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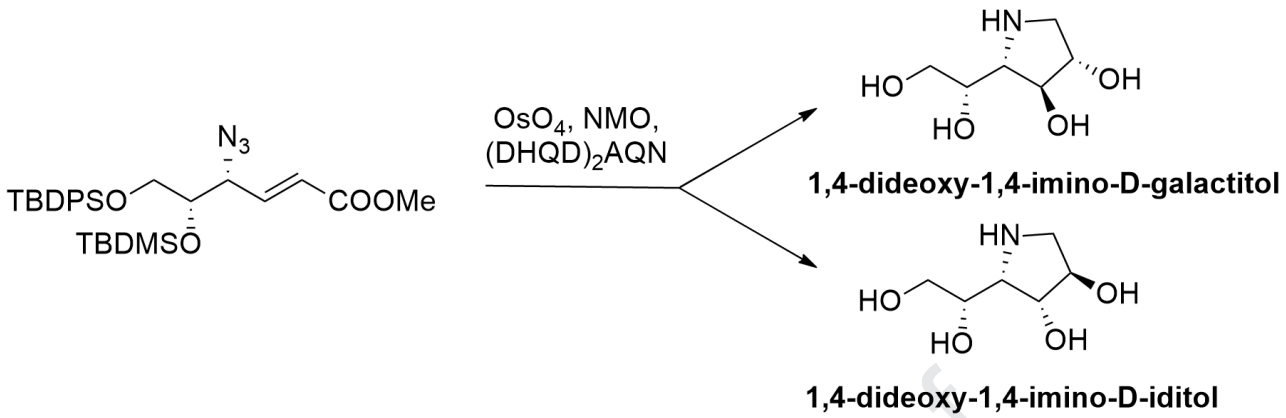

Stereocontrolled total synthesis of iminosugar 1,4-dideoxy-1,4-imino-D-iditol

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Abstract: The first stereocontrolled total synthesis of iminosugar 1,4-dideoxy-1,4-imino-D-iditol is described. The key step in our approach was the double diastereoselection in the asymmetric dihydroxylation (AD) of suitable optically active olefin, the chiral vinyl azido alcohol **9**. Performing the AD using the most common Cinchona alkaloids as ligands enabled us to identify the ligand of choice for the stereodivergent synthesis of 1,4-dideoxy-1,4-imino-D-iditol and 1,4-dideoxy-1,4-imino-D-galactitol. These type of iminosugars, both natural and unnatural, are intensively studied for their promising chemotherapeutic properties against viral infections, diabetes, cancer, and tuberculosis.

Keywords: iminosugars; 1,4-dideoxy-1,4-imino-D-iditol; 1,4-dideoxy-1,4-imino-D-galactitol; asymmetric dihydroxylation.

1. Introduction

Iminosugars, carbohydrate analogues in which the endocyclic oxygen is replaced by a nitrogen atom, are nowadays one of the most attractive class of sugar mimics because of their high glycosidase and glycosyltransferase inhibitor activity and hence their therapeutic potential in a vast array of diseases, such as diabetes, glycosphingolipid storage disorders, and viral infections (HIV, hepatitis B and C...) [1].

Among iminosugars, several five-membered pyrrolidine compounds are selective inhibitors of α- and β-glucosidases. For example, the (2*R*,5*R*)-bis(dihydroxymethyl)-(3*R*,4*R*)-dihydroxypyrrolidine, DMDP [2], the first pyrrolidine iminosugar discovered and isolated in 1976 from *Derris elliptica* [3], displays strong inhibition on glycosidases I and antiviral activity [4]. The 1-deoxy derivative of D-arabinosimine (DAB-1), isolated in 1985 from *Angylocalyx boutiqueanus*

[5], is a potent inhibitor of glycogen phosphorylase and is under study as a treatment for Type II diabetes and preventative of HIV replication. Its diastereoisomer, LAB-1, is a strong intestinal α-glucosidase inhibitor and a powerful anti-AIDS agent. The C-5 epimer of DMDP, 2,5-dideoxy-2,5-imino-D-glucitol (DGDP), recently isolated from traditional Thai folk medicine "Non tai yak" (*Stemona tuberosa*) [6], exhibited broad-spectrum inhibition against α- and β-glucosidases and α-mannosidases.

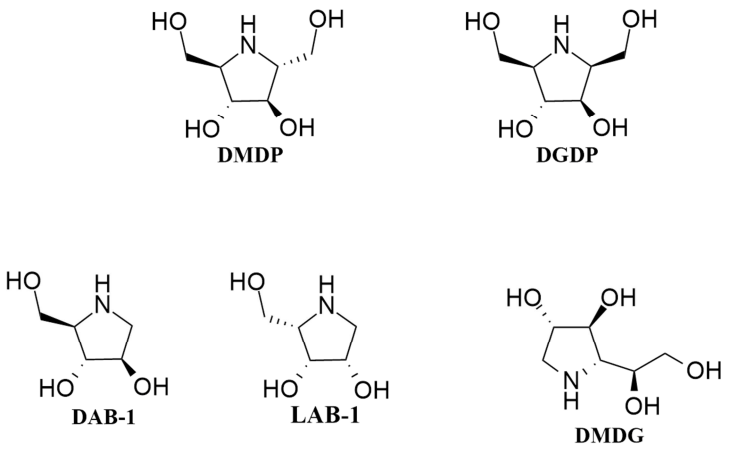


Figure 1

The 1,4-dideoxy-1,4-imino hexitols, are not only potent glycosidase inhibitors[7], but also promising inhibitors of mycobacterial galactan biosynthesis, probably by means of their inhibition of the mycobacterial UDP-Gal mutase. In particular, the 1,4-dideoxy-1,4-imino-D-galactitol (DMDG) is the first known inhibitor of E. coli K12 UDP-Gal mutase and mycobacterial galactan biosynthesis [8,9,10]. This activity may have therapeutic potential for the treatment of mycobacterial infections such as tuberculosis and leprosy, diseases that have become currently public health concerns one more due to the recent reappearance of multiresistances against most existing treatments.

2. Results and discussion

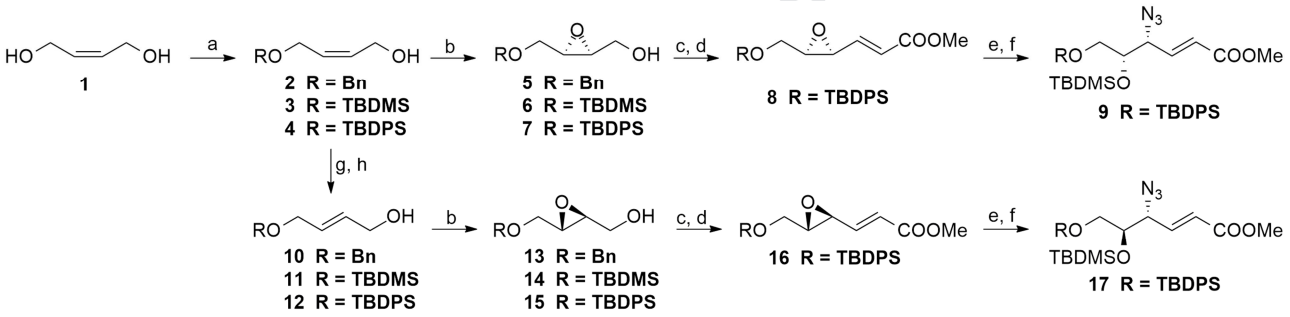
In our previous work we described the total synthesis of the pyrrolidine alkaloids 1,4-dideoxy-1,4-imino-D-galactitol and its diastereoisomer 1,4-dideoxy-1,4-imino-D-glucitol, exploiting as key steps two different regio- and stereoselective nucleophilic openings of a suitable chiral vinyl epoxide and subsequent double diastereoselection in the asymmetric dihydroxylation (AD). [11]

As already reported by us, using $(DHQ)_2PHAL$ as chiral ligand in the AD of the optically active vinyl azido alcohols **9** and **17**, we obtained an increase of the natural diastereoselection,

achieving almost exclusively the diols **A** and **C**. Instead, the use of $(DHQD)_2PHAL$ increased the production of the unnatural diols **B** and **D**, but was not able to reverse the diasteroisomeric ratio.

With the purpose of enhancing the amount of diols **B** and **D**, precursor of the iminosugars 1,4-dideoxy-1,4-imino-D-iditol and 1,4-dideoxy-1,4-imino-D-altritol respectively, in this work we performed the AD on substrates **9** and **17** using all the most common second generation Cinchona alkaloids, to test their influence on the diastereoselectivity.

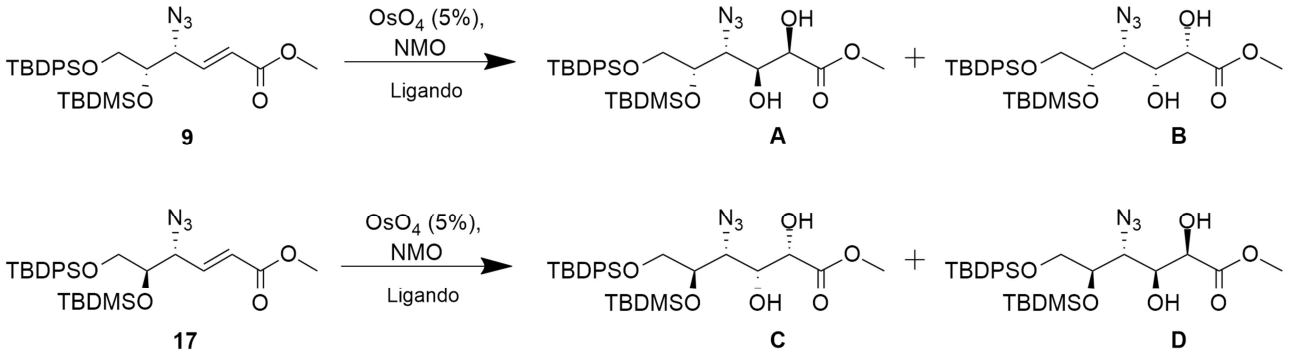
Azido alcohols **9** and **17** were prepared from *cis* 2-butene-1,4-diol **1** after careful selection of the suitable protecting group: the Sharpless asymmetric epoxidation on monobenzyl ethers **2** and **10** led to the corresponding epoxides **5** and **13** with moderate yields and enantiomeric excess, while on the *tert*-butyldimethylsilyl ethers **3** and **11** it never gave reproducible results. Finally, the protection as *tert*-butyldiphenylsilyl ethers (**4** and **12**) allowed us to obtain the optically active epoxides **7** and **15** in very good yields and excellent enantiomeric excess (Scheme 1).



Scheme 1. a) NaH, TBDPSCl (or TBDMSCl), THF, 0°C to rt, nearly quantitative yield; b) $Ti(O\text{-}i\text{-}Pr)_4$, (+)-DET, *t*-BuOOH, CH_2Cl_2, -20°C, **7** 87% and **15** 89%; c) TEMPO, IBDA, CH_2Cl_2, rt,; d) LiOH, TMPA, THF, reflux, (**8** 75% from **7** and **16** 77% from **15**); e) $TMSN_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, (**9** 74% from **8** and **17** 73% from **16**).

The subsequent oxidation to aldehyde of epoxy alcohols **7** and **15,** followed by a Horner-Emmons reaction, afforded the corresponding *trans* α,β-unsaturated epoxy esters **8** and **16**. The heterocyclic ring was then subjected to a regio and stereocontrolled nucleophilic opening using the $BF_3/TMSN_3$ system to give the target vinyl azido alcohols **9** and **17**.

Table 1. Asymmetric dihydroxylation of vinyl azido alcohols **9** and **17**



Entry	Ligand	A/B	C/D
1	//	75:25	90:10
2	$(DHQ)_2PHAL$	>95:5	>95:5
3	$(DHQD)_2PHAL$	70:30	75:25
4	$(DHQ)_2Pyr$	81:19	>95:5
5	$(DHQD)_2Pyr$	84:16	80:20
6	$(DHQ)_2AQN$	>95:5	>95.5
7	$(DHQD)_2AQN$	50:50	75:25

As shown in Table 1, all the dihydroquinin-derived ligands (DHQ) lead almost exclusively to the diastereoisomers **A** and **C** (*matched* case), which also remain predominant also with the use of the dihydroquinidine-derived ligands (DHQD).

Despite not being able to overturn the diastereomeric ratio, a larger amount of the diastereoisomer **B** (*mismatched* case) was obtained by using $(DHQD)_2AQN$ in the dihydroxylation of the *syn* azido alcohol **9**, giving an equimolar mixture of the two diastereoisomeric triols.

The diastereomeric ratio was determined by integration of the two methyl signals on silicon (two singlets at about 0.02 and -0.13ppm) of the TBSO group of each diastereoisomer on the ^1H NMR spectra of the crude mixture.

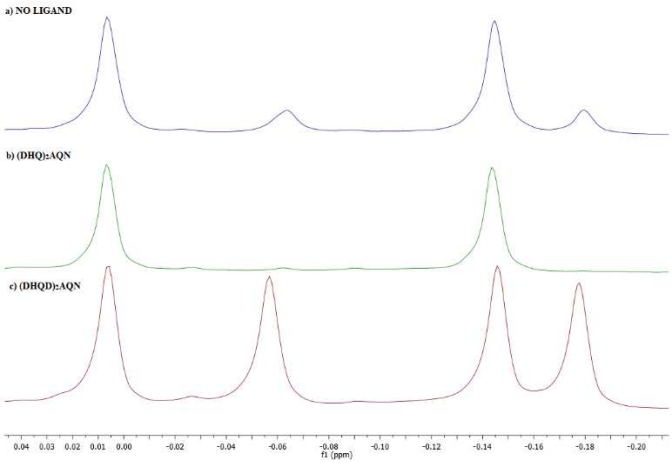
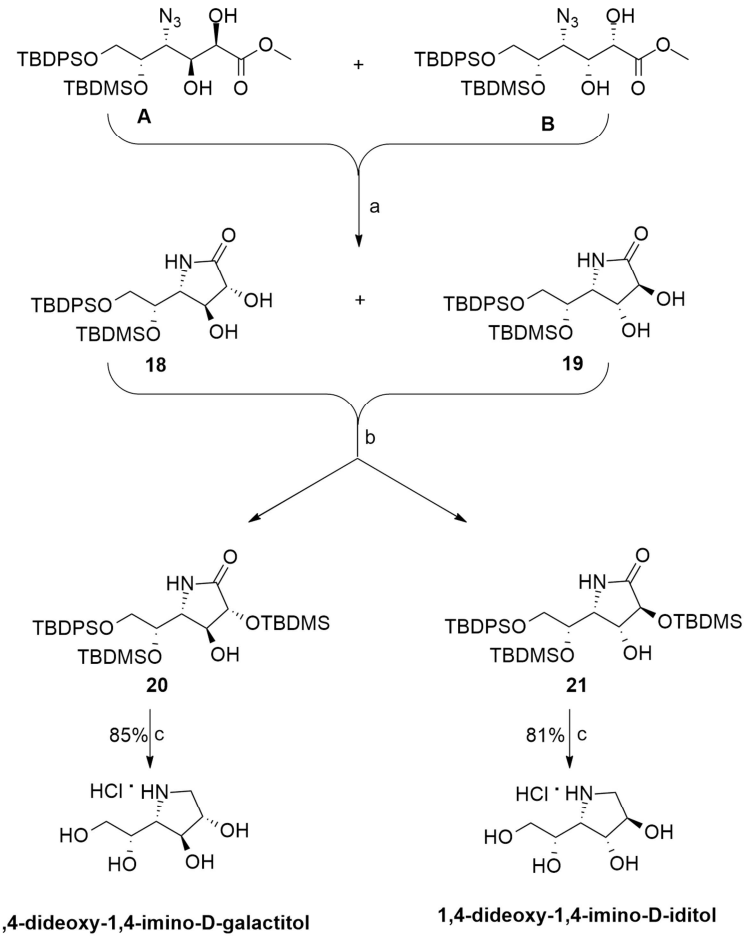


Fig. 2. Comparison between the signals of the two methyls on the silicon of the hydroxylation products of **9** (**A** + **B**): a) without ligand; b) with $(DHQ)_2AQN$; c) with $(DHQD)_2AQN$.

The diastereomeric ratio obtained in the last case is to be considered a convenient way to achieve at the same time 1,4-dideoxy-1,4-imino-D-galactitol [8,9] and 1,4-dideoxy-1,4-imino-D-iditol (an inhibitor of α-L-fucosidase and α-D-arabinosidase) [12], employing the azidotriol **B** as the common precursor and by exploiting the same synthetic route until the separation of the two diastereoisomers in the final steps of the synthesis. For this purpose, following a sequence of steps already performed, the inseparable mixture of **A** and **B** was subjected to the *one-pot* reduction of the azide moiety and subsequent ring closure using triphenylphosphine to obtain an inseparable mixture of the polar lactams **18** and **19** (Scheme 2) [13]. Fortunately, the monosilylation of the lactams **18** and **19**, obtained treating the mixture with *t*-butyldimethylsilyl chloride in the presence of imidazole, enabled separation of the protected lactams **20** and **21** as single diastereomers. In both diastereoisomers the hydroxyl group in α to the carbonyl was selectively silylated, as proven through the corresponding acetyl derivatives.

A borane–dimethyl sulfide reduction in refluxing THF[14], followed by a work-up sufficiently acidic to remove the silyl protecting groups (HCl 37% in MeOH), enabled us to synthesize 1,4-dideoxy-1,4-imino-D-galactitol and its diastereoisomer 1,4-dideoxy-1,4-imino-D-iditol as hydrochlorides in excellent yield, with analytical data in accordance with those previously published[11,15].



Scheme 2. a) PPh_3, THF dry, rt; b) TBDMSCl, imidazole, THF dry, reflux, (**20** 27% from **9** and **21** 28% from **9**); c) BH_3-SMe_2, THF dry, rt; then HCl (37%), MeOH, 70 °C.

3. Conclusion

In conclusion, after testing the influence of different ligands on the diastereoselectivity in the asymmetric dihydroxylation of the suitable chiral vinyl azido alcohol, we reported the first total synthesis of the pyrrolidine iminosugar 1,4-dideoxy-1,4-imino-D-iditol.

Contrary to the expectations raised by our previous work, no Cinchona ligand was able to reverse the stereochemistry of the AD reaction. In fact, after testing the influence of different ligands on the diastereoselectivity of the AD, only the use of $(DHQD)_2AQN$ furnished an equimolar mixture of the two diastereoisomeric triols. However, this result is to be considered a convenient strategy to realise the first total synthesis of the pyrrolidine iminosugar 1,4-dideoxy-1,4-imino-D-iditol, in addition of 1,4-dideoxy-1,4-imino-D-galactitol, with a total satisfactory yield (11%), by exploiting a single synthetic route until the final separation of the diastereoisomers through a simple monosilylation of the corresponding lactams.

4. Experimental section

4.1. General methods

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 visualization 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 an acetone bath. Unless otherwise stated, reactions were carried out under standard atmosphere. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Mercury 300 (1H, 300 MHz; ^{13}C, 75 MHz), Bruker 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) and Bruker 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) instruments. Residual solvent peaks were used as internal references: chloroform (^{1}H, d 7.26 ppm; ^{13}C, δ 77.00 ppm), acetone (^{1}H, δ 2.05 ppm; ^{13}C, δ 30.83 ppm) and deuterium oxide (^{1}H, 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 *J*asco 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.

Compound **3** [16], **4** [17], **5** [18], **6** [14], **7** [19], **8** [11], **9** [18], **10** [20], **11** [19], **12** [21], **13** [22], **14** [23], **15** [11], **16** [21], are known.

*4.2 (E,4R,5S)-Methyl 4-azido-5-(t-butyldimethylsilyloxy)-6-(t-butyldiphenylsilyloxy)hex-2-enoate (**17**).* To a stirred solution of 16 (1 mmol) in dry CH_2Cl_2 (3 mL) were added $TMSN_3$ (1 mmol, 115 mg, 0.13 mL) and BF_3•OEt (2 mmol, 283 mg, 0.25 mL) dropwise and the mixture left stirring at room temperature. After complete consumption of the substrate (12 h, TLC monitoring), the mixture was diluted with CH_2Cl_2 and washed with aq $NaHCO_3$ and brine until pH 7. The organic layer was dried over Na_2SO_4 and after filtration the solvent evaporated under vacuum. The crude,

used without purification, was subjected to the hydroxyl group protection as silyl ether. In a two neck flask under argon atmosphere the azido alcohol was dissolved in 6 ml of CH_2Cl_2 and 2 mmol (214 mg, 0.23 mL) of 2,6-lutidine and 3 mmol (793 mg, 0.69 mL) of tert-butyldimethylsilyl triflate were added and the mixture stirred at r.t. until completion (12 h, TLC monitoring). The reaction was quenched with water, then the two phases were separated and the aqueous layer was extracted twice with CH_2Cl_2, 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 vacuum. The crude was purified by flash chromatography on silica gel (hexane/ethyl acetate 90:10) to afford **17** (74% from **8**).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75-7.66 (m, 4H, Ar), 7.50-7.27 (m, 6H, Ar), 6.98 (dd, 1H, *J* = 15.7, 7.3 Hz,CH=CHCOOCH$_3$), 6.13 (d, 1H, *J* = 15.7 Hz, CH=CHCOOCH), 4.45-4.36 (m, 1H, CHN$_3$), 3.90-3.80 (m, 1H, CHOTBS), 3.78 (s, 3H, COOCH$_3$), 3.65-3.53 (m, 2H, CHaOTBDPS, CHbOTBDPS), 1.08 (s, 9H, C(CH$_3$)$_3$), 0.86 (s, 9H, C(CH$_3$)$_3$), 0.06 (s, 3H, SiCH$_3$), -0.07 (s, 3H, SiCH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.0; 141.4; 135.5; 132.9; 132.8; 129.9; 129.9; 127.8; 127.8;124.5; 74.6; 64.4; 51.7; 26.8; 25.7; 19.2; 18.0; -4.7; -5.0. $C_{29}H_{43}N_3O_4Si_2$ (553.28): C 62.89, H 7.83, N 7.59; found C 62.91, H 7.85, N 7.63.

4.3 (2R,3S,4R,5S)-Methyl 4-azido-5-(t-butyldimethylsilyloxy)-6-(t-butyldiphenylsilyloxy)-2,3-dihydroxyhexanoate ***A*** [11] *and (2S,3R,4R,5S)-Methyl 4-azido-5-(t-butyldimethylsilyloxy)-6-(t-butyldiphenylsilyloxy)-2,3-dihydroxyhexanoate* ***B*** *(mixture 50:50).* To a solution of 1 mmol of **9** in 9 mL of acetone/water (8:1) were added 2 mmol (270 mg) of NMO, ligand $(DHQD)_2AQN$ (0.15 mmol, 129 mg) and 0.05 mmol of OsO_4 (0.63 mL of a 2.5% solution of OsO_4 in *tert*-butanol).) The mixture left stirring overnight at room temperature. The reaction was then quenched with 5 mL $Na_2S_2O_3$ saturated solution, the mixture left stirring for 1 h and then transferred in a separating funnel. The aqueous layer was extracted with 10 mL of EtOAc, the combined organic layers dried over Na_2SO_4 and the solvent removed under reduced pressure. The product was used without chromatographic purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70-7.64 (m, 8H, Ar), 7.47-7.33 (m, 12H), 4.52 (d 1H, *J* =1.3 Hz, C<u>H</u>OH **A**), 4.50 (d 1H, *J* = 1.3 Hz, C<u>H</u>OH **B**), 4.28-4.22 (m 2H, C<u>H</u>OH **B**, C<u>H</u>OTBS **B**) 4.20-4.11 (m, 3H, C<u>H</u>OH **A,** C<u>H</u>OTBS **A**, O<u>H</u>), 3.96 (bs, 1H, O<u>H</u>) 3.83-3.80 (m, 2H, C<u>H$_a$H$_b$</u>OTBDPS **A**, C<u>H$_a$H$_b$</u>OTBDPS **B**) 3.73 (s, 3H, OCH$_3$ **A**), 3.72 (s, 3H, OCH$_3$ **B**), 3.70-3.57 (m, 4H, CH$_a$<u>H$_b$</u>OTBDPS **A**, CHN$_3$ **A**, CH$_a$<u>H$_b$</u>OTBDPS **B,** CHN$_3$ **B**), 1.04 (s, 18H, (C<u>H</u>$_3$)$_3$C **A**, (C<u>H</u>$_3$)$_3$C **B**), 0.82 (s, 9H, (C<u>H</u>$_3$)$_3$C **A**), 0.81 (s, 9H, (C<u>H</u>$_3$)$_3$C **B**), 0.01 (s, 3H, C<u>H</u>$_3$ **A**), -0.06 (s, 3H, C<u>H</u>$_3$ **B**), -0.13 (s, 3H, C<u>H</u>$_3$ **A**), -0.17 (s, 3H, C<u>H</u>$_3$ **B**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.3, 135.8, 135.7,

133.2, 133.2, 133.0, 133.0, 130.0, 130.0, 127.9, 72.8, 72.2, 71.7, 71.4, 71.1, 71.0, 70.5, 64.6, 64.6, 64.3, 62.0, 53.0, 52.9, 26.9, 25.8, 25.7, 19.2, 18.1, 18.0, 14.3, 12.1, -4.1, -4.6, -5.2, -5.2.

*4.4 (1'S,3R,4S,5R)-5-[1'-(t-Butyldimethylsilyloxy)-2'-(t-butyldiphenylsilyloxy)-ethyl]-3,4-dihydroxypyrrolidin-2-one (**18**) and (1'S,3S,4R,5R)-5-[1'-(t-Butyldimethylsilyloxy)-2'-(t-butyldiphenylsilyloxy)-ethyl]-3,4-dihydroxypyrrolidin-2-one (**19**)*

To a solution of the inseparable mixture of diols **A** and **B** (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 then 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 80:20) to give an inseparable mixture of the polar lactams **18** and **19**.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70-7.62 (m, 8H, Ar), 7.47-7.33 (m, 12H, Ar), 5.98 (bs, 1H, NH **18**), 5.85 (bs, 1H, NH **19**), 4.95 (bs, 1H, OH **18**), 4.77-4.53 (m, 2H, OH **18**, OH **19**), 4.53-4.40 (m, 2H, C<u>H</u>O<u>H</u> **19**), 4.37 (d, 1H, *J* = 7.8 Hz, C<u>H</u>OH **18**), 4.16 (dd, 1H, J_1=J_2=7.8 Hz, C<u>H</u>OH **18**), 4.13-4.07 (m, 1H, C<u>H</u>OH **19**), 3.93 (m, 1H, C<u>H</u>OTBS **19**) 3.80-3.57 (m, 5H, C<u>H</u>OTBS **18,** C<u>H$_a$H$_b$</u>OTBDPS **18**, C<u>H$_a$H$_b$</u>OTBDPS **19**), 3.54-3.42 (m, 2H, C<u>H</u>NH **18**, C<u>H</u>NH **19**), 1.06 (s, 9H, (C<u>H$_3$</u>)$_3$C **18**), 1.05 (s, 9H, (C<u>H$_3$</u>)$_3$C **19**), 0.82 (s, 9H, (C<u>H$_3$</u>)$_3$C **18**), 0.75 (s, 9H, (C<u>H$_3$</u>)$_3$C **19**), -0.01 (s, 3H, C<u>H$_3$</u> **19**), -0.05 (s, 3H, C<u>H$_3$</u> **18**), -0.16 (s, 3H, C<u>H$_3$</u> **19**), -0.24 (s, 3H, C<u>H$_3$</u> **18**). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.5, 135.7, 135.6, 135.6, 130.2, 130.1, 130.1, 130.0, 128.1, 128.0, 76.6, 76.1, 75.3, 71.6, 69.0, 66.9, 65.2, 60.1, 56.0, 27.0, 26.9, 25.8, 25.8, 19.2, 19.1, 18.0, 17.9, -4.3, -4.4, -4.6, -5.0

*4.5 (1'S,3R,4S,5R)-5-[1'(tert-Butyl-dimethyl-silyloxy)-2'-(tert-butyl-diphenyl-silyloxy)-ethyl] -3-(tert-butyl-dimethyl-silyloxy)-4-hydroxypyrrolidin-2-one (**20**) and (1'S,3S,4R,5R)-5-[1'-(tert-Butyl-dimethyl-silyloxy)-2'-(tert-butyl-diphenyl-silyloxy)-ethyl]-3-(tert-butyl-dimethyl-silyloxy)-4-hydroxypyrrolidin-2-one (**21**)*

In a two neck flask under argon atmosphere 1 mmol of lactam was dissolved in 6 ml of dry THF. 2,2 mmol of imidazole (150 mg) and 1,1 mmol (166 mg) of tert-butyldimethylsilyl chloride were added and the mixture stirred at reflux temperature until completion (12 h, TLC monitoring). The THF was evaporated, the reaction mixture was dissolved in CH_2Cl_2 and washed with HCl 1M, then with $NaHCO_3$ saturated solution and finally with brine. The organic layer was dried over Na_2SO_4

and after filtration the solvent evaporated in vacuum. The crude was purified by flash chromatography on silica gel (hexane/ethyl acetate 85:15).

20: yield 27% from **17**; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70-7.60 (m, 4H, Ar), 7.53-7.37 (m, 6H), 5.55 (bs, 1H, NH), 4.33 (d, 1H, *J* = 7.9 Hz C<u>H</u>OTBS), 4.15 (dd, 1H, *J* = 7.9, 7.0 Hz, C<u>H</u>OH), 3.69 (dd, 1H, *J* = 10.9, 8.6 Hz, C<u>H</u>$_a$OTBDPS), 3,60 (dd, 1H, *J* = 10.9, 3.7 Hz, C<u>H</u>$_b$OTBDPS), 3.51 (td, 1H, *J* = 8.6, 3.7 Hz, C<u>H</u>OTBS), 3.30 (dd, 1H, *J* = 8.6, 7.0 Hz, C<u>H</u>NH), 1.07 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.96 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.75 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.22 (s, 3H, C<u>H</u>$_3$ C), 0.19 (s, 3H, C<u>H</u>$_3$ C), -0.12 (s, 3H, C<u>H</u>$_3$ C), -0.40 (s, 3H, C<u>H</u>$_3$ C). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.7, 135.8, 135.6, 132.0, 132.0, 130.6, 130.4, 128.3, 128.2, 77.3, 76.7, 74.5, 66.7, 62.1, 26.9, 25.9, 25.7, 19.2, 18.5, 17.9, -4.3, -4.6, -4.9, -5.0. $C_{34}H_{57}NO_5Si_3$ (643.35): C 63.40, H 8.92, N 2.17; found C 63.70, H 9.36, N 2.03.

21: yield 28% from **17**;^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.60 (m, 4H, Ar), 7.51-7.38 (m, 6H), 5.44 (bs, 1H, NH), 4.36 (dd, 1H, *J* = 6.5, 5.0 Hz, C<u>H</u>OH), 4.21 (d, 1H, *J* = 5.0 Hz, C<u>H</u>OTBS), 4.04 (dt, 1H, *J* = 8.8, 4.4 Hz, C<u>H</u>OTBS), 3,86 (dd, 1H, *J* = 6.5, 4.4 Hz, C<u>H</u>NH), 3.66 (dd, 1H, *J* = 10.4, 4.2 Hz, C<u>H</u>$_a$OTBDPS), 3.48 (dd, 1H, *J* = 10.4, 8.8 Hz, C<u>H</u>$_b$OTBDPS), 1.07 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.93 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.78 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.17 (s, 3H, C<u>H</u>$_3$ C), 0.16 (s, 3H, C<u>H</u>$_3$ C), 0.02 (s, 3H, C<u>H</u>$_3$ C), -0.14 (s, 3H, C<u>H</u>$_3$ C). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3, 135.9, 135.8, 132.6, 132.5, 130.6, 130.5, 128.4, 128.3, 128.2, 76.6, 76.0, 70.5, 65.7, 58.4, 27.1, 26.1, 26.0, 19.4, 18.6, 18.1, -4.1, -4.1, -4.2, -4.7. $C_{34}H_{57}NO_5Si_3$ (643.35): C 63.40, H 8.92, N 2.17; found C 63.78, H 9.31, N 2.00.

*4.6 (1'S,3R,4S,5R)-5-[1'(tert-Butyl-dimethyl-silyloxy)-2'-(tert-butyl-diphenyl-silyloxy)-ethyl] -3-(tert-butyl-dimethyl-silyloxy)-4-acetoxypyrrolidin-2-one **22** (acetyl derivative of **20**) and (1'S,3S,4R,5R)-5-[1'-(tert-Butyl-dimethyl-silyloxy)-2'-(tert-butyl-diphenyl-silyloxy)-ethyl]-3-(tert-butyl-dimethyl-silyloxy)-4-acetoxypyrrolidin-2-one **23** (acetyl derivative of **21**)*

1 mmol of substrate (**20** or **21**) was dissolved in 1 ml of pyridine and 0.5 ml of acetic anhydride was added. The mixture left stirring overnight at room temperature. The reaction mixture was transferred in a separating funnel with ethyl acetate and washed with HCl 2M. 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. The product was analyzed without chromatographic purification.

22: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71-7.55 (m, 4H, Ar), 7.51-7.35 (m, 6H), 5.85 (bs, 1H, NH), 5.21 (dd, 1H, J_1=J_2= 4.5 Hz, C<u>H</u>OAc), 4.29 (d, 1H, *J* = 4.5 Hz C<u>H</u>OTBS), 3.91 (m, 1H, C<u>H</u>OTBS), 3,60 (m, 2H, C<u>H</u>NH, C<u>H</u>$_a$OTBDPS), 3.54 (dd, 1H, J_1 = 11.0 J_2 = 5.7 Hz, C<u>H</u>$_b$OTBDPS), 2.06 (s, 3H, COC<u>H</u>$_3$) 1.05 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.89 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.84 (s, 9H, (C<u>H</u>$_3$)$_3$C), 0.16 (s, 3H, C<u>H</u>$_3$ C), 0.13 (s, 3H, C<u>H</u>$_3$ C), -0.06 (s, 3H, C<u>H</u>$_3$ C), -0.12 (s, 3H, C<u>H</u>$_3$ C).

***23**:* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65-7.56 (m, 4H, Ar), 7.49-7.35 (m, 6H), 5.63 (bs, 1H, NH), 5.31 (dd, 1H, J_1=J_2=7.8 Hz, CHOAc), 4.51 (d, 1H, *J* = 7.8 Hz, CHOTBS), 4.18 (m, 1H, CHOTBS), 3.62-3.55 (m, 2H, CHNH, CH_aOTBDPS), 3.45-3.66 (m, 1H, CH_bOTBDPS), 2.12 (s, 3H, $COCH_3$) 1.05 (s, 9H, $(CH_3)_3C$), 0.88 (s, 9H, $(CH_3)_3C$), 0.79 (s, 9H, $(CH_3)_3C$), 0.15 (s, 3H, CH_3 C), 0.09 (s, 3H, CH_3 C), -0.02 (s, 3H, CH_3 C), -0.20 (s, 3H, CH_3 C).

As is widely known, the acetylation of a secondary alcoholic function results in a deshielding of about 1.1 ppm of the CHOAc signal compared to the original CHOH one. By comparing the ^{1}H NMR of **20** and **21** with the respective acetyl derivatives **22** and **23**, it is possible to observe the expected deshielding for two dd systems, from 4.15 ppm of **20** to 5.21 ppm of **22** and from 4.36 ppm of **21** to 5.31 of **23**, respectively. The multiplicity of the deshielded systems is consistent with the CHOH in C-3 position, thus proving that the hydroxyl groups in α to the carbonyl, which have doublet multiplicity, were selectively silylated for both **20** and **21**.

4.7 1,4-dideoxy-1,4-imino-D-iditol hydrochloride [12, 15]

To a solution of **21** (1 mmol) in dry THF (4.34 mL) was added BH_3·DMS (5 mmol, 0.15 mL) at 0 °C. The reaction mixture was stirred under nitrogen at reflux temperature for 5 hours and then at room temperature until complete consumption of the substrate (TLC monitoring); the reaction was quenched by cautiously adding 1,5 ml of HCl 1M. The mixture was refluxed for 2 hours and after cooling, was concentrated to dryness. The mixture was coevaporated 4 times with a solution of MeOH/HCl 37% (1:1). The product was washed 3 times with hexane removing the supernatant and the solid residue was crystallized from MeOH/H_2O 90:10 affording 1,4-dideoxy-1,4-imino-D-iditol·HCl salt as white crystals (85%). mp = 154-156 °C; (lit [15] mp=157-158 °C). α_D= + 3.2 (*c*= 1.5, H_2O); (lit [15] α_D= +3.7, *c*= 3, H_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ:4.31 (bd, 1H, *J* = 3.9 Hz, H-2), 4.20 (bd, 1H, J = 2.5 Hz, H-3), 4.04 (ddd, 1H, *J* = 8.5, 4.8, 3.3 Hz, H-5), 3.75-3.66 (m, 2H, H-4 + H-6), 3.58-3.55 (m, 2H, H-6'+ H-5), 3.19 (bd, 1H, *J* = 13.1 Hz, H-5') . ^{13}C NMR (100 MHz, $CDCl_3$) δ:75.0, 74.4, 68.3, 63.5, 63.3, 50.5. $C_6H_{14}ClNO_4$ (199.06): C 36.10, H 7.07, N 7.02; found C 36.14, H 7.11, N 6.98. $C_6H_{14}ClNO_4$ (199.06): C 36.10, H 7.07, N 7.02; found C 36.14, H 7.11, N 6.98.

4.8 1,4-dideoxy-1,4-imino-D-galactitol hydrochloride [8, 9, 10]

Following the same procedure already described for ***1,4-dideoxy-1,4-imino-D-iditol·HCl*** salt, after crystallization from MeOH/H_2O 90:10, ***1,4-dideoxy-1,4-imino-D-galactitol·HCl*** salt) was obtained as white crystals (81%). mp = 100-103 °C; (lit [11] mp=100-102 °C). α_D= -23 (*c*= 1.5, H_2O); (lit [11] α_D= -22, *c*= 1,5, H_2O)

^{1}H NMR (400 MHz, D_2O) δ: 4.24 (1H, dt, *J* = 5.0, 3.2 Hz, H-2), 4.08 (1H, br t, *J* = 3.5 Hz, H-3), 3.93-3.88 (1H, m, H-5), 3.69 (1H, dd, *J* = 12.2, 3.6 Hz, H-6), 3.58 (1H, dd, *J* = 12.2, 4.9 Hz, H-6'), 3.49-3.43 (2H, m, H-4+H-1), 3.25 (1H, dd, *J* = 12.4, 3.2 Hz, H-1'). ^{13}C NMR (100 MHz, D_2O) δ: 76.5, 74.5, 69.1, 66.7, 63.3, 49.9. $C_6H_{14}ClNO_4$ (199.06): C 36.10, H 7.07, N 7.02; found C 36.13, H 7.09, N 6.99.

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The first stereocontrolled total synthesis of iminosugar 1,4-dideoxy-1,4-imino-D-iditol is described. The key step was the asymmetric dihydroxylation (AD) of suitable optically active vinyl azido alcohol. In particular using $(DHQD)_2AQN$ as chiral ligand it was possible to realise the stereodivergent synthesis of 1,4-dideoxy-1,4-imino-D-iditol and 1,4-dideoxy-1,4-imino-D-galactitol,
iminosugars with promising chemotherapeutic properties.

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: