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Synthesis of a bicyclic analog of L-iduronic acid adopting the biologically relevant $^2S_0$ conformation

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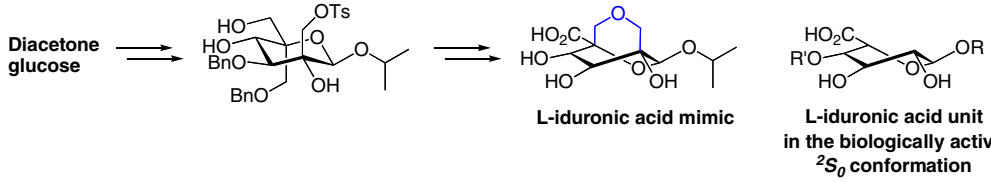
Abstract—The synthesis of a bicyclic analogue of the naturally occurring α-L-iduronic acid locked in a biologically active $^2S_0$ skew-boat conformation is disclosed. The desired $^2S_0$ conformation has been obtained by tethering the C-2 and C-5 carbon atoms of the sugar ring with a dimethyloxy bridge and confirmed by NMR and molecular modeling. The new mimic displays the exact hydroxyl pattern of α-L-iduronic acid, a major monosaccharide component of glycosaminoglycans and thus represents a closer mimic of the latter, compared to previously reported bicyclic analogs.



Keywords: Conformation; Glycosaminoglycans; Heparin; Iduronic acid; Scaffold

1. Introduction

The conformation of L-iduronic acid residues in glycosaminoglycans (GAGs) such as heparin, heparan sulfate, and dermatan sulfate was earlier the cause of a long controversy.[1,2] Thanks to the availability of well defined synthetic oligosaccharides, it has been unambiguously demonstrated that such residues are in equilibrium between three conformations: $^1C_4$, $^4C_1$, and $^2S_0$.[3] This unique conformational flexibility emerged as a new concept for explaining the recognition and biological properties of GAGs containing L-iduronic acid.[4] More specifically, NMR studies[5] on the synthetic pentasaccharide **1**[6] (Fig. 1), representing the antithrombin binding site of heparin and containing only one L-iduronic acid residue, suggested a large contribution of the unusual $^2S_0$ skewboat conformer[7] in such a pentamer where it is adjacent to a 3-O-sulfonated aminosugar residue.[4a]

To establish a correlation between conformation and antithrombotic activity, the total synthesis of the three pentasaccharides **2**–**4** was achieved,[8] in which the L-iduronic acid residue was conformationally locked, either in a $^1C_4$, $^4C_1$ or $^2S_0$ form. In these compounds, several hydroxyl groups and all the *N*-sulfonates were replaced by methoxy groups and *O*-sulfonates, respectively, a change that greatly simplified the synthetic route but

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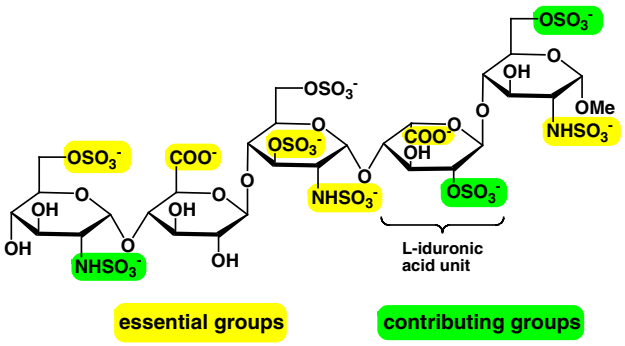


Figure 1. Structure of pentasaccharide **1** with essential and contributing groups (reproduced from Petitou and van Boeckel).[12b]

which did not affect their biological activity.[9,10] It was concluded that antithrombin-bound L-iduronic acid adopts the $^2S_0$ skewboat conformation, which thus governs the antithrombotic activity of heparin (Fig. 2). Another pentasaccharide, **5**, containing a slightly more flexible L-iduronic acid unit was later prepared.[11] In these first- and second-generation pentamers **3** and **5**, respectively, and as the logical result of the selected synthetic strategy, the hydroxyl group at C-2 of the parent L-iduronic acid was missing. In the specific case of antithrombin mediated activity, this substituent was shown not to be essential, albeit contributing to an increase of the activity;[12] actually, the effect of the missing substituent is compensated by the sulfate group located at C-3 of the D-glucosamine unit.[13] In the more general context of GAGs biological studies, the synthesis of a closer mimic of L-iduronic acid locked around the $^2S_0$ conformation and retaining all the hydroxyl groups is of interest and is disclosed in this piece of work. Our selected new third-generation scaffold **6** has its oxygen atom of the bridging unit moved one atom away from C-2, to generate a stable structure of ether type (Fig. 2).

2. Results and discussion

2.1. First approach

The first approach started from the known D-glucose derivative **7**[14] available from diacetone glucose. The choice of the isopropyl group as the anomeric substituent was imposed by the poor glycosylation step of the thiophenyl glycosyl donor with methanol. Alkene **7** was ozonolyzed and further reduced with $LiAlH_4$ to yield primary alcohol **8** in 70% yield. O-Benzylation followed by silyl group removal with TBAF afforded alcohol **9**. The required stereoselective installation of a latent leaving group at position 2 while retaining a D-*gluco* configured scaffold having two extra substituents at positions 2 and 5 was performed as follows. Swern oxidation of alcohol **9** furnished the corresponding ketone, which was directly used without purification and treated with vinyl magnesium bromide to afford the allylic alcohol **10** as a single product in 75% yield, the stereochemistry at C-2 for this compound being not firmly established at this stage.[‡] Ozonolysis followed by reduction with $NaBH_4$ yielded diol **11** (37% yield over two steps, unoptimized). Regioselective tosylation at the primary position afforded tosylate **12**, from which the isopropylidene group was removed under mild acidic conditions to furnish triol **13** in excellent yield.

The key cyclization step was then achieved by treatment of triol **13** under basic conditions with NaH in dry DMF to afford **14** in a modest 20% yield along with more polar unidentified products. Its structure was firmly established as follows: hydrogenolysis of the benzyl groups and subsequent per-acetylation of the crude compound afforded a crystalline compound **15**, the X-ray structure of which was solved (Fig. 3).[§] The structure of tetracetate **15** clearly indicates that the bicyclic compound **14** arises from displacement of the tosyl group at C-2 in **13** by the OH group at C-4. This in turn demonstrates addition of the Grignard reagent from the α-face of the transient ketone yielding the undesired D-*manno* configured isomer, **10**. As described by Ley and co-workers in a paper that appeared after we undertook this research,[15] the stereoselectivity of the addition of the Grignard reagent can be rationalized by the β-configuration of the anomeric substituent in the ketone favoring a trans addition at C-2 (see Scheme 1).

2.2. Second approach

Another route, based on the dihydroxylation of an exomethylene installed at C-2, was envisioned to provide the desired D-*gluco* configured stereoisomer (Scheme 2). Cis dihydroxylation of *C*-alkylidene carbohydrates with OsO_4 has been shown to proceed from the less hindered face of the olefin.[16] In our case, the isopropylidene group and the β-anomeric isopropyl group should favor a dihydroxylation from the α face of the sugar ring to produce the desired D-*gluco* stereoisomer.

[‡] NOE experiments gave ambiguous results on this structure.

[§] Selected crystal structure data for **15**; crystal system orthorhombic; space group $P2_12_12_1$; $Z = 4$; cell parameters: $a = 10.485(5)$, $b = 14.231(10)$, $c = 14.836(10)$, $\alpha = 90$, $\beta = 90$, $\gamma = 90$; radiation (Mo Kα) $\lambda = 0.71069$ Å; 193 variables for 1169 reflections; final $R = 0.1142$, $R_W = 0.1327$; crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 604630. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

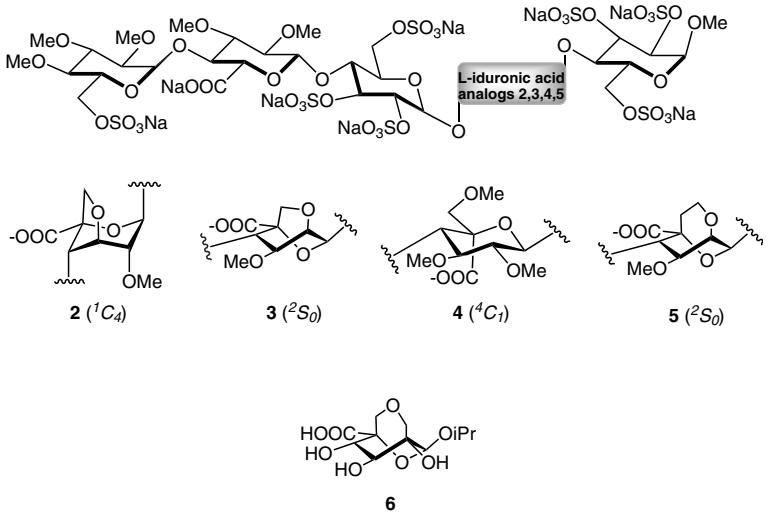


Figure 2. Structure of pentasaccharides **2**–**5** and new L-iduronic acid mimic **6**.

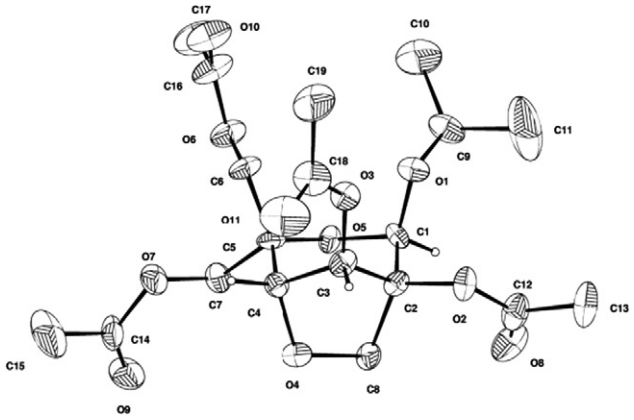


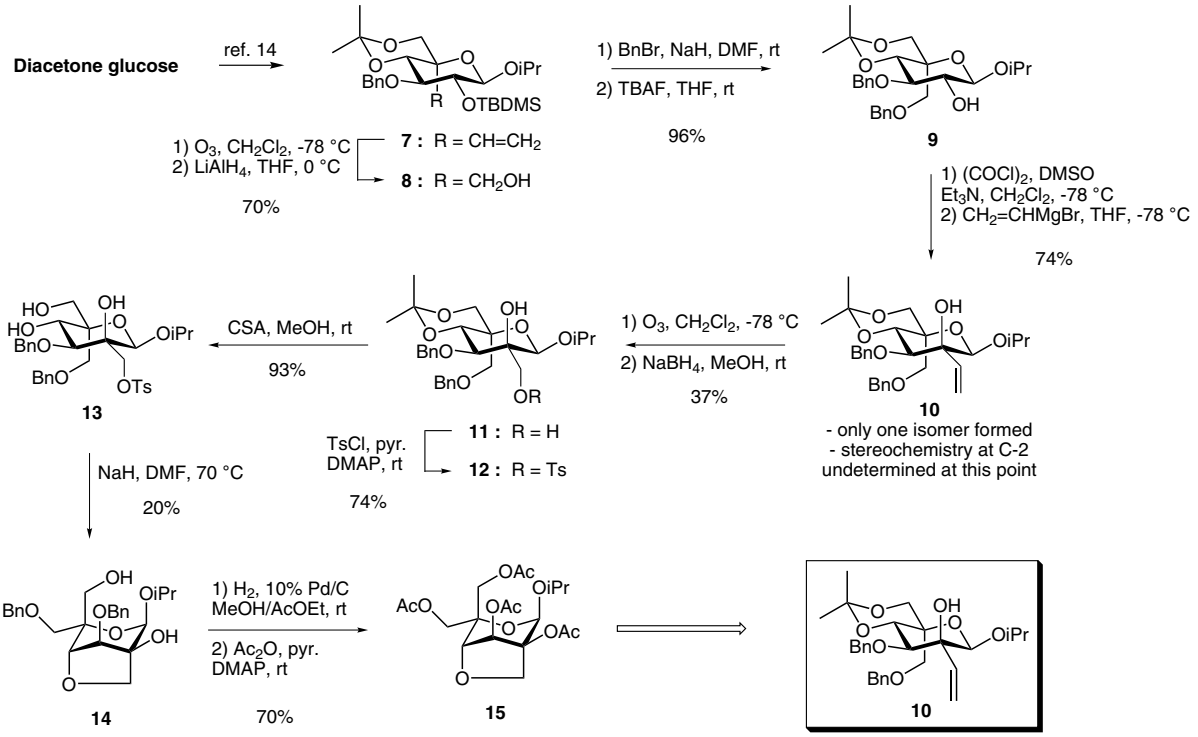
Figure 3. X-ray structure of compound **15**.

Starting from alcohol **9**, Wittig olefination of the transient ketone described above furnished the C-2 methylene glycoside **16** in 86% yield[17] which, upon dihydroxylation, gave a single diol **17** in 85% yield. A sequence similar as the one described above was then applied. Regioselective tosylation of the primary alcohol yielded tosylate **18** in 83% yield and subsequent removal of the isopropylidene group under mild acidic conditions afforded triol **19** in 96% yield. Comparison of the spectroscopic data obtained for the new diol **17**, tosyl derivative **18** and triol **19** with the previous D-*manno* configured diol **11**, tosyl derivative **12** and triol **13** showed significant discrepancies that confirmed the D-*gluco* configuration for the molecules obtained with the second route.

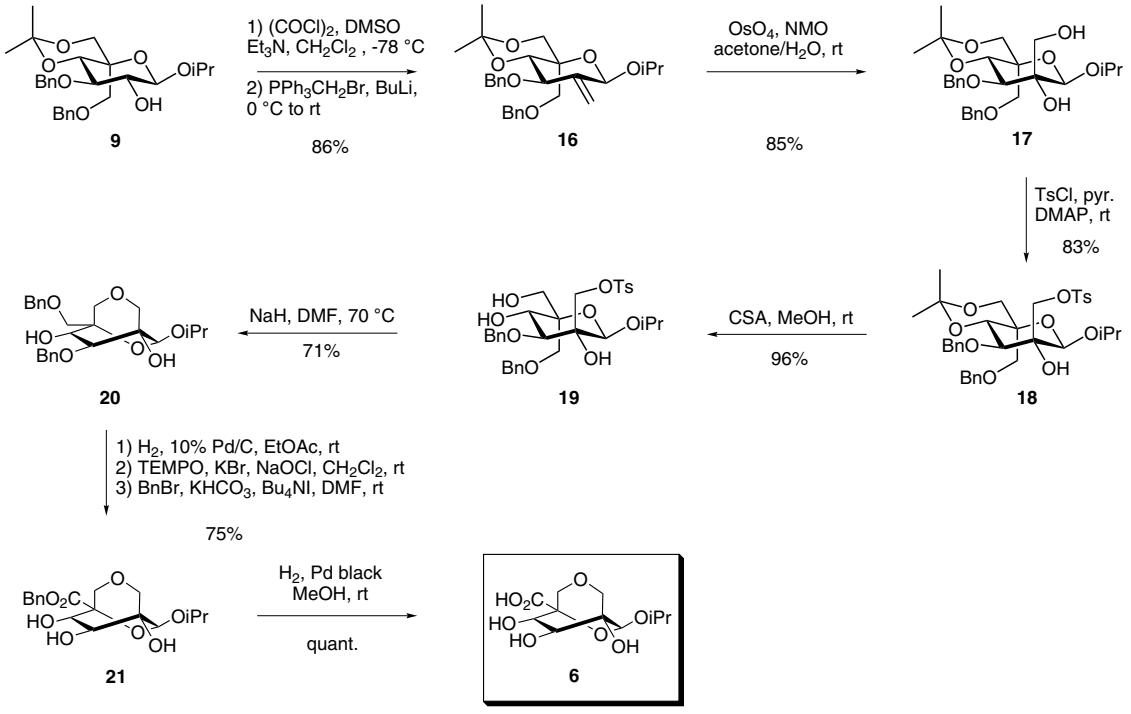
The key cyclization of triol **19** under basic conditions smoothly afforded a less polar compound **20**, the NMR data of which were in accordance with the expected bicyclic structure. This cyclization step may possibly occur via transient spiroepoxide formation at C-2 followed by subsequent intramolecular opening with the alkoxide at C-6. Finally, hydrogenolysis of the benzyl groups followed by chemoselective oxidation of the primary alcohol with TEMPO[18] afforded the corresponding crude carboxylic acid, which was protected as its benzyl ester **21** (75% yield over three steps) for ease of purification. Hydrogenolysis of the benzyl group furnished the desired α-L-iduronic acid analog **6** in pure form and excellent yield. Several attempts to crystallize derivatives of **6** were unsuccessful.

However, the $^2S_0$ skewboat conformation of compound **6** was confirmed by NMR and molecular modeling (Table 1). L-Iduronic acid mimic **6** exists as an equilibrium between two $^2S_0$-like skewboat conformers, **A** and **B**, that simply differ by the orientation of the bridged oxygen which is pointing either towards the anomeric oxygen or toward the carboxylic group, respectively. For each conformer, there is a slight difference in the shape of the six-membered ring, as deduced from the expected $J_{3,4}$ coupling values for the two conformers (which only differ by 0.3 kJ/mol according to MM3* calculations). According to the MM3* energies and, more importantly, to the experimental NOEs (Table 1), conformer **A** is predominant (Fig. 4). Due to the flexibility of the three atom bridge in compound **6** and as observed in bicycle **5**,[11] $^5S_1$ and ^{1,5}B conformations cannot be excluded for the pyranose ring of **6**.

In conclusion, the synthesis of a α-L-iduronic acid mimic **6** locked in the biologically relevant $^2S_0$ skewboat conformation and displaying the full hydroxyl pattern of L-iduronic acid has been achieved for the first time. Fine tuning of the biological activities of GAGs fragments may result from a freezing of appropriate locked conformations of their residues. In this respect, the availability of this third generation L-iduronic acid scaffold is of interest.



Scheme 1.



Scheme 2.

3. Experimental

3.1. General methods

Solvents were freshly distilled from Na/benzophenone (THF), or P_2O_5 (CH_2Cl_2). Reactions were carried under Ar, unless stated. Melting points were recorded on a Büchi 535 and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 digital polarimeter with a path length of 1 dm. Mass spectra were recorded on a JMS-700 spectrometer, using chemical ionization with ammonia or FAB. NMR spectra were recorded

Table 1. Experimental and calculated NMR data for L-iduronic acid analog **6**[a]

Experimental		Calculated (MM/MC/MD)	
		Conformer **A**	Conformer **B**
$^3J_{H,H}$ (Hz)		$^3J_{H,H}$ (Hz)	$^3J_{H,H}$ (Hz)
$J_{3,4}$ 2.0		$J_{3,4}$ 0.7	$J_{3,4}$ 4.0
NOE		Key interproton distances[b] (Å)	
Proton pair	*Intensity*		
H1/H3	s	2.5	2.5
H3/H4	mw	2.9	3.0
H1/CH isopropyl	s	2.5	2.5
H7/CH isopropyl	mw	3.0	3.8
CH isopropyl/H1	w	3.2	3.2

[a] Experimental and calculated J_{34} values and experimental (s, strong, m, medium and w, weak) NOEs observed for compound **6**.

[b] Key interproton distances that may be correlated with the experimental NOEs.

on a Bruker DRX-400 (400 and 100.6 MHz, for ^1H and ^{13}C, respectively) or a Bruker AC-250 (250 and 63 MHz, for ^1H and ^{13}C, respectively). TLC was performed on silica gel 60 F_{254} (Merck) and developed by charring with H_2SO_4 in ethanol. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck).

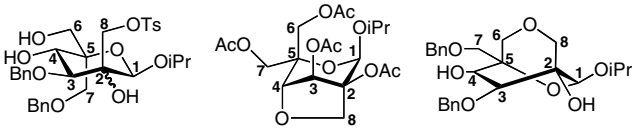
3.2. NMR and molecular modeling of 6

NMR spectra were recorded at 298 K in D_2O on Bruker AVANCE 500 MHz spectrometers. TOCSY[19] and HSQC[20] experiments were performed using the standard sequences. Selective 1D and 2D NOESY[21] were performed with mixing times of 350, 500, and 600 ms. The selective 1D NOESY versions of the experiments used a double pulse field gradient spin echo[22] for selection of the chosen resonance followed by the corresponding mixing sequence.

Molecular mechanics calculations were performed using the MacroModel/Batchmin[23] package (version 7.0) and the MM3* force field.[24] Bulk water solvation was simulated using MacroModel's generalized Born GB/SA continuum solvent model.[25] Energy minimizations were conducted using the conjugate gradient method until convergence according to the internal criterion of the program. Experimental and expected *J* and NOE data were compared as described.[26] *J* Values were estimated from the MM3* geometries by applying the generalized Karplus equation proposed by Altona and co-workers.[27]

3.3. Structure numbering

The following numberings by analogy with the parent sugars were used:



3.4. NMR Assignments

Assignment of protons and carbons at C-6, C-7, and C-8 for some compounds proved to be difficult and these signals are therefore sometimes not unambiguously assigned.

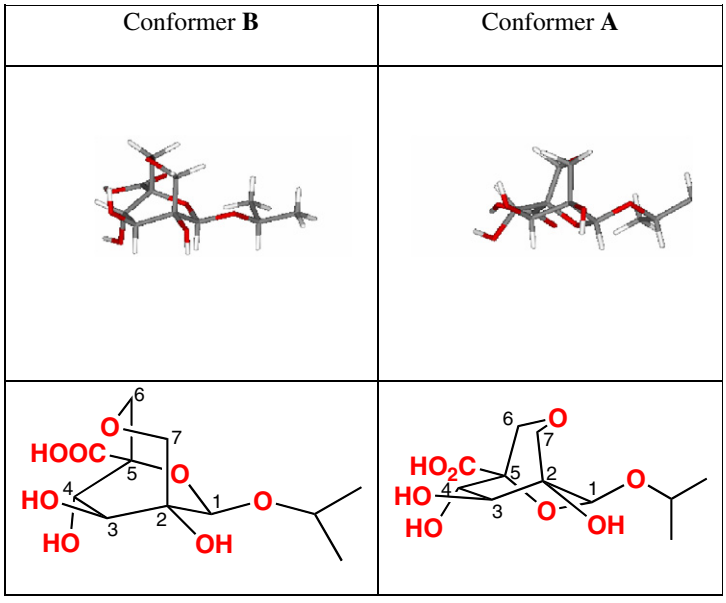


Figure 4. Conformations **A** and **B** adopted by L-iduronic acid mimic **6**.

3.5. Isopropyl 3-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-4,6-*O*-isopropylidene-5-*C*-hydroxymethyl-β-D-glucopyranoside (8)

Vinyl derivative **7** (450 mg, 0.9 mmol) was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to −78 °C. Ozone was bubbled through the solution under stirring until persistence of a pale blue color (10 min). Excess of ozone was quenched by the addition of Me_2S and the reaction mixture was stirring for 1 h and allowed to reach rt. The solvent was removed under reduced pressure and the crude aldehyde was directly used for the next reaction. The crude aldehyde was dissolved in dry THF (35 mL) under argon and the solution was cooled to −10 °C. Lithium aluminum hydride (34 mg, 0.9 mmol) was added slowly and the reaction mixture was stirred for 1 h and warmed to 0 °C. The reaction was quenched at 0 °C by adding a few drops of water followed by a few drops of a 15% w/v solution of NaOH. After stirring for 5 min at 0 °C and 30 min at rt, a white precipitate was formed and filtered off. The filtrate was concentrated and the residue was purified by flash column chromatography (cyclohexane–EtOAc, 4:1) to afford alcohol **8** (312 mg, 0.63 mmol, 70%) as a white solid. $[\alpha]_D$ −59 (*c* 1.0, $CHCl_3$); mp 78–79 °C (EtOAc–cyclohexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.30 (m, 5H, Ph), 4.81 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.77 (d, 1H, $J = 7.1$ Hz, H-1), 4.67 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.13 (m, H-7), 4.07–4.00 (m, 3H, H-4, H-7′, CH isopropyl), 3.97 (d, $J = 10.7$ Hz, H-6), 3.63 (dd, $J = 7.5$ Hz, $J = 10.2$ Hz, H-3), 3.62 (dd, $J = 0.8$ Hz, $J = 10.7$ Hz, H-6′), 3.56 (t, 1H, $J = 7.1$ Hz, H-2), 1.49 (s, 3H, CH_3 isopropylidene), 1.44 (s, 3H, CH_3 isopropylidene), 1.28 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl), 1.23 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl), 0.93 (s, 9H, *t*-Bu), 0.12 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.76 (C_{ipso}), 128.09–127.36 (Ph), 100.23 (C isopropylidene), 97.77 (C-1), 78.76 (C-3), 75.93 (C-2), 75.85 (C-4), 74.34 (CH_2Ph) 70.93 (CH isopropyl), 70.53 (C-5), 64.83 (C-6), 57.73 (C-7), 29.32 (CH_3 isopropylidene), 25.86 (*t*-Bu), 23.46, 21.45 ($2 \times CH_3$ isopropyl), 18.95 (CH_3 isopropylidene), −4.22, −4.41 ($2 \times SiCH_3$); *m*/*z* (CI, NH_3): 514 ($[M+NH_4]^+$, 100%); HRMS (CI, NH_3): calcd for $C_{26}H_{48}NO_7Si$ $[M+NH_4]^+$: 514.3200. Found: 514.3204.

3.6. Isopropyl 3-*O*-benzyl-4,6-*O*-isopropylidene-5-*C*-benzyloxymethyl-β-D-glucopyranoside (9)

Alcohol **8** (1.30 g, 2.62 mmol) and BnBr (0.6 mL, 5.2 mmol) were dissolved in dry DMF (26 mL) under argon. NaH (209 mg, 5.2 mmol) was added by portions at 0 °C. After stirring for 90 min at rt, the reaction mixture was quenched by the addition of MeOH (5 mL). The solvent was evaporated to afford the crude benzyl ether, which was directly dissolved in dry THF (10 mL) under argon. Tetrabutylammonium fluoride (8.0 mL, 8.0 mmol, 1 M in THF) was added and the reaction mixture was stirred overnight at rt and then quenched by the addition of water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (cyclohexane–EtOAc, 4:1) afforded alcohol **9** (1.20 g, 96%) as a white crystalline compound. $[\alpha]_D$ −17 (*c* 0.8, $CHCl_3$); mp 97–98 °C (EtOAc–*n*-pentane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.30 (m, 10H, $2 \times$ Ph), 4.87 (d, H, $J = 11.8$ Hz, CH_2Ph), 4.85 (d, H, $J = 7.8$ Hz, H-1), 4.76 (d, H, $J = 11.8$ Hz, CH_2Ph), 4.68 (d, 1H, $J = 11.9$ Hz, CH_2Ph), 4.61 (d, 1H, $J = 11.9$ Hz, CH_2Ph), 4.00 (sept., $J = 6.1$ Hz, CH isopropyl), 3.96 (d, 1H, $J = 10.7$ Hz, H-6), 3.95 (d, 1H, $J = 10.6$ Hz, H-4), 3.94 (d, 1H, $J = 10.7$ Hz, H-7), 3.90 (d, 1H, $J = 10.7$ Hz, H-6′), 3.84 (dd, 1H, $J = 8.2$ Hz, 10.6 Hz, H-3), 3.69 (d, 1H, $J = 10.7$ Hz, H-7′), 3.55 (dt, 1H, $J = 2.8$ Hz, $J = 7.8$ Hz, H-2), 2.50 (d, 1H, $J = 2.8$ Hz, OH), 1.52 (s, 3H, CH_3 isopropylidene), 1.45 (s, 3H, CH_3 isopropylidene), 1.27 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.21 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.85, 137.84 ($2 \times C_{ipso}$), 128.38–127.49 ($2 \times$ Ph), 100.31 (C isopropylidene), 97.92 (C-1), 77.52 (C-3), 75.85 (C-4), 75.37 (C-2), 73.96, 73.63 ($2 \times C$H$_2$Ph), 71.95 (CH isopropyl), 70.56 (C-5), 66.17 (C-6), 65.73 (C-7), 29.33 (CH_3 isopropylidene), 23.32 (CH_3 isopropyl), 21.92 (CH_3 isopropyl), 19.01 (CH_3 isopropylidene); *m*/*z* (CI, NH_3): 490 ($[M+NH_4]^+$, 100%), 473 ($[M+H]^+$, 10%); HRMS (CI, NH_3): calcd for $C_{27}H_{40}NO_7$ $[M+NH_4]^+$: 490.2805. Found: 490.2807.

3.7. Isopropyl 3-*O*-benzyl-5-*C*-benzyloxymethyl-4,6-*O*-isopropylidene-2-*C*-vinyl-β-D-mannopyranoside (10)

Oxalyl chloride (1.17 mL, 13.7 mmol) was added dropwise under argon to a stirred solution of dry DMSO (1.62 mL, 22.8 mmol) in dry CH_2Cl_2 (10 mL) cooled to −78 °C, and the reaction mixture was stirred for 30 min at −78 °C. A solution of alcohol **9** (2.15 g, 4.56 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to the solution and the reaction mixture was stirred for 1 h at −78 °C. Triethylamine (3.8 mL, 27.4 mmol) was added and the reaction mixture was warmed to rt for 30 min. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$ and concentrated to afford the rather unstable ketone that was dissolved in dry THF (20 mL) under argon. This solution was cooled to −78 °C and vinyl magnesium bromide (16 mL, 16 mmol, 1 M solution in THF) was added and the reaction mixture was stirred for 4 h at −78 °C under argon. Ammonium chloride (satd aq solution) was added to

quench the reaction and the reaction mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (cyclohexane–EtOAc, 5:1 then 3:1) afforded alcohol **10** (1.67 g, 3.36 mmol, 74%) as a solid. $[\alpha]_D$ −31 (*c* 1.0, $CHCl_3$); mp 81–82 °C (EtOAc–cyclohexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.31 (m, 10H, 2 × Ph), 5.63 (dd, 1H, $J = 10.7$ Hz, $J = 17.3$ Hz, CH═), 5.36 (dd, 1H, $J = 1.3$ Hz, $J = 17.3$ Hz, ═CH_2), 5.23 (dd, 1H, $J = 1.3$ Hz, $J = 10.7$ Hz, ═CH_2), 4.93 (s, 1H, H-1), 4.78 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.65 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.63 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.58 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.42 (d, 1H, $J = 10.2$ Hz, H-4), 4.09 (d, 1H, $J = 10.7$ Hz, H-6), 3.95 (d, 1H, $J = 10.2$ Hz, H-3), 3.90 (sept., $J = 6.1$ Hz, CH isopropyl), 3.87 (d, 1H, $J = 10.7$ Hz, H-6′), 3.79 (s, 2H, H-7, H-7′), 2.75 (s, 1H, OH), 1.57 (s, 3H, CH_3 isopropylidene), 1.48 (s, 3H, CH_3 isopropylidene), 1.23 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.09 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.04 (CH═), 138.42, 137.77 (2 × C_{ipso}), 128.34–127.42 (2 × Ph), 116.13 (CH_2═), 100.51 (C isopropylidene), 97.13 (C-1), 77.29 (C-2), 76.02 (C-3), 74.62 (*C*H_2Ph), 73.90 (C-4), 73.75 (*C*H_2Ph), 72.03 (CH isopropyl), 70.04 (C-5), 68.44 (C-6), 66.22 (C-7), 29.47 (CH_3 isopropylidene), 23.06 (CH_3 isopropyl), 21.56 (CH_3 isopropyl), 19.29 (CH_3 isopropylidene); *m*/*z* (CI, NH_3): 516 ($[M+NH_4]^+$, 100%); HRMS (CI, NH_3): calcd for $C_{29}H_{42}O_7N$ $[M+NH_4]^+$: 516.2961. Found: 516.2963.

3.8. Isopropyl 3-*O*-benzyl-5-*C*-benzyloxymethyl-4,6-*O*-isopropylidene-2-*C*-hydroxymethyl-β-D-mannopyranoside (11)

Vinyl derivative **10** (1.67 g, 3.36 mmol) was dissolved in CH_2Cl_2 (300 mL) and the solution was cooled to −78 °C. Ozone was bubbled through the solution under stirring until persistence of a pale blue color (10 min). Excess of ozone was quenched by the addition of Me_2S and the reaction mixture was stirring for 1 h and allowed to reach rt. The solvent was removed under reduced pressure and the crude aldehyde was directly used for the next reaction. The crude aldehyde was dissolved in MeOH (35 mL) and the solution was cooled to 0 °C. Sodium borohydride (255 mg, 6.74 mmol) was added and the reaction mixture was stirred for 3 h at rt and then concentrated. Purification of the residue by flash column chromatography (cyclohexane–EtOAc, 3:1) afforded the corresponding diol **11** (625 mg, 1.24 mmol, 37% over two steps, unoptimized) as a solid. $[\alpha]_D$ +17 (*c* 1.0, $CHCl_3$); mp 131–132 °C (EtOAc–cyclohexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.30 (m, 10H, 2 × Ph), 5.02 (s, 1H, H-1), 4.88 (d, 1H, $J = 11.7$ Hz, CH_2Ph), 4.65 (d, 1H $J = 11.7$ Hz, CH_2Ph), 4.64 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.61 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.48 (d, 1H, $J = 10.4$ Hz, H-4), 4.02–3.88 (m, 5H, H-3, H-6, H-6′, H-7, CH isopropyl), 3.77 (d, 1H, $J = 10.6$ Hz, H-7′), 3.46 (m, 2H, H-8, H-8′), 1.58 (s, 3H, CH_3 isopropylidene), 1.48 (s, 3H, CH_3 isopropylidene), 1.24 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.13 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.19, 137.90 (2 × C_{ipso}), 128.85–127.36 (2 × Ph), 100.49 (C isopropylidene), 94.82 (C-1), 76.91 (C-3), 74.85 (C-2), 74.16 (C-4), 74.08 (*C*H_2Ph), 73.70 (*C*H_2Ph), 71.20 (CH isopropyl), 70.88 (C-5), 66.80 (C-6), 65.82 (C-7), 62.89 (C-8), 29.52 (CH_3 isopropylidene), 23.17 (CH_3 isopropyl), 21.55 (CH_3 isopropyl), 19.33 (CH_3 isopropylidene); *m*/*z* (CI, NH_3): 520 ($[M+NH_4]^+$, 100%); HRMS (CI, NH_3): calcd for $C_{28}H_{42}O_8N$ $[M+NH_4]^+$: 520.2910. Found: 520.2914.

3.9. Isopropyl 3-*O*-benzyl-5-*C*-benzyloxymethyl-4,6-*O*-isopropylidene-2-*C*-tosyloxymethyl-β-D-mannopyranoside (12)

Diol **11** (497 mg, 1 mmol) was dissolved in dry pyridine (2 mL) under argon and TsCl (570 mg, 0.3 mmol) followed by a catalytic amount of DMAP were added. The reaction mixture was stirred for 24 h and more TsCl (570 mg, 0.3 mmol) was added to complete the reaction. After 48 h, the reaction was quenched by the addition of water and extracted with EtOAc. The solvents were removed under reduced pressure and the residue purified by flash column chromatography (cyclohexane–EtOAc, 2:1) to afford tosylate **12** (484 mg, 0.73 mmol, 74%) as a solid along with starting material **11** (122 mg, 0.24 mmol). $[\alpha]_D$ −19 (*c* 1.0, $CHCl_3$); mp 91–92 °C (EtOAc–cyclohexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, 2H, CH aromatic), 7.44–7.22 (3 × Ph), 5.13 (s, 1H, H-1), 4.80 (d, 1H, $J = 10.9$ Hz, CH_2Ph), 4.66 (m, 2H, CH_2Ph), 4.44 (d, 1H, $J = 10.9$ Hz, CH_2Ph), 4.34 (d, 1H, $J = 10.3$ Hz, H-3), 4.13 (d, 1H, $J = 10.3$ Hz, H-4), 4.11 (d, 1H, $J = 8.9$ Hz, H-8), 3.99 (d, 1H, $J = 10.8$ Hz, H-6), 3.93 (d, 1H, $J = 8.9$ Hz, H-8′), 3.90 (d, 1H, $J = 10.8$ Hz, H-6′), 3.89 (sept., 1H, $J = 6.1$ Hz, CH isopropyl), 3.88 (d, 1H, $J = 10.6$ Hz, H-7), 3.72 (d, 1H, $J = 10.6$ Hz, H-7′), 2.72 (s, 1H, OH), 2.44 (s, 3H, CH_3 tosyl), 1.52 (s, 3H, CH_3 isopropylidene), 1.43 (s, 3H, CH_3 isopropylidene), 1.19 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.07 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.09, 138.11, 137.83, 132.40 (4 × C_{ipso}), 129.89–127.62 (3 × Ph), 100.47 (C isopropylidene), 93.63 (C-1), 75.02 (*C*H_2Ph), 74.48 (C-2), 74.02 (C-3), 73.62 (*C*H_2Ph), 72.75 (C-4), 72.39 (CH isopropyl), 70.02 (C-5), 67.04 (C-8), 66.41 (C-6), 65.68 (C-7), 29.38 (CH_3 isopropylidene), 23.11 (CH_3 isopropyl), 21.55 (CH_3 isopropyl, CH_3 tosyl), 19.24 (CH_3 isopropylidene); *m*/*z* (CI, NH_3): 674 ($[M+NH_4]^+$, 28%), 502 (100%); HRMS (CI, NH_3): calcd for $C_{35}H_{48}O_{10}NS$ $[M+NH_4]^+$: 674.2999. Found: 674.2997.

3.10. Isopropyl 3-*O*-benzyl-5-*C*-benzyloxymethyl-2-*C*-tosyloxymethyl-β-D-mannopyranoside (13)

Tosyl derivative **12** (392 mg, 0.60 mmol) was dissolved in MeOH (5 mL) and camphorsulfonic acid (10 mg) was added. The reaction mixture was stirred for 90 min, quenched by the addition of Amberlite IRA-400 resin, filtered and the solvent was evaporated under reduced pressure. Purification of the residue by flash column chromatography (cyclohexane–EtOAc, 2:1) afforded triol **13** (344 mg, 0.56 mmol, 93%) as a colorless syrup. $[\alpha]_D$ −38 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, 2H, Ts), 7.45–7.19 (3 × Ph), 5.11 (s, 1H, H-1), 4.76 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.61 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.48 (d, 1H, $J = 12.1$ Hz, CH_2Ph), 4.38 (d, 1H, $J = 11.0$ Hz, CH_2Ph), 4.22 (d, 1H, $J = 9.7$ Hz, H-4), 4.03 (d, 1H, $J = 9.7$ Hz, H-3), 4.11 (d, 1H, $J = 8.9$ Hz, H-7), 3.92 (d, 1H, $J = 8.9$ Hz, H-7′), 3.81 (sept., 1H, $J = 6.1$ Hz, CH isopropyl), 3.78 (d, 1H, $J = 10.8$ Hz, H-8), 3.55 (m, 3H, H-6, H-6′, H-8′), 3.30–3.12 (br, 3H, 3 × OH), 2.39 (s, 3H, CH_3 Ts), 1.13 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.03 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.01, 137.99, 137.48, 132.13 (4 × C_{ipso}), 129.79–127.57 (3 × Ph), 93.88 (C-1), 77.50 (C-3), 77.48 (C-2), 75.40 (*C*H_2Ph), 74.09 (C-5), 73.71 (*C*H_2Ph), 72.15 (C-4), 69.88 (C-8), 69.20 (CH isopropyl), 67.00 (C-7), 64.33 (C-6), 23.10 (CH_3 isopropyl), 21.59 (CH_3 isopropyl); *m*/*z* (CI, NH_3): 634 ($[M+NH_4]^+$, 70%); HRMS (CI, NH_3): calcd for $C_{32}H_{44}O_{10}NS$ $[M+NH_4]^+$: 634.2686. Found: 634.2690.

3.11. Isopropyl 2-*C*-4-*O*-anhydro-3-*O*-benzyl-5-*C*-benzyloxymethyl-2-*C*-hydroxymethyl-β-D-mannopyranoside (14)

Sodium hydride (60 mg, 0.90 mmol, 60% in oil) was added to a solution of compound **13** (185 mg, 0.30 mmol) in very dry DMF (8 mL) under argon. The reaction mixture was heated at 70 °C and stirred for 2 h. The reaction was quenched by the addition of MeOH and concentrated. The residue was purified by flash column chromatography (cyclohexane–EtOAc, 5:1 then 2:1) to afford bicyclic compound **14** (27 mg, 0.06 mmol, 20%) as a colorless syrup. $[\alpha]_D$ −22 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.25 (m, 10H, 2 × Ph), 5.18 (s, 1H, H-1), 4.92 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.79 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.76 (d, 1H, $J = 10.9$ Hz, CH_2Ph), 4.65 (d, 1H, $J = 10.9$ Hz, CH_2Ph), 4.48 (m, 2H, H-3, H-4), 4.39 (d, 1H, $J = 11.4$ Hz, H-6 or H-7 or H-8), 4.21 (d, 1H, $J = 11.4$ Hz, H-6′ or H-7′ or H-8′), 4.09 (d, 1H, $J = 7.8$ Hz, H-6 or H-7 or H-8), 4.08 (sept., 1H, $J = 6.1$ Hz, CH isopropyl), 3.89 (d, 1H, $J = 7.8$ Hz, H-6′ or H-7′ or H-8′), 3.80 (d, 1H, $J = 8.5$ Hz, H-6 or H-7 or H-8), 3.58 (d, 1H, $J = 8.5$ Hz, H-6′ or H-7′ or H-8′), 3.20 (br s, 1H, OH), 1.33 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.26 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 138.34, 137.89 (2 × C_{ipso}), 128.75–127.18 (2 × Ph), 100.13 (C-1), 78.99 (C-3 or C-4), 78.52, 78.50 (C-2, C-5), 73.85 (C-3 or C-4), 73.64 (*C*H_2Ph), 70.25 (CH isopropyl), 72.68, 72.35, 64.12 (C-6, C-7, C-8), 72.29 (*C*H_2Ph), 23.43, 21.39 (2 × CH_3 isopropyl); *m*/*z* (CI, NH_3): 445 ($[M+H]^+$, 15%), 462 ($[M+NH_4]^+$, 76%); HRMS (CI, NH_3): calcd for $C_{25}H_{36}NO_7$ $[M+NH_4]^+$: 462.2495. Found: 462.2492.

3.12. Isopropyl 2-*C*-4-*O*-anhydro-2,3,6-tri-*O*-acetyl-5-*C*-acetoxymethyl-2-*C*-hydroxymethyl-β-D-mannopyranoside (15)

Compound **14** (25 mg, 0.056 mmol) was dissolved in MeOH–EtOAc (2 mL, 1:1) and Pd/C (10 mg) was added. The reaction vessel was purged from air and the reaction mixture was stirred overnight under hydrogen, filtered through a Celite plug eluted with MeOH. The solvent was removed under reduced pressure and the crude oil was dissolved in dry pyridine (1 mL). The solution was cooled to 0 °C and Ac_2O (0.5 mL) followed by a catalytic amount of DMAP were added under argon. The reaction mixture was stirred at rt overnight and concentrated. Purification of the residue by flash column chromatography (cyclohexane–EtOAc, 1:1) afforded tetracetate **15** (17 mg, 0.039 mmol, 70%) as colorless crystals. $[\alpha]_D$ −40 (*c* 0.2, $CHCl_3$); mp 120–121 °C (EtOAc–cyclohexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.56 (d, 1H, $J = 1.0$ Hz, H-1), 5.51 (dd, 1H, $J = 1.0$ Hz, $J = 5.6$ Hz, H-3), 4.63 (d, 1H, $J = 8.9$ Hz, H-6 or H-7 or H-8), 4.56 (s, 2H, H-6 or H-7 or H-8), 4.32 (d, 1H, $J = 10.9$ Hz, H-6 or H-7 or H-8), 4.28 (d, $J = 5.6$ Hz, H-4), 4.19 (d, 1H, $J = 10.9$ Hz, H-6 or H-7 or H-8), 3.97 (sept., 1H, $J = 6.2$ Hz, CH isopropyl), 3.91 (d, 1H, $J = 8.9$ Hz, H-6 or H-7 or H-8), 2.16, 2.11, 2.09, 2.07 (4 × s, 12H, 4 × OAc), 1.26 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl), 1.11 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.36, 170.31, 170.10, 170.00 (4 × C=O), 97.40 (C-1), 78.01, 76.51 (C-2, C-5), 71.30, 71.13, 70.49 (C-3, C-4, CH isopropyl), 71.02, 63.58, 62.43 (C-6, C-7, C-8), 23.01, 21.01 (2 × CH_3 isopropyl), 20.92, 20.81, 20.74, 20.68 (4 × CH_3CO). Anal. Calcd for $C_{19}H_{28}O_{11}$: C, 52.77, H, 6.53. Found, C, 52.74, H, 6.59.

3.13. Isopropyl 3-*O*-benzyl-5-*C*-benzyloxymethyl-4,6-*O*-isopropylidene-2-*C*-methylene-β-D-arabinoside (16)

Anhydrous DMSO (1.5 mL, 20.0 mmol) was added dropwise to a solution of oxalyl chloride (1.2 mL, 13.3 mmol) in dry CH_2Cl_2 (13 mL) under argon and stirred for 30 min at −60 °C. The reaction mixture was cooled to −78 °C and a solution of alcohol **9** (2.10 g,

4.45 mmol) in dry CH_2Cl_2 (32 mL) was added slowly via a dropping funnel. After stirring for 90 min at −78 °C, Et_3N (3.7 mL, 26.7 mmol) was added and the reaction mixture was stirred for 30 min at −78 °C and then allowed to reach rt for 15 min. The reaction mixture was then diluted with CH_2Cl_2, washed with water and brine, and dried over $MgSO_4$. The organic extracts were evaporated to afford crude ketone, which was directly engaged in the next step. *n*-Butyl lithium (5.3 mL, 13.3 mmol, 2.5 M solution in THF) was added dropwise to a solution of Ph_3PCH_2Br (4.8 g, 13.3 mmol) in dry THF (25 mL) at 0 °C under argon. The reaction mixture was stirred for 30 min at 0 °C until persistence of a pale orange color. A solution of the crude ketone in THF (20 mL) was transferred by cannula into the solution and the reaction mixture was stirred overnight at rt. The reaction was quenched by the addition of satd aq NH_4Cl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (cyclohexane–EtOAc, 9:1) afforded exomethylene derivative **16** (1.80 g, 86%) as a solid. $[\alpha]_D$ −36 (*c* 1.0, $CHCl_3$); mp 83–84 °C (EtOAc–cyclohexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42–7.31 (m, 10H, 2 × Ph), 5.51 (m, 1H, =CH_2), 5.46 (m, 1H, =CH_2), 5.38 (s, 1H, H-1), 4.83 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.76 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.67 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.62 (d, 1H, $J = 12.3$ Hz, CH_2Ph), 4.33 (dt, 1H, $J = 1.8$ Hz, $J = 10.0$ Hz, H-3), 4.20 (d, 1H, $J = 10.0$ Hz, H-4), 4.06 (sept., 1H, $J = 6.1$ Hz, CH isopropyl), 4.01 (d, 1H, $J = 10.6$ Hz, H-6), 3.95 (d, 1H, $J = 10.5$ Hz, H-7), 3.90 (d, 1H, $J = 10.5$ Hz, H-7′), 3.70 (d, 1H, $J = 10.6$ Hz, H-6′), 1.53 (s, 3H, CH_3 isopropylidene), 1.48 (s, 3H, CH_3 isopropylidene), 1.33 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.22 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.83 (C-2), 138.88, 138.09 (2 × C_{ipso}), 128.27–127.30 (2 × Ph), 113.52 (=CH_2), 100.19 (C isopropylidene), 96.07 (C-1), 76.80 (C-4), 74.56 (C-3), 73.56 (*C*H_2Ph), 72.30 (*C*H_2Ph), 70.84 (CH isopropyl), 70.41 (C-5), 67.44 (C-6), 65.83 (C-7), 29.34 (CH_3 isopropylidene), 23.37 (CH_3 isopropyl), 21.73 (CH_3 isopropyl), 19.02 (CH_3 isopropylidene); *m*/*z* (CI, NH_3): 486 ($[M+NH_4]^+$, 10%), 426 (M−isopropyl, 100%); HRMS (CI, NH_3): calcd for $C_{28}H_{40}O_6N$ $[M+NH_4]^+$: 486.2856. Found: 486.2857.

3.14. Isopropyl 3-*O*-benzyl-5-*C*-benzyloxymethyl-2-*C*-hydroxymethyl-4,6-*O*-isopropylidene-β-D-glucopyranoside (17)

Exomethylene derivative **16** (467 mg, 1 mmol) was dissolved in a mixture of acetone–water (5:1, 2 mL) and NMO (270 mg, 2.0 mmol) followed by OsO_4 (2.5% in *t*-BuOH, 0.1 mL, 0.02 mmol) were added. The reaction mixture was stirred for 2 days under argon and quenched by adding an excess of a saturated solution of $Na_2S_2O_3$. The reaction mixture was stirred for 30 min, extracted with EtOAc, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (cyclohexane–EtOAc, 4:1) afforded diol **17** (438 mg, 85%) as a yellow syrup. $[\alpha]_D$ −41 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.40–7.30 (m, 10H, 2 × Ph), 4.95 (s, 1H, H-1), 4.80 (s, 2H, CH_2Ph), 4.69 (d, 1H, $J = 10.0$ Hz, CH_2Ph), 4.61 (d, 1H, $J = 10.0$ Hz, CH_2Ph), 4.12 (d, 1H, $J = 11.5$ Hz, H-8), 4.03–3.92 (m, 6H, H-3, H-6, H-6′, H-7, H-8′, CH isopropyl), 3.85 (d, 1H, $J = 10.9$ Hz, H-4), 3.65 (d, 1H, $J = 10.2$ Hz, H-7′), 2.90 (br s, 2H, 2 × OH), 1.51 (s, 3H, CH_3 isopropylidene), 1.43 (s, 3H, CH_3 isopropylidene), 1.24 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.19 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 138.79, 137.76 (2 × C_{ipso}), 128.42–127.45 (2 × Ph), 100.47 (C isopropylidene), 100.37 (C-1), 79.24 (C-3), 75.40 (C-2), 75.15 (*C*H_2Ph), 74.30 (C-4), 73.77 (*C*H_2Ph), 72.63 (CH isopropyl), 70.40 (C-5), 66.12 (C-7), 65.81 (C-6), 60.83 (C-8), 29.38 (CH_3 isopropylidene), 23.31 (CH_3 isopropyl), 21.68 (CH_3 isopropyl), 19.14 (CH_3 isopropylidene); *m*/*z* (CI, NH_3): 520 ($[M+NH_4]^+$, 100%); HRMS (CI, NH_3): calcd for $C_{28}H_{42}O_8N$ $[M+NH_4]^+$: 520.2910. Found: 520.2906.

3.15. Isopropyl 3-*O*-benzyl-5-*C*-benzyloxymethyl-4,6-*O*-isopropylidene-2-*C*-tosyloxymethyl-β-D-glucopyranoside (18)

To a solution of diol **17** (1.80 g, 3.58 mmol) in dry pyridine (7 mL) was added at 0 °C under argon recrystallized TsCl (2.0 g, 10.7 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred overnight at rt, quenched by the addition of ice, stirred for another 20 min and extracted with EtOAc. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (cyclohexane–EtOAc, 9:1) to afford tosylate **18** (1.95 g, 2.97 mmol, 83%) as a white solid. $[\alpha]_D$ −56 (*c* 0.6, $CHCl_3$); mp 117–118 °C (EtOAc–cyclohexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90–7.00 (m, 14H, 3 × Ph), 4.87 (s, 1H, H-1), 4.80–4.60 (m, 5H, 2 × CH_2Ph, H-4), 4.50 (d, 1H, $J = 9.8$ Hz, H-6), 4.22 (d, 1H, $J = 10.3$ Hz, H-7), 4.20 (d, 1H, $J = 9.8$ Hz, H-6′), 4.05 (d, 1H, $J = 10.1$ Hz, H-3), 3.95 (sept., 1H, $J = 6.2$ Hz, CH isopropyl), 3.66 (d, 1H, $J = 10.6$ Hz, H-8), 3.64 (d, 1H, $J = 10.6$ Hz, H-8′), 3.60 (d, 1H, $J = 10.3$ Hz, H-7′), 2.50 (s, 3H, CH_3 tosyl), 1.80 (s, 1H, OH), 1.48 (s, 3H, CH_3 isopropylidene), 1.38 (s, 3H, CH_3 isopropylidene), 1.24 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl), 1.15 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.40, 138.42, 136,74, 132.95 (4 × C_{ipso}), 129.61–127.49 (3 × Ph), 100.71 (C isopropylidene), 99.55 (C-1), 80.02 (C-3), 75.21 (C-2), 75.04 (*C*H_2Ph), 73.54 (*C*H_2Ph), 73.03 (C-4), 71.62 (C-5), 70.58 (C-8), 70.43 (CH isopropyl),

69.71 (C-6), 68.08 (C-7), 29.20 (CH_3 isopropylidene), 23.46 (CH_3 isopropyl), 21.57 (CH_3 tosyl), 21.15 (CH_3 isopropyl), 19.14 (CH_3 isopropylidene); *m/z* (CI, NH_3): 674 ($[M+NH_4]^+$, 22%), 502 (100%); HRMS (CI, NH_3): calcd for $C_{35}H_{48}O_{10}NS$ $[M+NH_4]^+$: 674.2999. Found: 674.2995.

3.16. Isopropyl 3-*O*-benzyl-5-*C*-benzyloxymethyl-2-*C*-tosyloxymethyl-β-D-glucopyranoside (19)

A catalytic amount of camphorsulfonic acid was added to a stirred solution of compound **18** (460 mg, 0.70 mmol) in MeOH (7 mL). After 90 min, the reaction was quenched by adding slowly solid $NaHCO_3$ at 0 °C until neutral pH of the solution. The reaction mixture was diluted with EtOAc and filtered through a Celite plug. The solvent was evaporated and the residue was purified by flash column chromatography (cyclohexane–EtOAc, 3:2) to afford triol **19** (422 mg, 0.68 mmol, 96%) as a white solid. $[\alpha]_D$ −35 (*c* 0.8, $CHCl_3$); mp 85–86 °C (EtOH); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, 2H, $J = 8.2$ Hz, Ts), 7.27–7.15 (m, 12H, 3 × Ph), 4.96 (s, 1H, H-1), 4.85 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.65 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.58 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.53 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.34 (d, 1H, $J = 10.0$ Hz, H-6), 4.31 (d, 1H, $J = 10.0$ Hz, H-6′), 3.95–3.88 (m, 3H, H-3, H-4, CH isopropyl), 3.82 (d, 1H, $J = 10.5$ Hz, H-7), 3.70 (d, 1H, $J = 11.4$ Hz, H-8), 3.62 (d, 1H, $J = 11.4$ Hz, H-8′), 3.60 (d, 1H, $J = 10.5$ Hz, H-7′), 2.45 (s, 3H, CH_3 tosyl), 1.20 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl), 1.14 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.67, 138.12, 137.33, 132.77 (4 × C_{ipso}), 129.67–127.70 (3 × Ph), 98.19 (C-1), 81.75 (C-3 or C-4), 77.46 (C-2), 74.72 (*C*H_2Ph), 74.15 (C-5), 73.82 (*C*H_2Ph), 71.52 (C-3 or C-4), 70.28 (C-7), 68.96 (CH isopropyl), 67.92 (C-6), 65.04 (C-8), 23.09 (CH_3 isopropyl), 21.59 (CH_3 tosyl), 21.46 (CH_3 isopropyl); *m/z* (CI, NH_3): 634 ($[M+NH_4]^+$, 35%); HRMS (CI, NH_3): calcd for $C_{32}H_{44}O_{10}NS$ $[M+NH_4]^+$: 634.2686. Found: 634.2687.

3.17. Isopropyl 3,6-*O*-dibenzyl-2-*C*-5-*C*-dimethyloxy-α-L-idopyranoside (20)

Sodium hydride (19 mg, 0.49 mmol) was added to a solution of compound **19** (86 mg, 0.14 mmol) in very dry DMF (10 mL) under argon. The reaction mixture was introduced immediately in a preheated bath at 70 °C and stirred for 90 min. The reaction was quenched by the addition of MeOH and concentrated. The residue was purified by flash column chromatography (cyclohexane–EtOAc, 9:1 then 4:1) to afford bicyclic compound **20** (63 mg, 0.10 mmol, 71%) as a colorless syrup. $[\alpha]_D$ −3 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.30 (m, 10H, 2 × Ph), 5.01 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.83 (s, 1H, H-1), 4.76 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.59 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.54 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.45 (app. t, 1H, $J = 3.5$ Hz, H-4), 4.19 (d, 1H, $J = 10.9$ Hz, H-6), 4.02 (sept., 1H, $J = 6.1$ Hz, CH isopropyl), 4.00 (d, 1H, $J = 12.7$ Hz, H-7), 3.85 (d, 1H, $J = 12.7$ Hz, H-7′), 3.67 (d, 1H, $J = 10.9$ Hz, H-6′), 3.59 (d, 1H, $J = 3.5$ Hz, H-3), 3.53 (d, 1H, $J = 9.2$ Hz, H-8), 3.21 (d, 1H, $J = 9.2$ Hz, H-8′), 2.37 (d, 1H, $J = 3.9$ Hz, OH-4), 2.35 (s, 1H, OH-2), 1.26 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.18 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.09, 137.17 (2 × C_{ipso}), 128.62–127.73 (2 × Ph), 99.98 (C-1), 85.05 (C-3), 82.28 (C-2), 74.71 (C-5), 73.94 (C-4), 73.64 (*C*H_2Ph), 73.22 (C-7), 72.24 (*C*H_2Ph), 69.92 (CH isopropyl), 69.84 (C-8), 67.25 (C-6), 23.60 (CH_3 isopropyl), 21.53 (CH_3 isopropyl); *m/z* (CI, NH_3): 462 ($[M+NH_4]^+$, 100%); HRMS (CI, NH_3): calcd for $C_{25}H_{36}O_7N$ $[M+NH_4]^+$: 462.2486. Found: 462.2490.

3.18. Isopropyl 6-*O*-benzoate-2-*C*-5-*C*-dimethyloxy-α-L-iduronic acid (21)

Compound **20** (450 mg, 1.0 mmol) was dissolved in EtOAc (35 mL) and 10% Pd/C (50 mg) was added. The reaction mixture was stirred for 3 h under H_2 atmosphere and filtered through a Celite plug eluted with MeOH. The solvent was removed under reduced pressure to afford a tetrol (267 mg, quant.) as an oil. This tetrol was directly engaged in the next oxidation reaction. The tetrol (267 mg, 1.0 mmol) was suspended in CH_2Cl_2 (3 mL) and TEMPO (2.4 mg) followed by a saturated solution of $NaHCO_3$ (2.2 mL), KBr (11.2 mg) and *n*-Bu_4NCl (17 mg) were added at rt. The reaction mixture was cooled to 0 °C and a saturated solution of $NaHCO_3$ (1.1 mL), brine (2.2 mL) and NaClO (1.5 mL, bleach commercial solution) were added dropwise and stirred for 30 min. The two layers were separated and the organic phase was extracted with water and the combined aqueous extracts were acidified to pH ∼ 4 with aq HCl. The aqueous extracts were concentrated and the crude acid was dissolved in DMF (20 mL) and $KHCO_3$ (683 mg, 5.5 mmol) followed by *n*-Bu_4NI (2.0 g, 5.5 mmol) and BnBr (0.7 mL, 5.5 mmol) were added at rt under argon. The reaction mixture was stirred overnight. After completion of the reaction, DMF was removed under reduced pressure and the residue was dissolved in EtOAc and washed with a satd aq $Na_2S_2O_3$ and brine. The organic layer was concentrated and purification by flash column chromatography (cyclohexane–EtOAc, 1:1 then 1:4) afforded the benzyl ester **21** (280 mg, 0.75 mmol, 75%) as a colorless oil. $[\alpha]_D$ −24 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30 (m, 5H, Ph), 5.21 (d, 1H, $J = 12.4$ Hz, CH_2Ph), 5.19 (d, 1H, $J = 12.4$ Hz, CH_2Ph), 4.98 (s, 1H, H-1), 4.60 (s, 1H, OH), 4.45 (br s, 1H, H-4), 4.30 (br s, 1H, OH),

4.20 (d, 1H, $J = 12.8$ Hz, H-8), 4.19–4.10 (m, 2H, H-7, CH isopropyl), 3.99 (d, 1H, $J = 12.8$ Hz, H-8′), 3.85 (br s, 1H, H-3), 3.72 (d, 1H, $J = 11.2$ Hz, H-7′), 3.50 (br s, 1H, OH), 1.29 (d, 3H, $J = 6.1$ Hz, CH_3 isopropyl), 1.19 (3H, d, $J = 6.1$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.41 (C=O), 135.15 (C_{ipso}), 128.53–128.05 (Ph), 99.89 (C-1), 86.67 (C-2), 79.77 (C-3), 76.25 (C-4), 75.03 (C-5), 73.69 (C-6), 70.85 (CH isopropyl), 67.48 (CH_2Ph), 66.65 (C-7), 23.58 (CH_3 isopropyl), 21.67 (CH_3 isopropyl); *m/z* (CI, NH_3): 386 ($[M+NH_4]^+$, 100%); HRMS (CI, NH_3): calcd for $C_{18}H_{28}NO_8$ $[M+NH_4]^+$: 386.1815. Found: 386.1818.

3.19. Isopropyl 2-*C*-5-*C*-dimethyloxy-α-L-iduronic acid (6)

Benzyl ester **21** (64 mg, 0.174 mmol) was dissolved in MeOH (3 mL) and Pd black (7 mg) was added. The reaction vessel was purged from air and stirred overnight under a hydrogen atmosphere. Filtration through a Celite plug eluted with MeOH and concentration afforded the L-iduronic acid analog **6** (48 mg, 0.173 mmol, quant.) as an oil. $[\alpha]_D$ −41 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.88 (s, 1H, H-1), 4.27 (d, 1H, $J = 13.1$ Hz, H-6), 4.26 (d, 1H, $J = 3.4$ Hz, H-4), 4.11 (sept., 1H, $J = 6.2$ Hz, CH isopropyl), 4.08 (d, 1H, $J = 11.3$ Hz, H-8), 3.93 (d, 1H, $J = 13.1$ Hz, H-6′), 3.67 (d, 1H, $J = 11.3$ Hz, H-8′), 3.66 (d, 1H, $J = 3.4$ Hz, H-3), 1.24 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl), 1.16 (d, 3H, $J = 6.2$ Hz, CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.70 (C=O), 99.81 (C-1), 87.13 (C-2), 79.36 (C-3), 76.04 (C-4), 75.24 (C-5), 74.13 (C-6), 71.79 (CH isopropyl), 66.23 (C-8), 22.85 (CH_3 isopropyl), 20.95 (CH_3 isopropyl); *m/z* (CI, NH_3): 296 ($[M+NH_4]^+$, 100%); HRMS (CI, NH_3): calcd for $C_{11}H_{22}O_8N$ $[M+NH_4]^+$: 296.1345. Found: 296.1348.

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Supplementary data

^1H and ^{13}C NMR spectra for compounds **6**, **8**–**20**; crystallographic information file for **15**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.02.025.

References

1. Rees, D. A.; Morris, E. R.; Stoddart, J. F.; Stevens, E. S. *Nature* **1985**, *317*, 480.
2. Casu, B.; Choay, J.; Ferro, D. R.; Gatti, G.; Jacquinet, J.-C.; Petitou, M.; Ragazzi, A. M.; Sinaÿ, P.; Torri, G. *Nature* **1986**, *322*, 215–216.
3. Ferro, D. R.; Provasoli, A.; Ragazzi, M.; Torri, G.; Casu, B.; Gatti, G.; Jacquinet, J.-C.; Sinaÿ, P.; Petitou, M.; Choay, J. *J. Am. Chem. Soc.* **1986**, *108*, 6773–6778.
4. (a) Casu, B.; Petitou, M.; Provasoli, A.; Sinaÿ, P. *Trends Biochem. Sci.* **1988**, *13*, 221–225; (b) Canales, A.; Angulo, J.; Lozano, R.; Ojeda, R.; Fayos, R.; Martín-Lomas, M.; Giménez-Gallego, G.; Nieto, P. M.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **2005**, *127*, 5778–5779.
5. Torri, G.; Casu, B.; Gatti, G.; Petitou, M.; Choay, J.; Jacquinet, J.-C.; Sinaÿ, P. *Biochem. Biophys. Res. Commun.* **1985**, *128*, 134–140.
6. Sinaÿ, P.; Jacquinet, J.-C.; Petitou, M.; Duchaussoy, P.; Lederman, I.; Choay, J.; Torri, G. *Carbohydr. Res.* **1984**, *132*, C5–C9.
7. For a discussion on the emergence of $^2S_0$ or $^0S_2$ conformation in the idopyranose series, see: Augé, J.; David, S. *Tetrahedron* **1984**, *40*, 2101–2106.
8. (a) Das, S. K.; Mallet, J.-M.; Esnault, J.; Driguez, P.-A.; Duchaussoy, P.; Sizun, P.; Hérault, J.-P.; Herbert, J.-M.; Petitou, M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1670–1673; (b) Das, S. K.; Mallet, J.-M.; Esnault, J.; Driguez, P.-A.; Duchaussoy, P.; Sizun, P.; Herbert, J.-M.; Petitou, M.; Sinaÿ, P. *Chem. Eur. J.* **2001**, *7*, 4821–4833.
9. Westerduin, P.; van Boeckel, C. A. A.; Basten, J. E. M.; Broekhoven, M. A.; Lucas, H.; Rood, A.; van der Heijden, H.; van Amsterdam, R. G. M.; van Dinther, T. G.; Meuleman, D. G.; Visser, A.; Vogel, G. M. T.; Damm, J. B. L.; Overklift, G. T. *Bioorg. Med. Chem.* **1994**, *2*, 1267–1280.
10. Herbert, J. M.; Hérault, J. P.; Bernat, A.; van Amsterdam, R. G. M.; Lormeau, J. C.; Petitou, M.; van Boeckel, C. A. A.; Hoffmann, P.; Meuleman, D. G. *Blood* **1998**, *91*, 4197–4205.
11. Kovensky, J.; Mallet, J.-M.; Esnault, J.; Driguez, P.-A.; Sizun, P.; Hérault, J.-P.; Herbert, J.-M.; Petitou, M.; Sinaÿ, P. *Eur. J. Org. Chem.* **2002**, 3595–3603.
12. (a) van Boeckel, C. A. A.; Petitou, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1671–1690; (b) Petitou, M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3118–3133.
13. (a) Desai, U. R.; Petitou, M.; Björk, I.; Olson, S. T. *Biochemistry* **1998**, *37*, 13033–13041; (b) Desai, U. R.; Petitou, M.; Björk, I.; Olson, S. T. *J. Biol. Chem.* **1998**, *273*, 7478–7487.
14. Blériot, Y.; Vadivel, S. K.; Herrera, A. J.; Grieg, I. R.; Kirby, A. J.; Sinaÿ, P. *Tetrahedron* **2004**, *60*, 6813–6828.
15. Cleator, E.; McCusker, C. F.; Steltzer, F.; Ley, S. V. *Tetrahedron Lett.* **2004**, *45*, 3077–3080.
16. (a) Walker, D. L.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 6251–6253; (b) Yoshimura, J.; Matsuzawa, M. *Carbohydr. Res.* **1981**, *96*, 7–20; (c) Dyong, I.; Weygand, J.; Meyer, W. *Tetrahedron Lett.* **1981**, *22*, 2969–2970; (d) Zagar, C.; Scharf, H.-D. *Liebigs Ann. Chem.* **1992**, 693–697.
17. These conditions of methylenation compete well with the use of Lombardo reagent. See: Hollingworth, G. J.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 703–706; For Lombardo reagent, see: Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293–4296.

18. (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562; (b) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970–2972; (c) Siedlecka, R.; Skarzewski, J.; Mlochowski, J. *Tetrahedron Lett.* **1990**, *31*, 2177–2180; (d) Davis, N. J.; Flitsch, S. L. *Tetrahedron Lett.* **1993**, *34*, 1181–1184; (e) De Nooy, A. E. J.; Besemer, A. C. *Carbohydr. Res.* **1995**, *269*, 89–98; (f) Haller, M.; Boons, G.-J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 814–822; (g) Litjens, R. E. J. N.; Den Heeten, R.; Timmer, M. S. M.; Overkleeft, H. S.; Van der Marel, G. A. *Chem. Eur. J.* **2005**, *11*, 1010–1016.
19. Braunschweiler, L.; Ernst, R. R. *J. Magn. Res.* **1983**, *53*, 521–527.
20. Bodenhausen, G.; Reuben, D. J. *Chem. Phys. Lett.* **1980**, *69*, 185–189.
21. Macura, S.; Ernst, R. R. *Mol. Phys.* **1980**, *41*, 95–108.
22. Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 3157–3158.
23. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440–467.
24. Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8559.
25. Still, W. C.; Tempzyk, A.; Hawley, R.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127–6129.
26. Poveda, A.; Asensio, J. L.; Martín-Pastor, M.; Jimenez-Barbero, J. *J. Biomol. NMR* **1997**, *10*, 29–43.
27. Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2794.