Carbohydrate Research 346 (2011) 569–576

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

A comparative study of the O-3 reactivity of isomeric *N*-dimethylmaleoyl-protected D-glucosamine and D-allosamine acceptors

María I. Colombo [a], Carlos A. Stortz [b], Edmundo A. Rúveda [a,*]

[a] Instituto de Química Rosario (CONICET-UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Suipacha 531, 2000 Rosario, Argentina
[b] Departamento de Química Orgánica-CIHIDECAR, Facultad de Ciencias Exactas y Naturales, UBA, Ciudad Universitaria, Pab. 2, 1428, Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 6 December 2010
Received in revised form 13 January 2011
Accepted 16 January 2011
Available online 23 January 2011

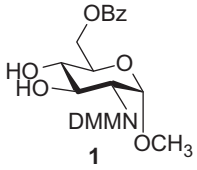
Keywords:
Glucosamine/allosamine acceptors
N-Dimethylmaleoyl group
Galactopyranosyl donor
Competitive glycosylations
Molecular modeling

ABSTRACT

Four isomeric *N*-dimethylmaleoyl 4,6-*O*-benzylidene-protected D-hexosamine acceptors (**2**, **3**, **4**, and **5**) with all possible configurations at C-1 and C-3 (e.g., derived from D-glucosamine and D-allosamine) were prepared, and the assessment of their O-3 relative reactivity through competition experiments using the known per-O-acetylated D-galactopyranosyl trichloroacetimidate donor (**15**) was then carried out. The reactivities are in the order **4** ≫ **2** > **5** > **3**. The analysis of the NMR spectra of **2**–**5** at different temperature and modeling experiments carried out on analogs of **2**–**5** (DFT) and on the acceptors themselves (MM) are coincident, and have helped to establish the stability of the different hydrogen bonds, and of the conformers which carry them. The whole results suggest that the electronic effects (hydrogen bonds) are required to explain the observed trend, in spite of the axial conformation of the most reactive hydroxyl group. The steric effects appear only when hydrogen bonds are weak.

1. Introduction

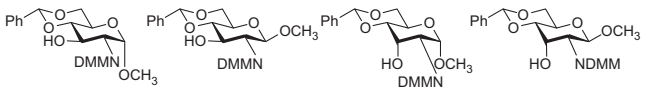
In the course of a systematic analysis of the influence of the configuration of the anomeric carbons and the effect of the protecting groups on O-6 on the relative reactivity of the hydroxyl groups of *N*-dimethylmaleoyl-protected (DMM) D-glucosamine derivatives, Bohn et al. observed that methyl α-glucoside acceptors gave preferentially substitution at O-3, whereas the β-anomers gave mainly substitution at O-4.[1] In an attempt to rationalize these regioselectivities we postulated, on the basis of DFT calculations, that in the α-anomers, a strong hydrogen bond between the H(O)-3 and one of the DMM carbonyl groups, could activate O-3 by increasing its nucleophilicity.[2] More recently, a temperature dependence NMR experiment for both hydroxyl groups of acceptor **1** in DMSO-d_6 solution, gave values that indicated -at best- only weak intramolecular hydrogen bonds (Colombo et al., unpublished results), as was also shown in other studies.[3,4]



1

Herein we present the preparation of the known acceptors **2** and **3**,[1,5] and the synthesis of **4** and **5**, with all possible configurations at C-1 and C-3, a study of their NMR spectra at different temperatures to establish if their hydroxyl groups show different abilities to form intramolecular hydrogen bonds in solution, a series of competition experiments using the same trichloroacetimidate donor to compare the reactivity of the isomeric acceptors, under standard glycosylation conditions, and the molecular modeling of analogs of the four DMM-hexosamine derivatives. Taking into account that the reactivity of any acceptor is both dependent on steric and electronic variables, which are often related, we hope that these results might help to understand the predominant variables in each case.

Competition experiments on D-glucosamine derivatives carrying different N-protected groups have been previously carried out by Crich et al. to explain the influence of hydrogen bonds on the reactivity of the O-4 group.[6]



2 **3** **4** **5**

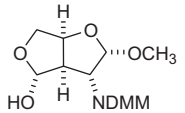
2. Results and discussion

Acceptors **2** and **3** were prepared following sequences recently described.[1,5] For the preparation of the α-D-allosamine derivative **4**, we initially attempted to start from **2**, and invert the stereochemistry at C-3 following the strategy described by Vasella et al.,[7] but

* Corresponding author. Tel./fax: +54 341 4370477.
E-mail address: ruveda@iquir-conicet.gov.ar (E.A. Rúveda).

0008-6215/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2011.01.017

using milder conditions. To this end, the triflate activation nitrite-mediated epimerization seemed to be the appropriate methodology.[8] However, when the triflate of **2** was treated with $NaNO_2$ in DMF over 4 days at room temperature, compound **6** was obtained as the major product. Clearly, this triflate followed the ring-contraction pathway instead of the expected substitution one.[9]

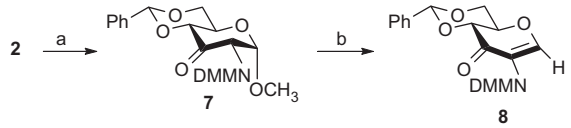


6

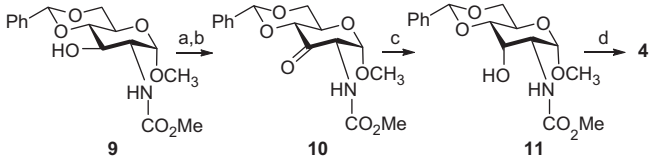
The structure and stereochemistry of **6** was deduced from its ^1H NMR data. The signals at δ 5.41 (s, H-6) and at δ 5.05 (d, $J_{3,4}$ 4.5 Hz, H-3) indicated the presence of two anomeric-like protons and the coupling constants of the signal at δ 4.95 (dd, $J_{1,5}$ 7.1, $J_{1,8a}$ 4.1 Hz) assigned to H-1, clearly showed that **6** was a *cis*-fused compound. Furthermore, the presence of a singlet for the signal at δ 5.41 suggested a dihedral angle H-5/H-6 of around 90°, indicating that O-6 is in the *exo* face of the bicyclo[3.3.0] structure.[9] An NOE study on compound **6** confirmed the above assignment. Thus, the most important NOE relations were observed between the H-1/H-5, H-3/H-4, and H-6/H-4.

We then attempted the classical oxidation–reduction methodology to epimerize the hydroxyl group of **2**. Surprisingly, from the reaction mixture of the Swern oxidation[10] we isolated the amino-glycal **8**, suggesting that the expected ketone **7** is prone to beta-elimination under basic conditions, because of the increasing acidity of H-2 and the release of the steric congestion between the bulky DMM group and the anomeric substituent (Scheme 1). Amino-glycals are well-known side products of glycosylations with 2-phthalimidoglycosyl donors.[11]

In view of these results, we decided to use **9**, carrying a sterically less demanding N-protecting group,[12] as starting material for the preparation of **4**. In fact, when **9** was submitted to Swern oxidation followed by $NaBH_4$ reduction,[10] the allosamine derivative **11** was obtained in good overall yield. The coupling constants of the signal at δ 4.22 (ddd, $J_{3,4}$ 2.9 Hz, $J_{3,2}$ 6.1 Hz, $J_{3,OH}$ 6.6 Hz) assigned to H-3 in the ^1H NMR spectrum of **11** clearly indicated that the O-3 was axial. Finally, removal of the carbamate protecting group under reflux with KOH in a mixture of dioxane-methoxyethanol,[13] followed by treatment of the resulting product with dimethylmaleic anhydride,[14] afforded **4** (Scheme 2).



Scheme 1. Reagents and conditions: (a) CH_2Cl_2, $(ClCO)_2$, DMSO, −78 °C to −65 °C, **2**, −45 °C, DIPEA; (b) work-up, silica gel column chromatography (58% from **2**).

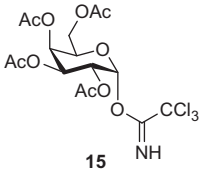


Scheme 2. Reagents and conditions: (a) CH_2Cl_2, $(ClCO)_2$, DMSO, −78 °C to −65 °C, **9**, −45 °C, DIPEA; (b) CH_3OH, $NaBH_4$, 0 °C to rt, 1 h; (c) 1,4-dioxane–methoxyethanol, KOH, 120 °C, 7 h, rt overnight; (d) CH_3OH, dimethylmaleic anhydride, rt, 20 min, 60 °C, 4 h (32% from **9**).

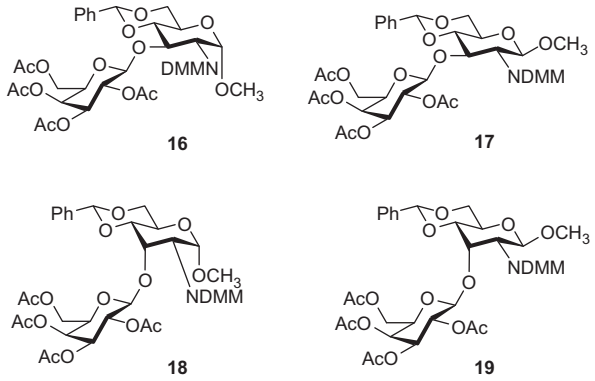
In an attempt to prepare **5** from **3** by the oxidation–reduction sequence, the corresponding ketone was smoothly obtained under the Swern conditions. However, its reduction with sodium borohydride in MeOH led to an over-reduction product, because one of the carbonyl groups of the DMM protecting group was also reduced.

In view of this result, we turned our attention to the triflate activation nitrite-mediated epimerization sequence,[8] starting with the known triol **12**[15] which, by 4,6-*O*-benzylidene protection, was transformed into **13**. The application of the above sequence to **13** gave **14** in reasonable yield. The signal at δ 4.26 (dd, with appearance of broad triplet, $J_{3,2} \approx J_{3,4}$ 2.4 Hz) assigned to H-3 in the ^1H NMR spectrum of **14** also indicated that O-3 was axial. Again, the removal of the carbamate protecting group followed by treatment of the resulting product with dimethylmaleic anhydride afforded **5** (Scheme 3).

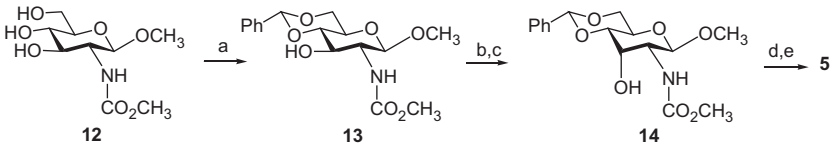
The ^1H NMR spectra for the acceptors **2–5** in DMSO-d_6 solution were then obtained. From the plots of δ (OH) versus temperature (from 298 to 350 K), for **2**, **3**, **4**, and **5** we obtained slopes of −5.1, −4.6, −3.5, and −5.0 ppb/K, respectively. The value for **4** is characteristic of an OH proton participating in a strong hydrogen bond, whereas the OH groups of the remaining acceptors may only be engaged in weak intramolecular hydrogen bonds,[3,4] at most. It is worthwhile mentioning that the low-field signal of the H(O)-3 (δ = 5.79) of **4** in $CDCl_3$ solution further confirmed that it is participating in a strong intramolecular hydrogen bond.[16]



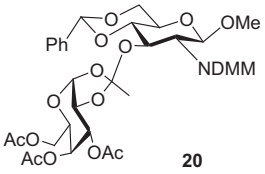
To compare the reactivity of the isomeric acceptors under standard glycosylation reaction conditions, the known per-*O*-acetylated D-galactopyranosyl trichloroacetimidate **15**[17] was chosen as the donor. In order to control these reactions, we decided first to prepare authentic samples of disaccharides **16**, **17**, **18,** and **19**.



The treatment of **3** with **15** under standard reaction conditions (CH_2Cl_2, MS, TMSOTf at −45 °C) led unexpectedly to the orthoester **20** as the major product of the reaction (59% yield). However, by working at a higher temperature (−25 °C) and with the slow addition of the promoter in a dilute solution of CH_2Cl_2 (TMSOTf, 0.02 M), **17** was obtained, albeit in only 46% yield. By using these reaction conditions, the remaining acceptors were converted into their corresponding disaccharides in excellent yield and all of them were fully characterized as β-galactosides.



Scheme 3. Reagents and conditions: (a) CH_3CN, benzaldehyde dimethyl acetal, CSA, reflux, 3 h, 69%; (b) CH_2Cl_2, pyridine, Tf_2O, 0 °C; (c) DMF, $NaNO_2$, rt, 4 days, 61% (from **13**); (d) 1,4-dioxane–methoxyethanol, KOH, 120 °C, 3.5 h; (e) CH_3OH, dimethylmaleic anhydride, rt, 20 min, 60 °C, 4 h, 38% (from **14**).



A series of competition glycosylation experiments were then carried out. In those experiments a limited amount of donor **15** was allowed to react, under the conditions described above, with an equimolecular mixture of two acceptors. The crude reaction mixtures were analyzed by ^1H NMR and the ratios of the disaccharides obtained were determined on the basis of the relative areas of the methoxyl group signals.

The analysis of the results of these competition experiments (Table 1) clearly showed that the order of reactivity of the isomeric acceptors was **4** ≫ **2** > **5** > **3**. The highest reactivity of acceptor **4** indicated that there is a clear relationship between the strength of the hydrogen bond detected in the acceptor and its reactivity. In this acceptor, the strong hydrogen bond was attributed to the interaction between the H(O)-3 group with the C=O group of the DMM moiety, that by increasing its nucleophilicity compensated by far the expected steric hindrance of an axial OH group. The axial nature of both, the O-3 and the anomeric MeO (which tilts the DMM group[2]), undoubtedly favors the strong hydrogen bond observed in **4**. In spite that there are other possibilities that might contribute to the strong hydrogen bond observed in **4**, as the H(O)-3 to O-1, a classical 1,3-diaxial interaction, and the H(O)-3 to O-4, an axial/equatorial *cis*-1,2 hydroxy-ether interaction,[18] their contributions should not be very relevant because of the slope (−5.3 ppb/K) obtained with compound **11** (without the DMM group) in a temperature dependence NMR experiment in DMSO solution that showed, at best, weak hydrogen bonds. The analysis of the relative reactivities of acceptors **2** and **5** that showed only weak hydrogen bonds, is not as clear as that of **4**. It could be argued however, that in **2** the axial MeO tilts the DMM group, as in **4**, favoring a weak hydrogen bond of the H(O)-3 with its C=O while in **5**, the axial O-3 group and the C=O of the DMM moiety are close enough to suggest also a weak hydrogen bond. The slightly higher reactivity of **2** in comparison with **5** could be attributed to the equatorial nature of the O-3 group of the former acceptor. Finally, in **3**, the electronic factors support its lower reactivity.

To rationalize the stability of the intramolecular hydrogen bonds present in **2**–**5**, a theoretical study was carried out. Quantum mechanics calculations were carried out on different conformations (allowing for different exocyclic angles) of analogs of **2–5** where, for the sake of simplicity, the phenyl moieties were replaced by methyl groups (**2e**–**5e**, that is, having ethylidene groups instead of benzylidene groups) using DFT at the B3LYP/6-31+G** level. This level was already tested on carbohydrates and considered to give good geometries and fair energy values.[19] The full results of energies and geometries of the calculations can be found as Supplementary data, whereas Table 2 summarizes the relative energies, exocyclic angles, and hydrogen bond features of the different conformers found for each compound. The only hydrogen possibly participating in hydrogen bonds is H(O)-3. It can engage in bonding with O-4 for all compounds, with the carbonyl group of DMM (theoretically for all compounds), and with O-1 just for compound **4e**, with axial groups on C-1 and C-3. The hydrogen bonds on O-4 correspond to axial/equatorial *cis*-1,2-hydroxy-ether in **4** and **5** which are considered to be weak ones, whereas those in **2** and **3**, being diequatorial *trans*-1,2 are even weaker interactions.[18] Furthermore, it has been suggested that these interactions should not even be called hydrogen bonds.[20] The strength of the hydrogen bonds can be estimated by the distance between the H and the H-acceptor (O in this case), being stronger when this distance is shorter. The other parameter to estimate the hydrogen bond strength is the O–H···O angle (θ), being the bond stronger when this angle gets closer to 180°, and very weak with θ lower than 110°. Table 2 shows that compound **3e** is unable to establish strong hydrogen bonds: the β-configuration of the anomeric carbon and the equatorial conformation of the C-3 substituent do not allow for a hydrogen bond between H(O)-3 and the carbonyl group of DMM. As expected, the H(O)-3 to O-4 hydrogen bond detected in its most stable conformation should be very weak (2.54 Å, θ = 103°). The other three compounds show both conformers with bonds to the carbonyl group and to O-4. As stated previously, the latter can be classified as weak bonds, with distances in the range 2.31–2.60 Å and angles θ smaller than 110°. The calculations find a very strong hydrogen bond for the most stable conformer of **4e** (Fig. 1) and for the less stable conformer of **5e** (d = 1.80–1.87 Å; θ = 160–161°), and a weaker one for the less stable conformer of

Table 1
Ratios of disaccharides obtained after reaction of donor **15** with different mixtures of the isomeric acceptors

Entry	Acceptors	Products	Ratio
i	**2**, **3**	**16** + **17**	**5**:**1**
ii	**4**, **5**	**18** + **19**	**13**:**1**
iii	**4**, **2**	**18** + **16**	**10**:**1**
iv	**5**, **3**	**19** + **17**	**3**:**1**
v	**2**, **5**	**16** + **19**	**2**:**1**

Table 2
Relative energies and geometries of the conformers found by B3LYP/6-31+G** on compounds **2e**–**5e**

	ΔE (kcal)	$\chi_2/\chi_{2'}$ (°)	χ_3 (°)	Hydrogen bond		
					$d_{O\cdots H}$ (Å)	θ (°)
2e						
Conf. 1	0.00	155/−20	−58	H(O)-3 to O-4	2.60	100
Conf. 2	0.69	134/−47	28	H(O)-3 to O=C	2.18	129
3e						
Conf. 1	0.00	180/2	−63	H(O)3 to O-4	2.54	103
Conf. 2	2.00	−174/11	177	None		
4e						
Conf. 1	0.00	162/−26	−79	H(O)-3 to O=C	1.80	160
Conf. 2	2.75	−107/64	−163	H(O)-3 to O-1	1.96	139
Conf. 3	4.25	−89/83	61	H(O)-3 to O-4	2.43	103
Conf. 4	5.17	180/3	71	H(O)-3 to O-4	2.31	109
5e						
Conf. 1	0.00	−151/30	71	H(O)-3 to O-4	2.36	107
Conf. 2	0.59	−175/−8	−87	H(O)-3 to O=C	1.87	161

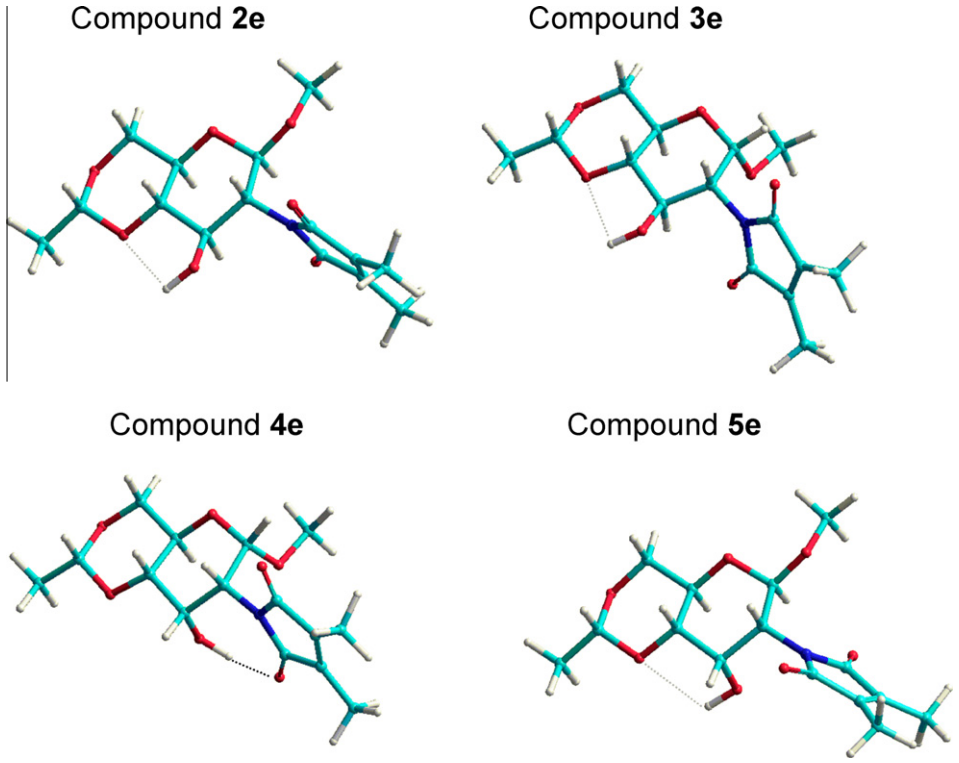


Figure 1. Molecular representation of the most stable conformers of compound **2e**–**5e** calculated at the B3LYP/6-31+G** level. The stronger hydrogen bond is indicated by a black dotted line, whereas the weaker ones are indicated by a gray dotted line.

2e (d = 2.18 Å; θ = 129°). They all correspond to bonds with the DMM carbonyl group. The most stable conformers of **2e**, **3e**, and **5e** show only weak hydrogen bonds (Table 2, Fig. 1).

Another calculation approach is the use of a simple empirical method (molecular mechanics, MM), not useful for transient species, but of fair use for stable compounds. As these methods allow for variations in the dielectric constant, the stability of the different hydrogen bonds can also be easily tested. Thus, the different conformations of **2**, **3**, **4**, and **5** (full molecules, containing the benzylidene groups) were studied using MM3 at both dielectric constants 1.5 (default) and 3. The MM3 force-field[21] has been widely used for carbohydrates.[22,23] Given its particular attention to the directionality of hydrogen bonding, it has already been used by different groups in order to explain features related to the hydrogen bonding of carbohydrates.[24,25] It is expected to find a decrease in the strength of the hydrogen bonds (longer distance and smaller angle) when the dielectric constant is raised. The MM3 calculations repeat more or less the general features found by DFT (Table 2). However, the most interesting point is that for the calculation on **4**, the hydrogen bond to the carbonyl group remains almost unaltered by raising the dielectric constant, and that the conformer carrying this bond keeps its status of greater stability (though the differences with the remaining conformers are reduced). On the other hand, the calculation for **2** shows that the strength of the hydrogen bond of this conformer is reduced sharply by an increase in the dielectric constant (the distance raises from 1.98 to 2.74 Å, whereas the angle decreases from 133° to 113°), and at the same time, this conformer loses stability. These facts suggest that in dichloromethane solution, this hydrogen bond is weak or non-existent at all. For compound **5**, the MM3 calculation also shows a decrease in the strength of the hydrogen bond to the carbonyl group, although not so sharp as for **2** (the distance raises from 1.91 to 2.08 Å), but again this occurs on a minor conformer. These results match the experimental evidence that compound **4** carries a strong hydrogen bond, whereas they show that **2** and **5** have a weaker hydrogen bond for two reasons: the hydrogen bond is intrinsically weaker, and it appears for less populated conformers. These observations that suggest the **4** ≫ **5** ≈ **2** > **3** sequence for the hydrogen bond strengths complement the temperature dependence NMR experiments mentioned above.

Thus, the rather small difference in reactivity between **2** and **5** can be related not to their hydrogen bonding capabilities (weak for both), but to steric effects, larger in **5** (with an axial O-3) than in **2** (with an equatorial O-3). As anticipated, the hydrogen bond observed in conformer 2 of compound **4**/**4e** with O-1 also appears to be weaker than those to the carbonyl group, as it has larger distances, smaller angles and it disappears after raising the dielectric constant. It is worthwhile mentioning that the higher reactivity of **2** in comparison with **3**, is reminiscent to the reactivity that we have observed for α-anomers when we studied the influence of the anomeric carbon on the regioselectivity of 6-O-substituted *N*-dimethylmaleoyl-protected D-glucosamine acceptors.[1]

Recent computational studies[26] have advocated for the traditional higher reactivity of equatorial against axial hydroxyl groups. However, although much work should be done to fully understand the reactivity of acceptors showing only weak hydrogen bonds, our observations on the relevant influence of the electronic factors in these reactions extend the results published by other authors,[4,16,27,28] and give support to the statement of Fraser-Reid and López '*the generally accepted hydroxy preferences of organic structures, e.g., primary > secondary, and equatorial > axial, have proven to be unreliable with respect to glycosylation.*'[27]

3. Experimental

3.1. General methods

Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 spectrometer for $CDCl_3$ solutions

with Me_4Si as internal standard, except where noted. For the 2D experiments, Bruker standard software was employed. High resolution mass spectrometry (HRMS-ESI) was performed in a Bruker microTOF-Q II instrument. Optical rotations were measured with a Jasco DIP-1000 polarimeter. Column chromatography was performed on Silica Gel 60 H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of EtOAc in hexane as solvent. Analytical TLC was carried out using Kieselgel GF254 (E. Merck) with a thickness of 0.20 mm. The homogeneity of all compounds prior to the high-resolution mass spectral determination was carefully verified by TLC. Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. All chemicals were used as purchased or purified according to standard procedures.

3.2. Methyl 4,6-*O*-benzylidene-2-deoxy-2-dimethylmaleimido-α-D-glucopyranoside (2)

Compound **2** was prepared as described previously.[1]

3.3. Methyl 4,6-*O*-benzylidene-2-deoxy-2-dimethylmaleimido-β-D-glucopyranoside (3)

Compound **3** was prepared as described previously.[5]

3.4. [1*S*,3*S*,4*R*,5*S*,6*R*]-4-Dimethylmaleimido-6-hydroxy-3-methoxy-2,7-dioxabicyclo[3.3.4]octane (6)

A suspension of **2** (389 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (6 mL) and anhydrous pyridine (1.6 mL) was stirred and cooled to 0 °C, trifluoromethanesulfonic anhydride (0.36 mL, 2.18 mmol) was slowly added and the stirring was continued for 1 h at 0 °C. The mixture was then diluted with CH_2Cl_2, washed with icy 1 N HCl, satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated to give a brownish solid that was used in the next step without further purification. To a stirred solution of this solid (410 mg) in anhydrous DMF (10 mL) was added $NaNO_2$ (730 mg, 10.57 mmol) and the suspension was stirred for 4 days at room temperature. The reaction mixture was then diluted with CH_2Cl_2, washed with icy 1 N HCl, satd aq $NaHCO_3$, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed to give pure **6** (33.4 mg, 61%) as a solid: mp 183–185.5 °C; R_f 0.24 (1:1 hexane–EtOAc). ^{1}H NMR: δ 5.41(s, 1H, H-6), 5.05 (d, 1H, $J_{3,4}$ 4.5 Hz, H-3), 4.95 (dd, 1H, $J_{1,5}$ 7.1, $J_{1,8a}$ 4.1 Hz, H-1), 4.135 (dd, 1H, $J_{4,5}$ 8.0 Hz, H-4), 4.13 (dd, 1H, $J_{8a,8b}$ 10.6 Hz, H-8a), 4.01 (d, 1H, H-8b), 3.99 (dd, with appearance of t, 1H, H-5), 3.29 (s, 3H, OCH_3), 1.95 (s, 6H, $CCH_3 \times 2$). ^{13}C NMR: δ 172.05 (CO), 137.30 (C × 2), 103.95 (C-3), 102.68 (C-6), 81.37 (C-1), 71.55 (C-8), 57.16 (C-4), 55.14 (OCH_3), 49.30 (C-5), 8.75 ($CCH_3 \times 2$). ESI-HRMS: Calcd for $[C_{13}H_{17}NO_6+K]^+$: 322.06875. Found, *m/z*: 322.06934.

3.5. Amino-glycal 8

To a solution of oxalyl chloride (0.2 mL, 2.36 mmol) in anhydrous CH_2Cl_2 (6 mL) at −78 °C, anhydrous DMSO (0.327 mL, 4.60 mmol) was added and the resulting solution was stirred for 20 min allowing the temperature to warm up to −65 °C. To the reaction mixture, a solution of **2** (405 mg, 1.04 mmol) in anhydrous CH_2Cl_2 (2 mL) was added. The reaction mixture was then stirred for 30 min allowing the temperature to warm up to −45 °C. To this mixture anhydrous DIPEA (1.6 mL) was added, and the reaction was allowed to warm up to 0 °C in 1 h. The reaction mixture was then diluted with CH_2Cl_2 and the organic layer was washed with 1 N HCl, brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to give pure **8 (**208.7 mg, 58%) as a foamy solid: ^{1}H NMR: δ 7.52–7.48 (m, 2H, ArH), 7.42 (s, 1H, H-1), 7.37–7.35 (m, 3H, ArH), 5.96 (s, 1H, CHPh), 4.72–4.65 (m, 2H, H-4, H-5), 4.60–4.50 (m, 1H, H-6a), 4.15–4.05 (m, 1H, H-6b). ^{13}C NMR: δ 183.10 (CO), 161.98 (C-1), 138.27 (C × 2), 135.99, (C-Ar), 129.50–126.41 (C-Ar), 111.91 (C-2), 102.18 (CHPh), 73.68 (C-4), 67.65 (C-5), 67.60 (C-6), 9.00 ($CCH3 \times 2$). ESI-HRMS: Calcd for $[C_{19}H_{17}NO_6+H]^+$: 356.1129. Found, *m/z*: 356.1126.

3.6. Methyl 4,6-*O*-benzylidene-2-deoxy-2-dimethylmaleimido-α-D-allopyranoside (4)

To a solution of oxalyl chloride (1 mL, 11.81 mmol) in anhydrous CH_2Cl_2 (25.5 mL) at −78 °C, anhydrous DMSO (2.94 mL, 41.39 mmol) was added and the resulting solution was stirred for 20 min allowing the temperature to warm up to −65 °C. To the reaction mixture, a solution of **9**[11] (1.5 g, 4.42 mmol) in anhydrous CH_2Cl_2 (54 mL) was added. The reaction mixture was then stirred for 30 min allowing the temperature to warm up to −45 °C. To this mixture anhydrous DIPEA (8.1 mL) was added, and the reaction was allowed to warm up to 0 °C in 1 h. The reaction mixture was then diluted with CH_2Cl_2 and the organic layer was washed with 1 N HCl, brine, dried (Na_2SO_4), and evaporated. Although this residue was used in the next step without further purification, a small portion was chromatographed to give pure **10** as a foamy solid: R_f 0.24 (1:1 hexane–EtOAc). ^{1}H NMR: δ 7.55–7.45 (m, 2H, ArH), 7.50–7.30 (m, 3H, ArH), 5.58 (s, 1H, CHPh), 5.50 (d, 1H, $J_{NH,2}$ 8.2 Hz, NH), 5.19 (d, 1H, $J_{1,2}$ 4.2 Hz, H-1), 4.70 (dd, 1H, H-2), 4.41 (dd, 1H, $J_{6a,5}$ 4.4, $J_{6a,6b}$ 10.4 Hz, H-6a), 4.38 (d, 1H, $J_{4,5}$10.8 Hz, H-4), 4.15–4.04 (m, 1H, H-5), 3.96 (dd, with appearance of t, 1H, $J_{6b,5}$ 10.2 Hz, H-6b), 3.71 (s, 3H, OCH_3 ester), 3.40 (s, 3H, OCH_3). ^{13}C NMR: δ 194.81 (CO ketone), 156.49 (CO ester), 136.31 (C-Ar, C × 2), 129.40–126.39 (C-Ar), 102.25 (CHPh), 101.98 (C-1), 82.50 (C-4), 69.41 (C-6), 65.85 (C-5), 60.47 (C-2), 55.65 (OCH_3), 52.61 (OCH_3 ester). To the stirred solution of the crude ketosugar (**10**) from previous step (1.4 g) in MeOH (120 mL), cooled to 0 °C, $NaBH_4$ (510 mg, 13.48 mmol) was added in small portions. After 1 h of stirring at room temperature, the reaction was quenched with 1 N HCl to pH 7 and most the solvent was evaporated. The residue was diluted with EtOAc–MeOH (7:3) and filtered through a SiO_2 gel pad and washed with EtOAc–MeOH. Although this residue was used in the next step without further purification, a small portion was chromatographed to give pure **11** as a solid: mp 117.5–120 °C; R_f 0.19 (1:1 hexane–EtOAc). ^{1}H NMR: δ 7.60–7.45 (m, 2H, ArH), 7.40–7.30 (m, 3H, ArH), 5.61 (s, 1H, CHPh), 5.53 (d, 1H, $J_{NH,2}$ 9.1 Hz, NH), 4.75 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 4.38 (dd, 1H, $J_{6a,5}$ 5.0, $J_{6a,6b}$ 10.3 Hz, H-6a), 4.22 (ddd, 1H, $J_{3,4}$ 2.9, $J_{3,2}$ 6.1, $J_{3,OH}$ 6.6 Hz, H-3), 4.12 (ddd, 1H, $J_{5,4}$ 10.1, $J_{5,6b}$ 10.3 Hz, H-5), 3.98 (ddd, 1H, H-2), 3.79 (dd, with appearance of t, 1H, H-6b), 3.71 (s, 3H, OCH_3 ester), 3.64 (dd, 1H, H-4), 3.45 (s, 3H, OCH_3), 2.61 (d, 1H, OH). ^{13}C NMR: δ 156.46 (CO), 137.09 (C × 2), 129.24–126.27 (C-Ar), 101.93 (CHPh), 99.48 (C-1), 78.54 (C-4), 69.16 (C-6), 68.32 (C-3), 57.40 (C-5), 56.19 (OCH_3), 52.29 (OCH_3 ester), 51.29 (C-2). ESI-HRMS: Calcd for $[C_{16}H_{21}NO_7–CH_3O]^+$: 308.1129. Found, *m/z*: 308.1118. To a stirred solution of KOH (3.5 g) in 1,4-dioxane:methoxyethanol (7.5:4.5 mL, v/v) **11** (1.4 g) was added and the mixture was refluxed at 120 °C for 7 h and stirred overnight at room temperature. The reaction mixture was then neutralized with 1 N HCl until slightly basic to avoid amine hydrochloride formation. Most of the solvents were evaporated and the residue was dissolved in H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed to yield the amine as a brownish solid that was used in the next step without further purification. A solution of this product (587 mg, 1.73 mmol) in MeOH (28 mL) was treated with dimethylmaleic anhydride (431 mg, 3.42 mmol) and stirred for 20 min at room temperature. Et_3N (0.7 mL, 5.02 mmol) was then added and the reaction mixture was again treated with

dimethylmaleic anhydride (241 mg, 1.91 mmol). The reaction was warmed to 60 °C with stirring for 4 h, then the solvent was evaporated and the residue in CH_2Cl_2 was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed to give pure **4** (554 mg, 32% from **9**) as a solid: mp 169.8–170.9 °C; $[\alpha]_D^{32}$ +122.9 (*c* 0.58, $CHCl_3$); R_f 0.33 (1:1 hexane–EtOAc). ^{1}H NMR: δ 7.60–7.50 (m, 2H, ArH), 7.40–7.30 (m, 3H, ArH), 5.79 (s, 1H, OH), 5.59 (s, 1H, CHPh), 4.65 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.50 (m, 1H, H-5), 4.44 (br s, 1H, H-3), 4.42–4.30 (m, 2H, H-6a, H-2), 3.78 (dd, with appearance of t, 1H, $J_{6b,5} \approx J_{6b,6a}$ 10.2 Hz, H-6b), 3.72 (br dd, 1H, $J_{4,3}$ 2.3, $J_{4,5}$ 9.5 Hz, H-4), 3.35 (s, 3H, OCH_3), 2.01 (s, 6H, $CCH_3 \times 2$). ^{13}C NMR: δ 172.48 (CO × 2), 137.88 (C-Ar, C × 2), 137.29 (C-Ar) 129.05–126.47 (C-Ar), 102.07 (CHPh), 99.10 (C-1), 79.95 (C-4), 69.15 (C-6), 67.39 (C-3), 58.06 (C-5), 55.97 (OCH_3), 55.04 (C-2), 8.99 ($CCH_3 \times 2$). ESI-HRMS: Calcd for $[C_{20}H_{23}NO_7+H]^+$: 390.1547. Found, *m/z*: 390.1548.

3.7. Methyl 4,6-*O*-benzylidene-2-deoxy-2-dimethylmaleimido-β-D-allopyranoside (5)

To a stirred suspension of **12**[15] (1.32 g, 5.26 mmol) in CH_3CN (100 mL) were added benzaldehyde dimethylacetal (3 mL, 19.7 mmol) and a catalytic amount of camphorsulfonic acid. The mixture was heated at reflux for 3 h, then neutralized with Et_3N and evaporated. The residue was crystallized (MeOH) to give **13** (750 mg). The mother liquors were evaporated and the residue was chromatographed to give an additional amount of pure **13** (481 mg, 69%) as a solid: mp 189.0–193 °C; R_f 0.10 (1:1 hexane–EtOAc). ^{1}H NMR: δ 7.53–7.46 (m, 2H, ArH), 7.40–7.34 (m, 3H, ArH), 5.56 (s, 1H, CHPh), 4.93 (d, 1H, $J_{NH,2}$ 3.4 Hz, NH), 4.55 (d, 1H, $J_{1,2}$ 8.0 Hz, H-1), 4.36 (dd, 1H, $J_{6a,5}$ 5.0, $J_{6a,6b}$ 10.7 Hz, H-6a), 4.10 (dd, with appearance of br t, 1H, $J_{3,2} \approx J_{3,4}$ 8.7 Hz, H-3), 3.80 (dd, with appearance of t, 1H, $J_{6b,5}$ 10.1 Hz, H-6b), 3.70 (s, 3H, OCH_3 ester), 3.56 (dd, with appearance of t, 1H, $J_{4,5}$ 9.5 Hz, H-4), 3.53 (s, 3H, OCH_3), 3.52–3.45 (m, 1H, H-5), 3.43–3.25 (m, 1H, H-2). ^{13}C NMR: δ 157.21 (CO), 137.03–126.31 (C-Ar), 102.16, (C-1), 101.93 (CHPh), 81.51 (C-4), 71.23 (C-3), 68.65 (C-6), 66.17 (C-5), 58.92 (C-2), 57.21 (OCH_3), 52.50 (OCH_3, ester). ESI-HRMS: Calcd for $[C_{16}H_{21}NO_7+Na]^+$: 362.12102. Found, *m/z*: 362.12077. A suspension of **13** (1.91 g, 5.63 mmol) in anhydrous CH_2Cl_2 (33 mL) and anhydrous pyridine (9 mL) was stirred and cooled to 0 °C, trifluoromethanesulfonic anhydride (2.1 mL, 12.7 mmol) was slowly added and the stirring was continued for 1 h at 0 °C. The mixture was then diluted with CH_2Cl_2, washed with icy 1 N HCl, satd aq $NaHCO_3$, and brine, dried (Na_2SO_4) and evaporated to give a brownish solid that was used in the next step without further purification. To a stirred solution of this solid (2.6 g) in anhydrous DMF (15 mL) was added $NaNO_2$ (4 g, 57.97 mmol) and the suspension was stirred for 4 days at room temperature.[8] The reaction mixture was then diluted with CH_2Cl_2, washed with icy 1 N HCl, satd aq $NaHCO_3$, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed to give pure **14** (1.16 g, 61%) as a solid: mp 183–185.5 °C; R_f 0.24 (1:1 hexane–EtOAc). ^{1}H NMR: δ 7.51–7.45 (m, 2H, ArH), 7.40–7.35 (m, 3H, ArH), 5.59 (s, 1H, CHPh), 5.33 (d, 1H, $J_{NH,2}$ 8.9 Hz, NH), 4.55 (d, 1H, $J_{1,2}$ 8.2 Hz, H-1), 4.39 (dd, 1H, $J_{6a,5}$ 4.8, $J_{6a,6b}$ 10.3 Hz, H-6a), 4.26 (dd, with appearance of bt, 1H, $J_{3,2} \approx J_{3,4}$ 2.4 Hz, H-3), 3.97 (ddd 1H, $J_{5,4}$ 9.7, $J_{5,6b}$ 10.2 Hz, H-5), 3.90–3.70 (m, 1H, H-2), 3.79 (dd, with appearance of t, 1H, H-6b), 3.70 (s, 3H, OCH_3 ester), 3.63 (dd, 1H, H-4), 3.51 (s, 3H, OCH_3). ^{13}C NMR: δ 156.60 (CO), 136.94–126.15 (C-Ar), 101.76, (C × 2, C-1, CHPh), 78.79 (C-4), 69.10 (C-6), 68.94 (C-3), 63.26 (C-5), 57.23 (OCH_3), 53.87 (C-2), 52.99 (OCH_3, ester). ESI-HRMS: Calcd for $[C_{16}H_{21}NO_7+H]^+$: 340.1391. Found, *m/z*: 340.1390. To a stirred solution of KOH (2.4 g) in 1,4-dioxane–methoxyethanol (5:3 mL, v/v) **14** (1.16 g, 3.42 mmol) was added and the mixture was refluxed at 120 °C for 3.5 h. The reaction mixture was cooled and neutralized with 1 N HCl until slightly basic to avoid amine hydrochloride formation. Most of the solvents were evaporated and the residue was dissolved in H_2O and extracted with Cl_2CH_2. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was used in the next step without further purification. A solution of this product (842 mg, 2.48 mmol) in MeOH (40 mL) was treated with dimethylmaleic anhydride (615 mg, 4.87 mmol) and stirred for 20 min at room temperature. Et_3N (1 mL, 7.17 mmol) was then added and the reaction mixture was again treated with dimethylmaleic anhydride (353 mg, 2.80 mmol). The reaction was warmed to 60 °C with stirring for 4 h, then the solvent was evaporated and the residue in CH_2Cl_2 was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to give pure **5** (505 mg, 38%) as a solid: mp 169.8–172.5 °C; $[\alpha]_D^{32}$ −85.3 (*c* 0.58 , $CHCl_3$); R_f 0.45 (1:1 hexane–EtOAc). ^{1}H NMR: δ 7.55–7.45 (m, 2H, ArH), 7.40–7.30 (m, 3H, ArH), 5.69 (d, 1H, $J_{1,2}$ 8.7 Hz, H-1), 5.60 (s, 1H, CHPh), 4.43 (dd, 1H, $J_{6a,5}$ 5.2, $J_{6a,6b}$ 10.5 Hz, H-6a), 4.30 (dd, with appearance of br t, 1H, $J_{3,2} \approx J_{3,4}$ 2.4 Hz, H-3), 4.25–4.10 (m, 1H, H-5), 4.05 (dd, 1H, $J_{4,5}$ 8.6 Hz, H-4), 3.81 (dd, with appearance of t, 1H, $J_{6b,5}$ 10.3 Hz, H-6b), 3.73 (dd, 1H, H-2), 3.48 (s, 3H, OCH_3, 2.89 (br s, 1H, OH), 1.98 (s, 6H, $CH_3 \times 2$). ^{13}C NMR: δ 172.17 (CO), 137.02 (C × 2, C-Ar), 129.31–126.25 (C-Ar), 101.98, (CHPh), 97.87 (C-1), 79.04 (C-4), 69.43 (C-3), 69.11 (C-6), 63.63 (C-5), 57.12 (OCH_3), 55.98 (C-2), 8.87 ($CCH_3 \times 2$). ESI-HRMS: Calcd for $[C_{20}H_{23}NO_7+Na]^+$: 412.1367. Found, *m/z*: 412.1371.

3.8. Temperature dependence of the chemical shift of the hydroxyl groups of 2, 3, 4, and, 5 in ^{1}H NMR

^{1}H NMR (300 MHz) spectra were recorded for solutions of **2**, **3**, **4**, **5,** and **11** in DMSO-d_6 (internal standard, for the ^{1}H residual DMSO). Assignments of proton resonances were based on two-dimensional ^{1}H–^{1}H correlation experiments. Four spectra were recorded at different temperatures in the 298–350 K range. The $\Delta\delta/\Delta T$ [ppb/K] were obtained from a linear fit.

3.9. Data for 20

59%; as a foamy solid: $[\alpha]_D^{31}$ +27.7 (*c* 0.55, $CHCl_3$); R_f 0.29 (1:1 hexane–EtOAc). ^{1}H NMR: δ 7.50–7.45 (m, 2H, ArH), 7.35–7.30 (m, 3H, ArH), 5.62 (d, 1H, $J_{1',2'}$ 4.8 Hz, H-1′), 5.54 (s, 1H, CHPh), 5.34 (dd, with appearance of t, 1H, $J_{4',5'} \approx J_{4',3'}$ 3.0 Hz, H-4′), 5.00 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1), 4.90 (dd, 1H, $J_{3',2'}$ 6.5 Hz, H-3′), 4.46 (dd, 1H, $J_{3,4}$ 9.0, $J_{3,2}$ 10.0 Hz, H-3), 4.38 (dd, 1H, $J_{6a,5}$ 4.1, $J_{6a,6b}$ 10.3 Hz, H-6a), 4.19 (ddd, 1H, $J_{5',6'a}$, 6.4, $J_{5',6'b}$ 6.9 Hz, H-5′), 4.15–4.00 (m, 3H, H-6′a, H-6′b, H-2′), 3.96 (dd, 1H, H-2), 3.80 (dd, with appearance of t, 1H, H-6b), 3.65–3.55 (m, 2H, H-4, H-5), 3.42 (s, 3H, OCH_3), 2.07 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 1.99 (s, 6H, $CCH_3 \times 2$), 1.97 (s, 3H, $COCH_3$), 1.56 (s, 3H, $COCH_3$). ^{13}C NMR: δ 170.41–169.67 (CO), 137.20 (C × 2, C-Ar), 128.90–126.00 (C-Ar), 121.85 (C-orthoester), 101.26 (CHPh), 99.89 (C-1), 97.46 (C-1′), 80.40 (C-4), 73.86 (C-2′), 70.96 (C-3′), 70.32 (C-3), 68.96 (C-5′), 68.65 (C-6), 66.33 (C-5), 65.68 (C-4′), 61.21 (C-6′), 56.98 (OCH_3), 55.67 (C-2), 24.86–20.51 ($COCH_3 \times 4$), 8.73 ($CCH_3 \times 2$). ESI-HRMS: Calcd for $[C_{34}H_{41}NO_{16}+Na]^+$: 742.23176. Found, *m/z*: 742.23060.

3.10. General procedure for the synthesis of 16, 17, 18, and 19

A suspension of the corresponding acceptor (**2**, **3**, **4,** or **5**) (50 mg, 0.13 mmol), donor **15** (130 mg, 0.26 mmol) and activated 4 Å molecular sieves (200 mg) in anhydrous CH_2Cl_2 (7.8 mL) was stirred at room temperature. After 30 min, the mixture was cooled to −25 °C, TMSOTf (0.02 M in CH_2Cl_2, 3.6 mL) was slowly added and the stirring was continued for 30 min (TLC). The mixture was then neutralized by addition of Et_3N and filtered through a silica

gel pad with copious washings with EtOAc. The filtrate was evaporated and the residue was chromatographed to yield the corresponding disaccharides.

3.10.1. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-2-deoxy-2-dimethylmaleimido-4,6-*O*-benzylidene-α-D-glucopyranoside (16)

91%; as a foamy solid: $[\alpha]_D^{29}$ +84.2 (*c* 0.50, $CHCl_3$) R_f 0.30 (1:1 hexane–EtOAc). ^1H NMR: δ 7.55–7.45 (m, 2H, ArH), 7.40–7.25 (m, 3H, ArH), 5.56 (s, 1H, CHPh), 5.27 (dd, 1H, $J_{3,4}$ 8.9, $J_{3,2}$ 10.9 Hz, H-3), 5.22 (dd, 1H, $J_{4',5'}$ 1.0, $J_{4',3'}$ 3.5 Hz, H-4′), 4.98 (dd, 1H, $J_{2',1'}$ 8.0, $J_{2',3'}$ 10.3 Hz, H-2′), 4.83 (dd, 1H, H-3′), 4.75 (d, 1H, H-1′), 4.63 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.27 (dd, 1H, $J_{6a,5}$ 4.4, $J_{6a,6b}$ 10.2 Hz, H-6a), 4.23 (dd, 1H, H-2), 4.02 (dd, 1H, $J_{6'a,5'}$ 8.1, $J_{6'a,6'b}$ 11.1 Hz, H-6′a), 3.94 (dd, 1H, $J_{5,4}$ 9.7 Hz, H-5), 3.86 (dd, 1H, $J_{6'b,5'}$ 5.6 Hz H-6′b), 3.80 (dd, with appearance of t, 1H, $J_{6b,5}$ 10.2 Hz, H-6b), 3.76 (dd, with appearance of t, 1H, H-4), 3.50–3.40 (m, 1H, H-5′), 3.32 (s, 3H, OCH_3), 2.09 (s, 3H, COCH_3), 1.97 (s, 9H, COCH_3, CCH_3 × 2), 1.95 (s, 3H, COCH_3), 1.91 (s, 3H, COCH_3). ^{13}C NMR: δ 172.24–169.48 (CO), 138.42–135.89 (C × 2, C-Ar), 129.37–126.10 (C-Ar), 101.77 (CHPh), 99.79 (C-1′), 99.12 (C-1), 81.92 (C-4), 71.90 (C-3), 71.27 (C-3′), 70.09 (C-5′), 69.28 (C-2′), 68.98 (C-6), 66.74 (C-4′), 62.36 (C-5), 60.96 (C-6′), 55.49 (OCH_3), 54.78 (C-2), 20.84–20.50 (COCH_3 × 4), 8.81 (CCH_3 × 2). ESI-HRMS: Calcd for $[C_{34}H_{41}NO_{16}$+Na$]^+$: 742.23176. Found, *m/z*: 7742.23142.

3.10.2. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-2-deoxy-2-dimethylmaleimido-4,6-*O*-benzylidene-β-D-glucopyranonoside (17)

46.5%; as a foamy solid: $[\alpha]_D^{29}$ −7.1 (*c* 0.49, $CHCl_3$) R_f 0.27 (1:1 hexane–EtOAc). ^1H NMR: δ 7.50–7.43 (m, 2H, ArH), 7.40–7.35 (m, 3H, ArH), 5.55 (s, 1H, CHPh), 5.22 (br d, 1H, $J_{4',3'}$ 3.4 Hz, H-4′), 5.00 (dd, 1H, $J_{2',1'}$ 7.9, $J_{2',3'}$ 10.3 Hz, H-2′), 4.92 (d, 1H, $J_{1,2}$ 8.5 Hz, H-1), 4.82 (dd, 1H, H-3′), 4.56 (dd, 1H, $J_{3,4}$ 8.5, $J_{3,2}$ 10.3 Hz, H-3), 4.54 (d, 1H, H-1′), 4.35 (dd, 1H, $J_{6a,5}$ 4.8, $J_{6a,6b}$ 10.5 Hz, H-6a), 4.04 (dd, 1H, $J_{6'a,5'}$ 8.5, $J_{6'a,6'b}$ 10.7 Hz, H-6′a), 4.04 (dd, with appearance of t, 1H, H-2), 3.89–3.78 (m, 2H, H-6b, H-6′b), 3.74 (dd, with appearance of t, 1H, $J_{4,5}$ 9.2 Hz, H-4), 3.56 (ddd, with appearance of dt, 1H, $J_{5,6b}$ 10.2 Hz, H-5), 3.54–3.46 (m, 1H, H-5′), 3.40 (s, 3H, OCH_3), 2.09 (s, 3H, COCH_3), 1.99 (s, 6H, CCH_3 × 2), 1.92 (s, 3H, COCH_3), 1.91 (s, 3H, COCH_3), 1.86 (s, 3H, COCH_3). ^{13}C NMR: δ 171.51–169.03 (CO), 137.02 (C × 2, C-Ar), 129.28–126.00 (C-Ar), 101.41 (CHPh), 100.26 (C-1′), 99.58 (C-1), 81.01 (C-4), 75.54 (C-3), 71.02 (C-3′), 70.29 (C-5′), 69.35 (C-2′), 68.71 (C-6), 66.67 (C-4′), 66.18 (C-5), 60.86 (C-6′), 56.86 (OCH_3), 54.98 (C-2), 20.62–20.51 (COCH_3 × 4), 8.84 (CCH_3 × 2). ESI-HRMS: Calcd for $[C_{34}H_{41}NO_{16}$+Na$]^+$: 742.23176. Found, *m/z*: 742.22953.

3.10.3. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-2-deoxy-2-dimethylmaleimido-4,6-*O*-benzylidene-α-D-allopyaronoside (18)

98%; as a foamy solid: $[\alpha]_D^{27}$ +9.7 (*c* 0.55, $CHCl_3$) R_f 0.18 (1:1 hexane–EtOAc). ^1H NMR: δ 7.55–7.48 (m, 2H, ArH), 7.42–7.35 (m, 3H, ArH), 5.54 (s, 1H, CHPh), 5.30 (br d, 1H, $J_{4',3'}$ 3.4 Hz, H-4′), 5.25 (dd, 1H, $J_{2',1'}$ 8.0, $J_{2',3'}$ 10.5 Hz, H-2′), 5.14 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.97 (dd, 1H, H-3′), 4.86 (dd, ,with appearance of br t, 1H, H-3), 4.63 (d, 1H, H-1′), 4.28 (dd, 1H, $J_{6'a,5'}$ 5.2, $J_{6'a,6'b}$ 10.0 Hz, H-6′a), 4.25–4.15 (m, 1H, H-5), 4.14 (dd, with appearance of t, 1H, $J_{2,3}$ 3.5 Hz, H-2), 3.95–3.72 (m, 4H, H-6a, H-6b, H-5′, H-6′b), 3.70 (dd, 1H, $J_{4,5}$ 9.1 Hz, H-4), 3.43 (s, 3H, OCH_3), 2.13 (s, 3H, COCH_3), 2.00 (s, 3H, COCH_3), 1.96 (s, 3H, COCH_3), 1.93 (s, 6H, CCH_3 × 2), 1.90 (s, 3H, COCH_3). ^{13}C NMR: δ 171.28–169.37 (CO), 137.20 (C-Ar), 137.05 (C × 2), 129.17–126.14 (C-Ar), 101.86 (CHPh), 101.35 (C-1′), 97.93 (C-1), 78.70 (C-4), 72.37 (C-3), 71.02 (C-3′), 70.03 (C-5′), 69.35 (C-6′), 68.80 (C-2′), 67.01 (C-4′), 61.24 (C-6), 57.89 (C-5), 55.39 (OCH_3), 54.70 (C-2), 20.89–20.60 (CO$CH3$ × 4), 8.71 (CCH_3 × 2). ESI-HRMS: Calcd for $[C_{34}H_{41}NO_{16}$+Na$]^+$: 742.23176. Found, *m/z*: 742.22970.

3.10.4. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-2-deoxy-2-dimethylmaleimido-4,6-*O*-benzylidene-β-D-allopyaronoside (19)

81%; as a foamy solid: $[\alpha]_D^{30.6}$ −64.2 (*c* 0.52, $CHCl_3$); R_f 0.31 (1:1 hexane–EtOAc). ^1H NMR: δ 7.48–7.42 (m, 2H, ArH), 7.40–7.33 (m, 3H, ArH), 5.80 (d, 1H, $J_{1,2}$ 8.9 Hz, H-1), 5.53 (s, 1H, CHPh), 5.31 (br d, 1H, $J_{4',3'}$ 3.5 Hz, H-4′), 5.13 (dd, 1H, $J_{2',1'}$ 7.8, $J_{2',3'}$ 10.5 Hz, H-2′), 4.95 (dd, 1H, H-3′), 4.51 (d, 1H, H-1′), 4.35 (dd, 1H, $J_{6'a,5'}$ 4.3, $J_{6'a,6'b}$ 9.7 Hz, H-6′a), 4.27 (dd, with appearance of t, 1H, $J_{3,2} \approx J_{3,4}$ 2.5 Hz, H-3), 3.97–3.72 (m, 5H, H-2, H-5, H-5′, H-6a, H-6′b), 3.69 (dd, 1H, $J_{4,5}$ 9.3 Hz, H-4), 3.56 (dd, 1H, $J_{6b,5}$ 6.6, $J_{6b,6a}$ 10.6 Hz, H-6b), 3.50 (s, 3H, OCH_3), 2.12 (s, 3H, COCH_3), 2.03 (s, 3H, COCH_3), 1.97 (br d, 3H, CCH_3), 1.95 (s, 3H, COCH_3), 1.93 (br d, 3H, CCH_3), 1.86 (s, 3H, COCH_3). ^{13}C NMR: δ 172.20–169.83 (CO), 137.96 (C), 137.04 (C), 136.02 (C-Ar), 129.10–125.96 (C-Ar), 101.53 (CHPh), 101.30 (C-1′), 98.55 (C-1), 78.23 (C-4), 74.92 (C-3), 70.66 (C-3′), 69.93 (C-5′), 69.19 (C-6′), 68.70 (C-2′), 66.77 (C-4′), 63.84 (C-5), 61.10 (C-6), 57.18 (OCH_3), 55.89 (C-2), 20.97–20.57 (COCH_3 × 4), 8.70 (CCH_3), 8.49 (CCH_3). ESI-HRMS: Calcd for $[C_{34}H_{41}NO_{16}$+K$]^+$: 758.20569. Found, *m/z*: 758.20438.

3.11. Competition experiments

The mixtures of acceptors **2** and **3**, **4** and **5**, **4** and **2**, **5** and **3**, **2** and **5** (0.13 mmol each) were glycosylated as described for the preparation of disaccharides **16**, **17**, **18,** and **19**, using donor **15** (0.14 mmol). The resulting mixtures of products were then analyzed by ^1H NMR spectroscopy. By the integration of the methoxyl group signals, the ratios were **16**:**17**, 5:1; **18**:**19**, 13:1; **18**:**16**, 10:1; **19**:**17**, 3:1 and **16**:**19**, 2:1, respectively.

3.12. Molecular modeling

Quantum mechanical calculations were carried out using Jaguar 6.0 (v. 6.0107, Schroedinger, Portland, USA) with standard basis sets and termination conditions. For molecular mechanics calculations, MM3(92) was used (QCPE, Indiana, USA), modified as indicated elsewhere.[21] MM3 was used to generate all the possible conformers of **2**–**5** by a systematic search. These were submitted to the DFT calculation. The dihedral χ_2 is defined by the atoms H-2–C-2–N-2–C(=O), whereas $\chi_{2'}$ corresponds to the same relationship but with the other carbonylic carbon of the dimethylmaleimido group.[2] As they appear to be interchangeable, the non-primed acronym was used for the angle with higher absolute value. The dihedral χ_3 is defined by the atoms H-3–C-3–O-3–H(O)-3. The methyl and phenyl groups in the ethylidene and benzylidene moieties were put with (*R*) stereochemistry (equatorial), as occurred for the synthesized compounds.

Acknowledgments

We thank Dr. Manuel González-Sierra for NMR spectral determinations and interpretation and to Drs. G. Labadie and C. Delpiccolo for HRMS determinations. Financial support from UNR, UBA, ANPCYyT and CONICET are also acknowledged. M.I.C., C.A.S, and E.A.R. are Research Members of the National Research Council of Argentina (CONICET).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.01.017.

References

1. Bohn, L. M.; Colombo, M. I.; Pisano, P. L.; Stortz, C. A.; Rúveda, E. A. *Carbohydr. Res.* **2007**, *342*, 2522–2536.
2. Bohn, M. L.; Colombo, M. I.; Rúveda, E. A.; Stortz, C. A. *Org. Biomol. Chem.* **2008**, *6*, 554–561.
3. (a) Kroon, J.; Kroon-Batenburg, L. M. J.; Leeflang, B. R.; Vliegenthart, J. F. G. *J. Mol. Struct.* **1994**, *322*, 27–31; (b) Muddasani, P. R.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 334–350; (c) Abraham, R. J.; Byrne, J. J.; Griffiths, L.; Koniotu, R. *Magn. Reson. Chem.* **2005**, *43*, 611–624.
4. Ulhmann, P.; Vasella, A. *Helv. Chim. Acta* **1992**, *75*, 1979–1994.
5. Bohn, M. L.; Colombo, M. I.; Stortz, C. A.; Rúveda, E. A. *Carbohydr. Res.* **2006**, *341*, 1096–1104.
6. Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819–6825.
7. Vasella, A.; Witzig, C.; Husi, R. *Helv. Chim. Acta* **1991**, *74*, 1362–1372.
8. (a) Dong, H.; Pei, A.; Ramström, O. *J. Org. Chem.* **2006**, *71*, 3306–3309; (b) Chen, H.-M.; Withers, S. G. *Carbohydr. Res.* **2007**, *342*, 2212–2222.
9. Kassou, M.; Castillón, S. *J. Org. Chem.* **1995**, *60*, 4353–4358.
10. Chang, C.-H. T.; Hui, Y.; Elchert, B. *Tetrahedron Lett.* **2001**, *42*, 7019–7023.
11. Maloisel, J.-L. *Vasella, Helv. Chim. Acta* **1992**, *75*, 1491–1514.
12. Bauer, T.; Tarasiuk, J.; Pasniczek, K. *Tetrahedron: Asymmetry* **2002**, *13*, 77–82.
13. Crich, D.; Vinod, A. U. *Org. Lett.* **2003**, *5*, 1297–1300.
14. Aly, M. R. E.; Castro-Palomino, J. C.; Ibrahim, E.-S. I.; El-Ashary, E.-S. H.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 2305–2316.
15. Otani, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 781–782.
16. Briner, K.; Bernet, B.; Maloisel, J.-L.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 1969–1984.
17. Schmidt, R. R.; Stumpp, M. *Justus Liebigs Ann. Chem.* **1983**, 1249–1256.
18. Muddasani, P. R.; Bozó, E.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 257–290. and references cited therein.
19. (a) Csonka, G. I. *J. Mol. Struct. (Theochem)* **2002**, *584*, 1–4; (b) Csonka, G. I.; French, A. D.; Johnson, G. P.; Stortz, C. A. *J. Chem. Theory Comput.* **2009**, *5*, 679–692.
20. (a) Klein, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 13931–13937; (b) Klein, R. A. *J. Comput. Chem.* **2003**, *24*, 1120–1131.
21. (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8566; (b) Allinger, N. L.; Rahman, M.; Lii, J.-H. *J. Am. Chem. Soc.* **1990**, *112*, 8293–8307.
22. (a) Dowd, M. K.; Zeng, J.; French, A. D.; Reilly, P. J. *Carbohydr. Res.* **1992**, *230*, 223–244; (b) Dowd, M. K.; French, A. D.; Reilly, P. J. *Carbohydr. Res.* **1992**, *233*, 15–34; (c) Stortz, C. A. *Carbohydr. Res.* **2006**, *341*, 663–671; (d) Stortz, C. A.; Johnson, G. P.; French, A. D.; Csonka, G. I. *Carbohydr. Res.* **2009**, *344*, 2217–2228.
23. Stortz, C. A. *J. Comput. Chem.* **2005**, *26*, 471–483.
24. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 995–1021.
25. López de la Paz, M.; Ellis, G.; Pérez, M.; Perkins, J.; Jiménez-Barbero, J.; Vicent, C. *Eur. J. Org. Chem.* **2002**, 840–855.
26. Kalikanda, J.; Li, Z. *Tetrahedron Lett.* **2010**, *51*, 1550–1553.
27. Uriel, C.; Gómez, A. M.; López, C. J.; Fraser-Reid, B. *Eur. J. Org. Chem.* **2009**, 403–411.
28. (a) Bozó, E.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 745–753; (b) Cid, M. B.; Alfonso, F.; Alonso, I.; Martín-Lomas, M. *Org. Biomol. Chem.* **2009**, *7*, 1471–1481; (c) Cmoch, P.; Pakulski, Z. *Tetrahedron: Asymmetry* **2008**, *19*, 1494–1503.