Intramolecular 1,5- versus 1,6-hydrogen abstraction reaction promoted by alkoxyl radicals in pyranose and furanose models

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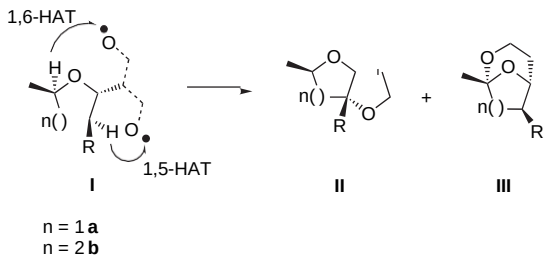
Received 11 May 2007; accepted 6 June 2007
Available online 12 June 2007

Abstract—The primary alkoxyl radical generated by reaction of 1-(2-hydroxyethyl)-glycosides with (diacetoxyiodo)benzene (DIB) and iodine can undergo regioselective intramolecular hydrogen abstraction (IHA) reactions to furnish four different dioxabicyclic systems derived from carbohydrates. The results strongly suggest that the regiocontrol and feasibility of the cyclisation are dependant not only on geometric and stereoelectronic factors, but also on polar and thermochemical factors. The correct selection of the substituents at the precursors can favour the 1,6-IHA against the 1,5-IHA pathway.

1. Introduction

Remote intramolecular free radical functionalisation of inactivated carbons via intramolecular hydrogen abstraction (IHA) from alkoxyl radicals has attracted considerable interest among synthetic organic chemists.[1] The (diacetoxyiodo)-benzene (DIB) in the presence of iodine is a convenient reagent to generate alkoxyl radicals from alcohols in mild conditions and has been widely used in synthesis. Earlier reports from this laboratory have described a new methodology to obtain various bicyclic polyhydroxylated systems, starting from a carbohydrate with a primary alkoxyl radical attached to one, two, three and four carbon tethers extended from the C1 of the sugar, through an IHA reaction.[2] The 1,5-hydrogen atom transfer (HAT) is by far the most common reaction and is particularly useful for the synthesis of tetrahydrofuran derivatives.[3,2f] 1,6-HAT has also been frequently observed, but high yields are only obtained when the transferring hydrogen is bonded to an oxygen-substituted carbon.[4,5] Among other factors such as geometry and stereoelectronic effects, the feasibility of the HAT reaction is dependant on polar effects and the C–H dissociation bond energy (DBE) involved in the process. To some extent the C–H DBE can be conditioned by the electron-donating ability of the substituents linked to the carbon atom. For instance, we can observe a decrease in the experimental C–H DBE values (kcal mol^{-1}) if the electron-donating ability of the *O*-substituent at the methane increases: CH_3C–H, 105; $C_6H_5COOCH_2$–H, 100.2 and CH_3OCH_2–H, 93.[6] In addition, the polarity of the substituents can alter the regioselectivity of the hydrogen atom transfer promoted by a highly electrophilic alkoxyl radical. We have also found that either the absence of a substituent or the presence of alcohols protected with electron-withdrawing groups (EWGs) inhibits oxidation of the radical in the alkoxyl radical b-fragmentation reaction, allowing faster reaction with radical species present in the medium, typically capturing iodine.[7,8]

With all this in mind, the purpose of the present work was to investigate whether substituents could be used to control the reaction course in an IHA reaction. With this aim, we synthesised a number of carbohydrate models possessing a primary alkoxyl radical attached at C1 of pyranose and furanose *C*-glycosides by a two-carbon tether. In these models the alkoxyl radical may abstract hydrogen from two different carbon atoms:[9] from C6 and C7, in furanoses and pyranoses, respectively, through a seven-membered transition state (TS) and from C4 through a, in principle, more favourable six-membered TS I (Scheme 1).



Scheme 1. Regioselectivity of the IHA reaction.

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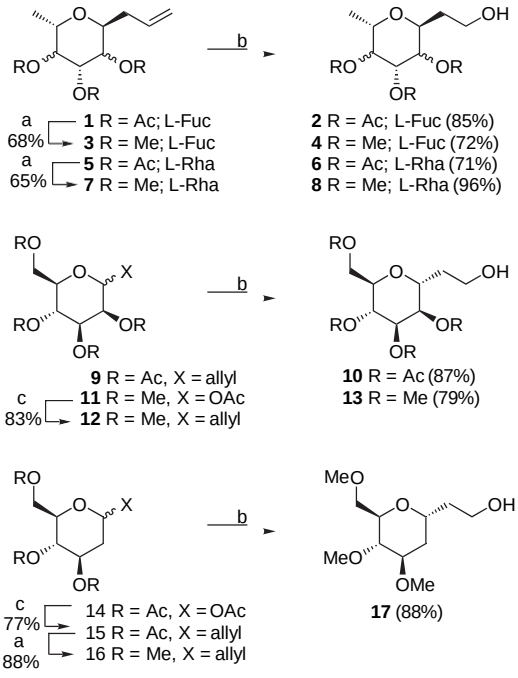
It therefore offers an opportunity to study the regioselectivity of the process (1,5- versus 1,6-HAT)[10] and at the same time to develop new methodology for the synthesis of four especially interesting dioxabicyclic systems: hexahydrofuro[3,2-*b*]furan **IIa**, hexahydro-2*H*-furo[3,2-*b*]pyran **IIb**, 2,8-dioxabicyclo[3.2.1]octane **IIIa** and 2,9-dioxabicyclo[3.3.1]nonane **IIIb**. These bicycles are substructural units of many natural products. An example is azaspiracid, a marine toxin, which has units **IIb** and **IIIb** in its molecule.[11] Units **IIa** and **IIb** are frequently related to ascorbic and zaragozic acid derivatives, respectively.[12]

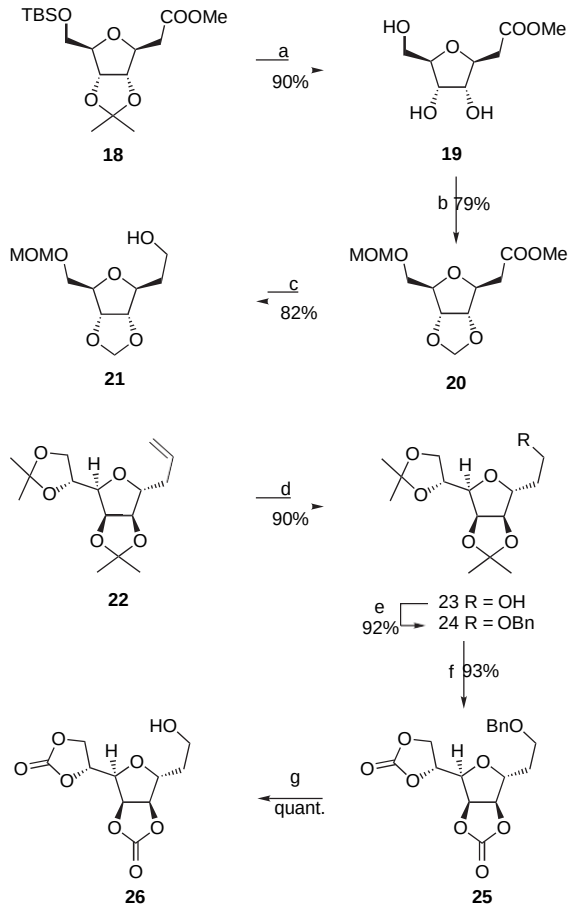
2. Synthesis of substrates and results

Preparation of the required octitols was accomplished following a well-established two-step protocol starting from suitably protected derivatives of L-fucose, L-rhamnose, D-mannose and 2-deoxy-D-arabinose. A Lewis acid-mediated *C*-glycosidation with allyltrimethylsilane afforded the non-8-enitols, in general with high stereoselectivity,[13,18] which upon subsequent ozonolysis followed by reductive workup with $NaBH_4$ provided the alcohols **2**, **4**, **6**, **8**, **10**, **13** and **17** in good yield (Scheme 2).



Scheme 2. Syntheses of 3,7-anhydrooctitols: (a) KOH/MeOH, rt followed by NaH, MeI, DMF, rt; (b) O_3, CH_2Cl_2/MeOH, —78 °C and then $NaBH_4$, MeOH, 0 °C; (c) ATMS, BF_3\$$OEt_2$, MeCN, 0 °C/rt.

We have also prepared three *C*-glycosides of the tetrahydrofuran series in order to extend this methodology for the synthesis of another two dioxabicyclic systems. The 3,6-anhydro-heptitol **21** was prepared from the known ester **18**[2c] by changing the protecting groups and subsequent reduction of carboxyl moiety with $LiAlH_4$. 3,6-Anhydro-octitol **23** was synthesised from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose by radical C-allylglycosidation as previously described[2a] followed by ozonolysis with a reductive workup with $NaBH_4$, which after suitable substitution of protecting groups yielded compound **26** (Scheme 3).



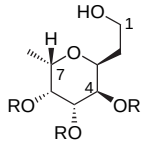
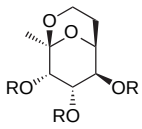
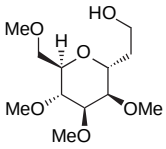
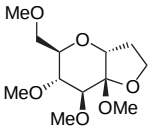
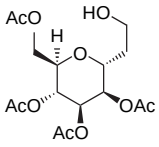
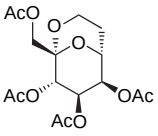
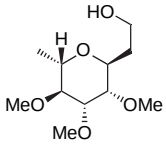
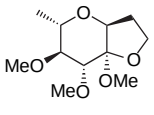
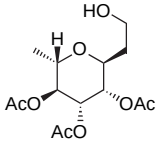
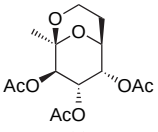
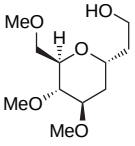
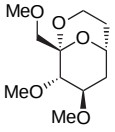
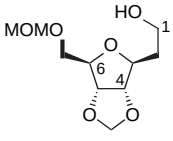
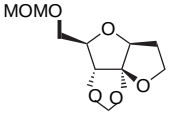
Scheme 3. Synthesis of 3,6-anhydroheptitols and 3,6-anhydrooctitols: (a) I_2, MeOH, reflux, 4 h; (b) $(MeO)_2CH_2$, P_2O_5, $CHCl_3$, rt, 3 h; (c) $LiAlH_4$, THF, rt, 1 h; (d) O_3, CH_2Cl_2/MeOH, —78 °C and then $NaBH_4$, MeOH, 0 °C; (e) NaH, BnBr, DMF, rt; (f) acid resin Dowex (50×8), MeOH, rt, 60 h followed by triphosgene, Py, CH_2Cl_2, —70 °C/rt, 30 min; (g) H_2, Pd–C, MeOH, rt, 8 h.

The IHA reactions were performed under the oxidative conditions stated in Table 1, with (diacetoxyiodo)benzene and iodine in CH_2Cl_2 at room temperature and irradiation with two 80 W tungsten filament lamps.

Since the synthesis of the 2,9-dioxabicyclo[3.3.1]nonane system has never been reported from an IHA reaction, we decided to perform preliminary experiments to verify the feasibility of this methodology. Alcohols **2** and **4** derived from L-fucose were selected since C4 abstraction is stereochemically blocked and the reaction, in a conformationally restricted $^1C_4$ pyranose ring, should proceed exclusively by abstraction of the hydrogen at C7 (entries 1 and 2). In both cases the reaction proceeded smoothly to give the expected dioxabicyclic products **27** and **28**, respectively, in moderate yield.

In entry 3 we describe an IHA reaction over a *C*-glycoside derived from D-mannose **13**. In this case, a restricted $^4C_1$ conformation of the pyranose ring allows the hydroxyl radical at C1 to abstract the hydrogen atoms located at either the C4 equatorial or C7 axial position. The hexahydro-2*H*-

Table 1. IHA reaction of 3,7-anhydrooctitols and 3,6-anhydroheptitols[a]

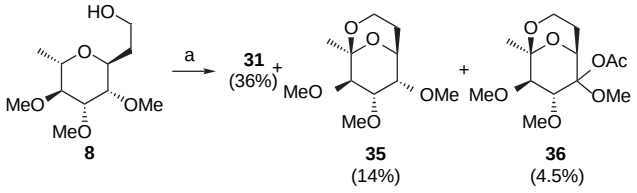
Entry	Substrate	DIB (mmol)	Time (h)	Products	Yield (%)
1	 **2** R = Ac **4** R = Me	1.5	1	 27 R = Ac 28 R = Me	47
2		1.5	1.5		57
3	 **13**	1.3	1.25	 **29**	70
4	 **10**	1.6	2.75	 **30**	48
5	 **8**	1.5	4.5	 **31**	45[b]
6	 **6**	1.3	9	 **32**	53
7	 **17**	1.5	1.5	 **33**	64
8	 **21**	1.5	1	 **34**	57

[a] Octitol or heptitol derivative (1 mmol) in CH_2Cl_2 (25 mL) containing DIB and iodine (1 mmol) was irradiated with two 80 W tungsten filament lamps at room temperature.
[b] 2,8-Anhydro-1,7-dideoxy-3,4,5-tri-*O*-methyl-b-L-*altro*-oct-2-ulopyranose (35, 11%) was also obtained.

furo[3,2-*b*]pyran derivative 29, generated by the transfer of the hydrogen at C4, was formed exclusively.

The influence of the protective group at C4 was subsequently studied in entry 4 of Table 1. The substitution of the methyl ether by an acetyl group (such as compound 10) affected the regiochemical course of the reaction; the H–C7 was now transferred and the 2,9-dioxabicyclo[3.3.1]nonane derivative 30 was obtained instead. Although the yield was moderate, no other compounds could be detected in the reaction mixture.

The results obtained with two differentially protected 3,7-anhydro-2,8-dideoxyoctitols 8 and 6 derived from L-rhamnose are shown in entries 5 and 6. The IHA reaction proceeded analogously; the ester group at C4 inhibited the reaction originated by hydrogen transfer from this position and functionalisation occurred at C7 through a seven-membered TS. The result obtained in the cyclisation of compound 8 merits a brief comment. Although the reaction gave mainly the expected product 31 corresponding to a H–C4 hydrogen transfer, a minor product 35, generated by a H–C7 hydrogen abstraction, was also obtained with a ratio 31/35¼44:1. Interestingly, compound 13 reacts more selectively than its pseudo-enantiomer 8 with which the only difference is the 8-methoxy group. Probably the presence of a supplementary b-oxygen retards further the rate of hydrogen abstraction at C7, favouring the exclusive abstraction at C4.[14] A third minor compound 36 was isolated as a single stereoisomer when $NaHCO_3$ was added to the reaction mixture, generated probably by a rarely observed double HAT as depicted in Scheme 4.[15] A possible explanation is that a preliminary H–C4 hydrogen abstraction was followed by an intermolecular nucleophilic attack of an acetoxy group, coming from the reagent (DIB), to the transient oxycarbenium intermediate generated, maintaining the primary hydroxyl group enabled to carry out a second HAT and cyclisation at C7.



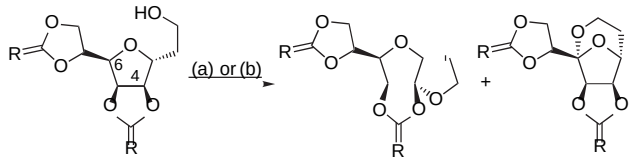
Scheme 4. (a) DIB (1.3 equiv), I_2 (1 equiv), $NaHCO_3$ (100%), CH_2Cl_2, 100 W tungsten filament lamp, 1 h.

Aware of the previously observed products of double IHA in our laboratory,[2a,b] where in the first instance a primary alkoxyl radical prefers a 1,5-HAT from a deoxygenated CH_2 position instead of a 1,6-HAT from a pseudoanomeric position similar to our cases, we decided to synthesise the precursor 17 with a deoxygenated C4 position. For this substrate, 1,6-HAT dominated, furnishing exclusively product 33 in good yield instead of 1,5-HAT, which was expected to insert an iodine atom at position C4 (entry 7). For this pyranose model, the approximation of the alkoxyl radical to the H–C7 atom in a respective 1,3-diaxial position is favoured with a smaller entropical penalty than in the case of a linear chain.

This IHA-cyclisation sequence was further extended to furanose models such as 21, 23 and 26. Model 21, derived from D-ribose, yielded smoothly the single expected compound 34 although with a quite tensioned tricyclic skeleton (entry 8). The use of acetal instead of methyl ethers as protecting group aimed to expand the scope of this methodology for further transformation of the products.

The D-mannofuranosyl derivatives 23 behaved similarly to the pyranose model 8 with poorer regiocontrol where 1,5-HAT dominated versus the 1,6-HAT, although both

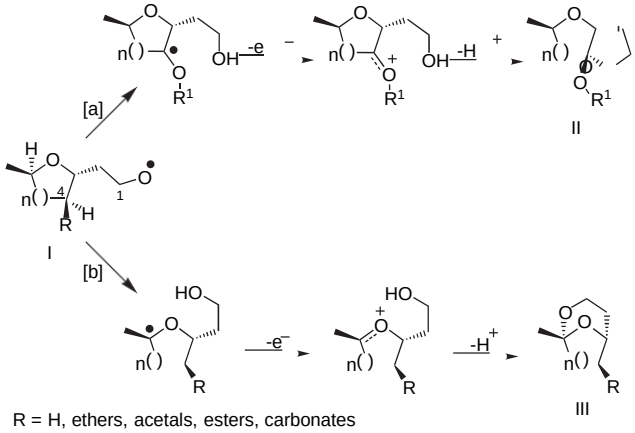
processes took place furnishing dioxabicyclic compounds 37 and 38 with a 67% yield in a ratio of (1.6:1) (Scheme 5). The regioselectivity decreased with respect to model 8 and no products of double HAT were observed. The yield of the re- action but not the products' ratio was optimised by neutral- ising the medium with a suspension of $NaHCO_3$.



Scheme 5. 1,5- versus 1,6-IHA of mannofuranosyl derivatives. Reagent and conditions: (a) 23, DIB (2 equiv), I_2 (1 equiv), $NaHCO_3$ (30%), CH_2Cl_2, 1×80 W tungsten filament lamps, rt, 1 h; (b) 26, DIB (1.5 equiv), I_2 (1 equiv), CH_2Cl_2, 1×80 W tungsten filament lamps, rt, 0.5 h, and then BF_3\$$OEt_2$ (1 equiv), CH_2Cl_2, 0 °C, 0.5h.

To our delight, we observed that upon switching the di-*O*-isopropylidene protecting group to carbonate, as depicted for model 26, the course of the reaction diverted exclusively to the 1,6-HAT at position C6 affording the product 40 in good yield. The carbonate group proved to be an EWG suf- ficient to inhibit the abstraction of H–C4 to give compound 39. This time, the reaction procedure was modified, and a second step was necessary to complete the cyclisation stage with the addition of the Lewis acid (BF_3\$$OEt_2$). Otherwise, intermediate products of acetylation at C6 were isolated.

A mechanism to explain the observed regioselectivity of these IHA reactions is depicted in Scheme 6. When the substituent at C4 was an oxygenated electron-releasing group (R¼ether or acetals), the alkoxyl radical I abstracted the hydrogen preferentially at this carbon atom through a six-membered TS. The [3.3.0] and [4.3.0] bicycle, *n*¼1 and 2 (II), respectively, were subsequently formed, after oxidation at the C4 radical and intramolecular attack of the nucleophilic alcohol (path [a], models 8, 13, 21 and 23). Neverthe- less, the situation changed dramatically when R was hydrogen or an alcohol protected with an EWG (acetate or carbonate). The electrophilic alkoxyl radical abstracted the hydrogen exclusively on the electron-richer C6 or C7, *n*¼1 or 2, respectively, despite the less favourable seven-membered TS, and the reaction went exclusively through path [b] to give the [3.3.1] or [3.2.1] bicycles (III) (models 6, 10, 17, 26).[16] No compounds derived from abstraction of the hydrogen at the C4 position were detected in this case.



Scheme 6. Mechanism of the IHA reaction.

Intermolecular nucleophilic attack of anion acetate on the transient oxycarbenium cation intermediate is possible, the acetyl derivatives being isolable in some cases.

3. Conclusions

With these examples we have now demonstrated the possibility of using an EWG substituent to avoid the intramolecular functionalisation at a favoured position and trigger the reaction in a less favoured carbon atom. Indeed, the correct choice of the C4 substituent has been the switch to either 1,5-HAT or 1,6-HAT control in the reaction and hence to the specific synthesis of hexahydrofuro[3,2-*b*]furan, hexahydro-2*H*-furo[3,2-*b*]pyran, 2,8-dioxabicyclo[3.2.1]octane or 2,9-dioxabicyclo[3.3.1]nonane systems.[17] As observed, the reaction, which may be conceptually considered to be an intramolecular glycosidation is, in reality, a selective oxidation of specific carbons of the carbohydrate skeleton and constitute a mild procedure for the synthesis of protected uloses, which are not readily accessible by other methods.

4. Experimental

4.1. General

Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature in $CHCl_3$ solutions. IR spectra were measured as thin films on NaCl plate. NMR spectra were determined at 500 MHz for ^1H and 125.7 MHz for ^{13}C in $CDCl_3$ unless otherwise stated, in the presence of TMS as internal standard. Mass spectra were determined at 70 eV. Merck silica gel 60 PF (0.063–0.2 mm) was used for column chromatography. Circular layers of 1 mm of Merck silica gel 60 PF_{254} were used on a Chromatotron for centrifugally-assisted chromatography. Commercially available reagents and solvents were of analytical grade or were purified by standard procedures prior to use. All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. The spray reagents for TLC analysis were conducted with 0.5% vanillin in H_2SO_4–EtOH (4:1) and further heating until development of colour.

4.2. Syntheses of precursors for cyclisation via IHA reaction

4.2.1. 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1,7-dideoxy-L-*glyc*-*ero*-D-*galacto*-octitol (2). General procedure for reductive ozonolysis. A solution of 3,4,5-tri-*O*-acetyl-2,6-anhydro- 1,7,8,9-tetradeoxy-L-*glycero*-D-*galacto*-non-8-enitol[13a] 1 (434 mg, 1.38 mmol) in dry CH_2Cl_2–MeOH (50 mL, 1:1) was cooled to —78 °C and ozone was introduced into the

solution until it became blue. Then nitrogen was bubbled through the solution to expel excess of ozone, and the mixture was heated to 0 °C. Afterwards, $NaBH_4$ (313 mg, 8.29 mmol) was added slowly and the solution stirred for 30 min at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. Column chromatography (hexanes–EtOAc, 25:75) of the residue afforded the title alcohol **2** (375 mg, 1.18 mmol, 85%) as a colourless oil: $[\alpha]_D$ —7.3 (*c*, 0.48); IR 3478, 2942, 1748, 1732, 1434, 1372, 1246, 1059 cm^{-1}; ^1H NMR 1.11 (3H, d, *J*¼6.3 Hz), 1.64 (1H, m), 1.93 (1H, m), 1.96 (3H, s), 2.01 (3H, s), 2.10 (3H, s), 3.69 (2H, m), 3.98 (1H, ddd, *J*¼1.9, 6.5, 6.5 Hz), 4.34 (1H, ddd, *J*¼3.3, 5.5, 5.5 Hz), 5.13 (1H, dd, *J*¼3.3, 9.9 Hz), 5.22 (1H, dd, *J*¼1.5, 5.4 Hz), 5.24 (1H, dd, *J*¼5.4, 9.9 Hz); ^{13}C NMR 15.8 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 27.8 (CH_2), 59.8 (CH_2), 66 (CH), 68 (CH), 68.5 (CH), 70.4 (CH), 70.6 (CH), 169.9 (C), 170.1 (C), 170.5 (C); MS (EI) *m/z* (rel intensity) 319 (M^++H, 1), 301 (<1), 273 (10); HRMS calcd for $C_{14}H_{23}O_8$ 319.1393, found 319.1359. Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97. Found: C, 52.72; H, 7.25.

4.2.2. 2,6-Anhydro-1,7,8,9-tetradeoxy-3,4,5-tri-*O*-methyl- L-*glycero*-D-*galacto*-non-8-enitol (3). A solution of 3,4,5-tri-*O*-acetyl-2,6-anhydro-1,7,8,9-tetradeoxy-L-*glycero*- D-*galacto*-non-8-enitol **1** (3.6 g, 11.45 mmol) in MeOH (25 mL) containing KOH (0.75 g, 0.013 mmol) was stirred at room temperature for 1 h. The reaction mixture was then neutralised with Dowex 50×8 acid resin, filtered and concentrated in vacuum to afford an oily residue, which was used in the following reaction without purification. To a suspension of NaH (1.65 g, 68.72 mmol) in dry DMF (50 mL) was added the crude triol previously obtained in DMF (50 mL) and the mixture stirred at 0 °C under nitrogen until hydrogen evolution had ceased. Then an excess of methyl iodide (4.3 mL, 69.9 mmol) was added dropwise and stirring continued at room temperature for 2 h. Excess reagent was destroyed by slow addition of MeOH and the solution poured into water and extracted with EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated in vacuum. Column chromatography (hexanes–EtOAc, 70:30) of the residue afforded the title compound **3** (1.81 g, 7.87 mmol, 68.6%) as a colourless oil: $[\alpha]_D$ —86.7 (*c*, 0.82); IR 2978, 2933, 2826, 1643, 1360, 1193, 1104 cm^{-1}; ^1H NMR 1.27 (3H, d, *J*¼6.6 Hz), 2.30 (1H, m), 2.37 (1H, m), 3.44 (3H, s), 3.48 (3H, s), 3.49 (3H, s), 3.51 (3H, m), 3.92 (1H, dq, *J*¼6.5, 3.3 Hz), 4.03 (1H, ddd, *J*¼9.1, 5.3, 3.8 Hz), 5.05 (1H, d, *J*¼10.2 Hz), 5.10 (1H, dd, *J*¼17.0, 1.5 Hz), 5.81 (1H, ddd, *J*¼17.0, 10.2, 6.8 Hz); ^{13}C NMR 15.0 (CH_3), 31.9 (CH_2), 58.3 (CH_3), 58.5 (CH_3), 59.5 (CH_3), 68.2 (CH), 70.0 (CH), 77.5 (CH), 77.6 (CH), 78.4 (CH), 116.6 (CH_2), 135.2 (CH); MS (EI) *m/z* (rel intensity) 230 (M^+, 21), 189 (29); HRMS calcd for $C_{12}H_{22}O_4$ 230.1518, found 230.1519. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.49; H, 9.65.

4.2.3. 2,6-Anhydro-1,7-dideoxy-3,4,5-tri-*O*-methyl- L-*glycero*-D-*galacto*-octitol (4). Following the general procedure for ozonolysis, 2,6-anhydro-1,7,8,9-tetradeoxy- 3,4,5-tri-*O*-methyl-L-*glycero*-D-*galacto*-non-8-enitol **3** (1.4 g, 6.08 mmol) afforded compound **4** (1.025 g, 4.38 mmol, 72%) as a colourless oil: $[\alpha]_D$ —65.5 (*c*, 0.6); IR 3444, 2936, 2829, 1732, 1651, 1463, 1362, 1362, 1194, 1102 cm^{-1}; ^1H NMR 1.28 (3H, d, *J*¼6.6 Hz), 1.73 (1H, m), 1.94 (1H, m), 3.46 (3H, s), 3.49 (3H, s), 3.51 (3H, s), 3.52 (3H, m), 3.77 (2H, m), 3.95 (1H, dq, *J*¼2.8, 6.6 Hz), 4.21 (1H, ddd, *J*¼3.6, 9.9, 9.9 Hz); ^{13}C NMR 15.4 (CH_3), 29.5 (CH_2), 58.3 (CH_3), 58.9 (CH_3), 59.9 (CH_3), 61.5 (CH_2), 68.5 (CH), 70.8 (CH), 77.7 (CH), 77.9 (CH), 78.9 (CH); MS (EI) *m/z* (rel intensity) 235 (M^++H, <1), 217 (<1), 202 (<1), 170 (1); HRMS calcd for $C_{11}H_{22}O_5$ 234.1467, found 234.1468. Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.20; H, 9.70.

4.2.4. 3,4,5-Tri-*O*-acetyl-2,6-anhydro-1,7-dideoxy-L-*glyc*- *ero*-L-*manno*-octitol (6). Following the general procedure, 3,4,5-tri-*O*-acetyl-2,6-anhydro-1,7,8,9-tetradeoxy-L-*glycero*- L-*manno*-non-8-enitol[13b] **5** (500 mg, 1.591 mmol) afforded compound **6** (361 mg, 1.13 mmol, 71%) as a colourless oil: $[\alpha]_D$ +0.6 (*c*, 0.36); IR 3479, 2940, 2889, 1746, 1372, 1228, 1048 cm^{-1}; ^1H NMR 1.21 (3H, d, *J*¼6.3 Hz), 1.77 (1H, m), 1.98 (3H, s), 2.00 (3H, m), 2.04 (3H, s), 2.08 (3H, s), 2.37 (1H, br d), 3.69–3.80 (3H, m), 4.08 (1H, ddd, *J*¼3.2, 3.2, 10.0 Hz), 4.99 (1H, dd, *J*¼8.5, 8.5 Hz), 5.14–5.17 (2H, m); ^{13}C NMR 17.4 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.1 (CH_2), 59.4 (CH_2), 68.4 (CH), 69 (CH), 70.9 (CH), 71.4 (CH), 72.6 (CH), 169.8 (C), 170 (C), 170.2 (C); MS (EI) *m/z* (rel intensity) 319 (M^++H, 1), 273 (2), 258 (1), 198 (32), 183 (48); HRMS calcd for $C_{14}H_{23}O_8$ 319.1393, found 319.1470. Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97. Found: C, 52.56; H, 7.27.

4.2.5. 2,6-Anhydro-1,7,8,9-tetradeoxy-3,4,5-tri-*O*-methyl- L-*glycero*-L-*manno*-non-8-enitol (7). A solution of 3,4,5-tri-*O*-acetyl-2,6-anhydro-1,7,8,9-tetradeoxy-L-*glycero*- L-*manno*-non-8-enitol[13b] **5** (11.5 g, 36.59 mmol) in MeOH (200 mL) containing KOH (6.0 g, 150.0 mmol) was stirred at room temperature for 1 h. The reaction mixture was then neutralised with Dowex 50×8 acid resin, filtered and concentrated in vacuum to give an oil (8.5 g), which was used in the following reaction without purification. To a suspension of NaH (5.26 g, 219.5 mmol) in dry DMF (350 mL) was added the crude triol previously obtained in DMF (150 mL) and the mixture stirred at 0 °C under nitrogen until all hydrogen evolution had ceased. Then an excess of methyl iodide (15.9 mL, 256.1 mmol) was added dropwise and stirring continued at room temperature for 3 h. Excess reagent was destroyed by slow addition of MeOH and the solution poured into water and extracted with EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated in vacuum. Column chromatography (hexanes–EtOAc, 85:15) of the residue afforded the title compound **7** (5.5 g, 23.88 mmol, 65.5%) as a colourless oil: $[\alpha]_D$ —8.2 (*c*, 0.73); IR 3077, 2977, 2933, 2825, 1644, 1455, 1382, 1196, 1102 cm^{-1}; ^1H NMR 1.28 (3H, d, *J*¼6.3 Hz), 2.27 (1H, m), 2.42 (1H, m), 3.16 (1H, dd, *J*¼7.7, 7.7 Hz), 3.43 (1H, m), 3.43 (3H, s), 3.45 (1H, m), 3.47 (3H, s), 3.52 (3H, s), 3.56 (1H, m), 4.02 (1H, dq, *J*¼6.5, 3.3 Hz), 5.09 (1H, dd, *J*¼17.0, 1.5 Hz), 5.12 (1H, d, *J*¼10.0 Hz), 5.79 (1H, ddd, *J*¼17.0, 10.2, 6.8 Hz); ^{13}C NMR 17.8 (CH_3), 34.1 (CH_2), 57.6 (2×CH_3), 60.2 (CH_3), 69.1 (CH), 71.9 (CH), 77.7 (CH), 80 (CH), 81.8 (CH), 117.1 (CH_2), 134.2 (CH); MS (EI) *m/z* (rel intensity) 189 (44), 157 (139); HRMS calcd for $C_9H_{17}O_4$ 189.1127, found 189.1155. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.61; H, 9.64.

4.2.6. 2,6-Anhydro-1,7-dideoxy-3,4,5-tri-*O*-methyl- L-*glycero*-L-*manno*-octitol (8). Following the general pro- cedure, 2,6-anhydro-1,7,8,9-tetradeoxy-3,4,5-tri-*O*-methyl- L-*glycero*-L-*manno*-non-8-enitol 7 (2.0 g, 8.685 mmol) afforded compound 8 (1.95 g, 8.32 mmol, 96%) as a colourless oil: $[a]_D$ —17.1 (*c*, 0.34); IR 3453, 2935, 2828, 1725, 1642, 1452, 1383, 1197, 1099 cm^{-1}; ^1H NMR 1.28 (3H, d, *J*¼6.5 Hz), 1.67 (1H, m), 1.89 (1H, m), 3.17 (1H, dd, *J*¼8.1, 8.1 Hz), 3.36 (1H, dd, *J*¼2.8, 3.7 Hz), 3.41 (3H, s), 3.45 (3H, s), 3.46 (3H, s), 3.47 (1H, m), 3.64 (1H, dq, *J*¼6.5, 8.1 Hz), 3.73 (2H, t, *J*¼6.0 Hz), 4.11 (1H, ddd, *J*¼3.7, 8.2, 8.2 Hz); ^{13}C NMR 17.5 (CH_3), 31.7 (CH_2), 57.6 (CH_3), 57.8 (CH_3), 59.7 (CH_3), 60.6 (CH_2), 69.3 (CH), 70.7 (CH), 78.6 (CH), 79 (CH), 81.1 (CH); MS (EI) *m*/*z* (rel intensity) 234 (M^+, 1), 202 (2), 189 (1); HRMS calcd for $C_{11}H_{22}O_5$ 234.1467, found 234.1487. Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.34; H, 9.45.

4.2.7. 1,3,4,5-Tetra-*O*-acetyl-2,6-anhydro-7-deoxy- D-*glycero*-D-*manno*-octitol (10). Following the general procedure, 1,3,4,5-tetra-*O*-acetyl-2,6-anhydro-7,8,9-trideoxy- D-*glycero*-D-*manno*-non-8-enitol[18] 9 (240 mg, 8.685 mmol) afforded compound 10 (212 mg, 0.56 mmol, 87%) as a colourless oil: $[a]_D$ —3.1 (*c*, 0.64); IR 3542, 2960, 2888, 1756, 1651, 1434, 1372, 1242, 1049 cm^{-1}; ^1H NMR 1.75 (1H, m), 1.92 (1H, m), 1.98 (3H, s), 2.01 (3H, s), 3.66 (2H, m), 3.90 (1H, ddd, *J*¼2.8, 7.5, 7.5 Hz), 4.00 (1H, dd, *J*¼2.8, 12.2 Hz), 4.13 (1H, ddd, *J*¼3.8, 10.3, 10.3 Hz), 4.41 (1H, dd, *J*¼7.5, 12.2 Hz), 5.06 (1H, dd, *J*¼7.5, 7.5 Hz), 5.09 (1H, dd, *J*¼3.8, 3.8 Hz), 5.18 (1H, dd, *J*¼3.8, 7.5 Hz); ^{13}C NMR 21.0 (2×CH_3), 21.1 (CH_3), 21.2 (CH_3), 32.0 (CH_2), 59.6 (CH_2), 62.4 (CH_2), 67.7 (CH), 68.8 (CH), 70.7 (CH), 71.7 (CH), 72.3 (CH), 170.2 (C), 170.5 (2×C), 171.2 (C); MS (EI) *m*/*z* (rel intensity) 377 (M^+—H, <1), 359 (<1), 345 (<1), 317 (1), 214 (73); HRMS calcd for $C_{16}H_{25}O_{10}$ 377.1448, found 377.1454. Anal. Calcd for $C_{16}H_{24}O_{10}$: C, 51.06; H, 6.43. Found: C, 50.70; H, 6.75.

4.2.8. 2,6-Anhydro-7,8,9-trideoxy-1,3,4,5-tetra-*O*-methyl- D-*glycero*-D-*manno*-non-8-enitol (12). To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-D-mannopyranose[19] 11 (104 mg, 0.374 mmol) in dry MeCN (1.5 mL) were added allyltrimethylsilane (0.176 mL, 1.122 mmol) and BF_3\$$OEt_2$ (0.114 mL, 0.935 mmol) at 0 °C. After 30 min at room tem- perature, the reaction mixture was poured into ice-water and extracted with EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography (hexanes–EtOAc, 1:1) of the residue af- forded the title compound 12 (82 mg, 0.31 mmol, 83%) as a colourless oil: $[a]_D$ +15.6 (*c*, 0.52); ^1H NMR 2.33 (1H, m), 2.41 (1H, m), 3.37 (3H, s), 3.40 (3H, s), 3.41 (1H, m), 3.43 (1H, m), 3.47 (3H, s), 3.47 (3H, s), 3.57 (1H, m), 3.58 (2H, d, *J*¼4.7 Hz), 3.63 (1H, m), 4.02 (1H, ddd, *J*¼1.9, 7.2, 7.2 Hz), 5.07 (1H, d, *J*¼9.9 Hz), 5.10 (1H, d, *J*¼17.1 Hz), 5.80 (1H, dddd, *J*¼7.3, 7.3, 10.0, 17.1 Hz); ^{13}C NMR 34.1 (CH_2), 57.4 (CH_3), 57.6 (CH_3), 58.9 (CH_3), 59.6 (CH_3), 71.5 (CH_2), 71.8 (CH), 72.6 (CH), 76.4 (CH), 77.1 (CH), 79.3 (CH), 117.1 (CH_2), 134.1 (CH); MS (EI) *m*/*z* (rel intensity) 219 (M^+—C_3H_5, 35), 187 (63), 183 (15); HRMS calcd for $C_{10}H_{19}O_5$ 219.1232, found 219.1218. Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.84; H, 9.14.

4.2.9. 2,6-Anhydro-7-deoxy-1,3,4,5-tetra-*O*-methyl- D-*glycero*-D-*manno*-octitol (13). Following the general procedure, 2,6-anhydro-7,8,9-trideoxy-1,3,4,5-tetra-*O*-methyl- D-*glycero*-D-*manno*-non-8-enitol 12 (500 mg, 1.921 mmol) afforded compound 13 (398 mg, 1.51 mmol, 79%) as a colourless oil: $[a]_D$ +19.2 (*c*, 0.24); IR 3471, 2930, 1738, 1454, 1093 cm^{-1}; ^1H NMR 1.63 (1H, m), 1.84 (1H, m), 3.29 (3H, s), 3.30 (1H, m), 3.32 (1H, m), 3.35 (3H, s), 3.39 (3H, s), 3.40 (3H, s), 3.45 (1H, m), 3.48 (1H, dd, *J*¼7.2, 10.0 Hz), 3.56 (1H, dd, *J*¼8.1, 10.0 Hz), 3.66 (1H, m), 3.68 (2H, t, *J*¼5.7 Hz), 4.06 (1H, ddd, *J*¼4.7, 9.5, 9.5 Hz); ^{13}C NMR 31.7 (CH_2), 57.5 (CH_3), 58.2 (CH_3), 58.9 (CH_3), 59.4 (CH_3), 60.5 (CH_2), 71.2 (CH), 71.4 (CH_2), 72.3 (CH), 76.6 (CH), 78.4 (CH), 78.9 (CH); MS (EI) *m*/*z* (rel intensity) 264 (M^+, <1), 232 (1), 219 (4), 200 (1), 187 (35); HRMS calcd for $C_{12}H_{24}O_6$ 264.1573, found 264.1530. Anal. Calcd for $C_{12}H_{24}O_6$: C, 54.53; H, 9.15. Found: C, 54.58; H, 9.18.

4.2.10. 6,7,9-Tri-*O*-acetyl-4,8-anhydro-1,2,3,5-tetra- deoxy-D-*manno*-non-1-enitol (15). To a solution of compound 14[20] (6.2 g, 18.6 mmol) in dry MeCN (60 mL) were added allyltrimethylsilane (9.3 mL, 58.5 mmol) and BF_3\$$OEt_2$ (6.2 mL, 48.9 mmol) at 0 °C. After 1 h at room temperature, the reaction mixture was poured into ice-water and extracted with EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography (hexanes–EtOAc, 7:3) of the residue afforded the title compound 15 (4.5 g, 14.3 mmol, 77%) as a colourless oil: $[a]_D$ +38.0 (*c*, 0.30); IR (CCl_4) 3080, 2955, 1748, 1643, 1433, 1367, 1231, 1050 cm^{-1}; ^1H NMR (400 MHz) 1.85 (1H, ddd, *J*¼4.8, 8.9, 13.6 Hz), 2.03 (1H, m), 2.05 (3H, s), 2.07 (3H, s), 2.08 (3H, s), 2.27 (1H, m), 2.51 (1H, m), 3.91 (1H, ddd, *J*¼3.3, 6.7, 6.7 Hz), 4.04 (1H, m), 4.08 (1H, dd, *J*¼3.4, 11.9 Hz), 4.38 (1H, dd, *J*¼6.3, 11.9 Hz), 4.86 (1H, dd, *J*¼7.3, 7.3 Hz), 5.08–5.16 (3H, m), 5.78 (1H, dddd, *J*¼7.0, 7.0, 10.2, 17.1 Hz); ^{13}C NMR (100.6 MHz) 20.8 (3×CH_3), 32.0 (CH_2), 36.7 (CH_2), 62.1 (CH), 68.7 (CH), 68.7 (CH_2), 69.8 (CH), 70.7 (CH), 117.6 (CH_2), 133.9 (CH), 169.7 (C), 169.9 (C), 170.6 (C); MS (EI) *m*/*z* (rel intensity) (FAB) 337 (M^++Na, 7), 315 (M^++H, 75); HRMS calcd for $C_{15}H_{22}NaO_7$ 337.1263, found 337.1258. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.05. Found: C, 57.40; H, 7.33.

4.2.11. 4,8-Anhydro-1,2,3,5-tetradeoxy-6,7,9-tri-*O*-meth- yl-D-*manno*-non-1-enitol (16). Compound 15 (4.3 g, 13.7 mmol) was stirred in a KOH–MeOH 3% solution (50 mL) at room temperature for 12 h. The reaction mixture was then neutralised with Dowex 50×8 acid resin, filtered and concentrated in vacuum to give an oily residue, which was used in the following reaction without purification. To a suspension of NaH (1.78 g, 74.2 mmol) in dry DMF (70 mL) was added the crude tetrol previously obtained in DMF (65 mL) and the mixture stirred at 0 °C under nitrogen until all hydrogen evolution had ceased. Then an excess of methyl iodide (5.2 mL, 83.2 mmol) was added dropwise and stirring continued at room temperature for 3 h. Excess reagent was destroyed by slow addition of MeOH and the solution poured into water and extracted with EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated in vacuum. Column chromatography (hexanes–EtOAc, 6:4) of the residue afforded 16 (2.8 g, 12.2 mmol, 88%) as

a colourless oil: [a]$_D$ +42.2 (*c*, 0.40); IR (CCl_4) 3078, 2981, 2929, 2822, 1642, 1446, 1377, 1193, 1107 cm^{-1}; ^{1}H NMR (400 MHz) 1.65 (1H, ddd, *J*¼4.8, 9.0, 13.5 Hz), 1.93 (1H, ddd, *J*¼4.4, 8.9, 8.9 Hz), 2.23 (1H, m), 2.45 (1H, m), 3.13 (1H, dd, *J*¼7.1, 7.1 Hz), 3.39 (3H, s), 3.41 (3H, s), 3.48 (1H, m), 3.49 (3H, s), 3.55 (1H, m), 3.62 (1H, dd, *J*¼4.9, 12.3 Hz), 3.65 (1H, m), 4.00 (1H, dddd, *J*¼4.7, 4.7, 7.4, 7.4 Hz), 5.04–5.11 (2H, m), 5.78 (1H, dddd, *J*¼6.9, 6.9, 10.1, 17.1 Hz); ^{13}C NMR (100.1 MHz) 32.0 (CH_2), 37.2 (CH_2), 57.1 (CH_3), 59.3 (CH_3), 59.8 (CH_3), 70.4 (CH), 71.8 (CH_2), 72.7 (CH), 78.2 (CH), 78.9 (CH), 117.2 (CH_2), 134.9 (CH); MS (EI) *m/z* (rel intensity) (FAB) 253 (M^++Na, 1), 231 (M^++H, 2); HRMS calcd for $C_{12}H_{22}NaO_4$ 253.1416, found 253.1441. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.41; H, 9.33.

4.2.12. 2,6-Anhydro-5,7-dideoxy-1,3,4-tri-*O*-methyl-D-*manno*-octitol (17). Following the general procedure for reductive ozonolysis, compound 16 (2.4 g, 10.6 mmol) afforded compound 13 (2.18 g, 9.3 mmol, 88%) as a colourless oil: [a]$_D$ +34.2 (*c*, 0.26); IR 3638, 3530, 2929, 2822, 1455, 1385, 1191, 1113 cm^{-1}; ^{1}H NMR 1.43 (1H, m), 1.56 (1H, ddd, *J*¼4.9, 8.2, 13.2 Hz), 1.73–1.86 (2H, m), 2.92 (1H, dd, *J*¼6.4, 6.4 Hz), 3.01 (1H, br s), 3.24 (3H, s), 3.26 (3H, s), 3.33 (3H, s), 3.34 (1H, m), 3.39 (1H, dd, *J*¼3.6, 10.2 Hz), 3.53 (1H, dd, *J*¼6.7, 10.0 Hz), 3.57 (2H, t, *J*¼6.0 Hz), 3.61 (1H, ddd, *J*¼3.5, 6.5, 6.5 Hz), 3.99 (1H, dddd, *J*¼4.8, 4.8, 4.8, 9.8 Hz); ^{13}C NMR 32.4 (CH_2), 34.5 (CH_2), 56.7 (CH_3), 58.8 (CH_3), 59.1 (CH_3), 60.2 (CH_2), 68.6 (CH), 71.2 (CH_2), 72.1 (CH), 77.3 (CH), 78.2 (CH); MS (FAB) *m/z* (rel intensity) 257 (M^++Na, 5), 235 (M^++H, 100); HRMS calcd for $C_{11}H_{22}NaO_5$ 257.1365, found 257.1340. Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.27; H, 9.48.

4.2.13. Methyl 3,6-anhydro-2-deoxy-D-*allo*-heptonate (19). A solution of 18[21] (214 mg, 0.44 mmol) and iodine (38 mg, 0.15 mmol) in methanol was refluxed for 4 h. A saturated solution of $Na_2S_2O_3$ was added dropwise while the reaction mixture was stirred until complete reduction of the remaining iodine and the solvent was removed in vacuum. Purification of the residue by column chromatography ($CHCl_3$–MeOH, 9:1) gave compound 19 (81.5 mg, 0.40 mmol, 90%) as a colourless oil: [a]$_D$ —2.3 (*c*, 2.05); IR (CCl_4) 3360, 2931, 1732, 1652, 1442, 1285, 1108, 1040 cm^{-1}; ^{1}H NMR 2.52 (1H, dd, *J*¼8.4, 15.4 Hz), 2.67 (1H, dd, *J*¼4.3, 15.5 Hz), 3.54 (1H, dd, *J*¼4.5, 12.0 Hz), 3.63 (1H, dd, *J*¼3.6, 12.0 Hz), 3.67 (3H, s), 3.76 (1H, dd, *J*¼6.0, 6.0 Hz), 4.80 (1H, ddd, *J*¼4.4, 4.4, 8.1 Hz), 3.95 (1H, dd, *J*¼4.4, 5.6 Hz), 4.09 (1H, m), 4.83 (3H, br s); ^{13}C NMR 37.7 (CH_2), 50.7 (CH_3), 61.9 (CH_2), 71.0 (CH), 74.4 (CH), 78.8 (CH), 84.8 (CH), 172.0 (C); MS (EI) *m/z* (rel intensity) (FAB) 229 (M^++Na, 100), 207 (M^++H, 100). Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.26; H, 7.22.

4.2.14. Methyl 3,6-anhydro-2-deoxy-7-*O*-(methoxymethyl)-4,5-*O*-methylen-D-*allo*-heptonate (20). To a solution of compound 19 (1.9 g, 9.4 mmol) in dry $CHCl_3$ (55 mL) was added an excess of dimethoxymethane (55 mL, 632.5 mmol), phosphorous pentoxide (28 g, 197 mmol) and stirred at room temperature under nitrogen atmosphere for 3 h. The reaction mixture was cooled to 0 °C and a saturated solution of Na_2CO_3 was added dropwise with vigorous stirring until the effervescence disappeared. The mixture was poured into water, extracted with CH_2Cl_2 and the organic layer was dried over Na_2SO_4 and concentrated in vacuum. Column chromatography of the residue (hexanes–EtOAc, 6:4) gave compound 20 (1.9 g, 7.4 mmol, 79%) as a yellow oil: [a]$_D$ —0.8 (*c*, 0.13); IR (CCl_4) 2955, 1747, 1438, 1393, 1343, 1036 cm^{-1}; ^{1}H NMR (400 MHz) 2.72 (2H, d, *J*¼6.3 Hz), 3.37 (3H, s), 3.66–3.73 (2H, m), 3.71 (3H, s), 4.03 (1H, ddd, *J*¼4.5, 4.5, 4.5 Hz), 4.23 (1H, ddd, *J*¼4.8, 6.3, 6.3 Hz), 4.49 (1H, dd, *J*¼4.8, 6.9 Hz), 4.56 (1H, dd, *J*¼4.8, 6.9 Hz), 4.66 (2H, s), 5.08 (1H, s), 5.13 (1H, s); ^{13}C NMR (100.6 MHz) 38.5 (CH_2), 52.2 (CH_3), 55.7 (CH_3), 68.1 (CH_2), 79.5 (CH), 81.9 (2×CH), 84.1 (CH), 95.8 (CH_2), 97.1 (CH_2), 171.1 (C); MS (EI) *m/z* (rel intensity) 261 (M^+—H, 1), 247 (1), 231 (6); HRMS calcd for $C_{11}H_{17}O_7$ 261.0974, found 261.1002. Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.38; H, 6.92. Found: C, 50.11; H, 7.10.

4.2.15. 3,6-Anhydro-2-deoxy-7-*O*-(methoxymethyl)-4,5-*O*-methylen-D-*allo*-heptitol (21). To a solution of compound 20 (992 mg, 3.78 mmol) in dry THF (100 mL) was added $LiAlH_4$ (574 mg, 15.1 mmol) in small portions and stirred for 1 h at room temperature under nitrogen atmosphere. The excess hydride was destroyed by adding a saturated aqueous solution of Na_2SO_4, and the white salts were separated by filtration. The solvent was evaporated in vacuo and the residue purified by column chromatography (hexanes–EtOAc, 2:8) to afford compound 21 (723 mg, 3.09 mmol, 82%) as a colourless oil: [a]$_D$ —5.5 (*c*, 0.20); IR 3637, 3549, 2941, 2884, 1424, 1214, 1154, 1081, 1043 cm^{-1}; ^{1}H NMR 1.84–1.97 (2H, m), 2.32 (1H, br s, OH), 3.34 (3H, s), 3.66 (1H, dd, *J*¼5.2, 11.0 Hz), 3.71 (1H, dd, *J*¼3.8, 11.0 Hz), 3.77 (2H, t, *J*¼5.7 Hz), 3.91–3.96 (2H, m), 4.36 (1H, dd, *J*¼5.5, 6.9 Hz), 4.48 (1H, dd, *J*¼5.0, 6.9 Hz), 4.63 (2H, s), 5.02 (1H, s), 5.10 (1H, s); ^{13}C NMR 35.5 (CH_2), 55.4 (CH_3), 60.1 (CH_2), 67.5 (CH_2), 81.2 (3×CH), 84.0 (CH), 95.3 (CH_2), 96.6 (CH_2); MS *m/z* (rel intensity) 219 (M^+ —CH_3, 1), 203 (7); HRMS calcd for $C_9H_{15}O_6$ 219.087, found 219.0827. Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.21; H, 8.09.

4.2.16. 3,6-Anhydro-7-deoxy-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-octitol (23). Following the general procedure for reductive ozonolysis, compound 22[2a] (154 mg, 0.54 mmol) afforded compound 23 (140 mg, 0.49 mmol, 90%) as a colourless oil: [a]$_D$ –17 (*c*, 0.6); IR 3552, 2987, 2873, 1350, 1215 cm^{-1}; ^{1}H NMR 1.30 (3H, s), 1.34 (3H, s), 1.40 (3H, s), 1.46 (3H, s), 1.58 (1H, m), 1.73 (1H, m), 2.20 (1H, br s, OH), 3.74 (2H, m), 3.81 (1H, dd, *J*¼4.2, 6.9 Hz), 3.96 (1H, dd, *J*¼4.9, 8.7 Hz), 4.05 (1H, dd, *J*¼6.4, 8.7 Hz), 4.23 (1H, ddd, *J*¼0.0, 4.4, 10.7 Hz), 4.36 (1H, ddd, *J*¼6.5, 6.5, 6.5 Hz), 4.51 (1H, dd, *J*¼0.0, 6.0 Hz), 4.73 (1H, dd, *J*¼3.8, 6.0 Hz); ^{13}C NMR 24.6 (CH_3), 25.1 (CH_3), 26.0 (CH_3), 26.7 (CH_3), 32.5 (CH_2), 60.3 (CH_2), 66.6 (CH_2), 73.3 (CH), 80.0 (CH), 80.5 (CH), 83.1 (CH), 85.4 (CH), 109.0 (C), 112.6 (C); MS (EI) *m/z* (rel intensity) 273 (M^+—CH_3, 50), 215 (22), 101 (100); HRMS calcd for $C_{13}H_{21}O_6$ 273.1338, found 273.1344. Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.25; H, 8.58.

4.2.17. 3,6-Anhydro-1-*O*-benzyl-2-deoxy-4,5:7,8-di-*O*- isopropylidene-D-*manno*-octitol (24). Alcohol 23 (1.64 g, 5.73 mmol) and BnBr (1.36 mL, 11.5 mmol) were dissolved in dry DMF (15 mL) under argon. NaH (60% in oil) (458 mg, 11.5 mmol) was added in portions at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was quenched with MeOH (5 mL), poured into an aqueous sat. solution of NH_4Cl and extracted with ether. The organic phase was separated, dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. Column chromatography (hexanes–EtOAc, 7:3) of the residue afforded compound 24 (1.98 g, 5.24 mmol, 92%) as a colourless oil: $[a]_D$ +18 (*c*, 0.5, EtOAc); ^{1}H NMR 1.33 (3H, s), 1.37 (3H, s), 1.44 (3H, s), 1.50 (3H, s), 1.73 (2H, ddd, *J*¼6.2, 6.4, 8.1 Hz), 3.55 (2H, dd, *J*¼6.5, 6.5 Hz), 3.72 (1H, dd, *J*¼3.7, 7.7 Hz), 4.01 (1H, dd, *J*¼4.5, 8.7 Hz), 4.09 (1H, dd, *J*¼6.4, 8.7 Hz), 4.24 (1H, dd, *J*¼7.4, 7.4 Hz), 4.39 (1H, ddd, *J*¼4.4, 6.2, 7.7 Hz), 4.50 (2H, s), 4.59 (1H, dd, *J*¼0.8, 6.1 Hz), 4.75 (1H, dd, *J*¼3.8, 6.2 Hz), 7.27–7.38 (5H, m); ^{13}C NMR 25.1 (CH_3), 25.6 (CH_3), 26.5 (CH_3), 27.3 (CH_3), 67.2 (CH_2), 67.4 (CH_2), 73.5 (CH_2), 73.9 (CH), 80.6 (CH), 81.1 (CH), 82.0 (CH), 85.9 (CH), 109.5 (C), 112.9 (C), 127.9 (3×CH), 128.7 (2×CH), 138.7 (C); MS (FAB^+) *m*/*z* (rel intensity) 401 (M^++Na, 1), 379 (M^++H, 4), 363 (6); HRMS calcd for $C_{21}H_{31}O_6$ 379.2121, found 379.2117. Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99. Found: C, 66.70; H, 7.91.

4.2.18. 3,6-Anhydro-1-*O*-benzyl-2-deoxy-4,5:7,8-di-*O*- oxomethylene-D-*manno*-octitol (25). Acid resin Dowex (50×8) (29.0 g, 9 equiv) was added to a solution of compound 24 (1.95 g, 5.15 mmol) in methanol (100 mL) and stirred for 60 h at room temperature. The reaction mixture was filtered and the solvent removed under vacuum. The residue (1.58 g) and pyridine (6.10 g, 77 mmol) dissolved in dry CH_2Cl_2 (21 mL) was added slowly to a solution of triphosgene (3.36 g, 11.3 mmol) in CH_2Cl_2 (15 mL) stirred at —70 °C. After the addition was completed, the reaction mixture was allowed to warm up to room temperature. The resulting solution was poured into aqueous sat. solution of NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with 1 N HCl, aqueous sat. solution of $NaHCO_3$ and brine successively, dried over Na_2SO_4 and concentrated under vacuum. Column chromatography (hexanes–EtOAc, 4:6) of the residue afforded compound 25 (1.68 g, 4.80 mmol, 93%) as a white crystalline compound: $[a]_D$ +13 (*c*, 0.5, EtOAc); mp 118–120 °C (EtOAc–*n*-pentane); ^{1}H NMR 1.81 (2H, m), 3.56 (2H, dd, *J*¼5.8, 5.8 Hz), 4.13 (1H, dd, *J*¼2.9, 5.6 Hz), 4.40 (1H, dd, *J*¼6.4, 8.7 Hz), 4.46 (1H, d, *J*¼11.7 Hz), 4.49 (1H, d, *J*¼11.7 Hz), 4.52 (1H, dd, *J*¼8.6, 8.6 Hz), 4.55 (1H, dd, *J*¼7.0, 7.0 Hz), 4.93 (1H, ddd, *J*¼5.6, 6.4, 8.2 Hz), 5.14 (1H, d, *J*¼9.8 Hz), 5.17 (1H, d, *J*¼9.8 Hz), 7.28–7.38 (5H, m); ^{13}C NMR 30.9 (CH_2), 66.0 (CH_2), 66.5 (CH_2), 73.5 (CH), 73.7 (CH_2), 79.2 (CH), 80.4 (CH), 83.0 (CH), 84.5 (CH), 128.2 (2×CH, 128.4 (CH), 128.9 (2×CH), 138.0 (C), 153.8 (C), 154.6 (C); MS (FAB^+) *m*/*z* (rel intensity) 373 (M^++Na, 7), 349 (M^+—H, 11); HRMS calcd for $C_{17}H_{17}O_8$ 349.0923, found 349.0915. Anal. Calcd for $C_{17}H_{18}O_8$: C, 58.28; H, 5.18. Found: C, 58.17; H, 5.45.

4.2.19. 3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-oxomethylene-D-*manno*-octitol (26). Benzyl ether 25 (170 mg, 0.49 mmol) was dissolved in MeOH (4 mL) and Pd black (17 mg) was added. The reaction vessel was purged from air and stirred for 8 h under a hydrogen atmosphere. Filtration through a Celite plug eluted with MeOH and concentration afforded the alcohol 26 (127 mg, 0.49 mmol, quant.) as a colourless crystalline compound: $[a]_D$ —7 (*c*, 0.4, EtOAc); mp 116–117 °C (EtOAc–*n*-pentane); ^{1}H NMR 1.80 (2H, ddd, *J*¼5.8, 6.0, 7.0 Hz), 3.82 (2H, dd, *J*¼5.7, 5.7 Hz), 4.28 (1H, dd, *J*¼3.6, 4.9 Hz), 4.51 (1H, dd, *J*¼6.2, 8.9 Hz), 4.60 (1H, dd, *J*¼8.4, 8.4 Hz), 4.64 (1H, dd, *J*¼7.3, 7.3 Hz), 5.01 (1H, ddd, *J*¼5.1, 6.2, 8.2 Hz), 5.20 (1H, d, *J*¼6.6 Hz), 5.27 (1H, dd, *J*¼3.7, 7.1 Hz); ^{13}C NMR (CD_3OD) 33.7 (CH_2), 59.0 (CH_2), 67.8 (CH_2), 75.5 (CH), 79.9 (CH), 82.2 (CH), 83.6 (CH), 86.1 (CH), 155.9 (C), 156.8 (C); MS (FAB^+) *m*/*z* (rel intensity) 283 (M^++Na, 38), 261 (M^++H, 100); HRMS calcd for $C_{10}H_{13}O_8$ 261.0610, found 261.0602. Anal. Calcd for $C_{10}H_{13}O_8$: C, 46.16; H, 4.65. Found: C, 45.91; H, 4.82.

4.3. IHA reaction of 3,7-anhydrooctitols and 3,6-anhydroheptitols

4.3.1. General procedure. A solution of 3,7-anhydrooctitols or 3,6-anhydroheptitols (1 mmol) in dry CH_2Cl_2 (25 mL) containing (diacetoxyiodo)benzene (DIB) and iodine (1 mmol) was irradiated with two 80 W tungsten filament lamps at room temperature under nitrogen until the reaction was completed. The reaction mixture was then poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried and concentrated under vacuum. Chromatotron chromatography of the residue (hexanes–EtOAc mixtures) afforded the anhydrosugars. Equivalents of DIB used and reaction times are shown in Table 1 and Schemes 4 and 5.

4.3.2. Tri-*O*-acetyl-2,8-anhydro-1,7-dideoxy-b-L-*gulo*- oct-2-ulopyranose (27). Following the general procedure, precursor 2 (33 mg, 0.104 mmol) afforded the anhydrosugar 27 (15 mg, 0.05 mmol, 47%) as a colourless oil: $[a]_D$ —18.1 (*c*, 0.16); IR 2978, 1732, 1715, 1372, 1234, 1064 cm^{-1}; ^{1}H NMR 1.25 (3H, s), 1.90 (1H, m), 1.98 (3H, s), 2.04 (3H, s), 2.11 (1H, m), 2.14 (3H, s), 3.76 (1H, dd, *J*¼7.1, 10.7 Hz), 3.87 (1H, ddd, *J*¼4.7, 11.3, 11.3 Hz), 4.51 (1H, ddd, *J*¼3.2, 5.9, 9.6 Hz), 5.22 (1H, d, *J*¼4.1 Hz), 5.24 (1H, dd, *J*¼5.9, 10.5 Hz), 5.68 (1H, dd, *J*¼4.0, 10.5 Hz); ^{13}C NMR (50.3 MHz) 20.7 (3×CH_3), 22.2 (CH_3), 23.6 (CH_2), 55.9 (CH_2), 65.9 (CH), 67.1 (CH), 67.8 (CH), 71.4 (CH), 98.3 (C), 169.7 (C), 169.9 (C), 170.1 (C); MS (EI) *m*/*z* (rel intensity) 316 (M^+, 1), 257 (17), 214 (5), 196 (16); HRMS calcd for $C_{14}H_{20}O_8$ 316.1158, found 316.1175. Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.06; H, 6.70.

4.3.3. 2,8-Anhydro-1,7-dideoxy-3,4,5-tri-*O*-methyl-b- L-*gulo*-oct-2-ulopyranose (28). Following the general procedure, precursor 4 (131 mg, 0.559 mmol) afforded the anhydrosugar 28 (75 mg, 0.32 mmol, 57%) as a colourless oil: $[a]_D$ —30.5 (*c*, 0.59); IR 2936, 2826, 1462, 1377, 1223, 1102, 1074 cm^{-1}; ^{1}H NMR 1.33 (3H, s), 1.76 (1H, m), 2.06 (1H, m), 3.37 (1H, d, *J*¼2.8 Hz), 3.4 (3H, s), 3.5 (3H, s), 3.56 (3H, s), 3.60 (1H, dd, *J*¼3.3, 9.9 Hz), 3.62 (1H, d, *J*¼6.1 Hz), 3.79 (1H, dd, *J*¼3.3, 9.9 Hz), 3.84 (1H, ddd, *J*¼4.3, 9.9, 9.9 Hz), 4.37 (1H, ddd, *J*¼3.8, 6.1,

10.0 Hz); ^{13}C NMR 22.6 (CH_3), 23.3 (CH_2), 55.9 (CH_2), 58.1 (CH_3), 58.4 (CH_3), 61.6 (CH_3), 66.3 (CH), 77 (CH), 79 (CH), 80.2 (CH), 99.5 (C); MS (EI) *m/z* (rel intensity) 231 (M^+, <1), 203 (4), 187 (4); HRMS calcd for $C_{11}H_{19}O_5$ 231.1232, found 231.1291. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.54; H, 9.02.

4.3.4. Methyl 3,7-anhydro-2-deoxy-5,6,8-tri-*O*-methyl-a- D-*manno*-oct-4-ulofuranoside (29). Following the general procedure, precursor 13 (249 mg, 0.942 mmol) afforded the anhydrosugar 29 (174 mg, 0.66 mmol, 70%) as a colour- less oil: $[a]_D$ +13.3 (*c*, 0.42); IR 2933, 2828, 1740, 1456, 1194, 1106 cm^{-1}; ^{1}H NMR 1.87 (1H, m), 2.27 (1H, m), 3.17 (1H, dd, *J*¼2.6, 6.9 Hz), 3.19 (3H, s), 3.30 (3H, s), 3.36 (3H, s), 3.42 (1H, dd, *J*¼3.3, 10.4 Hz), 3.45 (3H, s), 3.52 (1H, dd, *J*¼7.2, 10.4 Hz), 3.54 (1H, d, *J*¼2.6 Hz), 3.65 (1H, ddd, *J*¼3.4, 6.9, 6.9 Hz), 3.75 (1H, ddd, *J*¼6.4, 8.8, 8.8 Hz), 4.05 (1H, ddd, *J*¼5.8, 8.7, 8.7 Hz), 4.16 (1H, br d, *J*¼5.6 Hz); ^{13}C NMR 31.3 (CH_2), 48.4 (CH_3), 57.8 (CH_3), 58.1 (CH_3), 59.1 (CH_3), 66.4 (CH_2), 72.1 (CH_2), 72.3 (CH), 76.5 (CH), 76.9 (CH), 77.2 (CH), 105.1 (C); MS (EI) *m/z* (rel intensity) 262 (M^+, 17), 231 (1), 217 (23); HRMS calcd for $C_{12}H_{22}O_6$ 262.1416, found 262.1379. Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 55.27; H, 8.10.

4.3.5. 1,3,4,5-Tetra-*O*-acetyl-2,8-anhydro-7-deoxy-b- D-*altro*-oct-2-ulopyranose (30). Following the general procedure, precursor 10 (75 mg, 0.2 mmol) afforded the an- hydrosugar 30 (36 mg, 0.096 mmol, 48%) as a colourless oil: $[a]_D$ —36.9 (*c*, 0.36); IR 2966, 1747, 1434, 1372, 1225, 1056 cm^{-1}; ^{1}H NMR 1.97 (1H, m), 1.99 (3H, s), 2.07 (3H, s), 2.08 (1H, m), 2.11 (3H, s), 2.16 (3H, s), 3.92 (1H, ddd, *J*¼2.7, 10.8, 10.8 Hz), 3.93 (1H, d, *J*¼12.0 Hz), 3.98 (1H, ddd, *J*¼4.7, 11.2, 11.2 Hz), 4.17 (1H, d, *J*¼12.0 Hz), 4.36 (1H, ddd, *J*¼2.0, 3.7, 11.1 Hz), 5.25 (1H, dd, *J*¼2.1, 3.9 Hz), 5.38 (1H, d, *J*¼10.3 Hz), 5.66 (1H, dd, *J*¼3.9, 10.3 Hz); ^{13}C NMR 20.6 (2×CH_3), 20.7 (CH_3), 20.9 (CH_3), 26.1 (CH_2), 57.7 (CH_2), 63.4 (CH_2), 67.2 (CH), 67.8 (CH), 69.6 (CH), 71.9 (CH), 97.7 (C), 169.8 (C), 170.1 (C), 170.3 (C), 170.5 (C); MS (EI) *m/z* (rel intensity) 375 (M^++H, 1), 331 (2), 315 (14); HRMS calcd for $C_{16}H_{23}O_{10}$ 375.1291, found 375.1266. Anal. Calcd for $C_{16}H_{22}O_{10}$: C, 51.33; H, 5.92. Found: C, 51.48; H, 6.11.

4.3.6. Methyl 3,7-anhydro-2,8-dideoxy-5,6-di-*O*-methyl- a-L-*manno*-oct-4-ulofuranoside (31) and 2,8-anhydro- 1,7-dideoxy-3,4,5-tri-*O*-methyl-b-L-*altro*-oct-2-ulopyra- nose (35). Following the general procedure, precursor 8 (63 mg, 0.269 mmol) afforded the anhydrosugar 35 (7 mg, 0.03 mmol, 11%), and anhydrosugar 31 (28 mg, 0.12 mmol, 44.5%). Compound 35: crystalline compound, mp 80.5–82.5 °C; $[a]_D$ +97.8 (*c*, 0.45); IR 2940, 2885, 2831, 1469, 1378, 1119, 1064 cm^{-1}; ^{1}H NMR 1.37 (3H, s), 1.58 (1H, dddd, *J*¼3.5, 6.8, 10.3, 13.7 Hz), 2.04 (1H, dddd, *J*¼2.7, 4.8, 10.8, 13.5 Hz), 3.25 (1H, d, *J*¼9.2 Hz), 3.43 (1H, dd, *J*¼2.1, 3.8 Hz), 3.48 (3H, s), 3.51 (3H, s), 3.58 (3H, s), 3.74 (1H, ddd, *J*¼2.7, 6.7, 11.2 Hz), 3.87 (1H, dd, *J*¼3.8, 9.2 Hz), 3.90 (1H, ddd, *J*¼4.7, 11.0, 11.0 Hz), 4.36 (1H, ddd, *J*¼1.9, 3.6, 10.8 Hz); ^{13}C NMR 23.0 (CH_3), 25.7 (CH_2), 56.5 (CH_2), 57.9 (CH_3), 58.1 (CH_3), 61.4 (CH_3), 66.9 (CH), 78.7 (CH), 80.1 (CH), 82.7 (CH), 99.2 (C); MS (EI) *m/z* (rel intensity) 232 (M^+, <1), 217 (<1), 201 (2); HRMS calcd for $C_{11}H_{20}O_5$ 232.1310, found 232.1334. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.87; H, 8.58. Compound 31: colourless oil; $[a]_D$ —8.4 (*c*, 0.55); IR 2934, 2827, 1446, 1103, 1050 cm^{-1}; ^{1}H NMR 1.29 (3H, d, *J*¼6.7 Hz), 1.89 (1H, m), 2.35 (1H, m), 3.07 (1H, dd, *J*¼2.4, 6.2 Hz), 3.26 (3H, s), 3.45 (3H, m), 3.52 (3H, s), 3.61 (1H, d, *J*¼2.4 Hz), 3.66 (1H, dq, *J*¼6.2, 6.7 Hz), 3.82 (1H, ddd, *J*¼6.4, 8.8, 8.8 Hz), 4.11 (1H, ddd, *J*¼5.5, 8.8, 8.8 Hz), 4.21 (1H, dd, *J*¼1.7, 6.9 Hz); ^{13}C NMR 18.6 (CH_3), 31.4 (CH_2), 48.5 (CH_3), 57.9 (CH_3), 58.1 (CH_3), 66.4 (CH_2), 68.7 (CH_2), 76.7 (2×CH); MS (EI) *m/z* (rel intensity) 232 (M^+, 16), 217 (1), 201 (4), 185 (2), 169 (2); HRMS calcd for $C_{11}H_{20}O_5$ 232.1310, found 232.1282. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 57.08; H, 8.32.

4.3.7. Formation of compounds 31, 35 and 3-acetyl-2,8- anhydro-1,7-didesoxy-3,4,5-tri-*O*-methyl-L-*arabino*- octo-2,5-diulo-2,6-pyranose (36). Following the general procedure for IHA reactions adding $NaHCO_3$ (100%) to the reaction mixture, precursor 8 (360 mg, 1.53 mmol) af- forded anhydrosugars 35 (50 mg, 0.215 mmol, 14%), 31 (130 mg, 0.56 mmol, 37%) and 36 (20 mg, 0.07 mmol, 4.5%). Compound 36: $[a]_D$ +11.1 (*c*, 0.28); IR 2943, 2747, 1222, 1112 cm^{-1}; ^{1}H NMR 1.35 (3H, s), 1.77 (1H, dddd, *J*¼3.7, 6.8, 10.6, 14.2 Hz), 1.99 (1H, dddd, *J*¼2.8, 4.0, 10.5, 14.0 Hz), 2.10 (3H, s), 3.08 (1H, d, *J*¼8.9 Hz), 3.59 (3H, s), 3.62 (3H, s), 3.66 (3H, s), 3.72 (1H, ddd, *J*¼2.5, 6.7, 11.2 Hz), 3.82 (1H, ddd, *J*¼4.4, 10.8, 10.8 Hz), 3.85 (1H, d, *J*¼8.9 Hz), 5.21 (1H, dd, *J*¼3.8, 10.6 Hz), ^{13}C NMR 21.8 (CH_3), 22.7 (CH_3), 24.5 (CH_2), 53.3 (CH_3), 56.0 (CH_2), 61.6 (CH_3), 61.8 (CH_3), 67.1 (CH), 83.3 (CH), 84.4 (CH), 98.5 (C), 105.0 (C), 169.6 (C); MS (EI) *m/z* (rel intensity) 290 (M^+, 3), 259 (7), 231 (6), 199 (8); HRMS calcd for $C_{13}H_{22}O_7$ 290.1365, found 290.1314. Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64. Found: C, 53.80; H, 7.39.

4.3.8. 3,4,5-Tri-*O*-acetyl-2,8-anhydro-1,7-dideoxy-b-L- *altro*-oct-2-ulopyranose (32). Following the general pro- cedure, precursor 6 (52 mg, 0.163 mmol) afforded the anhydrosugar 32 (27 mg, 0.085 mmol, 53%) as a colourless oil: $[a]_D$ +65 (*c*, 0.36); IR 2972, 2747, 1372, 1226, 1059 cm^{-1}; ^{1}H NMR 1.31 (3H, s), 1.87 (1H, m), 1.98 (3H, s), 2.09 (3H, s), 2.11 (1H, m), 2.14 (3H, s), 3.83–3.94 (2H, m), 4.25 (1H, ddd, *J*¼2.2, 2.2, 10.8 Hz), 5.21 (1H, d, *J*¼9.9 Hz), 5.23 (1H, dd, *J*¼1.9, 3.9 Hz), 5.63 (1H, dd, *J*¼3.9, 9.9 Hz); ^{13}C NMR 20.6 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 22.9 (CH_3), 26 (CH_2), 56.8 (CH_2), 67.4 (CH), 69.4 (CH), 71.7 (CH), 72.2 (CH), 98.7 (C), 170.1 (C), 170.2 (C), 170.5 (C); MS (EI) *m/z* (rel intensity) 316 (M^+, 7), 273 (1), 257 (10), 197 (7), 155 (25); HRMS calcd for $C_{14}H_{20}O_8$ 316.1158, found 316.1189. Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.23; H, 6.10.

4.3.9. (2*R*)-2,8-Anhydro-5,7-dideoxy-1,3,4-tri-*O*-methyl- D-*arabino*-oct-2-ulopyranose (33). Following the general procedure, precursor 17 (140 mg, 0.60 mmol) afforded the cyclised compound 33 (88.3 mg, 0.38 mmol, 64%) as a colourless oil: $[a]_D$ —3.3 (*c*, 0.09); IR 2931, 2830, 1731, 1450, 1260, 1195, 1113 cm^{-1}; ^{1}H NMR 1.62 (1H, m), 1.83 (1H, m), 2.04 (1H, m), 2.17 (1H, m), 3.29–3.37 (2H, m), 3.39 (3H, s), 3.45 (1H, m), 3.45 (3H, s), 3.55 (3H, s), 3.75–3.86

(2H, m), 3.91 (1H, m), 4.34 (1H, m); ^{13}C NMR 28.9 (CH_2), 35.8 (CH_2), 57.4 (CH_3), 58.2 (CH_2), 59.3 (CH_3), 60.8 (CH_3), 66.3 (CH), 73.2 (CH_2), 78.1 (CH), 81.7 (CH), 98.5 (C); MS *m*/*z* (rel intensity) 232 (M^+, 1), 231 (2); HRMS calcd for $C_{11}H_{20}O_5$ 232.1310, found 232.1297. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.81; H, 8.90.

4.3.10. 3,6-Anhydro-2-deoxy-7-*O*-(methoxymethyl)-4,5- *O*-methylene-b-D-*ribo*-hept-4-ulofuranose (34). Following the general procedure, precursor **21** (66.2 mg, 0.28 mmol) afforded the cyclised compound **34** (37.4 mg, 0.16 mmol, 57%) as a colourless oil: $[a]_D$ +61.0 (*c*, 1.41); IR 2930, 2886, 1732, 1440, 1367, 1153, 1109 cm^{-1}; ^{1}H NMR 1.99–2.17 (2H, m), 3.37 (3H, s), 3.70 (1H, dd, *J*¼6.4, 10.7 Hz), 3.76 (1H, dd, *J*¼4.0, 10.7 Hz), 4.04–4.10 (2H, m), 4.18–4.22 (2H, m), 4.39 (1H, dd, *J*¼1.4, 5.7 Hz), 4.67 (2H, s), 5.25 (2H, s), 5.34 (2H, s); ^{13}C NMR 31.1 (CH_2), 55.4 (CH_3), 67.3 (CH_2), 69.5 (CH_2), 82.5 (CH), 84.0 (CH), 84.2 (CH), 96.6 (CH_2), 98.4 (CH_2), 123.2 (C); MS *m*/*z* (rel intensity) 232 (M^+, 2), 231 (7); HRMS calcd for $C_{10}H_{16}O_6$ 232.0947, found 232.0991. Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.62; H, 6.88.

4.3.11. (4*R*)-3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropyl- idene-a-D-*manno*-oct-4-ulofuranose (37) and 7-deoxy- 1,2:4,5-di-*O*-isopropylidene-D-*altro*-oct-3-ulofuranose (38). Following the general procedure, precursor **23** (90 mg, 0.31 mmol) afforded compounds **38** (23 mg, 0.08 mmol, 26%) and **37** (36 mg, 0.13 mmol, 41%). Compound **37**: amorphous solid; $[a]_D$ —19.0 (*c*, 0.5); IR 2988, 2891, 1374, 1210, 1085 cm^{-1}; ^{1}H NMR 1.34 (3H, s), 1.42 (3H, s), 1.46 (3H, s), 1.48 (3H, s), 1.93 (1H, m), 2.13 (1H, m), 4.04 (4H, m), 4.13 (1H, dd, *J*¼3.9, 7.3 Hz), 4.35 (1H, ddd, *J*¼4.8, 6.3, 7.3 Hz), 4.45 (1H, d, *J*¼3.9 Hz), 4.54 (1H, dd, *J*¼7.1, 7.1 Hz); ^{13}C NMR 25.0 (CH_3), 25.1 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 30.8 (CH_2), 66.4 (CH_2), 69.0 (CH_2), 73.1 (CH), 80.3 (CH), 83.5 (CH), 86.4 (CH), 109.1 (C), 114.0 (C), 122.8 (C); MS *m*/*z* (rel intensity) 271 (M^+—CH_3, 35), 213 (30); HRMS calcd for $C_{13}H_{19}O_6$ 271.1181, found 271.1192. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.85; H, 7.95. Compound **38**: amorphous solid; $[a]_D$ —24.1 (*c*, 0.8); IR 2986, 2873, 1732, 1378, 1260, 1209, 1077 cm^{-1}; ^{1}H NMR 1.34 (1H, m), 1.34 (3H, s), 1.36 (3H, s), 1.43 (3H, s), 1.46 (3H, s), 2.19 (1H, m), 3.70 (1H, ddd, *J*¼4.2, 12.5, 12.5 Hz), 3.98 (1H, ddd, *J*¼0.0, 6.7, 12.6 Hz), 4.03 (1H, dd, *J*¼7.5, 7.5 Hz), 4.20 (1H, dd, *J*¼5.6, 8.4 Hz), 4.33 (1H, ddd, *J*¼0.0, 6.0, 6.0 Hz), 4.36 (1H, m), 4.68 (1H, d, *J*¼5.6 Hz), 4.73 (1H, d, *J*¼5.6 Hz); ^{13}C NMR 24.4 (CH_3), 25.0 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 27.5 (CH_2), 59.9 (CH_2), 64.9 (CH_2), 74.7 (CH), 79.3 (CH), 82.2 (CH), 82.8 (CH), 105.6(C), 109.7 (C), 112.5 (C); MS *m*/*z* (rel intensity) 271 (M^+—CH_3, 47), 213 (86); HRMS calcd for $C_{13}H_{19}O_6$ 271.1181, found 271.1212. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.63; H, 7.70.

4.3.12. 7-Deoxy-1,2:4,5-di-*O*-oxomethylene-D-*altro*-oct-3- ulofuranose (40). A solution of the alcohol **26** (50 mg, 0.19 mmol) in dry CH_2Cl_2 (4 mL) containing DIB (93 mg, 0.29 mmol) and iodine (49 mg, 0.19 mmol) was stirred and irradiated with an 80 W tungsten filament lamp at room temperature under nitrogen atmosphere for 35 min. The reaction mixture was then poured into 10% aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic phase was concentrated in vacuum. The residue was dissolved in dry CH_2Cl_2 and BF_3\$$OEt_2$ (24 mL, 0.19 mmol) was added at 0 °C under nitrogen atmosphere. After 30 min at 0 °C, the reaction mixture was poured into aqueous sat. solution of $NaHCO_3$ and extracted with AcOEt. The organic phase was dried with Na_2SO_4 and concentrated under vacuum. Column chromatography of the residue (hexanes–EtOAc, 1:1) afforded the anhydrosugar **40** (32 mg, 0.12 mmol, 65%) as a colourless crystalline compound; $[a]_D$ —42.6 (*c*, 0.6, EtOAc); mp 209–213 °C (EtOAc–*n*-pentane); ^{1}H NMR 1.60 (1H, dddd, *J*¼0.8, 2.1, 3.9, 14.1 Hz), 2.38 (1H, dddd, *J*¼3.9, 6.9, 13.0, 14.0 Hz), 3.71 (1H, ddd, *J*¼3.9, 12.9, 12.9 Hz), 4.12 (1H, dddd, *J*¼1.1, 1.1, 6.8, 12.5 Hz), 4.52 (1H, dd, *J*¼8.6, 8.6 Hz), 4.70 (1H, ddd, *J*¼1.6, 1.6, 3.5 Hz), 4.73 (1H, dd, *J*¼4.5, 8.7 Hz), 4.88 (1H, dd, *J*¼4.5, 8.5 Hz), 5.20 (1H, d, *J*¼6.1 Hz), 5.26 (1H, d, *J*¼6.1 Hz); ^{13}C NMR 27.0 (CH_2), 60.6 (CH_2), 65.2 (CH_2), 73.2 (CH), 80.3 (CH), 81.2 (CH), 81.3 (CH), 104.5 (C), 153.5 (C), 154.8 (C); MS (FAB$^+$) *m*/*z* (rel intensity) 281 (M^++Na, 18), 259 (M^++H, 100); HRMS calcd for $C_{10}H_{11}O_8$ 259.0454, found 259.0445. Anal. Calcd for $C_{10}H_{10}O_8$: C, 46.52; H, 3.90. Found: C, 46.19; H, 4.20.

Acknowledgements

This work was supported by the investigation programmes CTQ2004-06381/BQU and CTQ20004-02367/BQU of the Direcci´on General de Investigaci´on Cient´ıfica y T´ecnica, Spain. A.J.H. and I.P.-M. thank the Ministerio de Educaci´on y Ciencia, Spain, and the programme I3P-CSIC, respectively, for fellowships.

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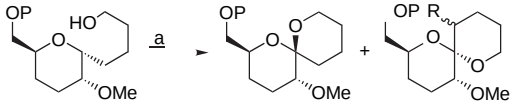
15. An example of a double IHA reaction:



(22%) R = H (29%) R = I (15%)

(a) DIB, I_2, cyclohexane, hν, 40 °C, 70 min

For other double IHA reactions in carbohydrate models, see Ref. 2a,b.

16. For studies of the influence of polar factors on, see: (a) Beckwith, A. L. J.; Zavitsas, A. A.; Chatgilialoglu, C. *J. Am. Chem. Soc.* 1995, *117*, 10645–10654; (b) Kaushal, P.; Mok, P. L. H.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* 1990, 1663–1670. For an example of correlation between proximity in the ground state and regioselectivity in an IHA reaction, see Ref. 3b.
17. Bicyclic ketals can be easily converted into the corresponding bicyclic ethers by stereoselective reduction: (a) Takemoto, Y.; Furuse, S.-I.; Hayase, H.; Echigo, T.; Iwata, C.; Tanaka, T.; Ibuka, T. *Chem. Commun.* 1999, 2515–2516; (b) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* 1989, *111*, 4136–4137.
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