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General synthesis and biological evaluation of α-1-*C*-substituted derivatives of fagomine (2-deoxynojirimycin-α-*C*-glycosides)

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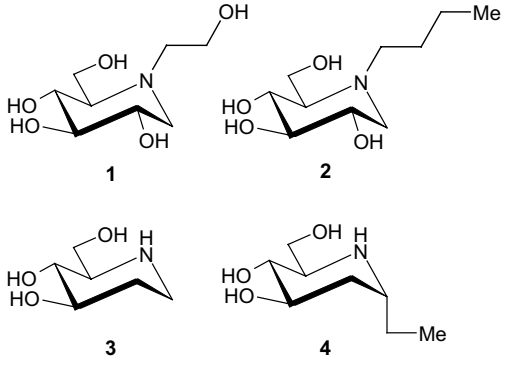
Abstract—A general synthesis of α-1-*C*-substituted derivatives of fagomine (2-deoxynojirimycin-α-*C*-glycosides) by ring-opening reactions of an aziridine with various heteroatomic nucleophiles, including thiol, amine, alcohol, carboxylate and phosphate, is described. The nine-step reaction sequence proceeded in an overall yield of 14–28% from tri-*O*-benzyl-D-glucal. Biological evaluation of α-1-*C*-substituted derivatives of fagomine, of the 2-deoxy analog of α-homonojirimycin **19** and its 1,*N*-anhydro derivative **22** as glycosidase inhibitors is reported. The glycosyl phosphate mimetic **15k** was found to display no inhibitory activity towards glycogen phosphorylase b and phosphoglucomutase.

1. Introduction

Since the discovery of their occurrence in 1966[1] and of their biological activity as glycosidase inhibitors by Bayer chemists ten years later, iminosugars have been the subject of intense studies.[2] Recently, the scope of their biological activity has been extended to the inhibition of a number of enzymes such as glycosyltransferases,[3] metalloproteinases,[4] glycogen phosphorylases,[5] a sugar nucleotide mutase[6] and nucleoside-processing enzymes.[7] These findings have triggered renewed interest in iminosugars. Since these enzymes are involved in numerous fundamental biological processes, carbohydrate mimetics with nitrogen instead of the ring oxygen constitute leads for the development of new therapeutic agents in a wide range of diseases.[8,9] Two iminosugar derivatives have already been approved as drugs: *N*-hydroxyethyl-1-deoxynojirimycin (Glyset™ **1**[10]) to treat complications associated with type II diabetes and *N*-butyl-1-deoxynojirimycin **2**[11] (Zavesca™) for the treatment of Gaucher's disease, a severe lysosomal storage disorder (Scheme 1). Further exciting applications are being uncovered: *N*-alkyliminosugars have been found to reversibly induce infertility in male mice, opening the way to a nonhormonal approach to male contraception.[12] Considering the high potential of 'azasugars' for drug discovery, diversity-oriented synthesis of stable derivatives, such as iminosugars *C*-glycosides, is still needed to accelerate the exploration of new biological targets and the finding of more selective/potent inhibitors. To achieve this goal and as part of our continuing studies on iminosugars,[13] we have designed a flexible strategy for the general synthesis of α-1-*C*-substituted derivatives of fagomine (1,2-dideoxynojirimycin, **3**).



Scheme 1.

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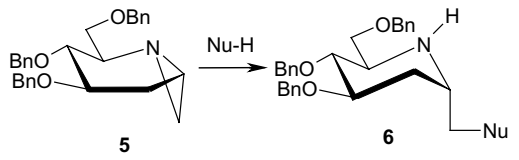


Scheme 2.

Recently, fagomine (**3**) was found to have potent antihyperglycemic effect in streptozocin-induced diabetic mice and to enhance glucose-induced insulin secretion.[14] To our knowledge, only one example of a natural fagomine *C*-glycoside (compound **4**)[15] has been reported to date. Our synthetic strategy hinges on the ring-opening reactions of the bicyclic aziridine **5**, which allows the introduction of structural diversity at the 'anomeric' position by using the wide library of nucleophiles available (Scheme 2). This point is crucial if one wants to explore the affinity of the aglycon binding site within a range of carbohydrate-processing enzymes. In addition, the key intermediate in our strategy, iminosugar-derived aziridine **5**,[16] once deprotected, is of biological interest as a potential irreversible inhibitor of glycosidases.

In a previous communication,[21] we have reported the first synthesis of 1,*N*-anhydro derivative of fagomine **5**, its deprotection and its use as an advanced intermediate for the synthesis of α-1-*C*-substituted derivatives by way of regioselective opening of the aziridine ring.[22] Herein, we wish to described the full details of theses studies as well as the biological evaluation of the compounds synthesized.

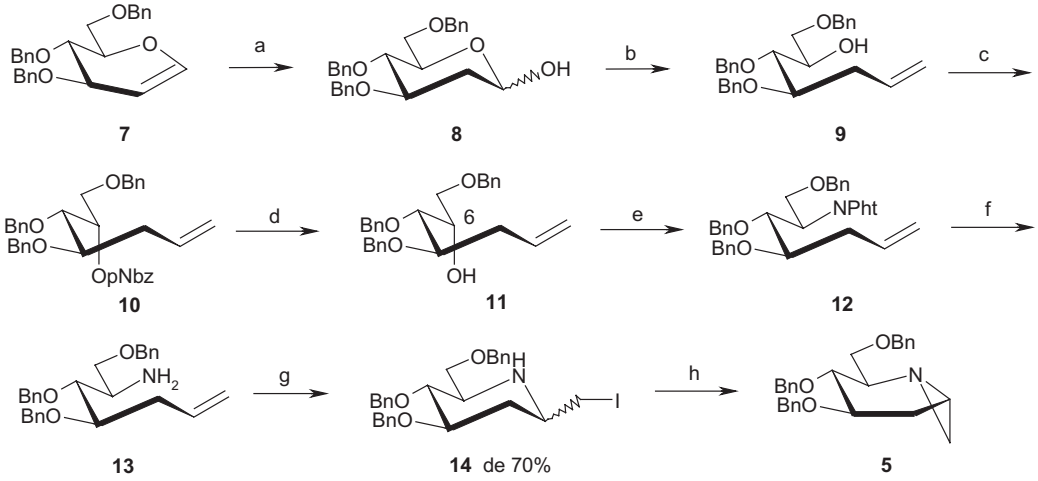
2. Results and discussion

2.1. Synthesis of the bicyclic aziridine 5

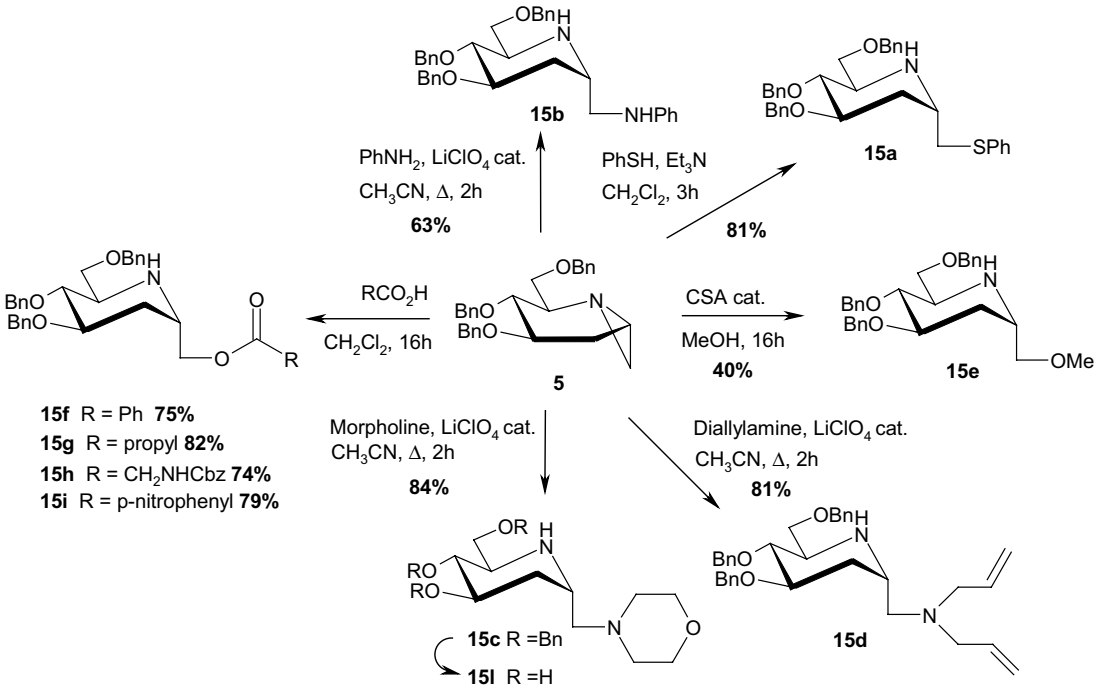
The synthesis of the key aziridine intermediate **5** was performed in eight steps and 34% overall yield from tri-*O*-benzyl-D-glucal (**7**) (Scheme 3). Hydration of **7** by a mild one-pot procedure[23] provided the corresponding 2-deoxysugar **8**, which was further transformed into alkene **9**[24] by Wittig methylenation. Introduction of the amino group at C-6 of the D-*arabino* heptenitol **9** was performed by way of a double Mitsunobu reaction. The configuration at C-6 of **9** was inverted efficiently in 79% yield by reaction with *p*-nitrobenzoic acid in the presence of Ph_3P and DIAD to provide **10**,[20a] followed by debenzoylation under basic conditions to give L-*xylo* heptenitol **11**. A second Mitsunobu reaction using phthalimide afforded the expected D-*arabino* amino sugar **13** in 72% yield after removal of the phthalimido group. The amino-heptenitol **13** was then cyclized using NIS to produce the relatively unstable 1-*C*-iodomethyl derivatives of fagomine **14** with a good diastereoselectivity in favour of the α-diastereoisomer (70% de). The two epimers could be separated by flash chromatography, even though partial decomposition occurred. By contrast, the NIS-promoted cyclization of the tetra-*O*-benzyl-D-*gluco* analogue of **14**[25] is completely diastereoselective: this comparison confirms the important role of the 3-*O*-benzyl group in the stereochemical outcome of the cyclization of the latter heptenitol. To avoid degradation, the mixture of the two stereoisomers **14** was engaged without purification, in the subsequent cyclization promoted by DBU. The aziridine **5** was isolated in 74% yield from **13** after purification by flash chromatography.

2.2. Ring opening reactions of aziridine 5

Baeyer strain combined with the electronegativity of the nitrogen atom explain the ability of aziridines to undergo ring opening under relatively mild conditions.[26] However, this process still remains challenging in comparison with the corresponding reaction of epoxides due to diminished electronegativity of the nitrogen atom and the presence of an additional valency.[26a] In addition, there have been few investigations on the ring-



Scheme 3. Reagents and conditions: (a) (i) NIS (1.1 equiv), CH_3CN/H_2O (95:5), 0 °C, 15 min; (ii) $Na_2S_2O_4$ (4 equiv), $NaHCO_3$ (10 equiv), DMF/H_2O (1:1), 5 h; (b) $Ph_3P^+CH_3Br^-$ (3.5 equiv), *n*-BuLi (3.5 equiv), THF, 0 °C to rt, 24 h, 81% (three steps); (c) PPh_3 (3 equiv), *p*-nitrobenzoic acid (3 equiv), DIAD (3 equiv), toluene, 0 °C to rt, 16 h; (d) Na (0.2 equiv), MeOH, 1 h, 79% (two steps); (e) phthalimide (3 equiv), PPh_3 (3 equiv), DIAD (3 equiv), toluene, 0 °C to rt, 16 h; (f) ethylenediamine (10 equiv), EtOH, 80 °C, 5 h, 72% (two steps); (g) NIS (1.2 equiv), CH_2Cl_2, 1 h; (h) DBU (10 equiv), THF, Δ, 6 h, 74% (two steps).

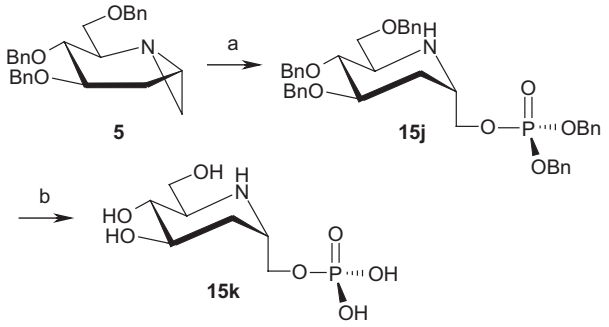


Scheme 4.

opening of *N*-alkylated aziridines in contrast to aziridines *N*-activated by sulfonyl, phosphoryl or carbonyl groups.[27,19]

We first investigated the reactions of aziridine **5** with various heteroatomic nucleophiles including thiol, amine, alcohol, carboxylate and phosphate (Scheme 4). We were pleased to find that the corresponding ring-opening products **15** could be obtained in good yields and with a high degree of regioselectivity (the seven-membered cyclic was not detected by NMR spectroscopy). Bicyclic iminosugar **5** was readily opened with thiophenol in the presence of triethylamine at room temperature. In the presence of a catalytic amount of lithium perchlorate, aziridine **5** underwent cleavage by primary or secondary amines under the mild conditions recently developed by Yadav et al. for *N*-tosyl aziridines.[28] The best yields were obtained with secondary amines. The ring opening proceeded much less satisfactorily with alcohols: aziridine **5** was opened by MeOH in the presence of camphorsulfonic acid to give **15e** in 40% yield whereas the reactions with phenol or butanol led to an untractable mixture of products.

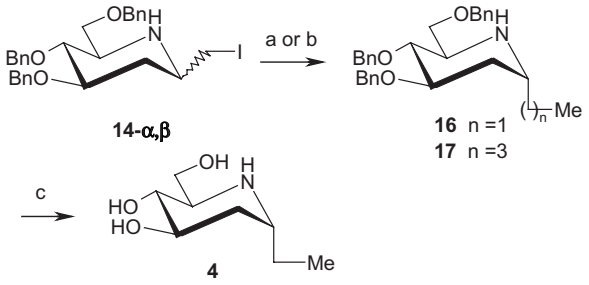
Regioselective ring opening occurred readily with various carboxylic acids in dichloromethane to provide the corresponding 2-deoxy-α-homonojirimycin derivatives **15f–i** in 74% to 82% yield.[19] No migration of the acyl group to the endocyclic nitrogen occurred as established unambiguously by IR and NMR spectral data. Under the same experimental conditions, the reaction with dibenzyl phosphate afforded protected iminosugar phosphate **15j**, which was debenzylated by hydrogenolysis to furnish the corresponding glycosyl phosphate mimetic **15k** in 85% yield (Scheme 5). To our knowledge, this



Scheme 5. Reagents and conditions: (a) $(BnO)_2P(O)OH$ (1.3 equiv), CH_2Cl_2, 16 h, 78%; (b) H_2, Pd/C, MeOH/HCl 4 N cat, 24 h, 85%.

is the first example of a ring-opening reaction of an *N*-alkylated aziridine by a phosphate.[29] Compound **15k** is a promising precursor of novel UDP-Glc analogs that could display interesting activity as glycosyltransferase inhibitors.[3]

We then turned our attention to organometallic nucleophiles in order to synthesize inter alia α-1-*C*-ethyl-fagomine **4**, a fagomine *C*-glycoside recently isolated from *Adenophora triphylla* var. *japonica*.[15a] The reaction of aziridine **5** with various organometallic reagents (MeLi, Me_2CuLi, $MeCeCl_2$) failed to give the desired product **16** under various conditions. However, **16** could be obtained in 65% yield by the reaction of Me_2CuLi with the mixture of the two stereoisomers **14** (Scheme 6).[30] The same process performed with Pr_2CuLi furnished the expected compound **17** in a less satisfactory yield of 32%. Removal of the benzyl groups in **16** provided α-1-*C*-ethyl fagomine **4** in 88% yield.



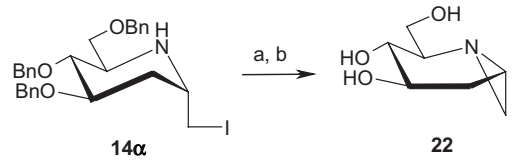
Scheme 6. Reagents and conditions: (a) Me_2 CuLi (1.1 equiv), THF, −50 °C to rt, 6 h, 65%; (b) *n*-Pr_2CuLi (1.3 equiv), THF, −60 °C to rt, 16 h, 32%; (c) H_2, Pd/C, EtOH, HCl 4 N cat, 24 h, 88%.

2.3. Access to 2-deoxy analogs of α-homonojirimycin

The 2-deoxy analog of α-homonojirimycin (**19**) was obtained by alkaline saponification of ester **15f** and hydrogenolysis of the resulting alcohol **18** under classical conditions (Scheme 7); the spectral parameters of **19** were found to be identical to those of naturally occurring 2-deoxy-α-homonojirimycin recently isolated.[31] A similar strategy was used to prepare the 2-deoxy analog of *N*-butyl-α-homonojirimycin **21**. The ester **15g** was first *N*-alkylated by reductive amination using butyraldehyde and $NaBH_3CN$ to provide **20** in 78% yield. Removal of the benzyl groups in **20** followed by saponification of the ester group using an ion-exchange resin [Dowex 1-X2, (OH^- form)] afforded the expected analog of *N*-butyl-α-homonojirimycin **21** in 88% yield for the two steps. Deprotection of the morpholino derivative **15c** by hydrogenolysis provided the corresponding piperidinol **15l** in 85% yield (Scheme 4).

2.4. Synthesis of the 1,*N*-anhydro derivative of fagomine 22

Finally, we investigated the deprotection of aziridine **5** in order to obtain the 1,*N*-anhydro derivative of fagomine **22**. Under usual debenzylation conditions, the reaction led to an untractable mixture of products (using Na/NH_3) or to the cleavage of the aziridine ring to give the α-1-*C*-methyl analogue of **4** in quantitative yield (using H_2, Pd/C). To overcome this difficulty, we first



Scheme 8. Reagents and conditions: (a) TMSI (8.5 equiv), CH_2Cl_2, 0 °C to rt, 16 h, 84%; (b) K_2CO_3 (1.8 equiv), H_2O, 4 h, 90%.

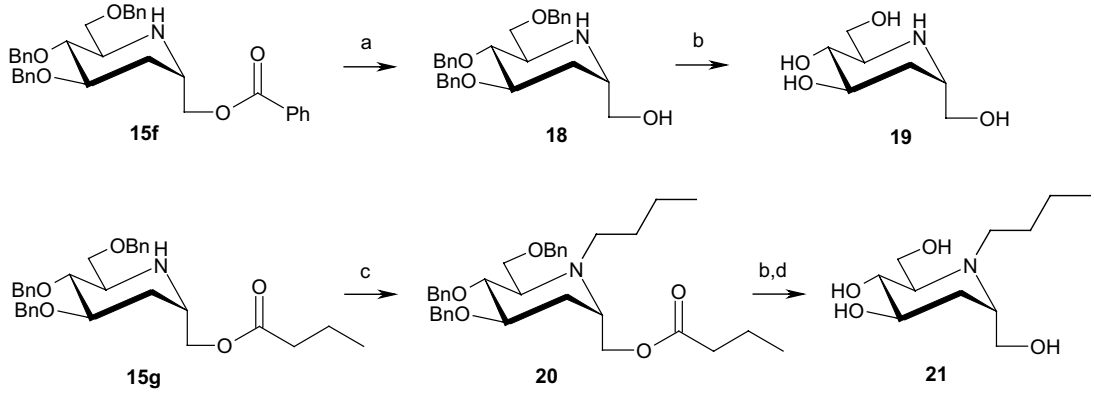
cleaved the benzyl groups at the stage of the α-1-*C*-iodomethyl derivative **14α**. The deprotection step was performed using a large excess of TMSI in dichloromethane. The expected bicyclic iminosugar **22** was then generated by intramolecular nucleophilic substitution promoted by K_2CO_3 in water in 75% yield for the two steps (Scheme 8).

2.5. Conformational analysis

^{1}H NMR Analysis (Table 1) of the 2-deoxy-α-homonojirimycin derivatives indicated that the molecules having free OH groups (**4**, **15l**, **19** as well as **21**) adopt in D_2O a nondistorted $^4C_1$ (D) conformation in which the C-1 substituent is in axial position. The benzylated derivatives (**15a–j**) exhibit however smaller values of $J_{2ax,3}$, $J_{3,4}$ and $J_{4,5}$ coupling constants, which indicate the existence of a conformational equilibrium with the alternate $^1C_4$ (D) conformation or of a nonchair conformation. The free 1-phosphate **15k** has a conformation more closely related to that of the protected derivatives **15a–j** than to the free iminoalditols.

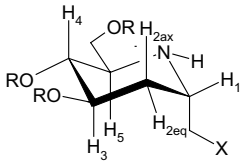
2.6. Screening of carbohydrate-processing enzymes

The inhibitory effect of fagomine analogs **15l**, **19**, **21**, **22** on various glycosidases has been examined (Tables 2 and 3). For comparison purposes, the IC_{50} values of fagomine (**3**), 1-deoxynojirimycin (**24**), *N*-butyl 1-deoxynojirimycin (**26**), α-homonojirimycin (**23**) and its *N*-butyl derivative **25** were also included in the tables. The aziridine **22** is a weak inhibitor of glycosidases but displays slightly better inhibitory activity than fagomine (**3**). This result may be explained by the flattened structure of the bicyclic aziridine **22** that may partially mimic the half



Scheme 7. Reagents and conditions: (a) MeONa (0.2 equiv), MeOH, 4 h, 86%; (b) H_2, Pd/C, MeOH, HCl 1 N cat, 16 h, 87%; (c) $C_3H_7CH{=}O$ (2 equiv), $NaBH_3CN$ (1.2 equiv), CH_3COOH (3 equiv), molecular sieves 4 Å, MeOH, 16 h, 78%. (d) Dowex 1-X2, (OH^- form), 1 h, 88% (from **20**).

Table 1. Coupling constants in 2-deoxy-α-homonojirimycin derivatives



J (Hz)	R = Bn **15a–j**	R = H **4**, **15l**, **19**
$J_{1,2ax}$	4.5–5.0	5.2–6.0
$J_{1,2eq}$	4.1–5.0	1.8–2.3
$J_{2ax,3}$	8.3–9.2	11.9–13.0
$J_{2eq,3}$	4.1–5.0	5.0
$J_{3,4}$	6.6–7.5	9.2–9.8
$J_{4,5}$	6.6–7.5	9.2–9.8

chair structure of the glycosyl cation involved in the mechanism of the enzymatic hydrolysis.[2a,36] There is however no indication of irreversible inhibition of the enzymes listed by compound **22**.

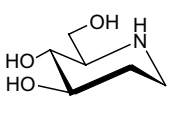
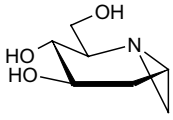
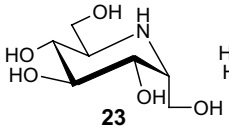
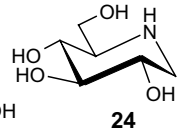
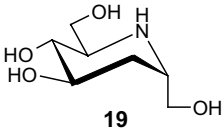
Comparison of the IC_{50} values between α-homonojirimycin (**23**) and its 2-deoxy analog **19** indicated that the α-glucosidase active sites can discriminate by over two or three orders of magnitude inhibitors differing by the absence of the hydroxyl group at C-2.[37] Interestingly, in the case of *N*-alkylated iminosugars, the absence of an OH group at C-2 does not seem to be detrimental for the inhibitory activity towards α-glucosidases. IC_{50} values found for *N*-butyl α-homonojirimycin (**25**) are indeed similar to those obtained for its 2-deoxy analog **21** with the exception of the rat intestinal maltase (Table 3). The homoazasugar **19** and its *N*-butyl analog **21** were designed in part to verify if a hydroxymethyl group at the pseudo-anomeric position could compensate for the missing OH group at C-2. Comparison of the inhibition constants between nojirimycin analogs **24** and **26** and the homoazasugars **19** and **21** demonstrates that the insertion of a hydroxymethyl group at C-1 is not sufficient to reinstate potent biological activity as α-glucosidase inhibitors (Tables 2 and 3).

Interconversion of the terminal hydroxyl group in **19** by a morpholino group does not change significantly the biological profile of the 2-deoxynojirimycin analogs as inhibitors of glucosidases (Tables 2 and 3).

Fagomine analogs **15l**, **19**, **21** and **22** did not display any significant inhibitory activity toward β-glucosidases and α-fucosidases. In addition, **15l** and **19** did not inhibit an α-L-rhamnosidase (*Penicillium decumbens*).

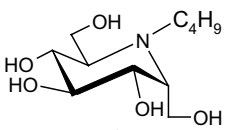
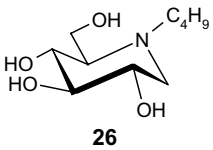
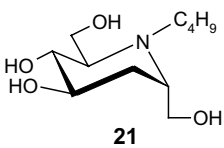
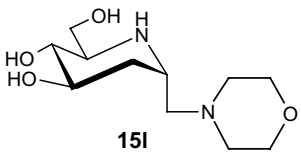
Compound **15k** was designed as a potential inhibitor of enzymes processing glucose 1-phosphate such as glycogen phosphorylase or phosphoglucomutase. Recent studies have demonstrated the interest of glycogen phosphorylase inhibitors as potential new hypoglycemic agents for the treatment of complications associated with type II diabetes.[5,38] Unfortunately, the glucose 1-phosphate mimetic **15k** did not display any inhibitory activity toward glycogen phosphorylase b nor towards phosphoglucomutase (Table 4). Further biological studies on α-glucosidases indicated that **15k** was a modest but selective inhibitor of rat intestinal isomaltase and sucrase.

Table 2. IC_{50} values for **19**, **22** and related compounds towards selected glycosidases

Enzyme	IC_{50} (μM)				
	 **3**	 **22**	 **23**	 **24**	 **19**
α-Glucosidase					
Rice	320[a]	(10.4)[d]	0.04[b]	0.05[e]	88
Yeast	880	NI	340	190[f]	NI
Rat intestinal maltase	820[b]	380	0.34[b]	0.36[b]	150
Rat intestinal isomaltase	460[b]	100	0.70	0.30[b]	9.2
Rat intestinal sucrase	90	(22.3)	0.17[b]	0.21[b]	45
β-Glucosidase					
Sweet almond	NI[a,c]	NI	NI	81[f]	NI
Caldocellum saccharolyticum	NI	(28.9)	NI	55	NI
α-Fucosidase					
Bovine epididymis	140[b]	NI	NI	NI	NI
Human placenta	NI	NI	NI	NI	NI

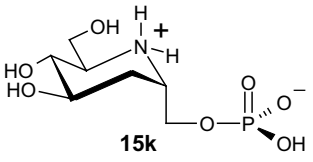
[a] Taken from Ref. 32.
[b] Taken from Ref. 33.
[c] NI: less than 50% inhibition at 1000 μM.
[d] % Inhibition at 1000 μM.
[e] Taken from Ref. 34.
[f] Taken from Ref. 35.

Table 3. IC_{50} values for **21**, **15l** and related compounds towards selected glycosidases

Enzyme	IC_{50} (μM)			
	 **25**	 **26**	 **21**	 **15l**
α-Glucosidase				
Rice	4.2[a]	0.42	6.6	145
Yeast	NI[b]	NI	NI	NI
Rat intestinal maltase	4.8[a]	2.1[a]	500	195
Rat intestinal isomaltase	100[a]	2.7[a]	120	25
Rat intestinal sucrase	3.0[a]	58[a]	12.5	48
β-Glucosidase				
Sweet almond	NI	1000	NI	NI
Caldocellum saccharolyticum (pH 5.0)	NI	NI	NI	NI
α-Fucosidase				
Bovine epididymis	NI	NI	NI	NI
Human placenta	NI	NI	NI	NI

[a] Taken from Ref. 33.
[b] NI: less than 50% inhibition at 1000 μM.

Table 4. IC_{50} values for **15k** towards selected enzymes

Enzyme	IC_{50} (μM)
	 **15k**
α-Glucosidase	
Rat intestinal maltase	NI[a]
Rat intestinal isomaltase	39
Rat intestinal sucrase	48
Rat trehalase	NI
Rat lactase	NI
Rat cellobiase	NI
Glycogen phosphorylase b	NI
Phosphoglucomutase	NI

[a] NI: less than 50% inhibition at 1000 μM.

3. Conclusion

In conclusion we have demonstrated that iminosugar-derived aziridine **5** was a versatile intermediate for the synthesis of fagomine *C*-glycosides and related compounds bearing a diverse range of functional groups at the 'anomeric' position. The nine-step reaction sequence proceeded in an overall yield of 14–28% from tri-*O*-benzyl-D-glucal (**7**). In the course of this study, the synthesis of a natural product, α-1-*C*-ethyl-fagomine (**4**), has been also achieved. The 1-*C*-substituted derivatives of fagomine **15l**, **19** and **21** were found to be modest inhibitors of α-glucosidases whereas the 1,*N*-anhydro derivatives of fagomine **22** displayed weak reversible inhibition values towards glycosidases. The glycosyl phosphate mimetic **15k** was found to have no inhibitory activity toward glycogen phosphorylase b or phosphoglucomutase. These results may be explained in part by the absence of the hydroxyl group corresponding to HO-2 in the parent glucosides. Interestingly, **15k** was found to be a modest but selective inhibitor of rat intestinal isomaltase and sucrase. Future work will focus on the extension of our synthetic strategy to other iminosugar *C*-glycosides bearing an OH group at C-2.

4. Experimental

4.1. General

Unless otherwise stated, all reactions requiring anhydrous conditions were carried out under argon. Tetrahydrofuran was freshly distilled from sodium/benzophenone under argon prior to use. Dichloromethane and toluene were distilled from calcium hydride. Infrared spectra were recorded using films on NaCl windows or KBr pellets. Low-resolution mass spectra (MS) were recorded with a Perkin–Elmer Sciex API 3000 in the ion spray (IS) mode. Specific rotations were measured at room temperature (20 °C) in a 1 dm cell with a Perkin–Elmer 241 polarimeter. Analytical thin layer chromatography was performed using silica gel $60F_{254}$ precoated plates (Merck). Flash Chromatography was performed on silica gel 60 (230-400 mesh) with ethyl acetate (AcOEt) and petroleum ether (PE) as eluants. ^1H and ^{13}C NMR spectra were recorded at 25 °C on Bruker DPX 250 Advance (250 MHz) and JEOL ECP-500 (500 MHz) spectrometers with Me_4Si as internal reference unless otherwise stated and *J* values are quoted in Hertz. Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Elemental analyses were carried out at the Service Central of Microanalyse du CNRS (Vernaison, France).

4.2. Chemistry

4.2.1. 4,5,7-Tri-*O*-benzyl-1,2,3-trideoxy-D-*arabino*-hept-1-enitol (9).[24] To a solution of methyltriphenylphosphonium bromide (8.62 g, 24.15 mmol) in THF (45 mL) was added dropwise at 0 °C 1.6 M BuLi in hexane (14.2 mL, 22.7 mmol). The reaction was stirred for 30 min at 0 °C and then for 30 min at room temperature. In another flask, a solution of BuLi in hexane (1.6 M, 4 mL, 6.5 mmol) was added dropwise at 0 °C to a solution of 2-deoxy sugar **8**[23] (3.0 g, 6.9 mmol) in THF (30 mL) and stirred for 30 min. The resulting solution was then cannulated into the THF solution of phosphorane. The reaction mixture was stirred for 24 h at room temperature, then quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with AcOEt (3×60 mL). The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and the residue was purified by column chromatography (9:1, PE/AcOEt) to give the desired compound **9** as a colourless oil (2.56 g, 86%); $[\alpha]_D^{20}$ −0.8 (c = 1.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 2.46 (m, 2H), 3.03 (d, 1H, J = 4.9 Hz), 3.61 (m, 2H), 3.72 (m, 1H), 4.02 (m, 1H), 4.50–4.62 (m, 6H), 5.02–5.11 (m, 2H), 5.78 (m, 1H), 7.26–7.31 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 34.4, 70.2, 71.0, 72.3, 73.2, 73.3, 78.0, 78.8, 117.1, 127.5–128.1, 134.8, 137.7, 137.9, 138.0; MS-IS m/z 455 $[M + Na]^+$, 432 $[M + H]^+$.

4.2.2. 4,5,7-Tri-*O*-benzyl-1,2,3-trideoxy-6-*O*-(4-nitrobenzoyl)-L-*xylo*-hept-1-enitol (10). To a solution of alcohol **9** (2.3 g, 5.3 mmol) in dry toluene (100 mL) were added triphenylphosphine (4.19 g, 15.9 mmol) and 4-nitrobenzoic acid (2.67 g, 15.9 mmol). The reaction was cooled to 0 °C and then DIAD (15.9 mmol, 3.22 g) was added slowly. The reaction mixture was stirred overnight at room temperature and the solvent was then removed under reduced pressure. The crude product was purified by column chromatography (9:1, PE/AcOEt) to give the desired compound **10** as a pale yellow oil (2.67 g, 87%); $[\alpha]_D^{20}$ +3.6 (c = 1.9, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 2.41 (m, 1H), 2.53 (m, 1H), 3.66 (m, 2H), 3.74 (dd, 1H, J = 4.2, 10.8 Hz), 3.95 (t, 1H, J = 4.9 Hz), 4.39–4.81 (m, 6H), 5.09–5.13 (m, 2H), 5.64 (∼q, 1H, J = 6.0 Hz), 5.80 (m, 1H), 7.26–7.32 (m, 15H), 8.13 (d, 2H, J = 9.0 Hz), 8.24 (d, 2H, J = 9.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 33.8, 67.8, 71.4, 72.5, 73.5, 74.2, 77.5, 77.6, 117.1, 122.9, 127.1–127.8, 130.3, 133.8, 135.0, 137.2, 137.5, 137.6, 149.9, 163.5; IR (film) ν 1710 cm^{-1} (C=O). Anal. Calcd for $C_{35}H_{35}NO_7$: C, 72.27; H, 6.07; N, 2.41. Found: C, 72.17; H, 6.18; N, 2.33.

4.2.3. 4,5,7-Tri-*O*-benzyl-1,2,3-trideoxy-L-*xylo*-hept-1-enitol (11). To a solution of ester **10** (1.28 g, 2.2 mmol) in dry MeOH under argon (75 mL) was added sodium (11 mg, 0.44 mmol). The reaction mixture was stirred for 4 h at room temperature and the solvent was then removed under reduced pressure. The crude product was purified by column chromatography (9:1, PE/AcOEt) to give the desired compound **11** as a colourless oil (0.86 g, 91%); $[\alpha]_D^{20}$ +5.2 (c = 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 2.35 (m, 1H), 2.47 (m, 1H), 2.55 (d, 1H, J = 7.9 Hz), 3.44 (m, 2H), 3.61 (dd, 1H, J = 3.0, 5.9 Hz), 3.72 (m, 1H), 3.95 (m, 1H), 4.45–4.65 (m, 5H), 4.75 (d, 1H, J = 11.2 Hz), 5.05–5.14 (m, 2H), 5.86 (m, 1H), 7.26–7.32 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 35.0, 69.6, 71.3, 72.5, 73.1, 74.5, 79.1, 79.4, 117.2, 127.5–128.3, 134.7, 137.9, 138.2, 138.3; MS-IS m/z 455 $[M + Na]^+$. Anal. Calcd for $C_{28}H_{32}O_4$: C, 77.75; H, 7.45. Found: C, 77.15; H, 7.63.

4.2.4. 4,5,7-Tri-*O*-benzyl-1,2,3,6-tetradeoxy-6-phthalimido-D-*arabino*-hept-1-enitol (12). To a solution of alcohol **11** (1.03 g, 2.38 mmol) in dry toluene (50 mL) were added triphenylphosphine (4.19 g, 7.15 mmol) and phthalimide (1.05 g, 7.15 mmol). The reaction was cooled at 0 °C and then DIAD (1.44 g, 7.15 mmol) was added slowly. The reaction was stirred overnight at room temperature and the solvent was then removed under reduce pressure. The crude product was purified by column chromatography (9:1, PE/AcOEt) to give the desired compound **12** as a colourless oil (1.61 g, 78%); $[\alpha]_D^{20}$ +42.5 (c = 1.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 2.42 (m, 2H), 3.54 (ddd, 1H, J = 3.2, 4.7, 8.0 Hz), 3.89 (dd, 1H, J = 4.0, 10 Hz), 4.11 (t, 1H, J = 10 Hz), 4.31–4.66 (m, 7H), 4.83 (ddd, 1H, J = 4, 9.7, 10 Hz), 4.98–5.10 (m, 2H), 5.77 (m, 1H), 7.11–7.29 (m, 15H), 7.55–7.67 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 33.6, 50.1, 67.2, 72.2, 73.3, 74.7, 78.4, 116.5, 122.6, 127.0–128.1, 131.9, 133.5, 135.3, 137.7, 137.8, 138.0, 168.4; IR (film) ν 1711 cm^{-1} (C=O). Anal. Calcd for $C_{36}H_{35}NO_5$: C, 76.98; H, 6.28; N, 2.49. Found: C, 76.39; H, 6.28; N, 2.74.

4.2.5. (2*R*,3*R*,4*R*,6*S*)-3,4-Di(benzyloxy)-2-benzyloxymethyl-1-azabicyclo[4.1.0]heptane (5). To a solution of compound **12** (530 mg, 0.94 mmol) in EtOH (30 mL) was added ethylenediamine (0.39 mL, 9.4 mmol). The reaction was heated at 80 °C overnight and, after cooling, the solvent was removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 (20 mL) and then NIS (254 mg, 1.12 mmol) was added. After 1 h at room temperature, a saturated aqueous solution of $Na_2S_2O_3$ was added (10 mL). The reaction was extracted with CH_2Cl_2 (2×30 mL), the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude iodomethyl derivative {**14**: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.81 (ddd, 1H, J = 4.4, 9.0, 13.2 Hz), 2.14 (dt, 1H, J = 4.7, 4.7, 13.4 Hz), 3.10 (m, 1H), 3.28–3.33 (m, 4H), 3.55–3.71 (m, 3H), 4.44–4.55 (m, 5H), 4.77 (d, 1H, J = 11.5 Hz), 7.25–7.28 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 11.8, 32.6, 50.5, 53.8, 69.9, 71.2, 72.9, 73.6, 76.6, 77.6, 127.3–128.6, 138.0, 138.1, 138.2; MS-IS m/z 558.5 $[M + H]^+$} was dissolved in THF (25 mL) and then DBU (1.40 mL, 9.4 mmol) was added. The reaction was refluxed for 5 h and, after cooling, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE/AcOEt 20:80 to 0:100) to give the aziridine **5** as a colourless oil (274 mg, 68% for the three steps); $[\alpha]_D^{20}$ +10.6 (c = 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 1.40 (d, 1H, J = 3.4 Hz), 1.97–2.22 (m, 4H), 2.54

(m, 1H), 3.56–3.72 (m, 4H), 4.39 (d, 1H, $J = 11.2$ Hz), 4.53–4.66 (m, 5H), 7.12–7.33 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 26.8, 30.4, 35.4, 64.8, 71.0, 72.3, 73.3, 73.4, 77.6, 79.5, 127.5–128.4, 138.3, 138.5, 138.6; MS-IS *m/z* 430.5 $[M + H]^+$; HRMS-CI *m/z* 430.2384 $[M + H]^+$ ($C_{28}H_{31}NO_3$ required 430.2382).

4.2.6. (2*R*,3*R*,4*R*,6*S*)-2-Hydroxymethyl-1-azabicyclo-[4.1.0]heptane-3,4-diol (22). To a solution of crude iodomethyl derivative **14** (100 mg, 0.18 mmol) in CH_2Cl_2 (4 mL) was added slowly at 0 °C iodotrimethylsilane (154 μL, 1.08 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 24 h. Water (10 mL) and diethylether (10 mL) were then added, the organic layer was separated and the aqueous layer was extracted with diethylether (10 mL). The aqueous layer was concentrated to a volume of 1 mL and K_2CO_3 (44.7 mg, 0.32 mmol) was added. After 3 h, the solvent was removed under reduced pressure and the crude product was purified on Dowex 1-X2 (OH^-) ion exchange resin (elution with water). The combined fractions were lyophilized to afford compound **22** as a white foam (21 mg, 75%); $[\alpha]_D^{20}$ +57.7 ($c = 0.4$, H_2O); ^1H NMR (500 MHz, D_2O–TSP:[39]) δ_H 1.66 (br d, 1H), 1.97 (ddd, 1H, $J = 6.0$, 9.6, 14.2 Hz), 2.02 (br d, 1H), 2.23 (m, 1H), 2.44 (ddd, 1H, $J = 2.3$, 3.5, 14.2 Hz), 2.57 (ddd, 1H, $J = 3.2$, 6.0, 9.6 Hz), 3.34 (dd, 1H, $J = 8.7$, 9.6 Hz), 3.76 (dd, 1H, $J = 6.0$, 11.5 Hz), 3.89 (dd, 1H, $J = 3.2$, 11.5 Hz); ^{13}C NMR (125 MHz, D_2O–TSP[39]): δ_C 32.1, 34.9, 36.8, 66.4, 69.5, 71.3, 74.7; HRMS-CI *m/z* 160.0976 $[M + H]^+$ ($C_7H_{14}NO_3$ required 160.0973).

4.2.7. 4,5,7-Tri-*O*-benzyl-2,3,6-trideoxy-2,6-imino-1-S-phenyl-1-thio-D-*manno*-heptitol (15a). To a solution of aziridine **5** (50 mg, 0.116 mmol) in CH_2Cl_2 (1 mL) were added triethylamine (21 μL, 0.15 mmol) and thiophenol (17 μL, 0.15 mmol). After 2 h at room temperature, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (8:2, PE/AcOEt) to give **15a** as a pale yellow oil (50.6 mg, 81%); $[\alpha]_D^{20}$ +18.2 ($c = 1.0$, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 1.72 (ddd, 1H, $J = 4.6$, 9.7, 13.2 Hz), 2.02 (br s, 1H), 2.12 (dt, 1H, $J = 4.2$, 4.2, 13.4 Hz), 2.94–3.09 (m, 3H), 3.21 (m, 1H), 3.33 (t, 1H, $J = 7.5$ Hz), 3.59 (d, 2H, $J = 5.1$ Hz), 3.65 (m, 1H), 4.41–4.57 (m, 5H), 4.79 (d, 1H, $J = 11.2$ Hz), 7.24–7.29 (m, 20H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 33.0, 37.5, 49.0, 54.2, 70.2, 71.4, 73.2, 74.2, 77.6, 78.9, 126.4, 127.5, 127.6, 127.7, 128.0, 128.3, 129.0, 130.1, 135.7, 138.2, 138.4; HRMS-ESI *m/z* 540.2575 $[M + H]^+$ ($C_{34}H_{38}NO_3S$ required 540.2572).

4.2.8. 4,5,7-Tri-*O*-benzyl-1,2,3,6-tetradeoxy-2,6-imino-1-phenylamino-D-*manno*-heptitol (15b). To a solution of aziridine **5** (30 mg, 0.07 mmol) in acetonitrile (2 mL) were added aniline (13 μL, 0.14 mmol) and $LiClO_4$ (0.007 mmol, 1.2 mg). The reaction was heated at 80 °C for 2 h and after cooling, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (1:9, PE/AcOEt) to give **15b** as a pale yellow oil (22 mg, 63%); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 33.3, 45.5, 48.8, 54.1, 69.5, 71.6, 73.2, 74.1, 77.9, 78.6, 112.9, 117.3, 127.4–129.3, 138.1, 138.5, 148.3. HRMS-ESI *m/z* 523.2962 $[M + H]^+$ ($C_{34}H_{39}N_2O_3$ required 523.2961).

4.2.9. 4,5,7-Tri-*O*-benzyl-1,2,3,6-tetradeoxy-2,6-imino-1-morpholino-D-*manno*-heptitol (15c). To a solution of aziridine **5** (50 mg, 0.116 mmol) in acetonitrile (3 mL) were added morpholine (13.2 mg, 0.15 mmol) and $LiClO_4$ (2 mg, 0.011 mmol). The reaction was heated at 80 °C for 4 h and after cooling, the solvent was removed under reduced pressure. The crude product was purified by column chromatography using AcOEt as eluant to give **15c** as a pale yellow oil (50 mg, 84%); $[\alpha]_D^{20}$ +22.6 ($c = 0.6$, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 1.67 (m, 1H), 1.90 (m, 1H), 2.15 (m, 2H), 2.30–2.52 (m, 5H), 3.09–3.25 (m, 2H), 3.35 (dd, 1H, $J = 6.6$ Hz), 3.55–3.73 (m, 7H), 4.42–4.62 (m, 5H), 4.77 (d, 1H, $J = 11.4$ Hz), 7.26–7.30 (m, 15H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ_C 31.9, 45.0, 53.9, 61.0, 67.0, 70.1, 71.3, 73.1, 73.7, 78.0, 127.5–128.3, 138.3, 138.5, 138.6; MS-IS *m/z* 539 $[M + Na]^+$, 517 $[M + H]^+$.

4.2.10. 1,2,3,6-Tetradeoxy-2,6-imino-1-morpholino-D-*manno*-heptitol (15l). To a solution of **15c** (20 mg, 0.038 mmol) in MeOH (1 mL) were added 1 N HCl (0.1 equiv) and 10% Pd/C (0.2 equiv). The reaction mixture was stirred under H_2 (1 atm) overnight and then the solids were removed by filtration on a pad of Celite. The solvent was removed under reduced pressure and the residue was purified on Dowex 1-X2 (OH^-) ion exchange resin (elution with water). The combined fractions were lyophilized to afford compound **15l** as a white foam (8 mg, 85%); $[\alpha]_D^{20}$ +23.6 ($c = 0.5$, H_2O); ^1H NMR (500 MHz, D_2O–TSP[39]): δ_H 1.67 (ddd, 1H, $J = 6.0$, 11.9, 13.3 Hz), 1.99 (ddd, 1H, $J = 2.3$, 5.0, 13.3 Hz), 2.50 (m, 1H), 2.57 (m, 2H), 2.64 (m, 2H), 2.73 (m, 1H), 2.82 (ddd, 1H, $J = 2.8$, 7.3, 9.2 Hz), 3.18 (dd, 1H, $J = 9.2$ Hz), 3.38 (m, 1H), 3.61 (dd, 1H, $J = 7.3$, 11.5 Hz), 3.73 (ddd, 1H, $J = 4.6$, 9.2, 11.9 Hz), 3.79 (t, 4H, $J = 5.0$ Hz), 3.91 (dd, 1H, $J = 2.8$, 11.5 Hz); ^{13}C NMR (125 MHz, D_2O–TSP[39]): δ_C 36.9, 49.9, 55.9, 58.0, 61.7, 64.8, 68.8, 72.2, 76.2; MS-IS *m/z* 247.5 $[M + H]^+$; HRMS-FAB *m/z* 247.1660 $[M + H]^+$ ($C_{11}H_{23}N_2O_4$ required 247.1658).

4.2.11. 4,5,7-Tri-*O*-benzyl-1,2,3,6-tetradeoxy-1-diallylamino-2,6-imino-D-*manno*-heptitol (15d). To a solution of aziridine **5** (30 mg, 0.07 mmol) in acetonitrile (2 mL) were added diallylamine (11 μL, 0.14 mmol) and $LiClO_4$ (0.007 mmol, 1.2 mg). The reaction was heated at 80 °C for 2 h and, after cooling, the solvent was removed under reduced pressure. The crude product was purified by column chromatography using AcOEt as eluant to give **15d** as a pale yellow oil (23 mg, 81%); $[\alpha]_D^{20}$ +9.6 ($c = 0.2$, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 1.75 (ddd, 1H, $J = 4.9$, 8.7, 13.7 Hz), 2.00 (dt, 1H, $J = 4.6$, 4.6, 13.4 Hz), 2.36 (dd, 1H, $J = 5.1$, 13.1 Hz), 2.63 (dd, 1H, $J = 9.9$, 13.1 Hz), 3.01–3.21 (m, 3H), 3.28 (m, 1H), 3.32 (t, 1H, $J = 7.4$ Hz), 3.64 (m, 3H), 4.50–4.62 (m, 5H), 4.76 (d, 1H, $J = 11.5$ Hz), 5.14 (m, 4H), 5.73 (m, 2H), 7.24–7.33 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 30.6, 47.3, 54.2, 54.3, 57.1, 71.5, 73.2, 74.0, 77.2, 118.3, 127.5–128.4, 134.8, 138.1,

138.4, 138.5; HRMS-ESI *m/z* 527.3252 $[M + H]^+$ ($C_{34}H_{43}N_2O_3$ required 527.3274).

4.2.12. 1-*O*-Benzoyl-4,5,7-tri-*O*-benzyl-2,3,6-trideoxy-2,6-imino-D-*manno*-heptitol (15f). To a solution of aziridine **5** (30 mg, 0.07 mmol) in CH_2Cl_2 (3 mL) was added benzoic acid (11.1 mg, 0.09 mmol). The reaction was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography (2:8, PE/AcOEt) to give **15f** as a white solid (29 mg, 75%); $[\alpha]_D^{20}$ +25.4 ($c = 0.5$, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 1.79 (ddd, 1H, $J = 4.7$, 9.0, 13.5 Hz), 2.06 (dt + br s, 2H, $J = 4.7$, 4.7, 13.4 Hz), 3.21 (dt, 1H, $J = 5.3$, 7.1 Hz), 3.38 (t, 1H, $J = 7.1$ Hz), 3.48 (m, 1H), 3.66 (d, 2H, $J = 5.3$ Hz), 3.77 (m, 1H), 4.34 (m, 2H), 4.46–4.60 (m, 5H), 4.82 (d, 1H, $J = 11.4$ Hz), 7.25–7.43 (m, 17H), 7.54 (m, 1H), 8.05 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 30.8, 48.2, 54.4, 65.5, 70.3, 71.6, 73.2, 73.9, 77.3, 78.3, 127.5–128.4, 129.6, 130.0, 133.0, 138.2, 138.4, 138.5, 166.2; MS-IS *m/z* 552 $[M + H]^+$. IR (film) *v* 1712 (C=O), 3346 (NH) cm^{-1}.

4.2.13. 4,5,7-Tri-*O*-benzyl-1-*O*-butanoyl-2,3,6-trideoxy-2,6-imino-D-*manno*-heptitol (15g). To a solution of aziridine **5** (30 mg, 0.07 mmol) in CH_2Cl_2 (3 mL) was added butanoic acid (7.9 mg, 0.09 mmol). The reaction was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography (7:3 to 5:5: PE/AcOEt) to give **15g** as a pale yellow oil (29.5 mg, 82%); $[\alpha]_D^{20}$ +19.6 ($c = 0.9$, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 0.90 (t, 3H, $J = 7.4$ Hz), 1.61 (m, 2H, $J = 7.4$ Hz), 1.71 (ddd, 1H, $J = 5.0$, 8.9, 13.6 Hz), 1.95 (dt, 1H, $J = 5.0$, 5.0, 13.5 Hz), 2.26 (t, 2H, $J = 7.4$ Hz), 2.45 (br, 1H, NH), 3.10 (dt, 1H, $J = 5.1$, 5.1, 7 Hz), 3.30 (m, 1H), 3.35 (t, 1H, $J = 7.3$ Hz), 3.61 (d, 2H, $J = 5.1$ Hz), 3.70 (m, 1H), 4.00 (dd, 1H, $J = 5.4$, 11.0 Hz), 4.14 (dd, 1H, $J = 8.5$, 11.0 Hz), 4.41–4.62 (m, 5H), 4.78 (d, 1H, $J = 11.3$ Hz), 7.24–7.28 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 13.6, 18.4, 30.8, 36.0, 48.1, 54.2, 64.7, 70.1, 71.6, 73.1, 73.9, 77.3, 78.3, 127.5–128.4, 138.2, 138.4, 173.4; MS-IS *m/z* 540 $[M + Na]^+$, 518 $[M + H]^+$; IR (film) *v* 1735 (C=O), 3352 (NH) cm^{-1}.

4.2.14. 4,5,7-Tri-*O*-benzyl-1-*O*-(benzyloxycarbonylamino-acetyl)-2,3,6-trideoxy-2,6-imino-D-*manno*-heptitol (15h). To a solution of aziridine **5** (25 mg, 0.058 mmol) in CH_2Cl_2 (3 mL) was added Z-glycine (18.2 mg, 0.087 mmol). The reaction was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography using AcOEt as eluant to give **15h** as a pale yellow oil (27 mg, 74%); $[\alpha]_D^{20}$ +20.4 ($c = 1.2$, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 1.72 (m, 1H), 1.92 (m, 1H), 2.07 (br s, 1H), 3.05 (m, 1H), 3.35 (m, 2H), 3.59–3.65 (m, 3H), 3.93 (m, 2H), 4.06 (dd, 1H, $J = 5.6$, 10.7 Hz), 4.22 (t, 1H, $J = 9.6$ Hz), 4.40–4.56 (m, 5H), 4.77 (d, 1H, $J = 11.4$ Hz), 5.11 (s, 2H), 5.21 (m, 1H), 7.25–7.33 (m, 20H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 30.9, 42.8, 48.1, 54.4, 65.9, 67.2, 70.0, 71.7, 73.2, 74.0, 77.3, 78.2, 127.7–128.6, 136.3, 138.3, 138.5, 156.3, 169.9; HRMS-ESI *m/z* 661.2883 $[M + Na]^+$ ($C_{38}H_{42}N_2O_7Na$ required 661.2890).

4.2.15. 4,5,7-Tri-*O*-benzyl-2,3,6-trideoxy-1-*O*-(4-nitro-benzoyl)-2,6-imino-D-*manno*-heptitol (15i). To a solution of aziridine **5** (30 mg, 0.070 mmol) in CH_2Cl_2 (2 mL) was added 4-nitrobenzoic acid (15.2 mg, 0.091 mmol). The reaction was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography (2/8, PE/AcOEt) to give **15i** as a solid (33 mg, 79%); $[\alpha]_D^{20}$ +28.2 ($c = 0.5$, $CHCl_3$); δ_H 1.79 (ddd, 1H, $J = 4.7$, 8.8, 13.7 Hz), 2.01 (dt, 1H, $J = 4.6$, 4.6, 13.7 Hz), 2.16 (br s, 1H), 3.20 ($\sim$ q, 1H), 3.38 (t, 1H, $J = 7.1$ Hz), 3.48 (m, 1H), 3.66 (d, 2H, $J = 5.5$ Hz), 3.76 (m, 1H), 4.29–4.55 (m, 5H), 4.59 (s, 2H), 4.80 (d, 1H, $J = 11.5$ Hz), 7.27–7.30 (m, 15H), 8.10 (s, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 30.7, 47.8, 54.3, 66.2, 70.2, 71.6, 73.2, 73.9, 77.1, 78.1, 123.5, 127.5–128.3, 130.6, 135.2, 138.1, 138.3, 150.4, 164.3; IR (film) *v* 1717 (C=O), 3352 (NH) cm^{-1}.

4.2.16. 4,5,7-Tri-*O*-benzyl-1-*O*-(dibenzyloxyphosphoryl)-2,3,6-trideoxy-2,6-imino-D-*manno*-heptitol (15j). To a solution of aziridine **5** (20 mg, 0.046 mmol) in CH_2Cl_2 (1 mL) was added dibenzyl phosphate (15.5 mg, 0.056 mmol). The reaction was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography using AcOEt as eluant to give **15j** as a colourless oil (25 mg, 78%); $[\alpha]_D^{20}$ +16.1 ($c = 1.3$, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 1.66 (ddd, 1H, $J = 4.8$, 9.2, 13.6 Hz), 1.90 (dt, 1H, $J = 4.7$, 4.7, 13.5 Hz), 2.27 (br s, 1H), 3.02 (m, 1H), 3.24 (m, 1H), 3.32 (t, 1H, $J = 7.2$ Hz), 3.56 (m, 2H), 3.61 (m, 1H), 3.85 (dt, 1H, $J = 6.0$, 6.0, 11.6 Hz), 4.02 ($\sim$ q, 1H), 4.37–4.57 (m, 5H), 4.76 (d, 1H, $J = 11.2$ Hz), 5.00 (d, 4H, $J = 8.4$ Hz), 7.25–7.29 (m, 25H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 30.1, 49.0 (d, $J = 7.8$ Hz), 54.0, 67.8 (d, $J = 6.0$ Hz), 69.2 (d, $J = 5.4$ Hz), 70.0, 71.3, 73.0, 73.8, 77.1, 78.1, 127.4–128.4, 135.6 (d, $J = 6.7$ Hz), 138.0, 138.3 (2C); HRMS-ESI *m/z* 708.3097 $[M + H]^+$ ($C_{42}H_{47}NO_7P$ required 708.3090).

4.2.17. 2,3,6-Trideoxy-2,6-imino-D-*manno*-heptitol-1-phosphate (15k). To a solution of **15j** (35 mg, 0.049 mmol) in MeOH (1 mL) were added 1 N HCl (0.1 equiv) and the filtrate was 10% Pd/C (0.2 equiv). The reaction mixture was stirred under H_2 (1 atm) overnight and then the catalyst was removed by filtration on a pad of Celite and neutralized with a minimal amount of Dowex 1-X2 (OH^-) ion exchange resin. The solvent was removed under reduced pressure to afford compound **15k** as a colourless oil (10.8 mg, 85%); $[\alpha]_D^{20}$ +25.5 ($c = 0.2$, H_2O); ^1H NMR (250 MHz, D_2O; ref. AcOH $\delta = 2.04$): δ_H 1.89 (ddd, 1H, $J = 5.3$, 9.7, 14.7 Hz), 2.22 (dt, 1H, $J = 4.2$, 4.2, 14.7 Hz), 3.44 (m, 1H), 3.63 (t, 1H, $J = 8.2$ Hz), 3.86–3.98 (m, 3H), 4.04 (m, 1H), 4.13 (m, 2H); ^{13}C NMR (62.9 MHz, D_2O–TSP[39]): δ_C 28.3 (CH_2), 50.3 (CH, d, $J = 7.8$ Hz), 56.0 (CH), 56.04 (CH_2), 61.9 (CH_2, d, $J = 7.8$ Hz), 66.2

(CH), 67.6 (CH); HRMS-FAB *m/z* 258.0741 $[M + H]^+$ ($C_7H_{17}NO_7P$ required 258.0743).

4.2.18. (2*R*,3*R*,4*R*,6*R*)-3,4-Di(benzyloxy)-2-benzyloxymethyl-6-ethylpiperidine (16). A solution of 1.4 M methyllithium (0.189 mmol, 0.135 mL) in diethylether was added at −50 °C to a slurry of CuI (0.117 mmol, 22.3 mg) in dry THF (1 mL). After 1 h a solution of crude iodomethyl derivative **14** (0.09 mmol, 50.1 mg) in THF (0.5 mL) was added slowly. The reaction was stirred overnight at room temperature, quenched with a saturated aqueous solution of NH_4Cl (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by column chromatography (100% AcOEt) to give the desired compound **16** as a colourless oil (16.9 mg, 65%); $[\alpha]_D^{20}$ +24.1 (*c* = 1.4, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 0.87 (t, 3H, *J* = 7.5 Hz), 1.35–1.50 (m, 2H), 1.65 (ddd, 1H), 1.93 (m, 2H), 2.90 (m, 1H), 3.00 (m, 1H), 3.34 (t, 1H, *J* = 7.9 Hz), 3.62 (d, 2H, *J* = 4.7 Hz), 3.70 (m, 1H), 4.41–4.60 (m, 5H), 4.82 (d, 1H, *J* = 11.0 Hz), 7.24–7.31 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 11.1, 25.5, 34.0, 51.5, 54.0, 70.4, 71.4, 73.1, 74.2, 78.0, 79.3, 127.5–128.3, 138.3, 138.6, 138.7; HRMS-CI *m/z* 446.2699 $[M + H]^+$ ($C_{29}H_{36}NO_3$ required 446.2695).

4.2.19. (2*R*,3*R*,4*R*,6*R*)-3,4-Di(benzyloxy)-2-benzyloxymethyl-6-butylpiperidine (17). A solution of 2.0 M propylmagnesium chloride (0.094 mL, 0.189 mmol) in diethylether was added at −50 °C to a slurry of CuI (22.3 mg, 0.117 mmol) in dry THF (1 mL). After 1 h a solution of crude iodomethyl derivative **14** (50.1 mg 0.09 mmol) in THF (0.5 mL) was added dropwise. The reaction was stirred overnight at room temperature, quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the residue was purified by column chromatography (5:5, PE/AcOEt) to give the desired compound **17** as a pale yellow oil (14 mg, 32%); $[\alpha]_D^{20}$ +21.6 (*c* = 0.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 0.88 (t, 3H, *J* = 6.3 Hz), 1.16–1.52 (m, 6H), 1.64 (m, 1H), 1.92 (m, 2H), 3.01 (m, 2H), 3.34 (t, 1H, *J* = 7.9 Hz), 3.63 (d, 2H, *J* = 4.7 Hz), 3.69 (m, 1H), 4.41–4.60 (m, 5H), 4.82 (d, 1H, *J* = 11.3 Hz), 7.25–7.31 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 14.1, 22.7, 28.9, 32.2, 34.3, 50.0, 54.1, 70.3, 71.5, 73.2, 74.3, 77.9, 79.4, 127.5–128.3, 138.3, 138.6, 138.7; MS-IS *m/z* 474.8 $[M + H]^+$.

4.2.20. (2*R*,3*R*,4*R*,6*R*)-2-Hydroxymethyl-6-ethylpiperidine-3,4-diol (4). To a solution of **16** (40 mg, 0.09 mmol) in MeOH (3 mL) were added 1 N HCl (0.1 equiv) and 10% Pd/C (0.2 equiv). The reaction mixture was stirred under H_2 (1 atm) overnight and the solids were removed by filtration on a pad of Celite. The solvent was removed under reduced pressure and the residue was purified on Dowex 1-X2 (OH^-) ion exchange resin (elution with water). The combined fractions were lyophilized to afford compound **4** as a white foam (13.8 mg, 88%); $[\alpha]_D^{20}$ +42.3 (*c* = 0.4, H_2O); ^1H NMR (250 MHz, D_2O–MeOH[39]): δ_H 0.88 (t, 3H, *J* = 7.5 Hz), 1.49–1.63 (m, 3H), 2.01 (ddd, 1H, *J* = 2.0, 5.0, 13.1 Hz), 2.79 (ddd, 1H, *J* = 3.0, 7.2, 10.0 Hz), 2.95 (m, 1H), 3.12 (t, 1H, *J* = 9.5 Hz), 3.55 (dd, 1H, *J* = 7.1, 11.9 Hz), 3.73 (ddd, 1H, *J* = 5.1, 9.1, 11.9 Hz), 3.89 (dd, 1H, *J* = 3.1, 11.9 Hz); ^{13}C NMR (62.9 MHz, D_2O–TSP[39]): δ_C 11.0, 24.0, 35.4, 53.1, 55.3, 62.9, 70.3, 74.5; MS-IS *m/z* 176.5 $[M + H]^+$; HRMS-CI *m/z* 176.1281 $[M + H]^+$ ($C_8H_{18}NO_3$ required 176.1286).

4.2.21. 4,5,7-Tri-*O*-benzyl-2,3,6-trideoxy-2,6-imino-D-*manno*-heptitol (18). To a solution of ester **15f** (24 mg, 0.44 mmol) in dry MeOH under argon (2 mL) was added sodium (2.2 mg, 0.088 mmol). The reaction was stirred 4 h at room temperature and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using AcOEt as eluant to give the desired compound **18** as a colourless oil (16.9 mg, 86%); $[\alpha]_D^{20}$ +29.5 (*c* = 0.4, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 1.67 (ddd, 1H, *J* = 5.5, 9.5, 13.7 Hz), 1.92 (dt, 1H, *J* = 4.2, 4.2, 13.5 Hz), 2.62 (br s, 2H), 2.89 (m, 1H), 3.14 (m, 1H), 3.36–3.69 (m, 5H), 3.81 (dd, 1H, *J* = 4.6, 9.0 Hz), 4.41–4.64 (m, 5H), 4.80 (d, 1H, *J* = 11.1Hz), 7.24–7.30 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 31.5, 51.0, 53.7, 61.7, 69.1, 71.5, 73.2, 74.2, 77.7, 78.5, 127.5–128.3, 138.0, 138.4 (2C); MS-IS *m/z* 448.5 $[M + H]^+$. HRMS-ESI *m/z* 448.2484 $[M + H]^+$ ($C_{28}H_{34}NO_4$ required 448.2488).

4.2.22. 2,3,6-Trideoxy-2,6-imino-D-*manno*-heptitol (19). To a solution of **18** (30 mg, 0.067 mmol) in MeOH (2 mL) were added 1 N HCl (0.1 equiv) and 10% Pd/C (0.2 equiv). The reaction mixture was stirred under H_2 (1 atm) overnight and then filtered on a pad of Celite. The solvent was removed under reduced pressure and the residue was purified on Dowex 1-X2 (OH^-) ion exchange resin (elution with water). The combined fractions were lyophilized to afford compound **19** as a colourless oil (10 mg, 87%); $[\alpha]_D^{20}$ +29.1 (*c* = 0.4, H_2O); ^1H NMR (500 MHz, D_2O–TSP[39]): δ_H 1.66 (ddd, 1H, *J* = 6.0, 11.9, 13.3 Hz), 2.01 (ddd, 1H, *J* = 1.8, 5.0, 13.3 Hz), 2.82 (ddd, 1H, *J* = 2.8, 7.8, 9.2 Hz), 3.18 (dd, 1H, *J* = 9.2 Hz), 3.16–3.21 (m, 1H), 3.60 (dd, 1H, *J* = 7.8, 11.5 Hz), 3.61 (dd, 1H, *J* = 6.0, 11.5 Hz), 3.69 (ddd, 1H, *J* = 5.0, 9.2, 11.9 Hz), 3.79 (dd, 1H, *J* = 9.2, 11.5 Hz), 3.91 (dd, 1H, *J* = 2.8, 11.5 Hz); ^{13}C NMR (125 MHz, D_2O–TSP[39]): δ_C 34.8, 54.8, 57.7, 63.1, 64.9, 72.3, 76.3; [Natural 2,3,6-trideoxy-2,6-imino-D-*manno*-heptitol[31] (same conditions): δ_C 34.9, 54.9, 57.7, 63.2, 65.0, 72.4, 76.4.]; MS-IS *m/z* 200 $[M + Na]^+$, 178 $[M + H]^+$; HRMS-FAB *m/z* 178.1078 $[M + H]^+$ ($C_7H_{16}NO_4$ required 178.1079).

4.2.23. 4,5,7-Tri-*O*-benzyl-1-*O*-butanoyl-*N*-butyl-2,3,6-trideoxy-2,6-imino-D-*manno*-heptitol (20). To a mixture of iminosugar **15g** (120 mg, 0.23 mmol), butanal (42 μL, 0.46 mmol), glacial acetic acid (40 μL, 0.7 mmol) and powdered 3 Å molecular sieves (125 mg) in anhydrous MeOH, was added $NaBH_3CN$ (18 mg, 0.28 mmol). The reaction mixture was stirred overnight at room temperature and then the solids were removed by filtration through a pad of Celite. The solids were washed with EtOAc (20 mL), the organic solvent was removed under reduced pressure and the residue was

purified by column chromatography (5:5, PE/AcOEt) to give the desired compound **20** as colourless oil (102 mg, 78%); $[\alpha]_D^{20}$ −18.0 (c = 0.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ_H 0.89 (t, 3H, J = 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz), 1.23–1.77 (m, 8H), 2.02 (m, 1H), 2.26 (t, 2H, J = 7.3 Hz), 2.68 (m, 2H), 2.85 (m, 1H), 3.24 (m, 1H), 3.58–3.75 (m, 4H), 4.06 (dd, 1H, J = 7.3, 11.1 Hz), 4.19 (dd, 1H, J = 5.5, 11.1 Hz), 4.46–4.62 (m, 5H), 4.83 (d, 1H, J = 11.1 Hz), 7.22–7.25 (m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C 13.6, 14.0, 18.3, 20.6, 29.1, 30.8, 36.1, 37.1, 48.7, 53.0, 59.4, 62.2, 67.2, 71.3, 73.1, 74.1, 78.0, 78.1, 127.4–128.2, 138.0, 138.6, 138.7, 173.4; MS-IS m/z 574.5 $[M + H]^+$; IR (film) ν 1737 (C═O) cm^{-1}.

4.2.24. *N*-Butyl-2,3,6-trideoxy-2,6-imino-D-*manno*-heptitol (21). To a solution of **20** (23 mg, 0.040 mmol) in MeOH (2 mL) were added 1 N HCl (0.1 equiv) and 10% Pd/C (0.2 equiv). The reaction mixture was stirred under H_2 (1 atm) overnight and the solids were removed by filtration on a pad of Celite. Dowex 1-X2 (OH^-) resin was added to the filtrate and after 1 h, the reaction mixture was filtered. The solvent was removed under reduced pressure to afford compound **21** as a colourless oil (8.2 mg, 88%); $[\alpha]_D^{20}$ −7.1 (c = 0.5, H_2O); ^1H NMR (250 MHz, D_2O): δ_H 0.91 (t, 3H, J = 7.0 Hz), 1.24–1.56 (m, 4H), 1.65 (dt, 1H, J = 5.2, 13.0, 13.0 Hz), 2.05 (ddd, 1H, J = 2.2, 5.0, 13.5 Hz), 2.55–2.75 (m, 3H), 3.17 (m, 1H), 3.40 (t, 1H, J = 9.8 Hz), 3.61–3.94 (m, 5H); ^{13}C NMR (62.5 MHz, D_2O): δ_C 15.5, 22.5, 31.7, 32.2, 50.1, 57.6, 60.0, 61.0, 63.5, 72.1, 73.8. HRFABMS m/z 234.1707 $[M + H]^+$ ($C_{11}H_{24}NO_4$ required 234.1705).

4.3. Biochemical assays

Brush border membranes prepared from rat small intestine according to the method of Kessler et al.[40] were used as the enzyme source of rat intestinal α-glucosidases. Other enzymes were purchased from Sigma Chemical Co. The activities of rice α-glucosidase and rat intestinal α-glucosidases were determined using an appropriate disaccharide as substrate. The released D-glucose was determined colourimetrically using glucose B-test Wako (Wako Pure Chemical Ind.). Other glycosidase activities were determined using an appropriate *p*-nitrophenyl glycoside as substrate. The reaction was stopped by adding 400 mM Na_2CO_3. The released *p*-nitrophenol was measured spectrometrically at 400 nm. Glycogen phosphorylase activity was assayed in the direction of glycogen breakdown from the photometrical determination of the rate of NADPH formation in an assayed coupled to phosphoglucomutase and glucose 6-phosphate dehydrogenase according to the method of Maddaiah and Madsen.[41]

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