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From D-glucuronic acid to L-iduronic acid derivatives via a radical tandem decarboxylation–cyclization

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ABSTRACT

A synthesis to L-iduronic derivatives, major components of heparin derived pentasaccharides was accomplished by formal inversion of configuration at C-5 of a D-glucuronic acid derivative through radical formation at C-5 using Barton decarboxylation followed by intramolecular radical addition on an acetylenic tether at O-4 giving exclusively a bicyclic sugar of L-*ido* configuration. Oxidation and ring opening of this bicyclic sugar led to a L-iduronate. This method opens the way to short syntheses of pentasaccharidic moiety of Idraparinux and congeners.

1. Introduction

L-Iduronic acid (L-idoA) is a major constituent of heparin, a highly sulfated linear polysaccharide belonging to the family of glycosaminoglycans, extensively used for its anticoagulant properties.[1,2] Structural elucidation of the active domain of heparin, a pentasaccharide referred to as **DEFGH**, along with SAR studies led to chemically defined synthetic heparin analogues such as Fondaparinux (**1**), the only commercial ultra low molecular weight heparin and Idraparinux (**2**), a more potent and easier to prepare analogue which is *O*-sulfated and *O*-methylated (Fig. 1).[3] Idraparinux, a long acting antithrombin-mediated inhibitor of factor Xa, is an efficient anticoagulant in deep venous thrombosis. Idraparinux binds to antithrombin more strongly than Fondaparinux because of a higher number of hydrophobic interactions due to extensive methylation. More complex constructions involving Idraparinux and thrombin inhibitors have been proposed. Biotinylated derivatives of these antithrombotics have been elaborated to allow their neutralization by injection of avidin.[4]

Many chemical syntheses of pentasaccharides related to heparin have been reported.[5] All synthetic approaches required the preparation of at least five monosaccharide building blocks often referred to as **DEFGH** (Fig. 1). One important building block is the L-iduronic moiety **G** which is needed for biological activity of the oligosaccharides and which is challenging in terms of synthesis. L-hexoses are rare sugars from natural sources and are often biosynthetized by epimerization of D-sugars as it is the case for L-iduronic acid.[6] However the chemical synthesis of the L-idoA moiety is more complex and remains the limiting step of the preparation of these pentasaccharides. Although chemoenzymatic syntheses have recently emerged,[7] efficient chemical syntheses of L-idose derivatives are needed. L-idose and D-glucose are epimers, differing only in their configuration at C-5, therefore, most of the strategies explored to reach L-idoA made use of a D-glucose derivative as starting material and proceeded via basic or radical epimerizations of pyranose derivatives,[8] diastereoselective hydroboration of 5,6 *exo*-glycals,[9] nucleophilic substitution[10] or nucleophilic addition on furanose aldehyde derivatives.[11] However, these strategies often suffer from modest diastereoselectivity affording mixtures of L-*ido* and D-*gluco* derivatives.

Examination of former syntheses of **DEFGH** pentasaccharides shows that a widely used strategy is the assembly of two blocks **DEF** and **GH**,[5] the **DEF** block being obtained from two other building blocks **D** and **EF**. It is clear that in these target structures **GH** and **EF** differ only by the stereochemistry at C-5 of **G**. Being able to prepare **GH** from **EF** in a completely stereospecific manner would be of tremendous interest in the context of a multistep synthesis. We attempted to tackle this problem in a model study and we report here some of our results obtained on a monosaccharide.

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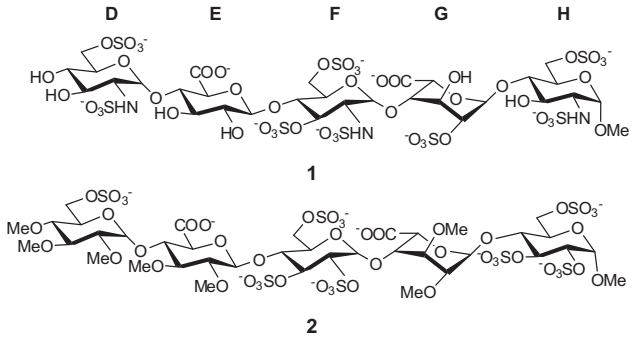


Figure 1. Structures of two synthetic heparin analogue pentasaccharides, Fondaparinux (**1**), and Idraparinux (**2**).

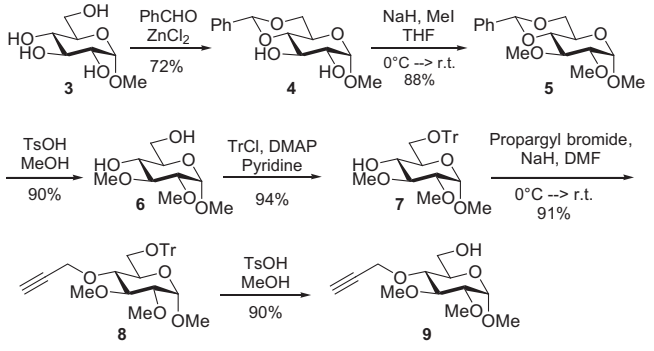
2. Results and discussion

It was reasoned that the inversion at C-5 would be better achieved on a pyranose structure owing to the strong tendency of L-idose derivative to exist as furanose derivatives. Basic epimerization of D-glucuronic acid or ester is difficult to drive to the L-*ido* derivative and β-elimination is often a side-reaction. Hydroboration of 5,6 *exo*-glycals is strongly dependent of the substrate in particular of the anomeric configuration, the β anomer (like in **GH**) giving mostly the D-*gluco* configuration.[9a,c,d]

Radical cyclization forming five-membered rings has been introduced by Stork et al. as an efficient way to control the stereochemistry of the newly formed C–C bond.[12a,b] This has been usefully applied to carbohydrate[12c–h] and carbocyclic chemistry.[12i,j] On the basis of our previous work on radical cyclization on sugar templates,[12c–e] we anticipated that a kinetically favoured 5-*exo* dig cyclization between a radical generated at C-5 and a suitable tether at O-4 would lead exclusively to a 4,5-*cis* fused-ring system, giving access to the desired L-*ido* configuration only. Moreover, the formation of a radical at C-5 has been invented by Barton et al. by decarboxylation of uronic acid via the corresponding thiohydroxamate, the so-called Barton ester.[13]

A D-glucuronic acid was thus a good starting point for our investigations. Starting from methyl α-D-glucopyranoside, the known 4,6-diol **6** was obtained in good yield on multi-gram scale, using only recrystallizations as a mean of purification. Selective protection of the primary hydroxyl group as a trityl ether followed by propargylation at O-4 and detritylation afforded alcohol **9** in excellent yield (Scheme 1).

Even though no selective oxidation was required, the primary alcohol was oxidized using the TEMPO/NaBr/NaOCl system allowing to work in water,[14] to give the corresponding carboxylic acid **10** which was just cleared of the inorganic salts and used as such in



Scheme 1. Synthesis of alcohol **9**.

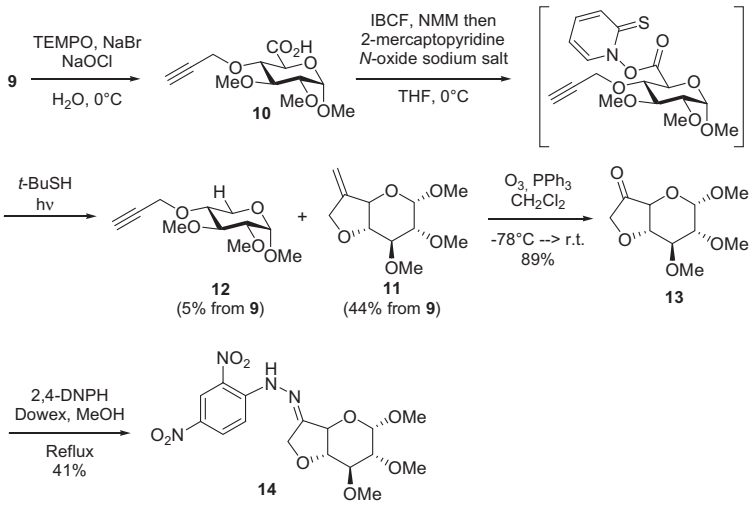
the next step. Two methods of radical decarboxylation were envisioned, the first used a classical Barton ester,[13] the second went through a stable *N*-(acyloxy)phthalimide activated ester as described by Okada et al.[15] The Barton decarboxylation method was eventually selected since it gave in our hands slightly better yields and easier purifications. Thus, acid **10** was converted to a mixed anhydride by treatment with isobutyl chloroformate (IBCF) in the presence of *N*-methyl-morpholine, then 2-mercaptopyridine *N*-oxide sodium salt was added to afford the Barton ester which was submitted to UV irradiation in the presence of *tert*-butylthiol, leading to the expected 5-*exo* dig cyclization adduct **11** in 44% yield from alcohol **9**, along with 5% of the reduced compound **12** (Scheme 2).

The moderate yield of the reaction was considered acceptable over 3 steps and it is worth noting that a single diastereomer was isolated. Yet, the configuration of the newly formed sugar could not be ascertained by NMR using the proton coupling constants due to a distortion of the carbohydrate ring (see Section 4). Hence, alkene **11** was submitted to ozonolysis and the resulting ketone **13** was condensed with 2,4-dinitrophenylhydrazine (2,4-DNPH) giving rise to the hydrazone **14**. Subsequent purifications and recrystalizations gave suitable crystals for X-ray diffraction analysis (Fig. 2).

X-ray crystallographic data showed the distorted $^4C_1$ conformation adopted by the carbohydrate, corroborating the observed coupling constants, and confirmed the desired stereochemistry at C-5 and consequently the L-*ido* configuration of the cyclization product (Fig. 2).

The opening of the oxolan ring and further excision of one carbon were attempted on ketone **13**. Enolization of this ketone was improductive, the equatorial H-5 proton being preferentially abstracted with LDA or weaker bases. Not unexpectedly Baeyer–Villiger oxidation of **13** gave the corresponding lactone with oxygen insertion between C-5 and C-6. We then attempted to reverse this situation by changing the methylene group of the five-membered ring for an acetal. For that purpose, the alkene **11** was efficiently transformed into its isomer **15** by treatment with dichlorotris(triphenylphosphine)ruthenium(II) catalyst in the presence of diisopropylethylamine in toluene at 80 °C. Treatment of **15** with NBS in the presence of ethanol gave the bromoacetal **16** as a single stereoisomer in 87% yield. On treatment with DBU in refluxing toluene for 4 days, the latter gave the alkene **17** in modest yield (29%) together with its 5,6 isomer (43% not shown). Finally, ozonolysis of **17** gave the expected ketone **18** in 80% yield. Gratifyingly, Baeyer Villiger oxidation of this ketone using *m*-CPBA and sodium bicarbonate in dichloromethane gave the expected unstable lactone which was not isolated since it cleaved spontaneously in situ to provide the L-iduronic acid **19** and the carbonate **21** according to proton NMR and mass spectrometry analyses on the crude mixture (see Supporting information). The presence of the ethoxycarbonate might result from a second Baeyer–Villiger reaction on the orthoester prior to decomposition, due to the slight excess of *m*-CPBA used.[16] The mixture was heated under reflux with a small amount of TsOH to cleave the carbonate group affording a single uronic acid **19** which was esterified under basic conditions to avoid furanose formation providing the methyl ester **20** in 56% yield from **18** (Scheme 3).

We then modified our route to **19** by installing the ethylacetal function as the tether earlier in the synthesis (Scheme 4). The ethoxypropyne group was introduced by a transacetalation reaction under acidic conditions. Hence, diol **6** was selectively oxidized with TEMPO[14] and the resulting carboxylic acid was protected as the methyl ester **22**. Transacetalation with 3,3-diethoxy-1-propyne gave the fully protected D-glucuronate **23** as a 2:1 mixture of diastereomers which was submitted to saponification to give carboxylic acid **24**. The radical tandem decarboxylation–cyclization



Scheme 2. Radical tandem decarboxylation–cyclization.

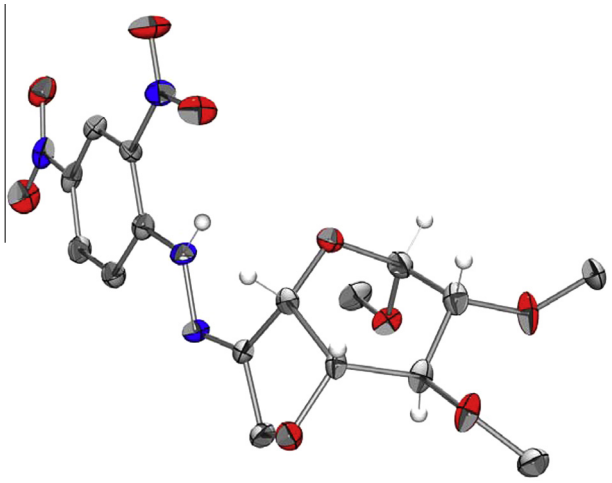
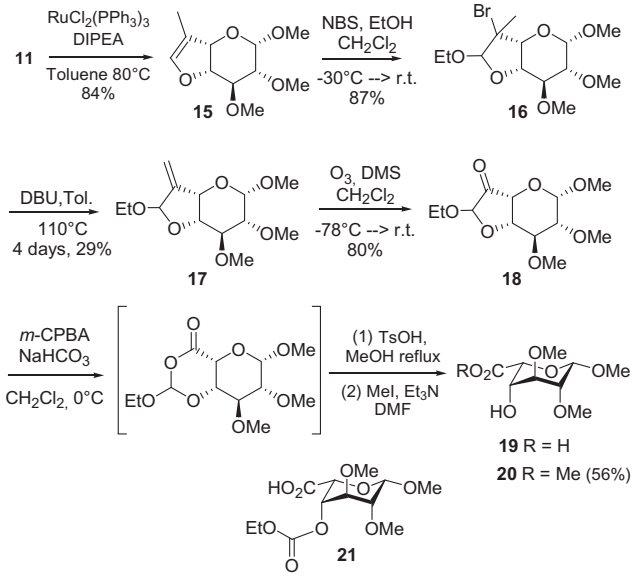
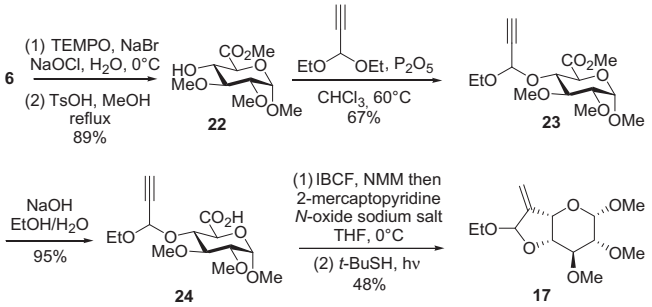


Figure 2. Crystal structure of hydrazone **14**. For clarity, (1) only one of the two independent molecules is shown and (2) only polar and methine hydrogen atoms are shown.



Scheme 3. First synthesis of L-iduronate **20**.



Scheme 4. Improved route to acetal **17**.

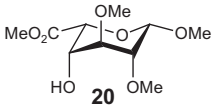
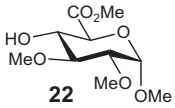
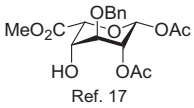
was performed on the crude acid resulting in the fused-ring compound **17**, in a yield that was comparable to the one observed with the propargylic ether. Eventually the remaining steps were performed on the mixture of diastereomers and furnished the L-iduronate in similar yields as previously described. This early functionalization allowed us to cut three steps in the synthesis, including the dehydrohalogenation which had the lowest yield (29%).

The L-*ido* configuration of the newly formed methyl uronate **20** was unambiguously confirmed by comparison of its proton coupling constants with those of the corresponding D-glucuronate **22** and those of a known yet differently protected methyl L-iduronate[17] (Table 1).

3. Conclusions

In conclusion, a new stereoselective method to reach an L-idoA derivative from its D-*gluco* counterpart has been achieved in five steps, the inversion of configuration being made during a tandem process involving the formation of a radical at C-5. Our method compares well with existing methods of epimerization involving a C-5 radical which always gave a mixture of D-*gluco* and L-*ido* derivatives depending on the solvent.[8d,e] The method described here offers the advantage of giving only the L-*ido* configuration. These results pave the way to a new process for the preparation of synthetic heparin analogues by direct transformation of **EF** building blocks into **GH** building blocks saving about ten steps of synthesis.

Table 1
$J_{(H,H)}$ coupling constants of methyl uronates (in Hz)

	 **20**	 **22**	 Ref. 17
$J_{1,2}$	0.9	3.4	1.4
$J_{2,3}$	3.5	9.3	3.3
$J_{3,4}$	3.5	9.5	3.3
$J_{4,5}$	1.6	9.6	1.8

4. Experimental

4.1. General methods

All commercial reagents were used as received. THF was distilled from sodium/benzophenone under argon, dichloromethane from P_2O_5, then calcium hydride and methanol from magnesium. DMF was stored over 4 Å MS. Pyridine and triethylamine were stored over KOH. TLC was performed on silica gel 60 F254, precoated plates. Compounds were visualized using UV254 and 30% H_2SO_4 MeOH with charring. Column chromatographies were performed using 63–200 μM or 40–63 μM or 5–40 μM silica gel. NMR spectra were recorded at 303 K at 250 or 400 MHz for ^1H and 62.9 or 100.6 MHz for ^{13}C. The chemical shifts are reported in ppm (δ) relative to residual solvent peak. Elucidations of chemical structures were based on ^1H, COSY, HSQC, ^{13}C, HMBC experiments. Mass spectra (MS) were recorded in ESI mode on quadrupole spectrometer or ESI/QqTOF spectrometer for HRMS. Optical rotations were obtained using sodium D line at rt. Melting points were determined in capillaries and are uncorrected. Infrared spectra were recorded on NaCl window. Compounds **4**,[18] **5**,[19] **6**,[20] **7**[21] and **22**[22] have been prepared according to literature procedures.

4.2. Methyl 2,3-di-*O*-methyl-4-*O*-propargyl-6-*O*-triphenyl methyl-α-D-glucopyranoside (8)

To a solution of alcohol **7** (9.72 g, 20.9 mmol) in DMF (100 mL), under argon at 0 °C, was added portionwise sodium hydride (60% in mineral oil, 1.26 g, 31.5 mmol, 1.5 equiv). After 30 min, propargyl bromide (4.5 mL, 41.8 mmol, 2.0 equiv) was added. After stirring for 17 h at room temperature, methanol (20 mL) was added to the reaction mixture then water (250 mL). The aqueous phase was extracted with Et_2O (4 × 120 mL) the combined organics were washed with water (100 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexane/EtOAc 90:10) to afford fully protected **8** as white solid (9.53 g, 19.0 mmol, 91%). Mp 120–121 °C; $[\alpha]_D^{20}$ 91.5 (*c* 1.0; $CHCl_3$); IR (film) 3293 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.48 (m, 6H, H_{Ar}), 7.32–7.21 (m, 9H, H_{Ar}), 4.91 (d, J_{1-2} = 3.6 Hz, 1H, H-1), 4.22, 4.14 (ABX system, J_{AB} = 15.3 Hz, J_{AX} = J_{BX} = 2.4 Hz, 2H, CH_2), 3.70 (ddd, J_{4-5} = 9.8 Hz, J_{5-6} = 5.0 Hz, $J_{5-6'}$ = 1.5 Hz, 1H, H-5), 3.62 (s, 3H, OCH_3), 3.57–3.43 (m, 3H, H-3, H-4, H-6′), 3.55 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.29 (dd, J_{2-3} = 9.5 Hz, J_{1-2} = 3.6 Hz, 1H, H-2), 3.13 (dd, $J_{6-6'}$ = 10.2 Hz, J_{5-6} = 5.0 Hz, 1H, H-6), 2.21 (t, *J* = 2.4 Hz, 1H, C≡C—H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 144.2, 128.9, 127.9, 127.1 (18 × C_{Ar}), 97.3 (C-1), 86.5 (*C*-Ph_3), 83.8 (C-3), 82.1 (C-2), 78.0 (H—C≡*C*—), 77.7 (C-4), 74.1 (H—*C*≡C—), 69.9 (C-5), 63.0 (C-6), 61.2 (OCH_3), 59.7 (≡C—*C*H_2), 59.1, 55.1 (2×OCH_3); Anal. Calcd for $C_{31}H_{34}O_6$ C: 74.08; H: 6.82. Found: C: 74.23; H: 6.88; MS (ESI): 525 $[M+Na]^+$.

4.3. Methyl 2,3-di-*O*-methyl-4-*O*-propargyl-α-D-glucopyranoside (9)

To a solution of **8** (2.00 g, 3.98 mmol) in methanol (40 mL) was added TsOH (80 mg, 0.42 mmol, 0.1 equiv). After 5 h at room temperature, sodium carbonate (78 mg) was added and stirring was continued for 15 min. After filtration through Celite® and concentration the residue was purified by chromatography (hexane/EtOAc 70:30), recrystallized in Et_2O, and washed with Et_2O/hexane (1:1). The filtrate was recrystallized twice from Et_2O to afford **9** as white crystals (936 mg, 3.60 mmol, 90%). Mp 97–98 °C; $[\alpha]_D^{20}$ 191.7 (*c* 1.0; $CHCl_3$); IR (film) 3477 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.81 (d, J_{1-2} = 3.6 Hz, 1H, H-1), 4.44, 4.39 (ABX system, J_{AB} = 15.3 - Hz, J_{AX} = J_{BX} = 2.4 Hz, 2H, CH_2), 3.84–3.80 (m, 2H, H-6, H-6′), 3.60 (s, 3H, OCH_3), 3.60–3.54 (m, 2H, H-3, H-5), 3.50 (s, 3H, OCH_3), 3.44–3.41 (m, 1H, H-4), 3.39 (s, 3H, OCH_3), 3.18 (dd, J_{2-3} = 9.6 Hz, J_{1-2} = 3.6 Hz, 1H, H-2), 2.47 (t, *J* = 2.4 Hz, 1H, C≡C—H), 1.97 (t, J_{CH-OH} = 6.6 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 97.5 (C-1), 83.7 (C-3), 82.1 (C-2), 80.3 (H—C≡*C*—), 76.7 (C-4), 74.5 (H—*C*≡C—), 70.4 (C-5), 61.9 (C-6), 61.1 (OCH_3), 59.8 (≡C—*C*H_2), 59.1, 55.3 (2×OCH_3); Anal. Calcd for $C_{12}H_{20}O_6$ C: 55.37; H: 7.74. Found: C: 55.69; H: 7.45; MS (ESI): 283 $[M+Na]^+$.

4.4. Methyl 4,7-anhydro-6-deoxy-6-methylene-2,3-di-*O*-methyl-β-L-*ido*-heptopyranoside (11)

To a solution of alcohol **9** (2.05 g, 7.88 mmol) in water (55 mL) were added NaBr (162 mg, 1.58 mmol, 0.2 equiv) and TEMPO (49 mg, 0.31 mmol, 0.04 equiv). The reaction mixture was cooled to 0 °C then a NaOCl aqueous solution (13% v/v, 18 mL, 31.4 mmol, 4.0 equiv) was added. After 5 h at 0 °C ethanol was added (96% v/v, 18 mL), the pH was reduced to 2–3 by the addition of 1 N HCl. The volatiles were removed in vacuo and the residue suspended in methanol, filtered to remove salts, and washed with dichloromethane and methanol. The filtrate was concentrated, dissolved in anhydrous THF (80 mL) under argon IBCF (1.00 mL, 7.72 mmol, 1.0 equiv) and *N*-methylmorpholine (0.87 mL, 7.91 mmol, 1.0 equiv) were added at 0 °C. After 20 min, the flask was covered with aluminum foil, 2-mercaptopyridine *N*-oxide sodium salt (2.35 g, 15.76 mmol, 2.0 equiv) was added, and the reaction mixture was stirred at rt. After 40 min anhydrous THF (200 mL) and *tert*-butylthiol (1.35 mL, 12.60 mmol, 1.6 equiv) were added. The foil was removed and the reaction mixture irradiated and heated with a UV lamp (300 W) for 30 min. The thiol excess was neutralized with a NaOCl aqueous solution (13% v/v, 20 mL). The reaction mixture was concentrated then dissolved in EtOAc (150 mL), washed successively with a 5% $NaHCO_3$ aqueous solution (2 × 25 mL), and brine (2 × 25 mL), then the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organics

were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (CH_2Cl_2/EtOAc 98:2) afforded the alkene **11** as (790 mg, 3.43 mmol, 44%) and the reduced **12** as colorless oils (90 mg, 0.39 mmol, 5%). $[\alpha]_D^{20}$ −38.0 (*c* 1.0; $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.30 (dd, J_{gem} = 4.1 Hz, *J* = 2.0 Hz, 1H, C=CH_aH_b), 5.09 (dd, J_{gem} = 4.1 Hz, *J* = 2.0 Hz, 1H, C=CH_aH_b), 4.69 (d, J_{1-2} = 2.4 Hz, 1H, H-1), 4.63–4.54 (m, 2H, H-5, H-7′), 4.27 (td, J_{gem} = 13.3 Hz, *J* = 2.0 Hz, 1H, H-7), 3.99 (br t, *J* = 5.4 Hz, 1H, H-4), 3.71 (dd, J_{2-3} = 7.5 Hz, J_{3-4} = 5.4 Hz, 1H, H-3), 3.56 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.24 (dd, J_{2-3} = 7.5 Hz, J_{1-2} = 2.4 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 147.5 (C-6), 108.0 (C=CH_2), 99.1 (C-1), 79.6 (C-4), 78.5 (C-2), 77.0 (C-3), 75.2 (C-5), 68.8 (C-7), 59.5, 59.4, 56.7 (3 × OCH_3); MS (HR-ESI) for $C_{11}H_{18}O_5Na$ $[M+Na]^+$: 253.1052, found: 253.1063.

4.5. Methyl 2,3-di-*O*-methyl-4-*O*-propargyl-α-D-xylopyranoside (12)

IR (film) 3251 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.76 (d, J_{1-2} = 3.5 Hz, 1H, H-1), 4.35, 4.29 (ABX system, J_{AB} = 15.8 Hz, J_{AX} = J_{BX} = 2.4 Hz, 2H, CH_2), 3.73 (dd, $J_{5-5'}$ = 10.5 Hz, $J_{4-5'}$ = 4.9 Hz, 1H, H-5′), 3.61 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.62–3.42 (m, 3H, H-3, H-4, H-5), 3.40 (s, 3H, OCH_3), 3.16 (dd, J_{2-3} = 9.0 Hz, J_{1-2} = 3.5 Hz, 1H, H-2), 2.45 (t, *J* = 2.4 Hz, 1H, C≡C—H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 97.6 (C-1), 82.9 (C-3), 81.9 (C-2), 80.1 (H—C≡*C*—), 77.6 (C-4), 74.5 (H—*C*≡C—), 61.2 (OCH_3), 59.8 (C-5), 59.2 (OCH_3), 58.9 (≡C—CH_2), 55.3 (OCH_3); MS (ESI): 253 $[M+Na]^+$.

4.6. Methyl 4,7-anhydro-2,3-di-*O*-methyl-β-L-*ido*-heptopyranosid-6-ulose (13)

Through a solution of alkene **11** (900 mg, 3.91 mmol) in anhydrous dichloromethane (20 mL), under argon and cooled to −78 °C, was bubbled ozone (0.2 L/min, 110 V). When the solution had turned dark blue, oxygen was bubbled through until the solution became colorless. Triphenylphosphine (1.14 g, 4.35 mmol, 1.1 equiv) was added and the solution was brought to room temperature for 1h30 and the reaction mixture was concentrated. Column chromatography (CH_2Cl_2/EtOAc 95:5) afforded **13** as colorless oil (807 mg, 3.48 mmol, 89%) which turned into a white solid at −18 °C. It was recrystallized from Et_2O/hexane, mp 66–67 °C; $[\alpha]_D^{20}$ −80.6 (*c* 1.0; $CHCl_3$); IR (film)): 1772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.76 (d, J_{1-2} = 2.8 Hz, 1H, H-1), 4.46 (dd, J_{4-5} = 9.3 Hz, J_{3-4} = 7.3 Hz, 1H, H-4), 4.28 (br d, J_{4-5} = 9.3 Hz, 1H, H-5), 4.11, 4.03 (ABX system, J_{AB} = 17.4 Hz, J_{AX} = 1.2 Hz, J_{BX} = 0 Hz, 2H, H-7, H-7′), 3.73 (dd, J_{2-3} = 10.0 Hz, J_{3-4} = 7.3 Hz, 1H, H-3), 3.63 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.14 (dd, J_{2-3} = 10.0 Hz, J_{1-2} = 2.8 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 210.4 (C-6), 98.9 (C-1), 79.7 (C-2), 79.2 (C-4), 76.9 (C-3), 72.5 (C-5), 66.9 (C-7), 60.4, 59.3, 57.0 (3 × OCH_3); Anal. Calcd for $C_{10}H_{16}O_6$: C: 51.72; H: 6.94, found: C: 51.80; H: 6.97; MS (ESI) 255 $[M+Na]^+$; 287 $[M+Na+MeOH]^+$.

4.7. Methyl 4,7-anhydro-2,3-di-*O*-methyl-β-L-*ido*-heptopyranosid-6-ulose 2,4-dinitrophenyl osazone (14)

To a solution of ketone **13** (396 mg, 0.96 mmol) in methanol (10 mL) were added 2,4-dinitrophenylhydrazine (66%, 356 mg, 1.20 mmol, 1.3 equiv) and Dowex® 50X8 (100 mg), then the reaction mixture was heated under reflux. After 4 h the reaction mixture was filtered and the precipitate washed with methanol. The filtrate was concentrated, the resulting residue dissolved in EtOAc (60 mL), and successively washed with a 5% $NaHCO_3$ aqueous solution (2 × 20 mL) and water (1 × 20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (CH_2Cl_2/EtOAc 95:5) then recrystallized first in methanol to provide **14** as yellow crystals (56 mg, 0.14 mmol, 41%). Suitable crystals for X-ray diffraction analysis were obtained from ethanol, mp 134–135 °C; $[\alpha]_D^{20}$ −602.1 (*c* 0.4; $CHCl_3$); IR (film) 3282 cm^{-1}; 1618 (C=N); 1519; 1505 (N=O); 1337; 1313 (N=O); ^1H NMR ($CDCl_3$, 400 MHz): δ 12.03 (s, 1H, NH), 9.13 (d, *J* = 2.4 Hz, 1H, H_{Ar}), 8.32 (dd, *J* = 9.6 Hz, *J* = 2.4 Hz, 1H, H_{Ar}), 7.90 (d, *J* = 9.6 Hz, 1H, H_{Ar}), 5.05 (dd, J_{4-5} = 8.4 Hz, J_{5-7} = 1.6 Hz, 1H, H-5), 4.95 (d, J_{1-2} = 2.7 Hz, 1H, H-1), 4.63 (dd, J_{gem} = 14.7 Hz, J_{5-7} = 1.6 Hz, 1H, H-7′), 4.42 (m, 2H, H-4, H-7), 3.81 (dd, J_{2-3} = 9.6 Hz, J_{3-4} = 6.4 Hz, 1H, H-3), 3.63 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.25 (dd, J_{2-3} = 9.6 Hz, J_{1-2} = 2.7 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 158.8 (C-6), 145.0 (6 × C_{Ar}), 138.5, 130.2, 129.9, 123.6, 116.2, 99.7 (C-1), 80.6 (C-4), 79.2 (C-2), 76.8 (C-3), 70.1 (C-5), 66.5 (C-7), 60.2, 59.4, 58.3 (3 × OCH_3); Anal. Calcd for $C_{16}H_{20}N_4O_9$: C: 46.60; H: 4.89; N: 13.59, found: C: 46.66; H: 4.89; N: 13.64; MS (ESI): *m*/*z* 435 $[M+Na]^+$.

4.8. Methyl-4,7-anhydro-6-deoxy-6-methyl-2,3-di-*O*-methyl-β-L-*ido*-hepto-6-enopyranoside (15)

To a solution of alkene **11** (900 mg, 3.91 mmol) in anhydrous toluene (20 mL), under argon, were added diisopropylethylamine (0.65 mL, 3.91 mmol, 1.0 equiv) and tris(triphenylphosphine) ruthenium dichloride (750 mg, 0.78 mmol, 0.2 equiv). The mixture was heated at 80 °C for 15 h then the volatiles were evaporated. The residue was purified by column chromatography (CH_2Cl_2/EtOAc 90:10) to afford alkene **15** as a green oil (760 mg, 3.30 mmol, 84%). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.19 (s, 1H, H-7), 4.74–4.71 (m, 2H, H-5, H-1), 4.23 (dd, J_{4-5} = 7.8 Hz, J_{3-4} = 3.0 Hz, 1H, H-4), 3.81 (dd, J_{2-3} = 7.4 Hz, J_{3-4} = 3.0 Hz, 1H, H-3), 3.52 (s, 6H, 2 × OCH_3), 3.42 (s, 3H, OCH_3), 3.31 (dd, J_{2-3} = 7.4 Hz, J_{1-2} = 2.2 Hz, 1H, H-2), 1.74 (s, 3H, CH_3); ^{13}C ($CDCl_3$, 100.6 MHz): δ 143.1 (C-7), 112.3 (C-6), 98.2 (C-1), 81.7 (C-4), 78.8 (C-3), 78.2 (C-2), 77.5 (C-5), 59.2, 58.3, 56.3 (3 × OCH_3), 9.1 (CH_3); MS (HR-ESI) for $C_{11}H_{18}O_5Na$ $[M+Na]^+$: 253.1052, found: 253.1057.

4.9. Methyl-4,7-anhydro-6-bromo-6-deoxy-6-methyl-7-ethoxy-2,3-di-*O*-methyl-β-L-*ido*-heptopyranoside (16)

To a solution of alkene **15** (151 mg, 0.66 mmol) in dichloromethane (5 mL) was added under argon, anhydrous ethanol (0.12 mL, 2.0 mmol, 3.0 equiv). The reaction mixture was cooled to −30 °C then *N*-bromosuccinimide (130 mg, 0.73 mmol, 1.1 equiv) was added. After 1h30 the mixture was kept at rt for 18 h then diluted with dichloromethane (25 mL) and washed with water (2 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (CH_2Cl_2/EtOAc 90:10) to afford **16** as a white solid (206 mg, 0.58 mmol, 87%).^1H NMR ($CDCl_3$, 400 MHz): δ 5.26 (s, 1H, H-7), 4.64 (d, J_{1-2} = 2.4 Hz, 1H, H-1), 4.39 (dd, J_{4-5} = 4.0 Hz, J_{3-4} = 2.8 Hz, 1H, H-4), 4.30 (d, J_{4-5} = 4.0 Hz, 1H, H-5), 3.79–3.71 (m, 2H, H-3, $OCH_aH_bCH_3$), 3.51–3.48 (m, 1H, $OCH_aH_bCH_3$), 3.50 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.29 (dd, J_{2-3} = 6.4 Hz, J_{1-2} = 2.4 Hz, 1H, H-2), 1.87 (s, 3H, CH_3), 1.18 (t, *J* = 6.8 Hz, 3H, OCH_2CH_3); ^{13}C ($CDCl_3$, 100.6 MHz): δ 109.9 (C-7), 98.9 (C-1), 80.3 (C-5), 79.4 (C-4), 78.4 (C-3), 77.0 (C-2), 69.9 (C-6), 64.0 (OCH_2CH_3), 59.1, 58.3, 56.5 (3 × OCH_3), 21.2 (CH_3), 15.1 (OCH_2CH_3); MS (HR-ESI) for $C_{13}H_{23}O_6BrNa$ $[M+Na]^+$: 377.0575 Found: 377.0548.

4.10. Methyl 4,7-anhydro-6-deoxy-6-methylene-7-ethoxy-2,3-di-*O*-methyl-β-L-*ido*-hepto pyranoside (17)

From **16**: To a solution of bromoacetal **16** (99 mg, 0.28 mmol) in toluene (5 mL) was added DBU (0.13 mL, 0.87 mmol, 3.0 equiv). After 36 h another batch of toluene (2 mL) and DBU (0.13 mL,

0.87 mmol, 3.0 equiv) was added. After 2 days at reflux the volatiles were evaporated. The residue was then dissolved in EtOAc (30 mL) and successively washed with a 5% aqueous citric acid (1 × 10 mL), a saturated aqueous $NaHCO_3$ (1 × 10 mL), and brine (1 × 10 mL). The aqueous phase was extracted with dichloromethane (2 × 20 mL) then the combined organics were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (CH_2Cl_2/EtOAc 98:2) to afford **17** as colorless oil (22 mg, 0.08 mmol, 29%). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.44 (t, J = 2.8 Hz, 1H, —C=CH_aH_b), 5.34–5.32 (m, 2H, H-7, —C=CH_aH_b), 4.79 (d, J_{1-2} = 2.8 Hz, 1H, H-1), 4.73 (td, J_{4-5} = 7.6 Hz, J = 2.8 Hz, 1H, H-5), 4.02 (t, J_{3-4} = J_{4-5} = 7.6 Hz, 1H, H-4), 3.95 (dd, J_{2-3} = 9.6 Hz, J_{3-4} = 7.6 Hz, 1H, H-3), 3.89–3.81 (m, 1H, OC$H_aH_bCH_3$), 3.63 (s, 3H, OCH_3), 3.62–3.57 (m, 1H, $OCH_aH_bCH_3$), 3.50 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.13 (dd, J_{2-3} = 9.6 Hz, J_{1-2} = 2.8 Hz, 1H, H-2), 1.23 (t, J = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C ($CDCl_3$, 100.6 MHz): δ 147.4 (C-6), 111.6 (—C=CH_2), 103.0 (C-7), 99.5 (C-1), 80.0 (C-2), 79.7 (C-4), 79.0 (C-3), 74.1 (C-5), 63.3 (OCH_2CH_3), 60.3, 59.0, 56.5 (3xOCH_3), 15.3 (OCH_2CH_3).

From **24**: Radical cyclization was carried out as described for **11** using acid **24** (1.89 g, 5.92 mmol) to afford **17** as colorless oil (218 mg, 0.79 mmol, 48%), in a 2:1 mixture of diastereomers as seen from ^1H NMR; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.57–5.35 (m, 3H, H-7, —C=CH_2), 4.79 (d, J_{1-2} = 3.0 Hz, 1H, H-1m), 4.73 (td, J_{4-5} = 7.9 Hz, J = 2.6 Hz, 1H, H-5m), 4.62 (d, J_{1-2} = 1.7 Hz, 1H, H-1M), 4.59 (br d, J_{4-5} = 4.0 Hz, 1H, H-5M), 4.07–3.93 (m, 2H, H-3, H-4), 3.90–3.78 (m, 1H, $OCH_aH_bCH_3$), 3.72 (dd, J_{2-3} = 5.0 Hz, J_{3-4} = 2.8 Hz, 1H, H-3M), 3.61–3.55 (m, 1H, OC$H_aH_bCH_3$), 3.53 (s, 3H, OCH_3M), 3.50 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3M), 3.41 (s, 3H, OCH_3m), 3.30 (dd, J_{2-3} = 5.0 Hz, J_{1-2} = 1.6 Hz, 1H, H-2M), 3.13 (dd, J_{2-3} = 9.6 Hz, J_{1-2} = 3.0 Hz, 1H, H-2m), 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 148.1 (C-6M), 147.4 (C-6m), 115.2 (—C=CH_2M), 111.6 (—C=CH_2m), 103.0 (C-7m), 102.2 (C-7M), 99.5 (C-1m), 99.3 (C-1M), 80.1 (C-2m), 79.7 (C-4m), 79.0 (C-3m), 77.7 (C-2M), 77.0 (C-4M), 76.4 (C-3M), 74.7 (C-5M), 74.2 (C-5m), 63.8 (OCH_2CH_3M), 63.3 (OCH_2CH_3m), 60.3 (OCH_3m), 59.9 (OCH_3M), 59.1 (OCH_3m), 58.6 (OCH_3M), 56.8 (OCH_3M), 56.5 (OCH_3m), 15.4 (OCH_2CH_3M), 15.3 (OCH_2CH_3m); MS (HR-ESI): m/z calcd for $C_{13}H_{22}O_6Na$ [M+Na]$^+$: 297.1309, found: m/z = 297.1318.

4.11. Methyl 4,7-anhydro-7-ethoxy-2,3-di-*O*-methyl-β-L-*ido*-heptopyranosid-6-ulose (18)

Through a solution of alkene **17** (449 mg, 1.64 mmol) in anhydrous dichloromethane (10 mL), under argon and cooled to −78 °C, was bubbled ozone (0.2 L/min, 110 V). When the solution had turned dark blue, oxygen was bubbled through in order to remove the excess ozone. When the solution became colorless dimethylsulfide (5 drops) was added and the solution was brought to room temperature. After 1h15 the reaction mixture was concentrated. Column chromatography (CH_2Cl_2/EtOAc 95:5) afforded **16** as white solid (364 mg, 1.32 mmol, 80%), in a mixture of diastereomers (4:1) (the relative composition of the mixture was determined by ^1H NMR from integrations of protons H-2); IR (film) 1783 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.93 (br s, 1H, H-7M), 4.89 (d, J = 1.1 Hz, 1H, H-7m), 4.79 (d, J_{1-2} = 2.9 Hz, 1H, H-1m), 4.76 (d, J_{1-2} = 2.8 Hz, 1H, H-1M), 4.50 (dd, J_{3-4} = 9.5 Hz, J_{4-5} = 6.2 Hz, 1H, H-4M), 4.44–4.39 (m, 2H, H-4m, H-5M), 4.34 (d, J_{4-5} = 9.1 Hz, 1H, H-5m), 4.07 (dd, J_{2-3} = 10.2 Hz, J_{3-4} = 7.7 Hz, 1H, H-3m), 3.10 (dd, J_{2-3} = 10.2 Hz, J_{1-2} = 2.9 Hz, 1H, H-2), 3.95–3.77 (m, 2H, OC$H_aH_bCH_3$), 3.73–3.48 (m, 3H, H-3M, OC$H_aH_bCH_3$), 3.66 (s, 3H, OCH_3m), 3.63 (s, 3H, OCH_3M), 3.50 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3m), 3.38 (s, 3H, OCH_3M), 3.17 (dd, J_{2-3} = 9.4 Hz, J_{1-2} = 2.8 Hz, 1H, H-2M), 1.28–1.24 (m, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 205.6 (C-6M), 205.3 (C-6m), 99.0 (C-1m), 98.7 (C-1M), 97.2 (C-7m), 96.1 (C-7M), 80.2 (C-2m), 79.8 (C-2M, C-3m), 79.4 (C-3M), 79.2 (C-4m), 75.9 (C-4M), 72.4 (C-5m), 70.2 (C-5M), 65.5 (OCH_2CH_3), 65.0 (OCH_2CH_3), 60.6 (OCH_3), 59.8 (OCH_3), 59.3 (OCH_3M), 57.2 (OCH_3m), 56.7 (OCH_3m), 15.2 (OCH_2CH_3M), 15.1 (OCH_2CH_3m). MS (ESI): 299 [M+Na]$^+$; 331 [M+Na+MeOH]$^+$.

4.12. Methyl (methyl 2,3-di-*O*-methyl-β-L-idopyranosid)uronate (20)

To a solution of ketone **18** (50 mg, 0.18 mmol) in dichloromethane (3 mL), under argon and cooled to 0 °C, were added *m*-CPBA (77%, 120 mg, 0.54 mmol, 3.0 equiv) and $NaHCO_3$ (20 mg, 0.23 mmol, 1.3 equiv). After 3 h stirring the volatiles were removed under vacuum. The resulting residue was dissolved in EtOAc (30 mL), extracted with distilled water, (2 × 10 mL) and the aqueous phase was concentrated. The crude mixture was dissolved in methanol (10 mL), TsOH was added (4 mg, 0.02 mmol, 0.1 equiv) then the reaction mixture was heated under reflux and the reaction monitored by ^1H NMR in deuterated methanol to check the disappearance of the carbonate. After 8 h the volatiles were evaporated. The residue was dissolved in DMF (5 mL) then triethylamine (28 μL, 0.20 mmol, 1.1 equiv) and methyl iodide (56 μL, 0.90 mmol, 5.0 equiv) were added. After 3h30 stirring at room temperature the reaction mixture was concentrated, dissolved in EtOAc (30 mL), and the organic phase was washed with a 5% $NaHCO_3$ aqueous solution (2 × 10 mL), a 5% citric acid aqueous solution (2 × 10 mL), and brine (1 × 10 mL). The aqueous phase was extracted with dichloromethane (5 × 10 mL) and the combined organics were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (CH_2Cl_2/EtOAc 85:15) afforded **20** as colorless oil (25 mg, 0.10 mmol, 56%). $[\alpha]_D^{20}$ 118.5 (*c* 0.4; $CHCl_3$); IR (film) 3491 cm^{-1}; 1765 (C=O); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.61 (d, J_{1-2} = 0.9 Hz, 1H, H-1), 4.42 (d, J_{4-5} = 1.6 Hz, 1H, H-5), 3.97 (m, 1H, H-4), 3.80 (s, 3H, OCH_3), 3.78–3.75 (m, 1H, OH), 3.69 (t, J_{2-3} = J_{3-4} = 3.5 Hz, 1H, H-3), 3.57 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.41 (br d, J_{2-3} = 3.5 Hz, 1H, H-2). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 169.6 (C=O), 100.9 (C-1), 77.5 (C-3), 77.2 (C-2), 74.8 (C-5), 67.7 (C-4), 60.8, 58.4, 57.5, 52.4 (4×OCH_3); Anal. Calcd for $C_{10}H_{18}O_7$: C: 48.00; H: 7.25, found: C: 47.62; H: 7.15; MS (ESI): 272 [M+Na]$^+$.

4.13. Methyl [methyl 4-*O*-(1′-ethoxy-2′-propyn-1′-yl)-2,3-di-*O*-methyl-α-D-glucopyranosid] uronate (23)

To a solution of methyl uronate **22** (4.56 g, 18.2 mmol) in chloroform (200 mL) were added, under argon, P_2O_5 (5.31 g, 36.3 mmol, 2.0 equiv), and propargylaldehyde diethylacetal (5.2 mL, 36.3 mmol, 2.0 equiv), then the reaction mixture was heated at 60 °C. After 4 h stirring, the cooled reaction mixture was filtered through a pad of Celite® then the volatiles were removed under vacuum. The crude mixture was suspended in EtOAc (300 mL), washed with a 5% $NaHCO_3$ aqueous solution (1 × 30 mL), and brine (1 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (hexane/EtOAc 80:20) afforded fully protected **23** as colorless oil (4.07 g, 12.2 mmol, 67%) in a diastereomeric mixture (2:1) determined by ^1H NMR from integrations of EtO-C*H* signal, along with some unreacted **20** (1.17 g, 4.7 mmol, 26%). IR (film) 1752 cm^{-1}; 3266 (≡C—H); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.58 (d, J = 1.7 Hz, 1H, EtO-C*H*M), 5.35 (d, J = 1.7 Hz, 1H, EtO-C*H*m), 4.88–4.86 (m, 1H, H-1), 4.18 (d, J_{4-5} = 10.0 Hz, 1H, H-5m), 4.15 (d, J_{4-5} = 10.0 Hz, 1H, H-5M), 3.86–3.78 (m, 1H, H-4), 3.80 (s, 3H, OCH_3m), 3.78 (s, 3H, OCH_3M), 3.73–3.65 (m, 1H, $OCH_aH_bCH_3$), 3.62 (s, 3H, OCH_3M), 3.62–3.47 (m, 2H, H-3, OC$H_aH_bCH_3$), 3.59 (s, 3H, OCH_3m), 3.50 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3m), 3.43 (s, 3H, OCH_3M), 3.31–3.26 (m, 1H, H-2), 2.56 (m, 1H, H—C≡C—), 1.25–1.18 (m, 3H, OCH_2CH_3);

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 169.9 (C═O), 169.6 (C═OM), 98.0 (C-1M), 97.9 (C-1m), 92.6 (EtO-*C*H), 82.9 (C-3M), 81.9 (C-3m), 81.8 (C-2m), 81.5 (C-2M), 78.9 (H—C≡*C*M), 78.6 (H—C≡*C*m), 76.7 (C-4M), 76.4 (C-4m), 74.2 (H—C≡Cm), 74.0 (H—C≡CM), 70.2 (C-5M), 70.1 (C-5m), 61.4 (OCH_3), 61.3 (OCH_2CH_3m), 60.4 (OCH_2CH_3M), 59.3 (OCH_3m), 59.2 (OCH_3M), 55.8 (OCH_3), 52.7 (OCH_3m), 52.6 (OCH_3M), 15.0 (OCH_2CH_3); Anal. Calcd for $C_{15}H_{24}O_8$: C: 54.21; H: 7.28, found: C: 54.17; H: 7.13; MS (ESI): 355 $[M+Na]^+$.

4.14. 4-*O*-(1′-Ethoxy-2′-propyn-1′-yl)-1,2,3-tri-*O*-methyl-α-D-glucopyranosiduronic acid (24)

To a solution of methyl uronate **23** (1.12 g, 3.37 mmol) in EtOH/H_2O (3:1 v/v, 100 mL) was added sodium hydroxide (156 mg, 3.90 mmol, 1.3 equiv). After 5 h stirring at room temperature the volatiles were evaporated. The residue was dissolved in water (50 mL), the pH was reduced to 2–3 with a 5% citric acid aqueous solution, then the aqueous layer was saturated with sodium chloride before extraction with dichloromethane (10 × 20 mL). If necessary the pH was adjusted by the addition of more citric acid aqueous solution. The combined organics were dried ($MgSO_4$), filtered, and concentrated to afford **24** without further purification as colorless oil (1.02 g, 3.20 mmol, 95%), in a mixture of diastereomers (3:1) as seen from ^{1}H NMR spectra; IR (film)) 1751 cm^{-1}; 3268 (≡C—H); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (d, J = 1.6 Hz, 1H, EtO-C*H*M), 5.45 (br s, 1H, EtO-C*H*m), 4.90–4.88 (m, 1H, H-1) (diastereomeric mixture), 4.18–4.13 (m, 1H, H-5), 3.87–3.81 (m, 1H, H-4), 3.77–3.68 (m, 1H, $OCH_aH_bCH_3$), 3.62 (s, 3H, OCH_3), 3.62–3.54 (m, 2H, H-3, $OCH_aH_bCH_3$), 3.51 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 3.33–3.25 (m, 1H, H-2), 2.62 (br s, 1H, H—C≡Cm), 2.59 (d, J = 1.6 Hz, 1H, H—C≡CM), 1.24–1.16 (m, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 174.0 (C═Om), 173.8 (C═OM), 98.0 (C-1M), 97.8 (C-1m), 92.5 (EtO-*C*H), 82.9 (C-3), 81.8 (C-3M), 81.7 (C-2m), 81.4 (C-2M), 78.8 (H—C≡*C*M), 78.5 (H—C≡*C*m), 76.4 (C-4M), 75.7 (C-4m), 74.8 (H—C≡CM), 74.3 (H—C≡Cm), 70.1 (C-5), 61.3 (OCH_3M), 61.2 (OCH_3m), 60.7 (OCH_2CH_3), 59.3 (OCH_3M), 59.2 (OCH_3m), 55.9 (OCH_3),14.9 (OCH_2CH_3); MS (ESI): 341 $[M+Na]^+$.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2014.01.006.

References

1. Casu, B. *Adv. Carbohydr. Chem. Biochem.* **1985**, *43*.
2. Musser, J. H.; Fugedi, P.; Anderson, M. B.; Rao, N.; Peto, C.; Tyrrell, D.; Holme, K.; Tressler, R. *Drug News Perspect.* **1996**, *9*, 133–141.
3. (a) Petitou, M.; Duchaussoy, P.; Lederman, I.; Choay, J.; Jacquinet, J. C.; Sinaÿ, P.; Torri, G. *Carbohydr. Res.* **1987**, *167*, 67–75; (b) Petitou, M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3118–3133.
4. (a) Petitou, M.; Nancy-Portebois, V.; Dubreucq, G.; Motte, V.; Meuleman, D.; de Kort, M.; van Boeckel, C. A. A.; Vogel, G. M.; Wisse, J. A. *Thromb. Haemost.* **2009**, *102*, 804–810; (b) Harenberg, J. *Expert Rev. Clin. Pharmacol.* **2010**, *3*, 9–16; (c) Richard, S.; El Hadri, A.; Goedheijt, M. S.; Heisen, M.; Vader, J.; Wiegerinck, P.; Petitou, M. *J. Labelled Compd. Radiopharm.* **2011**, *54*, 637–644; (d) Bianciotto, M.; Driguez, P. A.; Duchaussoy, P.; Lassalle, G.; Le-Dref, P.; Thiery, J.-C.; Trouilleux, P. PCT Int. Appl. 2012042123A1.
5. For leading references see: (a) Chen, C.; Yu, B. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3875–3879; (b) Herczeg, M.; Mezo, E.; Lazar, L.; Fekete, A.; Kover, K. E.; Antus, S.; Borbas, A. *Tetrahedron* **2013**, *69*, 3149–3158. and references cited therein.
6. Raedts, J.; Lundgren, M.; Kengen, S. W. M.; Li, J.-P.; Van der Oost, J. *J. Biol. Chem.* **2013**, *288*, 24332–24339.
7. (a) Zhang, Z.; McCallum, S. A.; Xie, J.; Nieto, L.; Corzana, F.; Jiménez-Barbero, J.; Chen, M.; Liu, J.; Linhardt, R. J. *J. Am. Chem. Soc.* **2008**, *130*, 12998–13007; (b) Xu, Y.; Masuko, S.; Takieddin, M.; Xu, H.; Liu, R.; Jing, J.; Mousa, S. A.; Linhardt, R. J.; Liu, J. *Science* **2011**, *334*, 498–501; (c) Masuko, S.; Linhardt, R. J. *Future Med. Chem.* **2012**, *4*, 289–296.
8. (a) Baggett, N.; Smithson, A. *Carbohydr. Res.* **1982**, *108*, 59–70; (b) Thiem, J.; Ossowski, P. *J. Carbohydr. Chem.* **1984**, *3*, 287–313; (c) Schell, P.; Orgueira, H. A.; Roehrig, S.; Seeberger, P. H. *Tetrahedron Lett.* **2001**, *42*, 3811–3814; (d) Chiba, T.; Sinaÿ, P. *Carbohydr. Res.* **1986**, *151*, 379–389; (e) Medakovic, D. *Carbohydr. Res.* **1994**, *253*, 299–300; (f) De Mesmaeker, A.; Hoffmann, P.; Ernst, B.; Hug, P.; Winkler, T. *Tetrahedron Lett.* **1989**, *30*, 6311–6314.
9. (a) Takeo, K. i.; Fukatsu, T.; Yasato, T. *Carbohydr. Res.* **1982**, *107*, 71–90; (b) Ichikawa, Y.; Monden, R.; Kuzuhara, H. *Tetrahedron Lett.* **1986**, *27*, 611–614; (c) Chiba, T.; Jacquinet, J.-C.; Sinaÿ, P.; Petitou, M.; Choay, J. *Carbohydr. Res.* **1988**, *174*, 253–264; (d) Rochepeau-Jobron, L.; Jacquinet, J. C. *Carbohydr. Res.* **1997**, *303*, 395–406; (e) Alper, P. B.; Hendrix, M.; Sears, P.; Wong, C. H. *J. Am. Chem. Soc.* **1998**, *120*, 1965–1978; (f) Deal, S. T.; Horton, D. *Carbohydr. Res.* **1999**, *315*, 187–191; (g) Hung, S.; Puranik, R.; Chi, F. *Tetrahedron Lett.* **2000**, *41*, 77–80; (h) Takahashi, H.; Miyama, N.; Mitsuzuka, H.; Ikegami, S. *Synthesis* **2004**, 2991–2994.
10. (a) Blanc-Muesser, M.; Defaye, J. *Synthesis* **1977**, *8*, 568–569; (b) Csuk, R.; Hönig, H.; Nimp, J.; Weidmann, H. *Tetrahedron Lett.* **1980**, *21*, 2135–2136; (c) Ke, W.; Whitfield, D. M.; Gill, M.; Larocque, S.; Yu, S. H. *Tetrahedron Lett.* **2003**, *44*, 7767–7770.
11. (a) Lubineau, A.; Gavard, O.; Alais, J.; Bonnaffé, D. *Tetrahedron Lett.* **2000**, *41*, 307–311; (b) Gavard, O.; Hersant, Y.; Alais, J.; Duverger, V.; Dilhas, A.; Bascou, A.; Bonnaffé, D. *Eur. J. Org. Chem.* **2003**, 3603–3620; (c) Hansen, S. U.; Barath, M.; Salameh, B. A. B.; Pritchard, R. G.; Stimpson, W. T.; Gardiner, J. M.; Jayson, G. C. *Org. Lett.* **2009**, *11*, 4528–4531; (d) Hansen, S. U.; Miller, G. J.; Barath, M.; Broberg, K. R.; Avizienyte, E.; Helliwell, M.; Raftery, J.; Jayson, G. C.; Gardiner, J. M. *J. Org. Chem.* **2012**, *77*, 7823–7843.
12. (a) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741–3742; (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500–501; For applications in carbohydrate chemistry see: (c) Moufid, N.; Chapleur, Y. *Tetrahedron Lett.* **1991**, *32*, 1799–1802; (d) Moufid, N.; Chapleur, Y.; Mayon, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 991–998; (e) Moufid, N.; Chapleur, Y.; Mayon, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 999–1007; (f) Audin, C.; Lancelin, J. M.; Beau, J. M. *Tetrahedron Lett.* **1988**, *29*, 3691–3694; (g) De Mesmaeker, A.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1988**, *29*, 6585–6588; (h) Lesueur, C.; Nouguier, R.; Bertrand, M. P.; Hoffmann, P.; De Mesmaeker, A. *Tetrahedron* **1994**, *50*, 5369–5380; For applications in carbocyclic chemistry see for example: (i) Clive, D. L. J.; Joussef, A. C. *J. Org. Chem.* **1990**, *55*, 1096–1098; (j) Clive, D. L. J.; Boivin, T. L. B.; Angoh, A. G. *J. Org. Chem.* **1987**, *52*, 4943–4953.
13. (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979–4982; (b) Barton, D. H. R.; Géro, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2123–2136.
14. (a) Györgydeák, Z.; Thiem, J. *Carbohydr. Res.* **1995**, *268*, 85–92; (b) Davis, N. J.; Flitsch, S. L. *Tetrahedron Lett.* **1993**, *34*, 1181–1184; (c) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1176; (d) Huang, L.; Teumelsan, N.; Huang, X. *Chem. Eur. J.* **2006**, *12*, 5246–5252.
15. (a) Okada, K.; Okamoto, K.; Oda, M. *J. Am. Chem. Soc.* **1988**, *110*, 8736–8738; (b) Okada, K.; Okubo, K.; Morita, N.; Oda, M. *Tetrahedron Lett.* **1992**, *33*, 7377–7380.
16. Bailey, W. F.; Shih, M.-J. *J. Am. Chem. Soc.* **1982**, *104*, 1769–1771.
17. Kuszmann, J.; Medgyes, G.; Boros, S. *Carbohydr. Res.* **2004**, *339*, 1569–1579.
18. Richtmyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1941**, *63*, 1727–1731.
19. Jedlinski, Z.; Maslinska, J. *Tetrahedron* **1963**, *19*, 1171–1173.
20. Nicoll-Griffith, D. A.; Weiler, L. *Tetrahedron* **1991**, *47*, 2733–2750.
21. Robertson, G. J. *J. Chem. Soc.* **1933**, 737–739.
22. Becher, J.; Seidel, I.; Plass, W.; Klemm, D. *Tetrahedron* **2006**, *62*, 5675–5681.