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Stereodivergent synthesis of piperidine iminosugars 1-deoxy-D-nojirimycin and 1-deoxy-D-altronojirimycin

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ABSTRACT

A stereodivergent approach for producing piperidine iminosugars has been developed employing a common optically active precursor. The key steps of the synthetic pathway are the double diastereoselection in the asymmetric dihydroxylation of the suitable chiral vinyl epoxy ester and the regio- and stereospecific opening of the epoxide ring with azide. The synthesis of two piperidine iminosugars, 1-deoxy-D-altronojirimycin and 1-deoxy-D-nojirimycin, was achieved by two related routes.

1. Introduction

Polyhydroxylated piperidines, pyrrolidines, pyrrolizidines, indolizidines and nortropanes, also known as azasugars or iminosugars, are widespread in plants and microorganisms. Their discovery dates back to 1965, when nojirimycin was isolated from Streptomyces and its biological properties were disclosed. This discovery triggered an enormous amount of interest in the isolation and synthesis of many other iminosugars, and subsequent investigation of their biological activity.[1]

As structural analogues of traditional carbohydrates where the endocyclic oxygen is replaced by a nitrogen atom, their most valuable property is the ability to inhibit glycosidase and glycosyltransferase enzymes by mimicking the corresponding natural carbohydrate substrates.[2] Therefore these sugar mimics have tremendous therapeutic potential for treating a vast array of diseases, from viral infections to tumoral metastases.[3] Nowadays, some piperidine azasugar derivatives are currently in the market: two different derivatives of 1-deoxynojirimycin: miglitol (Glyset®), a drug for treating type II diabetes mellitus,[4] and miglustat (Zavesca®) used for the treatment of Gaucher disease[5] and the 1-deoxygalactonojirimycin (migalastat-Galafold™)[6], a drug for the treatment of Fabry disease,[7] a rare genetic disorder.

Their low natural abundance has led to an increasing interest in their synthesis. Most of the syntheses reported to date make use of carbohydrates as precursors, due to their structural similarity.[8] Fewer syntheses start from linear molecules, and those often make use of the dihydroxylation reaction to generate new stereocenters.[9] Recently, we reported a study on double stereodifferentiation in the asymmetric dihydroxylation (AD) of optically active olefins.[10]

As already described by other authors,[11,12] the intrinsic diastereoselection of the substrate, due to its capability to interact with osmium tetroxide, and the chiral ligand effect can be combined in order to exalt the intrinsic stereofacial preference of the reaction (matched conditions) or even to override it, thereby obtaining the naturally less favoured product as the major one (mismatched conditions).[13] In our studies, among the tested cases, the most interesting results were obtained on trans α,β-unsaturated epoxy

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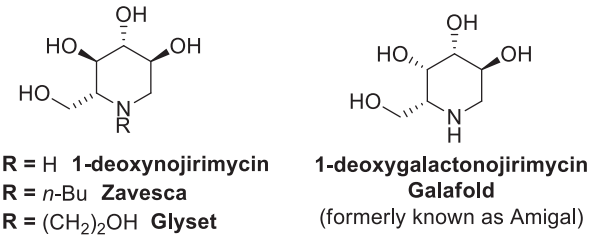


Figure 1. Piperidine Iminosugars

esters, which were successfully converted in the corresponding diols, through a matched or mismatched pathway, depending on the ligand used, with a considerable diastereomeric control (>80%). The molecules obtained, containing four adjacent stereogenic centers, could be further elaborated giving access to amino poly-alcoholic fragments, common motifs in many natural occurring and biologically active compounds, such as iminosugars.

We have previously reported the preparation of 1-deoxyaltronojirimycin[14] exploiting the intrinsic diastereoselection of the dihydroxylation of optically active *trans* α,β-unsaturated epoxy ester **7**, without considering the ligand's effect on the diastereocontrol of the reaction, which was still being studied. The synthetic pathway was the same as that described in route a of scheme 2, except for the selectivity obtained in the AD of **7**, significantly enhanced in the approach here described (from 60:40 to >95:5, Table 1).

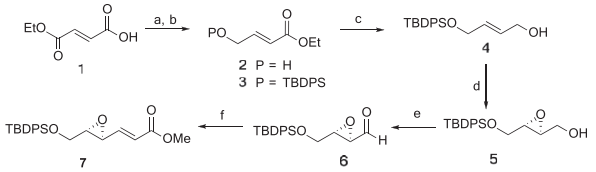
2. Results and discussions

Here, we report a stereodivergent synthesis, which, starting from the α,β-unsaturated epoxy ester **7**, allows preparation of 1-deoxynojirimycin or 1-deoxyaltronojirimycin simply by changing the ligand used in the asymmetric dihydroxylation reaction of the double bond of **7**.

Compound **7** was prepared from a suitable optically active 2,3-epoxy alcohol **5**, easily obtained from the commercially available fumaric acid monoethyl ester **1**,[15] which was first transformed in the (*E*)-ethyl 4-hydroxybut-2-enoate **2** by using $BH_3 \cdot DMS$. After converting **2** in the corresponding *tert*-butyldiphenylsilyl ether **3**, the DIBAL reduction furnished **4**, finally subjected to the Sharpless asymmetric epoxidation (AE) to give the epoxy alcohol **5**. The oxidation to aldehyde of **5**, followed by a Horner-Emmons reaction, afforded the corresponding *trans* α,β-unsaturated epoxy ester **7**, substrate of choice for the dihydroxylation reaction (Scheme 1).

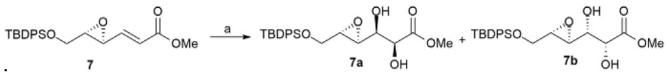
As observed previously, the dihydroxylation reaction without chiral ligand on substrate 7 led to a poor diastereomeric ratio (60:40). Considering that sometimes one ligand gives excellent results in the matched case, unlike its pseudoenantiomer in the mismatched case, we decided to perform the AD on substrate 7 using the most common second-generation *Cinchona* alkaloids (Table 1).

As expected, the ligand effect added to that of the stereogenic center, gave in all cases (except for entry 7) a double



Scheme 1. Preparation of epoxy ester 7

Table 1
Cinchona ligands catalyzed AD reaction.



a) OsO_4 (5%), NMO, acetone/H_2O 8:1, ligand

	Ligand	7a/7b[a]	
1	-	60:40	
2	$(DHQD)_2PHAL$	90:10	*matched*
3	$(DHQ)_2PHAL$	23:77	*mismatched*
4	$(DHQD)_2AQN$	>95:5	*matched*
5	$(DHQ)_2AQN$	14:86	*mismatched*
6	$(DHQD)_2PYR$	88:12	*matched*
7	$(DHQ)_2PYR$	50:50	

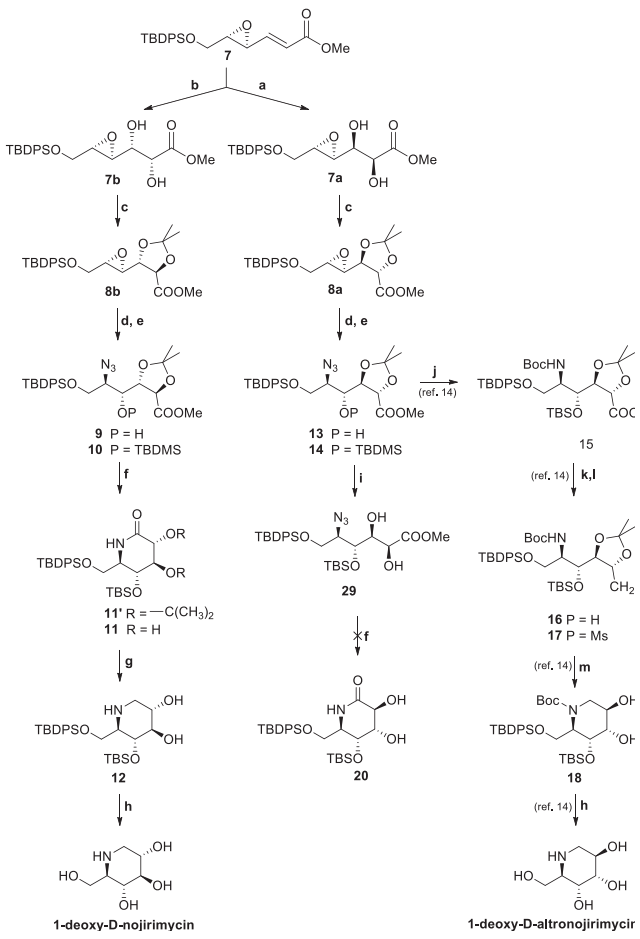
[a] Chromatographically inseparable mixtures. The ratio has been calculated by integration of the signals of the CHOH in α of the ester moiety on the ^1H NMR spectra of the crude mixture. The correct stereochemistry was assigned comparing the data of the final iminosugar with those reported in the literature[16]

diastereoselection: using the dihydroquinidine derivatives it was possible to greatly increase the diastereomeric ratio in favour of the natural diastereomer (matched reaction), whereas the dihydroquinine ones were able to override intrinsic diastereofacial preference (mismatched reaction) with very good d.r. This result is noteworthy because the enhancement, as well as the natural stereoselectivity inversion in AD, depending on the employed ligand, is not easily achievable on any chiral olefin.[17] In particular, the better results were obtained using anthraquinone core ligands (entry 4 and 5). Therefore, $(DHQD)_2AQN$ was the ligand of choice for *route b* (towards the 1-deoxy-D-altronojirimycin) and $(DHQ)_2AQN$ that for *route a* (towards the 1-deoxy-D-nojirimycin) (Scheme 2). The inseparable mixtures of diols, obtained from the AD of 7 catalyzed by the appropriate ligand, $(DHQD)_2AQN$ and $(DHQ)_2AQN$, were separately subjected to the same synthetic pathway until the compounds **10** and **14**.

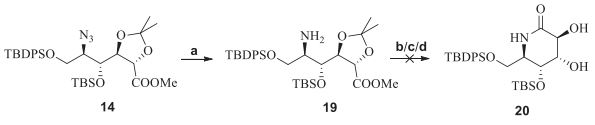
In order to provide good regioselectivity in the further azidolysis and protect the diolic moieties, the different mixtures of diols (**7a/7b** 14:86, *route b* and **7a/7b** >95:5, *route a*) in the corresponding acetonides were transformed.[18] The subsequent azidolysis of the epoxide ring was performed on the diastereomeric acetonide mixtures. The use of the system NaN_3/NH_4Cl in methanol at 70 °C[19] enabled the regioselective attack of C-5 (Scheme 2) and the chromatographic purification of the crudes allowed separation of the major diastereoisomer (**9** or **13**) from the minor one. The hindered alcoholic moiety of **9** and **13** was efficiently protected as tert-buthyldimethylsilyl ether employing tert-buthyldimethylsilyl ether triflate/2,6 lutidine[20] to produce **10** and **14**. The reduction of azide moiety and subsequent ring closure on the azido alcohol **10** was accomplished smoothly in a *one-pot* reaction by treatment with triphenylphosphine and water to produce the lactam **11'**. It turned into **11** through a spontaneous cleavage of the acetonide ring, probably caused by the *trans* bycyclic system tension. The subsequent amide reduction was carried out using borane—dimethyl sulfide to generate the corresponding piperidine **12**. Unfortunately, the same *one-pot* sequence failed on the azido alcohol **14**. Indeed, in these conditions only the reduction product **19** was isolated, and all the attempts to transform it in the lactam **20** failed (Scheme 3)[21-2.3].

According to the Staudinger reaction mechanism, it was hypothesized that the rate-determining step of the reaction is the nucleophilic intramolecular attack on the carbonyl leading to intermediates **22** and **24** (Scheme 4).

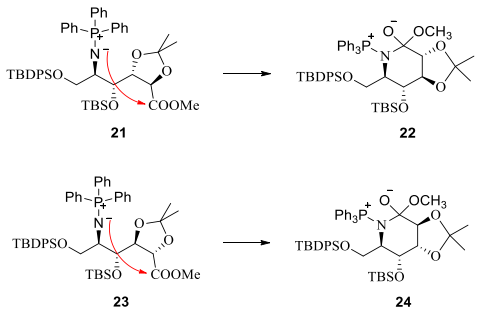
In order to find out whether the observed difference in behaviour between the ring closures of the two diastereoisomers was related to the different stabilities of **22** and **24**, Molecular Orbital



Scheme 2. Stereodivergent synthesis of 1-deoxy-D-nojirimycin and 1-deoxy-D-altronojirimycin starting from epoxy ester 7

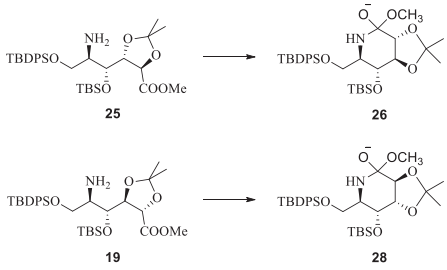


Scheme 3. Attempts to form lactam 20

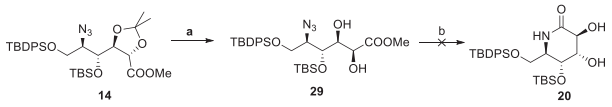


Scheme 4. Intramolecular cyclization of 21 and 23 intermediates

(MO) calculations have been carried out (see Supporting Information for computational details) on the simplified intermediates **26** and **28** (Scheme 5). The same calculations were also computed with regard to compounds **25** and **19**, which were chosen as simplified



Scheme 5. Simplified model of piperidine ring closure



Scheme 6. Attempts to form lactam 20

models of reagents **21** and **23**. Modeling of the actual reagents **21** and **23** and of the actual intermediates **22** and **24** was not carried out because the MO calculations were extremely slow (see Scheme 6).

The computational results indicated that compounds **25** and **19** have almost the same relative stabilities, **19** being more stable than **25** by just 0.13 kcal/mol. To the contrary, the stabilities of **26** and **28** are very different, the former being more stable by 7.79 kcal/mol. As hypothesized above, the ring closure of the two diastereoisomers is the rate-determing step of the reaction. In this step, the high energy intermediates **22** and **24** are formed. Therefore, according to the Hammond postulate, the transition state should have energy and structure similar to the intermediate. At this point, it is possible to estimate the relative energies of the two transition states by assuming that only 50% of the energy difference between the intermediates is found in the transition states. Consequently, the transition state for the process leading to **26** will be more stable than that leading to **28**, by 3.90 kcal/mol. Also, by taking into account the small energy difference (0.13 kcal/mol) between reagents **25** and **19**, the difference between the two activation energies (ΔEa) is 4.03 kcal/mol. This energy difference can be translated, by using the Arrhenius equation, into a reactivity ratio k25/k19 = 903. In other words, the ring closure reaction leading from **19** to **28** is about one thousand times slower than that leading from **25** to **26**. This result seems to clarify why the azido alcohol **14**, when treated with triphenylphosphine, does not undergo the ring closure reaction that should lead to compound **20**.

Hypothesizing that the presence of the acetonide ring could make lactamization more difficult, after several unsuccessful attempts at protecting the diol moiety as disilyl ether, the selective acetonide cleavage was performed. This step was not trivial, and after numerous trials the use of TFA in CH_2Cl_2[24] allowed us to obtain the desired diol **29** in satisfactory yield, together with a small amount of desilylated byproducts. However, here too, the lactam formation was not observed and the *one-pot* sequence on the azide diol **29** furnished a complex mixture of inseparable products.

Considering that removal of acetonide is not sufficient to allow ring closure, the related problem may be ascribed to the steric hindrance in the lactam **20** (see Fig. 1). In fact, as shown in figure 2, in the lactam **20** the hydroxyl groups would occupy pseudoaxial positions. To the contrary, in the easily formed lactam **11** the hydroxyl groups are in the more stable pseudoequatorial positions. To overcome the ring tension issues of the lactam **20** it was necessary

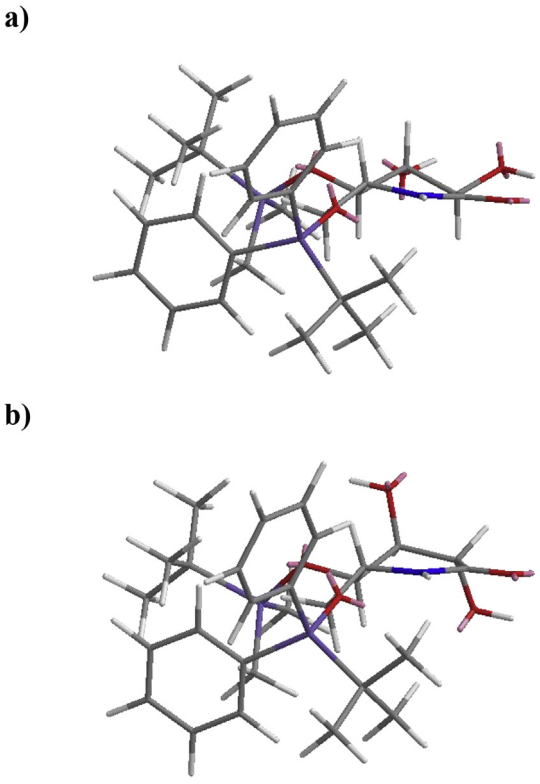


Figure 2. a) 3D model of lactam 11 b) 3D model of lactam 20

to employ a S_N2 type strategy to achieve the piperidine ring, the same one we developed.[14]

The *one pot* transformation of the azide **14** to N-(*t*-butoxycarbonyl)amine **15** was carried out for this purpose. The high yielding reduction of the ester moiety of **15** to alcohol **16** was performed with $NaBH_4$ in THF/H_2O 10:1 and, after functionalization of the alcoholic group as methanesulfonate, the closure of the piperidine ring was conducted with potassium tert-butoxide,[25] resulting in a good yield of protected 1-deoxy-D-altronojirimycin (Scheme 2). Finally, treating **12** and **18** with 37% HCl aq. in methanol at 70°C,[26] the 1-deoxy-D-nojirimycin and the (+)-1-deoxy-D-altronojirimycin were obtained as hydrochlorides in nearly quantitative yield. The iminosugars' physical data are consistent with those reported in the literature for the same compounds.[27,28,29]

3. Conclusions

In summary, the enantioselective stereodivergent approach for producing the piperidine iminosugars 1-deoxy-D-nojirimycin and 1-deoxy-D-altronojirimycin has been developed starting from a common suitable chiral vinyl epoxy ester through the double diastereoselective asymmetric dihydroxylation as the key step. Using *Cinchona* alkaloids derivatives as chiral ligands in the AD reaction, in particular $(DHQD)_2AQN$ and $(DHQ)_2AQN$, we have achieved both the *matched* and the *mismatched* pathway with excellent results. Further elaborations of the diastereomeric diols allowed isolation of the azido alcohols **10** and **14** as pure compounds, which, when submitted to different ring closure conditions, led to the synthesis of the two target iminosugars.

Note the wide applicability of the proposed approach that, simply by suitably choosing the chiral ligand in the two asymmetric reactions (AE and AD) or the nucleophile in the epoxy ring opening, provides access to different piperidine iminosugars. Halide opening of the oxirane and subsequent substitution with azide could lead, e.g., to 1-deoxy-galactonojirimycin or 1-deoxy-ido-nojirimycin. Studies pursuing these possibilities are ongoing in our laboratories.

4. Experimental section

General. Organic solvents and reagents were purchased and used without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light (254 nm) and visualisation was achieved by inspection under short-wave UV light (Mineralight UVG 11 254 nm) followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (5 g), ethanol (100 mL)] or ninhydrin dip [ninhydrin (5g), sulfuric acid (5 mL), n-butanol (100mL)] and heating. Low temperature reactions were performed in a Haake EK 101cryostat using anacetone bath. Unless otherwise stated, reactions were carried out under standard atmosphere. ^1H and ^{13}C NMR spectra were recorded using a Varian Mercury 300 (1H, 300 MHz; ^{13}C, 75 MHz), Bruker 300 (^1H, 300 MHz; ^{13}C, 75 MHz) and Bruker 400 (^1H, 400 MHz; ^{13}C, 100 MHz) instruments. Residual solvent peaks were used as internal references: chloroform (^1H, d 7.26 ppm; ^{13}C, δ 77.00 ppm), acetone (^1H, δ 2.05 ppm; ^{13}C, δ 30.83 ppm) and deuterium oxide (^1H, δ 4.79 ppm). Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard and coupling constant (*J*) in Hz. Splitting patterns are designated as s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet. Unless otherwise stated, all spectra are registered in deuterated chloroform. Optical rotations were measured with a Jasco Mod. DIP-370 polarimeter with a cell pathway length of 10 cm; solution concentrations are reported in grams per 100 mL. All chromatographic purifications were performed using forced flow on flash silica gel (Kiesegel 200–400 mesh from E. Merck, Germany). All procedures are referred to 1 mmol and the yields to isolated and spectroscopically homogeneous compounds.

Elemental analyses for C, H and N were performed on an EA 1110 CHNS-O instrument. All procedures are referred to 1 mmol and the yields to isolated and spectroscopically homogeneous compounds.

Synthetic Details. Compound **2**[30], **4**[31], **5**[32], **6**[28], and **7**[13] are known.

General Procedure A: Dihydroxylation Reaction. To a solution of 1 mmol of **7** in 9 mL of acetone/water (8:1) were added 2 mmol (270 mg) of NMO, ligand $(DHQD)_2AQN$ or $(DHQ)_2AQN$, (0.15 mmol) and 0.63 mL of a 2.5% solution of OsO_4 in tert-butanol (0.05 mmol of OsO_4). The mixture was left stirring overnight at room temperature. The reaction was then quenched with 5 mL of a saturated solution of $Na_2S_2O_3$ and the mixture left stirring for 1 h before transfer into a separating funnel. The aqueous layer was extracted with 10 mL of ethyl acetate, the combined organic layers dried over Na_2SO_4 and the solvent removed under reduced pressure.

General Procedure B: Diol protection as acetonide. 1 mmol of diols mixture (**7a**+**7b**) was dissolved in 2 ml of dichloromethane and 2 ml of 2,2-dimethoxypropane and 0.047 g of 4-toluenesulphonic acid were added and the mixture stirred at room temperature. until completion (24 h, TLC monitoring). The solvent was evaporated in vacuo and the mixture was dissolved in ethyl acetate, washed with brine and $NaHCO_3$ saturated solution until pH 7. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The crude, used without purification.

General Procedure C: Azidolysis Epoxide Ring. 1 mmol of **8a** and **8b** mixture was dissolved in 10 mL of MeOH and NaN_3 (5 mmol, 0.325 g) and NH_4Cl (2 mmol, 0.107 g) were added and the mixture

was left stirring at 70°C until complete consumption of the substrate (12 h, TLC monitoring). The mixture was filtered, concentrated in vacuo and the residue diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4 and after filtration the solvent evaporated under vacuum. The crude was purified by flash chromatography on silica gel (hexane/ethyl acetate 8:2).

General Procedure D: Hydoxyl Group Protection as Silyl Ether. In a two-neck flask under argon atmosphere 1 mmol of **9** or **13** was dissolved in 6 mL of anhydrous dichloromethane, and 2 mmol of 2,6-lutidine and 3 mmol of TBSOTf were added and the mixture stirred at room temperature. until completion (12 h, TLC monitoring). The reaction was quenched with water, the two phases were separated, and the aqueous layer was extracted twice with dichloromethane, and the combined organic layers were washed with brine and $NaHCO_3$ saturated solution until pH 7. The combined organic layers were dried over Na_2SO_4 and after filtration the solvent evaporated in vacuo. The crude was purified by flash chromatography on silica gel (hexane/ethyl acetate 95:5).

General Procedure E: Reduction with PPh_3. To a solution of azido derivative **10** or **14** (1 mmol) in THF (3 mL) was added triphenylphosphine (1 mmol, 223 mg) in one portion at 0 °C. After stirring at 0 °C for 10 min, the reaction mixture was warmed to room temperature and stirred for 48 h. Water (20 mL) was added. After stirring at room temperature for an additional 12 h, the reaction mixture was concentrated to dryness. The crude was purified by flash chromatography on silica gel (hexane/ethyl acetate 95:5).

General Procedure F: Total Deprotection. To piperidine derivatives **12** or **18** (1mmol) in MeOH (1 mL) was added HCl (37%, 1 mL) and the resultant mixture was stirred at 70 °C until complete consumption of the substrate (TLC monitoring). After cooling to room temperature, the mixture was diluted with EtOH (0.5 mL) and CH_3CN (5 mL) followed by removal of the solvents. The residual oil was purified by flash chromatography ($CHCl_3$—MeOH 1:1) to give the known iminosugars as hydrochlorides.

(E)-ethyl 4-hydroxybut-2-enoate ***2*** In a two-neck flask under argon atmosphere 27.75 mmol (4.00 g) of fumaric acid monoethyl ester **1** were dissolved in 14 mL of anhydrous THF and 27.75 mmol (2.6 mL) of $BH_3 \cdot DMS$ were slowly added at -40°C. The mixture was stirred at -40°C for 1 h, then warmed to room temperature and stirred until completion (TLC monitoring). The reaction mixture was cooled at 0°C, quenched with 17 mL of water and 6.66 g of K_2CO_3 and stirred for 15 min. THF was evaporated in vacuo, the mixture was transferred into a separative funnel with AcOEt and the aqueous layer was extracted three times with AcOEt. The combined organic layers were dried over Na_2SO_4 and after filtration the solvent evaporated in vacuo. The crude, used without purification, was subjected to protection of the alcoholic moiety as silyl ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (1H, dtd *J* 15.7, 4.0, 1.7 Hz, C<u>H</u>=CHCOOEt), 6.03 (1H, ddd, *J* 15.7, 3.8, 2.1 Hz, CH=C<u>H</u>COOEt), 4.27 (2H, bs, CH_2OH), 4.16-4.11 (2H, m, $COOC\underline{H}_2CH_3$), 3.1 (1H, bs, OH), 1.23 (3H, td, *J* 7.1, 1.5 Hz, $COOCH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, CDCl3) δ: 166.8, 147.4, 120.0, 61.6, 60.5, 14.2.

(E)-Ethyl 4-[(tert-butyldiphenylsilyl)oxy]but-2-enoate ***3*** In a round bottom flask the alcohol **2** was dissolved in 37.4 mL of CH_2Cl_2 and 41.6 mmol (10.7 mL) of tert-buthyldiphenylsilyl chloride, and 2.78 mmol (0.39 mg) of 4-(dimethylamino)pyridine (DMAP) and 19.3 mL of triethylamine were added. The mixture was stirred at room temperature for 12 hours (TLC monitoring). The reaction mixture was transferred into a separative funnel, HCl 0.1N was added, and the layers separated three times with CH_2Cl_2. The combined organic layers were washed with brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo to leave the crude, which was purified by flash chromatography on silica gel using a solvent mixture hexane/ethyl acetate 98:2 to produce the product as a yellow oil (5.93 g). Yield 58% from **1**.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72-7.66 (4H, m, Ar), 7.47-7.37 (6H, m, Ar), 7.02 (1 H, dt, *J* 15.5, 3.4 Hz, C<u>H</u>=CHCOOEt), 6.32 (1H, dt, *J* 15.5, 2.2 Hz, CH=C<u>H</u>COOEt), 4.38 (2H, dd, *J* 3.4, 2.3 Hz $C\underline{H}_2$OTBDPS), 4.25 (2H, q, *J* 7.1 Hz, $COOC\underline{H}_2CH_3$), 1.33 (3H, t, *J* 7.1 Hz, $COOCH_2C\underline{H}_3$), 1.11 (9H, s, $C(C\underline{H}_3)_3$).^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8, 146.9, 135.5, 133.1, 130.0, 127.9, 119.8, 63.0, 60.4, 26.9, 19.4, 14.4. $C_{22}H_{28}O_3Si$ (368.5): Calcd: 71.7, H 7.6 %. Found: C 71.7, H 7.7 %.

(E)-4-((tert-butyldiphenylsilyl)oxy)but-2-en-1-ol ***4*** In a three neck flask equipped with a dropping funnel under argon atmosphere, 16.09 mmol (5.93 g) of ester **3** were dissolved in 160.9 mL of dry THF and the reaction mixture was cooled at -40°C. 32.9 mL of a 25% solution of DIBAL in toluen (48.27 mmol of DIBAL) were added dropwise and the mixture was left stirring at -40°C for 12 hours (TLC monitoring). 110 mL of a saturated solution of Rochelle salt (sodium potassium tartrate tetrahydrate) were added at 0°C and stirred for 8 hours. THF was evaporated in vacuo, the mixture was transferred into a separative funnel with AcOEt and the aqueous layer was extracted four times with AcOEt. The combined organic layers were dried over Na_2SO_4 and after filtration the solvent evaporated in vacuo. The crude was purified by flash chromatography on silica gel (hexane/ethyl acetate 9:1) giving the product **4** (4.31 g). Yield 82%

^{1}H NMR (400 MHz, $CDCl_3$) δ:7.73—7.65 (4H, m, Ar), 7.46-7.34 (6H, m, Ar), 5.97-5.87 (1H, m, $CH_2C\underline{H}$=CH CH_2), 5.84-5.74 (1H, m, CH_2CH=C<u>H</u> CH_2), 4.25-4.23 (2H, m, TBDPSOC<u>H</u>$_2$), 4.16-4.14 (2H, m, $CHC\underline{H}_2OH$), 1.74 (1H, bs, OH), 1.09 (9H, s, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6, 133.7, 130.6, 129.8, 129.0, 127.8, 63.9, 63.2, 26.9, 19.3.

((2S,3S)-3-(((tert-butyldiphenylsilyl)oxy)methyl)oxiran-2-yl) methanol ***5*** In a three-neck flask equipped with a dropping funnel under argon atmosphere, 1.32 g of activated powdered 4Å molecular sieves were dissolved in 74.5 mL of dry CH_2Cl_2. The flask was cooled to -20 °C. 0.41 mL (2.37 mmol) of (+)-Diethyl L-tartrate, 0.59 mL (1.98 mmol) of Titanium(IV) isopropoxide. The reaction mixture was stirred at -20 °C as 4.81 mL of a tert-Butyl hydroperoxide solution 5.5 M in decane (26.38 mmol of *t*-BuOOH) were added through the addition funnel at a moderate rate (over ca. 5 min). The resulting mixture was stirred at -20 °C for 30 min. Allylic alcohol **4** (4.31 g, 13.19 mmol,), dissolved in 5.68 mL of CH_2C1_2, was then added dropwise through the same addition funnel over a period of 5 min, being careful to maintain the reaction temperature between -20 and -15 °C. The reaction mixture was left stirring for 8 hours (TLC monitoring). A freshly prepared solution of 9.21 g of ferrous sulfate heptahydrate and 8.68 g of tartaric acid in a total volume of 55.1 mL of deionized water is cooled to ca. 0 °C, by means of an ice water bath. The epoxidation reaction mixture was allowed to warm to ca. 0 °C and then was slowly poured into a beaker containing the precooled stirring ferrous sulfate solution (external cooling is not essential during or after this addition). The two-phase mixture was stirred for 5-10 min and then transferred into a separatory funnel. The phases were separated and the aqueous phase was extracted with ether. The combined organic layers were treated with 2.8 mL of a precooled (0 °C) solution of 30% NaOH (w/v) in saturated brine. The two-phase mixture was stirred vigorously for 1 h at 0 °C. Following transfer to a separatory funnel and dilution with water, the phases were separated and the aqueous layer was extracted with ether. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude was purified by flash chromatography on silica gel (hexane/ethyl acetate 6:4) affording epoxy alcohol **5** in 87% yield (3.93 g). $[\alpha]^{23}_D$= -13.8° (*c* 5.4, $CHCl_3$). ^{1}H NMR (300 MHz $CDCl_3$) δ: 7.71-7.68 (4H, m, Ar), 7.45-7.40 (6H, m,

Ar), 3.95-3.88 (2H, m, CH_2OH), 3.79 (1H, dd, *J* 12.3, 4.3 Hz, TBDPSOCHaHb), 3.62 (1H, dd, *J* 12.5, 4.3 Hz, TBDPSOCHaHb), 3.21-3.16 (1H, m, OCHCH$_2$OH), 3.13-3.08 (1H, m, TBSPSOCH$_2$CHO), 2.18 (1H, bs, OH), 1.07 (9H, s, C(CH_3)$_3$). ^{13}C NMR (75 MHz, CDCl3) δ: 135.7, 135.6, 133.3, 129.9, 127.9, 63.3, 61.4, 55.9, 55.8, 26.7, 19.2.

(2R,3S)-3-(((tert-butyldiphenylsilyl)oxy)methyl)oxirane-2-carbaldehyde ***6*** In a round bottom flask 11.48 mmol (3.93 g) of epoxy alcohol **5** were dissolved in 11.5 mL of CH_2C1_2. 1.15 mmol (179 mg) of TEMPO (2,2,6,6-Tetramethylpiperidinyloxy), and 12.63 mmol (4.07 g) of DIAB (Iodobenzene I,I-diacetate) were added. The mixture was stirred at room temperature for 2 hours (TLC monitoring). The reaction mixture was transferred into a separative funnel with CH_2Cl_2 and washed with a saturated solution of $Na_2S_2O_3$. The aqueous layer was extracted three times with CH_2Cl_2, the combined organic layers were washed with brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude was used without chromatographic purification. ^{1}H NMR (300 MHz, CDCl3) δ: 9.14 (1H, d, *J* 6.1 Hz, CHO), 7.83-7.70 (4H, m, Ar), 7.55-7.45 (6H, m, Ar), 3.99 (1H, dd, J 12.2, 1.9 Hz, TBDPSOCH$_2$-CHOCH), 3.90 (1H, dd, *J* 12.2, 4.3 Hz, TBDPSOCH$_2$CHOCH), 3.52-3.42 (2H, m, TBDPSOCH$_2$CHO), 1.16 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.2, 137.5, 135.6, 130.3, 130.0, 127.9, 61.9, 56.6, 56.2, 26.7, 19.3.

(E)-methyl 3-((2S,3S)-3-(((tert-butyldiphenylsilyl)oxy)methyl) oxiran-2-yl)acrylate ***7*** In a round bottom flask aldehyde **6** was dissolved in 29.4 mL of THF. 12.97 mmol (311 mg) of LiOH and 12.97 mmol (2.36 g) of TMPA (trimethylphosphonoacetate) were added. The mixture was stirred at room temperature for 12 hours (TLC monitoring). A saturated solution of NH_4Cl was added and the mixture was left stirring for 10 minutes. THF was evaporated in vacuo and the mixture was transferred into a separative funnel with AcOEt. The reaction mixture was transferred in a separative funnel, the phases are separated and the aqueous phase is extracted with AcOEt. the combined organic layers were washed with brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude was purified by flash chromatography on silica gel (hexane/ethyl acetate 98:2). Yield 77% from **5** (3.50 g). $[\alpha]^{23}_D$= -9.2° (*c* 3.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76-7.63 (4H, m, Ar), 7.47-7.36 (6H, m, Ar), 6.69 (1H, dd, *J* 15.7, 7.1 Hz, CH=CHCOOCH$_3$), 6.13 (1H, d, *J* 15.7 Hz, CH=CHCOOCH$_3$), 3.87-3.83 (2H, m, TBDPSOCH$_2$), 3.76 (3H, s, COOCH$_3$), 3.38 (1H, dd, *J* 7.1, 1.4 Hz, OCHCH=CH), 3.12-3.06 (1H, m, CHOCHCH=CH), 1.07 (9H, s, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.0, 144.4, 135.6, 135.5, 133.0, 132.9, 129.9, 127.8, 123.5, 62.9, 60.9, 53.8, 51.7, 26.7, 19.2. (2R,3R)-Methyl 3-{(2S,3S)-3-[(tert-butyldiphenylsilyl) oxymethyl] oxiran-2-yl}-2,3-dihydroxypropanoate **7A** and (2S,3S)-Methyl 3-{(2S,3S)-3-[(tert-butyldiphenylsilyl) oxymethyl]oxiran-2-yl}-2,3-dihydroxypropanoate **7B**.

Compound **7** was subjected to asymmetric dihydroxylation reaction according to **General Procedure A.** Diols **7a** and **7b** are obtained as chromatographically inseparable mixtures. The ratio has been calculated by integration of the signals of the CHOH in α of the ester moiety on the ^{1}H NMR spectra of the crude mixture. **7b** (data given for the inseparable mixture **7b/7a** 86:14): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68-7.66 (4H, m, Ar), 7.43-7.37 (6H, m, Ar), 4.26 (1H, d, *J* 2,3 Hz, CHOH-COOMe), 3.97-3.91 (1H, d, *J* 3,1 Hz, CHOH-CHOH), 3.83-3.68 (7H, m, CH$_2$OTBDPS, COOCH$_3$, OH, OH), 3.18-3.11 (2H, m, CH*ep*), 1.05 (9H, s, CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.9; 135.6; 134.8; 129.8, 129.6. 127.8, 127.7; 72.4; 70.2; 63.1; 55.6; 55.0; 53.1; 26.7; 19.6. **7a** (data given for the inseparable mixture **7a/7b** 90:10):^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72-7.70 (4H, m, Ar), 7.44-7.37 (6H, m, Ar), 4.38 (1H, d, *J* 3,5 Hz, CHOH-COOMe), 4.00-3.93 (2H, m, CHOH-CHOH, OH), 3.80-3.70 (5H, m, CH$_2$OTBDPS, COOCH$_3$), 3.37 (bs, 1H, OH), 3.33-3.29 (1H, m, CH*ep*), 3.20 (dd, 1H, *J* 5,0, 1,8 Hz, CH*ep*), 1.08 (9H, s, CH_3).^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.2; 135.6; 135.5, 133.2, 133.1, 129.8, 127.8; 71.7; 71.4; 63.3; 57.3; 55.0; 52.7; 26.8; 19.2.

(4R,5S)-Methyl 5-[(1R,2R)-2-azido-3-(tert-butyldiphenylsilyl)oxy-1-hydroxypropyl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate ***9*** *and (4S,5R)-Methyl-5-((1R,2R)-2-azido-3-[(tert-butyldiphenylsilyl)oxy-1-hydroxypropyl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate* ***13.*** Diols mixture (**7a:7b > 95:5, 7b:7a 86:14)** was subjected to diols protection reaction as acetonide according to **General Procedure B**. The crude, used without purification, was subjected to azidolysis of the epoxy ring according to **General Procedure C** to give **9** (55% from **7,** 2.42 g) and **13** (61% from **7,** 2.69 g) as yellow oils. **9**: $[\alpha]^{23}_D$= -25.2° (c 3.1, $CHCl_3$); IR (neat) ν cm^{-1} 3470, 3074, 3050, 2940, 2869, 2010, 1720, 1209, 1154; ^{1}H NMR (400 MHz $CDCl_3$) δ: 7.74-7.72 (4H, m, Ar), 7.46-7.40 (6H, m, Ar), 4.58 (1H, d, *J* 7.7 Hz, OCHCOOCH$_3$), 4.43 (1H, d, *J* 7.7, CHOCHOCOOCH$_3$), 4.09 (1H, dd, *J* 10.8, 3.0 Hz, OCH$_a$H$_b$CHN$_3$), 3.95 (1H, dd, *J* 10.8, 6.1 Hz, OCH$_a$H$_b$CHN$_3$), 3.81-3.71 (4H, m, COOCH$_3$, CHOH), 3.49-3.41 (1H, m, CHN$_3$), 2.29 (1H, bd, *J* 9.5 Hz, OH) 1.49 (3H, s, CH$_3$CCH$_3$), 1.47 (3H, s, CH$_3$CCH$_3$), 1.11 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3, 136.0, 136.0, 133.1, 133.1, 130.3, 130.2, 128.2, 128.1, 112.0, 78.3, 75.4, 68.9, 65.2, 64.6, 52.9, 27.1, 27.0, 26.0, 19.5. $C_{25}H_{32}N_3O_6Si$ (498.6): Calcd: C 60.2, H 6.5, N 8.4 %. Found: C 60.3, H 6.7, N 8.7 %. **13**: $[\alpha]^{23}_D$= -9.6° (c 1.1, $CHCl_3$); IR (neat) ν cm^{-1} 3475, 3065, 3050, 2940, 2858, 2095, 1730, 1209, 1154; ^{1}H NMR (300 MHz $CDCl_3$) δ: 7.73-7.69 (4H, m, Ar), 7.44-7.41 (6H, m, Ar), 4.55 (1H, d, *J 6.6* Hz, OCHCOOCH$_3$), 4.42 (1H, dd, *J* 6.6, 4.4 Hz, CHOCHOCOOCH$_3$), 4.04 (1H, dd, *J* 10.9, 3.3 Hz, OCH$_a$H$_b$CHN$_3$), 3.92 (1H, dd, *J* 10.9, 6.1 Hz, OCH$_a$H$_b$CHN$_3$), 3.87 (1H, dd, *J* 7.9, 4.4 Hz, CHOH), 3.83 (3H, s, COOCH$_3$), 3.63 (1H, ddd, J_1=J_2 7, 3.3 Hz, CHN$_3$), 2.62 (1H, d, *J* 4.0 Hz, OH) 1.45 (3H, s, CH$_3$CCH$_3$), 1.41 (3H, s, CH$_3$CCH$_3$), 1.09 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.8, 135.6, 129.9 127.8, 111.4, 79.2, 75.0, 70.4, 64.5, 63.4, 52.7, 26.8, 26.7, 25.4, 19.1. $C_{25}H_{32}N_3O_6Si$ (498.6): Calcd: C 60.2, H 6.5, N 8.4 %. Found: C 60.4, H 6.6, N 8.7 %.

(4R,5R)-Methyl 5-[(5R,6R)-6-azido-2,2,3,3,10,10-hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate **10** and (4S,5S)-Methyl-5-[(5R,6R)-6-azido-2,2,3,3,10,10-hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate **14**.

Compounds **9** and **13** were subjected to hydroxyl group protection as silyl ether according to **General Procedure D** to give **10** (76% from **9,** 2.32 g) and **14** (76% from **13,** 2.57 g) as yellow oils. **10:** $[\alpha]^{23}$D= -28.2° (c 3.7, $CHCl_3$); IR (neat) ν cm^{-1} 3038, 2935, 2860, 2116, 1755, 1201, 1150**;** ^{1}H NMR (300 MHz $CDCl_3$) δ: 7.74-7.66 (4H, m, Ar), 7.50-7.35 (6H, m, Ar), 4.44 (1H, d, *J* 7.5 Hz, OCHCOOCH$_3$), 4.28 (1H, dd, *J* 7.5, 3.6 Hz, CHOCHOCOOCH$_3$), 4.04 (1H, dd, *J* 10.3, 3.1 Hz, OCH$_a$H$_b$CHN$_3$), 3.87-3.63 (6H, m, OCH$_a$H$_b$CHN$_3$, COOCH$_3$, CHN$_3$, CHOTBS), 1.40 (3H, s, CH$_3$CCH$_3$), 1.10 (9H, s, (CH$_3$)$_2$SiC(CH$_3$)$_3$), 0.77 (9H, s, Ph$_2$SiC(CH$_3$)$_3$), 0.04 (3H, s, CH$_3$SiCH$_3$), -0.07 (3H, s, CH$_3$SiCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.2, 135.6, 133.0, 132.9, 129.8, 127.7, 111.1, 80.1, 74.9, 72.0, 66.1, 65.2, 52.5, 26.7, 26.6, 25.8, 25.7, 19.1, 18.1, -4.3, -4.6. $C_{32}H_{49}N_3O_6Si_2$ (627.9): Calcd: C 61.2, H 7.9, N 6.7 %. Found: C 61.4, H 8.0, N 6.9 %. **14**: $[\alpha]^{23}_D$= -11.3° (c 2.3, $CHCl_3$); IR (neat) ν cm^{-1} 3042, 2928, 2860, 2110, 1755, 1210, 1150; ^{1}H NMR (300 MHz $CDCl_3$) δ: 7.71-7.70 (4H, m, Ar), 7.45-7.36 (6H, m, Ar), 4.56 (1H, d, *J* 6.7 Hz, OCHCOOCH$_3$), 4.48 (1H, dd, *J* 6.7, 2.7 Hz, CHOCHOCOOCH$_3$), 3.93-3.62 (7H, m, OCH$_a$H$_b$CHN$_3$, OCH$_a$H$_b$CHN$_3$, COOCH$_3$, CHN$_3$, CHOTBS), 1.47 (3H, s, CH$_3$CCH$_3$), 1.39 (3H, s,

CH_3CCH_3), 1.10 (9H, s, $(CH_3)_2SiC(CH_3)_3$), 0.79 (9H, s, $Ph_2SiC(CH_3)_3$), 0.06 (3H, s, CH_3SiCH_3), -0.09 (3H, s, CH_3SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.9, 135.6, 132.9, 129.8, 127.8, 110.7, 79.1, 74.5, 71.3, 66.2, 65.0, 52.4, 26.7, 26.6, 25.7, 25.2, 19.1, 17.9, -4.3, -4.5. $C_{32}H_{49}N_3O_6Si_2$ (627.9): Calcd: C 61.2, H 7.9, N 6.7 %. Found: C 61.4, H 8.0, N 6.9 %.

(3*R*,4*R*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyl)oxy-6-[(*tert*-butyldiphenylsilyl)oxymethyl]-3,4-dihydroxypiperidin-2-one **11** and (4*S*,5*S*)-Methyl 5-[(5*R*,6*R*)-6-amino-2,2,3,3,10,10-hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate **19.** The azido derivatives **10** and **14** were subjected to the azide reduction reaction with PPh_3 according to **General Procedure E** to give **11** as colorless oil, yield 85% (1.66 g), and **19** as yellow oil, yield 78% (1.92 g). (The cleavage of acetonide ring in compound **11** occurred spontaneously, see Supporting Info.). **11**: $[\alpha]^{23}_D$= -17.1° (c 1.1, $CHCl_3$) IR (neat) ν cm^{-1} 3463, 3285, 3073, 3038, 1690, 1460, 1250, 1150 ^1H NMR (400 MHz $CDCl_3$) δ: 7.68-7.57 (4H, m, Ar), 7.50-7.32 (6H, m, Ar), 6.07 (1 H, bs NH), 3.91-3.84 (2H, m, $C6H_aH_b$, C2HOH), 3.73 (1H, dd, J_1=J_2=8.6 Hz, C3HOH), 3.59 (1H, dd J_1=J_2=8.6 Hz, C4HOTBS), 3.53 (1H, dd, J_1=J_2=8.8 C6-H_aH_b), 3.43-3,36 (1 H, m, C5HNH), 3.27 (1 H, bs, OH), 1.06 (9H, s, $(CH_3)_2SiC(CH_3)_3$), 0.74 (9H, s, $Ph_2SiC(CH_3)_3$), 0.09 (3H, s, CH_3SiCH_3), -0.12 (3H, s, CH_3SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ:171.1, 135.5, 135.4, 132.6, 130.1, 130.0, 128.0, 127.9, 74.4, 70.9, 70.4, 65.1, 58.3, 26.8, 25.7, 19.2, 18.1, -3.8, -5.1. $C_{28}H_{43}NO_5Si_2$ (529.8): Calcd: C 63.5, H 8.2, N 2.6 %. Found: C 63.6, H 8.3, N 2.9 %. **19**: IR (neat) ν cm^{-1} 3400, 3070, 2855, 1750, 1252, 1150; ^1H NMR (400 MHz $CDCl_3$) δ: 7.68-7.63 (4H, m, Ar), 7.45-7.34 (6H, m, Ar), 4.55 (2H, m, CHOCHOCOOCH$_3$), 3.94-3.92 (1H, m, CHOTBS), 3.81-3.73 (4H, $OCH_aH_bCHN_3$, $COOCH_3$, CHN_3,), 3.56 (1H, dd, J_1 10.0, J_2 8.2, $OCHaHbCHN_3$), 3.10 (1H, dt, J 8.1, J 5.2 Hz, $CHNH_2$) 1.44 (3H, s, CH_3CCH_3), 1.36 (3H, s, CH_3CCH_3), 1.08 (9H, s, $(CH_3)_2SiC(CH_3)_3$), 0.83 (9H, s, $Ph_2SiC(CH_3)_3$), 0.07 (3H, s, CH_3SiCH_3), -0.04 (3H, s, CH_3SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.6, 135.9, 135.9, 133.8, 133.7, 130.0, 128.0, 110.3, 79.2, 74.9, 73.0, 66.2, 56.6, 52.5, 27.2, 26.8, 26.2, 25.5, 19.6, 18.3, -3.8, -4.2. $C_{32}H_{51}NO_6Si_2$ (601.9): Calcd: C 63.85, H 8.5, N 2.3 %. Found: C 64.0, H 8.7, N 2.5 %.

(3S,4R,5R,6R)-5-[(tert-Butyldimethylsilyl)oxy-6-(tert-butyldiphenylsilyl)oxymethyl]-piperidine-3,4-diol **12.** To a solution of **11** (3.14 mmol) in dry THF (13.6 mL) was added BH_3.DMS (12.56 mmol, 1.1 mL) at 0 °C. After stirring under nitrogen at room temperature until complete consumption of the substrate (TLC monitoring), the reaction was quenched by cautiously adding methanol until gas evolution ceased. Additional methanol was added and the solvents were evaporated. The residue was dissolved in methanol and 2 N HCl was added to the solution. The mixture was refluxed for 10 min and, after cooling, the solution was evaporated and the pH was adjusted to 11–12 with a 15% sol of NH_4OH. The solution was evaporated and the residue purified by flash chromatography on silica gel ($CHCl_3$/CH_3OH 98:2) to afford **12** as colorless oil (1.10 g). Yield: 68%. IR (neat) ν cm^{-1} 3358, 3068, 2953, 2864, 1460, 1250, 1105; ^1H NMR (400 MHz $CDCl_3$) δ: 7.65-7.61 (4H, m, Ar), 7.42-7.37 (6H, m, Ar), 3.93 (1H, dd, J 9.7, 3.0 Hz, $C6H_aH_b$), 3.53 (2H, m, $C6H_aH_b$, C2HOH), 3.22 (3H, m, $C1H_aH_bNH$, C3HOH, C4HOTBS,), 2.64 (1H, ddd, J 11.3, 8.4, 2.9 Hz, C5HNH), 2.56 (1H, dd, J_1=J_2=10 Hz, $C1H_aH_b$), 1.07 (9H, s, $(CH_3)_2SiC(CH_3)_3$), 0.71 (9H, s, $(Ph_2SiC(CH_3)_3$), 0.03 (3H, s, CH_3SiCH_3), -0.21 (3H, s, CH_3SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6, 135.5, 133.2, 129.7, 127.7, 80.1, 73.6, 71.4, 65.3, 62.2, 49.6, 26.9, 25.8, 19.3, 18.0, -3.7, -4.9. $C_{28}H_{45}NO_4Si_2$ (518.8): Calcd: C 65.2, H 8.8, N 2.7 %. Found: C 65.4, H 9.0, N 2.9 %.

1-Deoxy-D-nojirimycin. Compound **12** was subjected to a total deprotection reaction according to **General Procedure F** to give the known iminosugar as hydrochloride (90% yield, 383 mg). ^1H NMR (400 MHz D_2O) δ: 3.99 (1H, dd, J 12.7, 3.1 Hz, $C6H_aH_b$), 3.91 (1H, dd, J 12.7, 5.1 Hz, $C6H_aH_b$) 3.82 (1H, ddd, J 11.9, 9.3, 5.1 Hz, C2HOH), 3.64 (1H, dd, J_1=J_2=9.3 Hz, C4HOH), 3.59-3.51 (2H, m, $C1H_aH_b$, C3HOH), 3.25 (1H, ddd, J 9.3, 5.1, 3.1 Hz, C5HNH) 3.01 (1H, dd, J_1=J_2=11.9 Hz, $C1H_aH_b$); ^{13}C NMR (100 MHz, D_2O) δ: 76.4, 68.0, 67.2, 60.2 (C-6), 57.9 (C-5), 46.1 (C-1).[33,34] mp= 201-203 °C; $[\alpha]^{25}_D$= +38.8° (*c* 0.7, H_2O), (lit.[35] mp: 200-202 °C; $[\alpha]^{23}D$= +36.9° (*c* 1.1, H_2O)); $C_6H_{14}ClNO_4$ (199.6): Calcd: C 36.1; H 7.1; N 7.0 %. Found C 36.4; H 7.4; N 7.4 %. (2S,3S,4R,5R)-Methyl 5-azido-4-[(tert-butyldimethylsilyl)oxy]-6-[(tert-butyldiphenylsilyl)oxy]-2,3-dihydroxyhexanoate **29**.

TFA (14.7 mL) was added to a cooled (0°C) solution of **14** (4.10 mmol) in CH_2Cl_2 (131 mL) and the mixture was left stirring at 0°C until completion (TLC monitoring). The reaction mixture was diluted with CH_2Cl_2, and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The crude was purified by flash chromatography on silica gel using a solvent mixture hexane/ethyl acetate 80:20 affording **29** in 52% yield (1.25 g). IR (neat) ν cm^{-1} 3080, 2980, 2870, 2100, 1710, 1250, 1150; ^1H NMR (400 MHz CDCl3) δ: 7.71- 7.66 (4H, m, Ar), 7.47-7.37 (6H, m, Ar), 4.39 (1H, d, J 0.9 Hz, CHOHCO), 4.00-3.92 (2H, m, CHOH, CHOTBS), 3.91-3.84 (2H, m, CHN_3, OCH_aH_b) 3.84-3.76 (4H, m, OCH_aH_b, OCH_3), 1.07 (9H, s, $(CH_3)_2SiC(CH_3)_3$), -0.85 (9H, s, $(Ph_2SiC(CH_3)_3$), -0.09 (6H, s, CH_3SiCH_3). ^{13}C NMR (100 MHz, CDCl3) δ 174.4, 135.8, 135.7, 133.0, 132.9, 130.0, 128.0, 72.5, 72.4, 70.0, 67.2, 63.6, 53.0, 26.8, 26.0, 19.2, 18.2, -4.0, -5.1.

$C_{29}H_{45}N_3O_6Si_2$ (587.85): Calcd: C 59.25, H 7.7, N 7.15 %. Found: C 59.5, H 7.8, N 7.3 %.

(4S,5S)-Methyl 5-[(5R,6R)-6-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2,3,3,10,10-hexamethyl-8-oxo-4,9-dioxa-7-aza-3-silaundecan-5-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate ***15****.* 4.10 mmol (2.57 g) of **14** were dissolved in 8.2 mL of ethyl acetate and 4.51 mmol (984 mg) of $(Boc)_2O$ were added, and the mixture was left stirring under H_2 atmosphere (1 atm) at room temperature until completion (6 h, TLC monitoring). The reaction mixture was filtered through a pad of celite and the solvent was evaporated in vacuo. The product was used without chromatographic purification. Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66-7.62 (4H, m, Ar), 7.42-7.33 (6H, m, Ar), 5.31 (1H, d, J 8.2 Hz, NH), 4.71 (1H, d, J 5.8 Hz, CHOCOOCH$_3$), 4.45 (1H, dd, J_1 5.8, J_2 2.9 Hz, CHOCHOCOOCH$_3$), 4.35 (1H, dd, J_1=J_2=2.9 Hz, CHOTBS), 4.21-4.15 (1H, m, CHNHBoc), 3.77-3.61 (5H, m, $OCH_aH_bCHNHBoc$, $COOCH_3$), 1.47 (3H, s, CH_3CCH_3) 1.30-1.24 (12H, m, $NHCOC(CH_3)_3$), 1.03 (9H, s, $Ph_2SiC(CH_3)_3$) 0.80 (9H, s, $Ph_2SiC(CH_3)_3$), CH_3OSi, 0.05 (3H, s, CH_3OSi), 0.04 (3H, s, CH_3OSi). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.1, 155.7, 135.9, 135.0, 133.4, 130.0, 129.9, 128.0, 127.9, 110.9, 80.0, 75.2, 72.2, 63.6, 63.2, 54.9, 52.7, 28.6, 27.1, 26.8, 26.0, 25.3, 19.4, 18.2, -4.2, -4.4.

tert-Butyl {(5R,6R)-5-[(4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2,3,3,10,10-hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-6-yl}carbamate ***16.*** **15** was dissolved in a solution of THF/H_2O 41 mL/4.1 mL and 12.3 mmol (465 mg) of $NaBH_4$ were added; the mixture was left stirring for four hours (TLC monitoring). 61.5 mL of water were added to the reaction mixture and it was subsequently transferred into a separative funnel, the layers separated, and the aqueous one extracted three times with ethyl acetate. The combined organic layers were washed with brine and $NaHCO_3$ until pH 7, then dried over Na_2SO_4. The solvent was evaporated in vacuo to leave the crude, which was purified by flash chromatography on silica gel using a solvent mixture hexane/ethyl acetate 95:5. Yellow oil, 85% yield from **14** (2.35 g). $[\alpha]^{23}_D$= -8.2° (c 1.4, $CHCl_3$) IR (neat) ν cm-1 3450, 3312, 3060, 2960, 1662, 1423, 1112

^{1}H NMR (300 MHz $CDCl_3$) δ: 7.78-7.55 (4H, m, Ar), 7.54-7.30 (6H, m, Ar), 4.72 (1H, d, J 8.12 Hz, CHNHBoc), 4.13-3.55 (9H, m $CH_2CHNHBocCHOTBSCHOCHOCH_2OH$), 3.15 (1H, br s, CH_2OH), 1.50-1.30 (15H, m, CH_3CCH_3, $NHCOC(CH_3)_3$), 1.07 (9H, s, $Ph_2SiC(CH_3)_3$), 0.79 (9H s $(CH3)_2SiC(CH_3)_3$, 0.08 (3H, s $CH_3CH_3SiC(CH_3)_3$), 0.02 (3H, s, $CH_3CH_3SiC(CH_3)_3$). ^{13}C NMR (75 MHz, C_3D_6O) δ: 156.9, 135.7, 135.0, 130.0, 129.4, 128.0, 127.7, 108.7, 79.1, 78.6, 77.9, 73.0, 64.0, 63.4, 55.6, 30.1, 28.0, 26.8, 26.6, 26.4, 25.7, 19.1, -4.4, -4.7. $C_{36}H_{59}NO_7Si_2$ (674.0): Calcd: C 64.15; H 8.8, N 2.1 %. Found C 64.3; H 9.0, N 2.2 %.

(4R,5S)-5-{[(5R,6R)-6-(tert-Butyldiphenylsilyloxymethyl)-2,2,3,3,10,10-hexamethyl-8-oxo-4,9-dioxa-7-aza-3-silaundecan-5-yl]-2,2-dimethyl-1,3-dioxolan-4-yl}methyl methanesulfonate ***17***. In a two-neck round bottom flask, under argon atmosphere, 3.49 mmol of **16** was dissolved in 104.7 mL of anhydrous CH_2Cl_2, and 4.19 mmol (0.32 mL) of MsCl, 6.98 mmol (0.97 mL) of Et_3N, and 0.03 mmol (0.004 g) of DMAP were subsequently added; the mixture was left stirring at room temperature until completion (6 h, TLC monitoring). The mixture was transferred into a separative funnel, water and ice were added, the layers were separated, and the organic one was washed with HCl 2N and brine until pH 7, then dried over Na_2SO_4. The solvent was evaporated in vacuo to produce the crude that was used without purification. Pale yellow oil. ^{1}H NMR (300 MHz $CDCl_3$) δ: 7.68-7.59 (4H, m, Ar), 7.45-7.31(6H, m, Ar), 4.54 (1H, d, *J* 8.22 Hz, CHNHBoc), 4.24-3.53 (8H, m $CH_2CHNHBoc-CHOTBSCHOCHOCH_2OMs$), 3.02 (3H, s, $CH_2OSO_2CH_3$), 1.46 (3H, s, CH_3CCH_3), 1.43-1.40 (12H, m, CH_3CCH_3, $NHCOC(CH_3)_3$), 1.04 (9H, s, $Ph_2SiC(CH_3)_3$), 0.80 (9H s $(CH_3)_2SiC(CH_3)_3$), 0.053 (3H, s, $CH_3CH_3SiC(CH_3)_3$), 0.037 (3H, s, $CH_3CH_3SiC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.4, 135.5, 133.1, 129.7, 127.7, 127.6, 127.6, 110.1, 79.5, 77.2, 73.0, 70.3, 62.6, 55.2, 45.9, 37.5, 28.3, 27.0, 26.8, 26.7, 25.8, 20.9, 19.1, 17.9, -4.2, -4.4.

(2R,3R,4S,5R)-tert-butyl-3-[(tert-Butyldimethylsilyl)oxy]-2-{[(tert-butyldiphenylsilyl)oxy]methyl}-4,5-dihydroxypiperidine-1-carboxylate ***18***. In a two-neck round bottom flask, under argon atmosphere, compound **17** was dissolved in 69.8 mL of anhydrous THF and 6.98 mmol (783 mg) of *t*BuOK were added at 0°C and the mixture was left stirring at room temperature until completion (8 h, TLC monitoring). 5 mL of saturated solution of NH_4Cl were added to the reaction flask, the mixture was left stirring for 5 minutes, and was was transferred into a separative funnel. The layers were separated, the aqueous one extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The crude was purified by chromatography on silica gel using a solvent mixture hexane/ethyl acetate 95:5. Yellow oil. Yield 64% from **16** (1.38 g).

The room temperature NMR of **18** was complicated by the existence of carbamate rotamers.[36] $[\alpha]^{23}_D$= -13.3° (c 1.1, $CHCl_3$). IR (neat) ν cm^{-1} 3458, 3065, 2953, 2864, 1660, 1465, 1250, 1110; ^{1}H NMR (300 MHz $CDCl_3$) δ: 7.69-7.59 (4H, m, Ar), 7.50-7.35 (6H, m, Ar), 4.68-4.07 (3H, m, C2H, C3H, C4H), 3.83- 3.52 (3H, m, C6Hb, C5H, C1Ha), 3.50-3.27 (1H, m,C6Hb), 2.62-2.44 (1H, m, C1Hb), 1.45-1.40 (9H, m, $NHCOC(CH_3)_3$), 1.06 (9H, s, $Ph_2SiC(CH_3)_3$), 0.94-0.88 (9H, m, $(CH_3)_2SiC(CH_3)_3$), 0.20-0.13 (6H, m, $CH_3CH_3SiC(CH_3)_3$.^{13}C NMR (75 MHz $CDCl_3$) δ: 154.9, 154.6, 135.6, 135.5, 135.4, 133.0, 132.7, 129.9, 127.9, 127.8, 80.1, 79.8, 73.6, 73.3, 70.1, 69.9, 68.2, 67-9 61.4, 60.3, 59.6, 58.0, 44.6, 43.9, 28.3, 26.8, 25.7, 21.0, 19.1, 18.0, 14.2, -4.6, -4.9. $C_{33}H_{53}NO_6Si_2$ (615.3): Calcd: C 64.35; H 8.7, N 2.3 %. Found C 64.6; H 8.9, N 2.5 %.

1-Deoxy-D-altronojirimycin. Compound **18** was subjected to a total deprotection reaction according to **General Procedure F** to give the known iminosugar as hydrochloride (92% yield, 407 mg). ^{1}H NMR (400 MHz D_2O) δ: 4.14-4.10 (1H, m, C4HOH), 4.03-3.94 (2H, m, C2HOH, C3HOH), 3.92 (1H, dd, *J* 3.4, 12.7 Hz, C6HaH$_b$), 3.79 (1H, dd, *J* 6.8, 12.7 Hz, C6HaH$_b$), 3.39- 3.30 (2H, m, C5HNH, C1H$_a$H$_b$), 3.18 (1H, dd, *J* 2.6 13.4 Hz, C1H$_a$H$_b$); ^{13}C NMR (100 MHz, D_2O) δ: 68.4 (C-4), 66.2 (C-2), 63.6 (C-3), 58.1 (C-6), 55.8 (C-5), 43.9 (C-1).[37,38] $C_6H_{14}ClNO_4$ (199.6): Calcd: C 36.1; H 7.1; N 7.0 %. Found C 36.4; H 7.3; N 7.4 %. Mp 102-104°C, (lit.[39]103-105°C); $[\alpha]^{25}_D$= +34.1° (*c* 1.7, MeOH), (lit[40]. $[\alpha]^{25}_D$ +33.2 (c 0.5, MeOH)).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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