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Asymmetric routes toward polyhydroxylated pyrrolidines: Synthesis of 1,4-dideoxy-1,4-imino-D-galactitol and 1,4-dideoxy-1,4-imino-D-glucitol

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ABSTRACT

Herein 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 is described, starting from a common optically active precursor. The key step in our approach was the double diastereoselection in the asymmetric dihydroxylation of chiral vinyl azido alcohols, obtained by means of two different regio- and stereoselective nucleophilic openings of the corresponding chiral vinyl epoxide.

1. Introduction

Polyhydroxylated pyrrolidines and piperidines, also know as azasugars or iminosugars, are known as specific and competitive inhibitors of glycosidases or glycosyl transferases [1]. Consequently they may have a potential for therapeutic applications, including treatment of diseases such as diabetes, cancer, inflammation, and viral and bacterial infections. These effects can be exploited to modify the glycosylation of eukaryotic cells, the metabolism of carbohydrates and glycoconjugates, the carbohydrate-dependent properties of glycoproteins (e.g. folding and transport) and the carbohydrate-mediated interaction of host cells with infectious agents.

The first pyrrolidine iminosugar discovered, isolated in 1976 from *Derris elliptica* [2], was the (2*R*,5*R*)-bis(dihydroxymethyl)-(3*R*,4*R*)-dihydroxypyrrolidine, DMDP [3]. Numerous similar molecules (Fig. 1) subsequently were found in many different plants and microorganisms. Although the structure of DMDP resembles that of β-D-fructofuranose, this iminosugar shows a strong inhibition of glycosidases I and displays antiviral activity [4].

1,4-Dideoxy-1,4-imino-D-galactitol, which bears an additional hydroxymethyl substituent, acts as a weak α-glycosidase inhibitor [5] and it has been the first known inhibitor of *E. coli* K12 UDP-Gal mutase and mycobacterial galactan biosynthesis [6]. Its inhibitory activities are highly specific and may represent a novel therapeutic strategy for the treatment of mycobacterial infections such as leprosy and tuberculosis.

Here, we report a versatile synthesis of 1,4-dideoxy-1,4-imino-D-galactitol [7,8] and its diastereoisomer 1,4-dideoxy-1,4-imino-D-

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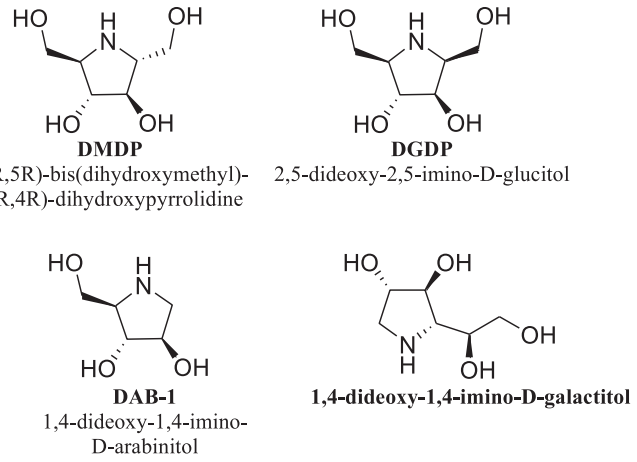


Fig. 1. Examples of naturally occurring polyhydroxylated pyrrolidines.

glucitol [9] from the common precursor chiral epoxide **5**, which was easily obtained by the Sharpless AE of monoprotected allylic alcohol **2** [10], starting from the commercial *cis*-but-2-en-1,4-diol **1** (Scheme 1).

The Sharpless asymmetric epoxidation was performed on the *cis* allylic alcohol **2** and, despite the sluggishness of the reaction (1–2 weeks), substrate conversion was complete and epoxy alcohol **3** was obtained with a good reproducibility and excellent *ee* [11]. After the oxidation of **3** to aldehyde **4**, followed by a Horner-Emmons reaction [12], the corresponding α,β-unsaturated epoxy ester **5** was obtained in good overall yield.

Recently, we reported a study on double stereodifferentiation in the asymmetric dihydroxylation of optically active olefins [13]. As already described by other authors [14], sometimes one ligand gives excellent results in the matched case, unlike its pseudoenantiomer in the mismatched case. On the optically active vinyl azido alcohols of type A (*syn* or *anti*), the use of $(DHQ)_2PHAL$ enhanced the intrinsic diastereofacial preference [15]. Instead, $(DHQD)_2PHAL$ increased the production of the unnaturaldiol **C**, but was not able to reverse the ratio of the diasteroisomers (Table 1).

The relevant diastereoselection obtained allowed us to prepare attractive compounds having four contiguous stereogenic centers, which are useful in the synthesis of a wide range of biologically active compounds. In particular, we considered that the asymmetric dihydroxylation on the suitable, optically active, unsaturated azido alcohols **7** and **11** could represent the key step to accessing different pyrrolidine iminosugars.

The regioselective azidolysis of vinyl epoxide **5,** performed using $BF_3{\cdot}OEt_2$ and $TMSN_3$ [16], afforded the *syn* azido alcohol **6** in quantitative yield. The *anti* relationship of the azido alcohol **10** was introduced through a regiocontrolled opening of epoxide by bromine, using the system LiBr/Amberlyst 15 [17], to give **9** and a subsequent substitution of the halogen by azide employing NaN_3 in DMF (Scheme 2) [18].

To achieve better handling of the subsequent dihydroxylation products, the hydroxyl group of **6** and **10** was protected by treating with *t*-butyldimethylsilyltrifluoromethanesulfonate/2,6-lutidine to provide the *tert*-butyldimethyl silyl ethers **7** and **11**.

The dihydroxylation reaction, with and without chiral ligands, was carried out on both substrates **7** and **11** (Table 2). On *syn* azido alcohol **7** a 90:10 diastereomeric ratio without chiral ligand was observed, while the presence of $(DHQ)_2PHAL$ or DHQ-CLB enhanced the intrinsic diastereofacial preference of the reaction which produced **8a** in almost quantitative yield. By using $(DHQD)_2PHAL$ or DHQD-CLB, the stereochemical outcome of the reaction was not reversed, and the percentage of the minor product **8b** was only slightly increased.

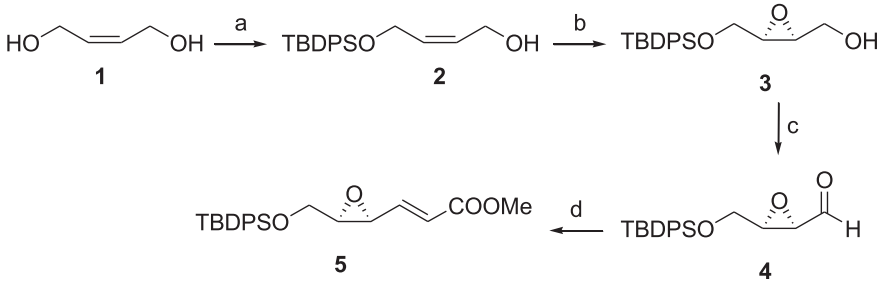
As shown in Table 2, similar results were obtained by performing the reactions on *anti* azido alcohol **11**: moreover, in this case the chiral ligand $(DHQ)_2PHAL$ enabled achievement of a diastereomeric ratio up to 95:5 for the intrinsically favored diol **12a.**

Reduction of the azide moiety and the subsequent ring closure was accomplished smoothly in a one-pot reaction by treating **8a** and **12a** with triphenylphosphine and then water to give lactams **13** and **15** (Scheme 3) [19]. When lactams **13** and **15** were subjected to the borane–dimethyl sulfide reduction in refluxing THF [20], the corresponding pyrrolidines **14** and **16** were obtained in good yield (68% and 71%, respectively). Finally, removal of the silyl protecting groups from the protected **14** and **16** by acid hydrolysis (HCl 37% in MeOH) gave 1,4-dideoxy-1,4-imino-D-galactitol and its diastereoisomer 1,4-dideoxy-1,4-imino-D-glucitolas hydrochlorides in excellent yield, with analytical data in accordance with those previously published [7b,9c].

2. Conclusion

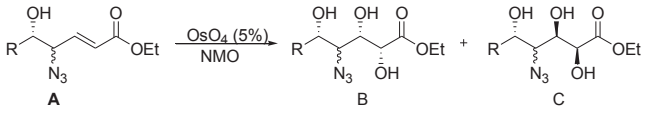
In conclusion, the total synthesis of the pyrrolidine alkaloids 1,4-dideoxy-1,4-imino-D-galactitol and 1,4-dideoxy-1,4-imino-D-glucitol was achieved starting from a common precursor: the optically active vinyl epoxide **5.** The key step in our approach was the double diastereoselection in the asymmetric dihydroxylation of the chiral vinyl azido alcohols **7** and **11,** obtained by two different regio- and stereoselective nucleophilic opening of the oxirane ring of **5**.

Note that the use of (−)-DET in AE would allow the access to the L-series. Moreover, if the suitable ligand able to reverse the stereochemical of the AD reaction could be found, the same synthetic sequence could lead to the 1,4-dideoxy-1,4-imino- iditol and 1,4-



Scheme 1. a) n-BuLi, TBDPSCl, THF, −50 °C to rt, > 90%; b) $Ti(O\text{-}i\text{-}Pr)_4$, (+)-DET, *t*-BuOOH, CH_2Cl_2, −20 °C, two weeks, 95%, ee 95%; c) TEMPO, IBDA, CH_2Cl_2, rt; d) LiOH, TMPA, THF, reflux, 75% from **3**.

Table 1
Dihydroxylation of vinyl azido alcohols of type **A**.



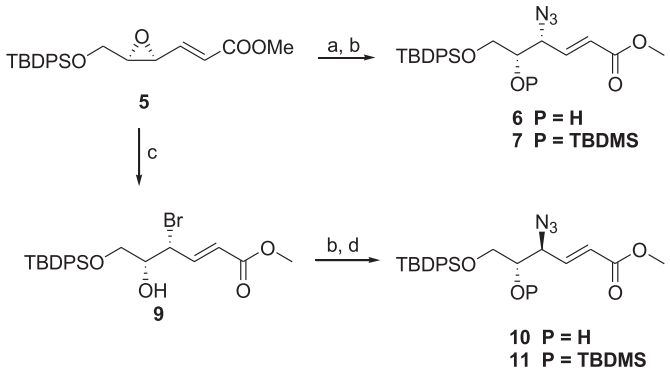
	A	B	C
L* = 0		90	10
L* = $(DHQ)_2PHAL$		>95	5
L* = $(DHQD)_2PHAL$		65	35

dideoxy-1,4-imino-altritol. Studies in this direction are currently under investigation.

3. Experimental section

3.1. 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 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 (5 g), sulfuric acid (5 mL), n-butanol (100 mL)] and heating. Low temperature reactions were performed in a Haake EK 101 cryostat using an acetone bath. Unless otherwise stated, reactions were carried out under standard atmosphere. ^1H and ^{13}C NMR spectra were recorded using a Varian Mercury 300 instrument (^1H, 300 MHz; ^{13}C, 75 MHz). Residual solvent peaks were used as internal references: chloroform (^1H, d 7.26 ppm; ^{13}C, d 77.00 ppm), Chemical shifts (d) 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.



Scheme 2. a) $TMSN_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 74% from **5**; c) LiBr, Amberlyst15, acetone, rt, >95%); d) NaN_3, dry DMF, rt, >95%.

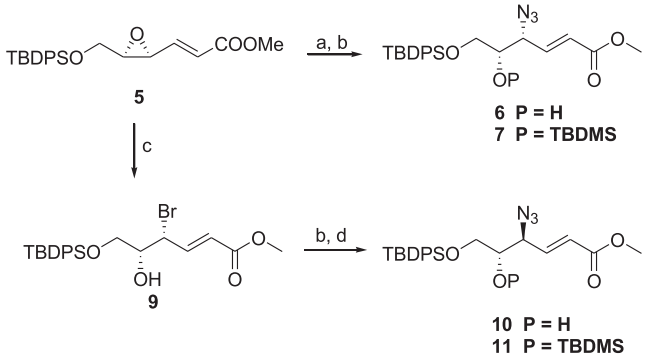
Compounds **2** [21], **3** and **4** [22] are known.

3.2. (E, 2′S,3′R)-3-[3′-(tert-Butyl-diphenyl-silanyloxymethyl)-oxiranyl]-acrylic acid methyl ester (**5**)

A suspension of **4** (1 mmol), TMPA (1.1 mmol, 0.250 g, 0.22 mL) and LiOH (1.1 mmol, 0.027 g) in THF (10 mL) was stirred at 70 °C until consumption of the substrate (TLC monitoring). Sat. NH_4Cl soln (20 mL) was then added and the mixture was concentrated under reduced pressure. The aqueous residue was then extracted with EtOAc (3 × 10 mL) and the combined organic extract was washed with sat. NH_4Cl soln and brine until pH 7. The organic extract was dried (Na_2SO_4) and concentrated under reduced pressure to leave the crude product, which was then purified by flash chromatography on silica gel (hexane–EtOAc, 9:1) to give **5** as yellow oil (75% from **3**).

^1H NMR (300 MHz, $CDCl_3$) δ: 7.78–7.57 (4H, m, Ar), 7.53–7.29 (6H, m, Ar), 6.70 (1H, dd, J = 5.6, 6.5 Hz, H-3), 6.05 (1H, d, J = 15.6 Hz, H-2), 3.86–3.65 (5H, m, H-$6_{a,b}$+OCH_3), 3.59–3.51 (1H, m, H-epox), 3.46–3.38 (1H, m, H-epox), 1.08 (9H, s, $(C\underline{H}_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.3, 135.5, 135.4, 134.7, 133.0, 132.8, 129.7, 127.7, 127.6, 124.8, 61.4, 59.1, 54.7, 51.5, 26.6, 19.1. $C_{23}H_{28}O_4Si$ (396.18): C 69.66, H 7.12; found C 69.70, H 7.16.

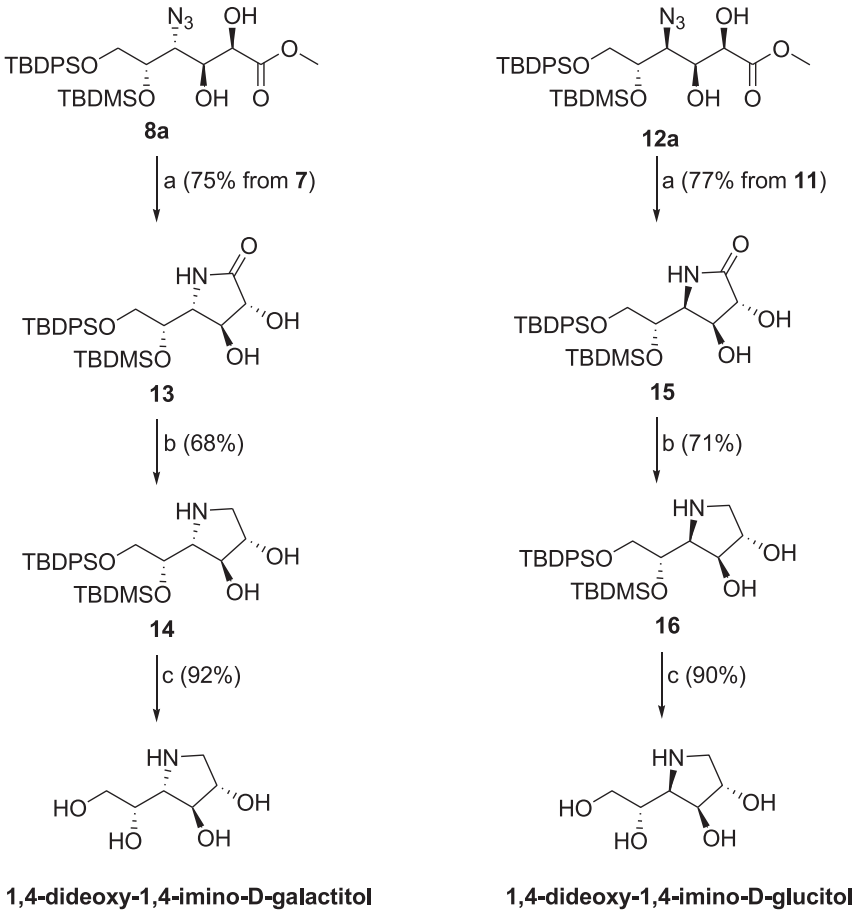
Table 2
Dihydroxylation of vinyl azido alcohols **7** and **11**.



Ligand	8a/8b[a,b]	12a/12b[a,b]
–	90:10	90:10
DHQ-CLB	>95:5	>95:5
$(DHQ)_2PHAL$	>95:5	>95:5
DHQD-CLB	85:15	87:13
$(DHQD)_2PHAL$	85:15	85:15

[a] The relative stereochemistry of the major diastereoisomer was confirmed by the structure of the final iminosugars, by comparing the physical data with those reported in literature.

[b] The ratio between the two diastereomers was determined by integration of the anisochronous C*H*OHCO$_2$Et signal for each diastereoisomer in the ^1H-NMR spectrum of the crude mixture.



Scheme 3. a) PPh_3, THF, rt; b) BH_3-SMe_2, THF, rt; c) HCl (37%), MeOH, 70 °C.

*3.3. (E,4R,5S)-4-Azido-6-(tert-butyl-diphenyl-silanyloxy)-5-hydroxy-hex-2-enoic acid methylester (**6**)*

To a stirred solution of **5** (1 mmol) in dry CH_2Cl_2 (3 mL) were added $TMSN_3$ (1 mmol, 115 mg, 0.13 mL) and $BF_3 \cdot OEt_2$ (2 mmol, 283 mg, 0.25 mL) dropwise and the reaction mixture was left stirring at room temperature. After complete consumption of the substrate (TLC monitoring), the mixture was diluted with CH_2Cl_2 (10 mL) and washed with aq $NaHCO_3$ soln (3 mL) and brine until pH 7. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the crude used without chromatographic purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68–7.61 (m, 4H, Ar), 7.50–7.36 (m, 6H, Ar), 6.87 (1H, dd, J = 15.8, 7.03 Hz, H-3), 6.10 (1H, d, J = 15.5 Hz, H-2), 4.27 (1H, dd, J = 6.05, 5.4 Hz, H-4), 3.80–3.63 (m, 6H, H-5+OCH_3+H-$6_{a,b}$), 2.12 (1H, br s, OH), 1.08 (9H, s, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.8, 141.3, 135.5, 129.9, 127.9, 124.5, 73.2, 64.04, 63.9, 51.8, 26.8, 19.2.

*3.4. (E,4R,5S)-4-Azido-5-(tert-butyl-dimethyl-silanyloxy)-6-(tert-butyl-diphenyl-silanyloxy)-hex-2-enoic acid methyl ester (**7**)*

To a solution of **6** (1 mmol) in dry CH_2Cl_2 (6 mL) under argon at 0 °C, were successively added 2,6-lutidine (2 mmol, 0.23 mL) and *t*-$BuMe_2SiOTf$ (3 mmol, 0.68 mL). The reaction mixture was stirred at room temperature until completion (TLC monitoring) and then diluted with 4 mL of distilled water. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude was purified by flash chromatography on silica gel (hexane/ethyl acetate 90:10) to give **7** as pale yellow oil (74% from **5**).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75–7.62 (4H, m, Ar), 7.50–7.34 (6H, m, Ar), 6.99 (1H, dd, J = 15.8, 6.7 Hz, H-3), 6.15 (1H, dd, J = 15.8, 1.4 Hz, H-2), 4.22 (1H, ddd, J = 6.7, 2.5, 1.4 Hz, H-4), 3.84–3.69 (4H, m, OCH_3+H-6_a), 3.62–3.54 (2H, m, H-5+H-6_b), 1.06 (9H, s, $(CH_3)_3C$), 0.81 (9H, s, $(CH_3)_3C$), −0.03 (3H, s, CH_3), −0.16 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ:166.06, 143.6, 135.5, 133.02, 132.8, 129.9, 129.9, 127.8, 127.8, 123.4, 75.3, 64.2, 63.01, 26.8, 25.7, 19.2, 17.9, −4.8, −5.1. $C_{29}H_{43}N_3O_4Si_2$ (553.28): C 62.89, H 7.83, N 7.59; found C 62.92, H 7.87, N 7.55.

*3.5. (4R,5R,E)-4-Bromo-6-(tert-butyl-diphenyl-silanyloxy)-5-hydroxy-hex-2-enoic acid methyl ester (**9**)*

LiBr (1 mmol, 65 mg) and Amberlyst15 (1 mmol, 212 mg) were added to **5** (1 mmol) dissolved in acetone (8 mL) and the mixture stirred overnight at room temperature. After filtration of the mixture, the solvent was removed in vacuum; the residue was dissolved in EtOAc (5 mL) and washed with brine until pH 7. The organic layer was dried on Na_2SO_4, filtered and concentrated in vacuo to give **9** that was used without any purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.74–7.59 (4H, m, Ar), 7.50–7.34 (6H, m, Ar), 7.09 (1H, dd, J = 15.5,9.4 Hz, H-3), 6.15 (1H, d, J = 15.5 Hz, H-2), 4.87 (1H, dd, J = 9.4, 3.3 Hz, H-4), 3.82–3.67 (5H, m, OCH_3+H-$6_{a,b}$+H-5), 2.58 (1H, br s, OH),1.08 (9H, s, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.9143.2, 135.5, 135.4, 128.9, 123.4, 73.0, 64.6, 54.5, 51.8, 26.8, 19.1.

3.6. (E,4S,5S)-4-Azido-6-(tert-butyl-diphenyl-silanyloxy)-5-hydroxy-hex-2-enoic acid methyl ester (**10**)

To a solution of **9** (1 mmol) in dry DMF (1 mL) under argon at 0 °C was added NaN_3 (2 mmol, 130 mg) and the mixture was left stirring until complete consumption of the substrate (TLC monitoring). The mixture was then diluted with EtOAc (3 mL) and washed with brine. The organic layer was dried on Na_2SO_4 and the solvent removed under reduced pressure to give **10** as pale yellow oil, which was used without any purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76–7.60 (4H, m, Ar), 7.52–7.27 (6H, m, Ar), 6.92 (1H, dd, J = 15.7, 6.8 Hz, H-3), 6.10 (1H, dd, J = 15.7, 1.2 Hz, H-2), 4.22 (1H, br t, J = 5.8 Hz, H-4), 3.76–3.66 (6H, m, OCH_3+H-$6_{a,b}$+H-5), 2.68 (1H, br s, OH), 1.09 (9H, s, $(CH_3)_3C$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.8, 141.4, 135.4, 132.5, 130.0, 127.8, 124.5, 72.9, 63.9, 63.6, 51.8, 26.8, 19.2.

3.7. (E,4S,5S)-4-Azido-5-(tert-butyl-dimethyl-silanyloxy)-6-(tert-butyl-diphenyl-silanyloxy)-hex-2-enoic acid methyl ester (**11**)

Following the same procedure already described for **7**, after purification by flash chromatography on silica gel (hexane/ethyl acetate 85:15) **11** was obtained as pale yellow oil (72% from **9**).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75–7.66 (4H, m, Ar), 7.50–7.27 (6H, m, Ar), 6.98 (1H, dd, J = 15.7, 7.3 Hz, H-3), 6.13 (1H, d, J = 15.7 Hz, H-2), 4.41 (1H, dd, J = 7.1, 3.3 Hz, H-4), 3.90–3.82 (1H, m, H-5), 3.78 (3H, s, OCH_3), 3.59 (1H, dd, J = 10.5, 4.5 Hz, H-6_a), 3.52 (1H, dd, J = 10.5, 7.4 Hz, H-6_b), 1.08 (9H, s, $(CH_3)_3C$), 0.86 (9H, s, $(CH_3)_3C$), 0.06 (3H, s, CH_3), −0.07 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7; 141.3; 135.5; 132.8; 132.8; 129.8; 129.7; 127.8; 127.7; 124.5; 74.6; 64.4; 51.6; 26.7; 25.6; 19.02; 17.9; −4.8; −5.1. $C_{29}H_{43}N_3O_4Si_2$ (553.28): C 62.89, H 7.83, N 7.59; found C 62.92, H 7.82, N 7.62.

3.8. (2R,3S,4R,5S)-4-Azido-5-(tert-butyl-dimethyl-silanyloxy)-6-(tert-butyl-diphenyl-silanyloxy)-2,3-dihydroxy-hexanoic acid methyl ester (**8a**)

To a solution of **7** (1 mmol) in 9 mL of acetone/water (8:1) were added NMO (2 mmol, 270 mg), $(DHQ)_2PHAL$ (0.15 mmol, 0.117 g) and OsO_4 (0.05 mmol, 0.63 mL of a 2,5% *tert*-butanol solution) and the mixture left stirring overnight at room temperature. The reaction was then quenched with $Na_2S_2O_3$ (2.5 mmol, 395 mg); the mixture left stirring for 1 h and then transferred in a separative funnel. The aqueous layer was extracted with EtOAc, the combined organic layers dried over Na_2SO_4 and the solvent removed under reduced pressure to give **8a** as colorless oil, which was used without any purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75–7.62 (4H, m, Ar), 7.50–7.32 (6H, m, Ar), 4.52 (1H, d, J = 1.2 Hz, H-2), 4.20–4.07 (2H, m, H-3+H-5), 3.83 (3H, s, OCH_3), 3.88–3.73 (1H, m, H-6_a), 3.68 (1H, dd, J = 9.5, 4.6 Hz, H-6_b), 3.60 (1H, dd, J = 3.6, 1.1 Hz, H-4), 2.46 (2H, br s, 2xOH), 1.06 (9H, s, $(CH_3)_3C$), 0.83 (9H, s, $(CH_3)_3C$), −0.05(3H, s, CH_3), −0.17 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.8, 135.5, 134.8, 129.9, 127.8, 72.1, 70.8, 70.3, 64.1, 61.9, 52.9, 26.8, 25.6, 19.1, 17.9, −4.8, −5.3.

3.9. (2R,3S,4S,5S)-4-Azido-5-(tert-butyl-dimethyl-silanyloxy)-6-(tert-butyl-diphenyl-silanyloxy)-2,3-dihydroxy-hexanoic acid methyl ester (**12a**)

Following the same procedure already described for **8a**, **12a** was obtained as colorless oil and used without any purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73–7.65 (4H, m, Ar), 7.55–7.27 (6H, m, Ar), 4.5 (1H, d, J = 1.01 Hz, H-2), 4.28 (1H, m, H-5), 4.10 (1H, dd, J = 10.2, 1.0 Hz, H-3), 3.99 (1H, dd, J = 9.7, 2.4 Hz, H-6_a), 3.93 (1H, dd, J = 9.7, 1.2 Hz, H-6_b), 3.78 (3H, s, $COOCH_3$), 3.55 (1H, dd, J = 10.2, 3.7 Hz, H-4), 3.32 (1H, br s, OH), 2.80 (1H, d, J = 6.4 Hz, OH), 1.06 (9H, s, $(CH_3)_3C$), 0.84 (9H, s, $(CH_3)_3C$), 0.02 (3H, s, CH_3), −0.13 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.6, 135.5, 135.4, 132.1, 130.0, 127.9, 72.9, 71.2, 70.9, 65.3, 64.2, 52.7, 26.6, 25.6, 18.9, 17.9, −2.9, −4.9, −5.1.

3.10. (1′S,3R,4S,5R)-5-[1′-(Tert-Butyl-dimethyl-silanyloxy)-2′-(tert-butyl-diphenyl-silanyloxy)-ethyl]-3,4-dihydroxy-pyrrolidin-2-one (**13**)

To a solution of **8a** (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, and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 70:30) to give **13** as colorless oil (75% from **7**).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70–7.62 (4H, m, Ar), 7.47–7.33 (6H, m, Ar), 6.1 (1H, s, NH), 5.12 (1H, br s, OH), 4.88 (1H, br s, OH), 4.36 (1H, d, J = 7.6 Hz, H-2), 4.15 (1H, dd, $J_1 = J_2$ = 7.6 Hz, H-3), 3.78 (1H, dd, J = 8.8, 4.5 Hz, H-5), 3.67 (2H, d, J = 4.7 Hz, H-$6_{a,b}$), 3.53 (1H, dd, J = 7.6, 4.5 Hz, H-4), 1.06 (9H, s, $(CH_3)_3C$), 0.82 (9H, s, $(CH_3)_3C$), −0.01 (3H, s, CH_3), −0.17 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.5, 135.4, 131.9, 131.8, 128.4, 128.3, 76.3, 75.9, 71.0, 66.7, 59.5, 27.7, 25.6, 18.8, 17.7, −4.6, −5.2. $C_{28}H_{43}NO_5Si_2$ (529.27): C 63.47, H 8.18, N 2.64; found C 63.51, H 8.20, N 2.68.

3.11. (1′S,2R,3S,4S)-2-[1′-(tert-Butyl-dimethyl-silanyloxy)-2′-(tert-butyl-diphenyl-silanyloxy)-ethyl]-pyrrolidine-3,4-diol (**14**)

To a solution of **13** (1 mmol) in dry THF (4.34 mL) was added BH_3.DMS (4 mmol, 0.15 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 (eluent: $CHCl_3$/CH_3OH 98:2) to afford **14** as colorless oil (68%).

^{1}H NMR (300 MHZ, $CDCl_3$) δ: 7.83–7.51 (4H, m, Ar), 7.51–7.32 (6H, m, Ar), 4.39–3.95 (2H, m, H-2+H-3), 3.95–3.51 (3H, m, H-$6_{a,b}$+H-5), 3.32–2.98 (3H,m, H-$1_{a,b}$+NH+H-4), 2.27 (2H, br s, 2xOH), 1.06 (9H, s, $(CH_3)_3C$), 0.76 (9H, s, $(CH_3)_3C$), −0.15 (3H, s, CH_3), −0.18 (3H,s, CH_3).^{13}C NMR (75 MHZ, $CDCl_3$) δ: 135.7, 135.5, 132.3, 132.1, 131.9, 129.9, 128.8, 128.6, 127.8, 127.8, 80.8, 75.8, 73.5, 70.2, 65.4, 60.7, 26.8, 25.8, 19.2, 17.9, −2.8, −5.1. $C_{28}H_{45}NO_4Si_2$ (515.29): C 65.20, H 8.79, N 2.72; found C 65.23, H 8.83, N 2.76.

3.12. 1,4-Dideoxy-1,4-imino-D-galactitol

To **14** (1 mmol) 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 **1,4-dideoxy-1,4-imino-D-galactitol·HCl** salt) as white crystals (92%). mp = 100–102 °C. $\alpha_D = -22$ (c = 1.5, H_2O). ^{1}H NMR (400 MHz, D_2O) δ: 4.27–4.19 (1H, br t, J = 2.8 Hz, H-2), 4.06 (1H, br t,

J = 3.5 Hz, H-3), 3.98–3.82 (1H, m, H-5), 3.68 (1H, dd, J = 12.1, 3.7 Hz, H-6), 3.56 (1H, dd, J = 12.2, 4.9 Hz, H-6′), 3.52–3.37 (2H, m, H-4+H-1), 3.23 (1H, dd, J = 2.6, 12.4 Hz, H-1′). ^{13}C NMR (100 MHz, D_2O) δ: 76.2, 74.2, 68.7, 66.4, 62.9, 49.6. HR-MS (ES Q-TOF) Calcd for $C_6H_{14}NO_4$ (M+H^+): 164.0971 Found: 164.0484.

3.13. (1′S,3R,4S,5S)-5-[1′-(tert-Butyl-dimethyl-silanyloxy)-2′-(tert-butyl-diphenyl-silanyloxy)-ethyl]-3,4-dihydroxy-pyrrolidin-2-one (**15**)

Following the same procedure already described for **13**, after purification by flash chromatography on silica gel (hexane/ethyl acetate 85:15) **15** was obtained as colorless oil (77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ:7.73–7.65 (4H,m), 7.55–7.27(6H,m), 6.20 (1H,d, J = 4.1 Hz,NH), 4.67 (1H, br s, OH), 4.45 (1H, br s, OH), 4.39 (1H, dd, $J_1 = J_2$ = 7.3 Hz, H-3), 4.33 (1H, d, J = 7.3 Hz, H-2), 3.82 (1H, ddd, J_1 = 7.7 Hz $J_2 = J_3$ = 4.1 Hz, H-5), 3.73 (1H, dd, J = 10.1, 7.8 Hz, H-6_a), 3.62–3.58 (2H, m, H-6_b+H-4), 1.06 (9H, s, $(CH_3)_3C$), 0.84 (9H, s, $(CH_3)_3C$), 0.07 (3H, s, CH_3), −0.05 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ:173.7, 135.4, 132.6, 131.9, 131.8, 131.6, 129.7, 128.4, 128.3, 127.7, 127.6, 76.4, 75.8, 72.3, 65.7, 59.9, 26.7, 25.7, 18.9, 17.7, −4.8, −5.1. $C_{28}H_{43}NO_5Si_2$ (529.27): C 63.47, H 8.18, N 2.64; found C 63.50, H 8.23, N 2.65.

3.14. (1′S,2S,3S,4S)-2-[1′-(tert-Butyl-dimethyl-silanyloxy)-2′-(tert-butyl-diphenyl-silanyloxy)-ethyl]-pyrrolidine-3,4-diol (**16**)

Following the same procedure already described for **14**, after purification by flash chromatography on silica gel (hexane/ethyl acetate 85:15) **16** was obtained as colorless oil (71%).

^{1}H NMR (300 MHZ, $CDCl_3$) δ:7.74–7.59 (4H, m), 7.59–7.36 (6H,m), 4.45–4.29 (2H, m, H-5+H-2),4.24 (1H, d, J = 4.4 Hz, H-3), 3.91(1H, br s, OH), 3.72–3.62 (2H, m, H-$6_{a,b}$), 3.25–3.07 (3H, m, H-4+H-$1_{a,b}$), 2.28 (1H, br s, OH), 1.62 (1H, br s, NH), 1.04 (9H, s, $(CH_3)_3C$), 0.76 (9H, s, $(CH_3)_3C$), 0.01 (3H,s, CH_3), −0.18 (3H, s, CH_3). ^{13}C NMR (75 MHZ, $CDCl_3$) δ:135.6, 135.5, 132.1, 132.0, 132.04, 131.9, 128.6, 128.4, 127.9, 127.8, 77.2, 75.6, 74.3, 67.8, 65.2, 60.2, 26.8, 25.6, 19.1, 17.8, −4.6, −5.1. $C_{28}H_{45}NO_4Si_2$ (515.29): C 65.20, H 8.79, N 2.72; found C 65.24, H 8.83, N 2.75.

3.15. 1,4-Dideoxy-1,4-imino-D-glucitol

Following the same procedure already described for ***1,4-dideoxy-1,4-imino-D-galactitol***, after purification by flash chromatography on silica gel ($CHCl_3$-MeOH 1:1) ***1,4-dideoxy-1,4-imino-D-galactitol·HCl*** salt) was obtained as white crystals (90%). mp = 138–140 °C.α_D = −26° (c = 2, H_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ:4.41–4.34 (2H, m, H-3+H-2), 4.09 (1H, ddd,$J_1 = J_2 = J_3$ = 5.5 Hz, H-5), 3.79 (1H, dd, J = 11.9,5.3 Hz, H-6_a), 3.75 (1H,dd$J$ = 11.9, 5.7 Hz, H-6_b), 3.63 (1H, dd, J = 10.1, 5.5 Hz,H-4), 3.60 (1H, dd, J = 12.4, 4.5 Hz, H-1_a), 3.40 (1H, dd, J = 12.4,2.7 Hz, H-1_b).^{13}C NMR (400 MHz, $CDCl_3$) δ: 75.3, 74.8, 68.7, 66.4, 62.9, 50.4. HR-MS (ES Q-TOF) Calcd for $C_6H_{14}NO_4$ (M+H^+): 164.0971 Found: 164.0415.

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