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A comparative study of the influence of some protecting groups on the reactivity of D-glucosamine acceptors with a galactofuranosyl donor

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

[a]*Instituto de Química Orgánica y de Síntesis (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*

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This paper is dedicated to Professor Rosa M. de Lederkremer for her outstanding contributions to the chemistry of carbohydrates

Abstract—Competitive glycosylation experiments with a galactofuranosyl trichloroacetimidate donor were performed with glucosamine acceptors having a free 4-OH group and carrying different protecting groups at N-2, O-3, and O-6. The most reactive acceptor is the *N*-dimethylmaleimido 3,6-di-O-benzylated derivative (**6c**), which reacts even faster than the oxazolidinone **1a**. Molecular orbital calculations have helped to rationalize these experimental facts in terms of a hard–hard reaction occurring between the donor and the acceptor.

Keywords: Glucosamine acceptors; *N*-Dimethylmaleoyl group; Galactofuranosyl donor; Competitive glycosylations; DFT

1. Introduction

Many oligosaccharides and glycoconjugates carry 4-linked *N*-acetylglucosamine moieties.[1] It is well known that the low reactivity at this 4-position carrying protecting groups at O-3 and O-6 sometimes hampers the synthesis of these biologically important compounds in acceptable yields.[2] This low reactivity has been attributed to steric factors and to the formation of a deactivating hydrogen bond in which the amido group is involved.[2,3] Recent observations that the amide group may itself be glycosylated by active species leading to *O*-glycosyl imidates provide a third explanation to the low reactivity of *N*-acetylglucosamine acceptors.[4,5] As a consequence, protection and synthetic strategies for the 2-amino moiety of D-glucosaminyl acceptors play a critical role in glycosylation reactions and post-glycosylation chemical manipulation to obtain target glycosides.[6]

To the best of our knowledge there are only two reports directed to assess the effect of N-protecting groups on the relative reactivity of glucosamine acceptors. In one of them, Crich and Dudkin[3] determined, through a competitive experiment, the acceptor reactivity of the 4-OH group of *N*-acetyl, *N*-phthalimido (Phth) and 2-azido-2-deoxyglucose derivatives when coupled with a mannosyl sulfoxide activated with triflic anhydride. They demonstrated that, under these conditions, the azido acceptor is 10 times more reactive than the *N*-acetylglucosamine acceptor, whereas the Phth acceptor has an intermediate reactivity. In addition, these authors have also shown that *N*,*N*-diacetylglucosamine and *N*-acetyl-*N*-benzylglucosamine derivatives, with a reactivity comparable to that of the Phth acceptor, were not worthwhile because of the instability of the imide function in the *N*,*N*-diacetyl derivative under those

* Corresponding author. Tel./fax: +54 341 4370477; e-mail addresses: eruveda@fbioyf.unr.edu.ar; ruveda@iquios.gov.ar

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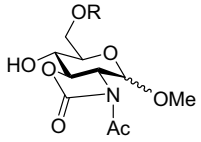
conditions. Furthermore, the complicated NMR spectra obtained for the *N*-acetyl-*N*-benzyl derivative indicates instability also for this compound.

More recently, in a comparative study of the reactivity of the *N*-acetyl, *N*-Phth, and *N*-2,2,2-trichloroethoxycarbonyl (Troc)-protected glucosamine derivatives, Matta and co-workers[7] showed that the *N*-Troc group afforded greater 4-OH reactivity than the *N*-Phth and *N*-acetylglucosamine acceptors when coupled with a galactopyranosyl imidate donor in a trimethylsilyl triflate (TMSOTf) promoted glycosylation. The 4-OH of tetrachlorophtaloyl[8] and sulfonamide[9] protected glucosamine derivatives appeared to have considerable potential as acceptor alcohols; however, the remarkable reactivity recently reported for the methyl glycosides of the *N*-acetyloxazolidinones (**1a** and **1b**)[10] suggested that these derivatives were the ideal acceptors for the synthesis of oligosaccharides carrying 4-linked *N*-acetylglucosamine moieties.

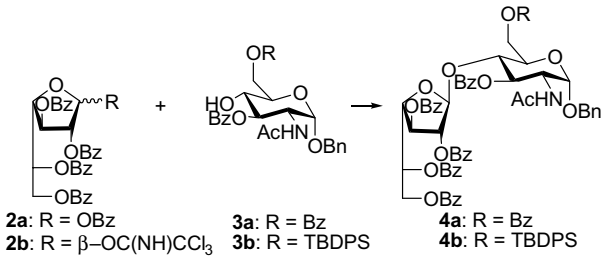


1a: R = Bn; α-OMe
1b: R = thexyldimethylsilyl; β-OMe
1c: R = Me; α-OMe

The high reactivity of **1a** and **1b** was demonstrated by a series of couplings with a range of thioglycosides and also with other glycosylation methods (i.e., Kahne's sulfoxide method, Gin's dehydrative coupling sequence, and Schmidt's trichloroacetimidate protocol). In all cases glycopyranosyl donors were used.[10]

The recent discovery of furanoside components in a wide variety of natural products of biological significance[11–13] prompted us to study the reactivity of some glucosamine derivative acceptors with a galactofuranosyl donor hoping to contribute to the synthesis of furanoside oligosaccharides, as modern methods are allowing such molecules to be isolated. It has been shown by de Lederkremer and co-workers[14] that galactofuranosides are good donors even when coupled with *N*-acetylglucosamine derivatives. They found that the coupling of penta-*O*-benzoyl-D-galactofuranose (**2a**) with benzyl 2-acetamido-3,6-di-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (**3a**), employing tin(IV) chloride as catalyst, gave the disaccharide **4a** in 85% yield. They also found that the coupling of tetra-*O*-benzoyl trichloroacetimidate **2b** with the glucosamine derivative **3b** in the presence of TMSOTf gave **4b** in 77% yield (Scheme 1). These disaccharides were shown to be the β-anomers on the basis of the small galactofuranose $^{1}J_{CH}$ anomeric coupling constant and by the C-1′ ^{13}C NMR chemical shift.[15]

Herein we report some observations, through competitive experiments with a galactofuranosyl trichloroacetimidate donor that clearly establish the influence of the *N*-dimethylmaleoyl group and electron-withdrawing and electron-donating groups at O-3 and O-6 on the reactivity of the 4-OH group of D-glucosamine acceptors.

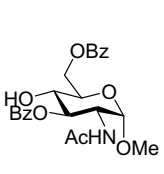


2a: R = OBz
2b: R = β–OC(NH)CCl$_3$
3a: R = Bz
3b: R = TBDPS
4a: R = Bz
4b: R = TBDPS

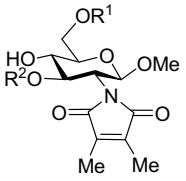
Scheme 1.

2. Results and discussion

The purpose of this work is to study the relative reactivity of acceptors **5**, **6a**, **6b**, and **6c** in competition with the highly reactive *N*-acetyloxazolidinone protected glucosamine **1a** by coupling with trichloroacetimidate **2b**. We considered it interesting to include in this study the *N*-dimethylmaleimido (DMM) glucosaminyl acceptors **6a**, **6b**, and **6c**, not only because this protecting group removes the deactivating hydrogen bond as well as the tendency toward amide glycosylation, but also because, as was shown by Schmidt and co-workers,[16] the *N*-DMM protected sugars are easily prepared, are stable enough to acid and nonnucleophilic bases, and are readily transformed into their corresponding *N*-acetyl derivatives.

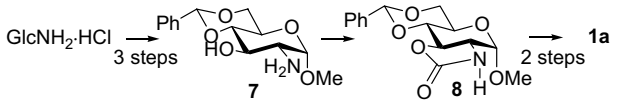


5



6a: R^1 = R^2 = Bz
6b: R^1 = Bn; R^2 = Bz
6c: R^1 = R^2 = Bn
6d: R^1 = R^2 = HCO
6e: R^1 = Me; R^2 = HCO
6f: R^1 = R^2 = Me

The acceptors **1a**, **5**, **6a**, **6b**, and **6c** were prepared by standard techniques. The preparation of **1a** was carried out following the sequence described by Crich and Vinod[10] from glucosamine hydrochloride, except that for the transformation of the 4,6-*O*-benzylidene-protected glucosamine **7** into the corresponding oxazolidinone **8** (Scheme 2), we found it more convenient to use triphosgene [bis(trichloromethyl)carbonate] in anhydrous EtOAc and Et_3N,[17] instead of *p*-nitrophenyl chloroformate and Amberlyst IR-120 resin. Under these

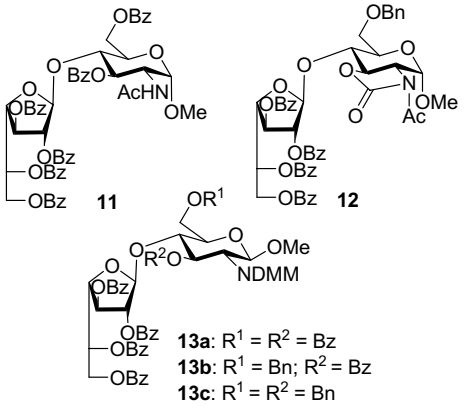


Scheme 2.

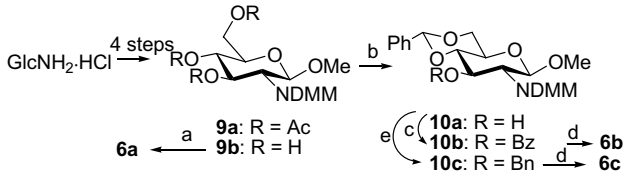
conditions the yield of **8** is excellent (87% after a column chromatography) and the workup is very simple.

For the preparation of **5** we have followed the sequence previously described.[18] Acceptors **6a**, **6b**, and **6c** were readily prepared from the known triol **9b**[16,19] (Scheme 3). Regioselective benzoylation of **9b** afforded **6a** in 69% yield, while 4,6-*O*-benzylidene protection of **9b**, followed by benzoylation or benzylation and reductive opening of the benzylidene group, gave **6b** or **6c** in 89% and 51% overall yield, respectively.

Each acceptor was then coupled with the tetra-*O*-benzoyl galactofuranosyl trichloroacetimidate donor (**2b**),[11,12,20] which was activated with TMSOTf to give the disaccharides **11**, **12**, **13a**, **13b**, and **13c** that were characterized by spectroscopic methods (see Section 3) as the β anomers.



With authentic samples of disaccharides **11**, **12**, **13a**, **13b**, and **13c** in hand, we carried out a series of competitive glycosylation experiments in which **2b** was allowed to react under the same reaction conditions with an equimolecular mixture of **1a** and acceptors **5**, **6a**, **6b**, and **6c**, respectively. The crude reaction mixtures were



Scheme 3. Reagents and conditions: (a) benzoyl chloride, Py, −40 °C; (b) benzaldehyde dimethyl acetal, CSA, DMF; (c) benzoyl chloride, Py, 0 °C; (d) $BH_3{\cdot}N(CH_3)_3$, $BF_3{\cdot}OEt_2$ CH_3CN; (e) $BnOC(NH)CCl_3$, TfOH, 0 °C.

then analyzed by HPLC to determine the ratios of the disaccharides obtained. As expected, the oxazolidinone-protected glucosamine acceptor **1a** was shown to be eleven times more reactive than the acetamido derivative **5** (**12**:**11**, 11:1), whereas **1a** was seven times more reactive than the *N*-DMM-protected acceptor **6a** (**12**:**13a**, 7:1).

Interestingly enough, the competitive experiment between **1a** and **6b** showed that both acceptors displayed rather similar reactivities (**12**:**13b**, 1.5:1), whereas **6c** was shown to be quite more reactive than **1a** (**12**:**13c**, 1:4). The ratios were also determined by ^{1}H NMR spectroscopy of the mixtures as explained in Section 3. Although the slightly higher reactivity of **1a** in comparison with **6b** can be attributed to the restricted nature of the protection on O-3 that minimizes the steric hindrance on 4-OH,[10] and the known activating and deactivating effect of electron-donating and electron-withdrawing groups can be invoked to explain that **6c** was the most reactive acceptor and that **6b** was more reactive than **6a** (3,6-di-*O*-benzyl in **6c** and 3-*O*-benzoyl-6-*O*-benzyl in **6b** vs 3,6-di-*O*-benzoyl in **6a**),[21] it seemed to us interesting to rationalize the differential reactivity of these acceptors.

Analogs of **1a**, **6a**, **6b**, and **6c** where the benzoyl groups were replaced by a formyl moiety, and the benzyl groups were replaced by a methyl group (**1c**, **6d**, **6e**, and **6f**, respectively) were submitted to minimization using DFT at the B3LYP/6-31+G** level. This level of basis set was considered necessary to yield good results on carbohydrates.[22] As Table 1 shows, the conformation showing a hydrogen bond between H(O)-4 and O-6 is preferential in the cases where a methyl group resides on O-6. Modeling of the compound **6d**, which carries a formyl group on C-6, shows the alternative conformation as the main one (Table 1), indicating than it can predict a weaker hydrogen bonding on a oxygen involved in an ester function. The same result is observed by looking at the distance between H(O)-4 and O-3 in the alternative conformation for the four compounds (Table 1): the shortest is that occurring for the 3-O-methylated compound, as expected considering its enhanced nucleophilic character.[23] Although it is not expected that a methyl or a formyl group can reproduce exactly the features of a benzyl or a benzoyl, respectively, it is expected that they should show the projected trend, considering that modeling of such large groups is difficult at this level of theory.

Chemical reactivity can be discussed within the framework of density functional theory (DFT).[24–26] The introduction of numerical descriptors[24–28] has provided quantitative concepts for the reactivity of different compounds, as well as of sites within the same compound with nucleophilic, electrophilic, and radical reagents. One of the more common descriptors of reactivity is the Fukui function, related to the electron density in

Table 1. Energy and selected geometry data on the two main conformers (a and b) obtained for compounds **1c**, **6d**, **6e**, and **6f** calculated at the B3LYP/6-31+G** level

	Relative E (kcal)	$\theta_{O\text{-}5\text{–}C\text{-}5\text{–}O\text{-}6\text{–}C\text{-}6}$ (°)	$\theta_{H\text{-}4\text{–}C\text{-}4\text{–}O\text{-}4\text{–}H\text{-}4}$ (°)	$d_{HO\text{-}4\text{–}O\text{-}3}$ (Å)	$d_{HO\text{-}4\text{–}O\text{-}6}$ (Å)
1c, a	2.76	73	−170	3.23	—
1c, b	0.00	178	69	—	2.04
6d, a	0.00	72	−94	2.78	—
6d, b	2.23	180	61	—	2.18
6e, a	0.83	70	−96	2.77	—
6e, b	0.00	−179	69	—	2.03
6f, a	1.31	71	−65	2.38	—
6f, b	0.00	180	70	—	2.01

the frontier molecular orbitals HOMO (for electrophilic attack) and LUMO (for nucleophilic attack).[24,26–28] However, this approach seems to be valid when, in the application of the hard and soft acids and base principle (HSAB), the interaction between nucleophile and electrophile corresponds to a soft–soft interaction.[26,29] On the other hand, the hard–hard interactions are not frontier controlled, and a different descriptor of reactivity is needed.[26] For such systems, it was postulated that either a minimal value of the Fukui function[26] or a maximum value of the net charge is required at the reaction site.[29]

For each conformer, charge and Fukui functions were determined. It is not expected that vacuum calculations will reproduce the behavior of these molecules in a dichloromethane solution (containing small amounts of acetonitrile). However, probably the low polarity of the solvent will not introduce large differences, and thus the present modeling can help just as an approximation to the real system. Table 2 shows the results for each of the compounds carrying conformation b as the main one (**1c**, **6e**, and **6f**), considering Boltzmann-averaged populations. The less reactive oxazolidinone derivative (**1a**/**1c**) shows a smaller charge and a higher Fukui function on O-4 (Table 2) than the more reactive **6c**/**6f**. Either data agree with a reaction that is not frontier controlled (hard–hard).[26,29] Charge considerations are also supportive of the similar reactivity of **1c** and **6f** analogs, but the Fukui function is always higher for the oxazolidinone derivatives. However, when the hardness/softness of the compound is taken into account,[29] the local softness on O-4 is smaller for the more reactive compound (analog of **6f**) and similar for the other two compounds, as expected for a hard–hard interaction. Within the *N*-DMM-substituted derivatives, calculations of the Fukui function made by evaluation of the HOMO orbital[28] also show decreasing values with increasing reactivity, as postulated by Li and Evans for hard–hard interactions.[26]

In conclusion, based on our experimental observations together with the rationalization of the differential reactivity of several glucosaminyl acceptors, we believe that the easily prepared acceptor **6c**, bearing Schmidt's *N*-DMM protecting group, represents an interesting alternative for the synthesis of 4-linked glucosamine oligosaccharides.

Table 2. Reactivity descriptors determined for the O-4 of compounds **1c**, **6e**, and **6f**

	1c	**6e**	**6f**
Charge $q_{O\text{-}4}$	−0.49	−0.50	−0.52
Fukui function $f^-_{O\text{-}4}$ [a]	0.100	0.074	0.054
Fukui function $f^-_{O\text{-}4}$ [b]	0.255	0.057	0.052
Softness $s^-_{O\text{-}4}$ [c]	0.41	0.44	0.33
Softness $s^-_{O\text{-}4}$ [d]	0.72	0.74	0.48
Softness $s^-_{O\text{-}4}$ [e]	0.63	0.69	0.44
Softness $s^-_{O\text{-}4}$ [f]	0.69	0.74	0.47

[a] Determined by the method of Yang and Mortier.[27]
[b] Determined by the method of Contreras et al.[28]
[c] Using the Fukui function determined from Mulliken charges.[27]
[d] Using the Fukui function determined from fitting to the electrostatic potential.[30]
[e] Using the Fukui function determined from charges obtained according to the CHelp scheme.[31]
[f] Using the Fukui function determined from charges obtained according to the CHelpG scheme.[32]

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 a Bruker AC 200 spectrometer for $CDCl_3$ solutions with Me_4Si as internal standard. For the 2D and COSY experiments, Bruker standard software was employed. Mass spectra were measured using MALDI-TOF HRMS and HRFABMS at the UCR Mass Spectrometry Facility (Department of Chemistry, University of California Riverside, USA) and Kent Mass Spectrometry (Kent, UK). Optical rotations were measured with a Jasco DIP-1000 polarimeter. High-performance liquid chromatography (HPLC) was performed using a HP 1100 with Lichrospher RP-8 (5 μm), a Quat pump, and gradient controller equipped with a variable wavelength UV detector. 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

(except where noted). Analytical TLC was carried out using Kieselgel GF254 (E. Merck) with a thickness of 0.20 mm. The homogeneity of all disaccharides 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 2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl-(1→4)-2-acetamido-3,6-di-*O*-benzoyl-2-deoxy-α-D-glucopyranoside (11)

A suspension of the known acceptor **5**[18] (248 mg, 0.56 mmol), donor **2b**[11,12,20] (436.5 mg, 0.59 mmol), activated 4 Å molecular sieves (127.5 mg) in anhyd CH_2Cl_2 (19 mL), and CH_3CN (640 μL) was stirred at room temperature. After 40 min, the mixture was cooled to −30 °C, TMSOTf (106 μL, 0.58 mmol) was slowly added, and the stirring was continued for 4 h. The mixture was then neutralized by addition of solid $NaHCO_3$ (225 mg) and filtered through a silica gel pad with copious washings with EtOAc. The filtrate was dried (Na_2SO_4) and evaporated. The residue was chromatographed to yield **11** (167 mg, 29%), as a foamy solid: $[\alpha]_D^{33}$ +57.7 (*c* 1.03, $CHCl_3$); R_f 0.44 (1:4 hexane–EtOAc); ^{1}H NMR: δ 8.15–7.00 (m, 30H, ArH), 5.77 (d, 1H, $J_{NH,2}$ 9.5 Hz, NH), 5.68–5.55 (m, 2H, H-5′, H-3′), 5.65 (dd, 1H, $J_{3,4}$ 9.0, $J_{3,2}$ 10.7 Hz, H-3), 5.43 (s, 1H, H-2′), 5.33 (s, 1H, H-1′), 4.89 (dd, 1H, $J_{6a,5}$ 1.5, $J_{6a,b}$ 12.0 Hz, H-6a), 4.78 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.64 (dd, 1H, $J_{6b,5}$ 3.6 Hz, H-6b), 4.58–4.44 (m, 1H, H-2), 4.37–4.16 (m, 5H, H-6′a, H-6′b, H-4′, H-4, H-5), 3.45 (s, 3H, OCH_3), 1.81 (s, 3H, CO*CH*$_3$); ^{13}C NMR: δ 169.65 (*CO*CH_3), 165.90–164.90 (CO × 6), 132.75–132.58, 129.50–127.31 (C–Ar), 106.51 (C-1′), 98.12 (C-1), 82.17 (C-2′), 81.92 (C-4′), 77.03 (C-3′), 74.54 (C-5), 71.82 (C-3), 69.64 (C-5′), 68.64 (C-4), 62.91 (C-6′), 62.44 (C-6), 54.79 (OCH_3), 51.64 (C-2), 22.22 (CO*CH*$_3$); MALDI-TOF HRMS: calcd for $C_{57}H_{51}NO_{17}$ $[M+Na]^+$, *m*/*z* 1044.3055; found, *m*/*z* 1044.3033.

3.3. Preparation of 1a

Compound **1a** was prepared essentially as previously described and identified by comparison of NMR data with that reported,[10] except for the transformation of **7** into **8**.

3.3.1. Preparation of 8. To a stirred solution of compound **7** (1.83 g, 6.51 mmol) in anhyd EtOAc (108 mL) was added anhyd Et_3N (1.8 mL, 12.8 mmol) and then triphosgene (644 mg, 14.6 mmol). The reaction mixture was stirred at room temperature for 1 h (TLC) after which time it was filtered, concentrated, and purified by flash chromatography with 55:45 hexane–EtOAc to give **8** as a white solid (1.74 g, 87%): mp 209.3–210.6 °C, lit.[10] 198 °C. This compound was identified by comparison of NMR data with that previously reported.

3.4. Methyl 2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl-(1→4)-2-acetamido-6-*O*-benzyl-2-*N*,3-*O*-carbonyl-2-deoxy-α-D-glucopyranoside (12)

A suspension of acceptor **1a**[10] (183.7 mg, 0.52 mmol), donor **2b**[11,12,20] (411.7 mg, 0.56 mmol), activated 4 Å molecular sieves (120 mg) in anhyd CH_2Cl_2 (10 mL), and CH_3CN (595 μL) was stirred at room temperature. After 40 min, the mixture was cooled to −30 °C, TMSOTf (100 μL, 0.55 mmol) was slowly added, and the stirring was continued for 4 h. The mixture was then neutralized by addition of solid $NaHCO_3$ (200 mg) and filtered through a silica gel pad with copious washings with CH_2Cl_2. The filtrate was dried (Na_2SO_4) and evaporated. The residue was chromatographed to yield **12** (308.6 mg, 64%), as a foamy solid: $[\alpha]_D^{29}$ +44.8 (*c* 1.01, $CHCl_3$); R_f 0.61 (1:4 hexane–EtOAc); ^{1}H NMR: δ 8.20–7.00 (m, 25H, ArH), 6.15–6.05 (m, 1H, H-5′), 5.60 (br s, 1H, H-1), 5.59 (d, 1H, $J_{3',4'}$ 3.2 Hz, H-3′), 5.31 (d, 1H, $J_{2',1'}$ 1.1 Hz, H-2′), 5.24 (br s, 1H, H-1′), 4.91 (dd, 1H, $J_{4',5'}$ 5.9 Hz, H-4′), 4.83 (s, 1H, H-6′b), 4.80 (br s, 1H, H-6′a), 4.64 (d, 1H, *J* 12.0 Hz, *CH*$_2$Ph), 4.63 (dd, 1H, $J_{3,4}$ 10.3, $J_{3,2}$ 12.0 Hz, H-3), 4.52 (d, 1H, *CH*$_2$Ph), 4.32 (dd with appearance of t, 1H, $J_{4,5}$ 9.2 Hz, H-4), 3.94 (dd, 1H, $J_{6a,5}$ 2.6, $J_{6a,b}$ 10.8 Hz, H-6a), 3.86–3.65 (m, 3H, H-2, H-5, H-6b), 3.44 (s, 3H, OCH_3), 2.50 (s, 3H, CO*CH*$_3$); ^{13}C NMR: δ 171.08 (*CO*CH_3), 165.96 (CO), 165.64 (CO × 2), 165.58 (CO × 2), 152.88 (CO), 137.65, 133.34–132.78, 129.97–127.57 (C–Ar), 105.37 (C-1′), 96.78 (C-1), 82.28 (C-2′), 81.12 (C-4′), 77.30 (C-3′), 75.48 (C-3), 73.40 (*CH*$_2$Ph), 72.52 (C-5), 72.43 (C-4), 70.14 (C-5′), 67.31 (C-6), 64.08 (C-6′), 59.97 (C-2), 55.81 (OCH_3), 23.64 (CO*CH*$_3$); MALDI-TOF HRMS: calcd for $C_{51}H_{47}NO_{17}$ $[M+Na]^+$, *m*/*z* 952.2793; found, *m*/*z* 952.2748.

3.5. Methyl 2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl-(1→4)-3,6-di-*O*-benzoyl-2-deoxy-2-dimethylmaleimido-β-D-glucopyranoside (13a)

A mixture of the triacetate **9a**[16,19] (1.54 g, 3.62 mmol), anhyd MeOH (36 mL) and NaOMe solution (0.169 M, 2.2 mL) was stirred at room temperature. After 2.30 h, the solution was neutralized with Amberlite IR-120 (H^+) resin, filtered, and evaporated. The residue was chromatographed (9:1 EtOAc–MeOH) to yield **9b** (1.1 g, 100%), as a foamy solid. To a stirred solution of **9b** (393 mg, 1.30 mmol) in anhyd pyridine (7.2 mL) at −40 °C was added dropwise freshly distilled benzoyl chloride (390 μL, 3.36 mmol). The reaction mixture was stirred for 2 h between −35 and −30 °C, and then

it was allowed to slowly warm to room temperature. After 15 h, water was added, the mixture was stirred for 10 min and then extracted with CH_2Cl_2. The organic layer was washed with 1 N HCl, satd aq $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to yield **6a** (454.6 mg, 69%), as a foamy solid: $[\alpha]_D^{18}$ +63.76 (*c* 1.01, $CHCl_3$); ^1H NMR: δ 8.17–7.98, 7.67–7.30 (2m, 10H, ArH), 5.72 (dd, 1H, $J_{3,4}$ 8.4, $J_{3,2}$ 10.7 Hz, H-3), 5.22 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1), 4.77 (dd, 1H, $J_{6a,5}$ 3.7, $J_{6a,b}$ 12.0 Hz, H-6a), 4.66 (dd, 1H, $J_{6b,5}$1.9 Hz, H-6b), 4.21 (dd, 1H, H-2), 3.90–3.75 (m, 1H, H-5), 3.83 (dd with appearance of t, 1H, $J_{4,5}$ 9.7 Hz, H-4), 3.47 (s, 3H, OCH_3), 1.87 (s, 6H, $CCH_3 \times 2$); ^{13}C NMR: δ 171.38 ($CO \times 2$), 167.01 (CO), 166.81 (CO), 137.28 ($C \times 2$), 133.43–128.33 (C–Ar), 99.08 (C-1), 74.48 (C-4), 74.28 (C-5), 70.28 (C-3), 63.44 (C-6), 56.77 (OCH_3), 54.09 (C-2), 8.60 ($CCH_3 \times 2$). A suspension of acceptor **6a** (70.4 mg, 0.14 mmol), donor **2b**[11,12,20] (124.2 mg, 0.17 mmol), activated 4 Å molecular sieves (50 mg) in anhyd CH_2Cl_2 (4.8 mL), and CH_3CN (160 μL) was stirred at room temperature. After 40 min, the mixture was cooled to −30 °C, TMSOTf (27 μL, 0.15 mmol) was slowly added, and the stirring was continued for 4 h. The mixture was then neutralized by addition of solid $NaHCO_3$ (245 mg) and filtered through a silica gel pad with copious washings with EtOAc. The filtrate was dried (Na_2SO_4) and evaporated. The residue was chromatographed to yield **13a** (67.1 mg, 56%), as a foamy solid: $[\alpha]_D^{34}$ +50.5 (*c* 1.02, $CHCl_3$); R_f 0.16 (7:3 hexane–EtOAc); ^1H NMR: δ 8.10–7.05 (m, 30H, ArH), 6.03 (dd, 1H, $J_{3,4}$ 8.9, $J_{3,2}$ 10.6 Hz, H-3), 5.65–5.54 (m, 1H, H-5′), 5.59 (d, 1H, $J_{3',4'}$ 4.1 Hz, H-3′), 5.42 (s, 1H, H-1′), 5.33 (br s, 1H, H-2′), 5.29 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1), 4.96 (dd, 1H, $J_{6a,5}$ 1.7, $J_{6a,b}$ 12.2 Hz, H-6a), 4.69 (dd, 1H, $J_{6b,5}$ 3.9 Hz, H-6b), 4.36–4.15 (m, 5H, H-2, H-4, H-4′, H-6′a,H-6′b), 4.08–3.97 (m, 1H, H-5), 3.46 (s, 3H, OCH_3), 1.84 (s, 6H, $CCH_3 \times 2$); ^{13}C NMR: δ 171.28 ($CO \times 2$), 165.85–165.42 ($CO \times 6$), 133.35 ($C \times 2$), 133.21–128.08 (C–Ar), 107.21 (C-1′), 99.07 (C-1), 82.72 (C-2′), 82.15 (C-4′), 77.03 (C-3′), 76.12 (C-4), 73.08 (C-5), 71.73 (C-3), 69.86 (C-5′), 63.25 (C-6′), 62.79 (C-6), 56.77 (OCH_3), 54.71 (C-2), 8.54 ($CCH_3 \times 2$); MALDI-TOF HRMS: calcd for $C_{61}H_{53}NO_{18}$ $[M+Na]^+$, *m*/*z* 1110.3155; found, *m*/*z* 1110.3130.

3.6. Methyl 2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl-(1→4)-3-*O*-benzoyl-6-*O*-benzyl-2-deoxy-2-dimethylmaleimido-β-D-glucopyranoside (13b)

To a stirred solution of **9b** (107 mg, 0.36 mmol), in anhyd DMF (1.8 mL) was added benzaldehyde dimethyl acetal (109 μL, 0.19 mmol) and a catalytic amount of camphorsulfonic acid, and the mixture was stirred overnight at room temperature. The reaction mixture was neutralized with solid Na_2CO_3 and diluted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to yield **10a** (116.9 mg, 85%), as a foamy solid: ^1H NMR: δ 7.52–7.32 (m, 5H, ArH), 5.55 (s, 1H, *CH*Ph), 5.03 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1), 4.46 (dd, 1H, $J_{3,4}$ 8.8, $J_{3,2}$ 10.5 Hz, H-3), 4.37 (dd, 1H, $J_{6a,5}$ 4.3, $J_{6a,b}$ 10.9 Hz, H-6a), 3.98 (dd, 1H, H-2), 3.83 (dd with appearance of t, 1H, $J_{4,5}$ 9.9 Hz, H-4), 3.61–3.51 (m, 2H, H-5, H-6b), 3.44 (s, 3H, OCH_3), 1.96 (s, 6H, $CCH_3 \times 2$); ^{13}C NMR: δ 171.61 ($CO \times 2$), 137.02 ($C \times 2$), 136.85, 128.96–126.07 (C–Ar), 101.51 (*CH*Ph), 99.65 (C-1), 81.88 (C-4), 68.27 (C-3), 68.36 (C-6), 65.81 (C-5), 56.64 (OCH_3), 56.10 (C-2), 8.48 ($CCH_3 \times 2$).

To a stirred suspension of **10a** (116.9 mg, 0.30 mmol) in anhyd pyridine (600 μL) in an ice-water bath was added dropwise freshly distilled benzoyl chloride (140 μL, 1.21 mmol). The reaction mixture was allowed to slowly warm to room temperature. After 15 h, water was added, and the mixture was stirred for 10 min and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to yield **10b** (119.3 mg, 81%), as a foamy solid: ^1H NMR: δ 8.00–7.90 (m, 2H, ArH), 7.60–7.25 (m, 8H, ArH), 5.98 (dd, 1H, $J_{3,4}$ 9.2, $J_{3,2}$ 10.3 Hz, H-3), 5.53 (s, 1H, *CH*Ph), 5.27 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1), 4.50–4.37 (m, 1H, H-5), 4.22 (dd, 1H, H-2), 3.89 (dd, 1H, $J_{6a,5}$ 2.5, $J_{6a,b}$ 9.4 Hz, H-6a), 3.87–3.52 (m, 2H, H-4, H-6b), 3.48 (s, 3H, OCH_3), 1.88 (br s, 6H, $CCH_3 \times 2$). ^{13}C NMR: δ 171.26 ($CO \times 2$), 164.47 (CO), 137.29 (C–Ar), 137.02 ($C \times 2$), 133.74–126.14 (C–Ar), 101.44 (*CH*Ph), 99.38 (C-1), 81.23 (C-4), 68.88 (C-6), 66.97 (C-5), 62.42 (C-3), 55.47 (OCH_3), 53.93 (C-2), 8.80 ($CCH_3 \times 2$).

To a solution of **10b** (29.5 mg, 0.06 mmol) and $BH_3{\cdot}N(CH_3)_3$ (9.8 mg, 0.14 mmol) in CH_3CN (600 μL) in an ice-water bath was added dropwise $BF_3{\cdot}OEt_2$ (15 μL, 0.14 mmol). After 1 h at this temperature, the solution was stirred at room temperature for an additional 0.5 h (TLC). $NaHCO_3$ (8.5 mg) was then added, and the solution was evaporated to dryness. The crude product in CH_2Cl_2 was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to yield **6b** (26.4 mg, 89%), as a foamy solid: $[\alpha]_D^{25}$ +48.95 (*c* 0.98, $CHCl_3$); ^1H NMR: δ 8.00–7.90 (m, 2H, ArH), 7.63–7.25 (m, 8H, ArH), 5.70 (dd, 1H, $J_{3,4}$ 8.6, $J_{3,2}$ 10.8 Hz, H-3), 5.17 (d, 1H, $J_{1,2}$ 8.6 Hz, H-1), 4.67 (d, 1H, *J* 12.2 Hz, CH_2Ph), 4.59 (d, 1H, CH_2Ph), 4.19 (dd, 1H, H-2), 3.97–3.82 (m, 3H, H-6a, H-6b, H-4), 3.80–3.67 (m, 1H, H-5), 3.47 (s, 3H, OCH_3), 3.24 (d, 1H, $J_{OH,4}$ 2.8 Hz, OH), 1.87 (s, 6H, $CCH_3 \times 2$); ^{13}C NMR: δ 171.32 ($CO \times 2$), 166.66 (CO), 137.65 ($C \times 2$), 137.12, 133.22–127.52 (C–Ar), 98.83 (C-1), 74.47 (C-5*), 74.38 (C-3*), 73.48 (CH_2Ph), 71.15 (C-4), 69.62 (C-6), 56.63 (OCH_3), 54.02 (C-2), 8.48 ($CCH_3 \times 2$) (the assignments for signals marked with an asterisk (*) may be reversed).

A suspension of acceptor **6b** (60 mg, 0.12 mmol), donor **2b**[11,12,20] (117 mg, 0.16 mmol), activated 4 Å molecular sieves (51 mg) in anhyd CH_2Cl_2 (4.6 mL), and CH_3CN (155 μL) was stirred at room temperature. After 40 min, the mixture was cooled to −30 °C, TMSOTf (26 μL, 0.15 mmol) was slowly added, and the stirring was continued for 4 h. The mixture was then neutralized by addition of solid $NaHCO_3$ (220 mg) and filtered through a silica gel pad with copious washings with EtOAc. The filtrate was dried (Na_2SO_4) and evaporated. The residue was chromatographed to yield **13b** (65.8 mg, 70% based on the recovered starting material, 16.8 mg), as a foamy solid: $[\alpha]_D^{27}$ +44.2 (*c* 1.00, $CHCl_3$); R_f 0.38 (1:1 hexane–EtOAc); ^{1}H NMR: δ 8.12–7.19 (m, 30H, ArH), 5.96 (dd, 1H, $J_{3,4}$ 9.2, $J_{3,2}$ 10.7 Hz, H-3), 5.59–5.51 (m, 2H, H-5′, H-3′), 5.45 (s, 1H, H-1′), 5.30 (br s, 1H, H-2′), 5.22 (d, 1H, $J_{1,2}$ 8.6 Hz, H-1), 4.64 (d, 1H, *J* 12.2 Hz, CH_2Ph), 4.55 (d, 1H, CH_2Ph), 4.36–4.07 (m, 5H, H-2, H-4, H-4′, H-6′a, H-6′b), 4.02 (dd, 1H, $J_{6a,5}$ 3.0, $J_{6a,b}$ 11.4 Hz, H-6a), 3.88 (dd, 1H, $J_{6b,5}$ 1.3 Hz, H-6b), 3.83–3.76 (m, 1H, H-5), 3.48 (s, 3H, OCH_3), 1.84 (br s, 6H, CCH_3 × 2); ^{13}C NMR: δ 171.28 (CO × 2), 165.69–165.28 (CO × 5), 137.13 (C × 2), 133.32–127.38 (C–Ar), 106.39 (C-1′), 99.05 (C-1), 82.28 (C-2′), 82.03 (C-4′), 77.18 (C-3′), 74.83 (C-4, C-5), 73.08 (CH_2Ph), 71.84 (C-3), 69.91 (C-5′), 67.94 (C-6′), 63.39 (C-6), 56.59 (OCH_3), 54.71 (C-2), 8.50 (CCH_3 × 2); MALDI-TOF HRMS: calcd for $C_{61}H_{55}NO_{17}$ $[M+Na]^+$, *m*/*z* 1096.3362; found, *m*/*z* 1096.3351.

3.7. Methyl 2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-dimethylmaleimido-β-D-glucopyranoside (13c)

To a solution of **10a** (198 mg, 0.51 mmol) in anhyd CH_2Cl_2 (1.0 mL) were added benzyl 2,2,2-trichloroacetimidate (190 μL, 1.02 mmol) and activated 4 Å molecular sieves (254 mg), and the mixture was stirred at room temperature for 45 min. Then the mixture was cooled in an ice-water bath, and a catalytic amount of TfOH (5.0 μL, 0.06 mmol) was added dropwise. After 2.30 h (TLC), a few drops of Et_3N were added, and the stirring was continued for a further 20 min. The mixture was then filtered through a silica gel pad with copious washings with CH_2Cl_2. The filtrate was evaporated, and the residue was chromatographed to yield **10c** (242 mg, 99%) as a foamy solid: ^{1}H NMR: δ 7.58–7.05 (m, 10H, ArH), 5.60 (s, 1H, *CH*Ph), 4.97 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1), 4.82 (d, 1H, *J* 12.4 Hz, CH_2Ph), 4.48 (d, 1H, CH_2Ph), 4.39 (dd, 1H, $J_{6a,5}$ 4.7, $J_{6a,b}$ 10.4 Hz, H-6a), 4.28 (dd, 1H, $J_{3,4}$ 8.8, $J_{3,2}$ 10.4 Hz, H-3), 3.96 (dd, 1H, H-2), 3.83 (t, 1H, H-6b), 3.74 (dd with appearance of t, 1H, $J_{4,5}$ 8.8 Hz, H-4), 3.63–3.51 (m, 1H, H-5), 3.40 (s, 3H, OCH_3), 1.84 (br s, 6H, CCH_3 × 2); ^{13}C NMR: δ 171.35 (CO × 2), 138.03, 137.12 (C–Ar), 136.81 (C × 2), 128.84–125.87 (C–Ar), 101.10 (*CH*Ph), 99.72 (C-1), 82.76 (C-4), 74.90 (C-3), 73.93 (CH_2Ph), 68.55 (C-6), 65.83 (C-5), 56.71 (OCH_3), 55.31 (C-2), 8.49 (CCH_3 × 2).

To a solution of **10c** (175 mg, 0.36 mmol) and $BH_3{\cdot}N(CH_3)_3$ (72 mg, 1.02 mmol) in CH_3CN (5.1 mL) in an ice-water bath was added dropwise $BF_3{\cdot}OEt_2$ (127 μL, 1.18 mmol). After 1 h at this temperature, the solution was stirred at room temperature for an additional 0.5 h (TLC). $NaHCO_3$ (72 mg) was then added, and the solution was evaporated to dryness. The crude product in CH_2Cl_2 was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to yield **6c** (90 mg, 51%), as a foamy solid: $[\alpha]_D^{32}$ +41.51 (*c* 0.40, $CHCl_3$); ^{1}H NMR: δ 7.40–7.08 (m, 10H, ArH), 4.90 (d, 1H, $J_{1,2}$ 8.4 Hz, H-1), 4.77 (d, 1H, *J* 12.2 Hz, 3-OCH_2Ph), 4.64 (d, 1H, *J* 12.2 Hz, 6-OCH_2Ph), 4.56 (d, 1H, 6-OCH_2Ph), 4.50 (d, 1H, 3-OCH_2Ph), 4.08 (dd, 1H, $J_{3,4}$ 8.1, $J_{3,2}$ 10.8 Hz, H-3), 3.91 (dd, 1H, H-2), 3.81–3.70 (m, 3H, H-4, H-6a, H-6b), 3.63–3.53 (m, 1H, H-5), 3.37 (s, 3H, OCH_3), 2.95 (br s, 1H, OH), 1.82 (s, 6H, CCH_3 × 2); ^{13}C NMR: δ 171.49 (CO × 2), 138.39, 137.50 (C–Ar), 136.77 (C × 2), 128.29–127.23 (C–Ar), 99.06 (C-1), 79.11 (C-4), 74.12 (CH_2Ph), 73.79 (C-3*), 73.54 (C-5*), 70.31 (C-6), 56.34 (OCH_3), 54.82 (C-2), 8.45 (CCH_3 × 2) (the assignments for signals marked with an asterisk (*) may be reversed).

A suspension of acceptor **6c** (53.5 mg, 0.10 mmol), donor **2b**[11,12,20] (101.6 mg, 0.14 mmol), activated 4 Å molecular sieves (56 mg) in anhyd CH_2Cl_2 (4.3 mL), and CH_3CN (139 μL) was stirred at room temperature. After 40 min, the mixture was cooled to −30 °C, TMSOTf (23 μL, 0.13 mmol) was slowly added, and the stirring was continued for 4 h. The mixture was then neutralized by addition of solid $NaHCO_3$ (196 mg) and filtered through a silica gel pad with copious washings with EtOAc. The filtrate was dried (Na_2SO_4) and evaporated. The residue was chromatographed to yield **13c** (82 mg, 70%), as a foamy solid: $[\alpha]_D^{32}$ +30.3 (*c*, 1.04, $CHCl_3$); R_f 0.11 (CH_2Cl_2); ^{1}H NMR: δ 8.05–7.10 (m, 30H, ArH), 5.91–5.83 (m, 1H, H-5′), 5.62 (d, 1H, $J_{3',4'}$ 4.9 Hz, H-3′), 5.59 (s, 1H, H-1′), 5.47 (s, 1H, H-2′), 4.89 (d, 1H, $J_{1,2}$ 8.2 Hz, H-1), 4.84 (d, 1H, *J* 12.0 Hz, 3-OCH_2Ph), 4.72 (t, 1H, $J_{4',5'}$ 4.3, H-4′), 4.60 (dd, 1H, $J_{6'a,5'}$ 7.3, $J_{6'a,b}$ 12.2 Hz, H-6′a), 4.60 (d, 1H, *J* 12.4 Hz, 6-OCH_2Ph), 4.51 (d, 1H, 6-OCH_2Ph), 4.49–4.37 (m, 1H, H-6′b), 4.41 (d, 1H, 3-OCH_2Ph), 4.25 (dd, 1H, $J_{3,4}$ 8.8, $J_{3,2}$ 10.3 Hz, H-3), 4.11 (dd with appearance of t, 1H, $J_{4,5}$ 8.8 Hz, H-4), 4.02 (dd, 1H, H-2), 3.96 (dd, 1H, $J_{6a,5}$ 3.4, $J_{6a,b}$11.2 Hz, H-6a), 3.82 (dd, 1H, $J_{6b,5}$ 0.9 Hz, H-6b), 3.68–3.57 (m, 1H, H-5), 3.39 (s, 3H, OCH_3), 1.78 (s, 6H, CCH_3 × 2); ^{13}C NMR: δ 171.53 (CO × 2), 165.82–165.60 (CO × 4), 138.22–137.94 (C–Ar), 136.81 (C × 2), 133.39–127.31 (C–Ar), 106.14 (C-1′), 99.15 (C-1), 82.38 (C-2′), 82.05 (C-4′), 78.78 (C-3), 77.79 (C-3′), 76.14 (C-4), 74.94 (C-5), 74.85 (3-OCH_2Ph), 73.05 (6-OCH_2Ph), 70.57 (C-5′), 68.11

(C-6), 63.63 (C-6′), 56.20 (OCH_3), 55.46 (C-2), 8.47 ($CCH_3 \times 2$); HRFABMS: calcd for $C_{61}H_{57}NO_{16}$ $[M+Na]^+$, *m*/*z* 1082.3575; found, *m*/*z* 1082.3582.

3.8. Competition experiments

The mixtures of acceptors **1a** and **5**, **1a** and **6a**, **1a** and **6b**, and **1a** and **6c** (1.0 equiv of each) were glycosylated as described for the preparation of disaccharides **11**, **12**, **13a**, **13b**, and **13c**, using 1.2 equiv of donor **2b**. The resulting mixtures of products were analyzed using HPLC. The ratios of disaccharides **12**:**11**,**12**:**13a**, **12**:**13b**, and **12**:**13c** were 11:1, 7:1, 1.5:1, and 1:4, respectively. The ratios of **12**:**13b** and **12**:**13c** were also determined by ^{1}H NMR spectroscopy of the mixtures of disaccharides after purification by column chromatography. By integration of the signals at 4.90 (dd, 1H, $J_{4',3'}$ 3.2, $J_{4',5'}$ 5.9 Hz, H-4′) in **12** and 5.45 (s, 1H, H-1′) in **13b** and at 5.24 (br s, 1H, H-1′) in **12** and 5.47 (s, 1H, H-2′) in **13c**, the ratios were **12**:**13b**, 1:1 and **12**:**13c**, 1:8, respectively.

3.9. Computational methods

Quantum mechanical calculations were performed using Gaussian 98W (version 5.2, revision A-7) with standard basis sets and default minimization methods and termination conditions.[33] In order to determine the best starting points for the QM calculations, a full search of the rotamers made by changing in turn all the exocyclic groups was done with MM3(92) (QCPE, Indiana University, USA).[34] The main conformers of **1c**, **6d**, **6e**, and **6f** were submitted to an AM1 calculation.[35] The conformer with the lowest energy in each case (using these methods) was used as one of the starting points for the DFT calculations (conformer a). The other one was selected to comply with a hydrogen bond between H(O)-4 and O-6 (conformer b). The Fukui functions were calculated as reported previously. With the Yang scheme,[27] the charge distribution was calculated for the ground-state molecules and for the radical cation (using an unrestricted calculation). The Fukui function was the difference between both values. Using the scheme of Contreras et al.,[28] the coefficients of the HOMO orbitals and the overlap integrals were taken from the output Gaussian file in an automatic fashion so as to determine the local values of the Fukui function on each atom. The determination of net charge attributed to each atom was made by several methods, including the regular Mulliken analysis, fits to the electrostatic potential according to the Merz–Singh–Kollman scheme,[30] the CHelp scheme,[31] and the CHelpG scheme.[32] The values of charge and Fukui function obtained for the O-4 of both conformers of each compound were Boltzmann averaged. Selected results are shown in Table 2. Global softness is the inverse of chemical hardness, which was calculated as $(E_{HOMO} + E_{LUMO})/2$, according to Pérez et al.[36] The local softness reported in the table is calculated by multiplying the global softness by the local Fukui function obtained using each charge distribution method.

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Supplementary data

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