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Carbohydrate Research 342 (2007) 1813–1830
Carbohydrate RESEARCH

Synthesis and biological evaluation of a small library of nojirimycin-derived bicyclic iminosugars

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Received 22 February 2007; received in revised form 4 April 2007; accepted 9 April 2007
Available online 18 April 2007

Abstract—Novel nojirimycin-derived bicyclic structures, containing cyclic carbamate, urea and guanidine moieties have been synthesised starting from suitably protected α-*C*-vinylnojirimycin and α-*C*-allylnojirimycin, respectively, and their biological activity against different glycosidases and as antibacterial agents tested.
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Keywords: Iminosugars; Nojirimycin; Glycosidases; Enzyme inhibitors; Glucuronidase; Antibacterial

1. Introduction

Polyhydroxylated alkaloids, usually referred to as iminosugars, display a wide range of interesting biological activities, suggesting their potential use in the treatment of a number of diseases. Mainly, they are known for their inhibitory activity towards carbohydrate-processing enzymes,[1] suggesting their use in different therapeutic applications, such as treatment of diverse viral infections,[2] that is, human immunodeficiency virus (HIV),[2a–d] human hepatitis B virus (HBV),[2b,d,e] human hepatitis C (HCV),[2f,g] bovine viral diarrhoea virus (BVDV),[2g] Japanese encephalitis virus (JEV)[2h] and dengue virus,[2h] as well as cancer,[3] diabetes,[4] tuberculosis,[5] malaria[5b] and lysosomal storage diseases.[6] Due to the tremendous potential of iminosugars, in the last several years a variety of monocyclic and bicyclic iminosugars have been synthesised[7] or isolated from natural sources.[1b] In particular, the *core* structure of a bicyclic iminosugar may contain various heterocyclic rings, such as the [4.3.0] indolizine system, or the [3.3.0] pyrrolizidine system. It has been suggested that their rigid, bicyclic structures are responsible for their potent activity, mimicking the flattened-chair transition state of the enzymatic reaction.[1e,8] In addition, it was demonstrated[1e] that the interaction between a heteroatom possessing a protonable lone pair suitably positioned in the molecule can influence the inhibitory activity. In connection with the design of more fine-tuned inhibitors, numerous syntheses of these alkaloids have been reported.[9] The design of non-natural bicyclic iminosugars has driven the synthesis of a number of different innovative structures.[10]

We report herein the synthesis of a variety of novel nojirimycin-derived bicyclic analogs, the six-membered ring of which has a flattened-chair conformation as a result of its fusion with the second ring. An innovative feature of these bicyclic structures is the introduction of pharmacophoric groups, such as cyclic carbamate, urea and guanidine moieties. Cyclic carbamates such as 1,3-oxazolidin-2-ones and 1,3-oxazinan-2-ones are important target molecules: oxazolidinones are relevant pharmacophores in antibiotics against highly resistant Gram-positive bacteria,[11] while 1,3-oxazinan-2-ones are important heterocycles present in several biologically active natural products such as maytansine and its analogues,[12] and are investigated as anti-cancer drugs.[12] In addition, ring-annulated 2-oxazolidinones

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doi:10.1016/j.carres.2007.04.002

can be used as precursors of iminosugar structures.[13] The urea pharmacophore is present in several molecules with therapeutic applications,[14] as far as the guanidinium group is included in many natural and unnatural derivatives, displaying an array of potent, selective and specific biological activities.[15] Preliminary biological evaluation of the synthesised compounds focused on glycosidase inhibition and antibacterial activity.

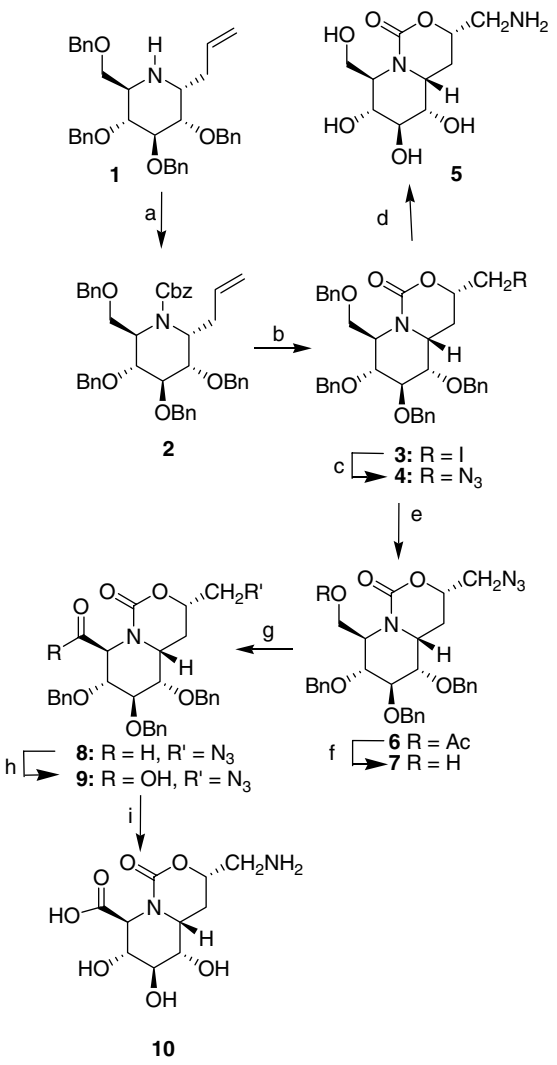
2. Results and discussion

To generate a small library of bicyclic iminosugars, five- or six-membered rings were fused to nojirimycin. Carbamate, urea, and guanidine functionality was introduced on the nitrogen atom, and amino, hydroxyl or carboxylic groups were positioned on the bicyclic scaffolds. Cyclic carbamates (1,3-oxazolidin-2-ones and 1,3-oxazinan-2-ones), cyclic ureas (1,3-diazolidin-2-ones and 1,3-diazinan-2-ones) and cyclic guanidines (2-imino-1,3-diazolidines and 2-imino-1,3-diazinanes) have been synthesised from key compounds α-*C*-allyl nojirimycin **1**,[16] and α-*C*-vinyl nojirimycin; the different position of the double bond afforded the six-membered or the five-membered nojirimycin-fused ring, respectively.

2.1. Synthesis of oxazolidinones and oxazinanones

α-*C*-Allyl nojirimycin **1**[16] was protected as carbobenzyloxy derivative **2** (58% yield, Scheme 1), with benzyl chloroformate and diisopropylethylamine (DIPEA), to allow an iodocyclisation reaction between the double bond and the benzyloxy group in position 2 producing a cyclic iodoether, as already reported for allyl-*C*-glycosides.[17] However, when compound **2** was reacted with iodine at 10 °C, a iodocyclisation reaction[18] occurred, affording the bicyclic iododerivative **3** (92% yield, de >95% in favour of *S* isomer). The stereochemical outcome of the reaction was determined by NOESY experiments on derivative **6**.

The nojirimycin-fused 1,3-oxazinan-2-one **3** was then further functionalised. Nucleophilic substitution of iodine with tetrabutylammonium iodide and sodium azide in dry *N*,*N*-dimethylformamide afforded the azido-bicyclic derivative **4** (reflux, 88% yield). Then, compound **4** was submitted to selective acetolysis of the primary benzyloxy group[19] using a mixture of acetic anhydride in trifluoroacetic acid obtaining compound **6** (72% yield). NOESY experiments on acetate **6** allowed the determination of the absolute configuration of the stereocentre generated in the iodocarbamoylation reaction, which was *S*. Oxazinanone **6** was further functionalised with a carboxyl group as follows. Compound **6** was deacetylated under Zémplen conditions (Na, MeOH)[20] affording alcohol **7** (95% yield). Alcohol **7** was then oxidised to the intermediate aldehyde **8** with



Scheme 1. Reagents and conditions. (a) CbzCl, DIPEA, dry MeCN, 58%; (b) I_2, dry CH_2Cl_2, 0 °C, 92%; (c) NaN_3, *n*-Bu_4NI, dry CH_2Cl_2, 88%; (d) H_2, $Pd(OH)_2$/C, 1:1 MeOH–H_2O, AcOH, quantitative yield; (e) Ac_2O, TFA, 72%; (f) dry MeOH, cat. Na, 95%; (g) IBX, DMSO; (h) $NaPO_4H_2.2H_2O$, $NaClO_2$, CH_3CN, 72% over two steps; (i) H_2, $Pd(OH)_2$/C, 1:1 acetone–H_2O, AcOH, quantitative yield.

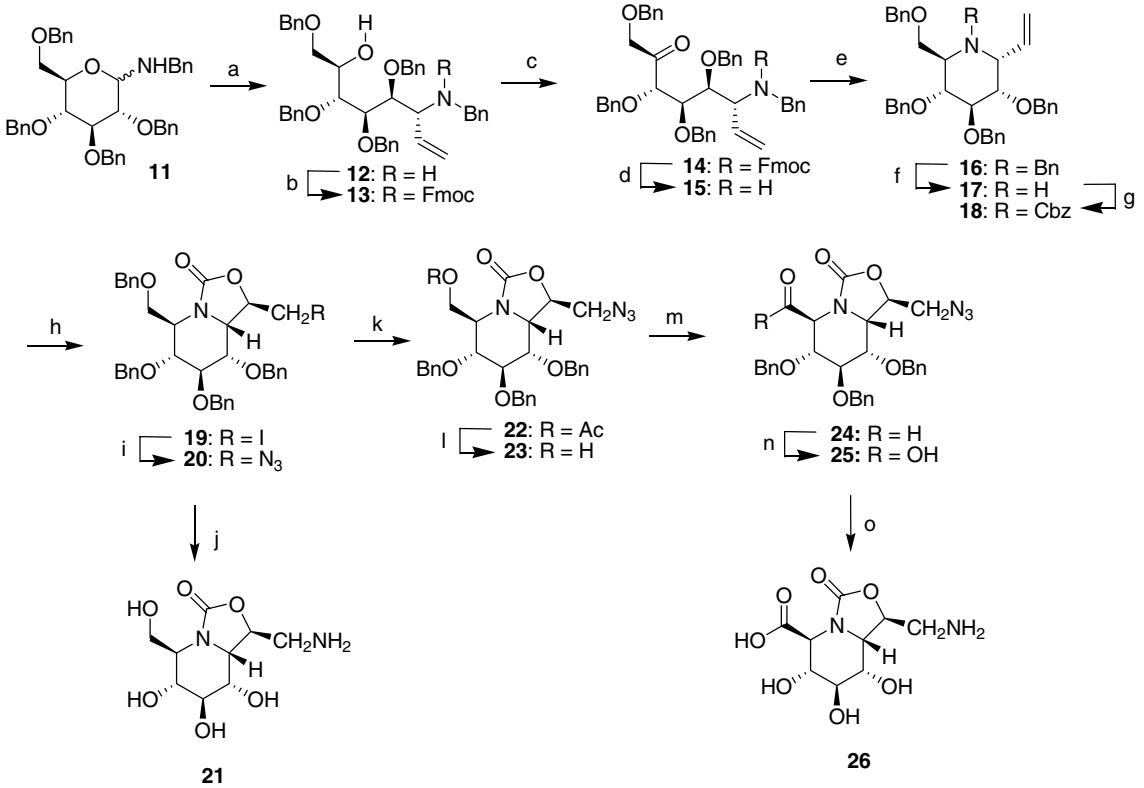
IBX in dimethylsulfoxide,[21] that was directly transformed into azido acid derivative **9** ($NaPO_4H_2{\cdot}2H_2O$, $NaClO_2$, CH_3CN, 72% yield over two steps).[22] Compounds **4** and **9** were finally deprotected by hydrogenolysis, with simultaneous reduction of the azido function to the corresponding amino group yielding compounds **5** and **10**, respectively.

Looking at the second ring potentiality, we thought that the five-membered 1,3-oxazolidin-2-one fused to the nojirimycin moiety could be of great interest. Starting from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, the corresponding glucosyl benzylamine **11**[16a] was formed in quantitative yields by reaction with benzylamine and catalytic camphor-10-sulfonic acid (CSA).

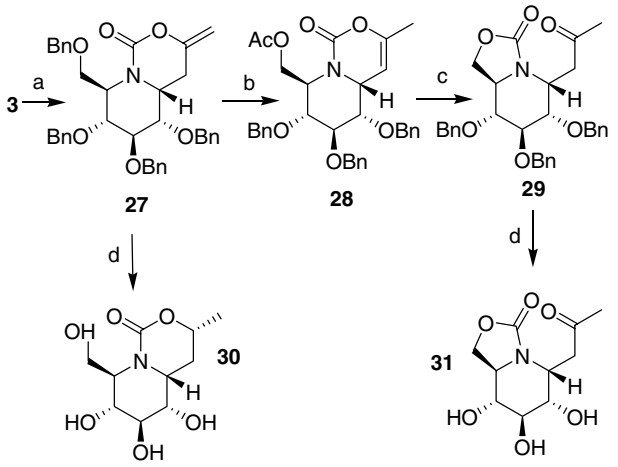
Reaction of **11** (Scheme 2) with vinylmagnesium bromide (1 M in THF) afforded the open-chain amino alcohol **12** (63% yield, 70% de). The stereochemistry of the newly formed stereocentre was determined only after ring closure by reductive amination. To oxidise the hydroxyl group of **12** into the corresponding ketone, protection of the nitrogen was needed.[16a] Compound **12** was therefore reacted with fluorenylmethyl chloroformate and diisopropylethylamine in dry acetonitrile, affording the Fmoc-protected amino alcohol **13** in quantitative yields. Oxidation of **13** with IBX in dry DMSO afforded compound **14** in 97% yield. Finally, in a two-step procedure, hydrolysis of the Fmoc protecting group, using diethylamine in dry acetonitrile, to the labile intermediate **15**, followed by intramolecular reductive amination (triacetoxyborohydride, glacial acetic acid) afforded the *C*-vinyl nojirimycin derivative **16** (65% yield over two steps, 60% de). ^{1}H NMR and NOESY analysis of **16** allowed the determination of the absolute configuration of the stereocentres derived from the previous Grignard reaction and the cyclisation reaction. *J* values between H-2/H-3, H-3/H-4 and H-4/H-5 (9.5 Hz) showed that the nojirimycin ring adopts a $^4C_1$ chair conformation; in addition, NOESY experiments and *J* values between H-4 and H-5 (9.5 Hz) indicate the D-configuration at C-5, while the *J* values between H-1/H-2 (5.5 Hz), suggest the α orientation of the vinyl group.

To further proceed to the bicyclic oxazolidinone derivative, selective debenzylation of the tertiary nitrogen of the ring was performed, by oxidative cleavage with ceric ammonium nitrate (CAN),[16b] affording the N-deprotected compound **17**. Carbamoylation of crude **17** with benzyl chloroformate afforded compound **18** (CbzCl, DIPEA in dry CH_3CN, 54% yield over two steps), the reaction of which at 0 °C with iodine in dry dichloromethane afforded, as expected, the bicyclic iodo derivative **19** (84% yield, de >95%). ^{1}H NMR and NOESY experiments allowed the determination of the absolute configuration of the new stereocentre, which in this case was *R*.

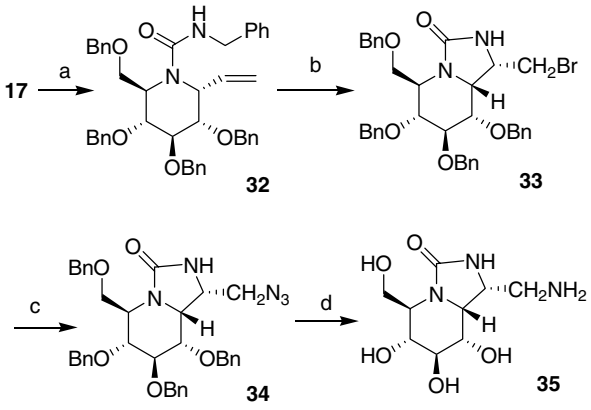
The oxazolidinone **19** was further functionalised first by nucleophilic substitution of the iodide with an azido function (tetrabutylammonium iodide and sodium azide in dry DMF, reflux) affording azido derivative **20** in 97% yield. The primary hydroxyl group at C-6 of compound **20** was selectively debenzylated by acetolysis (Ac_2O, TFA)[19] to give the acetylated compound **22** in 74% yield. Deacetylation at C-6, under Zémplen conditions[20] afforded alcohol **23** (78% yield). Finally, a two-step



Scheme 2. Reagents and conditions. (a) CH_2=$CHMgBr$, dry THF, 63%; (b) FmocCl, DIPEA, dry MeCN, quantitative yield; (c) IBX, DMSO, 97%; (d) DEA, dry MeCN; (e) $NaBH(OAc)_3$, Na_2SO_4, AcOH, 65% over two steps; (f) CAN, 5:1 THF–H_2O; (g) CbzCl, DIPEA, dry MeCN, 54% over two steps; (h) I_2, 0 °C, dry CH_2Cl_2, 84%; (i) NaN_3, *n*-Bu_4NI, dry CH_2Cl_2, 97%; (j) H_2, $Pd(OH)_2$/C, 1:1 MeOH–H_2O, AcOH, quantitative yield; (k) Ac_2O, TFA, 74%; (l) dry MeOH, cat. Na, 78%; (m) IBX, DMSO; (n) $NaPO_4H_2{\cdot}2H_2O$, $NaClO_2$, MeCN, 83% over two steps; (o) H_2, $Pd(OH)_2$/C, 1:1 acetone–H_2O, AcOH, quantitative yield.



Scheme 3. Reagents and conditions. (a) *n*-Bu_4NOH, CH_3CN, 98%; (b) Ac_2O, TFA, 59%; (c) dry MeOH, cat. Na, 70%; (d) H_2, $Pd(OH)_2$/C, AcOH, 1:1 MeOH–H_2O, quantitative yield.



Scheme 4. Reagents and conditions. (a) Benzyl isocyanate, dry DME, 80 °C, 94%; (b) NBS 2 equiv, dry CH_2Cl_2, 0 °C, 65%; (c) NaN_3, dry DMF, 79%; (d) H_2, $Pd(OH)_2$/C, AcOH, 1:1 MeOH–H_2O, quantitative yield.

oxidation procedure (IBX in DMSO to aldehyde **24**, then $NaPO_4H_2{\cdot}2H_2O$, $NaClO_2$, CH_3CN, 83% yield over two steps) afforded azido acid derivative **25**. Derivatives **20** and **25** were finally deprotected by hydrogenolysis, with simultaneous reduction of the azido function to the corresponding amino group to compounds **21** and **26**, respectively.

To introduce greater structural variation in the second ring, functionalisation with a hydroxyl group was attempted. Treatment of compound **3** with tetrabutylammonium hydroxide afforded compound **27** as the only product (Scheme 3), resulting from a β-elimination reaction, instead of the expected nucleophilic substitution product. With compound **27** in our hands, acetolysis was performed, affording compound **28** (59% yield), which gave, as expected, isomerisation of the double bond. Methanolysis under Zémplen conditions[20] afforded bicycle **29**, formed by intramolecular attack of the free hydroxyl group on the carbonyl group. Derivatives **27** and **29** were finally deprotected by hydrogenolysis, to generate bicyclic iminosugars **30** and **31**, respectively. Reduction of the double bond in **27** was diastereoselective (quantitative yield, de >98%) giving the stereoisomer with the *R* configuration at the newly generated stereocentre, as determined by ^{1}H NMR spectroscopy.

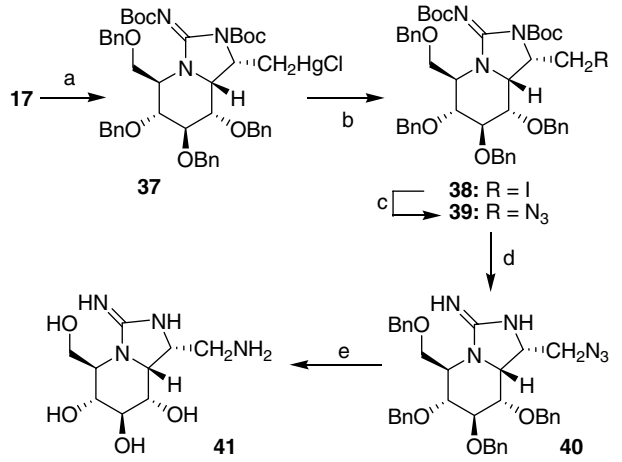
2.2. Synthesis of 1,3-diazolidin-2-ones and 1,3-diazinan-2-ones (cyclic ureas)

To generate a small iminosugar library, variations of the functionality in the second ring were made. First, a 1,3-diazolidin-2-one was synthesised (Scheme 4). Vinyl-*C*-nojirimycin **17** was reacted with benzyl isocyanate,[23] affording urea **32** in 94% yield. Treatment of **32** with *N*-bromosuccinimide in dry dichloromethane afforded the five-membered cyclic urea **33**. The cyclisation product originates from the nucleophilic attack of the nitrogen on the activated double bond; no traces of the product derived from the competing attack by the carbonyl oxygen could be detected. It is worth noting that during the cyclisation reaction the loss of the *N*-benzyl group was observed. ^{1}H NMR and NOESY experiments allowed the determination of the absolute configuration of the new stereocentre, which was *S*. Further functionalisation of the urea ring involved nucleophilic substitution of the bromine by an azido functionality to give derivative **34** (sodium azide, 79% yield), followed by complete deprotection and reduction to the corresponding amine **35** by hydrogenolysis (quantitative yield).

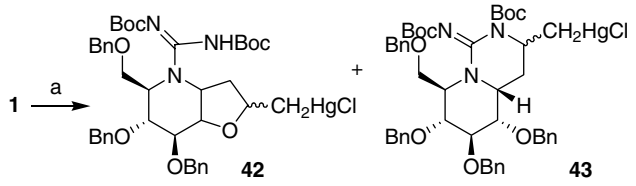
2.3. Synthesis of 2-imino-1,3-diazolidines and 2-imino-1,3-diazinanes (cyclic guanidines)

A cyclic guanidine functionality was also introduced on the nojirimycin ring (Scheme 5). Vinyl-*C*-nojirimycin **17** was reacted with *N*,*N*′-di-Boc-thiourea in the presence of mercuric chloride,[24] affording directly the cyclic protected guanidine derivative **37**, which was submitted without purification to the subsequent reaction. Double nucleophilic displacement, first with iodine to derivative **38** (46% yield over two steps), secondly with sodium azide (61% yield), afforded derivative **39**. The stereochemistry of the newly generated stereocentre was determined by NOESY experiments on derivative **39**. Hydrolysis of the carbamate protecting groups with trifluoroacetic acid to guanidine **40** (86% yield), followed by hydrogenolysis afforded compound **41** (quantitative yield). Attempts to oxidise the primary hydroxyl group of **41** with TEMPO[25] failed.

A guanidine functionality was also considered for the synthesis of six-membered bicyclic structures. Thus, treatment of **1** with *N*,*N*′-di-Boc-thiourea in the presence of mercuric chloride,[24] afforded a mixture of two



Scheme 5. Reagents and conditions. (a) *N*,*N*′-di-Boc-thiourea, $HgCl_2$, Et_3N, dry DMF; (b) I_2, CH_2Cl_2, 46% over two steps; (c) NaN_3, dry DMF, 100 °C, 61%; (d) 4:1 CF_3COOH–H_2O, 86%; (e) H_2, $Pd(OH)_2/C$, AcOH, 1:1 MeOH–H_2O, quantitative yield.



Scheme 6. Reagents and conditions. (a) *N*,*N*′-di-Boc-thiourea, $HgCl_2$, Et_3N, dry DMF.

different bicyclic structures **42** and **43** (Scheme 6), which slowly decomposed. Different reaction conditions were tested in order to selectively obtain only one compound, without any significant improvement.

2.4. Biological evaluation

Fully deprotected iminosugars were assayed as glycosidase inhibitors against commercially available α-glucosidase (yeast), β-glucosidase (almond) and β-glucuronidase (bovine liver). β-Glucuronidase was also tested because it is a target enzyme for anticancer chemotherapy.[26] To examine the potential of each member of the library as glycosidase inhibitor, preliminary screening assays at a fixed concentration (200 μM) of potential inhibitors were carried out. The inhibitory activity is shown as a percentage at the fixed concentration; inhibition data are summarised in Figure 1. The inhibitory activity against the corresponding *p*-nitrophenyl glycosides was estimated by measuring *p*-nitrophenol absorbance at 405 nm. 1-Deoxynojirimycin (DNJ) was used as the reference inhibitor. For compounds showing an interesting inhibitory effect, IC_{50} was also determined.

Compounds **10**, **21**, **26** and **31**, all featuring a cyclic carbamate group were active against α-glucosidase, with inhibition potency higher then the reference 1-deoxynojirimycin (56% inhibition, IC_{50} 180 μM). In particular, compounds **10** and **26** were the most active with 89% (IC_{50} 126 μM) and 82% (IC_{50} 140 μM) inhibition, respectively. Compound **21** and **31** showed 72% and 69% inhibition corresponding to 103 and 148 μM IC_{50}, respectively. Compounds **5** (23% inhibition), **10** (47% inhibition, IC_{50} 218 μM), **21** (11% inhibition) and **26** (45% inhibition, IC_{50} 259 μM) proved to inhibit β-glucuronidase, the best inhibitors being those possessing the carboxylic function at C-6 of the nojirimycin ring, as expected (IC_{50} were determined only for most significant inhibitors). None of the synthesised compounds resulted active against β-glucosidase.

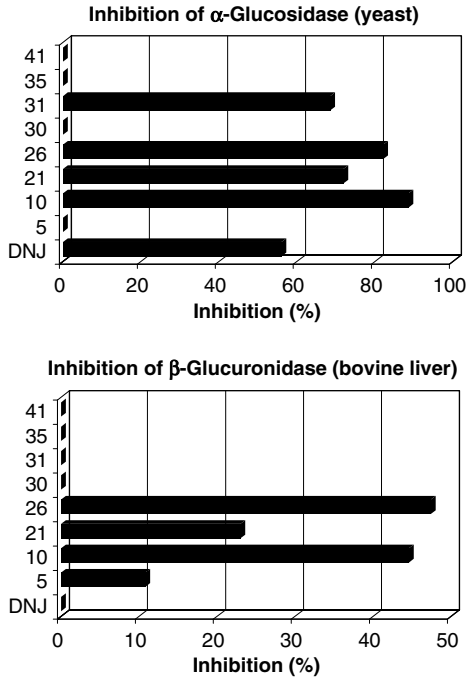


Figure 1. Inhibition of α-glucosidase and β-glucuronidase by bicyclic iminosugars.

Compounds **5**, **10**, **21**, **26**, **30** and **31** were also tested in antibacterial assays against *Enterococcus faecium* (Gram positive), *Staphylococcus aureus* (Gram positive), *Escherichia coli* (Gram negative) and *Pseudomonas aeruginosa* (Gram negative). However none showed antibacterial activity.

3. Experimental

3.1. General methods

All solvents were dried over molecular sieves, for at least 24 h prior to use. When dry conditions were required, the reaction was performed under Ar atmosphere. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} plates (Merck) with detection with UV light when possible, or charring with a solution containing concd H_2SO_4–EtOH–H_2O in a ratio of 5:45:45 or a solution

containing $(NH_4)_6Mo_7O_{24}$ (21 g), $Ce(SO_4)_2$ (1 g), concd H_2SO_4 (31 mL) in H_2O (500 mL). Flash column chromatography was performed on silica gel 230–400 mesh (Merck). NMR spectra were recorded at 400 MHz (^1H) and at 100.57 MHz (^{13}C) on a Varian Mercury instrument. Chemical shifts are reported in parts per million downfield from TMS as an internal standard; *J* values are given in Hz. Numbering refers to parent monosaccharide. Mass spectra were recorded on a MALDI2 Kompakt Kratos instrument, with gentisic acid (DHB) as the matrix. Optical rotations were measured at room temperature with a Krüss-Optronic P3002 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}.

3.2. General procedures for enzymatic assays

Inhibitory activity was determined spectrophotometrically, measuring the residual hydrolytic activities of the glycosidases against the corresponding *p*-nitrophenyl α- or β-D-glucopyranoside, and β-D-glucuronide. α-Glucosidase from yeast, β-glucosidase from almond and β-glucuronidase from bovine liver were used for the enzymatic assays. All enzymes and *p*-nitrophenyl glycosides were purchased from Sigma. Each experiment was carried out in triplicate.

The enzymatic assays were prepared as follow: (a) α-D-glucosidase: 0.94 U/mL in phosphate buffer (0.5 M with 0.244 M K_2HPO_4 and 0.256 M KH_2PO_4, pH 6.5); (b) β-D-glucosidase: 1.2 U/mL in citrate buffer 0.3 M, pH 5.0; (c) β-D-glucuronidase: 120 U/mL in acetate buffer 13.6 M, pH 5.0; (d) *p*-nitrophenyl glycosides (1 mM) were dissolved in water; (e) 1 mM stock solution of inhibitors in water were used for the determination of percentage of inhibition with a 200 μM concentration of the inhibitor in the assay cuvette; various inhibitor's concentrations (50–400 μM) were used to determine IC_{50} values. Each glycosidase assay was performed by preparing 1 mL samples in cuvettes, containing 0.2 mL of buffer, 0.1 mL of enzyme solution and 0.2 mL of water or stock solution with the inhibitor and finally each cuvette was filled up to a total volume of 0.9 mL with distilled water. The mixture was incubated for 10 min at 37 °C, the reaction was started by adding 0.1 mL of the glycoside solution. After 30 min, 0.1 mL of saturated aqueous solution of Na_2CO_3 was added and the absorbance of *p*-nitrophenate was measured at 405 nm. The percentage inhibition was calculated by the formula $(A - B)/A \times 100$, where *A* is the *p*-nitrophenol resulting from the enzymatic hydrolysis without inhibitor and *B* is that in the presence of the inhibitor. The IC_{50} value is the concentration of inhibitor at 50% of enzyme activity.

3.3. Antibacterial assays

Minimal inhibitory concentration (MIC) of the synthesised compounds was determined against four bacterial strains: *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecium*. The test strains were grown for 17–18 h at 37 °C in LB broth[27] and then diluted in the same medium to $OD_{600} = 0.05$. The bacteria (100 μL) were then inoculated in a microtitre plate containing serial dilutions (250–0.12 μg/mL) of the compound in 100 μL. The microtitre plates were incubated 18–20 h at 37 °C and the MIC was defined as the lowest concentration of test compound that inhibited bacterial growth.

3.4. (2*R*,3*R*,4*R*,5*S*,6*R*)-*N*-(Benzyloxycarbonyl)-3,4,5-tris(benzyloxy)-2-benzyloxymethyl-6-(prop-2-enyl)piperidine (2)

To a solution of compound **1** (0.133 g, 0.24 mmol) in dry CH_3CN (3 mL), DIPEA (0.168 mL, 0.98 mmol) and CbzCl (0.184 mL, 1.31 mmol) were added. After 4 h the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (petroleum ether–EtOAc, 85:15), affording compound **2** (0.096 g, 58%) as a yellowish oil. Due to conformational equilibrium between the two chair conformations, broad signals displayed at room temperature ^1H NMR spectrum; to have sharp and resolved signals for unambiguous assignments, the spectrum was recorded at 40 °C. $[\alpha]_D^{22}$ +8.6 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$; 40 °C): δ 7.41–7.25 (m, 25H, Ph), 5.94–5.88 (m, 1H, H-2′), 5.19 (br s, 2H, NCOOCH_2Ph), 5.03 (d, 1H, $J_{3'a,2'} = 17.3$ Hz, H-3′a), 4.95 (d, 1H, $J_{3'b,2'} = 10.1$ Hz, H-3′b), 4.73–4.50 (m, 8H, OC*H*Ph), 4.47–4.41 (m, 1H, H-1), 4.32 (dt, 1H, $J_{5,6} = 8.9$ Hz, $J_{5,4} = 3.8$ Hz, H-5), 4.05 (dd, 1H, $J_{4,5} = 3.8$ Hz, $J_{4,3} = 2.1$ Hz, H-4), 3.95 (br d, 1H, $J_{3,2} = 8.0$ Hz, H-3), 3.82 (dd, 1H, $J_{2,3} = 8.0$ Hz, $J_{2,1} = 5.4$ Hz, H-2), 3.73 (br dd, 1H, $J_{6a,5} = 8.9$ Hz, $J_{6a,6b} = 3.8$ Hz, H-6a), 3.64 (t, 1H, $J = 8.9$ Hz, H-6b), 2.73–2.58 (m, 2H, H-1′); ^{13}C NMR ($CDCl_3$): δ 156.20 (CO), 138.54, 138.46, 138.43, 138.05, 136.66 ($C_{quat.}$ arom.), 136.84 (2′-C), 128.75–127.72 (*C*H arom), 116.29 (C-3′), 81.81, 80.92, 77.38 (C-2, C-3, C-4), 73.30, 73.30, 72.85, 72.60, 72.01, 67.67 (O*C*H$_2$Ph, C-6), 54.92, 54.92 (C-1, C-5), 34.50 (C-1′); MALDI-MS *m*/*z* 721 $[M+Na]^+$; 737 $[M+K]^+$; $C_{45}H_{47}NO_6$ requires 697.86; Anal. Calcd for $C_{45}H_{47}NO_6$: C, 77.45; H, 6.79; N, 2.01. Found: C, 77.49; H, 6.81; N, 1.99.

3.5. (3*S*,4a*R*,5*S*,6*R*,7*R*,8*R*)-5,6,7-Tris(benzyloxy)-8-((benzyloxy)methyl)-hexahydro-3-(iodomethyl)pyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (3)

To a solution of compound **2** (0.597 g, 0.855 mmol) in dry CH_2Cl_2 at 0 °C (10 mL), I_2 was added (0.434 g, 1.71 mmol). After 3 h the reaction was quenched by the addition of aq sodium thiosulfate until a colourless solution was obtained, and then the mixture was extracted with CH_2Cl_2. The organic layer was dried over

Na_2SO_4, filtered and concentrated to dryness. The crude residue was purified by flash chromatography (petroleum ether–EtOAc, 7:3), affording compound **3** as a yellowish oil (0.795 g, 92%). $[\alpha]_D^{22}$ −12.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.35–7.28 (m, 20H, Ph), 4.78–4.74 (dt, 1H, $J_{5,6} = 6.5$ Hz, $J_{5,4} = 3.5$ Hz, 5-H), 4.62 (d, 1H, $J = 12.1$ Hz, OC*H*Ph), 4.58 (d, 1H, $J = 12.2$ Hz, OC*H*Ph), 4.47 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.43 (d, 1H, $J = 12.2$ Hz, OC*H*Ph), 4.38 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.33 (d, 1H, $J = 13.9$ Hz, OC*H*Ph), 4.30 (d, 1H, $J = 13.9$ Hz, OC*H*Ph), 4.26 (d, 1H, $J = 12.1$ Hz, OC*H*Ph), 4.01–3.95 (m, 1H, H-2′), 3.79 (t, 1H, $J = 3.5$ Hz, H-4), 3.72–3.68 (m, 1H, H-1), 3.66 (t, 1H, $J = 3.5$ Hz, H-3), 3.63 (dd, 1H, $J_{6a,6b} = 9.8$ Hz, $J_{6a,5} = 6.5$ Hz, H-6a), 3.59 (dd, 1H, $J_{6b,6a} = 9.8$ Hz, $J_{6b,5} = 6.5$ Hz, H-6b), 3.27 (dd, 1H, $J_{3'a,3'b} = 10.4$ Hz, $J_{3'a,2'} = 3.5$ Hz, H-3′a), 3.25 (br s, 1H, H-2), 3.10 (dd, 1H, $J_{3'b,3'a} = 10.4$ Hz, $J_{3'b,2'} = 7.5$ Hz, H-3′b), 2.09 (ddd, 1H, $J_{1'a,1'b} = 13.3$ Hz, $J = 11.2$ Hz, $J = 2.0$ Hz, H-1′a), 1.95 (ddd, 1H, $J_{1'b,1'a} = 13.3$ Hz, $J = 6.2$ Hz, $J = 2.0$ Hz, H-1′b); ^{13}C NMR ($CDCl_3$): δ 153.99 (CO), 138.31, 138.19, 137.57, 137.57 ($C_{quat.}$ arom.), 128.75–127.84 (*C*H arom.), 74.94, 74.58, 74.01, 72.18 (C-2, C-3, C-4, C-2′), 73.15, 72.67, 72.34, 72.25, 67.35 (O*C*H_2Ph, C-6), 53.90, 49.70 (C-1, C-5), 30.13 (C-1′), 6.23 (C-3′); MALDI-MS *m*/*z* 735 $[M+H]^+$; 757 $[M+Na]^+$; 773 $[M+K]^+$; $C_{38}H_{40}INO_6$ requires 733.63; Anal. Calcd for $C_{38}H_{40}INO_6$: C, 62.21; H, 5.50; N, 1.91. Found: C, 62.16; H, 6.79; N, 1.94.

3.6. (3*S*,4a*R*,5*S*,6*R*,7*R*,8*R*)-3-(Azidomethyl)-5,6,7-tris(benzyloxy)-8-((benzyloxy)methyl)-hexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (4)

To a solution of compound **3** (0.583 g, 0.795 mmol) in dry DMF (10 mL), *n*-Bu_4NI (0.147 g, 0.398 mmol) and NaN_3 (0.103 g, 1.59 mmol) were added and the reaction mixture heated to reflux. After 2 h, the solvent was evaporated, under reduced pressure. The crude residue was purified by flash chromatography (petroleum ether–EtOAc, 65:35), affording compound **4** as yellowish oil (0.697 g, 88%). $[\alpha]_D^{22}$ −9.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38–7.21 (m, 20H, Ph), 4.86–4.81 (m, 1H, H-5), 4.73–4.31 (m, 8H, $4 \times OCH_2Ph$), 4.21–4.15 (m, 1H, H-2′), 3.89 (t, 1H, $J = 3.6$ Hz, H-4), 3.87–3.78 (m, 1H, H-1), 3.76 (t, 1H, $J = 3.6$ Hz, H-3), 3.71–3.66 (m, 2H, H-6), 3.46 (dd, 1H, $J_{3'a,3'b} = 12.3$ Hz, $J_{3'a,2'} = 5.2$ Hz, H-3′a), 3.40 (dd, 1H, $J_{3'b,3'a} = 12.3$ Hz, $J_{3'b,2'} = 5.2$ Hz, H-3′b), 3.34 (dd, 1H, $J_{2,3} = 3.6$ Hz, $J_{2,1} = 2.6$ Hz, H-2), 2.28 (ddd, 1H, $J_{1'a,1'b} = 13.9$ Hz, $J = 11.6$ Hz, $J = 1.5$ Hz, H-1′a), 1.74 (ddd, 1H, $J_{1'b,1'a} = 13.9$ Hz, $J = 6.3$ Hz, $J = 1.9$ Hz, H-1′b); ^{13}C NMR ($CDCl_3$): δ 154.07 (CO), 138.33, 138.21, 137.61, 137.58 ($C_{quat.}$ arom.), 129.1–127.8 (*C*H arom.), 75.08, 74.84, 73.26, 72.33 (C-2, C-3, C-4, C-2′), 73.15, 72.73, 72.39, 72.22 (O*C*H_2Ph), 67.39 (C-6), 53.93, 49.77 (C-1, C-5), 54.10 (C-3′), 30.13 (C-1′); MALDI-MS *m*/*z* 649 $[M+H]^+$; 672 $[M+Na]^+$; 688 $[M+K]^+$; $C_{38}H_{40}N_4O_6$ requires 648.75; Anal. Calcd for $C_{38}H_{40}N_4O_6$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.25; H, 6.23; N, 8.65.

3.7. (3*S*,4a*R*,5*S*,6*R*,7*R*,8*R*)-3-(Aminomethyl)-hexahydro-5,6,7-trihydroxy-8-(hydroxymethyl)pyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (5)

To a solution of **4** (0.050 g, 0.077 mmol) in MeOH (2 mL), $Pd(OH)_2/C$ (0.050 g) and two drops of AcOH were added. The flask was purged three times with Ar and then filled with H_2. After 48 h, the catalyst was removed by filtration, and the filtrate concentrated under reduced pressure, affording compound **5** as a yellowish oil in quantitative yield. $[\alpha]_D^{22}$ −8.5 (*c* 1.00, MeOH); ^1H NMR (D_2O): δ 4.77–4.71 (m, 1H, H-2′), 4.62 (br t, 1H, H-5), 4.02 (ddd, 1H, $J = 9.8$ Hz, $J = 4.8$ Hz, $J_{1,2} = 1.6$ Hz, H-1), 3.98 (dd, 1H, $J_{6a,6b} = 11.8$ Hz, $J_{6a,5} = 8.5$ Hz, H-6a), 3.90 (dd, 1H, $J_{3,4} = 3.2$ Hz, $J_{3,2} = 1.6$ Hz, H-3), 3.87 (dd, 1H, $J_{4,3} = 3.2$ Hz, $J_{4,2} = 1.6$ Hz, H-4), 3.72 (dd, 1H, $J_{6b,6a} = 11.8$ Hz, $J_{6b,5} = 5.1$ Hz, H-6b), 3.53 (t, 1H, $J = 1.6$ Hz, H-2), 3.15 (dd, 1H, $J_{3'a,3'b} = 13.7$ Hz, $J_{3'a,2'} = 8.5$ Hz, H-3′a), 3.09 (dd, 1H, $J_{3'b,3'a} = 13.7$ Hz, $J_{3'b,2'} = 3.3$ Hz, H-3′b), 2.20 (br ddd, 1H, H-1′a), 2.02 (ddd, 1H, $J_{1'b,1'a} = 13.5$ Hz, $J_{1'b,1} = 4.8$ Hz, $J_{1'b,2'} = 1.7$ Hz, H-1′b); ^{13}C NMR (D_2O): δ 153.36 (CO), 69.73, 69.51, 69.03, 67.82 (C-2, C-3, C-4, C-2′), 60.19, 48.54 (C-1, C-5), 59.73, 59.17 (C-6, C-3′), 26.24 (C-1′); MALDI-MS *m*/*z* 285 $[M+Na]^+$; 301 $[M+K]^+$; $C_{10}H_{18}N_2O_6$ requires 262.26; Anal. Calcd for $C_{10}H_{18}N_2O_6$: C, 45.80; H, 6.92; N, 10.68. Found: C, 45.84; H, 6.91; N, 10.75.

3.8. ((3*S*,4a*R*,5*S*,6*R*,7*R*,8*R*)-3-(Azidomethyl)-5,6,7-tris(benzyloxy)-octahydro-1-oxopyrido[1,2-*c*][1,3]oxazin-8-yl)methyl acetate (6)

To compound **4** (0.120 g, 0.185 mmol), a mixture of Ac_2O–TFA, 4:1 (0.128 M) was added. After 9 h, the reaction was neutralised with a satd aq $NaHCO_3$, and extracted with EtOAc. Then, the organic phase was submitted to vacuum evaporation and flash chromatography (petroleum ether–EtOAc, 5:5) affording compound **6** as a yellowish oil (0.082 g, 72%). $[\alpha]_D^{22}$ −18.2 (*c* 0.8, $CHCl_3$); ^1H NMR (C_6D_6): δ 7.27–7.01 (m, 15H, Ph), 5.42 (dd, 1H, $J_{5,6a} = 10.0$ Hz, $J_{5,6b} = 4.2$ Hz, H-5), 4.83 (dd, 1H, $J_{6a,6b} = 11.3$ Hz, $J_{6a,5} = 10.0$ Hz, H-6a), 4.66 and 4.22 (ABq, 2H, $J = 11.6$ Hz, OCH_2Ph), 4.41 and 4.04 (ABq, 2H, $J = 11.6$ Hz, OCH_2Ph), 4.17 and 4.07 (ABq, 2H, $J = 11.8$ Hz, OCH_2Ph), 3.94 (dd, 1H, $J_{6b,6a} = 11.6$ Hz, $J_{6b,5} = 4.2$ Hz, H-6b), 3.88–3.83 (m, 1H, H-2′), 3.74 (ddd, 1H, $J_{1,1'a} = 10.6$ Hz, $J_{1,1'b} = 6.5$ Hz, $J_{1,2} = 1.7$ Hz, H-1), 3.70 (br t, 1H, $J = 3.1$ Hz, H-3), 3.48 (br s, 1H, H-4), 3.01 (br s, 1H, H-2), 2.65

(dd, 1H, $J_{3'a,3'b} = 12.8$ Hz, $J_{3'a,2'} = 6.0$ Hz, H-3′a), 2.56 (dd, 1H, $J_{3'b,3'a} = 12.8$ Hz, $J_{3'b,2'} = 4.8$ Hz, H-3′b), 2.01 (q, 1H, $J = 12.8$ Hz, H-1′a), 1.78 (s, 3H, CH_3CO), 1.02 (ddd, 1H, $J_{1'b,1'a} = 12.8$ Hz, $J_{1'b,1} = 6.5$ Hz, $J_{1'b,2'} = 1.7$ Hz, H-1′b); ^{13}C NMR ($CDCl_3$): δ 171.31 (CO), 154.15 (C-4′), 137.82, 137.47, 137.25 ($C_{quat.}$ arom.), 128.84–127.98 (*C*H arom.), 73.77, 73.18, 72.19, 72.18 (C-2, C-3, C-4, C-2′), 72.77, 72.25, 71.77, 61.60 (O*C*H_2Ph, C-6), 54.06 (C-3′), 53.52, 48.54 (C-1, C-5), 26.84 (C-1′), 21.39 (*C*H_3CO); MALDI-MS *m*/*z* 601 $[M+H]^+$; 624 $[M+Na]^+$; 640 $[M+K]^+$; $C_{33}H_{36}N_4O_7$ requires 600.62; Anal. Calcd for $C_{33}H_{36}N_4O_7$: C, 65.99; H, 6.04; N, 9.33. Found: C, 65.95; H, 6.00; N, 9.34.

NOESY experiments on acetate **6** allowed the determination of the absolute configuration of the stereocentre generated in the iodocarbamoylation reaction, which was *S*. ^{1}H NMR coupling constants, in agreement with some molecular mechanics calculations, showed that the nojirimycin ring has $^1C_4$ chair conformation, with some distortion and flattening of the chair around the C2–C3–C4 region, producing the lowering of the couplings, even below 3 Hz. In this case, there is a major conformer around C5–C6, because we have one large and one small coupling for H-5/H-6a and H-5/H-6b.

3.9. (3*S*,4a*R*,5*S*,6*R*,7*R*,8*R*)-3-(Azidomethyl)-5,6,7-tris(benzyloxy)-hexahydro-8-(hydroxymethyl)pyrido-[1,2-*c*][1,3]oxazin-1(3*H*)-one (7)

To a solution of **6** (0.050 g, 0.083 mmol) in dry MeOH (0.6 mL), catalytic Na was added. After 2 h, the reaction was neutralised with 5% aq HCl, and the solvent evaporated. Purification by flash chromatography (petroleum ether–EtOAc, 25:75) afforded compound **7** as a yellowish oil (0.046 g, 95%). $[\alpha]_D^{22}$ −24.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR (C_6D_6): δ 7.35–7.05 (m, 15H, Ph), 4.66–4.66 (m, 1H, H-5), 4.62 (d, 1H, $J = 12.4$ Hz, OC*H*Ph), 4.58 (d, 1H, $J = 12.2$ Hz, OC*H*Ph), 4.45 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.43 (m, 3H, OCH_2Ph, H-2′), 4.30 (d, 1H, $J = 11.6$ Hz, OC*H*Ph), 3.90–3.80 (m, 1H, H-1), 3.75 (d, 2H, $J = 6.0$ Hz, H-6), 3.70 (dd, 1H, $J_{3,4} = 3.0$ Hz, $J_{3,2} = 2.7$ Hz, H-3), 3.62 (dd, 1H, $J_{4,3} = 3.0$ Hz, $J_{4,5} = 2.8$ Hz, H-4), 3.39–3.38 (m, 2H, H-3′), 3.25 (br s, 1H, H-2), 2.32 (dd, 1H, $J_{1'a,1'b} = 13.4$ Hz, $J_{1'a,2'} = 11.0$ Hz, H-1'a), 1.72 (dd, 1H, $J_{1'b,1'a} = 13.4$ Hz, $J_{1'b,2'} = 5.5$ Hz, H-1′b); ^{13}C NMR ($CDCl_3$): δ 155.08 (CO), 138.08, 137.49, 137.26 ($C_{quat.}$ arom.), 131.10–127.07 (*C*H arom.) 74.36, 73.43, 73.02 (C-2, C-3, C-4, C-2′), 72.79, 72.24, 72.20 (O*C*H_2Ph), 61.49 (C-6), 56.43, 49.64 (C-1, C-5), 54.12 (*C*H_2N_3), 30.15 (C-1′); MALDI-MS *m*/*z* 559 $[M+H]^+$; 581 $[M+Na]^+$; 597 $[M+K]^+$; $C_{31}H_{34}N_4O_6$ requires 558.62; Anal. Calcd for $C_{31}H_{34}N_4O_6$: C, 66.65; H, 6.13; N, 10.03. Found: C, 66.60; H, 6.10; N, 10.04.

3.10. (3*S*,4a*R*,5*S*,6*R*,7*R*,8*S*)-3-(Azidomethyl)-5,6,7-tris(benzyloxy)-octahydro-1-oxopyrido[1,2-*c*][1,3]oxazine-8-carboxylic acid (9)

Alcohol **7** (0.072 g, 0.129 mmol) was dissolved in dry DMSO (1.3 mL), and IBX (0.180 g, 0.644 mmol) was added. After 6 h, the reaction was diluted with water, the precipitate filtered off, and the mixture extracted with Et_2O. Usual work up afforded aldehyde **8**, which was submitted to the subsequent reaction without any further purification. Aldehyde **8** was dissolved in CH_3CN (1.6 mL), then 1.25 M aq $NaH_2PO_4{\cdot}2H_2O$ (1.0 mL) and $NaClO_2$ (0.116 g, 1.29 mmol) were added. After 6 h, the reaction mixture was concentrated, the residue suspended in CH_2Cl_2, the precipitate filtered off, and the solvent evaporated under reduced pressure. Purification by flash chromatography (EtOAc/EtOH, 9:1) afforded azido acid **9** (0.053 g, 72%). $[\alpha]_D^{22}$ −23.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (C_6D_6): δ 7.20–6.85 (m, 15H, Ph), 5.82 (br s, 1H, H-5), 4.70–4.35 (m, 6H, 3 × OCH_2-Ph), 4.32–4.18 (m, 1H, H-2′), 4.17–4.00 (m, 2H, H-1, H-4), 3.80 (br s, 1H, H-3), 3.13 (br s, 1H, H-2), 2.78–2.60 (m, 2H, H-3′), 2.52 (br s, 1H, OH), 2.22–2.03 (m, 2H, H-1′); ^{13}C NMR ($CDCl_3$): δ 166.12, 155.80 (CO), 137.95, 137.40, 137.40 ($C_{quat.}$ arom.), 131.10–127.08 (*C*H arom.), 74.33, 74.33, 74.08, 73.83 (C-2, C-3, C-4, C-2′), 72.18, 72.09, 71.80 (O*C*H_2Ph), 54.19, 46.12 (C-1, C-5), 50.43 (*C*H_2N_3), 30.48 (C-1′); MALDI-MS *m*/*z* 573 $[M+H]^+$; 595 $[M+Na]^+$; 611 $[M+K]^+$; $C_{31}H_{32}N_4O_7$ requires 572.61; Anal. Calcd for $C_{31}H_{32}N_4O_7$: C, 65.02; H, 5.63; N, 9.78. Found: C, 64.98; H, 5.65; N, 9.81.

3.11. (3*S*,4a*R*,5*S*,6*R*,7*R*,8*S*)-3-(Aminomethyl)-octahydro-5,6,7-trihydroxy-1-oxopyrido[1,2-*c*][1,3]oxazine-8-carboxylic acid (10)

To a solution of **9** (0.037 g, 0.065 mmol) in acetone–H_2O, 1:1 (2 mL), $Pd(OH)_2$/C (0.030 g) and two drops of AcOH were added. The flask was purged three times with Ar and then filled with H_2. After 48 h, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure, affording compound **10** as a yellowish oil in quantitative yield. $[\alpha]_D^{22}$ −8.2 (*c* 1.0, MeOH); ^{1}H NMR (D_2O): δ 4.73–4.61 (m, 1H, H-2′), 4.51 (d, 1H, $J_{5,4} = 2.5$ Hz, H-5), 4.28 (br t, 1H, H-4), 3.96 (ddd, 1H, $J_{1,1'a} = 13$ Hz, $J_{1,1'b} = 5.6$ Hz, $J_{1,2} = 1.8$ Hz, H-1), 3.78 (t, 1H, $J = 7.1$ Hz, H-3), 3.51 (br s, 1H, H-2), 3.15 (dd, 1H, $J_{3'a,3'b} = 13.4$ Hz, $J_{3'a,2'} = 3.2$ Hz, H-3′a), 3.09 (dd, 1H, $J_{3'b,3'a} = 13.4$ Hz, $J_{3'b,2'} = 8.6$ Hz, H-3′b), 2.03–1.91 (m, 2H, H-1′); ^{13}C NMR (D_2O): δ 180.28, 169.45 (CO), 107.43 (C-2′), 70.00, 69.25, 67.95 (C-2, C-3, C-4), 61.18 (C-5), 49.99 (C-1), 47.95 (C-3′), 26.56 (C-1′); MALDI-MS *m*/*z* 278 $[M+H]^+$; 299 $[M+Na]^+$; 315 $[M+K]^+$; $C_{10}H_{16}N_2O_7$ requires 276.24; Anal. Calcd for $C_{10}H_{16}N_2O_7$: C, 43.48; H, 5.84; N, 10.14. Found: C, 43.45; H, 5.86; N, 10.17.

3.12. (2*R*,3*R*,4*R*,5*S*,6*R*)-6-(Benzylamino)-1,3,4,5-tetrakis(benzyloxy)oct-7-en-2-ol (12)

Compound **11** (3.15 g, 5.0 mmol) was dissolved in 1 M vinylmagnesium bromide in THF (25 mL, 25 mmol). After 48 h, the reaction was quenched by the addition of a satd aq soln of NH_4Cl and extracted with EtOAc. Usual workup and flash chromatography (petroleum ether–EtOAc, 75:25 + 0.5% Et_3N) afforded compound **12** as yellowish oil (2.06 g, 63%, 70% de). $[\alpha]_D^{22}$ −5.1 (*c* 0.7, $CHCl_3$); ^1H NMR (C_6D_6): δ 7.40–7.21 (m, 20H, Ph), 5.81–5.70 (m, 1H, H-2), 5.22 (d, 1H, $J_{1a,2}$ = 10.3 Hz, H-1a), 5.00 (d, 1H, $J_{1b,2}$ = 17.3 Hz, H-1b), 4.87 (d, 1H, J = 10.1 Hz, OC*H*Ph), 4.84 (d, 1H, J = 10.7 Hz, OC*H*Ph), 4.74 (d, 1H, J = 11.2 Hz, OC*H*Ph), 4.66 (d, 1H, J = 13.5 Hz, OC*H*Ph), 4.6 (d, 1H, J = 11.6 Hz, OC*H*Ph), 4.58–4.55 (m, 2H, 2 × OC*H*Ph), 4.35 (d, 1H, J = 11.4 Hz, OC*H*Ph), 4.27 (dd, 1H, $J_{5,4}$ = 7.2 Hz, $J_{5,6}$ = 3.2 Hz, H-5), 4.16–4.14 (m, 1H, H-7), 3.87 (d, 1H, J = 13.1 Hz, NHC*H*Ph), 3.86–3.84 (m, 1H, H-4), 3.68–3.63 (m, 2H, H-8), 3.58 (dd, 1H, J = 6.3 Hz, J = 3.1 Hz, H-6), 3.54 (d, 1H, J = 13.3 Hz, NHC*H*Ph), 3.09 (dd, 1H, J = 3.4 Hz, J = 8.3 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 140.67, 138.85, 138.59, 138.33, 138.28 ($C_{quat.}$ arom.), 138.27 (C-2), 128.86–126.99 (*C*H arom.), 117.59 (C-1), 83.26, 79.88, 78.13 (C-4, C-5, C-6), 75.40, 75.10, 73.81, 73.25, 71.89 (O*C*H_2Ph, C-8), 71.04 (C-7), 61.36 (C-3), 50.79 (N*C*H_2Ph); MALDI-MS *m*/*z* 659 $[M+H]^+$; 681 $[M+Na]^+$; 697 $[M+K]^+$; $C_{43}H_{47}NO_5$ requires 657.84; Anal. Calcd for $C_{43}H_{47}NO_5$: C, 78.51; H, 7.20; N, 2.13. Found: C, 78.47; H, 7.19; N, 2.13.

3.13. (2*R*,3*R*,4*R*,5*S*,6*R*)-6-[*N*-Benzyl-*N*-(fluoren-9-ylmethoxycarbonyl)amino]-1,3,4,5-tetrakis(benzyloxy)oct-8-en-2-ol (13)

To a solution of compound **12** (2.6 g, 3.13 mmol) in dry CH_3CN (30 mL), DIPEA (0.64 mL, 3.76 mmol) and FmocCl (1.6 g, 6.26 mmol) were added. After 6 h, the solvent was evaporated under reduced pressure; purification by flash chromatography (petroleum ether–EtOAc, 75:25 + 0.5% Et_3N) afforded compound **13** as a colourless oil (2.75 g, 99%). Due to conformational equilibria of the open-chain alcohol, ^1H NMR showed unclear resolution, and is not reported, whereas ^{13}C NMR refers to the major conformer at equilibrium. $[\alpha]_D^{22}$ +7.9 (*c* 0.8, $CHCl_3$); ^{13}C NMR (C_6D_6): δ 156.52 (CO), 144.42, 144.38, 141.62, 141.59, 139.17, 139.14, 139.01, 138.96, 138.66 ($C_{quat.}$ arom.), 135.45 (C-2), 128.61–119.92 (*C*H arom.), 118.32 (C-1), 80.89, 80.34, 79.16 (C-4, C-5, C-6), 75.27, 74.81, 74.13, 73.58, 71.91 (O*C*H_2Ph, 8-C), 71.75 (C-7), 67.15 (*C*H_2Fmoc), 62.22 (C-3), 51.90 (N*C*H_2Ph), 47.97 (*C*H Fmoc); MALDI-MS *m*/*z* 903 $[M+Na]^+$; 919 $[M+K]^+$; $C_{58}H_{57}NO_7$ requires 880.08; Anal. Calcd for $C_{58}H_{57}NO_7$: C, 79.15; H, 6.53; N, 1.59. Found: C, 79.07; H, 6.50; N, 1.61.

3.14. (3*R*,4*R*,5*S*,6*R*)-6-[*N*-Benzyl-*N*-(fluoren-9-ylmethoxycarbonyl)-amino]-1,3,4,5-tetrakis(benzyloxy)oct-8-en-2-one (14)

To a solution of compound **13** (0.100 g, 0.110 mmol) in DMSO (1 mL), IBX (0.130 g, 0.450 mmol) was added. After 21 h, the reaction was diluted with H_2O, filtered and extracted with Et_2O. After usual workup and flash chromatography (petroleum ether–EtOAc, 8:2) resulted compound **14** as a yellowish oil (0.097 g, 97%). Due to conformational equilibria of the open-chain ketone, ^1H NMR showed unclear resolution, and is not reported, whereas ^{13}C NMR refers to the major conformer at equilibrium. $[\alpha]_D^{22}$ −3.9 (*c* 0.7, $CHCl_3$); ^{13}C NMR (C_6D_6): δ 229.90, 165.70 (CO), 144.06, 144.06, 143.99, 141.51, 138.56, 137.77, 137.62, 137.62, 137.32 ($C_{quat.}$ arom.), 134.45 (C-2), 129.31–120.21 (*C*H arom.), 119.25 (C-1), 80.98, 80.01, 79.50 (C-4, C-5, C-6), 75.41, 74.81, 73.94, 73.31, 73.31 (O*C*H_2Ph, C-8), 65.48 (*C*H_2Fmoc), 60.14 (C-3), 51.00 (N*C*H_2Ph), 47.88 (*C*H Fmoc); MALDI-MS *m*/*z* 901 $[M+Na]^+$; $C_{58}H_{55}NO_7$ requires 878.06; Anal. Calcd for $C_{58}H_{55}NO_7$: C, 79.34; H, 6.31; N, 1.60. Found: C, 79.29; H, 6.25; N, 1.50.

3.15. (2*R*,3*R*,4*R*,5*S*,6*R*)-*N*-Benzyl-3,4,5-tris(benzyloxy)-2-benzyloxymethyl-6-(eth-2-enyl)piperidine (16)

To a solution of compound **14** (2.04 g, 2.32 mmol) in dry CH_3CN (18 mL), diethylamine (2 mL) was added. After 2 h, the solvent was evaporated to dryness and crude **15** directly submitted to the subsequent reaction. To a solution of crude **15** in dry DCE (30 mL) cooled to −35 °C were sequentially added glacial AcOH (1.33 mL, 23.2 mmol), anhydrous Na_2SO_4 (13.2 g, 92.8 mmol) and finally $NaHB(OAc)_3$ (1.97 g, 9.28 mmol). After 19 h, satd aq $NaHCO_3$ was added to neutrality; the suspension was then filtered, the mixture extracted with CH_2Cl_2. Usual work up followed by flash chromatography (toluene + 0.2% Et_3N) afforded compound **16** as a yellowish oil (0.960 g, 64% over two steps, 60% de). $[\alpha]_D^{22}$ +29.1 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.24–7.07 (m, 25H, Ph), 5.92 (dt, 1H, J = 16.6 Hz, J = 10.0 Hz, H-1′), 5.33 (dd, 1H, $J_{2'a,1'}$ = 10.0 Hz, $J_{2'a,2'b}$ = 2.0 Hz, H-2′a), 5.02 (dd, 1H, $J_{2'b,1'}$ = 16.6 Hz, $J_{2'b,2'a}$ = 2.0 Hz, H-2′b), 4.90 and 4.69 (ABq, 2H, J = 10.9 Hz, OCH_2Ph), 4.84 and 4.44 (ABq, 2H, J = 10.7 Hz, OCH_2Ph), 4.39 and 4.33 (ABq, 2H, J = 11.6 Hz, OCH_2Ph), 4.29 (br s, 2H, OCH_2Ph), 3.96 and 3.48 (ABq, 2H, J = 13.6 Hz, NCH_2Ph), 3.74 (dd, 1H, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 3.8 Hz, H-3), 3.67 (dd, 1H, $J_{6a,6b}$ = 10.5 Hz, $J_{6a,5}$ = 3.4 Hz, H-6a), 3.63 (dd, 1H, $J_{6b,6a}$ = 10.5 Hz, $J_{6b,5}$ = 1.9 Hz, H-6b), 3.59 (t, 1H, J = 9.5 Hz, H-4), 3.57 (dd, 1H, $J_{2,3}$ = 9.5 Hz,

$J_{2,1} = 5.5$ Hz, H-2), 3.34 (dd, 1H, $J_{1,1'} = 9.2$ Hz, $J_{1,2} = 5.5$ Hz, H-1), 2.89 (br d, 1H, $J_{5,4} = 9.5$ Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 140.22, 139.28, 139.28, 138.65, 138.24 ($C_{quat.}$ arom.), 131.16 (C-1′), 130.71–126.86 (*C*H arom.), 121.78 (C-2′), 84.12, 80.22, 79.64 (C-2, C-3, C-4), 75.74, 75.64, 73.32, 72.08, 68.04 (OCHPhO, C-6), 60.61, 59.61 (C-1, C-5), 52.63 (N*C*H_2Ph); MALDI-MS *m*/*z* 641 $[M+H]^+$; 664 $[M+Na]^+$; $C_{43}H_{45}NO_4$ requires 639.82; Anal. Calcd for $C_{43}H_{45}NO_4$: C, 80.72; H, 7.09; N, 2.19. Found: C, 80.77; H, 7.05; N, 2.21.

From *J* values between H-2/H-3, H-3/H-4 and H-4/H-5 (9.5 Hz) the nojirimycin ring has the $^4C_1$ conformation. In addition, from the NOESY experiments and from the *J* values between H-4/H-5 a D-configuration at C-5 after the ring closure was determined, while the *J* values between H-1/H-2, allowed the assignment of the α-vinyl appendage obtained in the Grignard reaction on the glycosyl amine.

3.16. (2*R*,3*R*,4*R*,5*S*,6*R*)-3,4,5-Tris(benzyloxy)-2-benzyloxymethyl-6-(eth-2-enyl)piperidine (17)

To a solution of *C*-vinyl derivative **16** (0.956 g, 1.49 mmol) in a 5:1 THF–H_2O mixture (40 mL) CAN was added (3.28 g, 5.98 mmol) portionwise. After 4 h, satd aq $NaHCO_3$ was added to basic pH. The suspension was filtered, extracted with Et_2O and usual work up afforded 0.800 g of crude **17**. An analytical sample was purified by flash chromatography (petroleum ether–EtOAc, 8:2 + 0.5% Et_3N). $[\alpha]_D^{22}$ +34.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.25–7.05 (m, 20H, Ph), 6.24–6.16 (m, 1H, 1′-H), 5.36 (d, 1H, $J_{2'a,1'} = 16.8$ Hz, H-2′a), 5.33 (d, 1H, $J_{2'b,1'} = 9.3$ Hz, H-2′b), 4.92 and 4.77 (Abq, 2H, $J = 10.8$ Hz, OCH_2Ph), 4.85 and 4.43 (Abq, 2H, $J = 10.7$ Hz, OCH_2Ph), 4.70 and 4.65 (ABq, 2H, $J = 11.5$ Hz, OCH_2Ph), 4.51 and 4.47 (Abq, 2H, $J = 10.0$ Hz, OCH_2Ph), 3.84 (br s, 1H, 1-H), 3.71–3.65 (m, 3H, H-2, H-3, H-6a), 3.51 (br dd, 1H, $J_{6b,6a} = 9.0$ Hz, $J_{6b,5} = 5.9$ Hz, H-6b), 3.40 (br t, 1H, H-4), 3.13–3.08 (m, 1H, H-5), 2.01 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 139.07, 138.57, 138.54, 138.24 ($C_{quat.}$ arom.), 134.43 (C-1′), 128.75–127.17 (CH arom.), 117.98 (C-2′), 83.97, 82.20, 80.86 (C-2, C-3, C-4), 76.01, 75.56, 73.62, 72.76, 70.75 (O*C*H_2Ph, C-6), 56.28, 53.80 (C-1, C-5); MALDI-MS *m*/*z* 551 $[M+H]^+$; 573 $[M+Na]^+$; $C_{36}H_{39}NO_4$ requires 549.71; Anal. Calcd for $C_{36}H_{39}NO_4$: C, 78.66; H, 7.15; N, 2.55. Found: C, 78.60; H, 7.10; N, 2.55.

3.17. (2*R*,3*R*,4*R*,5*S*,6*R*)-*N*-(Benzyloxycarbonyl)-3,4,5-tris(benzyloxy)-2-benzyloxymethyl-6-(eth-2-enyl)piperidine (18)

To a solution of crude **17** (0.800 g) in dry CH_3CN (15 mL), DIPEA (0.33 mL, 1.9 mmol) and CbzCl (0.36 mL, 2.54 mmol) were added. After 4 h, the solvent was evaporated to dryness. Flash chromatography (petroleum ether–EtOAc, 85:15) afforded the carbobenzyloxy derivative **18** as a yellowish oil (1.02 g, 54% over two steps). Due to conformational equilibrium between the two chair conformations, broad signals displayed at room temperature ^{1}H NMR; in order to have sharp and resolved signals for unambiguous assignments the spectrum was recorded at 55 °C. $[\alpha]_D^{22}$ +36.4 (*c* 0.72, $CHCl_3$); ^{1}H NMR (C_6D_6; 55 °C): δ 7.23–6.98 (m, 25H, Ph), 6.41–6.32 (m, 1H, H-1′), 5.40 (d, 1H, $J_{2'a,1'} = 17.1$ Hz, H-2′a), 5.20 (d, 1H, $J_{2'b,1'} = 10.3$ Hz, H-2′b), 5.15 and 5.05 (Abq, 2H, $J = 12.5$ Hz, NCOOCH_2Ph), 4.91 (br t, 1H, $J = 6.0$ Hz, H-1), 4.74–4.71 (m, 1H, H-5), 4.50–4.30 (m, 8H, 4 × OCH_2Ph), 4.14 (dd, 1H, $J = 2.5$ Hz, $J = 1.4$ Hz, H-4), 3.95 (br d, 1H, $J_{3,2} = 8.0$ Hz, H-3), 3.83 (dd, 1H, $J_{2,3} = 8.0$ Hz, $J_{2,1} = 6.0$ Hz, H-2), 3.70 (dd, 1H, $J_{6a,6b} = 9.0$ Hz, $J_{6a,5} = 3.9$ Hz, H-6a), 3.62 (t, 1H, $J = 9.0$ Hz, H-6b); ^{13}C NMR ($CDCl_3$): δ 155.86 (CO), 138.43, 138.41, 138.24, 137.95, 136.66 ($C_{quat.}$ arom.), 133.95 (C-1′), 128.70–127.68 (*C*H arom.), 119.62 (C-2′), 81.76, 79.85, 77.49 (C-2, C-3, C-4), 73.33, 73.33, 72.61, 72.46, 71.42, 67.73 (O*C*H_2Ph, C-6), 56.27, 55.03 (C-1, C-5); MALDI-MS *m*/*z* 707 $[M+Na]^+$; 723 $[M+K]^+$; $C_{44}H_{45}NO_6$ requires 683.83; Anal. Calcd for $C_{44}H_{45}NO_6$: C, 77.28; H, 6.63; N, 2.05. Found: C, 77.24; H, 6.61; N, 2.02.

3.18. (1*R*,5*R*,6*R*,7*S*,8*S*,8a*S*)-6,7,8-Tris(benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-1-(iodomethyl)-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (19)

To a solution of compound **18** (0.342 g, 0.500 mmol) in dry CH_2Cl_2 at 0 °C (17 mL), I_2 (0.254 g, 1.00 mmol) was added. After 4 h, the reaction was quenched by the addition of H_2O and sodium thiosulfate until the solution became colourless, then the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The crude residue was purified by flash chromatography (petroleum ether–EtOAc, 75:25), affording bicyclic compound **19** as a yellowish oil (0.323 g, 90%). $[\alpha]_D^{22}$ −34.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.30–7.16 (m, 20H, Ph), 4.62 (d, 1H, $J = 11.7$ Hz, OC*H*Ph), 4.59 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.88 (dt, 1H, $J = 10.1$ Hz, $J_{1',1} = 4.6$ Hz, H-1′), 4.55–4.38 (m, 5H, 5 × OC*H*Ph), 4.27 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.23–4.19 (m, 1H, H-5), 3.80 (t, 1H, $J = 2.8$ Hz, H-3), 3.77 (t, 1H, $J = 2.8$ Hz, H-4), 3.73 (dd, 1H, $J_{1,1'} = 4.6$ Hz, $J_{1,2} = 2.8$ Hz, H-1), 3.65 (dd, 1H, $J_{6a,6b} = 9.5$ Hz, $J_{6a,5} = 7.5$ Hz, H-6a), 3.59 (dd, 1H, $J_{6b,6a} = 9.5$ Hz, $J_{6b,5} = 6.1$ Hz, H-6b), 3.41 (t, 1H, $J = 2.8$ Hz, H-2), 3.22 (dd, 1H, $J_{2'a,2'b} = 10.1$ Hz, $J_{2'a,1'} = 3.9$ Hz, H-2′a), 3.08 (t, 1H, $J = 10.1$ Hz, H-2′b); ^{13}C NMR ($CDCl_3$): δ 156.78 (CO), 138.23, 138.04, 137.43, 137.43 ($C_{quat.}$ arom.), 128.80–127.81 (*C*H arom.), 74.45, 73.81, 73.67, 71.97 (C-2, C-3, C-4, C-1′), 73.30, 72.69, 72.32, 71.70, 67.63 (O*C*H_2Ph, C-6), 57.17, 52.49 (C-1, C-5), 7.09 (C-

2′); MALDI-MS *m/z* 743 $[M+Na]^+$; 759 $[M+K]^+$; $C_{37}H_{38}INO_6$ requires 719.60; Anal. Calcd for $C_{37}H_{38}INO_6$: C, 61.76; H, 5.32; I, 17.63; N, 1.95. Found: C, 61.81; H, 5.29; I, 17.58; N, 1.94.

^1H NMR and NOESY experiments allowed the determination of the absolute configuration of the new stereocentre, which in this case was *R*.

3.19. (1*S*,5*R*,6*R*,7*S*,8*S*,8a*R*)-1-(Azidomethyl)-6,7,8-tris(benzyloxy)-5-((benzyloxy)methyl)-tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (20)

To a solution of iodide **19** (0.85 g, 0.117 mmol) in dry DMF (2 mL), *n*-Bu_4NI (0.021 g, 0.058 mmol) and sodium azide (0.015 g, 0.234 mmol) were added and the reaction heated at reflux for 2 h. Evaporation of the solvent, followed by purification by flash chromatography (petroleum ether–EtOAc, 7:3) afforded azide **20** as a yellowish oil (0.072 g, 97%). $[\alpha]_D^{22}$ −61.0 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.23–7.04 (m, 20H, Ph), 4.61 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.59 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.47 (q, 1H, $J = 4.9$ Hz, H-1′), 4.42 (s, 2H, OCH_2Ph), 4.41 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.38 (d, 1H, $J = 10.9$ Hz, OC*H*Ph), 4.24 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.23 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.22–4.17 (m, 1H, 5-H), 3.81 (dd, 1H, $J_{4,3} = 3.4$ Hz, $J_{4,5} = 3.2$ Hz, H-4), 3.77 (dd, 1H, $J_{3,4} = 3.4$ Hz, $J_{3,2} = 3.0$ Hz, H-3), 3.73 (dd, 1H, $J_{1,1'} = 4.7$ Hz, $J_{1,2} = 1.6$ Hz, H-1), 3.65 (dd, 1H, $J_{6a,6b} = 9.7$ Hz, $J_{6a,5} = 7.6$ Hz, H-6a), 3.58 (dd, 1H, $J_{6b,6a} = 9.7$ Hz, $J_{6b,5} = 6.0$ Hz, H-6b), 3.33 (dd, 1H, $J_{2'a,2'b} = 13.0$ Hz, $J_{2'a,1'} = 5.0$ Hz, H-2′a), 3.30 (dd, 1H, $J_{2,3} = 3.0$ Hz, $J_{2,1} = 1.6$ Hz, H-2), 3.24 (dd, 1H, $J_{2'b,2'a} = 13.0$ Hz, $J_{2'b,1'} = 4.9$ Hz, H-2′b); ^{13}C NMR ($CDCl_3$): δ 156.85 (CO), 138.27, 138.04, 137.39, 137.36 ($C_{quat.}$ arom.), 128.81–127.84 (*C*H arom.), 74.43, 73.22, 73.19. 71.82 (C-2, C-3, C-4, C-1′), 73.37, 72.69, 72.39, 71.60 (O*C*H_2Ph), 67.66 (C-6), 54.08, 52.52 (C-1, C-5), 53.26 (C-2′); MALDI-MS *m/z* 658 $[M+Na]^+$; 674 $[M+K]^+$. $C_{37}H_{38}N_4O_6$ requires 634.72; Anal. Calcd for $C_{37}H_{38}N_4O_6$: C, 70.01; H, 6.03; N, 8.83. Found: C, 69.98; H, 6.00; N, 8.90.

3.20. (1*S*,5*R*,6*R*,7*S*,8*S*,8a*S*)-1-(Aminomethyl)-tetrahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-1*H*-oxazolo-[3,4-*a*]pyridin-3(5*H*)-one bicyclic (21)

To a solution of **20** (0.046 g, 0.072 mmol) in MeOH (2 mL), $Pd(OH)_2/C$ (0.046 g) and two drops of AcOH were added. The flask was purged three times with Ar and then filled with H_2. After 48 h, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure, affording compound **21** as a yellowish oil in quantitative yield. Due to conformational equilibria, the ^1H NMR showed broad signals, and is not reported. $[\alpha]_D^{22}$ −4.2 (*c* 1.0, MeOH); ^{13}C NMR (D_2O): δ 156.45, 71.25, 69.10, 69.04, 67.98 (C-2, C-3, C-4, C-1′), 60.16, 59.24 (C-6, C-2′), 59.06, 54.11 (C-1, C-5) MALDI-MS *m/z* 271 $[M+Na]^+$; $C_9H_{16}N_2O_6$ requires 248.23; Anal. Calcd for $C_9H_{16}N_2O_6$: C, 43.55; H, 6.50; N, 11.29. Found: C, 43.65; H, 6.43; N, 11.31.

3.21. ((1*S*,5*R*,6*R*,7*S*,8*S*,8a*R*)-1-(Azidomethyl)-6,7,8-tris(benzyloxy)-hexahydro-3-oxo-1*H*-oxazolo[3,4-*a*]pyridin-5-yl)methyl acetate bicyclic oxazolidinone azido acetyl derivative (22)

Compound **20** (0.181 g, 0.285 mmol) was dissolved in a 4:1 Ac_2O–TFA mixture (0.128 M). After 24 h, the reaction was neutralised with satd aq $NaHCO_3$, and extracted with EtOAc; the organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. Flash chromatography (petroleum ether–EtOAc, 7:3) afforded acetylated compound **22** as a yellowish oil (0.123 g, 74%). $[\alpha]_D^{22}$ −77.0 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.62–7.02 (m, 15H, Ph), 4.58 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.58 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.52–4.46 (m, 2H, H-6a, H-1′), 4.40 (d, 1H, $J = 12.1$ Hz, OC*H*Ph), 4.36 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.30 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.30–4.27 (m, 1H, H-5), 4.23 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 3.94 (dd, 1H, $J_{6b,6a} = 11.4$ Hz, $J_{6b,5} = 4.8$ Hz, H-6b), 3.89 (dd, 1H, $J = 4.7$ Hz, $J = 2.9$ Hz, H-1), 3.80 (dd, 1H, $J_{3,2} = 2.9$ Hz, $J_{3,4} = 2.2$ Hz, H-3), 3.45 (dd, 1H, $J_{4,3} = 2.2$ Hz, $J_{4,5} = 2.0$ Hz, H-4), 3.38 (dd, 1H, $J_{2'a,2'b} = 12.9$ Hz, $J_{2'a,1'} = 5.3$ Hz, H-2′a), 3.32–3.28 (m, 2H, H-2, H-2′b), 2.00 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$): δ 171.09, 156.82 (CO); 137.54, 137.28, 137.06 ($C_{quat.}$ arom.), 128.91–122.86 (*C*H arom.), 73.17, 72.52, 72.20, 71.96 (C-2, C-3, C-4, C-1′), 73.04, 71.94, 71.69 (O*C*H_2Ph), 61.26 (C-6), 53.19 (C-2′), 53.20, 52.17 (C-1, C-5), 21.27 (CH_3CO); MALDI-MS *m/z* 610 $[M+Na]^+$; 624 $[M+K]^+$; $C_{32}H_{34}N_4O_7$ requires 586.63; Anal. Calcd for $C_{32}H_{34}N_4O_7$: C, 65.52; H, 5.84; N, 9.55. Found: C, 65.55; H, 5.90; N, 9.50.

3.22. (1*S*,5*R*,6*R*,7*S*,8*S*,8a*R*)-1-(Azidomethyl)-6,7,8-tris(benzyloxy)-tetrahydro-5-(hydroxymethyl)-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (23)

To compound **22** (0.123 g, 0.21 mmol) in dry MeOH (3 mL), a catalytic amount of Na was added. After 3 h, 5% aq HCl was added to neutrality, and the solvent evaporated. Flash chromatography (petroleum ether–EtOAc, 45:55) afforded deacetylated compound **23** as a yellowish oil (0.090 g, 78%). $[\alpha]_D^{22}$ −22.9 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.29–7.04 (m, 15H, Ph), 4.62 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.61 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.47–4.42 (m, 3H, OCH_2Ph, H-1′), 4.45 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.37 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.26 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.03–3.98 (m, 1H, H-5), 3.84–3.81 (m, 2H, H-3, H-1), 3.78

(dd, 1H, $J_{6a,6b} = 11.6$ Hz, $J_{6a,5} = 5.0$ Hz, H-6a), 3.76 (dd, 1H, $J_{6b,6a} = 11.6$ Hz, $J_{6b,5} = 6.2$ Hz, H-6b), 3.61 (dd, 1H, $J = 3.8$ Hz, $J = 3.5$ Hz, H-4), 3.43 (dd, 1H, $J_{2'a,2'b} = 13.0$ Hz, $J_{2'a,1'} = 5.0$ Hz, H-2′a), 3.37 (dd, 1H, $J_{2'b,2'a} = 13.0$ Hz, $J_{2'b,1'} = 4.7$ Hz, H-2′b), 3.32 (dd, 1H, $J = 2.5$ Hz, $J = 2.3$ Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 157.67 (CO), 137.71, 137.19, 136.29 ($C_{quat.}$ arom.), 128.99–128.09 (*C*H arom.), 74.55, 73.58, 73.47, 73.05 (C-2, C-3, C-4, C-1′), 73.01, 72.60, 71.58 (O*C*H_2Ph), 62.00 (C-6), 54.99, 54.48 (C-1, C-5), 53.39 (C-2′); MALDI-MS *m*/*z* 568 $[M+Na]^+$; 584 $[M+K]^+$; $C_{30}H_{32}N_4O_6$ requires 544.60; Anal. Calcd for $C_{30}H_{32}N_4O_6$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.00; H, 5.90; N, 10.25.

3.23. (1*S*,5*S*,6*R*,7*R*,8*S*,8a*R*)-1-(Azidomethyl)-6,7,8-tris(benzyloxy)-hexahydro-3-oxo-1*H*-oxazolo[3,4-*a*]-pyridine-5-carboxylic acid (25)

To a solution of alcohol **23** (0.069 g, 0.126 mmol) in dry DMSO (1.2 mL), IBX (0.176 g, 0.630 mmol) was added. After 6 h, H_2O was added, the precipitate filtered off, and the mixture extracted with Et_2O. After usual work-up, crude product **24** was directly submitted to the subsequent reaction. To a solution of crude aldehyde **24** (0.126 mmol) in CH_3CN (1.6 mL) a 1.25 M aq solution of $NaH_2PO_4{\cdot}2H_2O$ (1.0 mL) and $NaClO_2$ (114 mg, 1.26 mmol) were added. After 7 h, the reaction mixture was concentrated, the residue suspended in CH_2Cl_2 and filtered, and the solvent evaporated under reduced pressure. Flash chromatography (EtOAc–EtOH, 9:1) afforded the amino acid derivative **25** as a yellowish oil (0.059 g, 83% over two steps). Due to conformational equilibria, the ^{1}H NMR showed broad signals, and is not reported. $[\alpha]_D^{22}$ −41.3 (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 188.12 (COOH), 167.89 (CO), 137.91, 137.38, 137.17 ($C_{quat.}$ arom.), 129.08–126.27 (*C*H arom.), 74.07, 73.17, 71.86, 71.28 (C-2, C-3, C-4, C-1′), 72.22, 71.86, 71.58 (O*C*H_2Ph), 54.89, 54.89 (C-1, C-5), 52.57 (C-2′); MALDI-MS *m*/*z* 582 $[M+Na]^+$; 598 $[M+K]^+$; $C_{30}H_{30}N_4O_7$ requires 558.58; Anal. Calcd for $C_{30}H_{30}N_4O_7$: C, 64.51; H, 5.41; N, 10.03. Found: C, 64.51; H, 5.41; N, 10.03.

3.24. (1*S*,5*S*,6*R*,7*R*,8*S*,8a*S*)-1-(Aminomethyl)-hexahydro-6,7,8-trihydroxy-3-oxo-1*H*-oxazolo[3,4-*a*]pyridine-5-carboxylic acid (26)

To a solution of **25** (0.047 g, 0.084 mmol) in 1:1 acetone–H_2O (2 mL), $Pd(OH)_2$/C (0.047 g) and two drops of AcOH were added. The flask was purged three times with Ar and then filled with H_2. After 48 h, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure, affording compound **26** as a yellowish oil in quantitative yield. Due to conformational equilibria, the ^{1}H NMR showed broad signals, and is not reported. $[\alpha]_D^{22}$ −1.7 (*c* 1.0, MeOH); ^{13}C NMR (D_2O): δ 192.93 (COOH), 74.39, 72.63, 70.33, 69.78 (C-2, C-3, C-4, C-1′), 61.89, 57.64 (C-1, C-5), 61.76 (C-6), 50.95 (C-2′); MALDI-MS *m*/*z* 285 $[M+Na]^+$; 301 $[M+K]^+$; $C_9H_{14}N_2O_7$ requires 262.22; Anal. Calcd for $C_9H_{14}N_2O_7$: C, 41.22; H, 5.38; N, 10.68. Found: C, 41.27; H, 5.41; N, 10.63.

3.25. (4a*R*,5*S*,6*R*,7*R*,8*R*)-5,6,7-Tris(benzyloxy)-8-((benzyloxy)methyl)-hexahydro-3-methylenepyrido[1,2-*c*]-[1,3]oxazin-1(3*H*)-one (27)

To a solution of **3** (0.359 g, 0.489 mmol) in CH_3CN (5.5 mL), *n*-Bu_4NOH (0.815 mL, 1.222 mmol) was added. After 4 h, the reaction was extracted with EtOAc; usual workup and flash chromatography (petroleum ether–EtOAc, 75:25) afforded compound **27** as a yellowish oil (0.292 g, 98%). $[\alpha]_D^{22}$ +14.4 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35–7.15 (m, 20H, Ph), 4.84 (m, 1H, H-5), 4.70 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.67 (d, 1H, $J = 11.8$, OC*H*Ph), 4.63 (d, 1H, $J_{3'a,3'b} = 1.4$ Hz, H-3′a), 4.57 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.52 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.51 (s, 1H, OC*H*Ph), 4.46 (s, 1H, OC*H*Ph), 4.45 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.39 (d, 1H, $J = 11.7$ Hz, OC*H*Ph), 4.21 (d, 1H, $J_{3'b,3'a} = 1.4$ Hz, H-3′b), 3.92 (t, 1H, $J = 3.9$ Hz, H-4), 3.77 (m, 2H, H-1, H-3), 3.75 (dd, 1H, $J_{6a,6b} = 9.8$ Hz, $J_{6a,5} = 7.0$ Hz, H-6a), 3.69 (dd, 1H, $J_{6b,6a} = 9.8$ Hz, $J_{6b,5} = 6.0$ Hz, H-6b), 3.45 (t, 1H, $J = 3.0$ Hz, H-2), 2.74 (dd, 1H, $J_{1'a,1'b} = 14.6$ Hz, $J_{1'a,1'} = 6.5$ Hz, H-1′a), 2.56 (dd, 1H, $J_{1'b,1'a} = 14.6$ Hz, $J_{1'b,1'} = 6.3$ Hz, H-1′b); ^{13}C NMR ($CDCl_3$): δ 151.85 (CO), 151.46 (C-2′), 138.28, 138.18, 137.70, 137.65 ($C_{quat.}$ arom.), 128.77–127.74 (*C*H arom.), 92.904 (C-3′), 76.74 (C-2), 75.91 (C-3), 72.74 (C-4), 73.23, 73.05, 72.52, 72.47 (O*C*H_2Ph), 67.70 (C-6), 55.24 (C-5), 49.06 (C-1), 27.74 (C-1′); MALDI-MS *m*/*z* 607 $[M+H]^+$; 629 $[M+Na]^+$; 645 $[M+K]^+$; $C_{38}H_{39}NO_6$ requires 605.72; Anal. Calcd for $C_{38}H_{39}NO_6$: C, 75.35; H, 6.49; N, 2.31. Found: C, 75.23; H, 6.50; N, 2.34.

3.26. ((4a*R*,5*S*,6*R*,7*R*,8*R*)-5,6,7-Tris(benzyloxy)-1,4a,5,6,7,8-hexahydro-3-methyl-1-oxopyrido[1,2-*c*]-[1,3]oxazin-8-yl)methyl acetate (28)

Compound **27** (0.262 g, 0.432 mmol) was dissolved in a 4:1 mixture of Ac_2O–TFA (0.128 M). After 24 h, the reaction was neutralised with satd aq $NaHCO_3$, and extracted with EtOAc; the organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. Flash chromatography (petroleum ether–EtOAc, 7:3) afforded acetate **28** as a yellowish oil (0.141 g, 59%). $[\alpha]_D^{22}$ +20.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.32–7.15 (m, 15H, Ph), 4.98 (m, 1H, H-5), 4.71 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.62 (d, 1H, $J = 12.2$ Hz, OC*H*Ph), 4.51 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.51 (m, 1H, H-1′), 4.48

(dd, 1H, $J_{6a,6b} = 11.6$ Hz, $J_{6a,5} = 8.3$ Hz, H6-a), 4.44 (d, 1H, $J = 11.6$ Hz, OC*H*Ph), 4.43 (d, 1H, $J = 12.2$ Hz, OC*H*Ph), 4.36 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.31 (m, 1H, H-1), 4.18 (dd, 1H, $J_{6b,6a} = 11.6$ Hz, $J_{6b,5} =$ 4.9 Hz, H-6b), 3.75 (t, 1H, $J = 3.1$ Hz, H-3), 3.58 (t, 1H, $J = 3.05$ Hz, H-4), 3.24 (br t, 1H, H-2), 2.02 (s, 3H, H-3′), 1.85 (s, 3H, CH_3Ac); ^{13}C NMR ($CDCl_3$): δ 170.86 (COAc), 151.09 (CO), 149.10 (C-2′), 138.06, 137.89, 137.35 ($C_{quat.}$ arom.), 128.75–127.80 (*C*H arom.), 95.50 (C-1′), 75.58 (C-2), 74.70 (C-3), 72.52 (C-4), 72.84, 72.47, 71.91 (O*C*H_2Ph), 60.94 (C-6), 53.30 (C-5), 50.25 (C-1), 21.25 (C-3′), 18.90 (*C*H_3Ac); MALDI-MS *m*/*z* 559 $[M+H]^+$; 581 $[M+Na]^+$; 597 $[M+K]^+$; $C_{33}H_{35}NO_7$ requires 557.63; Anal. Calcd for $C_{33}H_{35}NO_7$: C, 71.08; H, 6.33; N, 2.51. Found: C, 71.11; H, 6.45; N, 2.54.

3.27. (5*R*,6*S*,7*R*,8*R*,8a*R*)-6,7,8-Tris(benzyloxy)-tetrahydro-5-(2-oxopropyl)-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (29)

To compound **28** (0.180 g, 0.323 mmol) in dry MeOH (2.3 mL) a catalytic amount of Na was added. After 3 h, 5% aq HCl was added to neutrality, and the solvent evaporated. Flash chromatography (petroleum ether–EtOAc, 6:4) afforded deacetylated compound **29** as a white solid (0.110 g, 70%); mp 137–139 °C; $[\alpha]_D^{22}$ +65.3 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.36–7.23 (m, 15H, Ph), 4.95 (d, 1H, $J = 10.1$ Hz, OC*H*Ph), 4.88 (d, 1H, $J = 11.4$ Hz, OC*H*Ph), 4.77 (d, 1H, $J = 10.9$ Hz, OC*H*Ph), 4.76 (m, 1H, H-1), 4.65 (s, 2H, O*C*H_2Ph), 4.60 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.23 (dd, 1H, $J_{6a,6b} = 9.0$ Hz, $J_{6a,5} = 7.9$ Hz, H-6a), 3.79 (dd, 1H, $J_{6b,6a} = 9.0$ Hz, $J_{6b,5} = 3.8$ Hz, H6-b), 3.66 (m, 3H, H-2, H-3, H-5), 3.36 (dd, 1H, $J = 9.6$ Hz, $J = 8.4$ Hz, H-4), 2.98 (dd, 1H, $J_{1'a,1'b} = 15.6$ Hz, $J_{1'a,1'} = 5.7$ Hz, H-1′a), 2.50 (dd, 1H, $J_{1'b,1'a} = 15.6$ Hz, $J_{1'b,1'} = 8.7$ Hz, H-1′b), 2.14 (s, 3H, C-3′); ^{13}C NMR ($CDCl_3$): δ 205.21 (*C*O*C*H_3), 156.62 (CO), 138.83, 137.70, 137.50 ($C_{quat.}$ arom.), 128.84–128.04 (*C*H arom.), 81.85, 79.07 (C-2, C-3), 80.54 (C-4), 77.65, 77.33, 77.02 (O*C*H_2Ph), 66.22 (C-6), 53.65 (C-5), 48.28 (C-1), 41.46 (C-1′), 30.32 (C-3′); MALDI-MS *m*/*z* 517 $[M+H]^+$; 539 $[M+Na]^+$; $C_{31}H_{33}NO_6$ requires 515.60; Anal. Calcd for $C_{31}H_{33}NO_6$: C, 72,21; H, 6,45; N, 2,72. Found: C, 72.11; H, 6.45; N, 2.64.

3.28. (3*R*,4a*R*,5*S*,6*R*,7*R*,8*R*)-Hexahydro-5,6,7-trihydroxy-8-(hydroxymethyl)-3-methylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (30)

To a solution of **27** (0.050 g, 0.08 mmol) in MeOH (2 mL), $Pd(OH)_2$/C (0.050 g) and two drops of AcOH were added. The flask was purged three times with Ar and then filled with H_2. After 48 h, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure, affording compound **30** as a yellowish oil in quantitative yield. $[\alpha]_D^{22}$ +12.6 (*c* 0.5, MeOH); ^1H NMR (D_2O): δ 4.36 (m, 1H, H-2′), 4.31 (m, 1H, H-5), 3.83 (dd, 1H, $J_{6a,6b} = 12.1$ Hz, $J_{6a,5} = 9.8$ Hz, H-6a), 3.83 (m, 1H, H-1), 3.77 (m, 2H, H-3, H-4), 3.59 (dd, 1H, $J_{6b,6a} = 12.1$ Hz, $J_{6b,5} = 4.7$ Hz, H-6b), 3.53 (t, 1H, $J = 1.9$ Hz, H-2), 1.94 (m, 2H, H-1′), 1.21 (d, 3H, $J = 5.9$ Hz, H-3′); ^{13}C NMR (D_2O): δ 160.94 (CO), 75.46, 72.41, 72.06, 70.32 (C-2, C-3, C-4, C-2′), 62.26, 51.50 (C-1, C-5), 61.68 (C-6), 32.87 (C-1′), 22.42 (C-3′); MALDI-MS *m*/*z* 270 $[M+Na]^+$; $C_{10}H_{17}NO_6$ requires 247.25; Anal. Calcd for $C_{10}H_{17}NO_6$: C, 48.58; H, 6.93; N, 5.67. Found: C, 48.55; H, 6.91; N, 5.70. NOESY experiments on compound **30** allowed the determination of the absolute configuration of the stereocentre generated in the hydrogenation of the double bond, which was *R*.

3.29. (5*R*,6*S*,7*R*,8*R*,8a*R*)-Tetrahydro-6,7,8-trihydroxy-5-(2-oxopropyl)-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (31)

To a solution of **29** (0.030 g, 0.12 mmol) in MeOH (2 mL), $Pd(OH)_2$/C (0.030 g) and two drops of AcOH were added. The flask was purged three times with Ar and then filled with H_2. After 48 h, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure, affording compound **31** as a yellowish oil in quantitative yield. $[\alpha]_D^{22}$ +4.4 (*c* 0.80, H_2O); ^1H NMR ($CDCl_3$): δ 4.31 (m, 2H, H-1, H-3), 4.17 (dd, 1H, $J_{4,3} = 9.4$ Hz, $J_{4,5} = 4.2$ Hz, H-4), 3.62 (dt, 1H, $J_{5,6} = 10.3$ Hz, $J_{5,4} = 4.2$ Hz, H-5), 3.52 (dd, 1H, $J_{2,3} = 9.5$ Hz, $J_{2,1} = 6.2$ Hz, H-2), 3.35 (t, 1H, $J = 9.0$ Hz, H-6a), 3.27 (t, 1H, $J = 9.8$ Hz, H-6b), 2.89 (dd, 1H, $J_{1'a,1'b} = 17.3$ Hz, $J_{1'a,1} = 4.0$ Hz, H-1′a), 2.61 (dd, 1H, $J_{1'b,1'a} = 17.3$ Hz, $J_{1'b,1} = 9.9$ Hz, H-1′b), 2.07 (s, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 214.56 (CO ketone), 161.22 (CO), 75.81, 75.46, 72.31 (C-2, C-3, C-4), 69.26 (C-6), 56.51, 52.52 (C-1, C-5), 41.72 (C-1′), 32.45 (CH_3); MALDI-MS *m*/*z* 246 $[M+H]^+$; 284 $[M+K]^+$; $C_{10}H_{15}NO_6$ requires 245.23; Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.17; N, 5.71. Found: C, 48.90; H, 6.25; N, 5.78.

3.30. (2*R*,3*R*,4*R*,5*S*,6*R*)-*N*-Benzyl-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-6-vinylpiperidine-1-carboxamide (32)

To compound **17** (0.100 g, 0.18 mmol) in dry DME (2.5 mL), benzyl isocyanate (0.4 mL, 0.36 mmol) was added and the reaction mixture heated to reflux. After 2 h, the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (petroleum ether–EtOAc, 8:2), affording compound **32** (0.117 g, 94%) as a yellowish oil. $[\alpha]_D^{22}$ +38.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.33–7.19 (m, 25H, Ph), 6.17 (ddd, 1H, $J_{1',2'b} = 17.6$ Hz, $J_{1',2'a} = 10.5$ Hz,

$J_{1',1} = 7.4$ Hz, H-1′), 5.63 (t, 1H, $J = 5.3$ Hz, N*H*), 5.31 (dd, 1H, $J_{2'a,1'} = 10.5$ Hz, $J_{2'a,2'b} = 1.3$ Hz, H-2′a), 5.29 (dd, 1H, $J_{2'b,2'a} = 17.6$ Hz, $J_{2'b,2'a} = 1.3$ Hz, H-2′b), 4.72 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.64 (d, 1H, $J = 11.4$ Hz, OC*H*Ph), 4.59 (d, 1H, $J = 12.1$ Hz, OC*H*Ph), 4.52 (d, 1H, $J = 11.4$ Hz, OC*H*Ph), 4.56 (d, 1H, $J = 12.1$ Hz, OC*H*Ph), 4.55 (d, 1H, $J = 10.2$ Hz, OC*H*Ph), 4.51 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.42 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.58–4.54 (m, 1H, H-1), 4.40–4.35 (m, 3H, NCH_2Ph, H-5), 3.95 (dd, 1H, $J_{3,4} = 3.8$ Hz, $J_{3,2} = 2.3$ Hz, H-3), 3.86 (dd, 1H, $J_{2,1} = 5.7$ Hz, $J_{2,3} = 2.3$ Hz, H-2), 3.80 (br t, 1H, H-4), 3.78 (dd, 1H, $J_{6a,6b} = 9.7$ Hz, $J_{6a,5} = 4.9$ Hz, H-6a), 3.64 (dd, 1H, $J_{6b,6a} = 9.7$ Hz, $J_{6b,5} = 7.4$ Hz, H-6b); ^{13}C NMR ($CDCl_3$): δ 158.41 (CO), 139.52, 138.46, 138.24, 138.09, 138.00 ($C_{quat.}$ arom.), 135.06 (C-1′), 128.77–127.78 (*C*H arom.), 119.63 (C-2′), 83.33, 79.83, 78.94 (C-2, C-3, C-4), 73.41, 73.03, 72.79, 72.08, 71.89, 70.79 (*C*H_2Ph, C-6), 56.58, 54.76 (C-1, C-5); MALDI-MS *m*/*z* 706 $[M+Na]^+$; 721 $[M+K]^+$; $C_{44}H_{46}N_2O_5$ requires 682.85; Anal. Calcd for $C_{44}H_{46}N_2O_5$: C, 77.39; H, 6.79; N, 4.10. Found: C, 77.59; H, 6.81; N, 4.10.

3.31. (1*S*,5*R*,6*R*,7*R*,8*S*,8a*R*)-6,7,8-Tris(benzyloxy)-5-((benzyloxy)methyl)-1-(bromomethyl)-hexahydro-imidazo[1,5-*a*]pyridin-3(5*H*)-one (33)

To a solution of **32** (0.353 g, 0.517 mmol) in dry CH_2Cl_2 (8 mL) cooled to −20 °C, NBS (0.184 g, 1.03 mmol) was added. After 6 h, the reaction was quenched by the addition of H_2O and sodium thiosulfate until the solution became colourless, then the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The crude residue was purified by flash chromatography (petroleum ether–EtOAc, 6:4), affording compound **33** as a yellowish oil (0.225 g, 65%). $[\alpha]_D^{22}$ −9.4 (*c* 1.0, $CHCl_3$); IR (neat); *v* 1694 cm^{-1} (carbonyl); ^{1}H NMR ($CDCl_3$): δ 7.24–7.04 (m, 20H, Ph), 4.68 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.62 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.58 (m, 1H, H-1′), 4.49 (s, 1H, OC*H*Ph), 4.43 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.38–4.26 (m, 4H, 3 × OC*H*Ph, H-5), 4.30 (d, 1H, $J = 13.0$ Hz, OC*H*Ph), 3.90 (t, 1H, $J = 4.2$ Hz, H-4), 3.79 (m, 3H, H-1, H-3, H-6a), 3.67 (dd, 1H, $J_{6b,6a} = 9.4$ Hz, $J_{6b,5} = 5.1$ Hz, H-6b), 3.42 (t, 1H, $J = 2.5$ Hz, H-2), 3.31 (dd, 1H, $J_{2'a,2'b} = 10.4$ Hz, $J_{2'a,1'} = 4.5$ Hz, H-2′a), 3.23 (dd, 1H, $J_{2'b,2'a} = 10.4$ Hz, $J_{2'b,1'} = 7.8$ Hz, H-2′b); ^{13}C NMR ($CDCl_3$): δ 153.61 (CO), 138.74, 138.68, 138.46, 137.66 ($C_{quat.}$ arom), 126.18–128.84 (*C*H arom), 74.90, 75.12, 76.24, 76.34 (C-2, C-3, C-4, C-1′), 73.39, 72.77, 72.63, 71.64 (O*C*H_2Ph), 67.39 (C-6), 57.35, 53.26 (C-1, C-5), 29.99 (C-2′); MALDI-MS *m*/*z* 694 $[M+Na]^+$; 710 $[M+K]^+$; $C_{37}H_{39}BrN_2O_5$ requires 671.62; Anal. Calcd for $C_{37}H_{39}BrN_2O_5$: C, 66.17; H, 5.85; Br, 11.90; N, 4.17. Found: C, 66.21; H, 5.80; Br, 11.82; N, 4.11. NOESY experiments allowed the determination of the absolute configuration of the new stereocentre, which in this case was *S*.

3.32. (1*R*,5*R*,6*R*,7*R*,8*S*,8a*R*)-1-(Azidomethyl)-6,7,8-tris(benzyloxy)-5-((benzyloxy)methyl)-hexahydro-imidazo[1,5-*a*]pyridin-3(5*H*)-one (34)

To a solution of bromide **33** (0.128 g, 0.19 mmol) in dry DMF (2.3 mL), sodium azide (0.050 g, 0.76 mmol) was added and the reaction heated at reflux for 24 h. Evaporation of the solvent, followed by purification by flash chromatography (petroleum ether–EtOAc, 6:4) afforded azide **34** as a yellowish oil (0.095 g, 79%). $[\alpha]_D^{22}$ +13.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.24–7.09 (m, 20H, Ph), 4.66 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.626 (d, 1H, $J = 12.7$ Hz, OC*H*Ph), 4.49 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.49–4.45 (m, 1H, H-1′), 4.45–4.35 (m, 3H, 3 × OC*H*Ph), 4.31–4.20 (m, H-5), 4.294 (d, 1H, $J = 11.7$ Hz, OC*H*Ph), 4.24 (d, 1H, $J = 12$ Hz, OC*H*Ph), 3.94 (t, 1H, $J = 4.4$ Hz, H-4), 3.82 (dd, 1H, $J_{6a,6b} = 9.4$ Hz, $J_{6a,5} = 7.2$ Hz, H-6a), 3.77 (dd, 1H, $J_{3,4} = 4.4$ Hz, $J_{3,2} = 2.8$ Hz, H-3), 3.67 (dd, 1H, $J_{6b,6a} = 9.4$ Hz, $J_{6b,5} = 4.7$ Hz, H-6b), 3.64 (br t, 1H, H-1), 3.34 (t, 1H, $J = 2.6$ Hz, H-2), 3.19 (m, 2H, H-2′); ^{13}C NMR ($CDCl_3$): δ 153.64 (CO), 138.70, 138.45, 137.64, 137.60 ($C_{quat.}$ arom), 128.74–127.41 (*C*H arom), 76.30, 76.11, 74.36, 72.87 (C-2, C-3, C-4, C-1′), 73.40, 72.82, 72.55, 71.53 (O*C*H_2Ph), 67.37 (C-6), 50.02 (C-2′), 55.56, 53.14 (C-1, C-5); MALDI-MS *m*/*z* 657 $[M+Na]^+$; 673 $[M+K]^+$; $C_{37}H_{39}N_5O_5$ requires 633.74; Anal. Calcd for $C_{37}H_{39}N_5O_5$: C, 70.12; H, 6.20; N, 11.05. Found: C, 69.98; H, 6.20; N, 11.09.

3.33. (1*R*,5*R*,6*R*,7*R*,8*S*,8a*R*)-1-(Aminomethyl)-hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)imidazo-[1,5-*a*]pyridin-3(5*H*)-one (35)

To a solution of **34** (0.050 g, 0.079 mmol) in MeOH (2 mL), $Pd(OH)_2$/C (0.050 g) and two drops of AcOH were added. The flask was purged three times with Ar and then filled with H_2. After 48 h, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure, affording compound **35** as a yellowish oil in quantitative yield. $[\alpha]_D^{22}$ +14.8 (*c* 0.2, H_2O); ^{1}H NMR (D_2O): δ 5.40 (m, 1H, H-5), 4.76–4.62 (m, 1H, H-1′), 4.23 (dd, 1H, $J_{4,5} = 5.8$ Hz, $J_{4,3} = 2.2$ Hz, H-4), 3.90 (t, 1H, $J = 3.5$ Hz, H-2), 3.79 (m, 2H, H-1, H-3), 3.62 (dd, 1H, $J_{6a,6b} = 13.5$ Hz, $J_{6a,5} = 3.9$ Hz, H-6a), 3.42 (dd, 1H, $J_{6b,6a} = 13.5$ Hz, $J_{6b,5} = 1.8$ Hz, H-6b), 2.77–2.70 (m, 2H, H-2′); ^{13}C NMR (D_2O): δ 165.72 (CO), 77.25, 75.57, 74.22, 71.53 (C-2, C-3, C-4), 62.48 (C-6), 58.36, 51.08 (C-1, C-5), 42.45 (C-1′), 38.72 (C-2′); MALDI-MS *m*/*z* (MALDI-MS) 270 $[M+Na]^+$; $C_9H_{17}N_3O_5$ requires 247.25; Anal. Calcd for

$C_9H_{17}N_3O_5$: C, 43.72; H, 6.93; N, 17.00. Found: C, 43.81; H, 6.80; N, 17.08.

3.34. (2*R*,3*S*,4*R*,5*R*,6*R*)-2-Allyl-*N*-benzyl-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)piperidine-1-carboxamide (36)

To compound **1** (0.100 g, 0.18 mmol) in dry DME (2.5 mL), benzyl isocyanate (0.04 mL, 0.36 mmol) was added and the reaction mixture heated to reflux. After 2 h, the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (petroleum ether–EtOAc, 8:2), affording compound **36** (0.125 g, 99%) as a yellowish oil. $[\alpha]_D^{22}$ +22.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.21–7.15 (m, 25H, Ph), 6.32 (t, 1H, $J = 5.3$ Hz, NH), 5.76 (dddd, 1H, $J_{2',3'a} = 16.4$ Hz, $J_{2',3'b} = 10.0$ Hz, $J_{2',1'b} = 8.2$ Hz, $J_{2',1'a} = 6.1$ Hz, H-2′), 4.91 (m, 2H, H-3′), 4.64 (d, 1H, $J = 11.3$ Hz, OC*H*Ph), 4.61 (d, 1H, $J = 11.3$ Hz, OC*H*Ph), 4.583 (d, 1H, $J = 11.3$ Hz, OC*H*Ph), 4.54 (d, 1H, $J = 11.3$ Hz, OC*H*Ph), 4.50 (d, 1H, $J = 11.4$ Hz, OC*H*Ph), 4.48 (d, 1H, $J = 11.3$ Hz, OC*H*Ph), 4.23 (m, $2 \times$ OCH_2Ph, H-1), 3.76 (m, 3H, H-2, H-3, H-4), 3.70 (m, 1H, H-5), 3.62 (m, 2H, H-6), 2.53 (dt, 1H, $J_{1'a,1'b} = 14.4$ Hz, $J = 6.1$ Hz, H-1′a), 2.36 (dt, 1H, $J_{1'b,1'a} = 14.4$ Hz, $J = 8.2$ Hz, H-1′b); ^{13}C NMR ($CDCl_3$): δ 158.31 (CO), 139.49, 138.42, 138.19, 138.04, 137.95 ($C_{quat.}$ arom.), 135.03 (C-2′), 128.73–127.34 (*C*H arom), 119.57 (C-3′), 82.33, 79.80, 77.78 (C-2, C-3, C-4), 73.38, 73.33, 73.01, 72.76, 71.87, 70.77 (O*C*H$_2$Ph, C-6), 55.55, 54.72 (C-1, C-5), 45.37 (C-1′); MALDI-MS *m*/*z* 698 $[M+H]^+$; 720 $[M+Na]^+$; 736 $[M+K]^+$; $C_{45}H_{48}N_2O_5$ requires 696.87; Anal. Calcd for $C_{45}H_{48}N_2O_5$: C, 77,56; H, 6,94; N, 4,02. Found: C, 77.76; H, 6.69; N, 4.17.

3.35. *tert*-Butyl (1*S*,5*R*,6*R*,7*R*,8*S*,8a*R*)-2-(*tert*-butoxycarbonyl)-6,7,8-tris(benzyloxy)-5-((benzyloxy)methyl)-hexahydro-1-(iodomethyl)imidazo[1,5-*a*]pyridin-3(5*H*)-ylidenecarbamate (38)

To a solution of **17** (0.107 g, 0.195 mmol) in dry DMF (1 mL) cooled to 0 °C, di-Boc-thiourea (0.108 g, 0.39 mmol), Et_3N (0.54 mL, 0.39 mmol) and $HgCl_2$ (0.106 g, 0.39 mmol) were added sequentially. After 4 h, EtOAc was added and the precipitate filtered on a Celite pad. After usual workup, crude **37** was directly submitted to the subsequent reaction. To a solution of crude **37** (0.195 mmol) in dry CH_2Cl_2 (4.2 mL), I_2 (0.990 g, 0.390 mmol) was added. After 3 h, the reaction was quenched by the addition of H_2O and sodium thiosulfate until the solution became colourless, then the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The crude residue was purified by flash chromatography (petroleum ether–EtOAc, 8:2), affording bicyclic compound **38** as a yellowish oil (0.082 g, 46% over two steps). $[\alpha]_D^{22}$ +17.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.23 (m, 20H, Ph), 4.71 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.65 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.63 (s, 2H, OCH_2Ph), 4.52 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.46–4.37 (m, 2H, H-5, H-1′), 4.44 (d, 1H, $J = 11.7$ Hz, OC*H*Ph), 4.41 (d, 1H, $J = 11.6$ Hz, OC*H*Ph), 4.32 (d, 1H, $J = 11.7$ Hz, OC*H*Ph) 4.07 (dd, 1H, $J = 6.7$ Hz, $J = 5.7$ Hz, H-4), 3.95–3.78 (m, 3H, H-6a, H-3, H-1), 3.62–3.59 (m, 2H, H-6b, H-2), 3.47 (dd, 1H, $J_{2'a,2'b} = 9.6$ Hz, $J_{2'a,1'} = 3.02$ Hz, H-2′a), 3.08 (dd, 1H, $J_{2'b,1'} = 10.7$ Hz, $J_{2'b,2'a} = 9.7$ Hz, H-2′b), 1.50 (s, 9H, CH_3Boc), 1.492 (s, 9H, CH_3Boc); ^{13}C NMR ($CDCl_3$): δ 159.43 (CN), 149.54, 150.37 (CO), 138.28, 138.24, 137.86, 137.65 ($C_{quat.}$ arom.), 128.94–128.48 (*C*H arom.), 83.089, 79.134 ($C_{quat.}$ Boc), 79.90 (C-3), 78.53 (C-2), 73.45 (C-4), 73.86, 73.55, 73.30, 72.51 (O*C*H$_2$Ph), 67.62 (C-6), 58.46 (C-5), 57.99 (C-1), 53.51 (C-1′), 28.73, 28.68, 28.62, 28.51, 28.50, 28.34 (*C*H$_3$Boc), 8.47 (C-2′); MALDI-MS *m*/*z* 941 $[M+Na]^+$; 957 $[M+K]^+$; $C_{47}H_{56}IN_3O_8$ requires 917.87; Anal. Calcd for $C_{47}H_{56}IN_3O_8$: C, 61.50; H, 6.15; I, 13.83; N, 4.58. Found: C, 61.39; H, 6.18; I, 13.88; N, 4.56.

3.36. *tert*-Butyl (1*R*,5*R*,6*R*,7*R*,8*S*,8a*R*)-2-(*tert*-butoxycarbonyl)-1-(azidomethyl)-6,7,8-tris(benzyloxy)-5-((benzyloxy)methyl)-hexahydroimidazo[1,5-*a*]pyridin-3(5*H*)-ylidenecarbamate (39)

To a solution of iodide **38** (0.134 g, 0.146 mmol) in dry DMF (1.6 mL), sodium azide (0.038 g, 0.584 mmol) was added and the reaction heated at reflux for 24 h. Evaporation of the solvent, followed by purification by flash chromatography (petroleum ether–EtOAc, 8:2) afforded azide **39** as a yellowish oil (0.074 g, 61%). $[\alpha]_D^{22}$ −13.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34–7.14 (m, 20H, Ph), 4.68 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.66 (d, 1H, $J = 11.9$ Hz, OC*H*Ph), 4.61 (s, 2H, OCH_2Ph), 4.48 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.43 (d, 1H, $J = 12.8$ Hz, OC*H*Ph), 4.38 (d, 1H, $J = 12.4$ Hz, OC*H*Ph), 4.33 (d 1H, $J = 11.6$ Hz, OC*H*Ph), 4.27 (ddd, 1H, $J_{1',2'b} = 8.9$ Hz, $J_{1',2'a} = 3.9$ Hz, $J_{1',1} = 2.6$ Hz, H-1′), 3.99 (m, 2H, H-5, H-4), 3.79 (m, 3H, H-6a, H-3, H-1), 3.61 (dd, 1H, $J_{6b,6a} = 6.6$ Hz, $J_{6b,5} = 4.1$ Hz, H-6b), 3.59 (dd, 1H, $J_{2'a,2'b} = 10.5$ Hz, $J_{2'a,1'} = 3.9$ Hz, H-2′a), 3.53 (t, 1H, $J = 3.7$ Hz, H-2), 3.29 (dd, 1H, $J_{2'b,2'a} = 10.5$ Hz, $J_{2'b,1'} = 8.9$ Hz, H-2′b), 1.51 (s, 18H, CH_3Boc); ^{13}C NMR ($CDCl_3$): δ 159.53 (CN), 150.71, 149.67 (CO), 138.27, 138.25, 137.79, 137.61 ($C_{quat.}$ arom.), 128.70–127.77 (CH arom.), 83.07, 79.12 ($C_{quat.}$ Boc), 79.34, 77.78, 73.24 (C-2, C-3, C-4), 73.64, 73.43, 73.36, 72.17 ($4 \times$ O*C*H$_2$Ph), 67.60 (C-6), 56.36, 55.37, 53.28 (C-1, C-5, C-1′), 30.13 (C-2′); MALDI-MS *m*/*z* 857 $[M+Na]^+$; 873 $[M+K]^+$; $C_{47}H_{56}N_6O_8$ requires 832.98; Anal. Calcd for $C_{47}H_{56}N_6O_8$: C, 67.77; H, 6.78; N, 10.09. Found: C,

67.80; H, 6.75; N, 10.09; NOESY experiments on azide **39** allowed the determination of the absolute configuration of the stereocentre generated in the cyclisation, which was *S*.

3.37. (1*R*,5*R*,6*R*,7*R*,8*S*,8a*R*)-1-(Azidomethyl)-6,7,8-tris(benzyloxy)-5-((benzyloxy)methyl)-hexahydroimidazo[1,5-*a*]pyridin-3(5*H*)-imine (40)

Compound **39** (0.098 g, 0.116 mmol) was dissolved in a 4:1 TFA–H_2O mixture. After 1 h, the reaction was neutralised with satd aq $NaHCO_3$, and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness. Flash chromatography (petroleum ether–EtOAc, 75:25) afforded azide **40** as a yellowish oil (0.063 g, 86%). $[\alpha]_D^{22}$ −20.4 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.72–7.10 (m, 20H, Ph), 4.56 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.48 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.43 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.40 (s, 2H, OCH_2Ph), 4.33 (d, 1H, $J = 11.7$ Hz, OC*H*Ph), 4.28 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.26 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 3.89 (m, 1H, H-1′), 3.84 (m, 1H, H-5), 3.72 (dd, 1H, $J_{1,1'} = 4.6$ Hz, $J_{1,2} = 2.3$ Hz, H-1′), 3.67 (dd, 1H, $J_{3,4} = 4.4$ Hz, $J_{3,2} = 2.3$ Hz, H-3), 3.50 (m, 2H, H-6), 3.45 (t, 1H, $J = 4.4$ Hz, H-4), 3.32 (t, 1H, $J = 2.3$ Hz, H-2), 3.28 (d, 2H, H-2′); ^{13}C NMR ($CDCl_3$): δ 159.66 (CN), 137.18, 137.01, 136.92, 136.73 ($C_{quat.}$ arom.), 128.90–127.82 (*C*H arom.), 74.54, 73.47, 73.32 (C-2, C-3, C-4), 73.72, 72.93, 72.63, 72.06 (O*C*H_2Ph), 57.84, 55.20, 54.61 (C-1, C-5, C-1′), 53.19 (C-6), 30.16 (C-2′); MALDI-MS *m*/*z* 656 $[M+Na]^+$; 671 $[M+K]^+$; $C_{37}H_{40}N_6O_4$ requires 632.75; Anal. Calcd for $C_{37}H_{40}N_6O_4$: C, 70.23; H, 6.37; N, 13.28. Found: C, 70.27; H, 6.41; N, 13.30.

3.38. (1*R*,5*R*,6*R*,7*R*,8*S*,8a*R*)-1-(Aminomethyl)-octahydro-5-(hydroxymethyl)-3-iminoimidazo[1,5-*a*]pyridine-6,7,8-triol (41)

To a solution of **40** (0.054 g, 0.08 mmol) in MeOH (2 mL), $Pd(OH)_2$/C (0.050 g) and two drops of AcOH were added. The flask was purged three times with Ar and then filled with H_2. After 48 h, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure, affording compound **41** as a yellowish oil in quantitative yield. $[\alpha]_D^{22}$ +6.8 (*c* 0.2, H_2O); ^{1}H NMR (D_2O): δ 4.29 (m, 1H, H-1′), 4.10 (dd, 1H, $J_{1,1'} = 5.4$ Hz, $J_{1,2} = 2.2$ Hz, H-1), 3.86 (m, 2H, H-5, H-6a), 3.74 (m, 2H, H-2, H-3), 3.61 (m, 2H, H-4, H-6b), 3.23 (m, 2H, H-2′); ^{13}C NMR (D_2O): δ 165.57 (CN), 72.18, 71.81, 70.65 (C-2, C-3, C-4), 63.98, 62.13, 62.06 (C-5, C-1, C-1′), 57.74 (C-6), 49.13 (C-2′); MALDI-MS *m*/*z* 269 $[M+Na]^+$; 285 $[M+K]^+$; $C_9H_{18}N_4O_4$ requires 246.26; Anal. Calcd for $C_9H_{18}N_4O_4$: C, 43.89; H, 7.37; N, 22.75. Found: C, 43.91; H, 7.41; N, 22.70.

3.39. (3a*R*,5*R*,6*R*,7*R*,7a*S*)-[(6,7-Bis-benzyloxy-5-benzyloxymethyl-2-chloromercuriomethyl-hexahydro-furo[3,2-*b*]pyridin-4-yl)-*tert*-butoxycarbonylimino-methyl]-carbamic acid *tert*-butyl ester (42) and *tert*-butyl (4a*R*,5*S*,6*R*,7*R*,8*R*)-2-(*tert*-butoxycarbonyl)-5,6,7-tris(benzyloxy)-8-((benzyloxy)methyl)-3-(chloromercuriomethyl)-octahydropyrido[1,2-*f*]pyrimidin-1-ylidenecarbamate (43)

To a solution of **1** (0.041 g, 0.07 mmol) in dry DMF (0.35 mL) cooled to 0 °C, di-Boc-thiourea (0.019 g, 0.07 mmol), Et_3N (0.02 mL, 0.14 mmol) and $HgCl_2$ (0.019 g, 0.07 mmol) were added sequentially. After 24 h, EtOAc was added and the precipitate filtered on a Celite pad. Usual workup and flash chromatography (petroleum ether–EtOAc, 85:15) afforded compound **42** (0.015 g) and **43** (0.018 g) as a yellowish oils.

Compound **42**. ^{1}H NMR ($CDCl_3$): δ 7.24–7.17 (m, 15H, Ph), 4.75 (m, 1H, H-5), 4.62 (d, 1H, $J = 11.7$ Hz, OC*H*Ph), 4.58 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.52 (m, 1H, H-2′), 4.49 (d, 1H, $J = 11.4$ Hz, OC*H*Ph), 4.44 (d, 1H, $J = 11.4$ Hz, OC*H*Ph), 4.37 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.34 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.00 (dd, 1H, $J_{2,3} = 8.5$ Hz, $J_{2,1} = 6.4$ Hz, H-2), 3.91 (br t, 1H, H-4), 3.65 (m, 2H, H-3, H-6a), 3.53 (t, 1H, $J = 3.5$ Hz, H-6b), 3.45 (ddd, 1H, $J_{1,1'a} = 12.3$ Hz, $J_{1,2} = 6.4$ Hz, $J_{1,1'b} = 2.4$ Hz), 2.58 (ddd, 1H, $J_{1'a,2'} = 2.5$ Hz, $J_{1'a,1'b} = 10.9$ Hz, $J_{1'a,1} = 12.3$ Hz, H-1′a), 1.92 (dd, 1H, $J_{1'b,2'} = 4.1$ Hz, $J_{1'b,1'a} = 10.9$ Hz, H-1′b), 1.69 (m, 2H, H-3′), 1.45 (s, 9H, CH_3Boc), 1.44 (s, 9H, CH_3Boc); MALDI-MS *m*/*z* 952 $[M+H]^+$; 990 $[M+K]^+$. $C_{41}H_{52}ClHgN_3O_8$ requires 950.91.

Compound **43**. ^{1}H NMR ($CDCl_3$): δ 7.31–7.23 (m, 20H, Ph), 4.91 (m, 1H, H-5), 4.78 (d, 1H, $J = 11.3$ Hz, OC*H*Ph), 4.76 (d, 1H, $J = 11.6$ Hz, OC*H*Ph), 4.67 (m, 1H, H-2′), 4.65 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.61 (d, 1H, $J = 11.3$ Hz, OC*H*Ph), 4.60 (d, 1H, $J = 11.6$ Hz, OC*H*Ph), 4.41 (d, 1H, $J = 11.8$ Hz, OC*H*Ph), 4.39 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.29 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.03 (ddd, 1H, $J_{1,1'a} = 10.0$ Hz, $J_{1,1'b} = 9.7$ Hz, $J_{1,2} = 3.2$Hz, H-1), 3.95 (t, 1H, $J = 7.6$ Hz, H-4), 3.84 (m, 2H, H-3, H-6a), 3.73 (dd, 1H, $J_{6b,6a} = 10.1$ Hz, $J_{6b,5} = 4.3$ Hz, H-6b), 3.51 (t, 1H, $J = 3.2$ Hz, H-2), 2.54 (ddd, 1H, $J_{1'a,1'b} = 13.3$ Hz, $J_{1'a,1} = 10.0$ Hz, $J_{1'a,2'} = 5.4$ Hz, H-1′a), 2.25 (t, 1H, $J = 12.3$ Hz, H-3′a), 1.69 (m, 1H, H-1′b), 1.59 (dd, 1H, $J_{3'b,3'a} = 12.3$ Hz, $J_{3'b,2'} = 4.5$ Hz, H-3′b), 1.61 (s, 9H, CH_3Boc), 1.52 (s, 9H, CH_3Boc); MALDI-MS *m*/*z* 1042 $[M+H]^+$; 1080 $[M+K]^+$; $C_{48}H_{58}ClHgN_3O_8$ requires 1041.03.

Acknowledgements

The authors acknowledge the European Community's Human Potential Programme under contract HPRN-CT-2002-00173, [GLYCIDIC SCAFFOLDS], and the

Ministero dell'Università e della Ricerca under contract MIUR-PRIN 2005 No. 2005037725, Dr. Jesus Jiménez-Barbero for his contribution to conformational analysis, and Professor Alessandra Polissi for antibacterial tests.

References

1. For recent reviews on carbohydrate-processing enzymes inhibitors, see for example: (a) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553; (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (c) Asano, N. *J. Enzyme Inhib.* **2000**, *15*, 215–234; (d) Zechel, D. L.; Withers, S. G. *Acc. Chem. Res.* **2000**, *33*, 11–18; (e) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750–770; (f) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300–2324; (g) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, Germany, 1999; (h) Asano, N.; Nishida, M.; Kato, A.; Kizu, H.; Matsui, K.; Shimada, Y.; Watson, A.; Nash, R. J.; de Lilley, P. M. Q.; Itoh, T.; Baba, M.; Fleet, G. W. J. *J. Med. Chem.* **1998**, *41*, 2565–2571; (i) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340–347.
2. (a) Ratner, L.; Heyden, N. V.; Dedera, D. *Virology* **1991**, *181*, 180–192, and references cited therein; (b) Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, *291*, 2370–2376; (c) Chery, F.; Cronin, L.; O'Brien, J. L.; Murphy, P. V. *Tetrahedron* **2004**, *60*, 6597–6608; (d) Greimel, P.; Spreitz, J.; Stütz, A. E.; Wrodnigg, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513–523; (e) Alper, J. *Science* **2001**, *291*, 2338–2343; (f) Pavlovic, D.; Neville, D. C. A.; Argaud, O.; Blumberg, B.; Dwek, R. A.; Fischer, W. B.; Zitzmann, N. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 6104–6108; (g) Durantel, D.; Carrouée-Durantel, S.; Branza-Nichita, N.; Dwek, R. A.; Zitzmann, N. *Antimicrob. Agents Chemother.* **2004**, *48*, 497–504; (h) Wu, S.-F.; Lee, C.-J.; Liao, C.-L.; Dwek, R. A.; Zitzmann, N.; Lin, Y.-L. *J. Virol.* **2002**, *76*, 3596–3604.
3. (a) Paulsen, H.; Brockhausen, I. *Glycoconjugate J.* **2001**, *18*, 867–870; (b) Gross, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935–944.
4. (a) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539–2542; (b) Balfour, J. A.; McTavish, D. *Drugs* **1993**, *46*, 1025–1054.
5. (a) Cren, S.; Gurcha, S. S.; Blake, A. J.; Besra, G. S.; Thomas, N. R. *Org. Biomol. Chem.* **2004**, *2*, 2418–2420; (b) Wrodnigg, T. M.; Sprenger, F. K. *Mini-Rev. Med. Chem.* **2004**, *4*, 437–459.
6. (a) Butters, T. D.; van den Broek, L. A. G. M.; Fleet, G. W. J.; Krulle, T. M.; Wormald, M. R.; Dwek, R. A.; Platt, F. M. *Tetrahedron: Asymmetry* **2000**, *11*, 113–124; (b) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683–4696; (c) Cox, T. M.; Aerts, J. M. F. G.; Andria, G.; Beck, M.; Belmatoug, N.; Bembi, B.; Chertkoff, R.; Vom Dahl, S.; Elstein, D.; Erickson, A.; Giralt, M.; Heitner, R.; Hollak, C.; Hrebicek, M.; Lewis, S.; Mehta, A.; Pastores, G. M.; Rolfs, A.; Miranda, M. C. S.; Zimran, A. *J. Inherit. Metab. Dis.* **2003**, *26*, 513–526.
7. Cipolla, L.; La Ferla, B.; Nicotra, F. *Curr. Top. Med. Chem.* **2003**, *3*, 1349–1364, and references cited therein.
8. (a) Ermert, P.; Vasella, A.; Weber, M.; Rupitz, K.; Withers, S. G. *Carbohydr. Res.* **1993**, *250*, 113–128; (b) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171–1202; (c) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 21–41; (d) Takahata, H.; Momose, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: San Diego, 1993; Vol. 44,.
9. For a recent review on the synthesis of swainsonine and its analogues, see for example: (a) El Nemr, A. *Tetrahedron* **2000**, *56*, 8579–8629; For a review on the syntheses of polyhydroxindolizidine, see: (b) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045.
10. (a) Fernandez, J. M. G.; Mellet, C. O.; Benito, J. M.; Fuentes, J. *Synlett* **1998**, 316–318; (b) Berges, D. A.; Ridges, M. D.; Dalley, N. K. *J. Org. Chem.* **1998**, *63*, 391–392; (c) Berges, D. A.; Hong, L.; Dalley, N. K. *Tetrahedron* **1998**, *54*, 5097–5104; (d) Streith, J.; Rudyk, H.; Tschamber, T.; Tarnus, C.; Strehler, C.; Deredas, D.; Frankowski, A. *Eur. J. Org. Chem.* **1999**, 893–898; (e) Davis, B. G.; Nash, R. J.; Watson, A. A.; Smith, C.; Fleet, G. W. J. *Tetrahedron* **1999**, *55*, 4501–4520; (f) Lorthiois, E.; Meyyappan, M.; Vasella, A. *Chem. Commun.* **2000**, 1829–1830; (g) Berges, D. A.; Fan, J.; Devinck, S.; Liu, N.; Dalley, N. K. *Tetrahedron* **1999**, *55*, 6759–6770; (h) Kilonda, A.; Compernolle, F.; Peeters, K.; Joly, G. J.; Toppet, S.; Hoornaert, G. J. *Tetrahedron* **2000**, *56*, 1005–1012; (i) Flessner, T.; Wong, C.-H. *Tetrahedron Lett.* **2000**, *41*, 7805–7808; (j) Sondergaard, K.; Liang, X.; Bols, M. *Chem. Eur. J.* **2001**, *7*, 2324–2331.
11. (a) Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010–2023; (b) Diekem, D. J.; Jones, R. N. *Lancet* **2001**, *358*, 1975–1982; (c) Schierle-Arndt, K.; Kolter, D.; Danielmeier, K.; Steckhan, E. *Eur. J. Org. Chem.* **2001**, 2425–2433; (d) Ford, C. W.; Hamel, J. C.; Stapert, D.; Moerman, J. K.; Hutchinson, D. K.; Barbachyn, M. R.; Zurenko, G. E. *Trends Microbiol.* **1997**, *5*, 196–201; (e) Yagi, B. H.; Zurenko, G. E. *Anaerobe* **1997**, *3*, 301–306; (f) Zurenko, G. E.; Gibson, J. K.; Shinabarger, D. L.; Aristoff, P. A.; Ford, C. W.; Tarpley, W. G. *Curr. Opin. Pharmacol.* **2001**, *1*, 470–476.
12. (a) Gormley, G., Jr.; Chan, Y. Y.; Fried, J. *J. Org. Chem.* **1980**, *45*, 1447–1454; (b) Larson, G. M.; Schaneberg, B. T.; Sneden, A. T. *J. Nat. Prod.* **1999**, *62*, 361–363; (c) Cassady, J. M.; Chan, K. K.; Floss, H. G.; Leistner, E. *Chem. Pharm. Bull.* **2004**, *52*, 1–26.
13. (a) Campanini, L.; Duréault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1995**, *36*, 8015–8021; (b) McCort, I.; Duréault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1996**, *37*, 7717–7720; (c) Sung, H. K.; Do, H. R. *Tetrahedron Lett.* **1997**, *38*, 607–610.
14. (a) Crider, A. M.; Witt, K. A. *Mini-Rev. Med. Chem.* **2007**, *7*, 213–220; (b) Amtul, Z.; Atta-ur-Rahman; Siddiqui, R. A.; Choudhary, M. I. *Curr. Med. Chem.* **2002**, *9*, 1323–1348; (c) Eyermann, C. J.; Jadhav, P. K.; Hodge, C. N.; Chang, C.-H.; Rodgers, J. D.; Lam, P. Y. S. *Adv. Amino Acid Mimetics Peptidomimetics* **1997**, *1*, 1–40; (d) Cirillo, P. F.; Pargellis, C.; Regan, J. *Curr. Top. Med. Chem.* **2002**, *2*, 1021–1035.
15. (a) Berlinck, R. G. S.; Kossuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516–550, and references cited therein; (b) Nagasawa, K.; Hashimoto, Y. *Chem. Rec.* **2003**, *3*, 201–211; (c) Botta, B.; Carmignani, M.; Volpe, A. R.; Botta, M.; Corelli, F.; Delle Monache, G. *Curr. Med. Chem.* **2003**, *10*, 1845–1862.
16. (a) Cipolla, L.; La Ferla, B.; Peri, F.; Nicotra, F. *Chem. Commun.* **2000**, 1289–1290; (b) Cipolla, L.; Palma, A.; La Ferla, B.; Nicotra, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2161–2165.
17. Cipolla, L.; Lay, L.; Nicotra, F. *J. Org. Chem.* **1997**, *62*, 6678–6681.

18. Williams, A. L.; Abad Grillo, T.; Comins, D. L. *J. Org. Chem.* **2002**, *67*, 1972–1973, and references cited therein.
19. Sakai, J. I.; Takeda, T.; Ogihara, Y. *Carbohydr. Res.* **1981**, *95*, 125–131.
20. Zèmplen, G. *Chem. Ber.* **1926**, *59*, 1254–1266.
21. Frigerio, M.; Santagostino, M.; Sputare, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276.
22. Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637–2647.
23. Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055–4058.
24. Levallet, C.; Lerpiniere, J.; Ko, S. Y. *Tetrahedron* **1997**, *53*, 5291–5304.
25. de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174.
26. Chen, X.; Wu, B.; Wang, P. G. *Curr. Med. Chem.: Anti-Cancer Agents* **2003**, *3*, 139–150.
27. Kunz, D. A.; Chapman, P. J. *J. Bacteriol.* **1981**, *146*, 179–191.