Synthesis and Conformational Analysis of Fructose-Derived Scaffolds: Molecular Diversity from a Single Molecule

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Abstract: Bi- and tricyclic compounds were synthesized starting from fructose. The different hydroxyl groups present in fructose were exploited in the formation of a number of conformationally constrained sugar-based scaffolds, including azido acids. Introduction of an azido group and carboxy terminus into different bicyclic iodo ethers, allowed the synthesis of different conformationally constrained azido acids. Conformational analysis of compounds **10**, **11**, **17**, and **20** by NMR experiments assisted by molecular mechanics, allowed the determination of the distances between the relevant functional groups, that is the azido and carboxy functionalities.

Keywords: carbohydrates · C-glycosides · conformation analysis · NMR spectroscopy · scaffolds

Introduction

Carbohydrates are very abundant molecules and present many advantages for the construction of chiral scaffolds, cores, or templates over other biomolecules. Functionality, chirality, and structural diversity are all features of carbohydrate feedstock that are present to a lesser extent in other naturally occurring compounds such as amino acids. One of the common ways in which chirality is integrated into molecular targets is by carrying out transformations on a chiral core. Carbohydrates are probably the most abundant chiral molecules available naturally. They are, in fact, constituents of all major structural molecules in living systems. They occur alone in polymers such as starch, pectin, cellulose, and chitin. Carbohydrates can form a large portion of some glycoproteins and constitute much of the cell wall and extracellular slime of bacteria and other microorganisms.

The low cost, abundance, highest functional group density of any naturally occurring material, and the ease with which they can be obtained in a pure state are among the most important features that make carbohydrates prime candidates for the synthesis of chiral scaffolds,[1] with application in the areas of pharmaceutical and medicinal chemistry.[2] The key issue in this field is the development of better scaffolding structures for the presentation of binding functional groups in a specific orientation. For example, in the area of protein–protein interactions, it is generally believed that the size and the rigidity of the structural elements within a small molecule, such as monosaccharides, tend to provide better binding/interfering agents. β Turn mimetics for the inhibition of specific protein–protein interactions have been designed from carbohydrate cores; a β-D-glucose scaffold has been synthesized by Hirschmann et al.[3] and included in a cyclic peptide, as a mimetic of the natural somatostatin. So far, a number of monosaccharides has been used as scaffolds in mimetic construction aimed at the inhibition of receptor–ligand interactions.[4] The benefits of such carbohydrate scaffolds include an attractive balance between rigidity and diversity of functional group orientation. Sugar-derived scaffolds, such as tetrahydrofuran-based amino acid mimics,[5] have also been used for the preparation of unnatural oligomers as peptidomimetics, referred to as foldamers,[6] that is molecules that will adopt specific compact conformations. Besides the chemical synthesis of new molecules, elucidation of the three-dimensional structures is a prerequisite for a better understanding of biochemical recognition processes and for the rational design of carbohydrate-derived drugs. The recent advances in NMR spectroscopy, X-ray diffraction, and computer modeling methods[7] are nowadays supporting the development of new bioactive compounds.

In this context, we are interested in diversity-based organic synthesis aimed at synthesizing novel carbohydrate-based scaffolds as small molecules with structural rigidity, complex-

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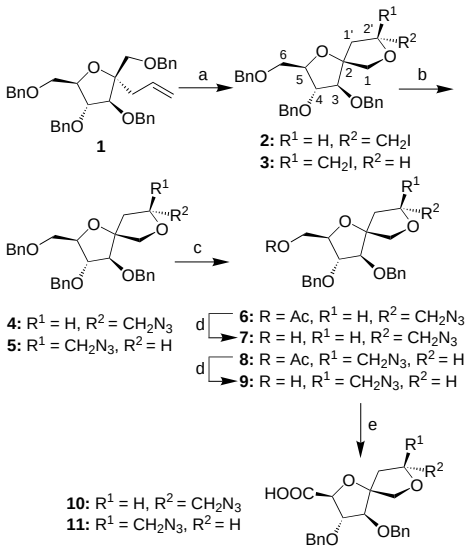
ity, and diversity. We present herein the synthesis and conformational analysis of polycyclic scaffolds derived from fructose, one of the most abundant natural sugars, focusing on the potentialities offered by the presence of two hydroxymethylene groups (the C-1 and C-6) and the unique reactivity of the anomeric position.

Results and Discussion

One possible method for the reduction of molecular flexibility is the introduction of a second, and possibly a third ring onto the sugar backbone. Towards this aim, bi- and tricyclic compounds were synthesized starting from fructose.

The different hydroxyl groups present in fructose (two primary, one secondary adjacent to the anomeric position, and the hemiacetal OH) were exploited in the formation of a number of conformationally constrained sugar-based scaffolds, including azido acids. The conformational rigidity was conferred by one or two additional rings in the carbohydrate skeleton, either fused or spiro, through the introduction of one or two suitably positioned double bonds into the molecule. Specifically, methyl fructofuranoside was benzylated according to the standard procedure (NaH, BnBr, DMF, quantitative yield), and an allylic group was then introduced at the anomeric position by Lewis acid-mediated C–C bond formation, one of the most widely used methods for C-glycosides synthesis.[8] The reaction usually proceeds via a cyclic oxocarbenium ion, which undergoes nucleophilic attack in a stereoelectronically controlled manner to provide the product with high stereoselectivity, both on pyranose[9] and furanose[10] rings. Hence, treatment of methyl 1,3,4,6-tetra-*O*-benzylfructofuranoside with allyltrimethylsilane in the presence of boron trifluoride etherate as Lewis acid catalyst afforded 2-(1′,3′,4′,6′-tetra-*O*-benzylfructofuranosyl)-2-propene (**1**) (98% yield, 60% *de*),[11] the only starting material used here for the creation of molecular diversity. The spatial relationship between the double bond and the oxygen at C-1 in the polybenzylated fructoside **1** is such that a 5-*exo* cyclization[12] can occur upon treatment with I_2 (1.2 equiv) in THF (Scheme 1) to afford two diastereoisomeric spiro compounds **2** and **3**, which were easily separated by chromatography (98% yield, in 3:2 ratio **2**:**3**). Once purified, the isomers were submitted to the same reaction sequence: Firstly, the iodide was displaced by an azido group (NaN_3, Bu_4NI) to afford derivatives **4** and **5** in 81% and 76% yield, respectively, then the primary hydroxyl group at C-6 was selectively debenzylated by acetolysis[13] to give compounds **6** and **8** in 93% and 86% yield, respectively. The acetate group was easily hydrolyzed under Zémplen[14] conditions (catalytic MeONa in MeOH) to afford the azidoalcohols **7** (87% yield) and **9** (82% yield), and subsequent Jones oxidation (CrO_3, H_2SO_4)[15] gave the corresponding spiroazido acids **10** (70% yield) and **11** (82% yield). The two azido acids **10** and **11** have different spatial arrangements of the azido groups with respect to the carboxy terminus, which makes these structures interesting scaffolds for inducing various pseudopeptide secondary structures.



Scheme 1. a) I_2, THF; b) NaN_3, Bu_4NI, DMF; c) Ac_2O/TFA 4:1; d) MeONa, MeOH; e) CrO_3, 3 M H_2SO_4, acetone/H_2O 2:1.

The absolute configuration of the new stereocenter generated in the iodocyclization reaction was determined by NOESY NMR experiments (included in the Supporting Information) performed on the azido-derivatives **4** and **5**: this was (*R*) in compound **2** and (*S*) in **3**. The iodo derivatives **2** and **3** are key intermediates for the whole synthesis, since all the products were derived from these two compounds by following different synthetic strategies. In fact, when a mixture of compounds **2** and **3** was treated with zinc in acetic acid, we obtained derivative **12**, in which the C-1 hydroxyl group is selectively deprotected and the double bond is reestablished. This selective deprotection was exploited for the introduction of a second double bond that, upon reaction with iodine, gave raise to a further cyclization. In more detail (Scheme 2), oxidation (DMSO/Ac_2O) of alcohol **12** afforded the corresponding aldehyde **13**, which reacted stereoselectively with vinylmagnesium bromide to give the (*R*) allylic alcohol **14** in 75% yield and 98% *de* (the absolute configuration was determined by ^1H NMR experiments; diastereomeric excess was determined by HPLC). The high stereoselectivity of this reaction can be ascribed to the formation of a Cram-chelated intermediate in which the magnesium ion coordinates the carbonyl group and the furanosidic oxygen, as depicted in Figure 1. Attack of the nucleophile is allowed only on the *Re* face of the carbonyl group of this intermediate, since the benzyloxy group at C-3 prevents the attack from the *Si* face.

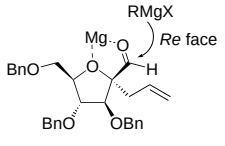


Figure 1. Chelated model for the attack of the Grignard reagent on aldehyde **13**.

Compound **14** was transformed into two different bicyclic structures. Treatment with I_2 in THF led to a 5-*exo* cyclization involving the unprotected hydroxyl group derived from the Grignard reaction to afford the spirobicyclic compound **15** (73% yield). Interestingly, in dichloromethane the iodocyc-

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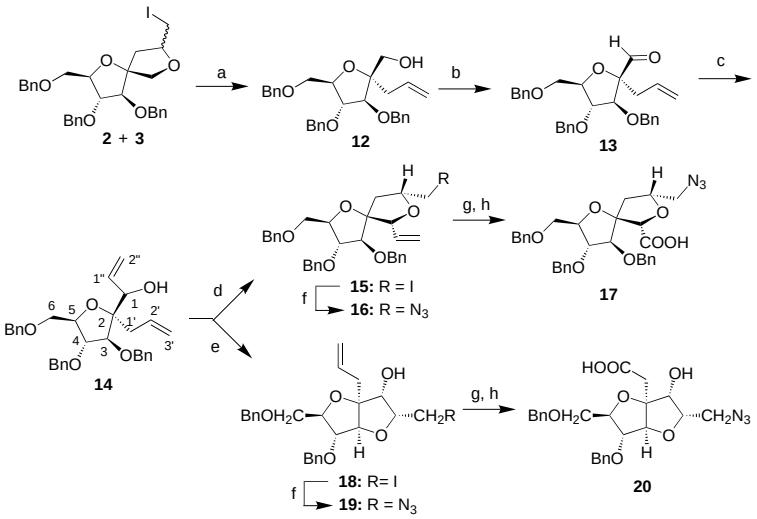
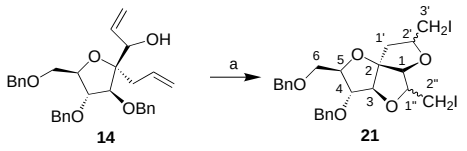


Scheme 2. a) Zn, AcOH, EtOH/Et_2O 1:1; b) DMSO/Ac_2O 2:1; c) 1M vinyl magnesium bromide in THF; d) I_2, THF, 0 °C; e) I_2, CH_2Cl_2, RT; f) NaN_3, Bu_4NI, DMF; g) OsO_4, $NaIO_4$, acetone/*t*BuOH/H_2O 1:1:1; h) $NaClO_2$, 1.25M aq. NaH_2PO_4, CH_3CN.

lization proceeded differently, and the benzyloxy group at C-3 was then involved in a 5-*exo* cyclization with the β-allylic substituent, to afford the fused bicyclic compound **18** (69% yield). It is noteworthy that different rigid bicyclic structures can be obtained just by switching the reaction medium. The iodine atom of compounds **15** and **18** was displaced with an azide group (NaN_3, Bu_4NI) to afford derivatives **16** and **19**, both in 70% yield. The vinylic and allylic group of compounds **16** and **19**, respectively, were subjected to degradative oxidation with osmium tetroxide/sodium periodate[16] followed by treatment with $NaH_2PO_4/NaClO_2$.[17]

Treatment of **14** with excess iodine in dichloromethane produced both the cyclization reactions and afforded the tricyclic compound **21** (Scheme 3) as a mixture of diastereomers (66% yield). The formation of the third ring



Scheme 3. a) I_2, CH_2Cl_2.

confirmed the (*R*) stereochemistry of the stereocenter generated at C-1 in the Grignard reaction, since the double bond is only properly oriented for the cyclization with the benzyloxy group at C-3 in this diastereomer.

The full characterization of compounds **15** and **18** was performed by 1D ^1H NMR and COSY experiments on a 400 MHz spectrometer. The absolute configurations of the new stereocenters were determined by NOESY experiments, using mixing time values optimized for these bicyclic structures; the analysis of NOE cross peak correlation allowed also the acquirement of fundamental information about the whole conformational arrangement of the bicyclic scaffolds.

The conformational preferences of the scaffolds were investigated by using NMR measurements, especially NOE and *J* analyses, assisted by molecular mechanics calculations. The assignment of the resonances was made through a combination of COSY, HSQC, NOESY, and TOCSY experiments at 500 MHz, recorded in a variety of solvents to try to avoid signal overlapping. The experimental couplings were compared to those expected from the geometries obtained by molecular mechanics calculations. In particular, the expected coupling constants were obtained by applying the generalized Karplus equation proposed by Altona[18] to the vicinal proton–proton torsion angles calculated by molecular mechanics calculations.

From data reported in Table 1 and in the Supporting Information, we deduced that for the ring protons a satisfactory match was observed between experimental and expected values. Thus, the molecular mechanics calculations predict a correct shape for the five-membered rings of the studied molecules, namely **10**, **11**, **17**, and **20**. Moreover, the NOE experimental contacts allowed us to deduce that the relative positions of the key protons at distances smaller than 3.5 Å (the experimental limit for NOE detection for molecules of

Table 1. Experimental and expected (in brackets) ^3J(H,H) values in Hz for the different molecules. If two values are given for the experimental *J* values, these correspond to the observed values in two solvents (deuterated benzene and chloroform).[a]

Compound	(3,4)	(4,5)	(5,6a)	(5,6b)	(1′a,2′)	(1′b,2′)	(2′,3′a)	(2′,3′b)	(1″,2″a)	(1″,2″b)
10	1.1	0.9	–	–	5.5	10.1	4.7	3.6	–	–
	(1.3)	(0.7)			(5.4)	(11.0)	(6.8)	(3.3)		
11	1.0	1.5	–	–	5.7	9.7	6.8	4.4	–	–
	(1.2)	(0.9)			(5.0)	(9.5)	(10.6)	(2.5)		
17	0.6/1.6	1.0/2.7	5.2/5.4	8.1/8.6	5.0/5.6	10.6/11.0	5.3	3.8	–	–
	(0.6)	(2.7)			(5.4)	(10.8)	(8.8)	(2.1)		
20	5.4	7.8	3.0	5.0	–	–	–	–	5.0	8.0
	(6.7)	(9.1)							(2.6)	(9.7)

[a] The expected coupling constants have been obtained by applying the generalized Karplus equation proposed by Altona to the vicinal proton–proton torsion angles calculated by molecular mechanics calculations for the five-membered rings. The corresponding values for the lateral chain have been calculated from the predicted vicinal proton–proton torsion angles and the corresponding probability distributions for the *gg*, *gt*, and *tg* rotamers (see text and Table 2 in Supporting Information).

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this size) were also in agreement with those predicted by the MM3* calculations (Figure 2), thus supporting the three-dimensional shape of the molecules (detailed Figure in the Supporting Information).

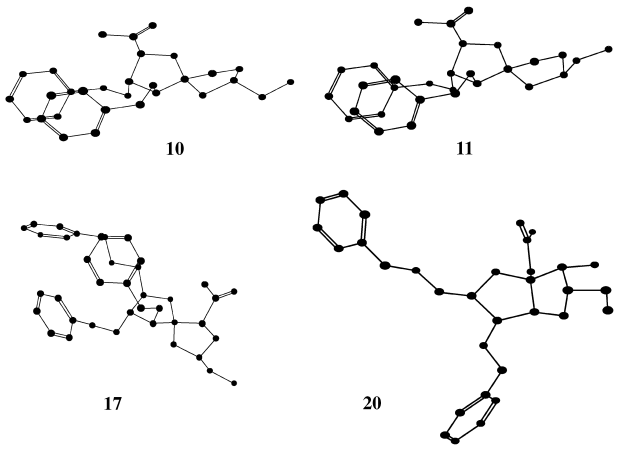

Figure 2. Schematic views of the major conformations of compounds **10**, **11**, **17**, and **20**, as provided by MM3* molecular mechanics calculations.

For the spiro compounds, the puckering of the five-membered rings depends on the substituents and the stereochemistry of the ring carbons (Table 2). Thus, most of the sugar rings may be defined as envelopes, positioning either C-4 (**10** and **11**) or C-2 (**17**) out of the plane defined by the other four atoms. Regarding the second five-membered ring, different envelope forms are also found, with C-1 (**10**), C-2 (**11**), or the oxygen (**17**) out of the plane defined by the other four atoms. The different fusion of the five-membered rings in **20** produces two envelope forms with atoms C-5 and C-2′ out of the plane, respectively.

With respect to the lateral chain at position C-5 – C-6 of the five-membered rings of **17** and **20**, the *J* values indicated the presence of more than one conformer in the conformational equilibrium in most of the cases. Indeed, for **17**, one large and one intermediate coupling were observed, indicating that the conformational equilibrium involved at least one of the *gt* or *tg* conformers, probably both. On the other hand, an important contribution of the *gg* conformer around the C-5 – C-6 linkage was detected for **20**, since the observed values were one small and one intermediate.

Table 2. Torsion angle values for the five-membered rings of compounds **10**, **11**, **17**, and **20**, according to MM3* calculations. The agreement between experimental and expected couplings is fair, and therefore, the MM3*-based model may be considered as a fair approximation of the actual situation.

Torsion angle	**10**	**11**	**17**	**20**
2-3-4-5	– 37	– 36	– 26	19
3-4-5-O	39	39	7	– 37
4-5-O-2	– 24	– 25	18	43
5-O-2-3	– 1	1	– 36	– 30
O-2-3-4	25	24	38	5
conformation	^4E	^4E	^2E	^5E
2-1′-2′-O	5	30	– 28	39
1′-2′-O-1	22	– 6	42	– 39
2′-O-1-2	– 41	– 21	– 38	23
O-1-2-1′	42	38	18	3
1-2-1′-2′	– 27	– 39	5	– 25
conformation	^1E	^2E	^OE	$^{2'}E$

The orientation of the lateral chain attached to the nitrogenated moiety is of key importance to deduce the interatomic distances between the N atom and the carboxylated fragment in the different compounds. For **10**, **11**, **17**, and **20**, the existing conformational equilibrium may be deduced from the coupling constants of the methylene protons to the ring proton. Again, one large and one small coupling would be expected for either the *gt* or *tg* conformers, and two small ones for the *gg* rotamer. Two intermediate to large values would be expected for a *gt*:*tg* conformational equilibrium, while one small and one intermediate value would be expected for a major presence of the *gg* rotamer. Intermediate values were observed for **10**, **11**, and **17** indicating a major conformational equilibrium. The correct prediction by molecular mechanics of the respective populations of the *gg*, *gt*, and *tg* conformations around the hydroxymethyl (azidomethyl in this case) lateral chain of carbohydrates is far from being solved.[19] A delicate balance between polar, steric, and solvent effects has been postulated to account for the observed distributions. The energy difference among the three forms is fairly low, and small deviations from the actual energy differences may provide population distributions far from the actual situation. Only very recently, and by using very long-solvated MD simulations,[19] the proper observed distribution of rotamers around the lateral chain of galactose and glucose has been accounted for. Therefore, by using regular molecular mechanics force fields, such as MM3*, only approximated values may be obtained,[20] although the comparison between experimental observables (i.e, *J* couplings) with those calculated from the computed geometries may be used to approximate the actual distribution. In fact, although the geometries of the five-membered rings is correct (good agreement between experimental and expected *J* couplings) with regard to the lateral chains, the comparison between the experimental and theoretical data indicates that the MM3*-derived values cannot explain the observed *J* values. In fact, the energy differences between the three rotamers are fairly small (smaller than 6 kJ mol^{-1}), and the presence of a conformational equilibrium is expected. According to the energy values provided by the MM3* molecular mechanics calculations, the *gt* rotamer is always the most stable rotamer (57, 96, 80 % for **10**, **11**, **17**, respectively), while the energy difference between the *gt* and the other *gg* and *tg* rotamers depends on the configuration at C-2′. For **10**, **17**, the *gg* is predicted to be second (41, 13 %, respectively) in stability, while for **11**, it is more destabilized than the *tg* (4 %) alternative. Indeed, this compound shows the highest coupling values, thus indicating a relatively small contribution of this rotamer with respect to **10** and **17**. Actually, the population distribution predicted for **10** (*gt*:*gg*:*tg*, 57:41:2) satisfactorily matches the observed data for **11**. In all three cases, the population of the *gt* conformer is overestimated by the MM3* calculations, since otherwise higher *J* values would be expected. The observed couplings for the lateral chains of **10** and

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17 may be satisfactorily explained for distributions around 60:35:5 of the *gt*:*gg*:*tg* rotamers. In contrast, **20** shows one large and one intermediate value of couplings, which indicates a major *gt* (or *tg*) rotamer. Since the MM3* energy values are in agreement with a major contribution of the *gt* rotamer (87%) versus the *tg* alternative (0%), the *gt* is possibly the major form around the nitrogen-containing lateral chain in this molecule. The tendency between the expected and observed couplings is satisfactory, although with a prediction of the *gt* higher than that actually existing (observed, 5 and 8 Hz; expected, 2.6 and 9.7 Hz). Indeed, the observed couplings for **20** are in between those predicted for **11** and **17**. A 88:8:4 distribution of the *gt*:*gg*:*tg* conformers produces a satisfactory fit of the observed *J* couplings.

Thus, considering that the shapes of the five-membered rings are well defined, as also deduced from the fair matching between experimental and expected coupling constants, a proper estimation of the distances between the two reactive centers may be provided (see Table in the Supporting Information).

For **10**, these are 5.2–7.0 Å, while for **11**, the distances are always around 7.4 Å. Smaller distances exist for **17** (around 5 Å, independent of the rotamer). A much wider array of values may take place for **20** as a result of the additional degree of freedom of the carboxyl group. In this case, the values may oscillate between 4 and 6 Å, although the energy values predict the latter to be the actual one.

Several possible diastereoisomers of compound **21**, in which two iodine atoms are attached to methylene fragments, were also included in the calculations (Figure 3 in Supporting Information). In this case, the possible distance oscillate by more than 4 Å, between 5.3 and 9.5 Å.

Experimental Section

General: All solvents were dried over molecular sieves, for at least 24 h prior to use. When dry conditions were required, the reaction was performed under Ar atmosphere. Thin-layer chromatography (TLC) was performed on silica gel $60F_{254}$ coated glass plates (Merck) with UV detection when possible, or charring with a conc. H_2SO_4/EtOH/H_2O solution (5:45:45 *v*/*v*/*v*). Flash column chromatography was performed on silica gel 230–400 mesh (Merck). Routine ^1H and ^{13}C NMR spectra were recorded at 400 MHz on a Varian Mercury instrument using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are reported in ppm downfield from TMS as an internal standard; aromatic signals are omitted. Mass spectra were recorded on a MALDI2 Kompakt Kratos instrument, using gentisic acid (DHB) as the matrix. IR spectra were recorded on Biorad FT/IR spectrometer FTS-40A coupled to an IR microscope Biorad UMA-40A. Optical rotations were measured at room temperature with a Perkin–Elmer 241 polarimeter.

Iodo ethers 2 and 3: C-glycoside **1**[11] (4.90 g, 8.68 mmol) was dissolved in dry THF (250 mL), and iodine (6.60 g, 26.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and then diluted with H_2O, and $Na_2S_2O_3$ was added until the organic phase turned colorless. The mixture was then extracted with AcOEt, the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated to dryness in vacuo. The crude residue was purified by flash chromatography (petroleum ether/AcOEt 8.5:1.5) to afford cyclic iodo ethers **2** (3.40 g) and **3** (1.70 g, 98%) as clear oils in 33% *de* in favor of isomer **2**.

Compound 2: $[\alpha]_D^{20} = +36.9$ ($c = 1.6$ in $CHCl_3$); ^1H NMR: $\delta = 4.59-4.48$ (m, 5H; PhCH_2O), 4.40 (d, $J = 11.6$ Hz, 1H; PhC*H*O), 4.25 (d, $J = 10.3$ Hz, 1H; H-1a), 4.18–4.16 (m, 1H; H-5), 4.12–4.06 (m, 1H; H-2′), 3.94 (dd, $J = 3.3$, 1.7 Hz, 1H; H-4), 3.92 (d, $J = 1.7$ Hz, 1H; H-3), 3.88 (d, $J = 10.3$Hz, 1H; H-1b), 3.58 (dd, $J = 9.9$, 5.5 Hz, 1H; H-6a), 3.50 (dd, $J = 9.9$, 6.6 Hz, 1H; H-6b), 3.30–3.18 (m, 2H; H-3′), 2.34 (dd, $J = 12.8$, 5.1 Hz, 1H; H-1′a), 1.64 (dd, $J = 12.8$, 9.9 Hz, 1H; H-1′b); ^{13}C NMR: $\delta = 92.94$ (s; C-2), 86.80, 83.84, 82.00, 78.31 (4d; C-3, C-4, C-5, C-2′), 74.46, 73.67, 72.06, 71.99, 70.83 (5t; Ph*C*H_2O, C-1, C-6), 43.68 (t; C-1′), 10.31 (t; C-3′); MALDI-MS: *m*/*z*: 623 $[M+Na]^+$, 639 $[M+K]^+$; elemental analysis calcd (%) for $C_{30}H_{33}0_5I$ (600.5): C 60.00, H 5.54; found: C 60.12, H 5.58. **Compound 3**: $[\alpha]_D^{20} = +24.7$($c = 1.2$ in $CHCl_3$); ^1H NMR: $\delta = 4.68-4.47$ (m, 5H; PhCH_2O), 4.38 (d, $J = 12.1$ Hz, 1H; PhC*H*O), 4.23–4.12 (m, 2H; H-5; H-2′), 4.11 (d, $J = 10.3$ Hz, 1H; H-1a), 4.03 (d, $J = 10.3$ Hz, 1H; H-1b), 3.96 (dd, $J = 3.4$, 1.5 Hz, 1H; H-4), 3.84 (d, $J = 1.5$ Hz, 1H; H-3), 3.58 (dd, $J = 10.0$, 5.4 Hz, 1H; H-6a), 3.48 (dd, $J = 10.0$, 6.5 Hz, 1H; H-6b), 3.34–3.22 (m, 2H; H-3′), 2.25 (dd, $J = 9.9$, 7.4 Hz, 1H; H-1′a), 2.06 (dd, $J = 9.9$, 5.1 Hz, 1H; H-1′b); ^{13}C NMR: $\delta =$ 91.96 (s; C-2), 86.59, 83.82, 81.91, 79.54 (4d, C-3, C-4, C-5, C-2′), 73.46, 73.37, 71.75, 71.58, 70.30 (5t; Ph*C*H_2O, C-1, C-6), 41.99 (t; C-1′), 9.33 (t; C-3′); MALDI-MS: *m*/*z*: 623 $[M+Na]^+$, 639 $[M+K]^+$; elemental analysis calcd (%) for $C_{30}H_{33}O_5I$ (600.5): C 60.00, H 5.54; found: C 60.14, H 5.55.

Azide 4: Iodo ether **2** (1.82 g, 3.03 mmol) was dissolved in dry DMF (19 mL), and Bu_4NI (0.56 g, 1.51 mmol) and NaN_3 (0.39 g, 6.06 mmol) were added. The reaction mixture was heated at reflux for 2 h and 30 min. The solvent was evaporated, and the residue was purified by flash chromatography (petroleum ether/AcOEt 9:1 → 7:3) to afford **4** (1.26 g, 81%) as a clear oil. $[\alpha]_D^{20} = +11.9$ ($c = 1.3$ in $CHCl_3$); ^1H NMR: $\delta = 4.68-4.52$ (m, 5H; PhCH_2O), 4.44 (d, $J = 11.9$ Hz, 1H; PhC*H*O), 4.38–4.30 (m, 1H; H-2′), 4.28 (d, $J = 10.3$ Hz, 1H; H-1a), 4.19 (dt, $J = 6.0$, 3.3 Hz, 1H; H-5), 3.98 (dd, $J = 3.4$, 1.7 Hz, 1H; H-4), 3.96 (d, $J = 1.7$ Hz, 1H; H-3), 3.90 (d, $J = 10.3$ Hz, 1H; H-1b), 3.62 (dd, $J = 9.9$, 6.0 Hz, 1H; H-6a), 3.53–3.46 (m, 2H; H-6b, H-3′a), 3.22 (dd, $J = 9.9$, 5.2 Hz, 1H; H-3′b), 2.19 (dd, 1H, $J = 13.0$, 5.7 Hz, 1H; H-1′a), 1.80 (dd, $J = 13.0$, 5.5 Hz, 1H; H-1′b); ^{13}C NMR $\delta = 92.94$ (s; C-2), 87.09, 84.09, 82.23, 78.37 (4d; C-3, C-4, C-5, C-2′), 74.12, 73.80, 72.18, 72.13, 71.00 (5t; C-1, C-6, Ph*C*H_2O), 54.22 (t, C-3′), 39.93 (t, C-1′); IR (neat): $\tilde{\nu} = 2095$ cm^{-1}; MALDI-MS: *m*/*z*: 538 $[M+Na]^+$, 554 $[M+K]^+$; elemental analysis calcd (%) for $C_{30}H_{33}0_5N_3$ (515.6): C 69.88, H 6.45, N 8.15; found: C 69.63, H 6.47, N 8.17.

Acetate 6: Azide **4** (0.81 g, 1.57 mmol) was dissolved in a 4:1 mixture of Ac_2O/TFA (15 mL). The solution was stirred for 1 h and then quenched by the addition of H_2O and solid $NaHCO_3$ to neutrality. The organic layer was extracted by CH_2Cl_2, then dried (Na_2SO_4) filtered, and evaporated. The resulting oil was purified by flash chromatography (petroleum ether/AcOEt 85:15 → 7:3) to afford acetate **6** (0.68 g, 93%) as colorless oil. $[\alpha]_D^{20} = +33.2$ ($c = 1.7$ in $CHCl_3$); ^1H NMR: $\delta = 4.59$, 4.47 (ABq, $J =$ 11.8 Hz, 2H; PhCH_2O), 4.53 (s, 2H; PhCH_2O), 4.32–4.29 (m, 1H; H-2′), 4.26 (d, $J = 10.2$ Hz, 1H; H-1a), 4.21–4.09 (m, 3H; H-5, H-6), 3.94 (d, $J =$ 1.7 Hz, 1H; H-3), 3.88 (d, $J = 10.2$ Hz, 1H; H-1b), 3.87 (dd, $J = 4.5$, 1.7 Hz, 1H; H-4), 3.50 (dd, $J = 13.0$, 3.6 Hz, 1H; H-3′a), 3.20 (dd, $J = 13.0$, 4.9 Hz, 1H; H-3′b), 2.18 (dd, $J = 13.0$, 5.7 Hz, 1H; H-1′a), 2.04 (s, 3H; CH_3CO), 1.75 (dd, $J = 13.0$, 9.9 Hz, 1H; H-1′b); ^{13}C NMR: $\delta = 170.76$ (s; CH_3*C*O), 92.88 (s; C-2), 86.30, 83.53, 80.52, 77.98 (4d; C-3, C-4, C-5, C-2′), 73.99, 73.65, 72.00, 64.64 (4t; C-1, C-6, Ph*C*H_2O), 53.72 (t; C-3′), 39.62 (t; C-1′), 20.85 (q; *C*H_3CO); MALDI-MS: *m*/*z*: 491 $[M+Na]^+$, 507 $[M+K]^+$; elemental analysis calcd (%) for $C_{25}H_{29}0_6N_3$ (467.5): C 64.23, H 6.25, N 8.99; found: C 64.55, H 6.23, N 9.01.

Alcohol 7: Acetate **6** (0.63 g, 1.36 mmol) was dissolved in dry MeOH (10 mL), and a catalytic amount of sodium was added. After 1 h, Amberlite IR-120 (H^+ form) was added and the mixture was stirred until the pH reached neutrality. The suspension was filtered and reduced in vacuo. Flash chromatography (petroleum ether/AcOEt 65:35) yielded alcohol **7** as a clear oil (0.50 g, 87%). $[\alpha]_D^{20} = +26.2$ ($c = 0.8$ in $CHCl_3$); ^1H NMR: $\delta = 4.61$, 4.42 (ABq, $J = 11.6$ Hz, 2H; PhCH_2O), 4.55 (br s, 2H; PhCH_2O), 4.35–4.29 (m, 1H; H-2′), 4.24 (d, $J = 10.3$ Hz, 1H; H-1a), 4.12–4.09 (m, 1H; H-5), 4.04 (dd, $J = 3.2$, 1.1 Hz, 1H; H-4), 3.92 (d, $J = 1.1$ Hz, 1H; H-3), 3.90 (d, $J = 10.3$ Hz, 1H; H-1b), 3.77 (dd, $J = 11.7$, 3.0 Hz, 1H; H-6a), 3.64 (dd, $J =$ 11.7, 3.9 Hz, 1H; H-6b), 3.50 (dd, $J = 12.9$, 3.6 Hz, 1H; H-3′a), 3.20 (dd, $J =$ 12.9, 5.0 Hz, 1H; H-3′b), 2.20 (dd, $J = 12.9$, 5.6 Hz, 1H; H-1′a), 1.74 (dd, $J =$ 12.9, 10.0 Hz, 1H; H-1′b), 1.65 (br s, 1H; OH); ^{13}C NMR: $\delta = 92.94$ (s; C-2), 86.18, 83.65, 82.95, 78.04 (4d; C-3, C-4, C-5, C-2′), 73.59, 72.19, 71.69, 63.07 (4t; C-1, C-6, PhCH_2O), 53.78 (t; C-3′), 38.87 (t; C-1′); MALDI-MS: *m*/*z*: 449 $[M+Na]^+$, 465 $[M+K]^+$; elemental analysis calcd (%) for $C_{23}H_{27}0_5N_3$ (425.5): C 64.93, H 6.40, N 9.88; found: C 65.06, H 6.37, N 9.92.

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Azido acid 10: Alcohol **7** (0.47 g, 1.03 mmol) was dissolved in acetone (22 mL) and the solution cooled to 0 °C before treating with CrO_3 (0.56 g, 5.64 mmol) dissolved in 3 M H_2SO_4 (11 mL). After 1 h, the reaction mixture was extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4), filtered, and then concentrated in vacuo. The crude residue was purified by flash chromatography ($CHCl_3$/0.5 % AcOH) to afford azido acid **10** as colorless oil (0.32 g, 70 %). $[\alpha]_D^{20} = +4.1$ ($c = 1.3$ in $CHCl_3$); ^{1}H NMR (C_6D_6): $\delta = 4.38$ (d, $J = 1.1$ Hz, 1H; H-5), 4.35, 4.20 (ABq, $J = 11.8$ Hz, 2H; PhCH_2O), 4.32 (br d, $J = 1.1$ Hz, 1H; H-4), 4.16, 3.97 (ABq, $J = 10.4$ Hz, 2H; PhCH_2O), 4.15 (d, $J = 11.9$ Hz, 1H; H-1a), 4.06 – 4.03 (m, 1H; H-2′), 3.85 (d, $J = 11.9$ Hz, 1H; H-1b), 3.55 (d, $J = 0.9$ Hz, 1H; H-3), 2.84 (dd, $J = 13.0$, 3.6 Hz, 1H; H-3′a), 2.50 (dd, $J = 13.0$, 4.7 Hz, 1H; H-3′b), 1.86 (dd, $J = 13.2$, 5.5 Hz, 1H; H-1′a), 1.48 (dd, $J = 13.2$, 10.1 Hz, 1H; H-1′b); ^{13}C NMR: (C_6D_6): $\delta = 172.33$ (s; C-6), 95.46 (s; C-2), 84.96, 84.74, 81.71, 78.48 (4d; C-3, C-4, C-5, C-2′), 73.81, 72.03, 71.70 (3t; C-1, PhCH_2O), 53.44 (t; C-3′), 39.88 (t; C-1′); MALDI-MS: m/z: 463 $[M+Na]^+$, 479 $[M+K]^+$; elemental analysis calcd (%) for $C_{23}H_{25}0_6N_3$ (439.5): C 62.86, H 5.73, N 9.56; found: C 63.12, H 5.75, N 9.54.

Azide 5: By using the experimental procedure used for the preparation of azide **4** [using Bu_4NI (0.26 g, 7.05 mmol) and NaN_3 (0.18 g, 2.76 mmol) in dry DMF (9 mL)], iodide **3** (0.85 g, 1.40 mmol) afforded azide **5** (0.55 g, 76 %) as colorless oil, after chromatographic purification (petroleum ether/AcOEt 9:1). $[\alpha]_D^{20} = +46.4$ ($c = 2.1$ in $CHCl_3$); ^{1}H NMR: $\delta = 4.68 – 4.47$ (m, 5H; PhCH_2O), 4.40 (d, $J = 12.0$ Hz, 1H; PhC*H*O), 4.17 – 4.12 (m, 2H; H-5, H-2′), 4.09 (d, $J = 10.2$ Hz, 1H; H-1a), 3.99 (dd, $J = 3.3$, 1.5 Hz, 1H; H-4), 3.98 (d, $J = 10.2$ Hz, 1H; H-1b), 3.86 (d, $J = 1.5$ Hz, 1H; H-3), 3.61 (dd, $J = 10.1$, 5.5 Hz, 1H; H-6a), 3.53 (dd, $J = 10.1$, 6.4 Hz, 1H; H-6b), 3.47 (dd, $J = 12.7$, 7.0 Hz, 1H; H-3′a), 3.28 (dd, $J = 12.7$, 4.4 Hz, 1H; H-3′b), 2.19 (dd, $J = 13.9$, 7.6 Hz, 1H; H-1′a), 1.95 (dd, $J = 13.4$, 6.2 Hz, 1H; H-1′b); ^{13}C NMR: $\delta = 91.84$ (s; C-2), 86.47, 83.87, 81.92, 78.26 (4d; C-3, C-4, C-5, C-2′), 73.42, 73.00, 71.79, 71.61, 70.55 (5t; C-1, C-6, PhCH_2O), 54.41 (t; C-3′), 39.74 (t; C-1′); IR (neat): $\tilde{\nu} = 2095$ cm^{-1}; MALDI-MS: m/z: 539 $[M+Na]^+$, 555 $[M+K]^+$; elemental analysis calcd (%) for $C_{30}H_{33}0_5N_3$ (515.6): C 69.88, H 6.45, N 8.15; found: C 69.95, H 6.44, N 8.18.

Acetate 8: Perbenzylated azide **5** (0.23 g, 0.45 mmol) was transformed into the corresponding acetate **8**, by acetolysis (Ac_2O/TFA, 5 mL) as described for derivative **6**. The crude residue was purified by flash chromatography (petroleum ether/AcOEt 8.5:1.5) to afford acetate **8** (0.18 g, 86 %) as a clear oil. $[\alpha]_D^{20} = +37.1$ ($c = 1.4$ in $CHCl_3$); ^{1}H NMR: $\delta = 4.58$, 4.45 (ABq, $J = 11.7$ Hz, 2H; PhCH_2O), 4.53 (br s, 2H; PhCH_2O), 4.24 – 4.12 (m, 4H; H-5, H-6, H-2′), 4.09 (d, $J = 10.2$ Hz, 1H; H-1a), 3.98 (d, $J = 10.2$ Hz, 1H; H-1′b), 3.88 (br d, $J = 5.5$ Hz, 1H; H-4), 3.86 (br s, 1H; H-3), 3.45 (dd, $J = 12.8$, 6.9 Hz, 1H; H-3′a), 3.29 (dd, $J = 12.8$, 4.8 Hz, 1H; H-3′b), 2.18 (dd, $J = 13.5$, 7.7 Hz, 1H; H-1′a), 2.04 (s, 3H; CH_3CO), 1.95 (dd, $J = 13.5$, 6.2 Hz, 1H; H-1′b); ^{13}C NMR: $\delta = 170.88$ (s; CH_3CO), 92.47 (s; C-2), 86.23, 83.88, 80.92, 78.51 (4d; C-3, C-4, C-5, C-2′), 73.19, 72.25, 72.13, 64.94 (4t; C-1, C-6, PhCH_2O), 54.60 (t; C-3′), 40.04 (t; C-1′), 21.29 (q; CH_3CO); MALDI-MS: m/z: 491 $[M+Na]^+$, 507 $[M+K]^+$; elemental analysis calcd (%) for $C_{25}H_{29}0_6N_3$ (467.5): C 64.23, H 6.25, N 8.99; found: C 64.06, H 6.26, N 8.97.

Alcohol 9: Deacetylation of acetate **8** (0.27 g, 0.59 mmol) with catalytic sodium methoxide, as described for **7**, afforded alcohol **9** (0.20 g, 82 %), after chromatographic purification (petroleum ether/AcOEt 7:3). $[\alpha]_D^{20} = +79.5$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR: $\delta = 4.62$, 4.41 (ABq, $J = 11.7$ Hz, 2H; PhCH_2O), 4.54 (br s, 2H; PhCH_2O), 4.16 – 4.10 (m, 1H; H-2′), 4.09 – 4.00 (m, 4H; H-1, H-4, H-5), 3.85 (d, $J = 0.83$ Hz, 1H; H-3), 3.78 (dd, $J = 11.7$, = 3.0 Hz, 1H; H-6a), 3.55 (dd, $J = 11.7$, 4.0 Hz, 1H; H-6b), 3.46 (dd, $J = 12.7$, 7.0 Hz, 1H; H-3′a), 3.30 (dd, $J = 12.7$, 4.4 Hz, 1H; H-3′b), 2.16 (dd, $J = 13.6$, 7.7 Hz, 1H; H-1′a), 2.10 (br s, 1H; OH), 1.95 (dd, $J = 13.6$, 6.0 Hz, 1H; H-1′b); ^{13}C NMR: $\delta = 92.62$ (s; C-2), 86.11, 83.99, 83.15, 78.69 (4d; C-3, C-4, C-5, C-2′), 73.40, 72.44, 71.75, 63.31 (4t; C-1, C-6, PhCH_2O), 54.60 (t; C-3′), 39.41 (t; C-1′); MALDI-MS: m/z: 448 $[M+Na]^+$; elemental analysis calcd (%) for $C_{23}H_{27}0_5N_3$ (425.5): C 64.93, H 6.40, N 9.88; found: C 64.82, H 6.43, N 9.97.

Azido acid 11: The same experimental procedure reported for the oxidation of alcohol **7** was applied to the oxidation of alcohol **9** (0.05 g, 0.11 mmol in 2 mL acetone) with CrO_3 (0.05 g, 0.54 mmol in 1 mL 3 M H_2SO_4). Purification by flash chromatography ($CHCl_3$/EtOH 9:1 containing 0.1 % AcOH) yielded azido acid **11** as a clear oil (0.04 g, 82 %). $[\alpha]_D^{20} = -2.4$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (C_6D_6): $\delta = 4.36$, 4.19 (ABq, $J = 11.8$ Hz, 2H; PhCH_2O), 4.34 (br d, $J = 1.5$ Hz, 1H; H-5), 4.31 (br t, $J = 1.1$ Hz, 1H; H-4), 4.18, 3.86 (ABq, $J = 12.0$ Hz, 2H; PhCH_2O), 4.03 (d, $J = 10.7$ Hz, 1H; H-1a), 3.83 (d, $J = 10.7$ Hz, 1H; H-1b), 3.68 – 3.64 (m, 1H; H-2′), 3.44 (d, $J = 1.1$ Hz, 1H; H-3), 2.95 (dd, $J = 12.7$, 6.8 Hz, 1H; H-3′a), 2.72 (dd, $J = 12.7$, 4.4 Hz, 1H; H-3′b), 1.72 – 1.67 (m, 2H; H-1′); ^{13}C NMR: $\delta = 171.32$ (s; C-6), 95.55 (s; C-2), 84.78, 84.31, 81.98, 78.74 (4d; C-3, C-4, C-5, C-2′), 73.96, 72.53, 72.02 (3t; C-1, PhCH_2O), 54.45 (t; C-3′), 40.22 (t; C-1′); MALDI-MS: m/z: 463 $[M+Na]^+$, 479 $[M+K]^+$; elemental analysis calcd (%) for $C_{23}H_{25}0_6N_3$ (439.5): C 62.86, H 5.73, N 9.56; found: C 62.78, H 5.70, N 9.59.

Alcohol 12: Iodo ethers **2** and **3** (1.48 g, 2.62 mmol) were dissolved in 1:1 Et_2O/EtOH (30 mL) and dust Zn (1.49 g, 22.8 mmol) and AcOH (0.26 mL) were added. After stirring for 24 h, the suspension was filtered, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and the solution was washed with 5 % aqueous HCl. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/AcOEt 8:2) to afford alcohol **12** (0.90 g, 80 %) as colorless oil. $[\alpha]_D^{20} = +12.9$ ($c = 1.6$ in $CHCl_3$); ^{1}H NMR: $\delta = 5.83 – 5.71$ (m, 1H; H-2′), 5.09 (d, $J = 10.3$ Hz, 1H; H-3′a), 4.97 (dd, $J = 17.2$, 1H; H-3′b), 4.72 – 4.46 (m, 6H; PhCH_2O), 4.45 (t, $J = 7.3$ Hz, 1H; H-4), 4.12 (d, $J = 7.3$ Hz, 1H; H-3), 3.92 (td, $J = 7.3$, 3.2 Hz, 1H; H-5), 3.72 – 3.64 (m, 2H; H-1a, H-6a), 3.52 – 3.46 (m, 2H; H-1b, H-6b), 2.30 (dd, $J = 13.9$, 6.2 Hz, 1H; H-1′a), 2.18 (dd, $J = 13.9$, 8.0 Hz, 1H; H-1′b), 1.60 (br s, 1H; OH); ^{13}C NMR: $\delta = 132.98$ (d; C-2′), 119.12 (t; C-3′), 84.33 (s; C-2), 86.71, 83.56, 79.40 (3d; C-3, C-4, C-5), 73.70, 73.23, 73.21, 69.71, 66.43 (5t; C-1, C-6, PhCH_2O), 40.41 (t; C-1′); MALDI-MS: m/z: 498 $[M+Na]^+$, 514 $[M+K]^+$; elemental analysis calcd (%) for $C_{30}H_{34}0_5$ (474.6): C 75.92, H 7.22; found: C 76.03, H 7.25.

Aldehyde 13: Alcohol **12** (1.57 g, 3.32 mmol) was dissolved in pre-dried (over molecular sieves) DMSO/Ac_2O (2:1, 77 mL). After 24 h, the mixture was diluted with AcOEt, extracted with ice-cold water, dried (Na_2SO_4) and concentrated in vacuo. The crude aldehyde was directly submitted to the next reaction.

Alcohol 14: Aldehyde **13** (0.47 g, 1.00 mmol) was dissolved in dry THF (13 mL), and the solution was cooled to 0 °C, and 1 M vinyl magnesium bromide in dry THF (2.0 mL) was then added. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The organic phase was dried over Na_2SO_4, filtered, and the solvent was evaporated to dryness. The crude residue was purified by flash chromatography (petroleum ether/AcOEt 9:1) to afford allylic alcohol **14** (0.375 g, 75 %, 98 % *de*) as a colorless oil. An analytical sample of crude **14** was analyzed by HPLC for quantification of diasteroselectivity (Waters HPLC system equipped with a Merck LiChrosorb Si-60 column (250 × 4 mm; 5 μm), and eluting with a flow rate of 1 mL min^{-1} with a linear gradient 0 → 100 % eluent B in eluent A; analysis time 30 min, eluent A: hexane and eluent B: AcOEt; detection at 280 nm with an absorbance detector Waters 2487 dual λ). $[\alpha]_D^{20} = +14.6$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR: $\delta = 5.99$ (ddd, $J = 17.3$, 9.9, 7.0 Hz, 1H; H-1″), 5.86 – 5.70 (m, 1H; H-2′), 5.25 (dd, $J = 17.3$, 1.4 Hz, 1H; H-2″a), 5.21 (br d, $J = 9.9$ Hz, 1H; H-2″b), 5.10 (br d, $J = 10.1$ Hz, 1H; H-3′a), 4.98 (br d, $J = 17.2$ Hz, 1H; H-3′b), 4.78 – 3.98 (m, 7H; H-4, PhCH_2O), 4.23 (d, $J = 7.0$ Hz, 1H; H-3), 4.19 (d, $J = 7.0$ Hz, 1H, H-1), 3.91 (dt, $J = 6.7$, 3.2 Hz, 1H; H-5), 3.71 (dd, $J = 10.5$, 3.2 Hz, 1H; H-6a), 3.50 (dd, $J = 10.5$, 6.7 Hz, 1H; H-6b), 2.40 (dd, $J = 14.2$, 5.9 Hz, 1H; H-1′a), 2.12 (dd, $J = 14.2$, 8.5 Hz, 1H; H-1′b); ^{13}C NMR: $\delta = 136.56$, 133.15 (2d; C-2′, C-1″), 118.99, 117.14 (2t; C-3′, C-2″), 86.88, 83.81, 79.48, 75.09 (4d; C-1, C-3, C-4, C-5), 85.15 (s; C-2), 73.48, 73.07, 72.96, 69.55 (4t; C-6, PhCH_2O), 40.55 (t; C-1′); MALDI-MS: m/z: 501 $[M+H]^+$, 524 $[M+Na]^+$, 539 $[M+K]^+$; elemental analysis calcd (%) for $C_{32}H_{36}0_5$ (500.6): C 76.77, H 7.25; found: C 76.92, H 7.26.

Spiroiodo ether 15: Allylic alcohol **14** (0.03 g, 0.06 mmol) was dissolved in dry THF (1 mL), then cooled to 0 °C and treated with iodine (0.02 g, 0.07 mmol). The solution was warmed to room temperature and stirred for 4 h. The reaction mixture was then diluted with H_2O, and $Na_2S_2O_3$ was added until the solution became colorless. The aqueous layer was extracted with AcOEt. The organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/Et_2O 8:2) to afford compound **15** (0.03 g, 73 %) as colorless oil, and its epimer (0.005 g), corresponding to 87 % overall yield, and 71 % *de* in favor of epimer **15**, as determined by ^{1}H NMR spectroscopy of the crude mixture. $[\alpha]_D^{20} = +76.9$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (C_6D_6): $\delta = 6.18$ (ddd, $J = 16.2$, 10.5, 5.0 Hz, 1H; H-1″), 5.55 (dt, $J = 16.2$, 1.5 Hz, 1H; H-2″a), 5.16 (dt, $J = 10.5$, 1.5 Hz, 1H; H-2″b), 5.05 (d, $J = 5.0$ Hz, 1H; H-1), 4.55 – 4.32 (m, 6H; H-5, H-2′, PhCH_2O), 4.28, 4.17 (ABq, $J = 11.3$ Hz, 2H; PhCH_2O), 4.10 (d, $J = 1.6$ Hz, 1H; H-4), 3.78 (dd, $J = 8.5$, 5.2 Hz, 1H;

H-6a), 3.74 (d, $J = 7.0$ Hz, 1H; H-3), 3.64 (t, $J = 8.5$ Hz, 1H; H-6b), 3.22 (dd, $J = 9.8$, 5.2 Hz, 1H; H-3′a), 3.08 (dd, $J = 9.8$, 7.2 Hz, 1H; H-3′b), 2.61 (dd, $J = 12.9$, 4.8 Hz, 1H; H-1′a), 1.52 (dd, $J = 12.9$, 8.7 Hz, 1H; H-1′b); ^{13}C NMR (C_6D_6): $\delta = 137.55$ (d; C-1″), 116.69 (t; C-2″), 95.89 (s; C-2), 86.23, 85.90, 83.69, 82.89, 78.66 (5d, C-1, C-3, C-4, C-5, C-2′), 73.63, 71.63, 71.63, 71.52 (4t; C-6, Ph*C*H$_2$O), 40.33 (t; C-1′), 9.66 (t; C-3′); MALDI-MS: m/z: 648 $[M+Na]^+$, 664 $[M+K]^+$; elemental analysis calcd (%) for $C_{32}H_{35}I0_5$ (626.5): C 61.35, H 5.63; found: C 61.42, H 5.68.

Spiroazide 16: Iodo ether **15** (0.02 g, 0.003 mmol) was dissolved in dry DMF (0.2 mL), and Bu_4NI (0.006 g, 0.002 mmol) and NaN_3 (0.004 g, 0.006 mmol) were added. The reaction mixture was heated at reflux for 2 h. Evaporation under reduced pressure and flash chromatography (petroleum ether/AcOEt 9:1) afforded azide **16** (0.01 g, 70%) as a clear oil. $[\alpha]_D^{20} = +79.8$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR: $\delta = 5.95$ (ddd, $J = 16.2$, 10.5, 5.5 Hz, 1H; H-1″), 5.36 (d, $J = 16.2$ Hz, 1H; H-2″a), 5.13 (d, $J = 10.5$ Hz, 1H; H-2″b), 4.61 – 4.45 (m, 5H; H-1, PhC*H*$_2$O), 4.41 – 4.36 (m, 1H; H-2′), 4.37, 4.30 (ABq, $J = 11.4$ Hz, 2H; PhC*H*$_2$O), 4.23 (brt, $J = 5.7$ Hz, 1H; H-5), 3.92 (d, $J = 1.6$ Hz, 1H; H-4), 3.76 (s, 1H; H-3), 3.65 (dd, $J = 9.5$, 5.7 Hz, 1H; H-6a), 3.52 – 3.46 (m, 2H; H-6b, H-3′a), 3.39 (dd, $J = 12.9$, 5.4 Hz, 1H; H-3′b), 2.26 (dd, $J = 12.8$, 4.8 Hz, 1H; H-1′a), 1.69 (dd, $J = 12.8$, 11.3 Hz, 1H; H-1′b); ^{13}C NMR: $\delta = 136.50$ (d; C-1″), 116.93 (t; C-2″), 95.25 (s; C-2), 85.37, 85.27, 83.47, 82.70, 77.33 (5d; C-1, C-3, C-4, C-5, C-2′), 73.65, 71.79, 71.71, 71.15 (4t; C-6, Ph*C*H$_2$O), 54.93 (t; C-3′), 36.46 (t; C-1′); IR (neat): $\tilde{\nu} = 2100$ cm^{-1}; MALDI-MS: m/z: 565 $[M+Na]^+$, 581 $[M+K]^+$; elemental analysis calcd (%) for $C_{32}H_{35}N_30_5$ (541.6): C 70.96, H 6.51, N 7.76; found: C 71.05, H 6.53, N 7.78.

Spiroazido acid 17: Azide **16** (0.05 g, 0.09 mmol) was dissolved in H_2O/acetone/*t*BuOH (1:1:1, 0.63 mL), and a 5 mg mL^{-1} solution of OsO_4 in *t*BuOH (0.80 mL) and $NaIO_4$ (0.06 g, 0.26 mmol) were then added. The suspension was stirred for 1 d, the salts were filtered off, and the solvent was evaporated under reduced pressure. The crude aldehyde was dissolved in CH_3CN (1.1 mL), and then $NaClO_2$ (0.03 g, 0.89 mmol) and a 1.25 M aqueous solution of $NaH_2PO_4 \cdot 2H_2O$ (0.14 g, 0.89 mmol) were added. The solution was stirred for 1 d, the solvent reduced in vacuo, and the crude residue was purified by flash chromatography (petroleum ether/AcOEt 1:1 → petroleum ether/AcOEt 2:8 containing 0.1% AcOH) to afford azido acid **17** (0.02 g, 45%) as a clear oil. $[\alpha]_D^{20} = -61.4$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (C_6D_6): $\delta = 4.82$ (s, 1H; H-1), 4.34 – 4.15 (m, 9H; H-4, H-5, H-2′, PhC*H*$_2$O), 3.99 (d, $J = 1.6$ Hz, 1H; H-3), 3.53 (dd, $J = 9.4$, 5.4 Hz, 1H; H-6a), 3.45 (dd, $J = 9.4$, 8.1 Hz, 1H; H-6b), 2.93 (dd, $J = 13.2$, 3.8 Hz, 1H; H-3′a), 2.78 (dd, $J = 13.2$, 5.3 Hz, 1H; H-3′b), 2.21 (dd, $J = 12.4$, 10.9 Hz, 1H; H-1′a), 2.10 (dd, $J = 12.4$, 5.0 Hz, 1H; H-1′b), 2.05 (brs, 1H; OH); ^{13}C NMR: $\delta = 175.05$ (s; C-1″), 95.835 (s; C-2), 86.93, 85.20, 83.41, 83.01, 80.43 (5d; C-1, C-3, C-4, C-5, C-2′), 73.35, 72.25, 71.51, 70.91 (4t; C-6, Ph*C*H$_2$O), 53.51 (t; C-3′), 38.82 (t; C-1′); MALDI-MS: m/z: 582 $[M+Na]^+$, 598 $[M+K]^+$; elemental analysis calcd (%) for $C_{31}H_{33}N_30_7$ (559.6): C 66.53, H 5.94, N 7.55; found: C 66.45, H 5.99, N 7.48.

Fused iodo ether 18: Allylic alcohol **14** (0.04 g, 0.007 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL), iodine (0.02 g, 0.009 mmol) was then added, and the solution was stirred for 2 h. The reaction mixture was diluted with H_2O, and $Na_2S_2O_3$ was added until the solution became colorless. The solution was extracted with CH_2Cl_2, and the organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/AcOEt 9:1) to afford iodo ether **18** (0.02 g, 56%) as a clear oil together with its epimer (4 mg), corresponding to 69% overall yield and 71% de in favor of isomer **18**, as determined by ^{1}H NMR spectroscopy. $[\alpha]_D^{20} = +20.8$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (C_6D_6): $\delta = 6.15 – 6.04$ (m, 1H; 2′), 5.15 (brd, $J = 16.1$ Hz, 1H; H-3′a), 5.10 (brd, $J = 9.6$ Hz, 1H; H-3′b), 4.70 – 4.63 (m, 1H; H-1″), 4.58 (brs, 1H; H-3), 4.55 – 4.32 (m, 5H; H-5, PhC*H*$_2$O), 4.20 (d, $J = 2.8$ Hz, 1H; H-1), 4.16 (d, $J = 4.4$ Hz, 1H; H-4), 3.66 – 3.50 (m, 2H; H-6), 3.31 (t, $J = 9.3$ Hz, 1H; H-2″a), 3.21 (dd, $J = 9.3$, 5.7 Hz, 1H; H-2″b), 2.82 (dd, $J = 14.2$, 5.9 Hz, 1H; H-1′a), 2.63 (dd, $J = 14.2$, 8.2 Hz, 1H; H-1′b), 1.45 (brs, 1H; OH); ^{13}C NMR (C_6D_6): $\delta = 134.93$ (d; C-2′), 118.40 (t; C-3′), 96.15 (s; C-2), 91.42, 87.43, 84.94, 83.62, 76.69 (5d; C-1, C-3, C-4, C-5, C-1″), 74.07, 72.64, 71.19 (3t; C-6, Ph*C*H$_2$O), 35.38 (t; C-1′), 1.71 (t; C-2″); MALDI-MS: m/z: 558 $[M+Na]^+$, 574 $[M+K]^+$; elemental analysis calcd (%) for $C_{25}H_{29}IO_5$ (536.4): C 55.98, H 5.45; found: C 56.05, H 5.41.

Fused azide 19: Nucleophilic substitution of iodide **18** (0.02 g, 0.06 mmol) by using NaN_3 (0.07 g, 0.11 mmol), Bu_4NI (0.01 g, 0.03 mmol) and dry DMF (0.24 mL)] as previously reported for **16**, affording azide **19** as clear oil (0.02 g, 70%) after purification by flash chromatography (petroleum ether/AcOEt 8:2). $[\alpha]_D^{20} = +69.4$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR: $\delta = 6.07 – 5.97$ (m, 1H; 2′), 5.20 (brd, $J = 17.2$ Hz, 1H; H-3′a), 5.16 (brd, $J = 9.9$ Hz, 1H; H-3′b), 4.62, 4.50 (ABq, $J = 11.7$ Hz, 2H; PhC*H*$_2$O), 4.54 (brs, 2H; PhC*H*$_2$O), 4.42 (brs, 1H; H-3), 4.37 – 4.25 (m, 1H; H-5), 4.20 (q, $J = 5.1$ Hz, 1H; H-1″), 4.09 (d, $J = 2.6$ Hz, 1H; H-4), 3.93 (d, $J = 4.8$ Hz, 1H; H-1), 3.60 – 3.51 (m, 2H; H-2″), 3.49 – 3.46 (m, 2H; H-6), 2.74 (dd, $J = 14.6$, 5.5 Hz, 1H; H-1′a), 2.58 (dd, $J = 14.6$, 8.8 Hz, 1H; H-1′b), 2.09 (brs, 1H; OH); ^{13}C NMR: $\delta = 134.01$ (d; C-2′), 118.28 (t; C-3′), 95.37 (s; C-2), 89.84, 86.22, 83.81, 80.31, 76.20 (5d; C-1, C-3, C-4, C-5, C-1″), 73.63, 72.28, 70.36 (3t; C-6, Ph*C*H$_2$O), 50.26 (t; C-2″), 34.71 (t; C-1′); IR (neat): $\tilde{\nu} = 2099$ cm^{-1}; MALDI-MS: m/z: 474 $[M+Na]^+$, 491 $[M+K]^+$; elemental analysis calcd (%) for $C_{25}H_{29}N_3O_5$ (451.5): C 66.50, H 6.47, N 9.31; found: C 66.61, H 6.49, N 9.35.

Fused azido acid 20: The same experimental procedure reported for the synthesis of **17** was applied to derivative **19** (0.05 g, 0.12 mmol) by using 0.60 mL of a solution of OsO_4, $NaIO_4$ (0.05 g, 0.02 mmol); then $NaClO_2$ (0.11 g, 1.19 mmol), a 1.25 M aqueous solution of $NaH_2PO_4 \cdot 2H_2O$ (0.97 mL)]. The crude residue was purified by flash chromatography (petroleum ether/AcOEt 2:8 containing 0.1% AcOH) to afford azido acid **20** (0.04 g, 77%) as a clear oil. $[\alpha]_D^{20} = -30.4$ ($c = 1.3$ in $CHCl_3$); ^{1}H NMR (C_6D_6): $\delta = 4.42$, 4.23 (ABq, $J = 11.7$ Hz, 2H; PhC*H*$_2$O), 4.21, 4.15 (ABq, $J = 12.0$ Hz, 2H; PhC*H*$_2$O), 4.11 (d, $J = 3.2$ Hz, 1H; H-3), 3.98 (d, $J = 3.6$ Hz, 1H; H-1), 3.90 – 3.80 (m, 3H; H-4, H-5, H-1″), 3.35 (dd, $J = 10.9$, 3.0 Hz, 1H; H-6a), 3.22 (dd, $J = 10.9$, 4.3 Hz, 1H; H-6b), 3.04 (dd, $J = 12.9$, 7.8 Hz, 1H; H-2″a), 2.76 (dd, $J = 12.9$, 4.7 Hz, 1H; H-2″b), 2.25 (s, 1H; H-1′); ^{13}C NMR: $\delta = 172.06$ (s; C-2′), 93.31 (s; C-2), 93.73, 86.54, 84.03, 82.72, 79.87 (5d; C-1, C-3, C-4, C-5, C-1″), 73.89, 72.52, 69.62 (3t; C-6, Ph*C*H$_2$O), 50.06 (t; C-2″), 38.99 (t; C-1′); MALDI-MS: m/z: 492 $[M+Na]^+$, 508 $[M+K]^+$; elemental analysis calcd (%) for $C_{24}H_{27}N_3O_7$ (469.5): C 61.40, H 5.80, N 8.95; found: C 61.39, H 5.82, N 9.00.

Tricycle 21: Alcohol **14** (0.03 g, 0.06 mmol) was dissolved in dry CH_2Cl_2 (1.4 mL), and iodine (0.09 g, 0.36 mmol) was added. After stirring the solution for 1 h, the reaction was diluted with H_2O, and $Na_2S_2O_3$ was added until the solution became colorless. The solution was extracted with AcOEt and the organic layer was dried (Na_2SO_4), filtered, and concentrated to dryness. The crude was purified by flash chromatography (petroleum ether/AcOEt 9:1) to afford tricycle **21** (0.03 g, 66%) as a clear oil, as a mixture of four non-separable diastereomers. NMR data refers to the major isomer. ^{13}C NMR: (C_6D_6): $\delta = 99.68$ (s; C-2), 99.09, 89.14, 84.11, 83.44, 83.25, 80.64 (6d; C-1, C-3, C-4, C-5, C-2′, C-1″), 74.26, 72.78, 70.89 (3t; C-6, Ph*C*H$_2$O), 44.09 (1t; C-1′), 9.35 (t; C-3′), 1.18 (t; C-2″); MALDI-MS: m/z: 686 $[M+Na]^+$, 702 $[M+K]^+$; elemental analysis calcd (%) for $C_{25}H_{28}I_2O_5$ (662.3): C 45.34, H 4.26; found: C 45.45, H 4.26.

Conformational analysis

Molecular mechanics and dynamics calculations: Molecular mechanics and dynamics calculations were performed using the MM3* force field as implemented in MACROMODEL 4.5.[21] Firstly, all the possible staggered orientations of the lateral chains were used for the constituent molecular fragments. *Gauche – gauche* (*gg*), *trans – gauche* (*tg*), and *gauche – trans* (*gt*) orientations are defined for the relative orientation (either *gauche* or *trans*) of the heteroatom (het) of the lateral chain with respect to the O and C-vicinal endocyclic atoms, respectively (see Figure 1). Separate calculations for a dielectric constant $\varepsilon = 10$ and for the continuum GB/SA solvent model were performed.[22] All the initial geometries of the different compounds (**3**, **8**, or **17**, depending on the number of lateral chains) were optimized using 200 steepest descent steps, followed by the number of conjugate gradient iterations required for complete convergence.

For the molecular dynamics (MD) simulations with the MM3* force field, 500 structures were sampled for the 1 ns simulation time. The time step was set to 1.5 fs and the SHAKE option was employed for the C–H bonds. The temperature was set to 300 K. Interproton distances and proton – proton torsion angles were then estimated from the output geometries to be compared with the experimental NOE and *J* NMR results.

NMR analysis: NMR experiments were recorded on Varian Unity and Bruker Avance 500 MHz spectrometers, using approximately 3 – 10 mg mL^{-1} solutions of the mimetics at different temperatures. Chemical shifts are reported in ppm, against the external reference TMS (0 ppm), independently of the solvent used. The double quantum-filtered COSY spectrum was performed with a data matrix of 256×1 K to digitize a

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spectral width of 4000 Hz. 16 scans were used with a relaxation delay of 1 s. The two-dimensional TOCSY experiment was performed using a data matrix of 256 × 2 K to digitize a spectral width of 4000 Hz. Four scans were used per increment with a relaxation delay of 2 s. MLEV 17 was used for the 100 ms isotropic mixing time. The one-bond proton–carbon correlation experiment was collected in the ^{1}H detection mode using the HSQC sequence and a reverse probe. A data matrix of was used to digitize a spectral width of 2000 Hz in F_2 and 10 000 Hz in F_1. Four scans were used per increment with a relaxation delay of 1 s and a delay corresponding to a J value of 145 Hz. A BIRD pulse was used to minimize the proton signals bonded to ^{12}C. ^{13}C decoupling was achieved by the WALTZ scheme.

NOESY experiments were performed with the selective one-dimensional double pulse field gradient spin echo module,[23] using four different mixing times, namely 150, 300, 450, and 600 ms. Two-dimensional NOESY and two-dimensional T-ROESY[24] experiments were also performed using mixing times of 450–800 ms.

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[1] S. Hanessian in *Total Synthesis of Natural Products*: *The "Chiron" Approac*h (Ed.: J. E. Baldwin), Pergamon, Oxford, **1983**.
[2] R. I. Hollingsworth, G. Wang, *Chem. Rev.* **2000**, *100*, 4267.
[3] a) R. Hirschmann, K. C. Nicolaou, S. Pietranico, J. Salvino, E. M. Leahy, P. A. Sprengeler, G. Furst, A. B. Smith III, C. D. Strader, M. A. Cascieri, M. R. Candelore, C. Donaldson, W. Vale, L. Maechler, *J. Am. Chem. Soc*. **1992**, *114*, 9217; b) R. Hirschmann, K. C. Nicolaou, S. Pietronico, E. M. Leahy, J. Salvino, B. Arison, M. A. Cichy, P. G. Spoors, W. C. Shakespeare, P. A. Sprengeler, P. Hamley, A. B. Smith III, T. Reisine, K. Raynor, L. Maechler, C. Donaldson, W. Vale, R. M. Freidinger, M. R. Cascieri, C. D. Strader, *J. Am. Chem. Soc*. **1993**, *115*, 12 550; c) R. Hirschmann, J. Hynes Jr., M. A. Cichy-Knight, R. D. van Rijn, P. A. Sprengeler, P. G. Spoors, W. C. Shakespeare, S. Pietronico-Cole, J. Barbosa, J. Liu, W. Yao, S. Rohrer, A. B. Smith III, *J. Med. Chem*. **1998**, *41*, 1382.
[4] a) T. Q. Dinh, C. D. Smith, X. Du, R. W. Armstrong, *J. Med. Chem.* **1998**, *41*, 981; b) H. P. Wessel, D. Banner, K. Gubernator, K. Hilpert, K. Müller, T. Tschopp, *Angew. Chem*. **1997**, *109*, 791; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 751; c) K. C. Nicolaou, J. Trujillo, K. Chibale, *Tetrahedron* **1997**, *53*, 8751; d) E. Graf von Roedern, H. Kessler, *Angew. Chem*. **1994**, *106*, 682; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 687; e) E. Graf von Roedern, E. Lohof, G. Hessler, M. Hoffmann, H. Kessler, *J. Am. Chem. Soc*. **1996**, *118*, 10 156; f) E. Lohof, E. Planker, C. Mang, F. Burkhart, M. A. Dechantsreiter, R. Haubner, H.-J. Wester, M. Schwaiger, G. Hölzemann, S. L. Goodman, H. Kessler, *Angew. Chem*. **2000**, *112*, 2868; *Angew. Chem. Int. Ed. Engl*. **2000**, *39*, 2761.
[5] N. L. Hungerford, G. W. J. Fleet, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3680.
[6] S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173.
[7] a) A. Imberty, S. Pérez, *Chem. Rev.* **2000**, *100*, 4567; b) A. Poveda, J. Jiménez-Barbero, *Chem. Soc. Rev*. **1998**, *27*, 133.
[8] H. M. D. Postema in *C-Glycosides Synthesis*, CRC, Boca Raton, FL, **1995** and references therein.
[9] A. Hosomi, Y. Sakata, H. Sakurai, *Tetrahedron Lett*. **1984**, *25*, 2383.
[10] a) F. Garcia-Tellado, P. de Armas, J. J. Marrero-Tellado, *Angew. Chem*. **2000**, *112*, 2839; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2727; b) C. H. Larsen, B. H. Ridgway, J. T. Shaw, K. A. Woerpel, *J. Am. Chem. Soc*. **1999**, *121*, 12 208.
[11] F. Nicotra, L. Panza, G. Russo, *J. Org. Chem.* **1987**, *52*, 5627.
[12] J. E. Baldwin, *Chem. Commun*. **1976**, 734.
[13] J. I. Sakai, T. Takeda, Y. Ogihara, *Carbohydr. Res.* **1981**, *95*, 125.
[14] G. Zémplen, *Chem. Ber*. **1926**, *59*, 1254.
[15] E. J. Eisenbrown, *Org. Synth*. **1973**, *4*, 310.
[16] R. Pappo, D. S. Allen, R. U. Lemieux, W. S. Johnson, *J. Org. Chem*. **1956**, *21*, 478.
[17] G. W. J. Fleet, J. C. Son, *Tetrahedron* **1988**, *44*, 2637.
[18] C. A. G. Haasnoot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron* **1980**, *36*, 2783.
[19] K. N. Kirschner, R. J. Woods, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 10 541.
[20] For a detailed discussion of the application of molecular mechanics force fields to carbohydrate molecules, see S. Pérez, A. Imberty, S. B. Engelsen, J. Gruza, K. Mazeau, J. Jiménez-Barbero, A. Poveda, J.-F. Espinosa, B. P. van Eyck, G. Johnson, A. D. French, M. L. C. E. Kouwijzer, P. D. J. Grootenuis, A. Bernardi, L. Raimondi, H. Senderowitz, V. Durier, G. Vergoten, K. Rasmussen, *Carbohydr. Res.* **1998**, *314*, 141.
[21] The MM3* force field (N. L. Allinger, Y. H. Yuh, J. H. Lii, *J. Am. Chem. Soc.* **1989**, *111*, 8551) implemented in MACROMODEL (F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440) differs from the regular MM3 force field in the treatment of the electrostatic term, since it uses charge–charge instead of dipole–dipole interactions. The MM3* force field was used since, except for the distribution around the lateral C-5–C-6 chains, it has provided a satisfactory agreement between experimental and theoretical data for a variety of saccharides and carbasugars. For specific cases, see: a) J. F. Espinosa, H. Dietrich, M. Martín-Lomas, R. R. Schmidt, J. Jiménez-Barbero, *Tetrahedron Lett.* **1996**, *37*, 1467; b) M. Martín-Pastor, J. F. J. Espinosa, L. Asensio, J. Jiménez-Barbero, *Carbohydr. Res.* **1997**, *298*, 15.
[22] W. C. Still, A. Tempczyk, R. C. Hawley, T. Hendrickson, *J. Am. Chem. Soc.* **1990**, *112*, 6127.
[23] K. Stott, J. Stonehouse, J. Keeler, T.-L. Hwang, A. J. Shaka, *J. Am. Chem. Soc*. **1995**, *117*, 4199.
[24] T. L. Hwang, A. J. Shaka, *J. Am. Chem. Soc*. **1992**, *114*, 3157.

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