ph), 4.32–4.26 (m, 1H, H-5), 4.19–4.16 (m, 1H, H-3), 4.15 (dd, *J* = 11.6, 1.9 Hz, 1H, H-6), 4.13–4.07 (m, 1H, H-1'), 4.02–3.88 (m, 3H, H-1, H-2, H-3'), 3.78 (dd, *J* = 6.5, 2.9 Hz, 1H, H-4), 3.69 (dd, *J* = 11.6, 2.1 Hz, 1H, H-6), 2.99–2.87 (m, 1H, H-2'), 2.80 (d, *J* = 5.0 Hz, 3H, CH<sub>3</sub>-N), 2.37 (ddd, *J* = 12.7, 9.2, 5.5 Hz, 1H, H-2'), 1.98 (s, 3H, CH<sub>3</sub>-CO). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  171.5 (C=O), 170.4 (C=O), 138.3 (C), 137.9 (C), 137.6 (C), 128.4 (2 CH), 128.2 (CH), 128.0 (CH), 127.8 (2 CH), 127.6 (2 CH), 127.5 (CH), 79.6 (C1'), 75.0 (C5), 73.3 (CH<sub>2</sub>), 73.2 (C3), 73.1 (CH<sub>2</sub>), 72.4 (C4), 70.9 (CH<sub>2</sub>), 68.2 (C1), 65.2 (C6), 62.4 (C3'), 52.6 (C2), 37.1 (C2'), 25.9 (CH<sub>3</sub>-N), 23.5 (CH<sub>3</sub>-CO).

**N-Methyl-5-(2-acetamido-3,4,6-tri-O-benzyl- $\beta$ -D-galactopyranos-1-yl)-isoxazolidine-3-amide (22):** The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 98:2 → 96:4) to provide compound **22** (178 mg, 0.295 mmol, 55 %). Yellow solid. M.p. 58.5–61.2 °C. *R*<sub>f</sub> = 0.13 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5). [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 31.9 (c 0.7, CHCl<sub>3</sub>). HRMS (ESI<sup>+</sup>): Calculated for C<sub>34</sub>H<sub>41</sub>N<sub>3</sub>NaO<sub>7</sub> [M + Na]<sup>+</sup>: *m/z* = 626.2837, found 626.2816. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.38–7.23 (m, 15H, ArH), 7.14 (br s, 1H, NHMe), 6.10 (br s, 1H, NHAc), 5.51 (d, *J* = 8.0 Hz, 1H, NH), 4.90 and 4.54 (AB syst. *J* = 11.7 Hz, 2H, CH<sub>2</sub>Ph), 4.69 and 4.39 (AB syst. *J* = 11.9 Hz, 2H, CH<sub>2</sub>Ph), 4.45 and 4.41 (AB syst. *J* = 10.7 Hz, 2H, CH<sub>2</sub>Ph), 4.25–4.18 (m, 1H, H1'), 3.99–3.94 (m, 1H, H4), 3.91–3.81 (m, 2H, H2, H3'), 3.77 (dd, *J* = 10.5, 1.6 Hz, 1H, H1), 3.64–3.56 (m, 2H, H3, H5), 3.50 (dd, *J* = 9.0, 5.8 Hz, 1H, H-6), 3.47 (dd, *J* = 9.0, 7.0 Hz, 1H, H-6), 2.77 (d, *J* = 5.0 Hz, 3H, CH<sub>3</sub>-N), 2.76–2.63 (m, 2H, H2'), 1.86 (s, 3H, CH<sub>3</sub>-CO). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  = 172.4 (C=O), 170.5 (C=O), 138.4 (C), 137.9 (C), 137.6 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.8 (3 CH), 127.5 (CH), 81.4 (C1), 79.4 (C5 or C3), 78.9 (C1'), 76.3 (C3 or C5), 74.4 (CH<sub>2</sub>), 73.4 (CH<sub>2</sub>), 72.1 (C4), 71.3 (CH<sub>2</sub>), 68.9 (C6), 62.8 (C3'), 49.3 (C2), 32.6 (C2'), 25.8 (CH<sub>3</sub>-N), 23.3 (CH<sub>3</sub>-CO).

## Acknowledgments

This work was supported by the Région des Pays de la Loire through the GlycoQuest program and the Ministère de l'Enseignement Supérieur et de la Recherche of France [Ph.D. fellowship (F. R.)]. We also thank Frédéric Legros for technical support, Sullivan Bricaud for the NMR analyses, Patricia Gangnery and Alexandre Bénard for the HRMS analyses.

**Keywords:** Amino acids · C-glycosides · Cycloaddition · Nitrones · TN antigen analog

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[35] For more details about DFT calculation data, see Supporting Information 2.

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Received: August 25, 2020