Synthesis of Carba- and C-Fucopyranosides and Their Evaluation as α-Fucosidase Inhibitors − Analysis of an Unusual Conformation Adopted by an Amino-C-fucopyranoside

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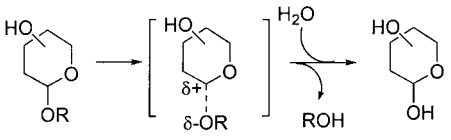
Dedicated to Professor Manuel Martín-Lomas on the ocassion of his 60th birthday

Keywords: Carbocycles / Conformational analysis / Glycosides / Inhibitors

Several carba- and C-fucopyranosides bearing a variety of substituents at their pseudoanomeric positions have been synthesized and tested as inhibitors of bovine kidney α-fucosidase. From the IC_{50} values, some conclusions about the structure-activity relationship could be drawn. The presence of a hydroxyl group close to the pseudoanomeric position, or the presence of an aromatic ring as substituent, were beneficial for inhibitory activity. A 1-(*R*)-amino-phenylmethyl C-fucopyranoside, the activity of which increased 40 times when the pH was changed from 5.0 to 7.0, adopted a $^4C_1$ conformation, in contrast to the $^1C_4$ form normally adopted by natural fucopyranosides. The conformation of this compound was analyzed in comparison with that of the 1-(*S*)-configured epimer, using NMR spectroscopy and molecular modeling.

Introduction

Carbohydrates play a broad range of biological roles, mainly related to cell recognition events,[1] many of which occur at very early stages of disease development and signaling processes. Control of such recognition processes has become an important target for new drug development. One strategy for intervention in these processes is to inhibit the enzymes involved in oligosaccharide synthesis and processing.[2] Glycosidases are the enzymes responsible for hydrolysis of the glycosidic bonds in oligosaccharides of glycoproteins and glycolipids; the reactions catalyzed by glycosidases proceed through cleavage of the bond between the anomeric carbon and the exo-anomeric oxygen atom (Scheme 1).[3] Many substrate and transition state analogue inhibitors of glycosidases have been developed; some of these appear to work by prevention of the processing of *N*-linked complex oligosaccharides.[4] In addition, glycosidase inhibitors have been used or proposed as antiviral agents,[5] antidiabetic compounds,[6] or as inhibitors of tumor metastasis.[7]



Scheme 1. Hydrolysis of glycosides

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The development of α-L-fucosidase inhibitors is of special interest because of the key role played by the fucopyranose moiety at the nonreducing end of many complex carbohydrates associated with antigenic determination,[8] tumorogenesis,[9] metastasis,[10] inflammatory processes,[11] etc. Many of the fucosidase inhibitors described in the literature are transition state analogs, with azasugar[12] or thioglycoside[13] structures. However, few examples of fucosidase inhibitors with C- or carba-fucopyranoside structures are known.[14]

We are involved in a project addressing the synthesis of fucose analogues, including thio-,[15] carba-,[16] and C-fucopyranosides.[17] We have reported a highly stereoselective synthesis of carba-α-L-fucopyranose (**1**, Scheme 2) from D-mannitol,[16b] and a new method for the synthesis of C-glycosides in a stereospecific manner from readily available glycosyl phenyl sulfoxides.[17] On this basis, we now report the preparation of a series of carba- and C-fucopyranosides with different substituents at their pseudoanomeric positions (Scheme 2). Because of the absence of anomeric carbon, these compounds are resistant to the action of fucosidases. Moreover, they can act as inhibitors of these enzymes, providing information about the influence on inhibitory properties of substituents around the anomeric center. In this paper we report on the activity of the new fucose analogs as inhibitors of bovine kidney α-fucosidase . Interestingly, a 1-(*R*)-amino-phenylmethyl C-fucopyranoside, the inhibitory activity of which was pH-dependent, had its pyranoid ring in a $^4C_1$ conformation, unlike the $^1C_4$ form normally adopted by natural fucopyranosides. A detailed conformational analysis of this compound by NMR spectroscopy and molecular modeling, in comparison with that of its 1-(*S*)-configured epimer, is reported.

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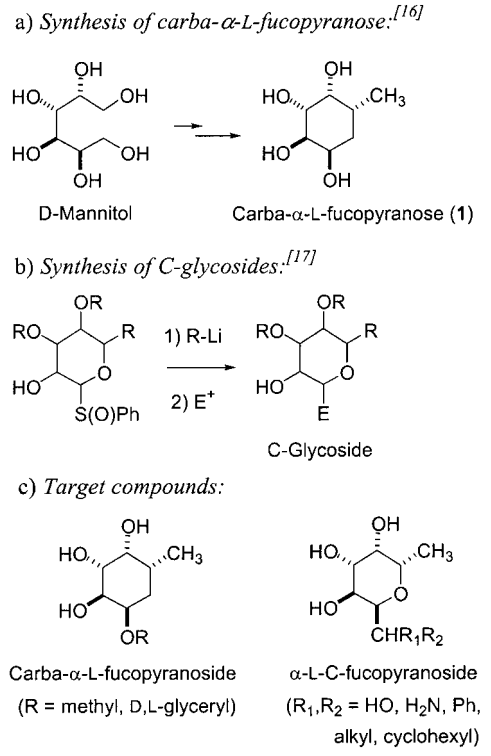
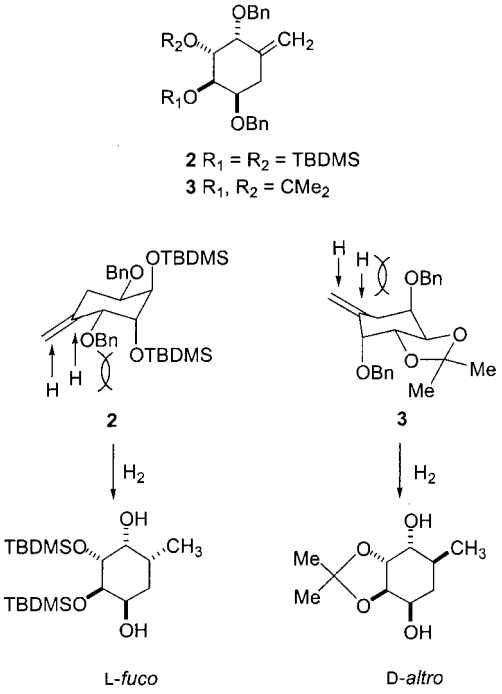


Scheme 2. Stereoselective routes for the synthesis of carba- and C-L-fucopyranosides

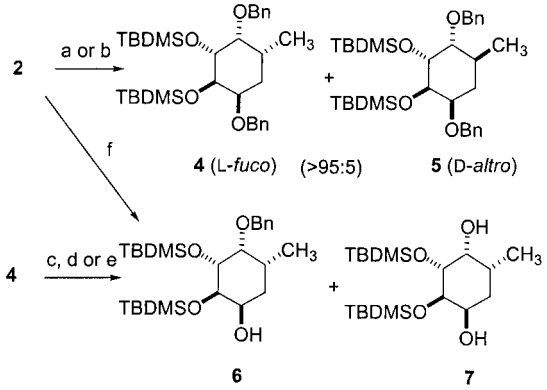
Results and Discussion

Synthesis of Carba- and C-Fucopyranosides

For the synthesis of the carba-fucopyranosides we used the *exo*-methylenecyclohexane **2** (Scheme 3). In previous work[16b] we have shown that the stereoselectivity of hydrogenation of **2** and **3** is determined by the type of substitution at the C(2) and C(3) positions (Scheme 3). In the case of **2**, the presence of two bulky *tert*-butyldimethylsilyloxy groups makes the cyclohexane ring adopt the conformation with the two silyloxy groups *trans*-diaxially disposed. In this conformation, the substituent at C(3) must preclude hydrogenation on the α-face, favoring addition on the opposite side to give the L-*fuco*-configured carbasugar, with simultaneous cleavage of the benzyl groups. In contrast, hydrogenation of the 2,3-*O*-isopropylidene derivative **3** gave the isomeric carba-D-altropyranose derivative. We have now performed hydrogenation of the double bond of **2** under conditions under which the benzyl groups remain (Scheme 4). This was efficiently accomplished by use of either Raney Ni or Pd−C in the presence of pyridine as catalysts, affording a mixture of *fuco*- and *altro*-configured compounds **4** and **5**, respectively, in which the carba-fucopyranose derivative **4** predominated (*fuco*:*altro* > 95:5). Regioselective hydrogenolysis of the benzyl group at C(1) under catalytic transfer hydrogenation conditions was next examined, using cyclohexene,[18] 2-propanol,[19] or $HCOONH_4$[20] as hydrogen donors. With the last reagent, use of a hydrogen atmosphere was necessary, probably due to inhibition of the catalyst (Pd−C) by the ammonium formate.[21] In all cases, a regioselective cleavage of the less sterically hindered benzyl group at C(1) took place, giving the alcohol **6**. The highest regioselectivity was obtained by use of $HCOONH_4$, which furnished **6** in 80% (Scheme 4). In view of the good result obtained with this reagent, together with the fact that the reaction needs a hydrogen atmosphere, we examined the possibility of performing both the hydrogenation of the double bond and the debenzylation of **2** under these conditions. Treatment of **2** with $HCOONH_4$ and H_2 gave the desired **6** with excellent stereo- and regioselectivity (**6** was isolated in 74% yield).

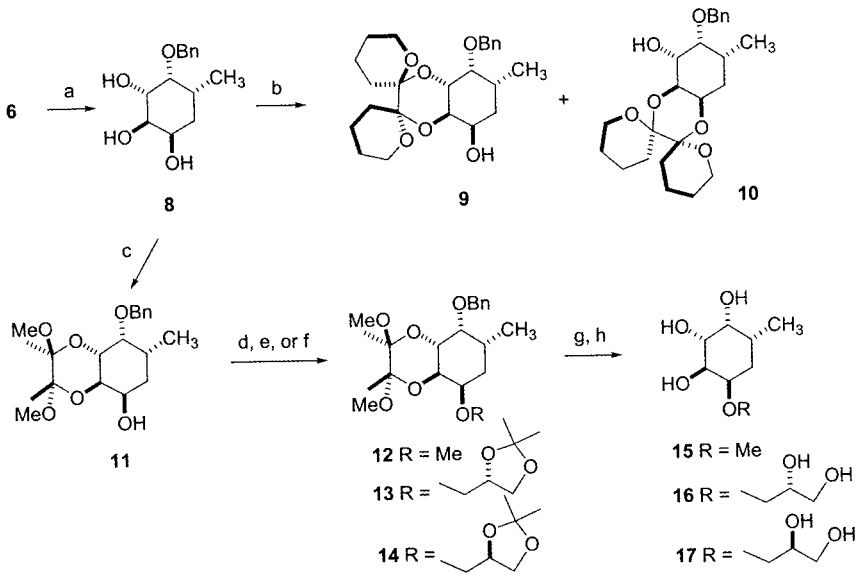


Scheme 3. Stereochemical outcome of the hydrogenation of **2** and **3**



Scheme 4. (a) Pd−C, H_2, MeOH/Py, 97%; (b) Raney Ni, H_2, MeOH, 70%; (c) $Pd(OH)_2$, cyclohexene, MeOH, 60 h, **6** (60%), **7** (26%); (d) Pd−C, *i*PrOH, 24 h, **6** (54%), **7** (40%); (e) Pd−C, $HCOONH_4$, H_2, MeOH, 4 h, **6** (80%), **7** (5%); (f) Pd−C, $HCOONH_4$, H_2, MeOH, 6 h, **6** (74%), **7** (18%)

With **6** in hand, we then examined its alkylation, to obtain the methyl and glyceryl carba-fucopyranosides shown in Scheme 2. All attempts to alkylate the hydroxyl moiety of **6** with MeI or with glycerol tosylates were unsuccessful,



Scheme 5. (a) Bu_4NF,THF, 98%; (b) bis-DHP, CSA, 61% (**9**:**10** = 1:1.2); (c) butane-2,3-dione, CSA, $CH(OMe)_3$, 94%; (d) MeI, NaH, DMF, 96%; (e) 2,3-*O*-isopropylidene-D-glyceryl tosylate, NaH, DMF, 70%; (f) 2,3-*O*-isopropylidene-L-glyceryl tosylate, NaH, DMF, 73%; (g) $AcOH/H_2O$, 100 °C; (h) H_2, Pd−C, MeOH, 73, 53, and 58% yields over two steps for **15**, **16**, and **17**, respectively

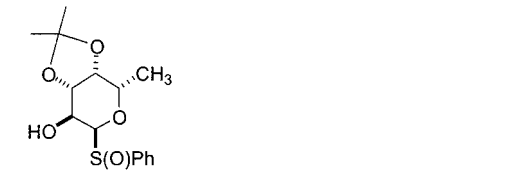
due to the instability of the silyloxy group under the basic conditions used. We therefore changed the protection at C(2) and C(3) to acetal groups (Scheme 5). Deprotection of **6** with tetrabutylammonium fluoride gave the triol **8**, with two vic-diol systems: 1,2-*cis*- and 2,3-*trans*-diequatorial diols. Selective protection of *trans* vicinal diols of carbohydrates by formation of dispiroacetals and 1,2-diacetals has been described by Ley et al.;[22] treatment of **8** with 3,3′,4,4′-tetrahydro-6,6′-bis-2*H*-pyran (bis-DHP)[22a] in the presence of camphorsulfonic acid (CSA) gave a 1:1.2 mixture of the 1,2-*cis* and 2,3-*trans* diol-protected ketals **9** and **10**, respectively, in 61% yield. Better results were obtained with butane-2,3-dione[22b] in the presence of CSA/$CH(OMe)_3$, which afforded the 2,3-protected derivative **11** in 94% yield. Compound **11** was alkylated with MeI, and also with 2,3-*O*-isopropylidene-D- and L-glyceryl tosylates to give the corresponding 1-*O*-alkylated derivatives **12**, **13**, and **14**, respectively. Acid hydrolysis of the acetal groups of **12**−**14** followed by debenzylation furnished the targets **15**, **16**, and **17**, respectively.

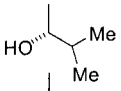
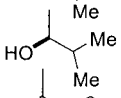
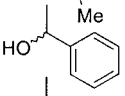
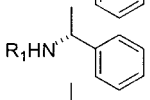
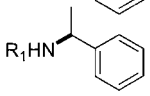
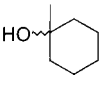
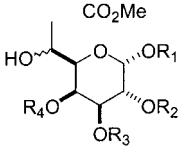
For the preparation of the α-L-C-fucopyranosides we used the products of our recent[17b] study on the synthesis of C-glycosides from glycosyl phenyl sulfoxides (compounds A in Scheme 6). These reactions proceeded through phenylsulfinyl-lithium exchange, to generate a configurationally stable anomeric carbanion, and subsequent treatment with carbon electrophiles. To obtain the *N*-protected amino-C-fucopyranosides **24** and **25**, the reaction mixture with benzonitrile as electrophile was hydrogenated, to reduce the generated imine, and subsequently treated with $(Boc)_2O$. The unprotected C-glycosides **30**−**38** (compounds B in Scheme 6) were obtained by treatment of **20**−**28** with trifluoroacetic acid in methanol.

Inhibition Studies

The carba-fucosides **1** and **15**−**17** and the C-fucopyranosides **30**−**38** were assayed as inhibitors of bovine kidney α-L-fucosidase at pH 5.5. As the substrate we used 4-nitrophenyl α-L-fucopyranoside, determining the release of nitrophenol in the presence or absence of inhibitor. The results are summarized in Table 1. The fucopyranoside analogs behaved only as moderate to weak inhibitors; nevertheless, some conclusions about the structure-activity relationship could be drawn. As general feature, the presence of a hydroxyl group near the pseudoanomeric position [C(1)] seemed to influence the inhibitory activity. For instance, the carba-fucopyranose **1**, with a hydroxyl group at C(1), was ten times better as an inhibitor than the 1-*O*-methyl derivative **15** and the 1-*C*-methyl and 1-deoxy-fucopyranosides **30** and **29**. Comparing the epimers **31** and **32**, a fivefold increase in the IC_{50} value was obtained on going from **31** to **32**. This seems to indicate that the inhibitory activity is dependent on the configuration of the stereocenter bearing the secondary hydroxyl group. However, the epimers **16** and **17**, in which the stereocenter is one bond further from the anomeric carbon, had similar inhibitory activities. Compound **33**, containing an aromatic ring in the aglycon, showed the highest activity among the C-glycosides. On the other hand, the inhibition properties of the C-disaccharide **38** were poor, and the 1-carboxymethyl C-fucoside **37** gave the lowest activity. Contrary to expectations, the amino C-glycoside analogs also gave weak inhibition, the isomer of *S* configuration at C(7) (compound **34**) being four times more active.

In order to examine the effect of pH changes on the amino derivatives **34** and **35**, the inhibition assay was also carried out at pH 7.0. Interestingly, while the inhibition



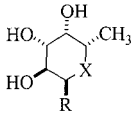
R	Compound A	Compound B (yield from A, %)
H	**19**	**29** (60)
Me	**20**	**30** (86)
	**21**	**31** (65)
	**22**	**32** (65)
	**23**	**33** (42)
	**24** R_1 = Boc	**34** (75) R_1 = H
	**25** R_1 = Boc	**35** (85) R_1 = H
	**26**	**36** (40)
CO_2Me	**27**	**37** (54)
	**28** R_1,R_2 = CMe_2 R_3,R_4 = CMe_2	**38** (72) R_1 = R_2 = H R_3 = R_4 = H

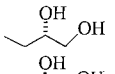
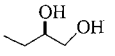
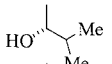
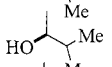
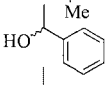
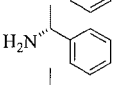
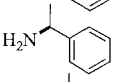
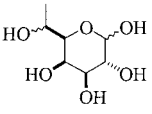
Scheme 6

produced by the *S* isomer **34** was unaltered after the pH increase, the activity of the *R* isomer **35** increased almost 40 times at pH 7.0. However, as detailed below, compound **35** is found in solution essentially in a $^4C_1$ chair at both pH values (5.5 and 7.0). This conformation is the opposite of the $^1C_4$ kind normally adopted by the natural fucopyranosides. The behavior of **35** as an inhibitor is difficult to explain without further kinetic studies.

In conclusion, the two series of fucopyranoside analogs have provided interesting data about the influence on enzyme inhibition of some functional groups close to the anomeric center. Their inhibitions are weak, however, compared to other compounds described in the literature, particularly compared to those aza-sugars that mimic the transition state. The fact that our compounds resemble the structure of the substrate rather than the transition state could account for their low inhibition properties.

Table 1. Inhibition of α-fucosidase at pH 5.5 by carba- and *C*-fucopyranosides.



R	X	Compound	IC_{50}[a] (mM)
OH	CH_2	**1**	0.6
OMe	CH_2	**15**	5.9
	CH_2	**16**	0.8
	CH_2	**17**	1.1
H	O	**29**	6.5
Me	O	**30**	7.0
	O	**31**	3.7
	O	**32**	20.0
	O	**33**	0.6
	O	**34**	6.7 (6.6)[b]
	O	**35**	28.0 (0.7)[b]
	O	**36**	3.9
CO_2Me	O	**37**	43.0
	O	**38**	10.3

[a] Concentration of fucose analog that inhibited the hydrolysis of 4-nitrophenyl α-L-fucopyranoside by 50%. – [b] The inhibition assay was performed at pH 7.0.

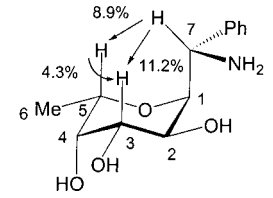
Conformational Analysis of 34 and 35

NMR Studies: NMR parameters, NOE and *J* values, were obtained in order to gain information on the conformational behavior of these compounds at the different pH values. The assignments of the resonances, made with the aid of COSY experiments at 500 MHz and the δ/*J* values, are shown in Table 2. For both compounds, independently of pH, the H(1)−H(7) coupling was very large (between 9.5 and 10.0 Hz), indicating an *anti*-like relationship between these two protons, also independently of the *R*/*S* configuration at C(7). The observed couplings for the ring system protons, however, were strikingly different in the two compounds. Indeed, the couplings for the *S* compound **34** were in agreement with those expected for a regular $^1C_4$(L) conformation, with large $J_{2,3}$, medium $J_{1,2}$, small

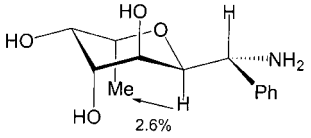
Table 2. Experimental chemical shifts (δ, ppm, pD 4.0), chemical shift variations between pD 4.0 and 10.0, and coupling constants (*J*, Hz) for the ring and H(7) protons of **34** and **35** in D_2O and 300 K.

34					**35**			
Proton	δ (ppm)	Δδ	$J_{H,H}$ [a]	(Hz)	δ (ppm)	Δδ	$J_{H,H}$	(Hz)
H(1)	4.638	0.57	$J_{1,2}$	5.5	4.554	0.61	$J_{1,2}$	0.8
H(2)	4.361	0.31	$J_{2,3}$	9.5	3.587	0.28	$J_{2,3}$	4.5
H(3)	4.186	0.23	$J_{3,4}$	3.0	4.059	0.34	$J_{3,4}$	4.0
H(4)	4.019	0.25	$J_{4,5}$	0.8	4.250	0.38	$J_{4,5}$	5.5
H(5)	3.935	0.19	$J_{5,6}$	6.5	4.431	0.39	$J_{5,6}$	6.2
H(7)	5.064	0.775	$J_{1,7}$	10.0	4.695	0.66	$J_{1,7}$	9.5

$J_{3,4}$, and very small $J_{4,5}$ couplings, values typical of an L-fucopyranosyl ring, with the C(6) methyl group adopting an equatorial orientation and the C(7) carbon in an axial disposition. In contrast, small, very small, small, and medium values were observed for the same coupling constants in the *R* analogue **35**. The observed couplings are in agreement with a drastic conformational change of the L-fucopyranosyl ring of the *R* compound, from the $^1C_4$(L) to the $^4C_1$(L) form. In this conformer, the C(6) methyl group now adopts an axial orientation, while the C(7) pseudoglycosidic carbon adopts an equatorial disposition. This conformation was confirmed by NOE measurements (Figure 1). Strong CH_3(6)/H(1) NOEs were observed only for the *R* analogue, as expected for a 1,3-syn diaxial orientation between the carbon and hydrogen atoms. Moreover, strong H(7)/H(5), H(5)/H(3), and H(7)/H(3) interactions were observed only for the *S* analogue, indicating close proximities between these proton pairs. This enhancement is only possible if H(3) and H(5) adopt an axial relationship, as in the $^1C_4$(L) form, and H(7) has an *anti*-like relationship with H(1). The NMR spectroscopic data therefore indicate that the fucopyranosyl chairs in these C-glycosides adopt different conformations, depending on the stereochemistry at the pseudoglycosidic C(7) center. An *anti*-like relationship exists between the anomeric H(1) and pseudoglycosidic H(7) protons in both compounds. Moreover, these conformational features are independent of the protonation state of the amine, since basically identical intra- and inter-ring *J* values are observed at pD values between 4 and 10 units. The conformational behavior of the *R* analogue **35** is markedly in contrast with that of a regular fucosyl glycoside, since to the best of our knowledge, no L-fucopyranosyl analogues with conformations other than $^1C_4$(L) have ever been reported.



34



35

Figure 1. NOE relationships in **34** and **35**

Molecular Mechanics Calculations: In the first step, the populations of the different staggered rotamers around φ angle were estimated for both *R*/*S* analogues **35**/**34** (Figure 2), by use of the MM3* force-field.[23] This glycosidic torsion angle is defined as Φ H(1′)−C(1′)−C(7)−CPh. The results are shown in Table 3. The rotamers were defined as g+ (60°), g− (−60°), and *anti* (180°). From the obtained energy values, two conclusions may be drawn: first, the typical L-fucopyranosyl $^1C_4$(L) conformer is more stable (ca. 5 kJ/mol) than the $^4C_1$(L) form, but only in the *S* analogue. The opposite trend is true for the *R* analogue (also ca. 5 kJ/mol), in close agreement with the experimental NMR observations. The *anti*-type relationship between H(1) and H(7) is also strongly favored in both cases, also in agreement with the NMR spectroscopic data. As far as the energy differences between the $^4C_1$(L) and $^1C_4$(L) forms are concerned, the major differences favoring the latter conformer in the *S* series are in the van der Waals term. For the *R* series, in contrast, the major differences favoring the $^4C_1$ conformers are in the solvation term. Indeed, when the MM3* calculations were performed in vacuo with no con-

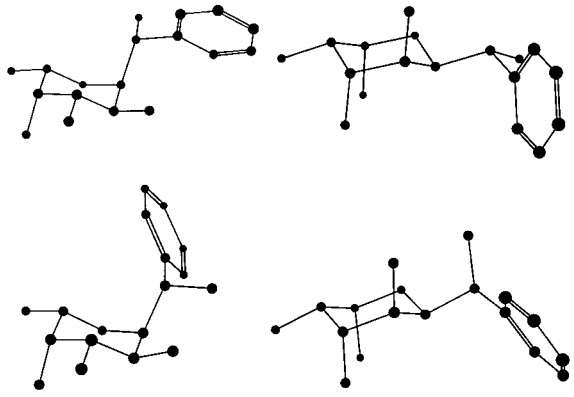


Figure 2. The four more stable conformers of **34** and **35**, according to MM3* calculations. Hydrogen atoms have been removed for sake of clarity. Top, isomer **35**, left, $^1C_4$ (L), and right, $^4C_1$ (L). Bottom, isomer **34**, left, $^1C_4$ (L), and right, $^4C_1$ (L)

Table 3. Steric energy values (kJ/mol, MM3*, GB/SA) calculated for the rotations around φ and the $^1C_4$ and $^4C_1$ conformations of **35** and **34**.

Energy (kJ/mol)				
Conformation (φ)	**35** $^1C_4$	**35** $^4C_1$	**34** $^1C_4$	**34** $^4C_1$
anti	338.2	333.3	333.2	339.9
g-	348.4	346.8	341.3	338.0
g+	349.5	341.6	346.5	348.1

tinuum GB/SA solvent model, the $^1C_4$ form was then 5 kJ/mol more stable than the experimentally observed $^4C_1$ conformer. The relative orientation of the amino group and the Ph ring and their interactions with the pyranoid ring and the environment may therefore be responsible for the observed conformational change in the *R* compound towards an unnatural $^4C_1$(L) conformation.

Experimental Section

General Methods: The methods described[16b] previously were applied.

4-*O*-Benzyl-2,3-di-*O*-(*tert*-butyldimethyl)silyl-5a-carba-α-L-fucopyranose (6)

Method A: A solution of **2**[16b] (80 mg, 0.14 mmol) and pyridine (5.3 μL, 0.07 mmol) in MeOH (1.6 mL) was hydrogenated in the presence of 10% Pd−C (6.5 mg, 0.007 mmol) at room temperature for 2 h. The reaction mixture was then diluted and filtered through a pad of Celite, and the solvent was evaporated. The residue was dissolved in MeOH (2 mL) and treated with $HCOONH_4$ (20 mg, 0.316 mmol) and 10% Pd−C (48 mg, 0.048 mmol) under a hydrogen atmosphere at 70 °C for 4 h. The reaction mixture was cooled and diluted with MeOH (4 mL), filtered, and concentrated to give a residue, which was purified by FC (hexane/CH_2Cl_2, 2:1) to give **6** (54 mg, 74%) as syrup, and **7** (4 mg, 5%).

Compound 6: $[\alpha]_D$ = −47.7 (*c* = 0.4, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (m, 12 H), 0.89 (s, 18 H), 1.04 (d, *J* = 6.7 Hz, 3 H), 1.62−1.64 (m, 1 H), 1.65−1.82 (m, 1 H), 2.09−2.23 (m, 1 H), 3.57−3.64 (m, 1 H), 3.77−3.85 (m, 1 H), 3.95−4.08 (m, 2 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.60−4.72 (m, 1 H), 7.26−7.35 (m, 5 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.6, −4.2, −4.1, −3.8, 18.1, 18.2, 26.1, 26.2, 30.0, 32.7, 73.8, 74.5, 127.2, 127.3, 128.1, 139.8. − $C_{26}H_{48}O_4Si_2$ (480.8): calcd. C 64.95, H 10.06, Si 11.68; found C 65.21, H 10.32, Si 11.99.

Compound 7: M.p. 95−96 °C. − $[\alpha]_D$ = −39.6 (*c* = 0.8, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (m, 12 H), 0.91 (s, 18 H), 1.03 (d, *J* = 7.0 Hz, 3 H), 1.59−1.70 (m, 2 H), 2.01−2.06 (m, 1 H), 2.34 (br. s, 1 H), 2.50 (br. s, 1 H), 3.67−3.68 (m, 1 H), 3.71−3.74 (m, 2 H), 3.88 (m, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.6, −4.6, −3.9, −3.9, 17.1, 17.9, 26.0, 28.3, 31.4, 73.2, 73.9, 70.5, 75.0. − $C_{19}H_{42}O_4Si_2$ (390.7): calcd. C 58.41, H 10.83, Si, 14.38; found C 58.36, H 11.15, Si 14.05.

Method B: A mixture of **2** (1.115 g, 195 mmol), MeOH (22 mL), $HCOONH_4$ (271 mg, 4.29 mmol), and 10% Pd−C (663 mg, 0.663 mmol) was hydrogenated at 70 °C for 6 h. The reaction mixture was cooled and diluted with MeOH (15 mL), filtered, and concentrated to give a residue, which was purified by FC (hexane/CH_2Cl_2, 2:1) to give first **4** (15 mg, 1%), then **6** (693 mg, 74%), and then **7** (137 mg, 18%).

4-*O*-Benzyl-5a-carba-α-L-fucopyranose (8): A solution of **6** (375 mg, 0.778 mmol), and Bu_4NF (815 mg, 3.112 mmol) in THF (25 mL), was stirred at room temperature for 3 h. After this time, the mixture was concentrated and the residue was purified by FC (hexane/EtOAc, 1:10) to give **8** (193 mg, 98%): m.p. 146−148 °C. − $[\alpha]_D$ = −50.4 (*c* = 0.6, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 7.0 Hz, 3 H,), 1.64−1.70 (m, 2 H), 1.91 (d, *J* = 8.8 Hz, 1 H), 2.08−2.26 (m, 1 H), 2.32 (br. s, 1 H), 2.48 (d, *J* = 2.4 Hz, 1 H), 3.69−3.75 (m, 3 H), 4.06−4.10 (m, 1 H), 4.64 (d, *J* = 11.6 Hz, 1 H), 4.78 (d, *J* = 11.7 Hz, 1 H), 7.38 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.8, 29.7, 32.9, 68.9, 72.7, 75.8, 72.9, 82.8, 127.3, 127.5, 128.3. − $C_{14}H_{20}O_4$ (252.3): calcd. C 66.63, H 7.99; found C 66.35, H 8.12.

4-*O*-Benzyl-2,3-*O*-(2,3-dimethoxybutane-2,3-diyl)-5a-carba-α-L-fucopyranose (11): 2,3-Butanedione (139 mg, 1.615 mmol), CSA (34 mg, 0.145 mmol), and $CH(OMe)_3$ (534 μL, 4.844 mmol) were added to a solution of **8** (185 mg, 0.734 mmol) in dry MeOH (1.5 mL), and the mixture was stirred at 60 °C for 12 h. The reaction mixture was quenched with Et_3N and concentrated. The residue was purified by FC (hexane/EtOAc, 10:1) to give **11** (234 mg, 94%): m.p. 54−56 °C. − $[\alpha]_D$ = +94.5 (*c* = 1.5, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.5 Hz, 3 H), 1.31 (s, 6 H), 1.6−1.64 (m, 2 H), 2.04−2.15 (m, 1 H), 2.36 (s, 1 H), 3.26 (s, 6 H), 3.60 (t, *J* = 2.1 Hz, 1 H), 3.98 (dd, *J* = 2.2, 3.4 Hz, 1 H), 3.99 (dd, *J* = 2.2, 10.3 Hz, 1 H), 4.04 (dd, *J* = 2.8, 10.5 Hz, 1 H), 4.55 (d, *J* = 11.2 Hz, 1 H), 5.01 (d, *J* = 11.2 Hz, 1 H), 7.28−7.37 (m, 3 H), 7.45−7.48 (m, 2 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 17.7, 17.8, 30.0, 33.3, 47.6, 47.7, 68.2, 68.4, 69.8, 74.0, 79.8, 99.3, 99.6, 127.1, 128.0, 128.0, 139.7. − $C_{20}H_{30}O_6$ (366.4): calcd. C 65.54, H 8.26; found C 65.72, H 8.35.

Methyl 4-*O*-Benzyl-2,3-*O*-(2,3-dimethoxybutane-2,3-diyl)-5a-carba-α-L-fucopyranoside (12): A solution of **11** (30 mg, 0.089 mmol) in THF (0.5 mL) was treated at room temperature with 95% NaH (3 mg, 0.106 mmol). After 30 min, CH_3I (6.6 μL, 0.106 mmol) was added and the reaction was allowed to proceed for 24 h. After this time, more 95% NaH (3 mg, 0.106 mmol) and CH_3I (6.6 μL, 0.106 mmol) were added and the reaction was allowed to continue for a further 4 h. The reaction mixture was then quenched with MeOH (1 mL) and the solvents were evaporated. The residue was purified by FC (hexane/EtOAc, 10:1) to give **12** (30 mg, 96%) as a syrup: $[\alpha]_D$ = +11.1 (*c* = 0.4, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.6 Hz, 3 H), 1.30 (s, 3 H), 1.33 (s, 3 H), 1.51 (td, *J* = 2.3, 14.4 Hz, 1 H), 1.67 (dt, *J* = 3.7, 14.3 Hz, 1 H), 1.91−1.99 (m, 1 H), 3.27 (s, 6 H), 3.39 (s, 3 H), 3.55 (d, *J* = 2.5 Hz, 1 H), 3.59 (m, 1 H), 4.02 (dd, *J* = 2.3, 10.6 Hz, 1 H), 4.12 (dd, *J* = 2.8, 10.6 Hz, 1 H), 4.53 (d, *J* = 11.1 Hz, 1 H), 5.02 (d, *J* = 11.0 Hz, 1 H), 7.23−7.52 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.4, 17.9, 29.9, 30.9, 47.6, 57.3, 74.4, 66.7, 70.1, 77.2, 79.9, 99.0, 99.4, 127.1, 128.0, 128.1, 140.0. − $C_{21}H_{32}O_6$ (380.5): calcd. C 66.29, H 8.48; found C 66.72, H 8.20.

D-*glycero*-2,3-Dihydroxy-2,3-*O*-isopropylidenepropyl 4-*O*-Benzyl-2,3-di-*O*-(2,3-dimethoxybutane-2,3-diyl)-5a-carba-α-L-fucopyranoside (13): A solution of **11** (75 mg, 0.2 mmol) in DMF (2 mL) was treated at room temperature with 95% NaH (21 mg, 0.888 mmol). After 20 min, a solution of Bu_4NI (82 mg, 0.222 mmol) and D-*glycero*-2,3-dihydroxy-2,3-*O*-isopropylidenepropyl *p*-toluenesulfonate (190 mg, 0.666 mmol) in DMF (0.9 mL) was added and the reaction was allowed to proceed at 90 °C for 8 h. The reaction was cooled to room temperature, treated again with 95% NaH (21 mg, 0.888 mmol), and heated to 90 °C for 20 h. After this time, the reaction mixture was cooled and quenched with MeOH (1 mL). The solvents were evaporated and the residue was purified by FC (hexane/EtOAc, 20:1→10:1→5:1) to give **13** (70 mg, 70%) as a syrup: $[\alpha]_D$ = +101.2 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.7 Hz, 3 H), 1.28 (s, 3 H), 1.29 (s, 3 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 1.54−1.62 (m, 2 H), 1.91−2.11 (m, 1 H), 3.24 (s, 6 H), 3.56−3.66 (m, 3 H), 3.79 (dd, *J* = 3.7, 10.7 Hz, 1 H), 3.94−4.12 (m, 4 H), 4.24−4.38 (m, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 5.01 (d, *J* = 11.1 Hz, 1 H), 7.30−7.49 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.3. 17.7, 17.8, 25.5, 26.7, 30.3,

35.2, 47.5, 47.6, 67.2, 69.2, 70.0, 72.1, 74.3, 75.0, 76.4, 79.9, 98.9, 99.0, 109.0, 127.9, 127.1, 128.1, 139.9. − $C_{26}H_{40}O_8$ (480.6): calcd. C 64.98, H 8.39; found C 64.60, H 8.21.

L-*glycero*-2,3-Dihydroxy-2,3-*O*-isopropylidenepropyl 4-*O*-Benzyl-2,3-di-*O*-(2,3-dimethoxy-butane-2,3-diyl)-5a-carba-α-L-fucopyranoside (14): With use of the same procedure as described for **13**, compound **11** was treated with L-*glycero*-2,3-dihydroxy-2,3-*O*-isopropylidenepropyl *p*-toluenesulfonate (190 mg, 0.666 mmol), to give **14** (73 mg, 73%) as a syrup: ^{1}H NMR(300 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.8 Hz, 3 H), 1.27 (s, 3 H), 1.28 (s, 3 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.51−1.59 (m, 2 H), 1.95−2.05 (m, 1 H), 3.23 (s, 6 H), 3.56−3.66 (m, 3 H), 3.81 (dd, *J* = 3.7, 10.7 Hz,1 H,), 3.94−4.09 (m, 4 H), 4.28−4.35 (m, 1 H), 4.51 (d, *J* = 11.2 Hz, 1 H), 5.00 (d, *J* = 11.0 Hz, 1 H), 7.28−7.48 (m, 5 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.4, 17.8, 25.7, 26.6, 30.4, 33.2, 47.5, 66.8, 70.8, 74.3, 68.9, 69.4, 70.1, 72.9, 74.9, 98.9, 99.0, 108.9, 127.1, 128.0, 128.1, 140.0. − $C_{26}H_{40}O_8$ (480.6): calcd. C 64.98, H 8.39; found C 65.12, H 8.31.

Methyl 5a-Carba-α-L-fucopyranoside (15): A solution of **12** (40 mg, 0.114 mmol) in AcOH/H_2O (2:1, 1 mL) was stirred at 100 °C for 2 h, and the solvents were then evaporated. The residue was purified by FC (CH_2Cl_2/MeOH, 20:1) to give methyl 4-*O*-benzyl-5a-carba-α-L-fucopyranoside: ^{1}H NMR (200 MHz, CD_3OD): δ = 0.96 (d, *J* = 6.8 Hz, 3 H), 1.55 (td, *J* = 2.4, 1.4 Hz, 1 H), 1.75 (dt, *J* = 1.2, 12.4 Hz, 1 H), 1.82−1.91 (m, 1 H), 3.35(s, 3 H), 3.53 (d, *J* = 1.8 Hz, 1 H,), 3.65 (s, 1 H), 3.77 (d, *J* = 1.2 Hz, 2 H), 4.56 (d, *J* = 11.4 Hz, 1 H), 4.93 (d, *J* = 11.4 Hz, 1 H), 7.24−7.40 (m, 5 H). − ^{13}C NMR (50 MHz, CD_3OD): δ = 18.2, 31.2, 57.7, 73.3, 75.0, 76.7, 81.2, 84.3, 128.6, 129.0, 129.4, 141.1. This compound was dissolved in MeOH (0.5 mL), and 10% Pd−C (20 mg, 0.020 mmol) was added. The mixture was hydrogenated at room temperature for 2 h, then filtered and concentrated to give **15** (22 mg, 73%): m.p. 101−103 °C. − $[\alpha]_D$ = −39.5 (*c* = 0.2, $CHCl_3$). − ^{1}H NMR (200 MHz, CD_3OD): δ = 1.17 (d, *J* = 7.0 Hz, 3 H), 1.64 (ddd, *J* = 2.5, 15.0 Hz, 1 H), 1.92 (ddd, *J* = 1.2, 4.0, 15.0 Hz, 1 H), 1.99−2.14 (m, 1 H), 3.54 (s, 3 H), 3.71 (q, *J* = 2. 8 Hz, 1 H), 3.81 (t, *J* = 2.1 Hz, 2 H), 3.90 (m, 1 H). − ^{13}C NMR (50 MHz, CD_3OD): δ = 15.6, 28.0, 28.4, 55.4, 70.5, 71.6, 73.2, 78.9. − $C_8H_{16}O_4$ (176.2): calcd. C 54.51, H 9.16; found C 54.60, H 9.20.

D-*glycero*-2,3-Dihydroxypropyl 5a-Carba-α-L-fucopyranoside (16): A solution of **13** (80 g, 0.155 mmol) in AcOH/H_2O (2:1, 1 mL) was stirred at 100 °C for 2 h. After this time, the solvents were evaporated, and the residue was purified by FC (CH_2Cl_2/MeOH, 20:1) to give D-*glycero*-2,3-dihydroxypropyl 4-*O*-benzyl-5a-carba-α-L-fucopyranoside (40 mg, 69%) as a syrup. − ^{1}H NMR (200 MHz, CD_3OD): δ = 0.96 (d, *J* = 6.8 Hz, 3 H), 1.51 (dt, *J* = 2.0, 12.6 Hz, 1 H), 1.70 (dt, *J* = 3.7, 12.3 Hz, 1 H), 1.85−2.05 (m, 1 H), 3.44 (dd, *J* = 4.1, 9.9 Hz, 2 H), 3.55−3.81 (m, 7 H), 4.56 (d, *J* = 11.4 Hz, 1 H), 4.95 (d, *J* = 11.4 Hz, 1 H), 7.23−7.40 (m, 5 H). − ^{13}C NMR (50 MHz, CD_3OD): δ = 18.2, 31.3, 31.9, 64.9, 71.8, 72.5, 73.4, 75.0, 76.8, 80.1, 84.4, 128.6, 129.0, 129.4, 141.1. Next, 10% Pd−C (20 mg, 0.020 mmol) was added to a solution of this compound in MeOH (0.5 mL). The mixture was hydrogenated at room temperature for 2 h, and then filtered and concentrated to give **16** (22 mg, 76%) as a syrup: $[\alpha]_D$ = − 65.1 (*c* = 0.4, $CHCl_3$). − ^{1}H NMR (500 MHz, D_2O): δ = 0.95 (d, *J* = 6.8 Hz, 3 H), 1.40 (dt, *J* = 1.9, 14.7 Hz, 1 H), 1.80 (dt, *J* = 2.6, 14.6 Hz, 1 H), 1.89−1.99 (m, 1 H), 3.49 (dd, *J* = 4.0, 11.0 Hz, 1 H), 3.60 (dd, *J* = 6.5, 11.0 Hz, 1 H), 3.62 (dd, *J* = 5.7, 10.2 Hz, 1 H), 3.66 (dd, *J* = 4.5, 11.7 Hz, 1 H), 3.69 (d, *J* = 3. 5 Hz, 1 H), 3.74−3.78 (m, 2 H), 3.85 (m, 1 H), 3.89 (dddd, *J* = 4.0, 5.7, 4.5, 6.5 Hz, 1 H). − ^{13}C NMR (75 MHz, D_2O): δ = 16.5, 28.8, 28.9, 62.9, 69.8, 71.0, 71.1, 71.9, 74.2, 78.3. − $C_{10}H_{20}O_6$ (236.3): calcd. C 50.83, H 8.53; found C 51.03, H 8.25.

L-*glycero*-2,3-Dihydroxypropyl 5a-Carba-α-L-fucopyranoside (17): This compound was prepared from **14** according to the method described above for the preparation of **16**. Compound **17** (58%) was obtained as a syrup: $[\alpha]_D$ = −42.3 (*c* = 0.6, $CHCl_3$). − ^{1}H NMR (500 MHz, D_2O): δ = 0.95 (d, *J* = 6.8 Hz, 3 H), 1.40 (t, *J* = 14.7 Hz, 1 H), 1.80 (dt, *J* = 2.2, 14.7 Hz, 1 H), 1.90−1.98 (m, 1 H), 3.40 (dd, *J* = 6.5, 8.2 Hz, 1 H), 3.56 (dd, *J* = 6.0, 11.5 Hz, 1 H), 3.65 (d, *J* = 4.0 Hz, 1 H), 3.69 (dd, *J* = 3.5, 10.5 Hz, 2 H), 3.75−3.77 (m, 2 H), 3.84 (m, 1 H), 3.88 (dddd, *J* = 4.0, 4.5, 6.0, 6.7 Hz, 1 H). − ^{13}C NMR (75 MHz, D_2O): δ = 11.7, 24.0, 24.2, 58.1, 65.5, 66.4, 66.4, 67.1, 73.8. − $C_{10}H_{20}O_6$ (236.3): calcd. C 50.83, H 8.53; found C 50.75, H 8.66.

Deprotection of *C*-Fucopyranosides. − General Procedure: A solution of *C*-fucopyranoside[17b] (0.2 mmol) in MeOH (2 mL) was treated with CF_3COOH (0.8 mmol) at 50 °C for the time indicated. The reaction mixture was then allowed to cool to room temperature and concentrated. The residue was purified by FC (EtOAc) to give **29−38**.

1,5-Anhydro-L-fucitol (29): The general procedure was used; compound **19** was treated with CF_3COOH for 24 h to give **29** (60%): m.p. 119−121 °C. − $[\alpha]_D$ = −61.2 (*c* = 0.5, MeOH). − ^{1}H NMR (300 MHz, CD_3OD): δ = 1.13 (d, *J* = 6.5 Hz, 3 H), 3.06 (t, *J* = 10.5 Hz, 1 H), 3.37 (dd, *J* = 3.3, 9.3 Hz, 1 H), 3.50 (q, *J* = 6.5 Hz, 1 H), 3.63 (d, *J* = 3.3 Hz, 1 H), 3.68−3.78 (m, 1 H), 3.83 (dd, *J* = 5.6, 10.6 Hz, 1 H). − ^{13}C NMR (50 MHz, CD_3OD): δ = 17.3, 68.5, 71.4, 73.7, 76.7, 77.0. − $C_6H_{12}O_4$ (148.2): calcd. C 48.64, H 8.16; found C 48.90, H 8.30.

2,6-Anhydro-1,7-dideoxy-L-*glycero*-D-*gluco*-heptitol (30): The general procedure was used; *C*-fucopyranoside **20** was treated with CF_3COOH for 48 h to give **30** (86%): m.p. 124−126 °C. − $[\alpha]_D$ = −82.7 (*c* = 0.5, MeOH). − ^{1}H NMR (200 MHz, CD_3OD): δ = 1.19 (d, *J* = 6.8 Hz, 6 H), 3.61−3.69 (m, 2 H), 3.80−3.91 (m, 2 H), 4.08 (dq, *J* = 3.3, 6.8 Hz, 1 H). − ^{13}C NMR (50 MHz, CD_3OD): δ = 12.5, 17.0, 68.7, 70.3, 72.0, 72.7, 73.2. − $C_7H_{14}O_4 \cdot 1/2\ H_2O$ (162.2): calcd. C 49.12, H 8.77; found C 49.00, H 8.56.

4,8-Anhydro-2-*C*-methyl-1,2,9-trideoxy-L-*threo*-D-*gulo*-nonitol (31): The general procedure was used; *C*-fucopyranoside **21** was treated with CF_3COOH for 48 h to give **31** (65%): m.p. 38−40 °C. − $[\alpha]_D$ = −51.1 (*c* = 1.5, MeOH). − ^{1}H NMR (300 MHz, CD_3OD): δ = 1.05 (d, *J* = 6.7 Hz, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 1.39 (d, *J* = 6.8 Hz, 3 H), 2.05 (m, *J* = 6.7 Hz, 1 H), 3.63 (dd, *J* = 4.3, 6.5 Hz, 1 H), 3.95 (dd, *J* = 3.4, 5.6 Hz, 1 H), 3.98 (t, *J* = 3.5 Hz, 1 H), 3.99 (t, *J* = 2.7 Hz, 1 H), 4.06 (dd, *J* = 3.6, 5.7 Hz, 1 H), 4.34 (qd, *J* = 2.0, 6.8 Hz). − ^{13}C NMR (50 MHz, CD_3OD): δ = 15.4, 18.5, 20.6, 34.5, 69.8, 70.6, 72.9, 73.4, 73.5, 78.5. − $C_{10}H_{20}O_5$ (220.3): calcd. C 54.53, H 9.15; found C 54.17, H 9.49.

4,8-Anhydro-2-*C*-methyl-1,2,9-trideoxy-L-*threo*-D-*ido*-nonitol (32): The general procedure was used; *C*-fucopyranoside **22** was treated with CF_3COOH for 48 h to give **32** (65%): m.p. 45−47 °C. − $[\alpha]_D$ = −38.1 (*c* = 0.3, MeOH). − ^{1}H NMR (300 MHz, CD_3OD): δ = 1.09 (d, *J* = 6.7 Hz, 3 H), 1.18 (d, *J* = 7.1 Hz, 3 H), 1.47 (d, *J* = 6.6 Hz, 3 H), 2.12 (dd, *J* = 2.6, 7.0 Hz, 1 H), 3.95−4.02 (m, 2 H), 4.04−4.11 (m, 3 H), 4.18−4.22 (m, 1 H). − ^{13}C NMR (75 MHz, CD_3OD): δ = 15.3, 15.4, 20.3, 30.5, 70.0, 70.7, 71.2, 72.6, 73.2, 74.2. − $C_{10}H_{20}O_5$ (220.3): calcd. C 54.53, H 9.15; found C 54.25, H 9.53.

2,6-Anhydro-7-deoxy−1-*C*-phenyl-L-*threo*-D-*gulo*- and 2,6-Anhydro-7-deoxy-1-*C*-phenyl-L-*threo*-D-*ido*-heptitol (33): The general proced-

ure was used; *C*-fucopyranoside **23** was treated with CF_3COOH for 48 h to give **33** in an approximately 2:1 diastereomeric mixture (42%): m.p. 67−69 °C. − $[\alpha]_D$ = − 65.8 (*c* = 0.6, MeOH). − ^1H NMR (300 MHz, CD_3OD): δ = 1.28 (d, *J* = 6.5 Hz, 3H-B), 1.52 (d, *J* = 6.9 Hz, 3H-A), 3.65 (dd, *J* = 2.8, 5.2 Hz, 1H-A), 4.08−4.21 (m, 3H-A y 4H-B), 4.26 (dd, *J* = 3.4, 6.2 Hz, 1H-B), 4.46 (q, *J* = 6.3 Hz, 1H-A), 5.13 (d, *J* = 6.8 Hz, 1H-A), 5.17 (d, *J* = 8.3 Hz, 1H-B),7.42−7.64 (m, 5H-A and 5H-B),. − ^{13}C NMR (50 MHz, CD_3OD) A): δ = 14.8, 68.9, 71.3, 73.4, 73.7, 74.5, 75.3, 128.5, 129.4, 144.2. B): δ = 15.2, 70.1, 72.7, 73.4, 73.7, 7.06, 74.13, 128.4, 128.83, 143.2. − $C_{13}H_{18}O_5$ (254.3): calcd. C 61.41, H 7.13; found C 60.99, H 7.50.

2,6-Anhydro-1-(*tert*-butoxycarbonylamino)-1,7-dideoxy-4,5-*O*-isopropylidene-1-*C*-phenyl-L-*threo*-D-*gulo*-heptitol (24) and 2,6-Anhydro-(*tert*-butoxycarbonylamino)-1,7-dideoxy-4,5-*O*-isopropylidene-1-*C*-phenyl-L-*threo*-D-*ido*-heptitol (25): A solution of **19**[16b] (0.32 mmol) and MeLi·BrLi (1.5 M, 0.35 mmol) in the minimum amount possible of dry THF was added dropwise at −78 °C to a solution of *t*BuLi (1.4 M in hexane, 1.60 mmol) in dry THF (2 mL). After 5 min, PhCN (1.6 mmol) was added, and the mixture was stirred for 5 min at −78 °C. MeOH (1 mL) and $NaBH_4$ (60 mg, 1.6 mmol) were then added, and the reaction was allowed to proceed at room temperature for 2 h. After this time, AcOH was added (1 mL) and the solvents were evaporated. The residue was dissolved in MeOH/ Et_3N (9:1, 1.7 mL) and treated with di-*tert*-butyl dicarbonate (350 mg, 1.6 mmol), stirring at 50 °C for 2 h. After this time, the reaction mixture was concentrated and the residue was purified by FC (hexane/EtOAc, 5:1) to give **24** (22 mg, 18%) and **25** (25 mg, 21%) as solids.

Compound 24: M.p. 190−192 °C. − $[\alpha]_D$ = −5.0 (*c* = 0.9, $CHCl_3$). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.4 Hz, 3 H), 1.34 (s, 3 H), 1.41 (s, 3 H), 1.49 (s, 3 H), 3.93 (t, *J* = 2.2 Hz, 1 H), 4.03 (dd, *J* = 1.9, 9.7 Hz, 1 H), 4.13 (dd, *J* = 1.5, 7.8 Hz, 1 H), 4.28 (qd, *J* = 1.4, 6.6 Hz, 1 H), 4.44 (dd, *J* = 2.2, 7.8, 1 H), 4.75 (dd, *J* = 8.5, 9.7 Hz, 1 H), 4.82−4.96 (br. s, 1 H), 5.07−5.18 (br. s, 1 H), 7.15−7.35 (m, 5 H),− ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3, 24.0, 26.5, 26.6, 28.2, 28.3, 65.3, 66.2, 72.8, 73.9, 75.1, 80.8, 109.0, 127.6, 128.0, 128.0, 128.6, 139.5, 156.9. − $C_{21}H_{31}NO_6$ (393.5): calcd. C 64.10, H 7.94, N 3.56; found C 64.51, H 7.66, N 3.48.

Compound 25: M.p. 138−140 °C. − $[\alpha]_D$ = −57.3 (*c* = 0.8, $CHCl_3$). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.4 Hz, 3 H), 1.29 (s, 3 H), 1.38 (s, 6 H), 1.42 (s, 6 H), 2.96−3.12 (br. s, 1 H), 3.66−3.74 (m, 1 H), 4.05−4.11 (m, 1 H), 4.14 (dd, *J* = 1.5, 7.7 Hz, 1 H), 4.22−4.31 (m, 2 H), 4.22−4.82 (br. s, 1 H), 5.36 (d, *J* = 7.7 Hz, 1 H), 7.22−7.35 (m, 5 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 24.0, 26.5, 28.2, 66.3, 68.6, 72.5, 74.1, 75.0, 80.0, 109.5, 127.0, 127.5, 128.6, 140.9, 156.2. − $C_{21}H_{31}NO_6$ (393.5): calcd. C 64.10, H 7.94, N 3.56; found C 64.28, H 7.77, N 3.39.

1-Ammonio-2,6-anhydro-1,7-dideoxy-4,5-*O*-isopropylidene-1-*C*-phenyl-L-*threo*-D-*gulo*-heptitol Trifluoroacetate (34): A solution of **24** (20 mg, 0.053 mmol) in MeOH (1 mL) was treated with CF_3COOH (41 μL. 0.53 mmol) at room temperature for 24 h and then concentrated. The residue was purified by FC (CH_2Cl_2/MeOH, 10:1) to give **34** (10 mg, 75%): m.p. 142−144 °C. − $[\alpha]_D$ = −24.4 (*c* = 0.2, $CHCl_3$). − ^1H NMR (300 MHz, CD_3OD): δ = 1.31 (d, *J* = 6.4 Hz, 3 H), 4.04−4.13 (m, 4 H), 4.42 (dd, *J* = 2.5, 7.6 Hz, 1 H) 4.88 (d, *J* = 7.6 Hz, 1 H), 7.60−7.72 (m, 5 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0, 57.2, 69.4, 70.5, 70.9, 72.5, 72.7, 128.6, 130.0, 136.1. − $C_{15}H_{20}F_3NO_6$ (367.3): calcd. C 49.05, H 5.49, N 3.81; found C 48.74, H 5.88, N 3.68.

1-Ammonio-2,6-anhydro-1,7-dideoxy-4,5-*O*-isopropylidene-1-*C*-phenyl-L-*threo*-D-*ido*-heptitol Trifluoroacetate (35): The title compound was obtained from **25** by the method described for the preparation of **34** (85%): m.p. 113−115 °C. − $[\alpha]_D$ = −22.9 (*c* = 0.2, $CHCl_3$). − ^1H NMR (300 MHz, CD_3OD): δ = 1.64 (d, *J* = 6.4 Hz, 3 H), 4.01 (t, *J* = 3.5 Hz, 1 H), 4.25 (dd, *J* = 3.5, 6.4 Hz, 1 H), 4.42 (q, *J* = 6.9 Hz, 1 H), 4.45 (dd, *J* = 1.5, 8.9 Hz, 1 H), 4.64 (d, *J* = 8.2 Hz, 1 H), 5.08 (m, 1 H), 7.63−7.72 (m, 5 H). − ^{13}C NMR (75 MHz, CD_3OD): δ = 13.8, 57.5, 66.4, 68.9, 70.5, 73.0, 74.2, 129.2, 130.3, 130.6, 135.4. − $C_{15}H_{20}F_3NO_6$ (367.3): calcd. C 49.05, H 5.49, N 3.81; found C 48.61, H 5.79, N 3.63.

1-*C*-(α-L-fucopyranosyl)cyclohexan-1-ol (36): By using the general procedure, C-fucopyranoside **26** was treated with CF_3COOH for 72 h to give **36** (40%): m.p. 64−66 °C. − $[\alpha]_D$: = −30.1 (*c* = 1.1, MeOH). − ^1H NMR (300 MHz, CD_3OD): δ = 1.44 (d, *J* = 6.7 Hz, 3 H), 1.53−1.94 (m, 10 H), 3.78 (d, *J* = 1.1 Hz, 1 H), 3.93 (t, *J* = 3.4 Hz, 1 H), 4.09−4.14 (m, 2 H), 4.19 (dq, *J* = 2.9, 6.7 Hz, 1 H). − ^{13}C NMR (50 MHz, CD_3OD): δ = 12.9, 14.0, 23.1, 27.1, 35.8, 36.1, 67.2, 69.3, 72.5, 73.2, 73.8, 75.4. − $C_{12}H_{22}O_5$ (245.3): calcd. C 58.75, H 9.04; found C 59.12, H 9.26.

Methyl 2,6-Anhydro-7-deoxy-L-*glycero*-D-*gluco*-heptanoate (37): Following the general procedure, compound **27** was treated with CF_3COOH for 24 h. After column chromatography, the fractions containing C-glycoside were concentrated and the residue was dissolved in MeOH (1 mL) and treated with MeONa (1 M, 20 μL, 0.02 mmol) at room temperature for 3 h. The reaction mixture was neutralized with Amberlyst IR-120 (H^+), and concentrated to give **37** (54%): m.p. 102−105 °C. − $[\alpha]_D$ = −84.7 (*c* = 0.5, MeOH). − ^1H NMR (300 MHz, CD_3OD): δ = 1.22 (d, *J* = 6.6 Hz, 3 H), 3.72 (s, 3 H), 3.75 (t, *J* = 2.3 Hz, 1 H), 3.94 (dd, *J* = 3.2, 8.7 Hz, 1 H), 4.01 (dd, *J* = 5.9, 8.7 Hz, 1 H), 4.34 (qd, *J* = 2.3, 6.6 Hz, 1 H), 4.48 (d, *J* = 5.8 Hz, 1 H). − ^{13}C NMR (75 MHz, CD_3OD): δ = 16.2, 52.0, 68.9, 71.8, 72.1, 72.3, 72.3, 75.5, 172.7. − $C_8H_{14}O_6$ (206.2): calcd. C 46.60, H 6.84; found C 46.90, H 7.12.

(6*R* and 6*S*)-6-*C*-(α-L-Fucopyranosyl)-α,β-D-galactopyranose (38): The general procedure was used; *C*-disaccharide **28** was treated with CF_3COOH for 24 h to give **38** (72%): m.p. 105−107 °C. − $[\alpha]_D$ = −0.6 (*c* = 0.9, MeOH) − ^1H NMR (300 MHz, D_2O): δ = 1.06 (d, *J* = 6.7 Hz, <1 H), 1.08 (d, *J* = 6.3 Hz, <1 H), 3.30−3.42 (m, 1 H), 3.46−3.54 (m, 2 H), 3.56−3.63 (m, 1 H), 3.67−3.73 (m, 2 H), 3.78−3.88 (m, 1 H), 3.92−4.04 (m, 2 H), 4.09−4.21 (m, 1 H), 4.98−5.18 (m, 1 H). − ^{13}C NMR (75 MHz, D_2O): δ = 16.2, 17.0, 69.6, 70.1, 71.8, 72.0, 72.8, 73.1, 73.9, 74.1, 74.3, 76.8, 97.9. − $C_{12}H_{22}O_{10}$·3 H_2O (978.9): calcd. C 37.89, H 7.36; found C 36.70, H 6.32.

Inhibition Experiments: Bovine kidney α-L-fucosidase was purchased from Sigma. The reaction mixture (1 mL) contained sodium phosphate buffer (50 mM, pH 5.5), 4-nitrophenyl α-L-fucopyranoside (3 mM), and carba- or C-fucopyranoside at final concentrations of 0.1 mM, 1.0 mM, or 10.0 mM, together with the α-L-fucosidase ($2.2 \cdot 10^{-2}$ U). After 30 min incubation at 27 °C, the reaction was quenched by addition of 1 M Na_2CO_3 (400 μL). The optical absorbance at 410 nm was measured to determine the amount of liberated 4-nitrophenol, and the IC_{50} value was calculated.

Molecular Mechanics and Dynamics Calculations: Molecular mechanics and dynamics calculations were performed using the MM3* force-field as implemented in MACROMODEL 4.5.[23] The relevant glycosidic torsion angle is defined as Φ H(1)−C(1)−C(7)−CPh in each compound. The energy results for the three different orientations are shown in Table 1. Two sets of calculations, for a dielectric constant ε = 80 and for the continuum

GB/SA solvent model were performed. $^1C_4$ and $^4C_1$ conformations were selected as starting geometries. From the energy values, probability distributions were calculated for each conformer, according to a Boltzmann function at 300 K.

NMR Spectroscopy: NMR experiments with compounds **34** and **35** were recorded on a Varian Unity 500 spectrometer, using approximately 2 mg/mL solutions of the *C*-glycosides at different temperatures (299−313 K) and four different pH values (pD between 4−10 units). Chemical shifts are reported in ppm, using external TMS (δ = 0) as reference. Assignments were performed with the aid of COSY spectra, with a data matrix of 256×1 K to digitize spectral widths of 3000 Hz. Sixteen scans were made, with relaxation delays of 1 s.

NOESY experiments were performed with the selective 1D double pulse field gradient spin echo module,[24] using two different mixing times: 500 and 750 ms.

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