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Stereoselective synthesis of novel tetrahydroxypyrrolizidines

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Abstract—*N*-Benzyloxycarbonyl-2,5-dideoxy-2,5-imino-3,4-*O*-isopropylidene-L-ribose **12a** has been converted into (1*R*,2*S*,6*R*,7*S*,7a*S*)-**5** and (1*R*,2*S*,6*S*,7*R*,7a*R*)-1,2,6,7-tetrahydroxypyrrolidin-5-ones **6** and (1*R*,2*S*,6*S*,7*S*,7a*S*)-**7** and (1*R*,2*S*,6*R*,7*R*,7a*S*)-1,2,6,7-tetrahydroxypyrrolizidines **8** following stereoselective paths. These new compounds have been assayed for their inhibitory activities towards 25 glycosidases. Pyrrolizidines **7** and **8** are moderate but selective inhibitors of amyloglucosidase from *Rhizopus mold* (**7**: $IC_{50} = 130\,\mu M$, $K_i = 120\,\mu M$; **8**: $IC_{50} = 200\,\mu M$, $K_i = 180\,\mu M$, mixed type of inhibition).

1. Introduction

Pyrrolizidine alkaloids form a class of important natural compounds.[1] Their common skeleton (1-azabicyclo-[3.3.0]octane) can be hydroxylated at different positions and possess a further hydroxymethyl group at C-1 (necines), at C-3 (alexines), or at C-3 and C-5 (hyacinthacines). Many pyrrolizidine alkaloids are selective glycosidase inhibitors, and, as consequence, display a range of important biological activities.[2] This fact, together with their functional and stereochemical complexities, has promoted the development of a variety of synthetic routes and a number of synthetic analogues has been prepared.[3] The formation of the pyrrolizidine framework generally takes place by cyclization of a conveniently substituted pyrrolidine moiety. Several types of processes, for example, radical and ionic cyclizations, carbene insertions and acylimmnium cyclizations have been reviewed.[4] Other procedures such as Claisen-like intramolecular acylation involving α-pyrrolidinyl sulfones,[5] ring-closing metathesis of disubstituted ethenyl pyrrolidines,[6] or intramolecular titanium-mediated coupling reactions of α-substituted succinimides[7] have been described. Other processes include the *cis*-allylation of a chiral lactam skeleton derived from D-malic acid,[8] cyclizations of acetylenic sulfones with β-chloroamines,[9] cyclizations of *N*-propargylaminyl radicals[10] and cycloaddition processes including tandem inter[4+2]/inter[3+2],[11] hetero Diels–Alder reactions,[12] and [2+2],[13] and 1,3-dipolar cycloadditions.[14–16] Recently a chemo-enzymatic process involving an enzymatic aldol reaction followed by double reductive amination has been described for the synthesis of several tetrahydroxylated pyrrolizidine alkaloids, such as 3-*epi*-australine, australine and 7-*epi*-alexine.[17]

Sugars have been extensively used as starting materials in most syntheses in this area, and highly stereocontrolled routes for the preparation of new series of pyrrolizidine alkaloids using readily available carbohydrates have been reported. For instance, L-xylofuranose derivatives have been used for the preparation of novel pyrrolizidines structurally related to (+)-alexine and (+)-australine.[18] D-arabinose has been used for the preparation of (+)-hyacinthacine.[19] The syntheses of 7a-*epi*-hyacinthacine A_2, 5,7a-di*epi*-hyacinthacine A_3 and (+)-hyacinthacine A_3[20] have been carried out starting from D-fructose. Fleet et al. have described the synthesis of 1,2,6,7-tetrahydroxypyrrolizidines **1** and **2** starting from D-*glycero*-D-*gulo*-heptono-1,4-lactone[21] and D-*glycero*-D-*talo*-heptono-1,4-lactone,[22] respectively. The synthesis of four diastereoisomers of (+)-casuarine, starting from octonolactones[23] has also been reported. Some of the above syntheses imply the

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preparation of iminoalditols as intermediates such as 1,4-imino-L-*glycero*-D-*ido* **3** and 1,4-imino-L-*glycero*-D-*gluco*heptitols **4**[24] presenting these compounds the additional advantage of being good and selective inhibitors of α- and β-D-glucosidases (Fig. 1).

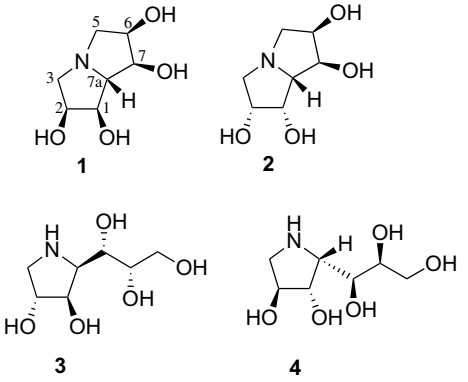


Figure 1.

It is known that small modifications on the structure of iminosugars may significantly change their enzymatic inhibitory properties,[25] therefore the development of new stereocontrolled synthetic routes for the preparation of novel natural polyhydroxylated pyrrolizidine alkaloids or of their unnatural isomers, is a task of interest for SAR studies.

Recently we have described[26] a stereoselective method for the preparation of hydroxylated indolizidines from the readily available 3,6-imino-2,3,6-trideoxy-L-*arabino* and D-*arabino*-hexose. By using a similar approach we describe herein a stereoselective route for the synthesis of two new enantiopure tetrahydroxy pyrrolizidin-5-ones **5** and **6** and two tetrahydroxypyrrolizidines **7** and **8**, starting from D-allitol and based on elongation of azasugar–carbaldehydes followed by stereoselective hydroxylation and cyclization (Fig. 2).

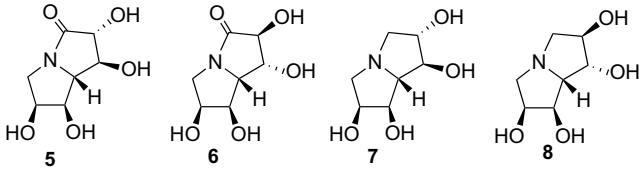


Figure 2.

2. Results and discussion

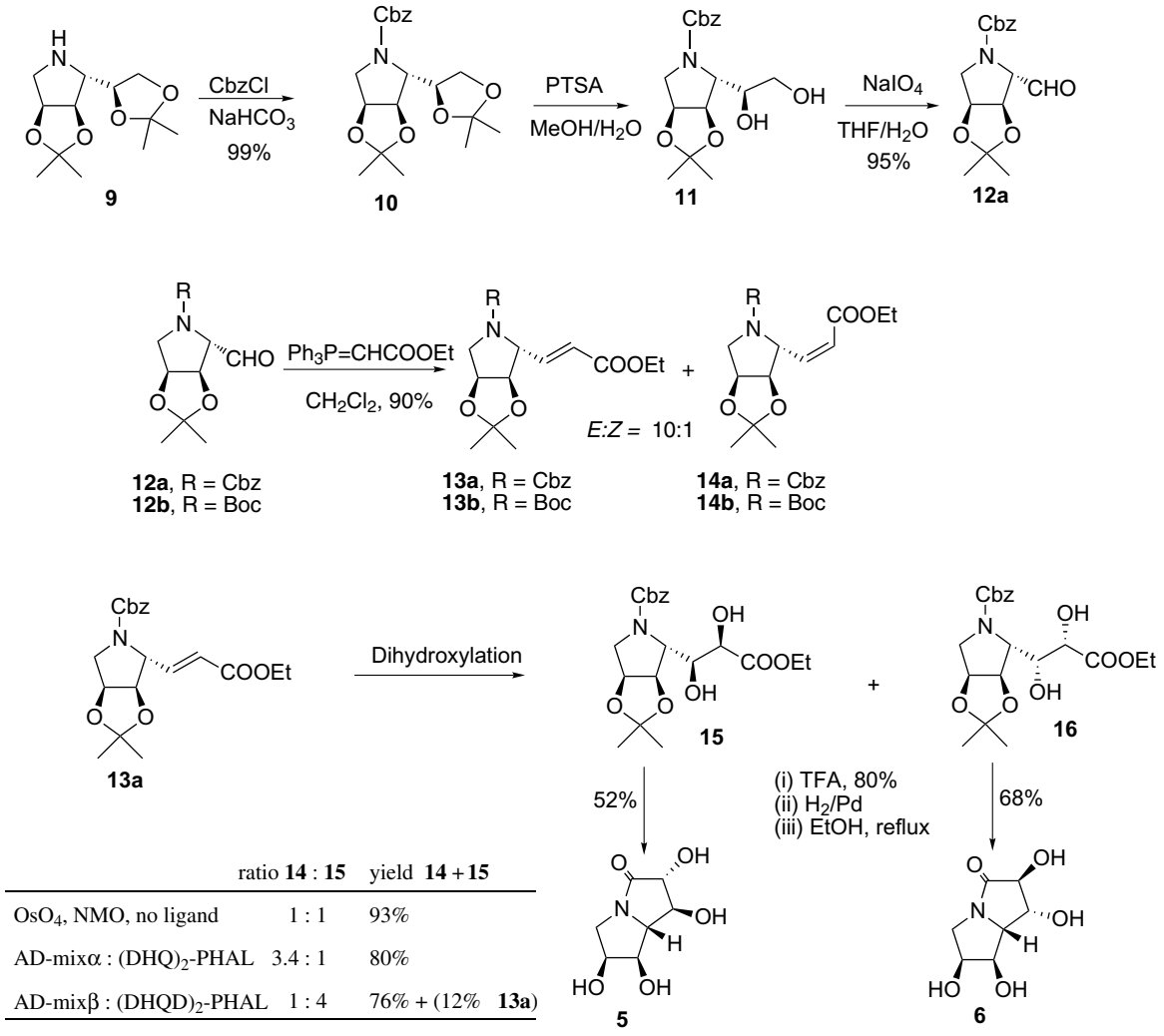
The synthesis begins from 2,5-imino-L-ribose **12a** and **12b** that were obtained according to Fleet's methodology.[27] Compound **12a** was prepared starting from 1,4-dideoxy-1,4-imino-2,3:5,6-di-*O*-isopropylidene-D-allitol[26] **9** by protection with benzyloxycarbonyl group to give successively compound **11**. Wittig reaction on **12** with two different protecting groups for nitrogen gave a mixture of alkenes **13** and **14** in a ratio *E*/*Z* 10:1. Direct hydroxylation reaction on **13a** with osmium tetroxide and morpholine-*N*-oxide gave a mixture of the corresponding *syn*-diastereoisomers **15** and **16** in a ratio 1:1, indicating that the sugar moiety does not exert any induction onto the stereoselectivity. When the reaction was carried out in the presence of the commercially available catalysts for asymmetric Sharpless dihydroxylations, good yields and a moderate selectivity were observed in both cases. *syn*-Diols **15** and **16** were obtained in a ratio 3.4:1 using AD-mixα and 1:4 with AD-mixβ. In the case of the reaction using AD-mixβ 12% of the starting material was recovered (Scheme 1).

The relative configurations of the polyhydroxylated pyrrolidine derivatives are based upon the empirical mnemonic device proposed by Sharpless[28] and have been confirmed by deprotection and cyclization reactions. Thus treatment of **15** and **16** with aq TFA, followed by hydrogenolysis and refluxing with ethanol gave pyrrolizidinones **5** and **6** in 52% and 68% yield, respectively.

The ^{1}H NMR data of **5** and **6** confirmed the proposed structures (Fig. 3, see experimental). In the case of compound **5** an NOE between pair of protons H-7a ($\delta = 3.53$)/H-6 ($\delta = 4.33$) confirmed the (*R*)-configuration of C-6. In addition, for compound **6** dihedral angle between H-6/H-7 on the one hand and between H-1/H-7a on the other hand must both approach 90° as $J_{6,7} = J_{1,7a} = 0$ Hz were observed. For compound **5**, an antiperiplanar relationship between proton pairs H-6/H-7 and H-1/H-7a ($J_{6,7} = 8.6$ Hz, $J_{1,7a} = 6.9$ Hz) is confirmed. These data are compatible with an envelope conformation for both five-membered rings in the pyrrolizidine moiety occupying C-2 and C-6 the apical positions in **5** and C-1 and C-6 in compound **6**.

In order to improve the diastereoselectivity in the Sharpless dihydroxylation with the commercial reagents AD-mixα and AD-mixβ, we decided to carry out the reaction with the *p*-methoxybenzoylic ester **18** obtained after reduction and protection. Compound **18** is a good substrate for asymmetric dihydroxylation, because it is known that aromatic moieties attached to allylic alcohols exert an excellent control of the diastereoselectivity when using the pseudoenantiomeric Cinchona alkaloid ligands for Sharpless reagents.[29] In the case of the reaction with AD-mixα, compound **19** was obtained as major compound, with a 90% d.e. Reaction with AD-mixβ gave diastereoisomer **20** with a d.e. of 99%. Hydroxylation with osmium tetroxide gave a 1:1 mixture of diastereoisomers. Zemplén methanolysis of **19** and **20** gave **21** and **22** in 91% and 84% yield, respectively, that after acidic deprotection gave the iminoalditols **23** and **24** (Scheme 2).

The configurations for the glycol moieties were based on the Sharpless mnemonic device[27] and have been confirmed by cyclization into different pyrrolizidine derivatives. This has been carried out by regioselective tosylation and Boc cleavage of **19** and **20**. The pyrrolizidines **7** and **8** were obtained in quantitative yields.



	ratio **14** : **15**	yield **14** + **15**
OsO_4, NMO, no ligand	1 : 1	93%
AD-mixα : $(DHQ)_2$-PHAL	3.4 : 1	80%
AD-mixβ : $(DHQD)_2$-PHAL	1 : 4	76% + (12% **13a**)

Scheme 1.

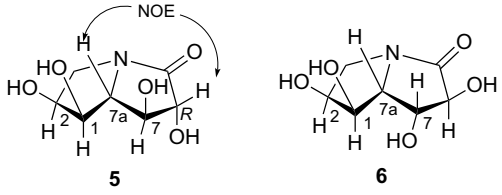
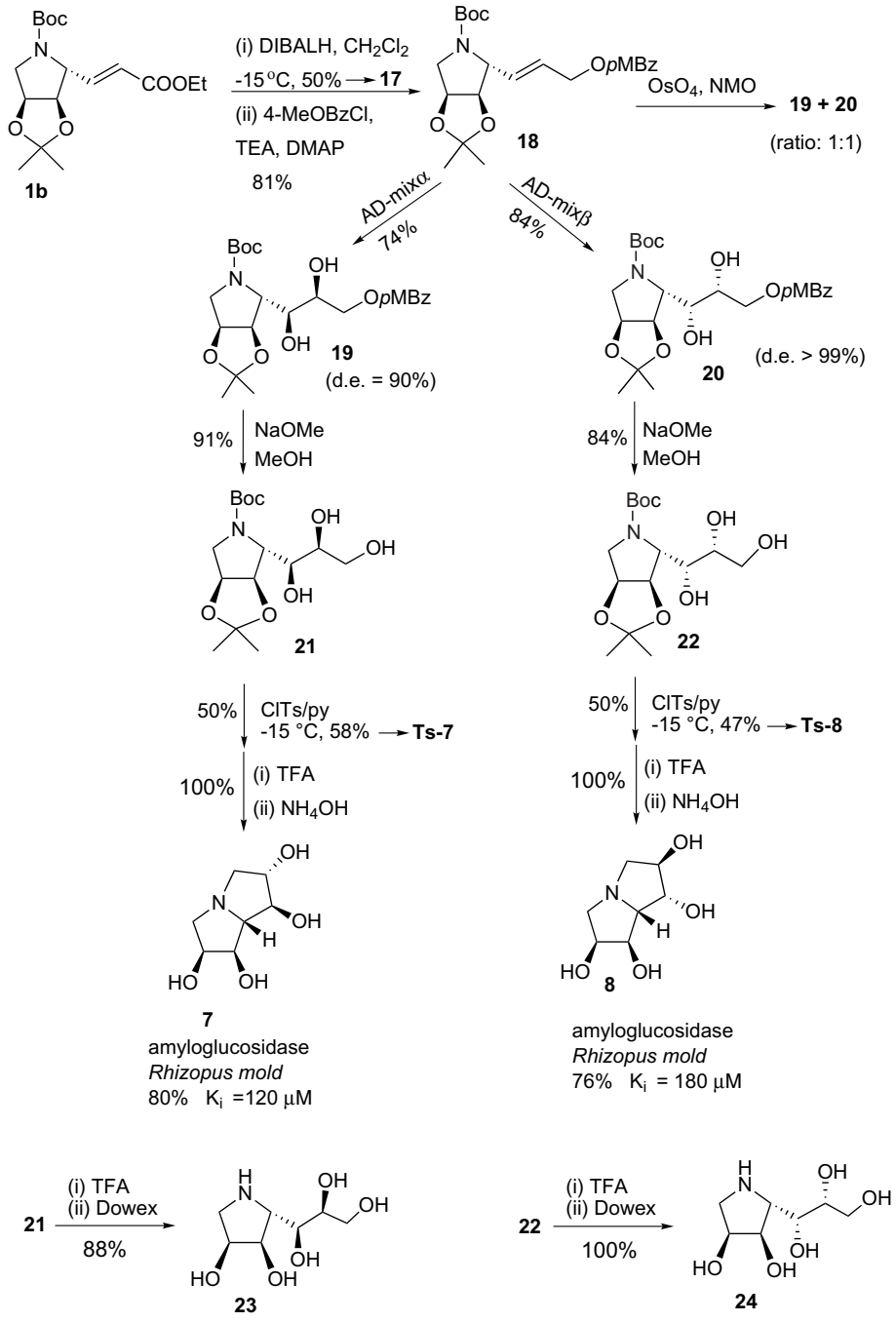


Figure 3.

The ^{1}H NMR data of **7** and **8** are in accordance with the proposed structure (Fig. 4, see experimental). The NOE observed between the ^{1}H NMR signals of H-7 ($\delta = 4.16$)/H-7a ($\delta = 3.99$) indicated the *R* configuration for C-6 and C-7 in compound **8**. For compound **7**, NOEs observed between pairs of protons H-1 ($\delta = 4.26$)/H-7 ($\delta = 4.07$) and H-6 ($\delta = 4.13$)/H-7a ($\delta = 3.41$) are compatible with the proposed *S* configuration for C-7. The average coupling constant values for these pyrrolizidines indicate higher conformational flexibility than in the case of pyrrolizidinones **5** and **6**.

Compounds **5**, **6**, **7** and **8** were assayed as enzymatic inhibitors towards 25 commercially available glycosidases. These compounds did not show any inhibitory activity at 1 mM concentration towards the following enzymes: α-L-fucosidase from bovine epididymis, and human placenta, α-galactosidases from coffee beans, *Aspergillus niger* and from *Escherichia coli*, β-galactosidases from *E. coli*, *A. niger*, *Aspergillus orizae* and from 'Jack bean', α-glucosidase (maltase) from yeast, α-glucosidase (isomaltase) from baker yeast, amyloglucosidase from *A. niger*, β-glucosidase from almond, α-mannosidase from 'Jack bean' and from almond, β-mannosidase from *Helix pomatia*, β-xylosidase from *A. niger*, α-*N*-acetylgalactosaminidase from chicken liver and β-*N*-acetylglucosaminidase from 'Jack bean' and bovine epididymis A and B. Furthermore pyrrolizidinones **5** and **6** ignored α-glucosidase from rice and amyloglucosidase from *Rhizopus mold*, presenting only weak inhibition activity towards β-galactosidase from bovine liver ($IC_{50} = 305\,\mu M$ for **5** and $IC_{50} = 470\,\mu M$ for **6**). Compound **6** presented a competitive inhibition towards β-glucosidases from *Caldocellum saccharolyticum* ($IC_{50} = 365\,\mu M$, $K_i = 117\,\mu M$). Pyrrolizidines **7** and **8** did not inhibit β-galactosidase



Scheme 2.

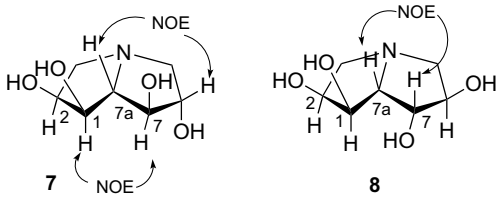


Figure 4.

from bovine liver and β-glucosidase from *C. saccharolyticum*, but presented moderate and specific inhibition activities towards amyloglucosidase from *Rhizopus mold* [$IC_{50} = 130\,\mu M$, $K_i = 120\,\mu M$ (M) for **7**; $IC_{50} = 200\,\mu M$, $K_i = 180\,\mu M$ (M) for **8**]. Compound **7** additionally presented a weak inhibition activity towards α-glucosidase from rice ($IC_{50} = 325\,\mu M$).

The methodology presented here has given access to novel pyrrolizidine derivatives, important compounds for structure–activity studies in the inhibition of glycosidases. Modification of the configuration of the tetrahydroxypyrrolizidines may induce significant changes in their inhibitory activities as demonstrated in this work.

3. Experimental

3.1. General

Optical rotations were measured in a 1.0 cm tube with a Perkin–Elmer 241 MC spectropolarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$, DMSO-d_6, CD_3OD and D_2O, J values are given in Hz and δ in ppm. All the assignments were confirmed by two-dimensional NMR experiments. The FAB mass spectra were obtained with glycerol or 3-nitrobenzyl alcohol as matrix. TLC was performed on silica gel HF_{254} (Merck), with detection by UV light and Pancaldi reagent ($(NH_4)_6MoO_4$, $Ce(SO)_4$, H_2SO_4, H_2O). Silica gel 60 (Merck, 230 mesh) was used for preparative chromatography. Anhyd solvents and reagents were freshly distilled under N_2 prior to use. The inhibition constants (K_i) and the type of inhibition (competitive, noncompetitive, mixed) were determined from Lineweaver–Burk plots.[30] For each plot, a blank and two concentrations of inhibitor were used corresponding to IC_{50} and $IC_{50}/2$.

3.2. *N*-Benzyloxycarbonyl-1,4-dideoxy-1,4-imino-2,3:5,6-di-*O*-isopropylidene-D-allitol 10

To a stirred solution of 1,4-dideoxy-1,4-imino-2,3:5,6-di-*O*-isopropylidene-D-allitoll[26] (1.50 g, 6.17 mmol) in EtOH/H_2O 1:1 (40 mL), $NaHCO_3$ (0.88 g, 10.5 mmol) and CbzCl (0.96 mL, 6.8 mmol) were added. After stirring for 2 h at rt, the mixture was poured into satd aq soln of $NaHCO_3$ (130 mL) and extracted with AcOEt (3×100 mL). The organic phases were dried over Na_2SO_4, filtered and concentrated. Column chromatography (ether/petroleum ether 1:3 → 1:1), afforded **10** (2.30 g, 99%). $[\alpha]_D^{22} = -60.5$ (c 1.2, CH_2Cl_2). IR (film) 2986, 2940, 1707 (C=O), 1418, 1103, 1057, 760, 698 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, J Hz) δ 7.36–7.31 (m, 5H, Ph), 5.14 (d, 1H, $^2J_{H,H} = 12.8$, C*H*-Ph), 5.09 (d, 1H, C*H*-Ph), 4.73 (td, 1H, $J_{2,1} = 0.8$, $J_{2,3} = J_{2,1'} = 5.8$, H-2), 4.68 (d, 1H, H-3), 4.16 (q, 1H, $J_{5,4} = J_{5,6} = J_{5,6'} = 5.8$, H-5), 4.02–3.93 (m, 2H, H-4, H-6), 3.77 (dd, 1H, $^2J_{1,1'} = 12.8$, H-1), 3.75 (dd, 1H, $^2J_{6',6} = 11.7$, H-6′), 3.42 (dd, 1H, H-1′), 1.37 and 1.30 (2s, 3H each, C(C*H*$_3$)$_2$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 153.9 (C=O), 136.4 (C-1 of Ph), 127.8, 127.2, 126.8 (Ph), 110.3 (*C*(CH$_3$)$_2$), 108.4 (*C*(CH$_3$)$_2$), 80.2 (C-2), 78.5 (C-3), 74.1 (C-5), 65.8, 65.7, 65.3 (*C*H$_2$-Ph, C-4, C-6), 51.8 (C-1), 26.2, 25.8 and 24.2 (2C(*C*H$_3$)$_2$). FABMS m/z 378 [100%, (M+H)$^+$], 400 [20%, (M+Na)$^+$]. CIMSHR m/z found 378.1913 (calcd for $C_{20}H_{27}NO_6$+H: 378.1916).

3.3. *N*-Benzyloxycarbonyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-allitol 11

To a solution of **10** (2.30 g, 6.10 mmol) in MeOH/H_2O 9:1 (30 mL), PTSA (115 mg, 0.61 mmol) was added. After 16 h at rt the reaction mixture was neutralized with IRA-68 (OH^-) resin. Filtration of the resin and evaporation of the filtrate gave a residue that, after column chromatography (ether/petroleum ether 1:2 → 3:1 and ether/acetone 6:1 → 4:1), gave **11** (0.76 g, 37%) as an oil and 1.26 g (55%) of recovered **10**. $[\alpha]_D^{22} = -34.5$ (c 1.3, CH_2Cl_2). IR (film) 3347 (OH), 2938, 1676 (C=O), 1433, 1109, 1063, 756, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, J Hz) δ 7.37–7.26 (m, 5H, Ph), 5.17 (s, 2H, C*H*$_2$-Ph), 4.87 (d, 1H, $J_{3,2} = 5.9$, H-3), 4.74 (td, 1H, $J_{2,1} = 0.8$, $J_{2,1'} = 5.8$, H-2), 4.07 (d, 1H, $J_{4,5} = 8.9$, H-4), 3.97 (dd, 1H, $^2J_{1,1'} = 13.0$, H-1), 3.60–3.55 (m, 2H, H-6, OH), 3.38 (dd, 1H, H-1′), 3.41–3.35 (m, 1H, H-5), 2.91 (br s, 1H, OH), 1.42 and 1.35 (2s, 3H each, C(C*H*$_3$)$_2$). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ ppm) δ 156.1 (C=O), 136.1 (C-1 of Ph), 128.4, 128.0, 127.5 (Ph), 111.7 (*C*(CH$_3$)$_2$), 81.9 (C-3), 79.0 (C-2), 70.4 (C-5), 67.4 (*C*H$_2$-Ph), 65.1 (C-4), 62.5 (C-6), 52.0 (C-1), 26.7 and 24.6 (C(*C*H$_3$)$_2$). FABMS m/z 338 [90%, (M+H)$^+$], 360 [100%, (M+Na)$^+$]. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.27; H, 7.17; N, 4.21.

3.4. *N*-Benzyloxycarbonyl-2,5-dideoxy-2,5-imino-3,4-*O*-isopropylidene-L-ribose 12a

A solution of $NaIO_4$ (1.31 g, 6.14 mmol) in water (20 mL) was added dropwise to a solution of **11** (1.03 g, 3.07 mmol) in THF (15 mL) cooled at 0 °C. After stirring for 1.5 h at that temperature, THF was evaporated and the residue dissolved in CH_2Cl_2 (80 mL) and washed successively with water, satd aq soln of $NaHCO_3$ and brine. The organic phase was dried, filtered and concentrated to afford crude aldehyde **12a** (0.88 g, 95%) which was used for the next step without further purification. FABMS m/z 306 [50%, (M+H)$^+$], 328 [100%, (M+Na)$^+$]. CIMSHR m/z found 306.1344 (calcd for $C_{16}H_{19}NO_5$+H: 306.1341).

3.5. Ethyl (*E*) and (*Z*)-*N*-benzyloxycarbonyl-2,3,4,7-tetradeoxy-4,7-imino-5,6-*O*-isopropylidene-L-*ribo*-hept-2-enonate 13a and 14a

To a solution of **12a** (0.88 g, 2.88 mmol) in dry CH_2Cl_2 (20 mL), ethoxycarbonyltriphenylmethylenephosphorane (1.5 g, 4.30 mmol) was added and the mixture was heated under reflux for 2 h. After evaporation of the solvent, the residue was treated with ether, filtered and concentrated. Column chromatography (ether/petroleum ether 1:5 → 1:2) afforded **13a** (956 mg, 88%) and **14a** (96 mg, 9%), both as oils.

Data for **13a**: $[\alpha]_D^{23} = -47$ (c 1, CH_2Cl_2). IR (film) 2984, 2936, 1715 (C=O), 1663 (C=C), 1109, 1051, 976, 750, 700 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, J Hz) δ 7.35–7.28 (m, 5H, Ph), 6.79 (dd, 1H, $J_{3,2} = 15.7$, $J_{3,4} = 5.7$, H-3), 5.85 (dd, 1H, $^4J_{2,4} = 1.6$, H-2), 5.14 (d, 1H, $^2J_{H,H} = 12.7$, C*H*-Ph), 5.08 (d, 1H, C*H*-Ph), 4.77 (ddd, 1H, $J_{6,5} = 5.7$, $J_{6,7'} = 4.9$, $J_{6,7} = 0.7$, H-6), 4.66–4.63 (m, 2H, H-4 and H-5), 4.15 (q, 2H, $^3J_{H,H} = 7.1$, C*H*$_2$CH$_3$), 3.77 (dd, 1H, $^2J_{7,7'} = 12.9$, H-7), 3.47 (dd, 1H, H-7′), 1.27 and 1.25 (2s, 3H each, C(C*H*$_3$)$_2$), 1.23 (t, 3H, CH$_2$C*H*$_3$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 164.6 (*C*OOEt), 153.7 (C=O of Cbz), 142.8 (C-3), 127.8, 127.2, 126.8 (Ph), 121.5 (C-2), 110.7 (*C*(CH$_3$)$_2$), 82.9 (C-5), 70.1 (C-6), 65.9 (*C*H$_2$-Ph), 63.9

(C-4), 59.6 (CH_2CH_3), 51.0 (C-7), 26.3 and 24.4 ($C(CH_3)_2$), 13.5 (CH_2CH_3). FABMS m/z 376 [10%, $(M+H)^+$], 398 [60%, $(M+Na)^+$]. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73. Found: C, 63.75; H, 6.78; N, 3.69. Data for **14a**: $[\alpha]_D^{24} = +65.6$ (c 1.8, CH_2Cl_2). IR (film) 2986, 2940, 1713 (C=O), 1196, 1117, 1053, 824, 760, 700 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, J Hz) δ 7.36–7.25 (m, 5H, Ph), 6.13 (dd, 1H, $J_{3,2} = 11.6$, $J_{3,4} = 8.7$, H-3), 5.88 (dd, 1H, $^4J_{2,4} = 1.5$, H-2), 5.49 (dd, 1H, H-4), 5.06 (s, 2H, CH_2-Ph), 4.76 (dd, 1H, $J_{6,5} = 5.2$, $J_{6,7'} = 4.9$, H-6), 4.45 (d, 1H, H-5), 4.13 (q, 2H, $^3J_{H,H} = 7.0$, CH_2CH_3), 3.74 (d, 1H, $^2J_{7,7'} = 12.9$, H-7), 3.56 (dd, 1H, H-7′), 1.35 and 1.25 (2s, 3H each, $C(CH_3)_2$), 1.22 (t, 3H, CH_2CH_3). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 164.4 (COOEt), 153.7 (C=O of Cbz), 144.3 (C-3), 136.5 (C-1 of Ph), 127.8, 127.2, 126.7 (Ph), 120.9 (C-2), 110.6 ($C(CH_3)_2$), 84.8 (C-5), 77.9 (C-6), 65.7 (CH_2-Ph), 61.6 (C-4), 59.4 (CH_2CH_3), 50.7 (C-7), 26.3 and 24.5 ($C(CH_3)_2$), 13.5 (CH_2CH_3). FABMS m/z 376 [100%, $(M+H)^+$], 398 [30%, $(M+Na)^+$]. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73. Found: C, 63.89; H, 6.81; N, 3.75.

3.6. Ethyl (*E*) and (*Z*)-*N*-(*tert*-butoxycarbonyl)-2,3,4,7-tetradeoxy-4,7-imino-5,6-*O*-isopropylidene-L-*ribo*-hept-2-enonate 13b and 14b

To a solution of **12b**[31] (1.30 g, 4.8 mmol) in dry CH_2Cl_2 (30 mL), ethoxycarbonyltriphenylmethylenephosphorane (2.34 g, 6.72 mmol) was added and the mixture was heated under reflux for 2 h. After evaporation of the solvent, the residue was treated with ether, filtered and concentrated. Column chromatography (ether/petroleum ether 1:5 → 1:2) afforded **13b** (1.27 g, 78%) and **14b** (119 mg, 7%), both as oils.

Data for **13b**: $[\alpha]_D^{24} = -39$ (c 1, CH_2Cl_2). IR (film) 1701 (C=O), 1663 (C=C), 1167, 1051, 976 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, J Hz) δ 6.77 (dd, 1H, $J_{3,2} = 15.7$, $J_{3,4} = 5.8$, H-3), 5.82 (dd, 1H, $^4J_{2,4} = 1.7$, H-2), 4.72 (ddd, 1H, $J_{6,5} = 5.2$, $J_{6,7} = 0.8$, $J_{6,7'} = 4.9$, H-6), 4.61 (dd, 1H, $J_{5,4} = 1.0$, H-5), 4.53 (dd, 1H, H-4), 4.14 (q, 2H, $^3J_{H,H} = 7.1$, CH_2CH_3), 3.67 (dd, 1H, $^2J_{7,7'} = 12.9$, H-7), 3.34 (dd, 1H, H-7′), 1.39 (s, 9H, $C(CH_3)_3$), 1.36 and 1.25 (2s, 3H each, $C(CH_3)_2$), 1.22 (t, 3H, CH_2CH_3). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 164.8 (COOEt), 153.4 (C=O of Boc), 143.6 (C-3), 121.3 (C-2), 110.8 ($C(CH_3)_2$), 83.0 (C-6), 79.0 (C-5), 78.3 ($C(CH_3)_3$), 63.9 (C-4), 59.8 (CH_2CH_3), 51.0 (C-7), 27.8 ($C(CH_3)_3$), 26.5 and 24.6 ($C(CH_3)_2$), 13.8 (CH_2CH_3). EIMS m/z 341 [7%, $(M)^{+\cdot}$], 326 [15%, $(M-CH_3)^{+\cdot}$]. Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.96; H, 7.90; N, 4.08.

Data for **14b**: $[\alpha]_D^{24} = +115$ (c 1, CH_2Cl_2). IR (film) 2985, 2936, 1715 (C=O), 1182, 1167, 1119, 1053, 714 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, J Hz) δ 6.07 (dd, 1H, $J_{3,2} = 11.6$, $J_{3,4} = 8.8$, H-3), 5.88 (dd, 1H, $^4J_{2,4} = 1.4$, H-2), 5.40 (ddd, 1H, $J_{4,5} = 0.8$, H-4), 4.72 (td, 1H, $J_{6,5} = J_{6,7'} = 5.1$, $J_{6,7} = 1.1$, H-6), 4.42 (dd, 1H, H-5), 4.16 (q, 2H, $^2J_{H,H} = 7.1$, CH_2CH_3), 3.65 (dd, 1H, $^2J_{7,7'} = 13.0$, H-7), 3.46 (dd, 1H, H-7′), 1.36 (s, 9H, $C(CH_3)_3$), 1.38 and 1.25 (2s, 3H each, $C(CH_3)_3$), 1.25 (t, 3H, CH_2CH_3). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 164.4 (COOEt), 153.2 (C=O of Boc), 144.7 (C-3), 120.4 (C-2), 110.5 ($C(CH_3)_2$), 84.7 (C-5), 78.5 ($C(CH_3)_3$), 77.9 (C-6), 61.4 (C-4), 59.3 (CH_2CH_3), 50.4 (C-7), 27.6 ($C(CH_3)_3$), 26.3 and 24.6 ($C(CH_3)_2$), 13.4 (CH_2CH_3). FABMS m/z 242 [60%, $(M-Boc+H)^+$], 364 [100%, $(M+Na)^+$]. Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.52; H, 8.01; N, 4.16.

3.7. Asymmetric dihydroxylation reactions. General procedure

To a solution of the olefin (1 mmol) in t-BuOH/H_2O 1:1 (10 mL), AD-mix (α or β) (1.4 g/mmol olefin) and $MeSO_2NH_2$ (1 mmol) were added. The reaction mixture was stirred at 0 or 25 °C until no more evolution was detected by TLC. After that, Na_2SO_3 (1.1 g/g AD-mix) was added at 0 °C and the mixture was stirred at 25 °C for 45 min. Then, it was diluted with AcOEt (20 mL) and extracted. The organic phases were washed with KOH 2 N and brine, dried over Na_2SO_4, filtered and concentrated.

3.8. General procedure for the deacylations

To a solution of the substrate (0.1 mmol) in dry MeOH (7 mL), NaOMe/MeOH (1 M) (0.03 mmol) was added until basic pH. After stirring for 3 h at 25 °C, the mixture was neutralized with IR-120 (H^+) resin, filtered and concentrated.

3.9. Boc and isopropylidene groups hydrolysis. General procedure for deprotection

The protected pyrrolidine (0.05 mmol) was stirred in a solution of 80% aqueous TFA (1.5 mL) for 2 h at 25 °C. The mixture was then poured into a Dowex 50WX8 (100–200 mesh) ion-exchange column and sequentially washed with MeOH (30 mL), H_2O (30 mL) and NH_4OH 10% (50 mL). The fractions containing the unprotected product were concentrated under vacuum.

3.10. Ethyl *N*-benzyloxycarbonyl-4,7-dideoxy-4,7-imino-5,6-*O*-isopropylidene-L-*glycero*-L-*altro*-heptanonate 15 and ethyl *N*-benzyloxycarbonyl-4,7-dideoxy-4,7-imino-5,6-*O*-isopropylidene-L-*glycero*-L-*gluco*-heptanonate 16

Asymmetric dihydroxylation of **13a** (156 mg, 0.416 mmol) with AD-mixα (16 h, rt) afforded, after work-up and column chromatography (CH_2Cl_2/acetone 25:1 → 20:1), **15** (123 mg, 61%) and **16** (40 mg, 20%). Same reaction of **13a** (156 mg, 0.416 mmol) with AD-mixβ (20 h, rt) afforded, after work-up and column chromatography (CH_2Cl_2/acetone 25:1 → 20:1), **16** (103.2 mg, 61%), **15** (25.8 mg, 15%) and a 12% of recovered **13a**.

Data for **15**: $[\alpha]_D^{25} = -32$ (*c* 0.6, CH_2Cl_2). IR (film) 3443 (OH), 2986, 2938, 1738 (C=O), 1703 (C=O), 1125, 1055, 862, 766, 698 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, *J* Hz) δ 7.36–7.30 (m, 5H, Ph), 5.10 (s, 2H, CH_2-Ph), 4.95 (d, 1H, $J_{5,6} = 5.9$, H-5), 4.93 (br d, 1H, $J_{OH,3} = 6.5$, OH-3), 4.87 (br d, 1H, $J_{OH,2} = 6.8$, OH-2), 4.69 (ddd, 1H, $J_{6,7'} = 5.1$, $J_{6,7} = 1.3$, H-6), 4.11 (q, 2H, $^3J_{H,H} = 7.1$, CH_2CH$_3$), 4.14–4.05 (m, 2H, H-4, H-2), 3.86 (m, 1H, H-3), 3.69 (dd, 1H, $^2J_{7,7'} = 12.4$, H-7), 3.48 (dd, 1H, H-7′), 1.29 and 1.25 (2s, 3H each, C(CH_3)$_2$), 1.20 (t, 3H, CH$_2$CH_3). ^{13}C NMR (125.7 MHz, DMSO-d_6 90 °C, δ ppm) δ 171.5 (*C*OOEt), 153.8 (C=O of Cbz), 136.6 (C-1 of Ph), 127.8, 127.2, 126.7 (Ph), 109.7 (*C*(CH$_3$)$_2$), 80.3 (m, C-5), 78.7 (m, C-6), 71.9, 65.9 (C-4, C-2), 71.3 (m, C-3), 65.6 (*C*H$_2$-Ph), 59.8 (*C*H$_2$CH$_3$), 52.3 (C-7), 26.4 and 24.4 (C(*C*H$_3$)$_2$), 13.5 (CH$_2$*C*H$_3$). CIMS *m*/*z* 410 [65%, (M+H)$^+$]. CIMSHR *m*/*z* found 410.1818 (calcd for $C_{20}H_{27}NO_8$+H: 410.1815).

Data for **16**: $[\alpha]_D^{19} = -47$ (*c* 1, CH_2Cl_2). IR (film) 3499, 3324 (OH), 1725 (C=O), 1678 (C=O), 1105, 1069, 878, 764, 698 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, *J* Hz) δ 7.35–7.28 (m, 5H, Ph), 5.10 (s, 2H, CH_2-Ph), 4.95 (d, 1H, $J_{5,6} = 6.0$, H-5), 4.92 (br d, 1H, $J_{OH,2} = 7.3$, OH-2), 4.86 (br d, 1H, $J_{OH,3} = 6.4$, OH-3), 4.68 (ddd, 1H, $J_{6,7'} = 5.1$, $J_{6,7} = 0.9$, H-6), 4.17 (d, 1H, $J_{4,3} = 6.0$, H-4), 4.12 (q, 2H, $^3J_{H,H} = 7.1$, CH_2CH$_3$), 4.05 (ddd, 1H, $J_{3,2} = 3.2$, H-3), 3.98 (dd, 1H, H-2), 3.73 (dd, 1H, $^2J_{7,7'} = 12.4$, H-7), 3.48 (dd, 1H, H-7′), 1.30 and 1.24 (2s, 3H each, C(CH_3)$_2$), 1.20 (t, 3H, CH$_2$CH_3). ^{13}C NMR (125.7 MHz, DMSO-d_6 90 °C, δ ppm) δ 171.7 (*C*OOEt), 154.1 (C=O of Cbz), 136.7 (C-1 of Ph), 127.8, 127.1, 126.6 (Ph), 109.8 (*C*(CH$_3$)$_2$), 80.3 (m, C-5), 78.6 (m, C-6), 70.4 (C-4), 69.6 (C-3), 66.0 (C-2), 65.6 (*C*H$_2$-Ph), 59.8 (*C*H$_2$CH$_3$), 52.6 (C-7), 26.4 and 24.3 (C(*C*H$_3$)$_2$), 13.5 (CH$_2$*C*H$_3$). FABMS *m*/*z* 432 [100%, (M+Na)$^+$]. Anal. Calcd For $C_{20}H_{27}NO_8$: C, 58.67; H, 6.65; N, 3.42. Found: C, 58.43; H, 6.84; N, 3.66.

3.11. (*E*)-*N*-(*tert*-Butoxycarbonyl)-2,3,4,7-tetradeoxy-4,7-imino-5,6-*O*-isopropylidene-L-*ribo*-hept-2-enitol 17

To a solution of **13b** (600 mg, 1.76 mmol) in dry CH_2Cl_2 (12 mL), cooled at −20 °C, DIBALH (1 M in CH_2Cl_2, 3.5 mL) was added dropwise under argon. After 20 min, the reaction was quenched with MeOH (3 mL) and allowed to warm to 25 °C. The mixture was diluted with ether (15 mL), satd aq soln of NaCl (3 mL) and $MgSO_4$ (3 g) were added and stirred for 1 h at 25 °C. After filtration and evaporation, the residue was chromatographed on silica gel (CH_2Cl_2/acetone 20:1 → 12:1) to give **17** (260 mg, 50%) as an oil. $[\alpha]_D^{25} = -30.2$ (*c* 1.8, CH_2Cl_2). IR (film) 3486 (OH), 2980, 2934, 1694 (C=O), 1410, 1215, 1165, 1055, 972 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, *J* Hz) δ 5.63 (dddd, 1H, $J_{2,3} = 15.5$, $J_{2,1} = J_{2,1'} = 4.7$, $^4J_{2,4} = 1.2$, H-2), 5.53 (dddd, 1H, $J_{3,4} = 5.4$, $^4J_{3,1} = {}^4J_{3,1'} = 1.3$, H-3), 4.70 (ddd, 1H, $J_{6,5} = 5.8$, $J_{6,7'} = 5.2$, $J_{6,7'} = 0.9$, H-6), 4.49 (d, 1H, H-5), 4.38 (m, 2H, H-4 and OH), 3.96–3.92 (m, 2H, H-1, H-1′), 3.64 (dd, 1H, $^2J_{7,7'} = 12.8$, H-7), 3.28 (dd, 1H, H-7′), 1.40 (s, 9H, C(CH_3)$_3$), 1.35 and 1.25 (2s, 3H each, C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 153.3 (C=O of Boc), 131.6 (C-2), 124.9 (C-3), 110.3 (*C*(CH$_3$)$_2$), 83.7 (C-5), 78.23 (*C*(CH$_3$)$_3$), 78.16 (C-6), 63.7 (C-4), 60.3 (C-1), 50.7 (C-7), 27.6 (C(*C*H$_3$)$_3$), 26.3 and 24.5 (C(*C*H$_3$)$_2$). FABMS *m*/*z* 322 [60%, (M+Na)$^+$], 200 [70%, (M−Boc+H)$^+$]. Anal. Calcd For $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.90; H, 8.55; N, 4.66.

3.12. (*E*)-*N*-(*tert*-Butoxycarbonyl)-2,3,4,7-tetradeoxy-4,7-imino-5,6-*O*-isopropylidene-1-*O*-(*p*-methoxybenzoyl)-L-*ribo*-hept-2-enitol 18

A solution of allylic alcohol **17** (222.5 mg, 0.744 mmol) in dry CH_2Cl_2 (3.5 mL) was treated with Et_3N (210 μL), *p*-methoxybenzoyl chloride (152 mg, 0.89 mmol) and DMAP (cat). After stirring for 4 h at 25 °C, the mixture was diluted with CH_2Cl_2 (30 mL), poured into water (40 mL) and extracted with CH_2Cl_2. The organic phase was washed with 1 M HCl (20 mL), satd aq soln of $NaHCO_3$ (2 × 30 mL) and brine (30 mL), dried, filtered and concentrated. Chromatography purification (ether/petroleum ether 1:3 → 1:2) of the residue afforded **18** (261 mg, 81%) as an oil. $[\alpha]_D^{23} = -19$ (*c* 1.5, CH_2Cl_2). IR (film) 1715 (C=O), 1597, 1404, 1260, 1165, 1066, 851, 768, 723 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, *J* Hz) δ 7.93–7.89 (m, 2H, Ph), 7.05–7.00 (m, 2H, Ph), 5.80 (dt, 1H, $J_{2,3} = 15.6$, $J_{2,1} = 4.5$, H-2), 5.73 (ddt, 1H, $J_{3,4} = 5.8$, $^4J_{3,1} = 1.0$, H-3), 4.76 (dd, 2H, H-1), 4.72 (ddd, 1H, $J_{6,5} = 5.8$, $J_{6,7'} = 5.0$, $J_{6,7} = 0.8$, H-6), 4.54 (dd, 1H, $J_{5,4} = 0.6$, H-5), 4.42 (br d, 1H, H-4), 3.85 (s, 3H, CH_3O), 3.65 (dd, 1H, $^2J_{7,7'} = 12.8$, H-7), 3.32 (dd, 1H, H-7′), 1.38 (s, 9H, C(CH_3)$_3$), 1.36 and 1.26 (2s, 3H each, C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 164.6 (C=O), 162.9 (C-1 of Ph), 153.3 (C=O of Boc), 130.7 (Ph), 129.8 (C-3), 125.3 (C-2), 121.7 (C-4 of Ph), 113.6 (Ph), 110.4 (*C*(CH$_3$)$_2$), 83.4 (C-5), 78.4 (*C*(CH$_3$)$_3$), 78.1 (C-6), 63.8 (C-4), 63.3 (C-1), 55.1 (*C*H$_3$O), 50.7 (C-7), 27.6 (C(*C*H$_3$)$_3$), 26.3 and 24.5 (C(*C*H$_3$)$_2$). FABMS *m*/*z* 456 [10%, (M+Na)$^+$], 334 [25%, (M−Boc+H)$^+$]. Anal. Calcd For $C_{23}H_{31}NO_7$: C, 63.72; H, 7.21; N, 3.23. Found: C, 63.17; H, 7.30; N, 3.17.

3.13. *N*-(*tert*-Butoxycarbonyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-7-*O*-(*p*-methoxybenzoyl)-L-*glycero*-D-*allo*-heptitol 19

To a solution of **18** (83.5 mg, 0.193 mmol) in *t*-BuOH/H_2O 1:1 (2 mL) stirred at 0 °C, AD-mixα (0.270 g) and $MeSO_2NH_2$ (18 mg, 0.193 mmol) were added. The mixture was vigorously stirred at 0 °C for 5 d and quenched by addition of Na_2SO_3 (0.35 g). After warming to 25 °C, the mixture was stirred for 45 min, diluted with AcOEt (10 mL) and H_2O (5 mL) and extracted with AcOEt (3 × 25 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. Column chromatography (CH_2Cl_2/acetone 20:1) afforded **19** (67 mg, 74%, d.e.: 90%) as a solid. $[\alpha]_D^{22} = -20$ (*c* 1, CH_2Cl_2). IR (film) 3436 (OH), 1667 (C=O), 1605, 1420, 1105 (C–O), 870, 770 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, *J* Hz) δ 7.98–7.92 (m, 2H, Ph), 7.06–6.98 (m, 2H, Ph),

4.94 (br d, 1H, $J_{3,2} = 5.8$, H-3), 4.79 (br d, 1H, $J_{OH,5} = 5.8$, OH-5), 4.67 (m, 2H, H-2, OH-6), 4.23 (d, 2H, $J_{7,6} = 5.9$, H-7), 4.01 (br d, 1H, $J_{4,5} = 3.7$, H-4), 3.84 (s, 3H, CH_3O), 3.80 (m, 1H, H-6), 3.64 (m, 1H, H-5), 3.61 (dd, 1H, $J_{1,2} = 0.8$, $^2J_{1,1'} = 12.4$, H-1), 3.41 (dd, 1H, $J_{1',2} = 5.0$, H-1′), 1.38 (s, 9H, C(CH_3)$_3$), 1.33 and 1.25 (2s, 3H each, C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 164.9 (C=O), 162.8 (C-1 of Ph), 153.7 (C=O of Boc), 130.9 (Ph), 121.9 (C-4 of Ph), 113.4 (Ph), 109.7 (*C*(CH$_3$)$_2$), 80.5 (C-3), 78.7 (C-2), 78.6 (*C*(CH$_3$)$_3$), 69.0 (C-5, C-6), 65.2 (C-4, C-7), 55.1 (*C*H$_3$O), 52.0 (C-1), 27.6 (C(*C*H$_3$)$_3$), 26.4 and 24.6 (C(*C*H$_3$)$_2$). FABMS m/z 490 [70%, (M+Na)$^+$], 368 [80%, (M−Boc+H)$^+$]. CIMS m/z 468 [10%, (M+H)$^{+\cdot}$]. CIMSHR m/z found 468.2225 (calcd for $C_{23}H_{33}NO_9$+H: 468.2233).

3.14. *N*-(*tert*-Butoxycarbonyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-7-*O*-(*p*-methoxybenzoyl)-D-*glycero*-L-*talo*-heptitol 20

To a 0 °C solution of **18** (100 mg, 0.231 mmol) in *t*-BuOH/H$_2$O 1:1 (3 mL), AD-mixβ (0.323 g) and MeSO$_2$NH$_2$ (22 mg, 0.231 mmol) were added. The mixture was vigorously stirred at 0 °C for 3 d and quenched by addition of Na$_2$SO$_3$ (0.35 g). After warming to 25 °C, the mixture was stirred for 45 min, diluted with AcOEt (10 mL) and H$_2$O (5 mL) and extracted with AcOEt (3×25 mL). The organic phase was dried (Na$_2$SO$_4$), filtered and concentrated. Column chromatography (CH$_2$Cl$_2$/acetone 20:1), afforded **20** (90.3 mg, 84%, d.e. > 99%) as a solid. $[\alpha]_D^{23} = -37$ (*c* 0.5, CH$_2$Cl$_2$). IR (film) 3464 (OH), 1697 (C=O), 1605, 1408, 1262, 1167, 1045, 853, 768, 694 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, δ ppm, *J* Hz) δ 7.96–7.91 (m, 2H, Ph), 7.04–6.99 (m, 2H, Ph), 4.70–4.60 (m, 3H, H-2, OH-5, OH-6), 4.34 (dd, 1H, $^2J_{7,7'} = 11.1$, $J_{7,6} = 6.0$, H-7), 4.72 (dd, 1H, $J_{7',6} = 5.0$, H-7′), 4.11 (br d, 1H, $J_{4,5} = 4.8$, H-4), 3.85 (s, 3H, CH_3O), 3.82–3.71 (m, 2H, H-5, H-6), 3.68 (br d, 1H, $^2J_{1,1'} = 12.6$, H-1), 3.44 (dd, 1H, $J_{1',2} = 5.0$, H-1′), 1.39 (s, 9H, C(CH_3)$_3$), 1.33 and 1.25 (2s, 3H each, C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 164.9 (C=O), 162.8 (C-1 of Ph), 153.8 (C=O of Boc), 130.8 (Ph), 122.0 (C-4 of Ph), 113.5 (Ph), 110.0 (*C*(CH$_3$)$_2$), 81.9 (C-3), 78.9 (C-2), 78.4 (*C*(CH$_3$)$_3$), 69.6 (C-5), 68.0 (C-6), 65.3 (C-4, C-7), 55.1 (*C*H$_3$O), 52.9 (C-1), 27.6 (C(*C*H$_3$)$_3$), 26.4 and 24.5 (C(*C*H$_3$)$_2$). FABMS m/z 490 [100%, (M+Na)$^+$], 368 [15%, (M−Boc+H)$^+$]. CIMSHR m/z found 468.2226 (calcd for $C_{23}H_{33}NO_9$+H: 468.2234).

3.15. *N*-(*tert*-Butoxycarbonyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-L-*glycero*-D-*allo*-heptitol 21

Conventional deacylation of **19** (43.6 mg, 0.093 mmol) with NaOMe/MeOH following the general procedure afforded, after chromatography column (CH$_2$Cl$_2$/MeOH 25:1 → 20:1), **21** (28.4 mg, 91%) as a solid. $[\alpha]_D^{25} = -17$ (*c* 0.77, CH$_2$Cl$_2$). IR (film) 3441 (OH), 2920, 1665 (C=O), 1111 (C–O), 1053 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6+D$_2$O 90 °C, δ ppm, *J* Hz) δ 4.84 (d, 1H, $J_{3,2} = 5.9$, H-3), 4.64 (td, 1H, $J_{2,1'} = 5.9$, $J_{2,1} = 0.9$, H-2), 3.94 (d, 1H, $J_{4,5} = 4.4$, H-4), 3.60 (dd, 1H, $^2J_{1,1'} = 12.5$, H-1), 3.53 (dd, 1H, $J_{5,6} = 3.5$, H-5), 3.47–3.43 (m, 2H, H-7, H-6), 3.39 (dd, 1H, $J_{7',6} = 3.5$, $^2J_{7',7} = 11.3$, H-7′), 3.36 (dd, 1H, H-1′), 1.39 (s, 9H, C(CH_3)$_3$), 1.31 and 1.23 (2s, 3H each, C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 153.6 (C=O of Boc), 109.6 (*C*(CH$_3$)$_2$), 80.6 (C-3), 78.7 (C-2), 78.2 (*C*(CH$_3$)$_3$), 71.6 (C-6), 70.5 (C-5), 65.6 (C-4), 62.5 (C-7), 52.2 (C-1), 27.6 (C(*C*H$_3$)$_3$), 26.4 and 24.5 (C(*C*H$_3$)$_2$). CIMS m/z 334 [20%, (M+H)$^{+\cdot}$], 234 [100%, (M−Boc+H)$^{+\cdot}$]. CIMSHR m/z found 334.1861 (calcd for $C_{15}H_{27}NO_7$+H: 334.1866). Anal. Calcd For $C_{15}H_{27}NO_7$: C, 54.04; H, 8.16; N, 4.20. Found: C, 53.62; H, 7.98; N, 4.19.

3.16. *N*-(*tert*-Butoxycarbonyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-*glycero*-L-*talo*-heptitol 22

Conventional deacylation of **20** (212 mg, 0.454 mmol) with NaOMe/MeOH following the general procedure afforded, after chromatography column (CH$_2$Cl$_2$/MeOH 25:1 → 20:1), **22** (126.5 mg, 84%) as a solid. $[\alpha]_D^{28} = -53.8$ (*c* 1.3, CH$_2$Cl$_2$). IR (film) 3407 (OH), 2978, 2930, 1674 (C=O), 1593, 1219, 1167, 1057 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6+D$_2$O 90 °C, δ ppm, *J* Hz) δ 4.75 (d, 1H, $J_{3,2} = 5.9$, H-3), 4.67 (td, 1H, $J_{2,1} = 5.7$, $J_{2,1'} = 0.6$, H-2), 4.02 (d, 1H, $J_{4,5} = 4.6$, H-4), 3.66–3.62 (m, 2H, H-5, H-1), 3.49 (dd, 1H, $J_{7,6} = 5.4$, $^2J_{7,7'} = 10.8$, H-7), 3.43 (dd, 1H, $J_{7',6} = 6.0$, H-7′), 3.41–3.33 (m, 2H, H-6 and H-1′), 1.37 (s, 9H, C(CH_3)$_3$), 1.29 and 1.21 (2s, 3H each, C(CH_3)$_2$). ^{13}C NMR (75.4 MHz, DMSO-d_6 90 °C, δ ppm) δ 153.2 (C=O), 109.7 (*C*(CH$_3$)$_2$), 82.0 (C-3), 78.9 (*C*(CH$_3$)$_3$), 78.3 (C-2), 70.6 (C-6), 69.6 (C-5), 65.3 (C-4), 62.5 (C-7), 52.9 (C-1), 27.7 (C(*C*H$_3$)$_3$), 26.4 and 24.5 (C(*C*H$_3$)$_2$). CIMS m/z 334 [50%, (M+H)$^{+\cdot}$]. CIMSHR m/z found 334.1869 (calcd for $C_{15}H_{27}NO_7$+H: 334.1866).

3.17. 1,4-Dideoxy-1,4-imino-L-*glycero*-D-*allo*-heptitol 23

Conventional acidic deprotection of **21** (20 mg, 0.06 mmol) with 80% aqueous TFA gave **23** (10.2 mg, 88%) as a solid. $[\alpha]_D^{25} = +17$ (*c* 1, H$_2$O). ^{1}H NMR (300 MHz, D$_2$O, δ ppm, *J* Hz) δ 4.14–4.08 (m, 2H, H-2, H-3), 3.77 (ddd, 1H, $J_{6,7} = 4.6$, $J_{6,H} = 3.2$, $J_{6,H} = 7.2$, H-6), 3.66 (dd, 1H, $^2J_{7,7'} = 11.6$, H-7), 3.64–3.57 (m, 2H, H-5, H-7′), 3.14 (t, 1H, $J_{4,5} = J_{4,3} = 6.0$, H-4), 3.11 (dd, 1H, $J_{1,2} = 5.2$, $^2J_{1,1'} = 12.1$, H-1), 2.82 (dd, 1H, $J_{1',2} = 3.7$, H-1′). ^{13}C NMR (75.4 MHz, D$_2$O, δ ppm) δ 75.3, 73.8 (C-2, C-3), 74.1 (C-6), 73.5 (C-5), 65.2 (C-4, C-7), 52.1 (C-1). CIMS m/z 194 [100%, (M+H)$^{+\cdot}$]. CIMSHR m/z found 194.1027 (calcd for $C_7H_{15}NO_5$+H: 194.1028).

3.18. 1,4-Dideoxy-1,4-imino-D-*glycero*-L-*talo*-heptitol 24

Conventional acidic deprotection of **22** (24 mg, 0.093 mmol) with 80% aqueous TFA gave **24** (14 mg, 100%) as a solid. $[\alpha]_D^{22} = +27$ (*c* 1, MeOH). ^{1}H NMR (300 MHz, MeOD, δ ppm, *J* Hz) δ 4.07 (td, 1H, $J_{2,1'} = 3.0$, $J_{2,1} = J_{2,3} = 4.8$, H-2), 3.96 (dd, 1H,

$J_{3,4} = 7.6$, H-3), 3.77 (t, 1H, $J_{5,4} = J_{5,6} = 3.0$, H-5), 3.69–3.59 (m, 3H, H-6, H-7, H-7′), 3.17 (dd, 1H, H-4), 3.18 (dd, 1H, $^2J_{1,1'} = 12.1$, H-1), 2.90 (dd, 1H, H-1′). ^{13}C NMR (75.4 MHz, MeOD, δ ppm) δ 75.0 (C-3), 74.8 (C-6), 72.1 (C-2), 70.3 (C-5), 65.0 (C-4), 64.0 (C-7), 52.4 (C-1). CIMS m/z 194 [100%, $(M+H)^{+\cdot}$]. CIMSHR m/z found 194.1034 (calcd for $C_7H_{15}NO_5$+H: 194.1028).

3.19. (1*R*,2*S*,6*R*,7*S*,7a*S*)-1,2,6,7-Tetrahydroxypyrrolizidin-5-one 5

A suspension of **15** (60 mg, 0.147 mmol) in 80% aqueous TFA (1.5 mL) is stirred at 25 °C for 2 h. Evaporation of the solvent gave a residue that after column chromatography (CH_2Cl_2/MeOH 25:1) afforded a crude product that was hydrogenated for 4 h (abs EtOH, 3 mL; Pd/C, 10%, 18 mg). The reaction mixture was filtered and the filtrate heated under reflux for 24 h. Evaporation of the solvent and column chromatography (CH_2Cl_2/MeOH/NH_4OH 10% 4:2:0.5) led to **5** (9 mg, 52%). $[\alpha]_D^{22} = +25$ (*c* 0.24, MeOH). IR (film) 3333 (OH), 1688 (C=O), 1441, 1379, 1115 (C–O) cm^{-1}. ^{1}H NMR (300 MHz, MeOD, δ ppm, *J* Hz) δ 4.33 (br d, 1H, $J_{6,7} = 8.6$, H-6), 4.15 (td, 1H, $J_{2,3} = J_{2,1} = 4.9$, $J_{2,3'} = 2.7$, H-2), 3.90 (dd, 1H, $J_{7,7a} = 7.0$, H-7), 3.85 (dd, 1H, $J_{1,7a} = 6.9$, H-1), 3.75 (dd, 1H, $J_{3,2} = 5.2$, $^2J_{3,3'} = 12.5$, H-3), 3.53 (t, 1H, H-7a), 3.03 (dd, 1H, H-3′). ^{13}C NMR (75.4 MHz, MeOD, δ ppm) δ 175.2 (C=O), 82.3 (C-7), 80.2 (C-6), 77.6 (C-1), 73.5 (C-2), 67.4 (C-7a), 50.0 (C-3). CIMS m/z 190 [100%, $(M+H)^{+\cdot}$]. CIMSHR m/z found 190.0717 (calcd for $C_7H_{12}NO_5$+H: 190.0715).

3.20. (1*R*,2*S*,6*S*,7*R*,7a*S*)-1,2,6,7-Tetrahydroxypyrrolizidin-5-one 6

A suspension of **16** (60.8 mg, 0.149 mmol) in 80% aqueous TFA (1.5 mL) is stirred at 25 °C for 2 h. Evaporation of the solvent gave a residue that after column chromatography (CH_2Cl_2/MeOH 30:1) afforded a crude product that was hydrogenated for 4 h (abs EtOH, 3 mL; Pd/C, 10%, 18 mg). The reaction mixture was filtered and the filtrate heated under reflux for 24 h. Evaporation of the solvent led to **6** (15 mg, 68%). $[\alpha]_D^{23} = -5.4$ (*c* 0.75, MeOH). IR (film) 3360 (OH), 1676 (C=O), 1451, 1090 (C–O) cm^{-1}. ^{1}H NMR (500 MHz, MeOD, δ ppm, *J* Hz) δ 4.25 (td, 1H, $J_{2,1} = J_{2,3} = 4.8$, $J_{2,3'} = 2.7$, H-2), 4.21 (dd, 1H, $J_{1,7a} = 7.0$, H-1), 4.17 (dd, 1H, $J_{7a,7} = 3.8$, H-7a), 4.14 (d, 1H, H-7), 3.92 (s, 1H, H-6), 3.66 (dd, 1H, $J_{3,2} = 5.1$, $^2J_{3,3'} = 12.7$, H-3), 3.08 (dd, 1H, $J_{3',2} = 2.6$, H-3′). ^{13}C NMR (75.4 MHz, MeOD, δ ppm) δ 175.8 (C=O), 82.9 (C-6), 74.5 (C-2), 73.0 (C-7), 69.9 (C-1), 69.0 (C-7a), 49.2 (C-3). CIMS m/z 190 [100%, $(M+H)^{+\cdot}$]. CIMSHR m/z found 190.0716 (calcd for $C_7H_{12}NO_5$+H: 190.0715).

3.21. (1*R*,2*S*,6*S*,7*S*,7a*S*)-1,2,6,7-Tetrahydroxypyrrolizidine 7

To a −20 °C solution of **21** (91.5 mg, 0.275 mmol) in dry pyridine (2.5 mL), TsCl (104.8 mg, 0.55 mmol) was added. After 1.5 h at −20 °C, water was added (0.5 mL) and the mixture was allowed to warm to 25 °C. Solvent was removed and the residue was diluted with AcOEt, washed successively with 1 M HCl, satd aq soln of $NaHCO_3$ and brine, dried and concentrated. Purification by column chromatography (CH_2Cl_2/MeOH 80:1 → 20:1) afforded tosylate **Ts-7** (78 mg, 58%) and 17 mg (18%) of recovered **21**. Tosylate **Ts-7** (59.3 mg, 0.122 mmol) was then treated with TFA 80% at 25 °C for 2 h and then evaporated. The residue was dissolved in water and treated with NH_4OH until basic pH. Solvent evaporation and purification by column chromatography (CH_2Cl_2/MeOH/NH_4OH 10% 4:2:0.5) afforded **7** (21 mg, 100%). $[\alpha]_D^{22} = +24$ (*c* 0.72, MeOH). ^{1}H NMR (300 MHz, MeOD, δ ppm, *J* Hz) δ 4.26 (dd, 1H, $J_{7,7a} = 6.9$, $J_{7,6} = 4.1$, H-7), 4.20 (ddd, 1H, H-6), 4.13 (ddd, 1H, H-2), 4.07 (t, 1H, $J_{1,2} = J_{1,7a} = 2.8$, H-1), 3.41 (dd, 1H, H-7a), 3.34 (dd, 1H, $J_{3,2} = 4.3$, $^2J_{3,3'} = 11.8$, H-3), 3.30 (dd, 1H, $J_{5,6} = 2.6$, H-5), 3.09 (dd, 1H, $^2J_{5',5} = 11.4$, $J_{5',6} = 3.9$, H-5′), 2.83 (dd, 1H, $J_{3',2} = 3.1$, H-3′). ^{13}C NMR (75.4 MHz, MeOD, δ ppm) δ 80.0 (C-1), 79.3 (C-2), 76.7 (C-7a), 76.4 (C-7), 73.4 (C-6), 61.5 (C-5), 60.2 (C-3). CIMS m/z 176 [100%, $(M+H)^{+\cdot}$]. CIMSHR m/z found 176.0921 (calcd for $C_7H_{13}NO_4$+H: 176.0923).

3.22. (1*R*,2*S*,6*R*,7*R*,7a*S*)-1,2,6,7-Tetrahydroxypyrrolizidine 8

To a solution of **22** (75 mg, 0.225 mmol) in dry pyridine (2 mL) stirred at −20 °C, TsCl (85.8 mg, 0.45 mmol) was added. After 1.5 h at −20 °C, water was added (0.5 mL) and the mixture was allowed to warm to 25 °C. Solvent was removed and the residue was diluted with AcOEt, washed successively with 1 M HCl, satd aq soln of $NaHCO_3$ and brine, dried and concentrated. Purification by column chromatography (CH_2Cl_2/MeOH 80:1 → 20:1) afforded the corresponding tosylate **Ts-8** (51 mg, 47%) and 21 mg (28%) of recovered **22**. Tosylate **Ts-8** (35.6 mg, 0.073 mmol) was then treated with 80% aqueous TFA at 25 °C for 2 h and then evaporated. The residue was dissolved in water and treated with NH_4OH until basic pH. Solvent evaporation and purification by column chromatography (CH_2Cl_2/MeOH/NH_4OH 10% 4:2:0.5) afforded **8** (12.8 mg, 100%). $[\alpha]_D^{23} = +31$ (*c* 0.9, MeOH). ^{1}H NMR (300 MHz, MeOD, δ ppm, *J* Hz) δ 4.46 (t, 1H, $J_{1,2} = J_{1,7a} = 4.4$, H-1), 4.38 (q, 1H, $J_{2,3} = J_{2,3'} = 4.5$, H-2), 4.25 (br t, 1H, H-6), 4.16 (dd, 1H, $J_{7,7a} = 4.4$, $J_{7,6} = 1.5$, H-7), 3.99 (t, 1H, H-7a), 3.38 (dd, 1H, $^2J_{3,3'} = 11.5$, H-3), 3.35 (dd, 1H, $J_{5,6} = 1.4$, H-5), 3.08 (dd, 1H, $J_{5',6} = 3.1$, $^2J_{5',5} = 11.6$, H-5′), 3.00 (dd, 1H, H-3′). ^{13}C NMR (75.4 MHz, MeOD, δ ppm) δ 79.2 (C-6), 75.1 (C-7a), 74.6, 74.5 (C-2, C-7), 70.6 (C-1), 60.7 (C-5), 59.3 (C-3). CIMS m/z 176 [100%, $(M+H)^{+\cdot}$]. CIMSHR m/z found 176.0920 (calcd for $C_7H_{13}NO_4$+H: 176.0923).

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