A versatile stereocontrolled synthesis of 2-deoxyiminosugar C -glycosides and their evaluation as glycosidase inhibitors

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Alexandre Lumbroso,[a] Clément Berthonneau,[a] Isabelle Beaudet,[a] Jean-Paul Quintard,[a] Aurélien Planchat,[a] M. Isabel García-Moreno,[b] Carmen Ortiz-Mellet,[b] Erwan Le Grognec[a]*

[a] Université de Nantes, CNRS, CEISAM, UMR 6230, 44000 Nantes, France.
e-mail: erwan.legrognec@univ-nantes.fr

[b] Department of Organic Chemistry, Faculty of Chemistry, University of Seville, c/ Professor García Gonzalez 1, 41012, Seville, Spain

Abstract

A highly enantioselective synthesis of *(R,S)* or *(S,S)*-2,6-disubstituted dehydropiperidines has been previously achieved through Sn/Li transmetalation of the corresponding stannylated dehydropiperidines or of their precursors. Herein, we successively consider their Upjohn's *syn* dihydroxylation and their *anti* dihydroxylation via an epoxidation reaction followed by epoxide opening reaction. The stereochemical course of these reactions was first reported including the use of appropriate protecting groups before considering the conversion of the obtained compounds into NH or NMe iminosugar hydrochlorides. A primary evaluation of the designed iminosugar C-glycosides as glycosidase inhibitors suggests candidates for the selective inhibition of α-galactosidase, amyloglycosidase and naringinase. Beyond the reported results, the method constitutes a highly modulable route for the synthesis of well stereodefined iminosugar C-glycosides, an advantage which might be used for the design of iminosugars to enhance their biological properties.

Keywords: *Iminosugar C-glycosides, Stereoselective Synthesis, Dihydroxylation, Epoxidation, Inhibition of glycosidases, Piperidine, Tetrahydropyridine, Dehydropiperidine*

1. Introduction

Iminosugars are the most attractive class of glycomimetics for inhibiting glycosidases due to a structural resemblance with the sugar moiety of the natural substrates.[1] The marketing of three iminosugar-based drugs for the treatment of type II diabete (Miglitol),[2] Gaucher disease (Miglustat),[3] or Fabry disease (Migalastat)[4] demonstrates the role that iminosugars can play in the therapy of diseases associated with carbohydrates metabolism.[1c, 5] A huge number of studies have been carried out to exploit the potential of iminosugars as antivirals[6] or antidiabetic agents[7] and to promote them in cancer therapy[8] or for the treatment of lysosomal storage disorders.[9] Therefore, numerous syntheses of iminosugars have been developed to improve the potency and selectivity of these inhibitors but also to better understand the structure-activity relationships.[1c, 10] The influence of ring size and rigidity have been studied through the synthesis of 4-membered,[11] 5-membered[12] and 7-membered rings,[13] through bicyclic locked deoxy-iminosugars,[14] hydrazine type bicyclic iminosugars[15], constrained fused bicyclic iminosugars[16] or sp^2-iminosugars.[17]

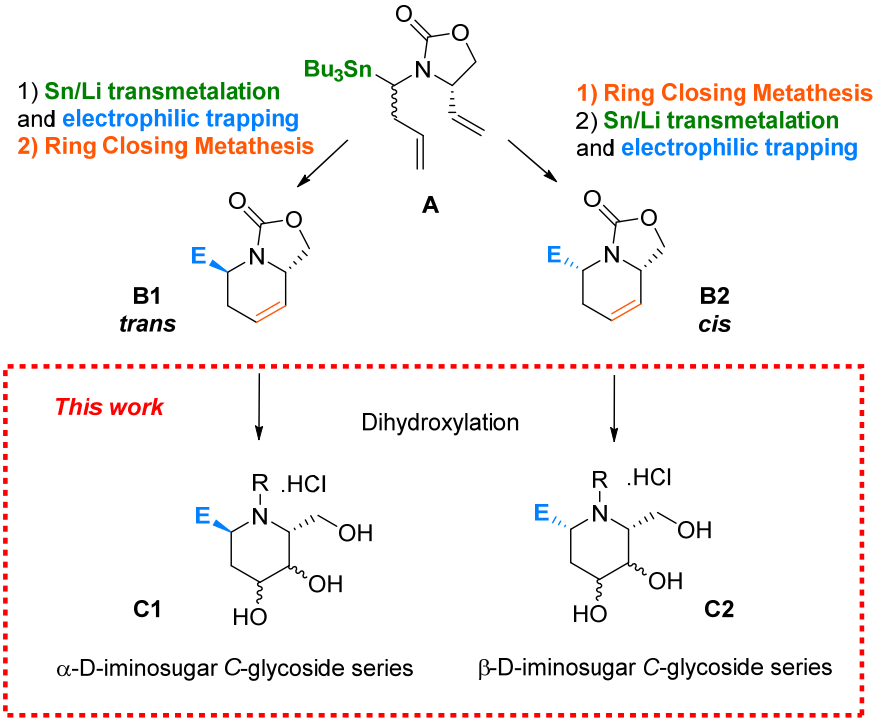
Many of the reported syntheses use carbohydrates as starting materials[18] including stannylated ones[19] but others start from simple organic molecules.[20] The use of carbohydrates as starting materials allows an access to modified compounds of well-defined configuration while the use of simple organic starting materials offer the opportunity to insert a wide variety of substituents.

Among the different classes of iminosugars, iminosugar C-glycosides display promising biological activities. They are supposed to allow an easier locking through a favorable conformation of the piperidine ring inducing a better ligand-enzyme interaction.[21] While naturally occurring C-glycosides iminosugars have been isolated,[22] versatile approaches to this type of compounds are required for the validation of these assessments.[23]

On our side, we have first developed a diastereoselective approach involving *syn*-allylstannation of *N*-acyliminium derivatives combined with a ring-closing metathesis and a dihydroxylation to obtain (±)-1-deoxy-6,8a-di-epi-castanospermine and (±)-1-deoxy-gulonojirimycine.[24] However, an enantioselective version of this approach was shown to be hardly developed and we considered a second method based on the stannylated platform **A** derived from (*S*)-vinylglycinol (scheme 1).[25] The 2,6-disubstituted dehydropiperidines **B** were obtained using two key reactions: 1) a Sn-Li transmetalation followed by an electrophilic trapping and 2) a ring-closing metathesis. The high stereoselectivity of the sequence was found to be governed by the chelation occurring between lithium and oxazolidinone carbonyl, revealing the importance of the relative order in which these two reactions are carried out and affording an opportunity for a selective preparation of (*S*,*S*)-*trans* dehydropiperidines **B1** and (*R*,*S*)-*cis* dehydropiperidines **B2**.[25b]

Herein, we report with further details the functionalization of these dehydropiperidines which constitutes the late stage of the stereocontrolled synthesis of iminosugar C-glycosides **C1** and **C2**

which has been briefly reported.[26] Furthermore, due to the high polarity of iminosugars, the removal of tetrabutyltin and other residual organotins can be easily achieved by biphasic partition or liquid chromatography,[27] allowing preliminary biological assays of these iminosugar C-glycosides toward a set of glycosidases.



Scheme 1. Syntheses of the two series of D-iminosugar *C*-glycosides

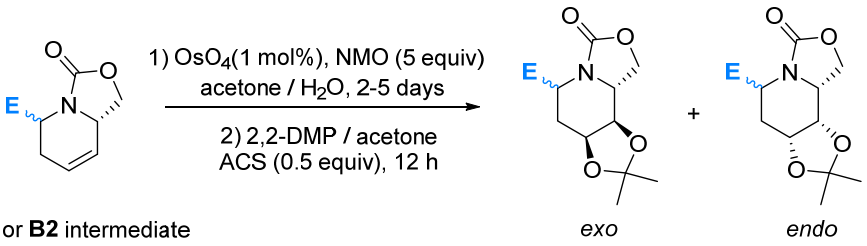
2. Synthesis of iminosugar *C*-glycoside analogs

2.1. Functionalization of intermediates **B1** and **B2** by *syn*-dihydroxylation

The functionalization of intermediates **B1** and **B2** was first considered through an Upjohn's dihydroxylation reaction achieved according to information reported in Table 1.[28] A subsequent conversion into acetonides was carried out to facilitate further characterizations (except for **5** and **11**). Accordingly, starting from dehydropiperidines **B1**, acetonides **1-6** were obtained in 55% to 94% yield as a mixture of two diastereomers which were fully characterized after separation by flash chromatography. Fortunately, suitable monocrystals for an X-ray diffraction analysis were obtained for the major diastereomer **2** resulting from the functionalization of **B1-b**, allowing its assignment as *endo* isomer.[26] On the basis of the similarity of their NMR data, the major diastereomers were always assigned to be *endo* in compounds **1** to **6** derived from **B1** type dehydropiperidines (*exo/endo* = 24/76 to 9/91).

When a similar procedure was applied to dehydropiperidines **B2**, acetonides **7-14** were obtained in good yields (62-89%) with a high preference for the *exo* isomers (91-98% when the side chain E contains an alcohol or an ester function (*vide infra* for the assignment of the *exo* configuration)). When E was an *n*-hexyl group, this *exo* preference (observed at the stage of the crude diol, without conversion into acetonide) appeared to be lower (*exo*/*endo* = 83/17). It is worth noting that the *exo* preference remained high (98%) when the product resulting from an acyl transfer reaction **B2-*d*** was considered for the dihydroxylation reaction.[29]

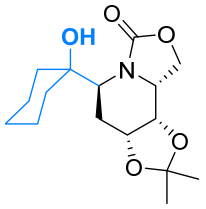
Table 1. *Syn*-Dihydroxylation of intermediates **B1** and **B2**



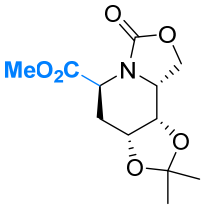
B1 or **B2** intermediate — *exo* — *endo*

E = ***a*** *c*Hex(OH), ***b*** CO_2Me, ***c*** (*S*)-$C_5H_{11}CH(OH)$, ***d*** (*R*)-$C_5H_{11}CH(OH)$, ***e*** *n*-$Bu_2C(OH)$, ***f*** *n*-C_6H_{13}, ***g*** (*S*)-PhCH(OH), ***h*** (*R*)-PhCH(OH), ***i*** (*S*)-*i*-BuCH(OH)

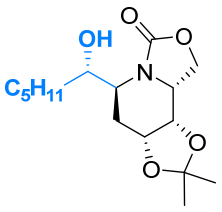
*From **B1** intermediates*



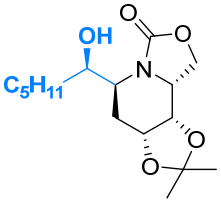
1 from **B1-*a*** 94%
exo/endo = 15/85[a]



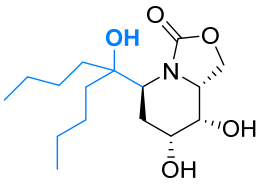
2 from **B1-*b*** 78%[b]
exo/endo = 17/83[a]



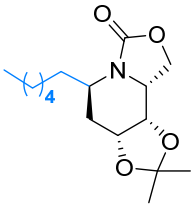
3 from **B1-*c*** 64%[c]
exo/endo = 28/72[d]



4 from **B1-*d*** 55%[c]
exo/endo = 15/85[d]

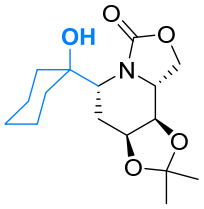


5 from **B1-*e*** 72%[e]
exo/endo = 9/91[a]

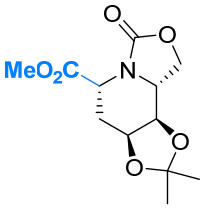


6 from **B1-*f*** 78%
exo/endo = 24/76[d]

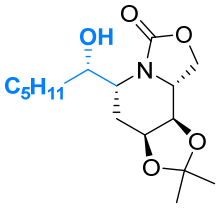
*From **B2** intermediates*



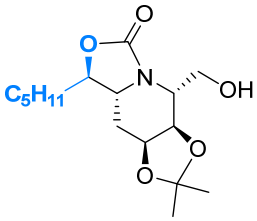
7 from **B2-*a*** 85%
exo/endo > 98/2[f]



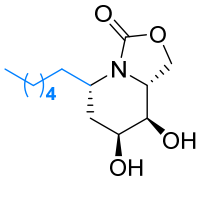
8 from **B2-*b*** 79%
exo/endo = 95/5[d]



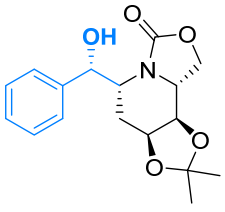
9 from **B2-*c*** 71%
exo/endo = 91/9[d]



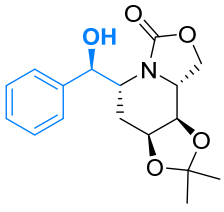
10 from **B2-*d*** 76%
exo/endo > 98/2[f]



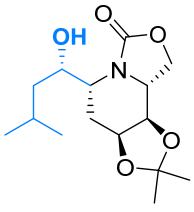
11 from **B2-*f*** 62%[e,g]
exo/endo = 83/17[d]



12 from **B2-*g*** 83%
exo/endo = 96/4[d]



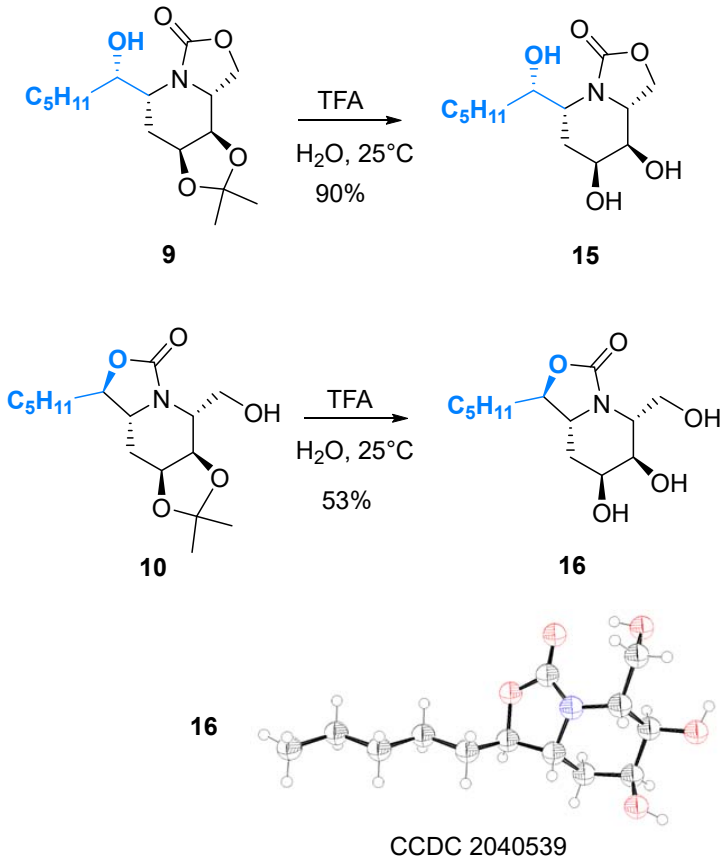
13 from **B2-*h*** 86%
exo/endo = 94/6[d]



14 from **B2-*i*** 89%
exo/endo = 96/4[d]

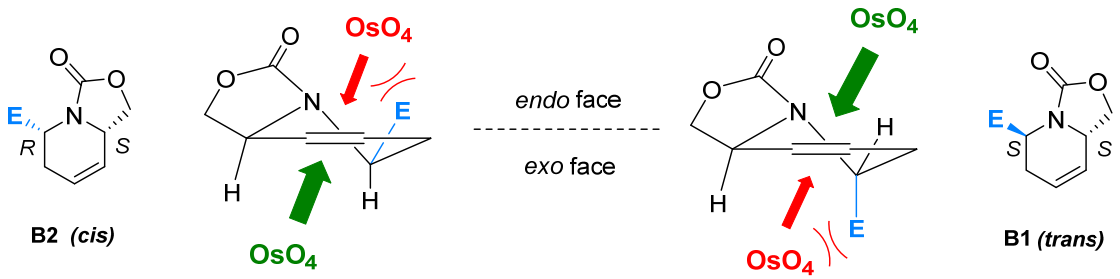
[a] *exo/endo* ratio was determined by GC analyses on the crude product.
[b] The absolute configuration of the *endo* compound was confirmed by X-ray analysis.[26]
[c] The *exo* isomer was not isolated after column chromatography.
[d] *exo/endo* ratio was determined by ^1H NMR analyses on the crude product.
[e] Without step 2, the obtained diol was not modified into acetonide.
[f] The minor compound was not observed in the ^1H NMR spectrum.
[g] The *endo* diol was not isolated after column chromatography.

At this stage, the deprotection of compounds **9** and **10** was performed with trifluoroacetic acid (TFA) in water and furnished **15** and **16** in good yields (scheme 2). Fortunately, suitable monocrystals for an X-ray diffraction analysis were obtained for the major isomer of **16** allowing assignment of its *exo* configuration. This assignment has been a key-information for further assignment of an *exo* configuration for the major diastereomer of compound **10** and subsequently for the major diastereomer of compounds **7**-**14** on the basis of the analogies encountered in their NMR data. Accordingly the Upjohn's dihydroxylation proceeded with a high *exo*-selectivity on intermediates **B2**. In addition, the X-ray analysis also corroborates the occurrence of the acyl transfer reaction during the synthesis of **B2-*d***.[29]



Scheme 2. Deprotection of acetonides **9** and **10** at 25°C and ORTEP view of compound **16**

The stereochemical trends of the Upjohn's dihydroxylation reaction can be explained by considering the approach of osmium tetroxide on the *exo* or *endo* face of the *cis* and *trans* dehydropiperidines in their half chair conformation (Scheme 3).[30] When the *cis* substrate is involved, the E group occupies a pseudo equatorial position which brings a steric hindrance on the *endo* face, inducing a prevalent reaction on the *exo* face. On the other hand, when the *trans* substrate is involved, the presence of the E group in a pseudo axial position strongly interferes with a reaction on the *exo* face, leading mainly to the reaction on the *endo* one. The higher preference for the *exo* approach starting from the *cis* dehydropiperidines **B2** (*exo*/*endo* ~ 95/5) compared to the *endo* preference for *trans* dehydropiperidines **B1** (*exo*/*endo* ~ 20/80) can be explained by a higher accessibility to the convex face (*exo* face) of these bicyclic molecules.

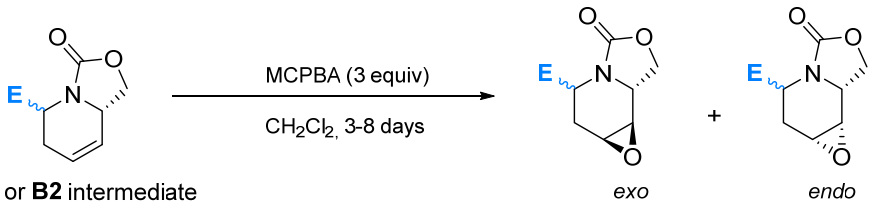


Scheme 3. Rationalization of the stereochemical trends for Upjohn's dihydroxylation

2.2 Functionalization of intermediates **B1** and **B2** by epoxidation and *anti* opening of the epoxides

This approach was recently reviewed and used for *anti* dihydroxylation and *anti* fluoro-hydroxylation of dehydropiperidines.[31] The epoxidation reaction was carried out on four different derivatives **B1-j**, **B2-b**, **B2-g** and **B2-i** in the presence of an excess of *meta*-chloroperbenzoic acid (MCPBA) in dichloromethane.[32] The results are reported in Table 2.

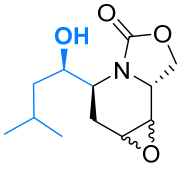
Table 2. Epoxidation of intermediates **B1** and **B2**



B1 or **B2** intermediate

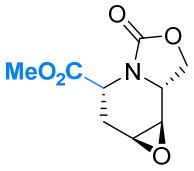
E = ***b*** CO_2Me, ***g*** (*S*)-PhCH(OH), ***i*** (*S*)-*i*-BuCH(OH), ***j*** (*R*)-*i*-BuCH(OH)

*From **B1-j***

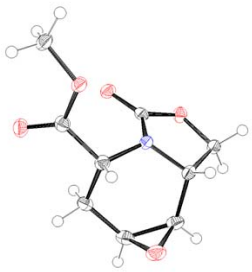


17, 73%
dr = 67/33[a]
unseparated mixture of diastereomers

*From **B2** intermediates*



18-*exo* from **B2-*b*,**
54%[b,c]
exo/endo = 87/13[a]



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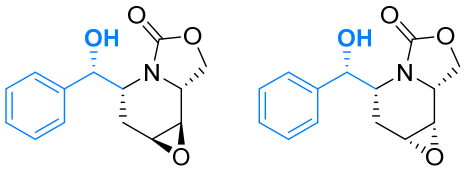
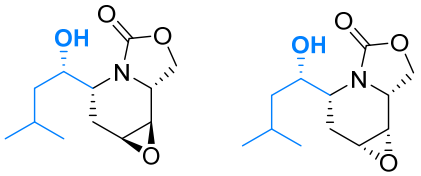
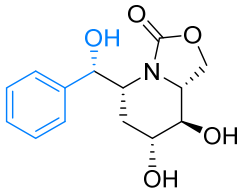


19-*exo* and **19-*endo*** from **B2-*g***, 58%[d]
exo/endo = 15/85[e]



20-*exo* and **20-*endo*** from **B2-*i***, 61%
exo/endo = 46/54[a]
Separated diastereomers



19' from **19-*exo***

[a] Ratios *exo/endo* were determined by ^{1}H NMR analyses on the crude product.
[b] The minor compound was not isolated.
[c] The absolute configuration of the exo compound was confirmed by X-ray analysis.
[d] Along the purification on silica gel, an *anti* opening reaction of the epoxide **19**-*exo* occurred, affording the corresponding diol **19'** characterized on the basis of its ^{1}H and ^{13}C NMR data.
[e] Ratio *exo/endo* was determined by HPLC analyses on the crude product and the configuration of the major epoxide was determined by NOESY experiments.

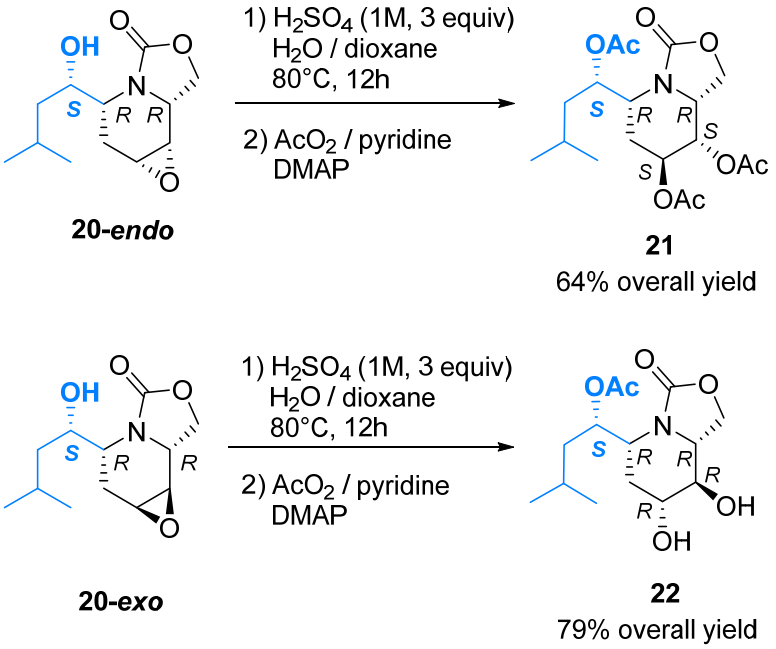
The reaction was found to proceed slowly affording the desired epoxides in moderate to good yields. Low stereoselectivities were obtained starting from **B2-*i*** and **B1-*j***, while a strong *exo*-preference was observed starting from **B2-*b*** and a strong *endo*-preference starting from **B2-*g*** as pointed out by X-ray and NMR analyses. Suitable monocrystals for an X-ray diffraction analysis were obtained for the major diastereomer of **18** allowing unambiguous assignment of its *exo*-configuration. Subsequent assignment of *exo* and *endo*-configurations of stereoisomers of **19** and **20** were deduced from their NMR data.

While the *exo* preference obtained for **18** can be explained on the basis of arguments used to justify the stereoselectivity of the Upjohn's dihydroxylation, the *endo* selectivity observed for **19** might find its explanation in a π-stacking interaction of the aromatic ring of the peracid with the phenyl group contained in the E substituent of **B2-*g***. Accordingly, the selectivity was low in the absence of this type of interaction as observed for **B2-*i*** and **B1-*j***.

The ring opening of these epoxides,[31a, 33] which occurred for **19-*exo*** (affording **19'**) during the purification by chromatography on silica gel, was then carried out on diastereomers **20-*exo*** and **20-*endo*** through hydrolysis with sulfuric acid followed by an acetylation reaction of the obtained diols to facilitate their NMR characterization (Scheme 4). While compound **20-*endo*** afforded the expected product **21** fully acetylated in 64% yield in two steps, the epoxide **20-*exo*** led to the monoacetylated product **22**. The *anti*-opening of the epoxide was pointed out in both cases from the NMR spectra of **21** and **22** on the basis of NOESY experiments (see SI). In this reaction the *anti* nucleophilic approach of water always occurs on the γ-position related to nitrogen (the less hindered site of the protonated epoxide).[31b, 33]

The different behaviour between *exo* and *endo* isomers in the acetylation reaction might be explained by a hydrogen bonding between the C3 hydroxyl and the carbonyl of the primary formed aglycon acetate (due to the higher accessibility of the aglycone hydroxyl) in the triol obtained from **20-*exo***. This hydrogen bond imposes also a distorted boat conformation which induces a higher steric hindrance (concave face) for the approach of the C4 hydroxyl (see SI).

Even not attempted here, the ring opening reaction of epoxides **18** and **19** should be performed in milder experimental conditions to avoid epimerization of the α-carbon related to nitrogen through enolization of labile hydrogens in **18** or formation of styryl type intermediate in **19**. Note that ring opening of the epoxide **19-*exo*** occurs in very mild experimental conditions (liquid chromatography on silica gel) to afford **19'**.



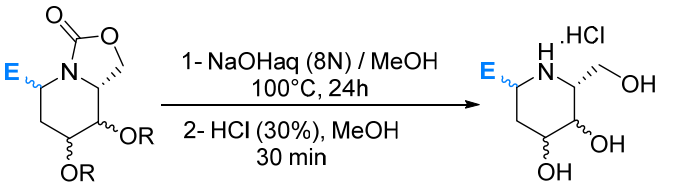
Scheme 4. Opening reaction of epoxides **20-*endo*** and **20-*exo***

In summary, while the *syn*-hydroxylation was found to be highly stereoselective, the *anti* hydroxylation often required a tedious separation of diastereomeric products.

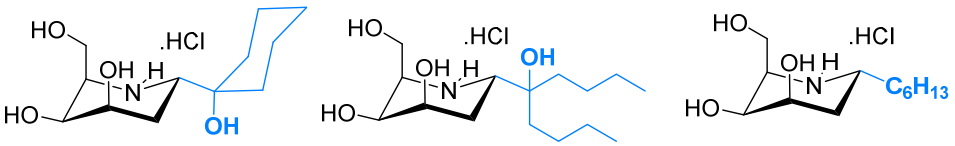
2.3 Access to the 2-deoxy(α or β)-*D*-iminosugar C-glycoside series

Having in hands the protected iminosugars **1-14** and **21**,**22**, the removal of protecting groups in illustrative examples was achieved (generally on the major isomer) by saponification of the carbamic ester (and eventually of other ester groups) using an hydro-alcoholic solution of sodium hydroxide followed by a treatment by hydrochloric acid to isolate the desired *NH*-iminosugars as hydrochloride salts (Table 3).

Table 3. Hydrolysis of the oxazolidinone function

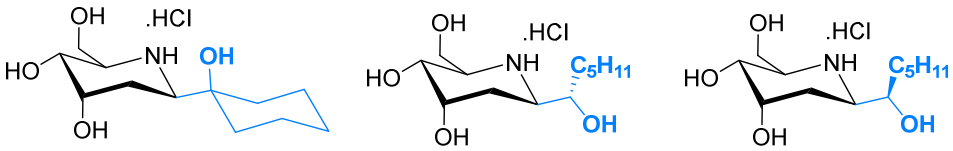


α-D-iminosugar C-glycoside series

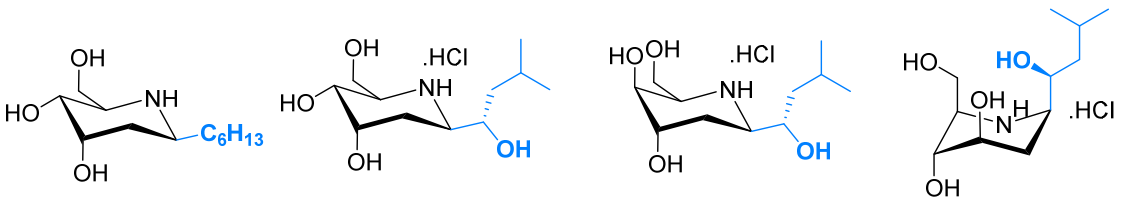


23 from **1** 85%[a] | **24** from **5** 79% | **25** from **6** 40%

β-D-iminosugar C-glycoside series



26 from **7** 81% | **27** from **9** 85% | **28** from **10** 91%

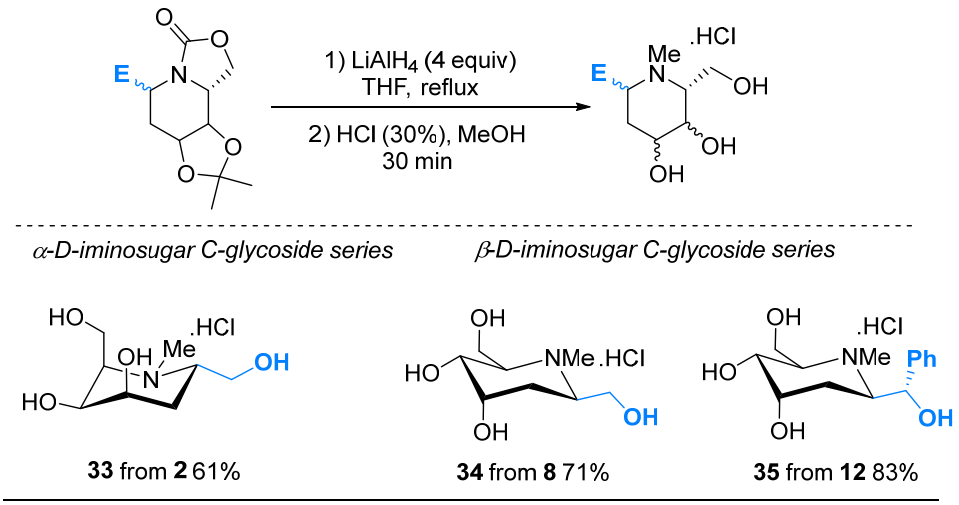


29 from **11** 76%[b] | **30** from **14** 69% | **31** from **21** 73% | **32** from **22** 63%

[a] Preliminary deprotection of the acetonide function (HCl 30% / MeOH), otherwise no opening of the oxazolidinone function occurred when NaOH treatment was directly applied.
[b] Without acid treatment (second step).

Furthermore, since inhibition properties are known to be modified by an alkyl substituent on nitrogen, *N*-methyl iminosugar analogs were also prepared from acetonides by achieving oxazolidinone removal in a reductive mode (with lithium aluminium hydride), followed with hydrochloric acid treatment.[23a, 34] Using this methodology, epimerization at the α-position of ester groups can be avoided, as for instance in **2** and **8** allowing preparation of **33** and **34**, at the difference of the previous method which would be complicated by side reactions involving labile hydrogen atoms when preparation of NH analogs was attempted. The obtained results are reported in Table 4.

Table 4. Reduction of the oxazolidinone function.



Following our synthetic strategy, from the same intermediate **A**, four classes of glycomimetics have been stereoselectively obtained in α- and β-series, depending on the type of functionalization. The *syn*- dihydroxylation of *trans*-dehydropiperidines **B1** (α-series) led to compounds corresponding to 2-deoxy-α-D-galactopyranosides (**23**-**25**, **33**), considering the configuration of the glycone stereogenic centers other than C-2 and the target enzymes. Starting from *cis*-dehydropiperidines **B2** (β-series), the *syn*-dihydroxylation led to 2-deoxy-β- D-allopyranosides (**26**-**30**, **34**, **35**) while the epoxidation and ring opening of epoxides afforded 2-deoxy-β- D-gulopyranoside (**31**) or 2-deoxy-β-D-glucopyranoside (**32**).

In summary, our methodology allows a versatile access to NH- or NMe-iminosugars in good isolated yields starting from 2-tributylstannyl-1,3-oxazolidine derived from (*S*)-vinylglycinol and its dienic derivative **A**. Furthermore, even not achieved in this work, the use of 2-tributylstannyl-1,3-oxazolidine derived from (*R*)-vinylglycinol[35] should open the route to the *L* series.

3. Biological evaluation

The inhibitory properties of the new 2-deoxygalactonojirimycin (2-DGJ; **23**-**25**, **33**), 2-deoxyallonojirimycin (2-DAJ; **26**-**30**, **34**, **35**), 2-deoxygulonojirimycin (2-DGUJ; **31**) or 2-deoxynojirimycin (2-DNJ; **32**) C-glycosides were tested towards a panel of commercial glycosidases including α-glucosidase (baker yeast) β-glucosidase (almonds), α-galactosidase from green coffee beans, β-galactosidase/β-glucosidase (bovine liver), β-galactosidase (*Escherichia coli*), isomaltase, trehalase, α- mannosidase from Jack beans, β-mannosidase from *Helix pomatia*, amyloglucosidase, naringinase and trehalase from pig kidney. The corresponding inhibition constant (K_i) values are collected in Tables 5 and 6.

2-DGJ derivatives **23** and **24**, sharing a configurational pattern of structural complementarity with α-D-galactopyranose, behave as potent inhibitors of α-galactosidase, with inhibition constants (K_i) values 33 and 36 μM, respectively, and an anomeric selectivity ratio over 10-fold related to β-galactoside. The aglycon structure has a marked impact in the ability to inhibit other enzymes. Thus compound **23** is specific for the galactosidase enzyme whereas the more flexible analogue **24** also inhibits β-glucosidase and, to a lesser extent, amyloglucosidase. Interestingly, compound **25**, lacking the hydroxyl group in the aglycon, showed a reversed selectivity, being a potent and selective inhibitor of β-galactosidase (K_i = 10.0 μM). *N*-methylation is detrimental for inhibition of α-galactosidase, cancelling the beneficial effect of the hydroxyl group in the aglycon, as inferred from data for **33** (K_i = 223 μM; Table 5).

The influence of the aglycon nature in the glycosidase inhibitory properties is also evident in the 2-DAJ series. The non *N*-methylated derivatives bearing linear hydrocarbon chains at the pseudoanomeric position in **27**-**30** behave as inhibitors of enzymes displaying β-glucosidase activity i.e. β-glucosidase from almonds, naringinase and β-glucosidase/β-galactosidase from bovine liver. The presence of an aglyconic hydroxyl group in **27** and **28** translates into modest inhibition of amyloglucosidase (K_i = 463 and 169 μM; Table 6). The branched isobutyl segment in **30** essentially cancels inhibition for all except the mammalian enzymes, whereas compound **26** bearing a more rigid cyclohexyl substituent was a very weak inhibitor of any of the β-glucosidases. *N*-methylation yield more selective inhibitors in this series. Thus, compound **35** bearing a phenyl residue in the aglycon selectively inhibits naringinase (K_i = 4.9 μM; Table 6). Notably, compound **34** missing the aromatic moiety is instead a very low micromolar inhibitor of amyloglucosidase, an enzyme displaying α-glucosidase activity (K_i = 1.4 μM; Table 6).

Compounds **31** and **32** share the same aglycon moiety than compound **30,** differing in the hydroxylation profile. The 2-DAJ derivative **30** is a modest inhibitor of the β-glucosidase/β-galactosidase (bovine liver) and show total anomeric selectivity when challenged against

amyloglucosidase. The 4-epimer 2-DGUJ derivative **31** did not inhibit any of the enzymes tested in this work. However, 3-epimer 2-DNJ derivative **32** was a selective inhibitor of amyloglucosidase (K_i = 22.8 μM; Table 6).

Altogether, the ensemble of results highlights the importance of developing methodologies compatible with structural diversity-oriented strategies allowing modification of the glycone and aglycone parts in glycomimetics to optimize the affinity and selectively towards glycosidase targets.

This set of tests which has been done in a screening mode from available synthetic products suffers from a lack of continuum in the modifications of the structures in order to attempt further rationalization. However, just on the basis of the reported results, several facts can be noted:

- No activity was observed on mannosidases regardless of the series and the nature of the aglycone, a result which is consistent with the non-hydroxylated C-2 position,[12a]
- The presence or the absence of an hydroxyl group on the aglycon can strongly modify the selectivitities (*Cf* **25** versus **23** and **24** in the α-series),
- The spatial position of an aglyconic hydroxyl can strongly modify the selectivities (**27** versus **28** in the β-series),
- While *N*-Me iminosugars appear generally to be less active in our tests, they are also able to exhibit simultaneously very high selectivity and efficiency on a single enzyme (*Cf* **34** against amyloglucosidase or **35** against naringinase).

Table 5. Glycosidase inhibitory activities (K_i, μM) of 2–deoxy-α-D-C-glycoside **23**-**25** and *N*-methyl 2-DGJ C-glycoside **33**. Values represent the mean ± SD (three independent determinations). Inhibition was competitive in all cases.[a]

Enzymes	**23**	**24**	**25**	**33**
β-galactosidase/ β-glucosidase (*bovine liver*)	473 ± 23	652 ± 40	10 ± 2	475 ± 39
β-glucosidase (*almonds*, pH 7.3)	n.i.	46 ± 3	252 ± 20	n.i.
α-galactosidase (*green coffee beans*)	33 ± 3	36 ± 5	313 ± 28	223 ± 20
Amyloglucosidase (*Asp. niger*)	n.i.	153 ± 12	n.i.	n.i.
Naringinase (*Penicilium decumbens*)	n.i.	n.i.	115 ± 10	n.i.

[a] No inhibition was observed for any compound at 1 mM concentration on baker yeast α-glucosidase, *E. coli* β-galactosidase, Jack bean α-mannosidase, *Helix pomatia* β-mannosidase, and pig kidney trehalase.

Table 6. Glycosidase inhibitory activities (K_i, μM) of 2–deoxy-β-D C-glycosides **26-30,** *N*-methyl 2-DAJ C-glycoside **34-35,** 2-DGUJ C-glycoside **31** and 2-DNJ C-glycoside **32**.
Values represent the mean ± SD (three independent determinations). Inhibition was competitive in all cases.[a]

Enzymes	**26**	**27**	**28**	**29**	**30**	**34**	**35**	**31**	**32**
β-galactosidase/ β-glucosidase (*bovine liver*)	301± 25	1.3 ± 0.1	42 ± 4	12.1 ± 1.3	58 ± 6	594 ± 50	195 ± 20	n.i	n.i.
β-glucosidase (*almonds*, pH 7.3)	693 ± 65	36 ± 4	11.4 ± 2	18 ± 2[b]	436 ± 41	537 ± 50	140 ± 11	n.i.	n.i.
Amyloglucosidase (*Asp. niger*)	116 ± 10	463 ± 40	169 ± 15	n.i.	n.i.	1.4± 0.1	550 ± 45	n.i.	22.8 ± 1.9
Naringinase (*Penicilium decumbens*)	76 ± 5	131 ± 11	45 ± 3	50 ± 4	224 ± 20	67 ± 5	4.9 ± 0.5	n.i.	272 ± 25

[a] No inhibition was observed for any compound at 2 mM concentration on baker yeast α-glucosidase, green coffe beans α-galactosidase, *E. coli* β-galactosidase, Jack bean α-mannosidase, *Helix pomatia* β-mannosidase, and pig kidney trehalase
[b] K_i = 102 ± 10 μM at pH 5.5.

4. Conclusion

The chelative stabilization of lithium by the oxazolidinone carbonyl has allowed the use of an organometallic route to selectively obtain *cis* or *trans* 2,6-disubstituted dehydropiperidines, precursors of the β- or α- series of 2-deoxyiminosugar *C*-glycosides, respectively. Herein, we report the possible *syn* or *anti* dihydroxylation of the double bond to obtain selectively several configurations of 2-deoxy iminosugar *C*-glycosides.

The screening of the inhibitory properties of the obtained *NH*- or *NMe*-iminosugar *C*-glycosides towards glycosidases has pointed out interesting features in terms of modulation of the activity by adjustment of the chemical structure of the aglycon.

While non-conclusive, these results are promising, because taking advantage of the generality of our synthetic method, it is possible to modulate the configuration of the pseudo-anomeric centre, the nature of the aglycon moiety as well as the configuration of the iminosugar itself. Furthermore, by starting from 2-tributylstannyl-1,3-oxazolidinones derived from (*R*) vinylglycinol instead of (*S*) vinylglycinol, this same strategy could provide access to *L* iminosugar series. On the basis of these results, we can envisage numerous adjustments in order to optimize the inhibition properties both in terms of efficiency and selectivity and also to allow access to new structures able to help in the understanding of the inhibition process itself.

5. Experimental section

General remarks for the following data: numbers, disconnected from the nomenclature, have been placed on the formula of the obtained compounds (given in supplementary information) in order to indicate the NMR assignments of protons and carbons.

5.1 General methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 or Bruker ARX 400 instruments. Chemical shifts are given in ppm as δ values related to tetramethylsilane (^{1}H, ^{13}C) and coupling constants are given in Hz. Mass spectra were obtained in EI (70 eV) and/or CI mode in direct introduction mode using a HP apparatus (Engine 5989A) or a DSQII (ThermoFisher Scientific). HRMS in ESI mode were recorded on a LTQ-Orbitrap (ThermoFisher Scientific) at Nantes-Atlantic National College of Veterinary Medicine, Food Science and Egineering (ONIRIS) or on a MicroTOFQII (ThermoFisher Scientific) at the University Claude Bernard Lyon 1. MALDI-TOF spectra were recorded on an Autoflex III apparatus (Bruker) in positive ionization mode and using DHB (dihydroxybenzoic acid) or DCTB (*trans*-2-[3-(4-*tert*-butyl-phenyl)-2-methyl-2-propenylidene]malononitrile) as matrix at the INRA of Nantes. IR spectra were recorded on a

Bruker IFS Vector 22 apparatus. Optical rotations were measured on a Perkin-Elmer 341 apparatus and melting points were determined with a Tottoli SMP3 Stuart apparatus. CH_2Cl_2 was dried on CaH_2 and distilled prior to use. Et_2O and THF were distilled on sodium-benzophenone. EtOH was dried over magnesium methoxide and distilled before use. TLC analyses were carried out on silica-coated plates (Merck Kieselgel $60F_{254}$) as well as LC purifications (silica gel 60 Merck Geduran). GC analyses were performed on a capillary column optima δ3 (long. 30 m, diameter 0.25 mm, stationary phase 0.25 μm) with the following parameters: flow = 1.3 mL/min of N_2; injector = 200°C; detector = 300°C. HPLC analyses were performed on an Inertsil 5Si column (250 mm x 3 mm) using an UV detector (254 nm) and 95/5 mixture of hexanes and AcOEt (Flow = 0.5 mL/min).

5.2 General Procedure for Inhibition Assay

Inhibition constant (K_i) values were determined by spectrophotometrically measuring the residual hydrolytic activities of the glycosidases against the respective o- (for β-galactosidase from E. coli) or p-nitrophenyl α- or β-D-glycopyranoside (for other glycosidases) in the presence of the iminosugars. Each assay was performed in phosphate buffer or phosphate-citrate buffer (for α- or β-mannosidase and amyloglucosidase) at the optimal pH for the enzymes. The reactions were initiated by addition of the enzyme to a solution of the substrate in the absence or presence of various inhibitor concentrations. The mixture was incubated for 10-30 min at 37 ºC or 55 ºC (for amyloglucosidase) and the reaction was quenched by addition of 1 M Na_2CO_3. Reaction times were appropriate to obtain 10–20% conversion of the substrate in order to achieve linear rates. The absorbance of the resulting mixture was determined at 405 nm. Approximate value of Ki was determined from the slope of Dixon plots using a fixed concentration of substrate (around the Km value for the different glycosidases) and various concentrations of inhibitor. Full Ki determinations and enzyme inhibition mode were determined from the slope of Lineweaver–Burk plots and double reciprocal analysis. Representative examples of Dixon and Lineweaver–Burk plots are shown in the Supplementary materials.

5.3 Preparation and Characterization of Compounds

5.3.1 Starting materials

The stannylated dienyloxazolidinones **A** were obtained by ring opening of 2-tributylstannyl-1,3-oxazolidine derived from N-protected (*S*)-vinylglycinol by soft nucleophiles in the presence of Lewis acids according to our previously described procedure.[36] The stereodefined platform **B1** (*trans* isomer) was obtained through a sequence transmetalation (and electrophilic trapping) followed by a ring closing metathesis, while stereodefined platform **B2** (*cis* isomer) was obtained through a reversed sequence (ring closing metathesis, then transmetalation and electrophilic trapping).[25b] Note that these syntheses have taken advantage of an improved preparation of *N*-Moc-

(*S*)-vinylglycinol[37] as well as of an improved cyclisation of the obtained tributylstannylated dienols into the corresponding oxazolidinones.[25a]

5.3.2 General procedure for the preparation of diols and acetonides

To a solution of dehydropiperidine (0.2 mmol) in acetone (3 mL) and H_2O (1 mL) were successively added NMO (135 mg, 1 mmol) and OsO_4 (20 mg of a 2.5% solution in *t*-BuOH, 1 mol%) at room temperature. The reaction was monitored by TLC and after complete dihydroxylation of the C=C double bond into diol, saturated aqueous $NaHCO_3$ solution was added. After further stirring for 1 h, the organic and aqueous phases were separated and the aqueous phase was extracted with AcOEt. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was used without further purification in the following procedure.

Crude diol was dissolved in acetone (2 mL) and 2,2-dimethoxypropane (2 mL) before addition of camphor sulfonic acid (23 mg, 0.1 mmol) to the mixture and stirring at room temperature for 12 h. The reaction mixture was subsequently partitioned between AcOEt (5 mL) and water (5 mL) and the organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Purification was carried out by chromatography on silica gel using hexanes/AcOEt as eluent.

5.3.3 Characterization of the obtained acetonides

Diastereomers **1-*endo***,**1-*exo***, **2-*endo*, 2-*exo***, **7**, **8**, **33** and **34** have been previously prepared and fully characterized.[26]

Acetonide 3. By using the above general procedure and starting from **B1-*c*** (48 mg, 0.2 mmol) as starting material, **3-*endo*** was isolated in 64% overall yield (R_f = 0.17, yellow oil, 40 mg) after purification on silica gel (eluent hexanes/AcOEt: 3/7). While observed in GC and NMR on the crude mixture, the *exo*-diastereomer was not isolated after liquid chromatography.

(3*aR*,5*S*,9*aR*,9*bS*)-5-((*S*)-1-hydroxyhexyl)-2,2-dimethylhexahydro-7*H*-[1,3]dioxolo[4,5-*c*]oxazolo[3,4-*a*]pyridin-7-one, 3-*endo*. $[\alpha]_D^{19}$ = -25.4 (*c* 1.0, $CHCl_3$); IR (neat): 3433, 2929, 2856, 1732, 1468, 1422, 1235, 1212, 1058, 1034, 1001 cm^{-1}; ^1H NMR (400 MHz, 300 K, $CDCl_3$): 4.54 (bdt, $^3J_{H3H2} = {}^3J_{H3H2'} = 2.7$, $^3J_{H3H4} = 7.8$, $1H_3$), 4.42 (dd, $^3J_{H6H5} = 2.3$, $^2J_{H6H6'} = -8.4$, $1H_6$), 4.35 (t, $^3J_{H6'H5} = 8.4$, $^2J_{H6'H6} = -8.4$, $1H_{6'}$), 4.17 (dd, $^3J_{H4H5} = 2.3$, $^3J_{H4H3} = 7.8$, $1H_4$), 3.85 (m, $2H_{1,5}$), 3.60-3.50 (m, $1H_8$), 2.1 (ddd, $^3J_{H2H3} = 2.7$, $^3J_{H2H1} = 5.3$, $^2J_{H2H2'} = -15$, $1H_2$), 1.7 (ddd, $^3J_{H2'H3} = 2.7$, $^3J_{H2'H1} = 12.2$, $^2J_{H2'H2} = -15$, $1H_{2'}$), 1.65-1.15 (m, $8H_{9,10,11,12}$), 1.40 (s, $3H_{15}$), 1.29 (s , $3H_{16}$), 0.87 (t, $^3J_{H13H12} = 6.9$, $3H_{13}$); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$): 160.5 (C_7), 109.2 (C_{14}), 75.0 (C_8), 73.6 (C_4), 71.0 (C_3), 64.2 (C_6), 53.4 (C_5), 51.4 (C_1), 33.9 (C_9), 31.9 (1C), 26.5 (C_2), 26.1 (C_{15}), 25.2 (1C), 24.0 (C_{16}), 22.7 (1C), 14.1 (C_{13}); HRMS (MALDI) calcd for $C_{16}H_{27}NO_5Na$ $[M+Na]^+$:

336.1781, found: 336.1790; MS (EI): *m/z* (%) 313 (0.2, $M^{+\bullet}$), 298 (20), 214 (15), 213 (100), 212 (70), 198 (13), 154 (11), 112 (13), 69 (11), 55 (11), 44 (14), 43 (14), 41 (11), 28 (12).
*Meaningful signals for the **isomer 3-exo** in the crude product:* 4.26 (dd, ^3J = 2.5, ^3J = 8.9, 1H), 1.86 (dt, ^3J = 8, ^2J = -15, $1H_2$) ppm.

Acetonide 4. By using the above general procedure and starting from **B1-*d*** (48 mg, 0.2 mmol) as starting material, **4** was isolated in 55% overall yield (yellow oil, 34 mg) after purification on silica gel (eluent hexanes/AcOEt: 3/7). While observed in GC and NMR on the crude mixture, the *exo*-diastereomer was not isolated after liquid chromatography.
(3*aR*,5*S*,9*aR*,9*bS*)-5-((*R*)-1-hydroxyhexyl)-2,2-dimethylhexahydro-7*H*-[1,3]dioxolo[4,5-*c*]oxazolo[3,4-*a*]pyridin-7-one, 4-*endo*. $[\alpha]_D^{19}$ = -20.1 (*c* 1.0, $CHCl_3$); IR (neat): 3568, 3445, 2930, 2857, 1732, 1433, 1383, 1247, 1211, 1034, 1001, 760 cm^{-1}; ^1H NMR (400 MHz, 300 K, $CDCl_3$): 4.57 (bdt, $^3J_{H3H2} = {}^3J_{H3H2'} = 2.6$, $^3J_{H3H4} = 7.9$, $1H_3$), 4.45-4.33 (m, $2H_{6,6'}$), 4.18 (dd, $^3J_{H4H5} = 2.3$, $^3J_{H4H3} = 7.9$, $1H_4$), 3.93-3.85 (m, $2H_{5,8}$), 3.82 (ddt, $^3J_{H1H8} = {}^4J_{H1\text{-}H9} = 2.1$, $^3J_{H1H2} = 5.0$, $^3J_{H1H2'} = 12.4$, $1H_1$), 2.01 (ddd, $^3J_{H2H3} = 2.6$, $^3J_{H2H1} = 5.0$, $^2J_{H2H2'} = -15.0$, $1H_2$), 1.79 (ddt, $^3J_{H2'H3} = 2.6$, $^3J_{H2'H1} = 12.4$, $^2J_{H2'H2} = -15.0$, $1H_{2'}$), 1.65-1.47 (m, $1H_9$), 1.43 (s, $3H_{15}$), 1.29 (s, $3H_{16}$), 1.42-1.15 (m, $7H_{9',10,11,12}$), 0.87 (t, $^3J_{H13H12} = 6.9$, $3H_{13}$); ^{13}C NMR (100 MHz, 300K, $CDCl_3$): 159.4 (C_7), 109.2 (C_{14}), 73.6 (C_4), 73.1 (C_8), 71.0 (C_3), 64.1 (C_6), 53.6 (C_5), 51.7 (C_1), 32.4 (1C), 32.0 (1C), 26.1 ($1C_{15}$), 26.0 (C_9), 24.1 (C_{16}), 23.4 (C_2), 22.7 (1C), 14.1 (C_{13}); HRMS (MALDI): calcd for $C_{16}H_{27}NO_5Na$ $[M+Na]^+$: 336.1781, found: 336.1792; MS (EI): m/z(%) 313 (0.2, $M^{+\bullet}$), 298 (18), 214 (15), 213 (100), 212 (77), 198 (13), 154 (12), 112 (13), 69 (11), 55 (10), 43 (13).
*Meaningful signals for **isomer 4-exo** in the crude product:* 4.51 (bd, ^3J = 8.4, 1H), 4.29 (dd, ^3J = 2.7, ^2J = -9.2, $1H_6$).

Diol 5 (*exo/endo*). Diol **5** was obtained according to the general procedure, but without the step of diol protection as acetonide, using **B1-*e*** (56 mg, 0.2 mmol) as starting material. Accordingly, **5** was prepared in 72% yield (*exo:endo* = 9:91) after purification on silica gel (eluent: AcOEt). HRMS (MALDI): calcd for $C_{16}H_{29}NO_5Na$ $[M+Na]^+$: 338.1943, found 338.1947.
(5*S*,7*S*,8*R*,8*aR*)-7,8-dihydroxy-5-(5-hydroxynonan-5-yl)hexahydro-3*H*-oxazolo[3,4-*a*]pyridin-3-one, 5-*exo*. colourless oil (4 mg, 7%); R_f = 0.39; $[\alpha]_D^{19}$ = -15 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, 300 K, $CDCl_3$): 4.42 (t, $^3J_{H6H5} = 8.8$, $^2J_{H6H6'} = -8.8$, $1H_6$), 4.35 (dd, $^2J_{H6'H6} = -8.8$, $^3J_{H6'H5} = 2.4$, $1H_{6'}$), 3.96 (bq, $^3J_{H3H2} = {}^3J_{H3H2'} = {}^3J_{H3H4} \sim 3.4$, $1H_3$), 3.92-3.88 (m, $1H_1$), 3.88 (bdd, $^3J_{H5H6} = 8.8$, $^3J_{H5H6'} = 2.4$, $1H_5$), 3.35-3.26 (m, $1H_4$), 2.65 (m, $1H_{OH}$), 2.35 (dt, $^2J_{H2H2'} = -16.0$, $^3J_{H2H1} = {}^3J_{H2H3} = 3.4$, $1H_2$), 1.98 (ddd, $^2J_{H2'H2} = -16.0$, $^3J_{H2'H1} = 8.4$, $^3J_{H2'H3} = 3.4$, $1H_{2'}$), 1.54-1.10 (m, $12H_{9,10,11}$), 0.96-0.88 (m, $6H_{12}$); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$): 158.0 (C_7), 78.1 (C_8), 70.3 (C_4), 66.0

(C_3), 65.6 (C_6), 53.0 and 52.6 ($2C_{1,5}$), 36.4 (1C), 35.3 (1C), 29.6 (1C), 28.8 (C_2), 25.8 (1C), 23.1 (2C), 14.0(C_{12}), 13.9 ($C_{12'}$).

(5*S*,7*R*,8*S*,8*aR*)-7,8-dihydroxy-5-(5-hydroxynonan-5-yl)hexahydro-3H-oxazolo[3,4-*a*]pyridin-3-one, 5-*endo*. colourless oil (41 mg, 65%); R_f = 0.29; $[\alpha]_D^{19}$ = -2.2 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, 300 K, $CDCl_3$): 4.41 (dd, $^2J_{H6H6'}$ = -8.4, $^3J_{H6H5}$ = 3.2, 1H_6), 4.36-4.32 (m, 1H_3, assigned by COSY experiment), 4.33 (t, $^3J_{H6'H5}$ = 8.4, $^2J_{H6'H6}$ = -8.4, 1$H_{6'}$), 4.24 (ddd, $^3J_{H5H6'}$ = 8.4, $^3J_{H5H6}$ = 3.2, $^3J_{H5H4}$ = 1.7, 1H_5), 3.83 (d, $^3J_{H1H2'}$ = 7.2, 1H_1), 3.76 (bs, 1H_4), 3.42 (bs, 1H_{OH}), 3.06-2.92 (m, 1H_{OH}), 1.95 (dd, $^2J_{H2H2'}$ = -13.2, $^3J_{H2H3}$ = 4.8, 1H_2), 1.84 (ddd, $^2J_{H2'H2}$ = -13.2, $^3J_{H2'H3}$ = 12.0, $^3J_{H2'H1}$ = 7.2, 1$H_{2'}$), 1.84-1.78 (m, 1H_{OH}), 1.60-1.10 (m, 12$H_{9,10,11}$), 0.93 (t, $^3J_{H12H11}$ = 7.2, 3H_{12}), 0.89 (t, $^3J_{H12'H11}$ = 7.2, 3$H_{12'}$); ^{13}C NMR ($CDCl_3$, 100 MHz, 300 K): 159.2 (C_7), 79.1 (C_8), 69.2 (C_5), 66.7 (C_3), 63.8 (C_6), 55.7 (C_4), 54.6 (C_1), 36.6 (1C), 35.9 (1C), 26.0 (C_2), 25.7(1C), 25.6 (1C), 23.4 (1C), 23.3 (1C), 14.2(C_{12}), 14.1 ($C_{12'}$).

Acetonide 6 (*exo/endo*). By using the general procedure and starting from **B1-*f*** (45 mg, 0.2 mmol), **6** was prepared in 78% yield (*exo:endo* = 24:76) after purification on silica gel (eluent hexanes/AcOEt: 3/7).

(3*aS*,5*R*,9*aR*,9*bR*)-5-hexyl-2,2-dimethylhexahydro-7*H*-[1,3]dioxolo[4,5-*c*]oxazolo[3,4-*a*]pyridin-7-one, 6-*exo*. colourless oil (11 mg, 19%); ^{1}H NMR (300 MHz, 300 K, $CDCl_3$): 4.46 (dd, $^2J_{H6H6'}$ = -9.0, $^3J_{H6H5}$ = 6.0, 1H_6), 4.30 (ddd, $^3J_{H3H2'}$ = 9.0, $^3J_{H3H4}$ = 7.2, $^3J_{H3H2}$ = 6.0, 1H_3), 4.26 (dd, $^2J_{H6H6'}$ = -9.0, $^3J_{H6'H5}$ = 3.0, 1$H_{6'}$), 4.02 (dd, $^3J_{H4H5}$ = 9.0, $^3J_{H3H4}$ = 7.2, 1H_4), 3.69 (ddd, $^3J_{H5H6'}$ = 3.0, $^3J_{H5H6}$ = 6.0, $^3J_{H5H4}$ = 9.0, 1H_5), 3.62 (dq, $^3J_{H1H2'}$ = 9.0, $^3J_{H1H2}$ == $^3J_{H1H8}$ = $^3J_{H1H8'}$ = 6.0, 1H_1), 2.19 (dt, $^2J_{H2H2'}$ = -12.0, $^3J_{H2H1}$ = $^3J_{H2H3}$ = 6.0, 1H_2), 1.68 (dt, $^2J_{H2H2'}$ = -12.0, $^3J_{H2'H1}$ = $^3J_{H2'H3}$ = 9.0, 1$H_{2'}$), 1.8-1.2 (m, 10$H_{8\ to\ 12}$), 1.47 (s, 3H_{15}), 1.33 (s, 3H_{16}), 0.87 (t, $^3J_{H12H13}$ = 6.5, 3H_{13}); ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K): 157.5 (C_7), 109.7 (C_{14}), 75.5 (C_4), 72.9 (C_3), 66.9 (C_6), 53.9 (C_5), 48.8 (C_1), 34.4 (1C), 31.8 (1C), 31.2 (C_2), 29.2 (1C), 27.4 (C_{15}), 25.4 (1C), 24.9 (C_{16}), 22.7 (1C), 14.2 (C_{13}).

(3*aR*,5*R*,9*aR*,9*bS*)-5-hexyl-2,2-dimethylhexahydro-7H-[1,3]dioxolo[4,5-c]oxazolo[3,4-a]pyridin-7-one, 6-*endo*. colourless oil (35 mg, 59%); ^{1}H NMR (300 MHz, 300 K, $CDCl_3$): 4.50 (dt, $^3J_{H3H2'}$ = $^3J_{H3H2}$= 3.0, $^3J_{H3H4}$ = 7.9, 1H_3), 4.39 (dd, $^2J_{H6H6'}$ = -8.5, $^3J_{H6H5}$ = 2.5, 1H_6), 4.3 (t, $^2J_{H6H6'}$ = -8.5, $^3J_{H6'H5}$ = 8.5, 1$H_{6'}$), 4.17 (dd, $^3J_{H4H5}$ = 2.5, $^3J_{H3H4}$ = 7.9, 1H_4), 3.82 (m, 1H_1), 3.77 (dt, $^3J_{H5H6'}$ = 8.5, $^3J_{H5H6}$ = $^3J_{H5H4}$ = 2.5, 1H_5), 2.16 (ddd, $^2J_{H2H2'}$ = -15.0, $^3J_{H2H1}$ = 5.0, $^3J_{H2H3}$ = 3.0, 1H_2), 1.65-1.05 (m, 1$H_{2'}$+ 10$H_{aliph.}$), 1.43 (s, 3H_{15}), 1.32 (s, 3H_{16}), 0.86 (t, $^3J_{H12H13}$ = 6.3, 3H_{13}); ^{13}C NMR (75 MHz, 300K, $CDCl_3$): 158.7 (C_7), 109.2 (C_{14}), 73.7 (C_4), 71.2 (C_3), 63.6 (C_6), 52.7 (C_5), 46.8 (C_1), 35.4 (1C), 31.9 (1C), 29.8 (1C), 29.5 (C_2), 26.1 (C_{15}), 24.9 (1C), 24.1 (C_{16}), 22.7 (1C), 14.1 (C_{13}).

(3*aS*,5*R*,9*aR*,9*bR*)-5-((*S*)-1-hydroxyhexyl)-2,2-dimethylhexahydro-7H-[1,3]dioxolo[4,5-*c*]oxazolo[3,4-*a*]pyridin-7-one, 9. By using the general procedure and starting from **B2-*c*** (49 mg, 0.2 mmol), **9** was isolated in 71% overall yield (R_f = 0.75, yellow oil, 53 mg) after purification on silica gel using AcOEt as eluent. Note that only *exo* isomer was isolated after liquid chromatography while crude mixture exhibited a 91/9 *exo/endo* ratio.

Isomer 9-exo, $[\alpha]_D^{19}$ = +36.5 (*c* 0.9; $CHCl_3$); IR (neat): 3407, 2988, 2926, 2859, 1741, 1420, 1215, 1060, 768, 761 cm^{-1}; ^1H NMR (400 MHz, 300 K, $CDCl_3$): 4.51 (m, $1H_3$), 4.50 (dd, $^2J_{H6H6'}$ = -8.9, $^3J_{H6H5}$ = 8.2, $1H_6$), 4.29 (m, $1H_8$), 4.17 (dd, $^3J_{H6'H5}$ = 5.5, $^2J_{H6H6'}$ = -8.9, $1H_{6'}$), 3.95 (dd, $^3J_{H4H3}$ = 5.5, $^3J_{H4H5}$ = 8.2, $1H_4$), 3.88 (d, $^3J_{OH\text{-}H8}$ = 3.3, $1H_{OH}$), 3.67 (td, $^3J_{H5H4}$ = $^3J_{H5H6}$ = 8.2, $^3J_{H5H6'}$ = 5.5, $1H_5$), 3.45 (ddd, $^3J_{H1H8}$ = 1.6, $^3J_{H1H2'}$ = 3.9, $^3J_{H1H2}$ = 9.6, $1H_1$), 2.30 (ddd, $^3J_{H2H3}$ = 4.6, $^3J_{H2H1}$ = 9.6, $^2J_{H2H2'}$ = -14.9, $1H_2$), 2.02 (td, $^3J_{H2'H1}$ = $^3J_{H2'H3}$ = 3.9, $^2J_{H2H2'}$ = -14.9, $1H_{2'}$), 1.61-1.46 (m, $8H_{9\text{ to }12}$), 1.48 (s, $3H_{15}$), 1.36 (s, $3H_{16}$), 0.88 (t, $^3J_{H13H12}$ = 6.8, $3H_{13}$); ^{13}C NMR (100 MHz, 300K, $CDCl_3$): 156.9 (C_7), 109.9 (C_{14}), 75.9 (C_4), 73.0 (C_3), 69.1 (C_8), 67.7 (C_6), 58.4 (C_5), 55.4 (C_1), 33.6 (C_9), 31.9 (1C), 28.1 (C_{16}), 26.3 (1C), 25.9 (C_{16}), 25.4 (C_2), 22.7 (1C), 14.2 (C_{13}); HRMS (MALDI): calcd for $C_{16}H_{27}NO_5Na$ $[M+Na]^+$: 336.1781, found 336.1769; MS (CI, NH_3): m/z 314 $(M+H)^+$; MS (EI): m/z (%) 313 (0.1, $M^{+\bullet}$), 298 (13), 242 (4), 213 (100), 154 (10), 94 (16).

*Meaningful signal for **isomer 9-endo** in the crude product:* 4.35 (m, 1H), 3.25 (dd, ^3J = 4.0, ^3J = 10.0, 1H).

(3*aR*,4*R*,8*R*,8*aR*,9*aS*)-4-(hydroxymethyl)-2,2-dimethyl-8-pentylhexahydro-6*H*-[1,3]dioxolo[4,5-*d*]oxazolo[3,4-*a*]pyridin-6-one, 10 (isomer 10-*exo*). By using the general procedure and starting from **B2-*d*** (49 mg, 0.2 mmol), **10-*exo*** was isolated in 76% overall yield (yellow oil, 48 mg) after purification on silica gel (eluent hexanes:AcOEt = 60:40). The *endo* isomer was not detected by ^1H NMR on the crude. $[\alpha]_D^{19}$ = + 20.6 (*c* 1.0 ; $CHCl_3$); IR (neat): 3431, 2931, 2858, 1732, 1422, 1382, 1260, 1212, 1163, 1047, 768 cm^{-1}; ^1H NMR (400 MHz, 300 K, $CDCl_3$): 4.41-4.36 (m, $1H_3$), 4.16 (dd, $^3J_{H4H3}$ = 5.6, $^3J_{H4H5}$ = 7.3, $1H_4$), 4.09-4.02 (m, $2H_{6,8}$), 3.86 (dd, $^3J_{H6'H5}$ = 5.3, $^2J_{H6'H6}$ = -12.2, $1H_{6'}$), 3.56 (ddd, $^3J_{H1H2}$ = 3.3, $^3J_{H1H8}$ = 7.5, $^3J_{H1H2'}$ = 11.8, $1H_1$), 3.34 (ddd, $^3J_{H5H6}$ = 3.0, $^3J_{H5H6'}$ = 5.3, $^3J_{H5H4}$ = 7.3, $1H_5$), 2.17 (ddd, $^3J_{H2H3}$ = 2.0, $^3J_{H2H1}$ = 3.3, $^2J_{H2H2'}$ = -14.4, $1H_2$), 1.79 (ddd, $^3J_{H2'H3}$ = 3.9, $^3J_{H2'H1}$ = 11.8, $^2J_{H2'H2}$ = -14.4, $1H_{2'}$), 1.79-1.58 (m, $2H_9$), 1.55-1.15 (m, $6H_{10\text{ to }12}$), 1.48 (s, $3H_{15}$), 1.34 (s, $3H_{16}$), 0.88 (t, $^3J_{H12H13}$ = 7.0, $3H_{13}$); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$): 156.8 (C_7), 108.9 (C_{14}), 81.2 (C_8), 72.3 (C_4), 71.8 (C_3), 60.0 (C_6), 57.9 (C_5), 55.8 (C_1), 34.0 (C_9), 32.4 (C_2), 31.5 (1C), 28.0 (C_{15}), 25.6 (C_{16}), 24.5 (1C), 22.5 (1C), 14.0 (C_{13}); HRMS (MALDI): calcd for $C_{16}H_{27}NO_5Na$ $[M+Na]^+$: 336.1781, found: 336.1775; MS (EI): m/z (%) 313 (9, $M^{+\bullet}$), 298 (11), 282 (100), 180 (40), 152 (8).

Diol 11. Diol **11** was obtained according to the general procedure, but without the step of diol protection as acetonide, using **B2-*f*** (45 mg, 0.2 mmol) as starting material. Accordingly, **11** was isolated in 62% overall yield (R_f = 0.36, colourless oil, 48 mg) after purification on silica gel (eluent hexanes:AcOEt = 20:80). Once more, the minor *endo*-diastereomer (*exo/endo* = 83/17 in the crude product) was not isolated after chromatography.

(5*S*,7*S*,8*R*,8*aR*)-5-hexyl-7,8-dihydroxyhexahydro-3*H*-oxazolo[3,4-*a*]pyridin-3-one, *11-exo*. $[\alpha]_D^{19}$ = +16.1 (*c* 0.5, $CHCl_3$); IR (neat): 3600-3100, 2985, 2934, 1734, 1651, 1455, 1381, 1248, 1218, 1041 cm^{-1}; ^1H NMR (400 MHz, 300 K, $CDCl_3$): 4.31 (dd, $^2J_{H6H6'}$ = -8.8, $^3J_{H6H5}$ = 7.2, $1H_6$), 4.19 (dd, $^2J_{H6'H6}$ = -8.8, $^3J_{H6'H5}$ = 3.2, $1H_{6'}$), 4.15 (m, $1H_3$), 3.72 (ddd, $^3J_{H5H4}$ = 10.0, $^3J_{H5H6}$ = 7.2, $^3J_{H5H6'}$ = 3.2, $1H_5$), 3.53 (dd, $^3J_{H4H5}$ = 10, $^3J_{H4H3}$ = 2.6, $1H_3$), 3.4 (m, $1H_1$), 2.36 (m, $1H_8$), 1.95 (ddd, $^2J_{H2H2'}$ = -14.4, $^3J_{H2H1}$ = 3.6, $^3J_{H2H3}$ = 2.8, $1H_2$), 1.66 (ddd, $^2J_{H2'H2}$ = -14.4, $^3J_{H2'H1}$ = 12.0, $^3J_{H2'H3}$ = 2.4, $1H_{2'}$), 1.68-1.58 (m, $1H_{8'}$), 1.40-1.23 (m, $8H_{9\,to\,12}$), 0.88 (t, $^3J_{H13H12}$= 7.2, $3H_{13}$); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$): 156.3 (C_7), 70.6 (C_4), 68.5 (C_3), 65.1 (C_6), 57.4 (C_5), 50.6 (C_1), 37.1 (C_2), 30.7 (C_8), 31.9 (1C), 29.3 (1C), 27.1 (1C), 22.7 (1C), 14.2 (C_{13}); HRMS (MALDI): calcd for $C_{13}H_{24}NO_4$ $[M+H]^+$: 258.1705, found: 258.1709; MS (CI, NH_3): m/z 258.20 $(M+H)^+$, 275.2 $(M+NH_4)^+$; MS (EI): m/z (%) 257 (4, $M^{+\bullet}$), 172 (100), 154 (10)3333, 91 (48), 82 (38), 67 (23), 55 (79), 41 (73).

*Meaningful signals for **isomer 11-endo** in the crude product:* 4.10 (dd, $^2J_{H6H6'}$ = -9, $^3J_{H6H5}$ = 5.1, $1H_6$), 3.95 (dd, $^2J_{H6H6'}$ = -9, $^3J_{H6H5}$ = 4.7, $1H_{6'}$), 3.65 (m), 3.90 (dd, $^3J_{H5H4}$ ~ 7, $^3J_{H3H4}$ ~ 1, H_4), 3.35 (m).

Acetonide 12. By using the general procedure and starting from **B2-*g*** (49 mg, 0.2 mmol) as starting material, **12** was isolated in 83% overall yield (R_f = 0.43, colourless oil, 53 mg) after purification on silica gel (eluent:hexanes/AcOEt = 50/50). Once more, the minor diastereomer (about 4%) was not isolated after liquid chromatography.

(3*aS*,5*R*,9*aR*,9*bR*)-5-((S)-hydroxy(phenyl)methyl)-2,2-dimethylhexahydro-7*H*-[1,3]dioxolo[4,5-*c*]oxazolo[3,4-*a*]pyridin-7-one, 12-*exo*. $[\alpha]_D^{19}$ = +37.1 (*c* 0.5, $CHCl_3$); IR (neat): 3432, 2926, 1734, 1653, 1422, 1058 cm^{-1}; ^1H NMR (300 MHz, 300 K, $CDCl_3$): 7.43-7.25 (m, $5H_{Ar}$), 5.55 (d, $^3J_{H8H1}$ = 1.9, $1H_8$), 4.60 (q, $^3J_{H3H4} \sim {}^3J_{H3H2} \sim {}^3J_{H3H2'} \sim 5.8$, $1H_3$), 4.59 (dd, $^2J_{H6'H6}$ = -8.7, $^3J_{H6H5}$ = 8.1, $1H_6$), 4.20 (dd, $^2J_{H6'H6}$ = -8.7, $^3J_{H6'H5}$ = 6.9, $1H_{6'}$), 4.09 (dd, $^3J_{H4H5}$ = 9.1, $^3J_{H4H3}$ = 5.8, $1H_4$), 3.87-4.00 (bs, $1H_{OH}$), 3.77 (ddd, $^3J_{H1H2}$ = 6.9, $^3J_{H1H2'}$ = 4.8, $^3J_{H8H1}$ = 1.9, $1H_1$), 3.74 (ddd, $^3J_{H5H4}$ = 9.1, $^3J_{H5H6}$ = 8.1, $^3J_{H5H6'}$ = 6.9, $1H_5$), 2.24 (ddd, $^2J_{H2H2'}$ = -15.0, $^3J_{H1H2}$ = 6.9, $^3J_{H3H2}$ = 5.8, $1H_2$), 1.74 (ddd, $^2J_{H2'H2}$ = -15.0, $^3J_{H3H2'}$ = 5.8, $^3J_{H1H2'}$ = 4.8, $1H_{2'}$), 1.43 (s, $3H_{14}$), 1.33 (s, $3H_{15}$); ^{13}C NMR (75 MHz, 300 K, $CDCl_3$): 157.1 (C_7), 140.4 (C_9), 128.5 ($2C_{Ar}$), 127.6 (C_{12}), 126.1 ($2C_{Ar}$), 109.7 (C_{13}), 76.5 (C_4), 72.6 (C_3), 71.2 (C_8), 68.0 (C_6), 57.4 (C_5), 56.4 (C_1), 27.8 (C_{14}), 25.4 (C_{15}), 25.1 (C_2); HRMS (MALDI): calcd for $C_{17}H_{21}NO_5Na$ $[M+Na]^+$: 342.1317, found: 342.1307;

MS (CI, NH_3): m/z 320 $(M+H)^+$, 337 $(M+NH_4)^+$; MS (EI): m/z (%) 262 (7), 213 (3), 212 (3), 175 (6), 173 (13), 172 (12), 141 (21), 115 (12), 107 (42), 105 (47), 91 (38), 79 (94), 77 (100), 68 (32), 55 (28), 43 (28).

Meaningful signals for minor ***isomer 12 endo*** *in the crude product:* 5.70 (bs, $1H_8$), 4.60 (m, 1H), 3.98 (m, 2H), 1.59 (s, 3H), 1.36 (s, 3H).

Acetonide 13. By applying the general procedure and using **B2-*h*** (49 mg, 0.2 mmol) as starting material, **13** was obtained in 86% overall yield (R_f = 0.28, colourless oil, 55 mg, *exo/endo* = 94/6). The purification on silica gel (eluent hexanes/AcOEt: 50/50) afforded the desired *exo* compound but the minor *endo* one was not isolated after flash chromatography.

(3aS,5R,9aR,9bR)-5-((R)-hydroxy(phenyl)methyl)-2,2-dimethylhexahydro-7H-[1,3]dioxolo[4,5-c]oxazolo[3,4-a]pyridin-7-one, 13-exo. $[\alpha]_D^{19}$ = +12.1 (*c* 0.5, $CHCl_3$) ; ^{1}H NMR (300 MHz, 300 K, $CDCl_3$): 7.50-7.25 (m, $5H_{Ar}$), 5.04 (d, $^3J_{H8H1}$ = 7.7, $1H_8$), 4.89 - 4.76 (bs, $1H_{OH}$), 4.54 (dd, $^2J_{H6H6'}$ = -8.8, $^3J_{H6H5}$ = 8.0, $1H_6$), 4.31 (dt, $^3J_{H3H4}$ = 5.5, $^3J_{H3H2'}$ = $^3J_{H3H2}$ = 4.7, $1H_3$), 4.20 (dd, $^2J_{H6'H6}$ = -8.8, $^3J_{H6'H5}$ = 5.3, $1H_{6'}$), 3.95 (dd, $^3J_{H4H5}$ = 8.7, $^3J_{H4H3}$ = 5.5, $1H_4$), 3.84 (ddd, $^3J_{H1H2}$ = 9.1, $^3J_{H1H8}$ = 7.7, $^3J_{H1H2'}$ = 3.9, $1H_1$), 3.68 (ddd, $^3J_{H5H4}$ = 8.7, $^3J_{H5H6}$ = 8.0, $^3J_{H5H6'}$ = 5.3, $1H_5$), 2.01 (ddd, $^2J_{H2H2'}$ = -15.0, $^3J_{H2H1}$ = 9.1, $^3J_{H2H3}$ = 4.7, $1H_2$), 1.79 (ddd, $^2J_{H2'H2}$ = -15.0, $^3J_{H2'H3}$ = 4.7, $^3J_{H2'H1}$ = 3.9, $1H_{2'}$), 1.46 (s, $3H_{14}$), 1.31 (s, $3H_{15}$) ; ^{13}C NMR (75 MHz, 300 K, $CDCl_3$): 157.6 (C_7), 140.7 (C_9), 128.8 ($2C_{10/11}$), 128.3 (C_{12}), 126.8 ($2C_{11/10}$), 110.1 (C_{13}), 75.5 (C_4), 74.7 (C_8), 72.4 (C_3), 68.2 (C_6), 58.6 (C_5), 56.9 (C_1), 34.6 (C_2), 29.2 (C_{14}), 28.0 (C_{15}) ; MS (CI, NH_3): m/z 320 $(M+H)^+$; MS (EI) m/z (%) 319 (14), 304 (20), 289 (23), 288 (91), 261 (23), 244 (93), 213 (26), 212 (20), 186 (66), 170 (25), 168 (100), 158 (26), 144 (27), 132 (45), 130 (57), 91 (87), 77 (35), 43 (49).

Meaningful signals for minor ***isomer 13-endo*** *in the crude product:* 5.06 (d, ^3J = 7.8, $1H_8$), 1.43 (s, 3H), 1.35 (s, 3H).

Acetonide 14. By applying the general procedure and using from **B2-*i*** (49 mg, 0.2 mmol) as starting material, **14** was obtained in 89% overall yield (R_f = 0.32, colourless oil, 53 mg, *exo/endo* = 96/4).The purification on silica gel (eluent hexanes/AcOEt: 50/50) afforded the desired *exo* compound but the minor *endo* one was not isolated after chromatography.

(3aS,5R,9aR,9bR)-5-((S)-1-hydroxy-3-methylbutyl)-2,2-dimethylhexahydro-7H-[1,3]dioxolo[4,5-c]oxazolo[3,4-a]pyridin-7-one, 14-exo. $[\alpha]_D^{19}$ = +26.9 (*c* 1, $CHCl_3$); IR (neat): 3387, 2982, 2924, 2854, 1748, 1721, 1441, 1218, 1043 cm^{-1}; ^{1}H NMR (400 MHz, 300 K, $CDCl_3$): 4.56-4.49 (m, $2H_{3,6}$), 4.40 (bd, $^3J_{H8H9}$ = 9.6, $^3J_{H8H9'}$ = 3.6, $^3J_{H8H1}$ = 1.6, $1H_8$), 4.17 (dd, $^2J_{H6'H6}$ = -9.2, $^3J_{H6'H5}$ = 5.2, $1H_{6'}$), 4.01 (dd, $^3J_{H4H5}$ = 8.8, $^3J_{H4H3}$ = 5.6, $1H_4$), 3.98-3.94 (m, $1H_{OH}$), 3.67 (dt, $^3J_{H5H4}$ = 8.8, $^3J_{H5H6}$ = $^3J_{H5H6'}$ = 5.2, $1H_5$), 3.42 (ddd, $^3J_{H1H2}$ = 9.6, $^3J_{H1H2'}$ = 3.8, $^3J_{H1H8}$ = 1.6, $1H_1$), 2.31 (ddd, $^2J_{H2H2'}$ = -15.2, $^3J_{H2H1}$ = 9.6, $^3J_{H2H3}$ = 4.8, $1H_2$), 2.02 (dt, $^2J_{H2'H2}$ = -15.2, $^3J_{H2'H3}$ = $^3J_{H2'H1}$

= 3.8, 1H$_{2'}$), 1.82 (m, 1H$_{10}$), 1.54 (ddd, $^{2}J_{H9H9'}$ = -14.0, $^{3}J_{H9H8}$ = 9.6, $^{3}J_{H9H10}$ = 5.2, 1H$_{9}$), 1.48 (s, 3H$_{15}$), 1.36 (s, 3H$_{16}$), 1.13 (ddd, $^{2}J_{H9'H9}$ = -14.0, $^{3}J_{H9'H10}$ = 8.8, $^{3}J_{H9'H8}$ = 3.6, 1H$_{9'}$), 0.95 (d, $^{3}J_{H11H10}$ = 6.4, 3H$_{11}$), 0.92 (d, $^{3}J_{H12H10}$ = 6.8, 3H$_{12}$); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$): 156.8 (C$_7$), 109.9 (C$_{14}$), 75.9 (C$_4$), 73.0 (C$_3$), 67.7 (C$_6$), 67.0 (C$_8$), 58.4 (C$_5$), 55.7 (C$_1$), 42.6 (C$_9$), 28.1 (C$_{15}$), 25.9 (C$_{16}$), 25.4 (C$_2$), 25.0 (C$_{10}$), 23.5 (C$_{11}$), 22.0 (C$_{12}$); MS (CI, NH_3): m/z 300 $(M+H)^+$; MS (EI): m/z (%) 284 (2), 213 (7), 184 (3), 94 (14), 69 (20), 59 (22), 43 (100).

*Meaningful signals for minor **isomer 14-endo** in the crude product:* 3.06 (ddd, ^{3}J = 9.5, ^{3}J = 3.8, ^{3}J = 1.5, 1H), 1.35 (s, 3H).

5.3.4 General procedure for the deprotection of acetonides

To a solution of acetonide in water (c = 0.1 M) was added TFA (5 equiv.) The reaction was monitored by TLC and the mixture was concentrated under reduced pressure after complete conversion of acetonide into diol. Then 2 mL of water and a saturated aqueous $NaHCO_3$ solution were sequentially added until neutral pH. The aqueous layer was extracted with dichloromethane (20 mL) and the organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum.

(5*R*,7*S*,8*R*,8*aR*)-7,8-dihydroxy-5-((*S*)-1-hydroxyhexyl)hexahydro-3*H*-oxazolo[3,4-*a*]pyridin-3-one, 15. By applying the above general procedure and using **9-*exo*** (31 mg, 0.1 mmol) as starting material, **15** was isolated in 90% yield (colourless oil, 25 mg) after purification on silica gel (eluent CH_2Cl_2/MeOH: 90:10); ^{1}H NMR (400 MHz, 300 K, CD_3OD): 4.41 (dd, $^{2}J_{H6H6'}$ = -8.6, $^{3}J_{H6H5}$ = 7.8, 1H$_6$), 4.39 (dt, $^{3}J_{H8H9}$ = 7.9, $^{3}J_{H8H9'}$ = $^{3}J_{H1H8}$ = 3.9, 1H$_8$), 4.27 (dd, $^{2}J_{H6H6'}$ = -8.6, $^{3}J_{H6'H5}$ = 3.9, 1H$_{6'}$), 4.11 (ddd, $^{3}J_{H3H4}$ = 2.8, $^{3}J_{H3H2}$ = 2.7, $^{3}J_{H3H2'}$ = 2.3, 1H$_3$), 3.90 (ddd, $^{3}J_{H5H4}$ = 10.1,$^{3}J_{H5H6}$ = 7.8, $^{3}J_{H5H6'}$ = 3.9, 1H$_5$), 3.55 (td, $^{3}J_{H1H2'}$ = 12.3, $^{3}J_{H1H2}$ = $^{3}J_{H1H8}$ = 3.9, 1H$_1$), 3.47 (dd, $^{3}J_{H4H5}$ = 10.1, $^{3}J_{H4H3}$ = 2.8, 1H$_4$), 1.96 (ddd, $^{2}J_{H2H2'}$ = -14.2, $^{3}J_{H2H1}$ = 3.9, $^{3}J_{H2H3}$ = 2.7, 1H$_2$), 1.82 (ddd, $^{2}J_{H2H2'}$ = -14.2, $^{3}J_{H2'H1}$ = 12.3, $^{3}J_{H2'H3}$ = 2.3, 1H$_{2'}$), 1.55-1.50 (m, 3H$_{9,10}$), 1.48-1.31 (m, 5H$_{9',11,12}$), 0.95 (t, $^{3}J_{H13H12}$ = 6.9, 3H$_{13}$); ^{13}C NMR (100 MHz, 300 K, CD_3OD): 161.0 (C$_7$), 72.9 (C$_4$), 71.1 (C$_8$), 69.8 (C$_3$), 68.0 (C$_6$), 59.2 (C$_5$), 57.0 (C$_1$), 35.6 (C$_{10}$), 33.8 (1C$_{11/12}$), 32.9 (C$_2$), 27.9 (C$_9$), 24.5 (1C$_{11/12}$), 15.2 (C$_{13}$); HRMS (MALDI): calcd for $C_{13}H_{23}NO_5Na$ $[M+Na]^+$: 296.1468, found: 296.1467; MS (CI): *m/z* 274.1 $[M + H]^+$.

(1*R*,5*R*,6*R*,7*S*,8*aR*)-6,7-dihydroxy-5-(hydroxymethyl)-1-pentylhexahydro-3*H*-oxazolo[3,4-*a*]pyridin-3-one, 16. By applying the above general procedure and using **10-*exo*** (31 mg, 0.1 mmol) as starting material, **16** was isolated in 53% yield (colourless oil, 23 mg) after purification on silica gel (eluent CH_2Cl_2/MeOH: 95:15). Suitable crystals of **16** were obtained from a diffusion of pentane in $CHCl_3$ allowing an X-ray structure (see supporting information). mp = 114°C; ^{1}H NMR (400 MHz, 300 K, CD_3OD): 4.28 (dd, $^{2}J_{H6H6'}$ = -12.5, $^{3}J_{H6H5}$ = 2.4, 1H$_6$), 4.15 (td, $^{3}J_{H8H1}$ = $^{3}J_{H8H9}$

= 7.2, $^{3}J_{H8H9'}$ = 5.4, 1H$_8$), 4.08 (m, 1H$_3$), 4.06 (dd, $^{2}J_{H6'H6}$ = -12.5, $^{3}J_{H6'H5}$ = 5.6, 1H$_{6'}$), 3.78 (ddd, $^{3}J_{H1H2'}$ = 11.6, $^{3}J_{H1H8}$ = 7.2, $^{3}J_{H1H2}$ = 3.2, 1H$_1$), 3.57 (dd, $^{3}J_{H4H5}$ = 10.2, $^{3}J_{H4H3}$ = 2.8, 1H$_4$), 3.41 (ddd, $^{3}J_{H5H4}$ = 10.2, $^{3}J_{H5H6'}$ = 5.6, $^{3}J_{H5H6}$ = 2.4, 1H$_5$), 2.03 (dt, $^{2}J_{H2H2'}$ = -13.5, $^{3}J_{H2H1}$ = $^{3}J_{H2H3}$ = 3.2, 1H$_2$), 1.79-1.68 (m, 2H$_9$), 1.69 (ddd, $^{2}J_{H2H2'}$ = -13.5, $^{3}J_{H2'H1}$ = 11.6, $^{3}J_{H2'H3}$ = 2.2, 1H$_{2'}$), 1.56-1.40 (m, 2H$_{10}$), 1.40-1.34 (m, 4H$_{11,12}$), 0.96 (t, $^{3}J_{H13H12}$ = 6.9, 3H$_{13}$); ^{13}C NMR (100 MHz, 300 K, CD$_3$OD): 159.8 (C$_7$), 82.7 (C$_8$), 70.2 (C$_4$), 69.5 (C$_3$), 60.7 (C$_6$), 59.4 (C$_5$), 58.6 (C$_1$), 37.3 (C$_2$), 35.6 (C$_9$), 33.5 (1C$_{11/12}$), 26.4 (C$_{10}$), 24.4 (1C$_{11/12}$), 15.1 (C$_{13}$); HRMS (MALDI): calcd for $C_{13}H_{23}NO_5Na$ $[M+Na]^+$: 296.1468, found: 296.1468; MS (CI, NH$_3$): m/z 274.2 $(M+H)^+$, 291.2 $(M+NH_4)^+$.

5.3.5 General procedure for the epoxidation of dehydropiperidines

To a solution of dehydropiperidine (0.5 mmol) in dichloromethane (5 mL) was added *m*-CPBA (275 mg, 70-75%, 1.2 mmol) at room temperature. The reaction was monitored by TLC and after complete conversion in epoxide, saturated aqueous $NaHCO_3$ (5mL) was added. The resulting mixture was vigorously stirred for 30 min before separation of the organic layer from the aqueous one which was re-extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum.

(3*R*,7a*R*)-3-((*S*)-1-hydroxy-3-methylbutyl)hexahydro-5*H*-oxazolo[3,4-*a*]oxireno[2,3-*c*]pyridin-5-one, 17. By applying the above procedure and using **B1-*j*-*trans*** (113 mg, 0.5 mmol) as starting material, **17** was obtained as a 67/33 diastereomeric mixture, in 73% yield after purification on silica gel using AcOEt as eluent (R_f = 0.37 for both isomers). ^{1}H NMR (300 MHz, 300 K, $CDCl_3$): *common signals*: 4.40-4.10 (m, 3H$_{6',5,8}$), 3.92-3.62 (m, 1H$_1$), 3.38 (m, 1H$_3$), 1.87-1.66 (1H$_{10}$), 1.45-1.10 (m, 2H$_{9/9'}$); *signals corresponding to the major isomer*: 4.48 (t,^{3}J = 8.0, 1H$_6$), 3.11 (d, $^{3}J_{H4H3}$ = 4.4, 1H$_4$, assigned by COSY experiment), 2.20-2.12 (m, 2H$_{2/2'}$), 0.95 (d, $^{3}J_{H11H10}$ = 6.5, 3H$_{11}$), 0.90 (d, $^{3}J_{H12H10}$ = 6.5, 3H$_{12}$); *signals corresponding to the minor isomer*: 4.59 (t, ^{3}J = 9.0,1H$_6$), 3.15 (d, $^{3}J_{H4H3}$ = 4.3, 1H$_4$, assigned by COSY experiment), 2.58 (bd, $^{2}J_{H2H2'}$ = -16.0, 1H$_2$), 2.09 (ddd, $^{2}J_{H2H2'}$ = -16.0, ^{3}J = 7.1, ^{3}J = 2.3, 1H$_{2'}$), 0.93 (d, $^{3}J_{H11H10}$ = 6.0, 3H$_{11}$), 0.89 (d, $^{3}J_{H12H10}$ = 6.0); ^{13}C NMR (75 MHz, 300 K, $CDCl_3$): 157.0 (C$_7$), 69.7, 66.6, 65.2, 62.7, 56.0, 54.7, 53.6, 52.0, 51.3, 50.8, 50.1, 44.7, 44.0, 25.0, 24.6, 23.9, 23.3, 22.5, 22.3, 21.9. Note that an additional signal near 80 ppm might be due to a partial conversion of **17** into triol **17'** (ring opening of the epoxide) along chromatography, by analogy with observations reported for compound **19-*exo*** (see below); MS (CI, NH$_3$): m/z 242 $(M+H)^+$, 259 $(M+NH_4)^+$; MS (EI): *m/z* (%) 242 (12), 241 (3), 223 (8), 155 (55), 154 (33), 126 (17), 125 (21), 91 (20), 83 (44), 82 (100), 80 (30), 68 (40), 67 (32), 57 (58), 55 (76), 54 (60), 43 (46), 41 (60). HRMS (ESI+): calcd for $C_{12}H_{19}NO_4Na$ $[M+Na]^+$: 264.1212, found: 264.1213;

Methyl (1*aS*,3*R*,7*aR*,7*bR*)-5-oxohexahydro-5*H*-oxazolo[3,4-*a*]oxireno[2,3-*c*]pyridine-3-carboxylate, 18. By applying the general procedure for the preparation of epoxides and starting from **B2-*b*-*cis*** (39 mg, 0.2 mmol), **18** was isolated in 54% yield (white crystals, 21 mg) after purification by recrystallisation in pentane/AcOEt. While contained in the crude mixture (about 13%), the minor diastereomer was not isolated. ***Isomer 18 exo***, mp = 164°C; $[\alpha]_D^{19}$ = -15 (*c* 0.125, $CHCl_3$); IR (neat): 2954, 2927, 2852, 1756, 1443, 1223, 1128, 1014 cm^{-1}; ^1H NMR (400 MHz, 300 K, $CDCl_3$): 4.59 (t, $^3J_{H6H5}$ = 8.7, $^2J_{H6H6'}$= -8.7, $1H_6$), 4.30 (dd, $^2J_{H6'H6}$ = -8.7, $^3J_{H6'H5}$ = 3.0, $1H_{6'}$), 4.26 (dd, $^3J_{H5H6}$ = 8.7, $^3J_{H5H6'}$ = 3.0, $1H_5$), 3.93 (dd, $^3J_{H1H2}$ = 9.3, $^3J_{H1H2'}$ = 6.0, $1H_1$), 3.79 (s, $3H_9$), 3.44 (m, $1H_3$), 3.16 (d, $^3J_{H4H3}$ = 3.6, $1H_4$), 2.45-2.40 (m, $2H_{2/2'}$); ^{13}C NMR (75 MHz, 300 K, $CDCl_3$): 168.8 (C_8), 157.5 (C_9), 65.4 (C_6), 54.8 (C_4), 54.6 (C_5), 52.8 (C_9), 52.5 (C_3), 50.1 (C_1), 24.8 (C_2); HRMS (CI): calcd for $C_9H_{12}NO_5$ $[M+H]^+$: 214.0715, found: 214.0715; MS (CI, NH_3): m/z 214 $(M+H)^+$, 231 $(M+NH_4)^+$; MS (EI): m/z (%) 154 (100), 110 (19), 98 (17), 82 (13), 67 (32), 54 (42). Structural information: see the radiocrystallographic structure in SI.
*Meaningful signals for minor **isomer 18-endo** in the crude product:* 4.50 (t, $^3J_{H6H5} = |^2J_{H6H6'}| = 8.4$, $1H_6$), 4.40 (dd, $^2J_{H6'H6}$ = -8.4, $^3J_{H6'H5}$ = 4.2, $1H_{6'}$), 3.78 (s, $3H_9$), 3.1 (d, ^3J = 3.1, $1H_4$).

Epoxide 19. By applying the general procedure for the preparation of epoxides and using **B2-*g*-*cis*** (123 mg, 0.5 mmol) as starting material, **19** was obtained as a diastereomeric mixture (*exo:endo* = 15:85). Both isomers were separated on silica gel (eluent = hexanes/AcOEt: 50/50) affording 11 mg of **19-*exo*** (9% yield) and 64 mg of **19-*endo*** (49% yield). In fact, isomer "**19-*exo***" is converted into triol **19'** (through an epoxide opening reaction) along the purification by chromatography on silica gel. MS (CI, NH_3): m/z 262 $(M+H)^+$, 279 $(M+NH_4)^+$; MS (EI): m/z (%) 155 (13), 154 (20), 136 (14), 108 (20), 107 (22), 105 (62), 91 (16), 82 (30), 79 (52), 77 (100), 55 (36).
***(5R,7S,8S,8aR)-7,8-dihydroxy-5-((S)-hydroxy(phenyl)methyl)hexahydro-3H-oxazolo[3,4-a]pyridin-3-one,* 19'**. Colourless oil (11 mg, 9%); R_f = 0.41; $[\alpha]_D^{19}$ = -8.0 (*c* 0.5, $CHCl_3$); IR (neat): 2954, 2927, 2852, 1756, 1443 cm^{-1}; *NMR spectra were recorded after purification on silica gel and for this isomer the purification step induced a ring opening of the epoxide as attested by ^{13}C NMR shifts near 80 ppm and $^3J_{H3H4}$ and $^3J_{H4H5}$ values which are 1.1 Hz and 7.5 Hz instead of about 4Hz and 1Hz respectively, as expected in this type of epoxides;* ^1H NMR (400 MHz, 300 K, $CDCl_3$): 7.40-7.26 (m, $5H_{Ar}$), 5.13 (bs,$1H_8$), 4.73 (t, $^3J_{H6H5}$ = 8.8, $^2J_{H6H6'}$ =-8.8, $1H_6$), 4.47 (dd, $^3J_{H3H2'}$ = 5.5, $^3J_{H3H4}$ = 1.1, $1H_3$), 4.21 (dd, $^2J_{H6'H6}$ = -8.8, $^3J_{H5H6'}$ = 7.5, $1H_{6'}$), 4.20 (dd, $^3J_{H1H2'}$ = 3.2, $^3J_{H1H2}$ = 1.1, $1H_1$), 3.98 (dt, $^3J_{H4H5}$ = 7.5, $^3J_{H4H3}$ = $^4J_{H4H2'}$ = 1.1, $1H_4$), 3.74 (dt, $^3J_{H5H4}$ = $^3J_{H5H6'}$ = 7.5, $^3J_{H5H6}$ = 8.8, $1H_5$), 2.10 (dd, $^2J_{H2H2'}$ =12.8, $^3J_{H1H2}$ = 1.1, $1H_2$), 1.97 (m, $^2J_{H2H2'}$ = -12.8, $^3J_{H2'H3}$ = 5.5, $^3J_{H2'H1}$ = 3.2, $^4J_{H2'H4}$ = 1.1, $1H_{2'}$), 1.78 and 1.20 (bs, $3H_{OH}$); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$): 156.9 (C_7), 139.6 (C_9), 128.5 ($2C_{Ar}$), 127.7 (C_{12}), 125.4 ($2C_{Ar}$), 84.1 (C_8), 80.6 ($C_{3/4}$), 79.0 ($C_{3/4}$), 69.4

(C_6), 57.7 (C_1), 54.2 (C_5), 25.4 (C_2). 18.9 (C_2). HRMS (ESI+): m/z calcd for $C_{14}H_{16}NO_4$ [M^++H-H_2O]: 262.1079, found: 262.1074.

(1*aR*,3*R*,7*aR*,7*bS*)-3-((*S*)-hydroxy(phenyl)methyl)hexahydro-5*H*-oxazolo[3,4-*a*]oxireno[2,3-*c*]pyridin-5-one, 19-*endo*. Colourless oil (64 mg, 49%); R_f = 0.19; $[\alpha]_D^{19}$ = +9.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, 300 K, $CDCl_3$): 7.44-7.27 (m, 5$H_{10,11,12}$), 5.38 (bs, 1H_8), 4.54 (t, $^3J_{H6H5}$ = 8.6, $^2J_{H6H6'}$ = -8.6, 1H_6), 4.42 (dd, $^2J_{H6'H6}$ = -8.6, $^3J_{H6H5}$ = 4.1, 1$H_{6'}$), 4.21 (ddd, $^3J_{H5H6}$ = 8.6, $^3J_{H5H6'}$ = 4.1, J_{H5H4} = 1, 1H_5), 3.34 (dd, $^3J_{H3H2'}$ = 5.4, $^3J_{H3H4}$ = 3.8, 1H_3), 3.26 (ddd, $^3J_{H1H2}$ = 12.5, $^3J_{H1H2'}$ = 4.8, J_{H1H8} = 1.6, 1H_1), 3.06 (dt, $^3J_{H4H3}$ = 3.8, $^3J_{H4H5}$ = $^4J_{H4H2}$ = 1, 1H_4), 2.53 (ddd, $^2J_{H2H2'}$ = -15.7, $^3J_{H2H1}$ = 12.5, $^4J_{H4H2}$ = 1, 1H_2), 1.65 (ddd, $^2J_{H2'H2}$ = -15.7, $^3J_{H2'H3}$ = 5.4, $^3J_{H2'H1}$ = 4.8, 1$H_{2'}$), 1.65 (bs, 1H_{OH}); ^{13}C NMR (75 MHz, 300 K, $CDCl_3$): 158.6 (C_7), 141.0 (C_9), 128.4 (2C_{Ar}), 127.7 (C_{12}), 126.2 (2C_{Ar}), 71.6 (C_8), 65.6 (C_6), 58.9 (C_1), 56.2 (C_5), 52.5 (C_3), 51.1 (C_4), 18.9 (C_2). HRMS (ESI+): m/z calcd for $C_{14}H_{16}NO_4$ [M^++H]: 262.1079, found: 262.1077.

Epoxide 20. By applying the general procedure for the preparation of epoxides and using **B2-*i*-*cis*** (113 mg, 0.5 mmol) as starting material, **20** was obtained as a diastereomeric mixture (*exo:endo* = 46:54). Both isomers were separated on silica gel (eluent = AcOEt) affording 34 mg of **20-*exo*** (28% yield) and 40 mg of **20-*endo*** (33% yield). IR (neat): 3440, 2955, 2924, 2869, 1738, 1435, 1248, 1058, 904, 762 cm^{-1}; HRMS (MALDI): m/z calcd for $C_{12}H_{20}NO_4$ $[M+H]^+$: 242.1392, found: 242.1397; MS (CI, NH_3): m/z 242 $(M+H)^+$, 259 $(M+NH_4)^+$.

(1*aS*,3*R*,7*aR*,7*bR*)-3-((*S*)-1-hydroxy-3-methylbutyl)hexahydro-5*H*-oxazolo[3,4-*a*]oxireno[2,3-*c*]pyridin-5-one, 20-*exo*. Colourless oil (34 mg, 28%); R_f = 0.38; $[\alpha]_D^{19}$ = +14.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, 300 K, $CDCl_3$): 4.60 (t, $^3J_{H6H5}$ = 8.7, $^2J_{H6H6'}$ = -8.7, 1H_6), 4.31 (ddd, $^3J_{H8H9'}$ = 8.8, $^3J_{H8H9}$ = 5.2, $^3J_{H1H8}$ = 1.6, 1H_8), 4.25 (dd, $^2J_{H6'H6}$ = -8.7, $^3J_{H6'H5}$ = 5.8, 1$H_{6'}$), 4.19 (ddt, $^3J_{H5H6}$ = 8.7, $^3J_{H5H6'}$ = 5.8, $^4J_{H5H3}$ = $^3J_{H5H4}$ = 0.8, 1H_5), 3.46 (m, 1H_3), 3.12 (d, $^3J_{H4H3}$ = 3.8, $^3J_{H5H4}$ = 0.8, 1H_4), 3.09 (ddd, $^3J_{H1H2}$ = 11.9, $^3J_{H1H2'}$ = 3.3, $^3J_{H1H8}$ = 1.6, 1H_1), 2.35 (ddd, $^2J_{H2H2'}$ = -15.3, $^3J_{H2H1}$ = 11.9, $^3J_{H2H3}$ = 1.6, 1H_2), 2.12 (ddd, $^2J_{H2'H2}$ = -15.3, $^3J_{H2'H1}$ = 3.3, $^3J_{H2'H3}$ = 1.7, 1$H_{2'}$), 1.80 (m, 1H_{10}), 1.55 (ddd, $^2J_{H9H9'}$ = -13.6, $^3J_{H9H10}$ = 9.7, $^3J_{H9H8}$ = 5.2, 1H_9), 1.07 (ddd, $^2J_{H9'H9}$ = -13.6, $^3J_{H9'H8}$ = 8.8, $^3J_{H9'H10}$ = 4.1, 1$H_{9'}$), 0.92 (d, $^3J_{H11H10}$ = 6.7, 3H_{11}), 0.91 (d, $^3J_{H12H10}$ = 6.7, 3H_{12}); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$): 157.7 (C_7), 67.3 (C_8), 65.4 (C_6), 55.8 (C_5), 54.8 and 54.6 (2$C_{1\text{ and }4}$), 53.0 (C_3), 43.0 (C_9), 24.9 (C_{10}), 23.5 (C_{11}), 23.2 (C_2), 22.0 (C_{12}).

(1*aR*,3*R*,7*aR*,7*bS*)-3-((*S*)-1-hydroxy-3-methylbutyl)hexahydro-5*H*-oxazolo[3,4-*a*]oxireno[2,3-*c*]pyridin-5-one, 20-*endo*. Colourless oil (40 mg, 33%); R_f = 0.33; $[\alpha]_D^{19}$ = +20.1 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, 300 K, $CDCl_3$): 4.82 (bs, 1H_{OH}), 4.49 (t, $^3J_{H6H5}$ = 8.6, $^2J_{H6H6'}$ = -8.6, 1H_6), 4.38 (dd, $^2J_{H6'H6}$ =- 8.6, $^3J_{H6'H5}$ = 4.1, 1$H_{6'}$), 4.25 (bdd, ^{3}J ~10 and ^{3}J ~ 4, 1H_8), 4.16 (ddd, $^3J_{H5H6}$ = 8.6, $^3J_{H5H6'}$ = 4.1, $^3J_{H5H4}$ = 1.1, 1H_5), 3.45 (dd, $^3J_{H3H2'}$ = 5.5, $^3J_{H3H4}$ = 3.9, 1H_3), 3.10 (dt, $^3J_{H4H3}$ = 3.9,

$^{3}J_{H4H5} \sim {}^{4}J_{H4H2} \sim 1.1$, $1H_4$), 2.99 (ddd, $^{3}J_{H1H2} = 12.4$, $^{3}J_{H1H2'} = 4.9$, $^{3}J_{H1H8} = 1.2$, $1H_1$), 2.48 (ddd, $^{2}J_{H2H2'} = -15.7$, $^{3}J_{H2H1} = 12.4$, $^{4}J_{H4H2} = 0.9$, $1H_2$), 1.86-1.74 (m, $1H_{10}$), 1.85 (ddd, $^{2}J_{H2'H2} = -15.7$, $^{3}J_{H2'H3} = 5.5$, $^{3}J_{H2'H1} = 4.9$, $1H_{2'}$), 1.54 (ddd, $^{2}J_{H9H9'} = -13.5$, $^{3}J_{H9H8} = 9.8$, $^{3}J_{H9H10} = 5.2$, $1H_9$), 1.05 (ddd, $^{2}J_{H9'H9} = -13.5$, $^{3}J_{H9'H10} = 8.9$, $^{3}J_{H9'H8} = 3.9$, $1H_{9'}$), 0.93 (d, $^{3}J_{H11H10} = 6.7$, $3H_{11}$), 0.91 (d, $^{3}J_{H12H10} = 6.7$, $3H_{12}$); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$): 158.3 (C_7), 67.4 (C_8), 65.4 (C_6), 57.1 (C_1), 56.1 (C_5), 52.5 (C_3), 51.2 (C_4), 43.3 (C_9), 24.9 (C_{10}), 23.5 (C_{11}), 21.9 (C_{12}), 20.0 (C_2).

Discrimination between *exo* and *endo* epoxides

Having in hand the radiocrystallographic structure of ***18-exo***, the assignment of the *exo* or *endo* epoxide was established on the basis of NMR spectra, including chemical shift of epoxide carbons in ^{13}C NMR spectrometry and meaningful vicinal coupling constants or meaningful NOE effects (see SI).

5.3.6 Ring Opening of Epoxides

(5*R*,7*S*,8*S*,8*aR*)-5-((*S*)-1-acetoxy-3-methylbutyl)-3-oxohexahydro-3*H*-oxazolo[3,4-*a*]pyridine-7,8-diyl diacetate, 21. An aqueous H_2SO_4 solution (1 M, 0.48 mL, 0.48 mmol) was added to a solution of epoxide **20-*endo*** (38 mg, 0.16 mmol) in a mixture of dioxane and water (1:1, 8 mL) before heating the mixture at 80°C for 12 h. Then, a saturated aqueous $NaHCO_3$ solution (3 mL) was added, and the mixture was stirred at room temperature for 10 min. The aqueous phase was extracted with AcOEt (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a crude intermediate triol. The latter was dissolved in pyridine, then acetic anhydride (0.5 mL) and DMAP (1% mol) were successively added before 4h stirring at room temperature. After concentration of the reaction mixture under reduced pressure, the chromatography on silica gel (eluent = AcOEt) afforded **21** as a colourless oil ($R_f = 0.63$, 39 mg, 64%); $[\alpha]_D^{19} = +16.3$ (*c* 0.5, $CHCl_3$); IR (neat): 2924, 2863, 2848, 1750, 1426, 1372, 1232 cm^{-1}; ^{1}H NMR (300 MHz, 300K, $CDCl_3$): 5.97 (dt, $^{3}J_{H8H9'} = {}^{3}J_{H8H1} = 9.3$, $^{3}J_{H8H9} = 2.1$, $1H_8$), 4.98 (q, $^{3}J_{H3H2} \approx {}^{3}J_{H3H2'} \approx {}^{3}J_{H3H4} \approx 3.0$, $1H_3$), 4.85 (m, $1H_4$), 4.19 (t, $^{3}J_{H6H5} = 9.0$, $^{2}J_{H6H6'} = -9.0$, $1H_6$), 4.00-3.92 (m, $2H_{5,6'}$), 3.32 (ddd, $^{3}J_{H1H2} = 12.0$, $^{3}J_{H1H8} = 9.3$, $^{3}J_{H1H2'} = 2.7$, $1H_1$), 2.04, 2.01 and 1.96 (3s, $9H_{14}$), 1.99-1.87 (m, $1H_2$), 1.68-1.33 (m, $4H_{2',9,9',10}$), 0.85 (d, $^{3}J_{H11H10} = 6.0$, $3H_{11}$), 0.81 (d, $^{3}J_{H12H10} = 6.3$, $3H_{12}$); ^{13}C NMR (75MHz, 300K, $CDCl_3$): 170.3, 170.2 and 169.1 (3C acetates), 155.6 (C_7), 70.2 (C_8), 67.8 (C_3), 67.0 (C_4), 63.4 (C_6), 56.1 (C_5), 54.1 (C_1), 41.6 (C_9), 26.9 (C_2), 24.7 (C_{10}), 23.7 (C_{11}), 21.2 (C_{12}), 21.1 ($2C_{14}$), 20.9 ($1C_{14}$); HRMS (MALDI): calcd for $C_{18}H_{27}NO_8Na$ $[M+Na]^+$: 408.1634, found: 408.1629; MS (CI, NH_3): m/z 386 $(M+H)^+$, 403 $(M+NH_4)^+$; MS (EI) m/z (%) 326 (3), 266 (1), 256 (2), 222 (8), 205 (16), 196 (100), 136 (17), 110 (10), 92 (18), 43 (80).

(*S*)-1-((5*R*,7*R*,8*R*,8*aR*)-7,8-dihydroxy-3-oxohexahydro-3*H*-oxazolo[3,4-*a*]pyridin-5-yl)-3-methylbutyl acetate, 22. Epoxide **20-*exo*** (27 mg, 0.11 mmol) was submitted to acidic treatment and acetylation according to the experimental conditions reported for **20-*endo***, the mono-acetylated compound **22** was obtained after liquid chromatography on silica gel (eluent = AcOEt) as a colourless oil (R_f = 0.31, 33 mg, 79%); $[\alpha]_D^{19}$ = -16.7 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, 300 K, $CDCl_3$): 4.58 (dd, $^2J_{H6H6'}$= -9.4, $^3J_{H6H5}$ = 8.7, 1H$_6$), 4.44 (dt, $^3J_{H4H5}$ = 6.7, $^3J_{H4H3} \approx {}^4J_{H4H2} \approx$ 1.4, 1H$_4$), 4.32 (m, 1H$_3$), 4.27 (t, $^3J_{H6H5}$ = 9.4, $^2J_{H6',H6}$ = -9.4, 1H$_{6'}$), 4.08 (bt, $^3J_{H1H2} = {}^3J_{H1H2'}$ = 2.4, 1H$_1$), 3.99 (dd, $^3J_{H8H9}$ = 7.4, $^3J_{H8H9'}$ = 6.6, 1H$_8$), 3.63 (ddd, $^3J_{H5H6'}$ = 9.4, $^3J_{H5H6}$ = 8.7, $^3J_{H5H4}$ = 6.7, 1H$_5$), 2.10-2.05 (m, 2H$_{2/2'}$), 2.07 (s, 3H$_{14}$), 1.73 (m, 1H$_{10}$ + 1H$_{OH}$), 1.63 (m, 1H$_{OH}$), 1.27-1.19 (m, 2H$_{9,9'}$ +1H$_{OH}$), 0.94 (d, $^3J_{H11H10}$ = 6.7, 3H$_{11}$), 0.92 (d, $^3J_{H12H10}$ = 6.7, 3H$_{12}$); ^{13}C NMR (100 MHz, 300 K, $CDCl_3$): 170.6 (C$_{13}$), 156.7 (C$_7$), 83.3 (C$_8$), 79.7 (C$_4$), 76.1 (C$_3$), 70.6 (C$_6$), 54.7 (C$_1$), 54.1 (C$_5$), 43.0 (C$_9$), 27.6 (C$_2$), 25.6 (C$_{10}$), 23.3 (1C$_{11/12}$), 22.7 (1C$_{11/12}$), 20.9 (C$_{14}$). MS (CI, NH_3): m/z 284 [$(M+H)^+$-H_2O], 301 [$(M+NH_4)^+$-H_2O]; MS (EI): m/z (%) 284(2), 223 (5), 137 (100), 125 (9), 93 (8), 79 (13), 67 (5), 43 (11).

5.3.7 Access to iminosugars

5.3.7.1 Basic hydrolysis of the oxazolidinone function

For this purpose four procedures have been used for the cleavage of the oxazolidinone function depending on the starting material and on the desired type of products.

Procedure A

The *N*-protected piperidine (0.17 mmol) was dissolved in MeOH (3 mL) and an aqueous solution of NaOH (8 M, 1 mL) was added. The mixture was stirred at 100°C for 24 h and the solvent was removed under reduced pressure. The resulting colourless oil was dissolved in AcOEt (10 mL) and water was added (10 mL). The basic aqueous phase was extracted with AcOEt (5 × 10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was dissolved without further purification in MeOH (17 mL) and HCl (30%, 1.7 mL), then stirred 30 min at room temperature. The solvent was removed under reduced pressure to obtain the polyhydroxy-piperidinium chloride.

(2*R*,3*S*,4*R*,6*R*)-3,4-dihydroxy-6-hexyl-2-(hydroxymethyl)piperidinium chloride, 25. By applying the procedure A to **6** (51 mg, 0.17mmol), **25** was obtained in 40% yield (white solid, 18 mg); $[\alpha]_D^{19}$ = +2.3 (*c* 0.3 , MeOH); IR (neat): 3420, 2956, 2927, 2855, 1576, 1064 cm^{-1}; ^{1}H NMR (400 MHz, 300 K, CD_3OD): 3.96 (m, 1H$_4$), 3.95-3.88 (m, 1H$_3$), 3.89 (dd, $^2J_{H6H6'}$ = -12.0, $^3J_{H6H5}$ = 8.4, 1H$_6$), 3.83 (dd, $^2J_{H6',H6}$ = -12.0, $^3J_{H6',H5}$ = 4.9, 1H$_{6'}$), 3.52-3.46 (m, 1H$_1$), 3.45-3.39 (m, 1H$_5$), 2.10 (ddd, $^2J_{H2H2'}$ = -14.7, $^3J_{H2H1}$ = 10.2, $^3J_{H2H3}$ = 2.8, 1H$_{2ax}$), 1.82 (dt, $^2J_{H2',H2}$ = -14.7, $^3J_{H2',H1} = {}^3J_{H2',H3}$ = 3.2, 1H$_{2'eq}$), 1.73-1.66 (m, 1H$_7$), 1.45-1.3 (m, 9H$_{7',8,9,10,11}$), 0.89 (t, $^3J_{H11H12}$ = 6.8, 3H$_{12}$);

^{13}C NMR (100 MHz, 300 K, CD_3OD): 68.9 (C_4), 66.7 (C_3), 61.2 (C_6), 58.4 (C_5), 54.2 (C_1), 33.5 (1C), 31.1 (1C), 30.9 (1C), 30.3 (C_2), 28.1 (1C), 24.4 (1C), 15.2 (C_{12}); HRMS (MALDI): m/z calcd for $C_{12}H_{26}NO_3$ [M - Cl^-]$^+$: 232.1907, found: 232.1908; MS (CI, NH_3): m/z 232 (M - Cl^-)$^+$.

(2*R*,3*R*,4*S*,6*R*)-3,4-dihydroxy-6-(1-hydroxycyclohexyl)-2-(hydroxymethyl)piperidinium chloride, 26. By applying the procedure A to **7** (53 mg, 0.17 mmol), **26** was obtained in 81% yield (white solid, 39 mg); $[\alpha]_D^{19}$ = +23.7 (*c* 1.22, MeOH); IR (neat): 3424, 3265, 2930, 2852, 1638, 1545, 1069, 1047 cm^{-1}; ^{1}H NMR (300 MHz, 300 K, CD_3OD): 4.12-4.06 (m, 1H$_3$), 3.98 (dd, $^2J_{H6H6'}$ = -12.0, $^3J_{H6H5}$ = 3.0, 1H$_6$), 3.86 (dd, $^2J_{H6'H6}$ = -12.0, $^3J_{H6'H5}$ = 6.0, 1H$_{6'}$), 3.71 (dd, $^3J_{H4H5}$ = 12.0, $^3J_{H4H3}$ = 3.0, 1H$_4$), 3.48-3.35 (m, 2H$_{1,5}$), 2.07 (dt, $^2J_{H2H2'}$ = -12.0, $^3J_{H2H1}$ = $^3J_{H2H3}$ = 3.0, 1H$_{2eq}$), 1.78 (bt, $^3J_{H2'H1}$ = 12, $^2J_{H2'H2}$ = -12.0, $^3J_{H2'H3}$ ~ 1.0, 1H$_{2'ax}$), 1.70-1.49 and 1.43-1.1 (m, 10H$_{8,9,10}$); ^{13}C NMR (75 MHz, 300 K, CD_3OD): 71.5 (C_7), 68.0 (C_4), 67.1 (C_3), 60.9 (C_1), 59.1 (C_6), 58.6 (C_5), 35.5 (C_8), 33.0 ($C_{8'}$), 30.4 (C_2), 26.4 (C_{10}), 22.4 (C_9), 22.1 ($C_{9'}$); HRMS (MALDI): calcd for $C_{12}H_{24}NO_4$ [M - Cl^-]$^+$: 246.1705, found: 246.1706; MS (CI, NH_3): m/z 246 (M - Cl^-)$^+$.

(2*R*,3*R*,4*S*,6*R*)-3,4-dihydroxy-6-((S)-1-hydroxyhexyl)-2-(hydroxymethyl)piperidinium chloride, 27. By applying the procedure A to **9** (53 mg, 0.17 mmol), **27** was obtained in 85% yield (white solid, 41 mg); $[\alpha]_D^{19}$ = +28.9 (*c* 0.425, MeOH); IR (neat): 3327, 2948, 2919, 2856, 1543, 1330, 1070, 1040 cm^{-1}; ^{1}H NMR (400 MHz, 300 K, CD_3OD): 4.14 (m, 1H$_3$), 4.00 (dd, $^2J_{H6H6'}$ = -12.0,$^3J_{H6H5}$ = 3.2, 1H$_6$), 3.99-3.95 (m, 1H$_7$), 3.88 (dd, $^2J_{H6'H6}$ = -12.0, $^3J_{H6'H5}$ = 6.2, 1H$_{6'}$), 3.72 (dd, $^3J_{H4H5}$ = 10.6, $^3J_{H4H3}$ = 2.6, 1H$_4$), 3.55-3.45 (m, 2H$_{5,1}$), 2.00 (dt, $^2J_{H2H2'}$ = -14.8, $^3J_{H2H1}$ = $^3J_{H2H3}$ = 3.5, 1H$_{2eq}$), 1.92(ddd, $^2J_{H2'H2}$ = -14.8, $^3J_{H2'H1}$ = 12.1, $^3J_{H2'H1}$ = 1.6, 1H$_{2'ax}$), 1.6-1.3 (m, 8H$_{8\ to\ 11}$), 0.95 (d, $^3J_{H11H12}$ = 6.8, 3H$_{12}$); ^{13}C NMR (100 MHz, 300 K, CD_3OD): 71.3 (C_7), 68.9 (C_4), 67.8 (C_3), 60.4 (C_6), 58.9 (C_1), 57.1 (C_5), 35.3 (1C), 33.6 (1C), 29.0 (C_2), 27.3 (1C), 24.4 (1C), 15.2 (C_{12}); HRMS (MALDI): m/z calcd for $C_{12}H_{26}NO_4$ [M - Cl^-]$^+$: 248.1856, found: 248.1866; MS (CI, NH_3): m/z 248 (M - Cl^-)$^+$.

(2*R*,3*R*,4*S*,6*R*)-3,4-dihydroxy-6-((R)-1-hydroxyhexyl)-2-(hydroxymethyl)piperidinium chloride, 28. By applying the procedure A to **10** (53 mg, 0.17 mmol), **28** was obtained in 91% yield (white solid, 44 mg); $[\alpha]_D^{19}$ = +12.4 (*c* 0.425, MeOH); IR (neat): 3396, 2956, 2932, 2859, 1629, 1429, 1072 cm^{-1}; ^{1}H NMR (400 MHz, 300 K, CD_3OD): 4.11 (m, 1H$_3$), 3.99 (dd, $^2J_{H6H6'}$ = -11.9, $^3J_{H6H5}$ = 3.2, 1H$_6$), 3.93 (dd, $^2J_{H6'H6}$ = -11.9, $^3J_{H6'H5}$ = 4.7, 1H$_{6'}$), 3.79 (dd, $^3J_{H4H5}$ = 10.7, $^3J_{H4H3}$ = 2.6, 1H$_4$), 3.67-3.60 (m, 1H$_7$), 3.41-3.35 (m, 2H$_{5,1}$), 2.07 (dt, $^2J_{H2H2'}$ = -14.7, $^3J_{H2H1}$ ≈ $^3J_{H2H3}$ = 3.2, 1H$_{2eq}$), 1.72 (ddd, $^2J_{H2'H2}$ = -14.7, $^3J_{H2'H1}$ = 12.5, $^3J_{H2'H3}$ = 1.4, 1H$_{2'ax}$), 1.65-1.3 (m, 8H$_{8\ to\ 11}$), 0.95 (d, $^3J_{H11H12}$ = 6.8, 3H$_{12}$); ^{13}C NMR (100 MHz, 300 K, CD_3OD): 72.6 (C_7), 68.6 (C_4), 67.9 (C_3), 59.8 (C_6), 58.4 (1C$_{1/5}$), 58.1 (1C$_{1/5}$), 35.5 (1C), 33.7 (1C), 33.3 (C_2), 26.3 (1C), 24.5 (1C),

15.2 (C_{12}); HRMS (MALDI): m/z calcd for $C_{12}H_{26}NO_4$ [M - Cl^-]$^+$: 248.1856, found: 248.1861; MS (CI, NH_3): m/z 248 (M - Cl^-)$^+$.

(2*R*,3*R*,4*S*,6*R*)-3,4-dihydroxy-6-[(S)-1-hydroxy-3-methylbutyl)-2-(hydroxymethyl] piperidinium chloride, 30. By applying the procedure A to **14** (51 mg, 0.17 mml), **30** was obtained in 69% yield (white solid, 32 mg); $[\alpha]_D^{19}$ = +21.4 (*c* 0.5 , MeOH) ; ^{1}H NMR (300 MHz, 300 K, CD_3OD): 4.15-4.03 (m, 2$H_{3,7}$), 3.98 (dd, $^2J_{H6H6'}$ = -11.8, $^3J_{H6H5}$ = 3.3, 1H_6), 3.86 (dd, $^2J_{H6'H6}$ = -11.8, $^3J_{H6'H5}$ = 6.0, 1$H_{6'}$), 3.70 (dd, $^3J_{H4H5}$ = 10.8, $^3J_{H4H3}$ = 2.7, 1H_4), 3.50-3.39 (m, 2$H_{5,1}$), 1.98 (dt, $^2J_{H2H2'}$ = -15.0, $^3J_{H2H1}$ = $^3J_{H2H3}$ = 3.3, 1H_{2eq}), 1.89 (bt, $^3J_{H2'H1}$ = 15.0, $^2J_{H2'H2}$ = -15.0, $^3J_{H2'H1}$ ~ 2.0, 1$H_{2'ax}$), 1.78 (m, 1H_9), 1.46 (ddd, $^2J_{H8H8'}$ = -13.8, $^3J_{H8H7/9}$ = 9.3, $^3J_{H8H9/7}$ = 5.4, 1H_8), 1.19 (ddd, $^2J_{H8'H8}$ = -13.8, $^3J_{H8'H7/9}$ = 8.7, $^3J_{H8'H9/7}$ = 4.2, 1$H_{8'}$), 0.96 (d, $^3J_{H10H9}$ = 6.9, 3H_{10}), 0.95 (d, $^3J_{H11H9}$ = 6.9, 3H_{11}); ^{13}C NMR (75 MHz, 300 K, CD_3OD): 68.4 (C_7), 68.0 (C_4), 67.1 (C_3), 59.6 (C_6), 58.1 (C_1), 56.6 (C_5), 43.4 (C_8), 28.3 (C_2), 25.5 (C_9), 23.6 (C_{10}), 22.3 (C_{11}). HRMS (CI, NH_3): m/z calcd for $C_{11}H_{24}NO_4$ [M - Cl^-]$^+$: 234.1705, found: 234.1706; MS (CI, NH_3): m/z 234 (M - Cl^-)$^+$.

Procedure B

An aqueous solution of NaOH (8 M, 0.6 mL) was added to a solution of protected piperidine (0.10 mmol) in MeOH (1.8 mL) before 24h stirring at 100°C. After cooling to room temperature and neutralization with a 6M HCl solution, the solvent was removed under reduced pressure and the crude product was dissolved in MeOH and filtered off through a pad of celite®. The solid residue was washed with MeOH (2 × 15 mL) and the combined filtrates were concentrated under reduced pressure. The crude product was then dissolved in MeOH (10 mL) and HCl (30%, 1.0 mL) and stirred 30 min at room temperature. The solvent was removed under reduced pressure to obtain the polyhydroxy-piperidinium chloride.

(2*R*,3*S*,4*R*,6*S*)-3,4-dihydroxy-2-(hydroxymethyl)-6-(5-hydroxynonan-5-yl)piperidinium chloride, 24. By applying procedure B to **5** (54 mg, 0.17 mmol), **24** was obtained in 79% yield (white solid, 44 mg); $[\alpha]_D^{19}$ = +4.8 (*c* 1.2, MeOH); IR (neat): 3404, 2956, 2929, 2870, 1639, 1453, 1041 cm^{-1}; ^{1}H NMR (400 MHz, 300 K, CD_3OD): 4.20 (dd, $^2J_{H6H6'}$ = -12.0, $^3J_{H6H5}$ = 10.4, 1H_6), 4.11 (bq, $^3J_{H3H4} \approx {}^3J_{H3H2} \approx {}^3J_{H3H2'}$ = 3.2, 1H_3), 4.03 (dd, $^3J_{H4H5}$ = 5.6, $^3J_{H4H3}$ = 3.2, 1H_4), 3.97 (dd, $^2J_{H6'H6}$ = -12.0, $^3J_{H6'H5}$ = 4.4, 1$H_{6'}$), 3.70 (ddd, $^3J_{H5H6}$ = 10.4, $^3J_{H5H4}$ = 5.6, $^3J_{H5H6'}$ = 4.4, 1H_5), 3.53 (dd, $^3J_{H1H2'}$ = 11.6, $^3J_{H1H2}$ = 2.8, 1H_1), 1.99 (ddd, $^2J_{H2H2'}$ = -14.8, $^3J_{H2H3}$ = 3.2, $^3J_{H2H1}$ = 2.8, 1H_{2eq}), 1.86 (ddd, $^2J_{H2'H2}$ = -14.8, $^3J_{H2'H1}$ = 11.6, $^3J_{H2'H3}$ = 3.2, 1$H_{2'ax}$), 1.60-1.20 (m, 12$H_{8\ to\ 10}$), 0.96 (t, $^3J_{H11H10}$ = 6.8, 6H_{11}); ^{13}C NMR (100 MHz, 300 K, CD_3OD): 74.0 (C_7), 67.6 (C_4), 67.4 (C_3), 59.6 (C_5), 57.3 (C_6), 53.5 (C_1), 36.3 (1C), 35.9 (1C), 30.0 (C_2), 26.2(1C), 26.1 (1C), 24.2(1C), 24.1 (1C), 14.3 (2C_{11}). HRMS (MALDI): calcd for $C_{15}H_{32}NO_4$ [M - Cl^-]$^+$: 290.2331, found: 290.2325; MS (CI, NH_3): m/z 290 (M - Cl^-)$^+$.

(2*R*,3*S*,4*S*,6*R*)-3,4-dihydroxy-6-[(*S*)-1-hydroxy-3-methylbutyl]-2-(hydroxymethyl) piperidinium chloride, 31. By applying procedure B to **21** (51 mg, 0.17 mmol), **31** was obtained in 73% yield (white solid, 33 mg); $[\alpha]_D^{19}$ = -0.3 (*c* 0.57, MeOH); IR (neat): 3372, 1633, 1075 cm^{-1}; ^1H NMR (400 MHz, 300 K, CD_3OD): 4.04 (m, $^3J_{H7H8'}$ = 8.8, $^3J_{H7H8}$ = 5.2, $^3J_{H7H1}$ = 2.7, $1H_7$), 3.98 (bq, $^3J_{H3H4} \approx {}^3J_{H3H2} \approx {}^3J_{H3H2'}$ = 2.4, $1H_3$), 3.92-3.77 (m, $3H_{6,6',4}$), 3.57 (bt, $^3J_{H5H6} \approx {}^3J_{H5H6'}$ = 6.4, $1H_5$), 3.39 (bdt, $^3J_{H1H2}$ = -12.8, $^3J_{H1H7} \approx {}^3J_{H1H2'}$ = 2.7, $1H_1$), 2.20 (ddd, $^2J_{H2H2'}$ = -14.2, $^3J_{H2H1}$ = 12.8, $^3J_{H2H3}$ = 2.4, $1H_2$), 1.83-1.70 (m, $1H_9$), 1.70 (dt, $^2J_{H2'H2}$ = -14.2, $^3J_{H2'H1}$ = 2.7, $^3J_{H2'H3}$ = 2.4, $1H_{2'}$), 1.46 (ddd, $^2J_{H8H8'}$ = -13.2, $^3J_{H8H9}$= 9.2, $^3J_{H8H7}$ = 5.2, $1H_8$), 1.18 (ddd, $^2J_{H8'H8}$ = -13.2, $^3J_{H8'H7}$ = 8.8, $^3J_{H8'H9}$ = 4.0, $1H_{8'}$), 0.96 (d, $^3J_{H10H9}$ = 6.8, $3H_{10}$), 0.94 (d, $^3J_{H11H9}$ = 6.9, $3H_{11}$); ^{13}C NMR (100 MHz, 300 K, CD_3OD): 69.0 (C_7), 66.9 ($1C_{3/4}$), 66.8 ($1C_{3/4}$), 60.6 (C_6), 58.0 (C_5), 57.4 (C_1), 43.0 (C_8), 25.5 (C_9), 24.5 (C_2), 23.6 (C_{10}), 22.2 (C_{11}); HRMS (MALDI): calcd for $C_{11}H_{24}NO_4$ $[M - Cl^-]^+$: 234.1705; found 234.1707; MS (CI, NH_3): m/z 234 $(M - Cl^-)^+$.

(2*R*,3*R*,4*R*,6*R*)-3,4-dihydroxy-6-[(*S*)-1-hydroxy-3-methylbutyl]-2-(hydroxymethyl) piperidinium chloride, 32. By using the procedure B and starting from **22** (51 mg, 0.17 mmol) as starting material, **32** was prepared in 63% yield (white solid, 29 mg); $[\alpha]_D^{19}$ = -10 (*c* 0.22, MeOH); IR (neat): 3418, 1644, 1069 cm^{-1}; ^1H NMR (400 MHz, 300 K, CD_3OD): 4.32 (dd, $^3J_{H3H2'}$ = 6.0, $^3J_{H3H4}$ = 3.6, $1H_3$), 4.19 (bdd, $^3J_{H7H8}$ = 9.0, $^3J_{H7H8'}$ = 5.0, $^4J_{H7H2'} \approx 0.7$, $1H_7$), 3.80 (dd, $^3J_{H6H5}$ = 5.6, $^2J_{H6H6'}$= -11.8, $1H_6$), 3.77 (dd, $^3J_{H1H2'}$ = 3.4, $^3J_{H1H2} \approx 0.7$, $1H_1$), 3.71 (dd, $^2J_{H6'H6}$ = -11.8, $^3J_{H6'H5}$ = 10.0, $1H_{6'}$), 3.65 (dd, $^3J_{H4H3}$ = 3.6, $^3J_{H4H5} \approx 2.7$, $1H_4$), 3.32-3.22 (m, $1H_5$), 2.44 (dd, $^2J_{H2H2'}$ = -13.6, $^3J_{H1H2} \approx 0.7$, $1H_2$), 2.09 (m, $1H_{2'}$), 1.75 (m, $^3J_{H9H8'}$ = 8.0, $^3J_{H9H10}$ = 6.8, $^3J_{H9H11}$ = 6.4, $^3J_{H9H8}$ = 6.0, $1H_9$), 1.36 (ddd, $^2J_{H8H8'}$ = -13.7, $^3J_{H8H7}$ = 9.0, $^3J_{H8H9}$ = 6.0, $1H_8$), 1.25 (ddd, $^2J_{H8'H8}$ = -13.7, $^3J_{H8'H9}$ = 8.0, $^3J_{H8'H7}$ = 5.0, $1H_{8'}$), 0.95 (d, $^3J_{H10H9}$ = 6.8, $3H_{10}$), 0.94 (d, $^3J_{H11H9}$ = 6.4, $3H_{11}$); ^{13}C NMR (100 MHz, 300 K, CD_3OD): 80.1 (C_7), 78.0 (C_3), 68.2 (C_4), 60.8 (C_6), 60.5 (C_5), 58.8 (C_1), 44.5 (C_8), 27.0 (C_2), 25.8 (C_9), 23.5 (C_{10}), 22.2 (C_{11}); HRMS (MALDI): calcd for $C_{11}H_{22}NO_3$ $[(M - Cl^-)^+ - (H_2O)]$: 216.1600, found: 216.1601; MS (CI, NH_3): m/z 216 $[(M - Cl^-)^+ - (H_2O)]$; Structural information: the adopted conformation is a distorted $_4C^1$ chair due to hydrogen bondings.

Procedure C

(2*R*,3*S*,4*R*,6*S*)-3,4-dihydroxy-6-(1-hydroxycyclohexyl)-2-(hydroxymethyl)piperidinium chloride, 23. The protected piperidine **1** (8 mg, 0.026 mmol) was dissolved in MeOH (3 mL) containing 0.25 mL of HCl 30%, and stirred for 2 h at room temperature before removal of the solvents under vacuum. The crude product was dissolved in MeOH (1 mL) without further purification and submitted to basic treatment (aqueous solution of NaOH 8M, 0.31 mL) upon stirring at 100°C for 24 h. After removal of the solvent, the resulting colourless oil was dissolved

in AcOEt (5 mL) and water was added (5 mL). The basic aqueous phase was extracted with AcOEt (5 × 5mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. Without further purification, the crude product was dissolved in 14.3 mL of a 10/1 mixture of MeOH and HCl 30% and stirred 2 h at room temperature. The solvent was removed under reduced pressure to obtain the polyhydroxy-piperidinium chloride **23** (6 mg; 85% yield); $[\alpha]_D^{19}$ = -0.6 (*c* 0.44, MeOH); ^{1}H NMR (400 MHz, 300 K, CD_3OD): 4.19 (dd, $^2J_{H6H6'}$ = -12.0, $^3J_{H6H5}$ = 10.0, 1H$_6$), 4.10 (m, 1H$_3$), 4.02 (dd, $^3J_{H4H5}$ = 5.6, $^3J_{H4H3}$ = 3.2, 1H$_4$), 3.95 (dd, $^2J_{H6'H6}$ = -12.0, $^3J_{H6'H5}$ = 4.4, 1H$_{6'}$), 3.68 (bddd, $^3J_{H5H6}$ = 10.0, $^3J_{H5H4}$ = 5.6, $^3J_{H5H6'}$ = 4.4, 1H$_5$), 3.39 (dd, $^3J_{H1H2'}$ = 10.7, $^3J_{H1H2}$ = 2.4, 1H$_1$), 2.05 (dt, $^2J_{H2H2'}$ = -14.4, $^3J_{H2H3}$ = $^3J_{H2H1}$= 2.4, 1H$_{2eq}$), 1.85 (ddd, $^2J_{H2'H2}$ = -14.4, $^3J_{H2'H1}$ = 10.7, $^3J_{H2'H3}$ = 2.4, 1H$_{2'ax}$), 1.75-1.20 (m, 10H$_{8,9,10}$); ^{13}C NMR (100 MHz, 300 K, CD_3OD): 71.5 (C$_7$), 67.7 (C$_4$), 67.4 (C$_3$), 59.5 (C$_5$), 57.4 (C$_6$), 55.9 (C$_1$), 35.3 (C$_8$), 33.3 (C$_{8'}$), 29.8 (C$_2$), 26.4 (C$_{10}$), 22.4 (C$_9$), 22.3 (C$_{9'}$); HRMS (MALDI): calcd for $C_{12}H_{24}NO_4$ $[M - Cl^-]^+$: 246.1705, found: 246.1695; MS (CI, NH_3): m/z 246 $M - Cl^-)^+$.

Procedure D

(2*R*,3*R*,4*S*,6*S*)-6-hexyl-3,4-dihydroxy-2-(hydroxymethyl)piperidine, 29.An aqueous solution of NaOH (8 M, 0.31 mL) was added to a solution of piperidine **11** (7.5 mg, 0.029 mmol) in MeOH (1 mL) and the mixture was stirred at 100°C for 24 h. After removal of the solvent under reduced pressure, the resulting colourless oil was dissolved in AcOEt (4 mL) and water (4 mL) was added. The basic aqueous phase was extracted with AcOEt (5 × 5 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure to afford the polyhydroxy-piperidine **29** as a colourless oil (5 mg, 76% yield); $[\alpha]_D^{19}$ = +28.8 (c 0.37 , $CHCl_3$); IR (neat): 3439, 2960, 2926, 2855, 1619, 1426, 1070 cm^{-1}; ^{1}H NMR (300 MHz, 300 K, CD_3OD): 3.96 (bq, $^3J_{H3H4} \approx {}^3J_{H3H2} \approx {}^3J_{H3H2'}$ = 2.8, 1H$_3$), 3.89 (dd, $^2J_{H6H6'}$ = -10.9, $^3J_{H6H5}$ = 3.3, 1H$_6$), 3.54 (dd, $^2J_{H6'H6}$ = -10.9, $^3J_{H6'H5}$ = 7.5, 1H$_{6'}$), 3.33-3.28 (m, 1H$_4$, masked by HCD_2OD), 2.98-2.90 (m, superimposed with H$_5$, 1H$_1$), 2.97 (ddd, $^3J_{H5H4}$ = 10.4, $^3J_{H5H6'}$ = 7.5, $^3J_{H5H6}$ = 3.3, 1H$_5$), 1.91 (ddd, $^2J_{H2H2'}$ = -13.9, $^3J_{H2H1}$ = 3.6, $^3J_{H2H3}$ = 2.8, 1H$_2$), 1.50-1.20 (m, 11H$_{2',7\text{ to }11}$), 0.91 (bt,$^3J_{2H11}$ = 6.5, 3H$_{12}$); ^{13}C NMR (100 MHz, 300 K, CD_3OD): 71.6 (C$_4$), 69.3 (C$_3$), 63.9 (C$_6$), 58.0 (C$_5$), 50.6 (C$_1$), 38.9 (C$_2$), 36.8, 32.9, 30.5, 27.1, 23.6 (5C$_{aliph.}$), 14.4 (C$_{12}$); HRMS (MALDI): m/z calcd for $C_{12}H_{26}NO_3$ $[M+H^+]$: 232.1913, found: 232.1910; MS (CI, NH_3): m/z 232$(M+H^+)$.

5.3.7.2 Reduction of the oxazolidinone function

(2*R*,3*R*,4*S*,6*R*)-3,4-dihydroxy-6-[(*S*)-hydroxy(phenyl)methyl]-2-(hydroxymethyl)-1-methylpiperidinium chloride, 35. To a solution of protected piperidine **12** (17 mg, 0.055 mmol) in THF (5 mL) was added $LiAlH_4$ (4 equiv., 92 µL of a 2.4M solution in THF) at room temperature.

After stirring for 4 hours at reflux, the mixture was cooled and H_2O (500 µL) was added dropwise. The crude product was filtrated through a pad of Celite®, washed with AcOEt and filtrated on alumina (eluent: methylene chloride/methanol: 9/1). The product was dissolved in a solution of MeOH/HCl(30%) (5:1, 5 mL) and stirred 3h at room temperature. The solvents were removed under reduced pressure to obtain compound **35** in 83% overall yield along the two steps (14 mg); $[\alpha]_D^{19}$ = +34 (*c* 0.4, CD_3OD); IR (neat): 3440, 3357, 3318, 3254, 2925, 2904, 1622, 1063, 703 cm^{-1}; ^1H NMR (400 MHz, 300 K, CD_3OD): 7.45-7.35 and 7.32-7.26 (2m, $5H_{10,11,12}$), 5.47 (d, $^3J_{H8H1}$ = 2.8, $1H_8$), 4.17-4.05 (m, $2H_{6/6'}$), 3.98-3.92 (m, $1H_3$), 3.79 (bdt, $^3J_{H1H2}$ = 12.0, $^3J_{H1H2'} \approx {}^3J_{H1H8}$ = 2.8, $1H_1$), 3.73 (dd, $^3J_{H4H5}$ = 11.0, $^3J_{H4H3}$ = 2.8, $1H_4$), 3.38 (bd, $^3J_{H5H4}$ = 11.0, $1H_5$), 3.25 (s, $3H_7$), 1.93 (ddd, $^2J_{H2H2'}$= -14.6, $^3J_{H2H1}$ = 12.0, $^3J_{H2H3}$ = 1.6, $1H_2$), 1.45 (bdt, $^2J_{H2'H2}$ = -14.6, $^3J_{H2'H1} \approx {}^3J_{H2'H3}$ = 2.8, $1H_{2'}$); ^{13}C NMR (100 MHz, 300 K, CD_3OD): 141.3 (C_9), 129.6 ($2C_{10/11}$), 128.9 (C_{12}), 126.8 ($2C_{10/11}$), 69.1 (C_8), 67.3 (C_4), 67.2 (C_5), 66.4 (C_3), 65.3 (C_1), 56.7 (C_6), 37.3 (C_7), 28.6 (C_2); HRMS (MALDI): calcd for $C_{14}H_{22}NO_4$ $(M - Cl^-)^+$: 268.1549, found: 268.1549; MS (CI, NH_3): m/z 268 $(M - Cl^-)^+$.

Compounds **33** and **34** have been obtained previously according to the same procedure and have been fully characterized.[26]

NMR spectra and NOESY analysis of new compounds are given in supplementary information.

CCDC 710420 and 2040539 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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