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The Synthesis of Ester and Ketone Analogues of 1-Deoxynojirimycin and Castanospermine

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Abstract: 1-Amino-1-deoxy-D-glucitol (**3**) was converted into the 3,4;5,6-di-*O*-isopropylidene protected ammonium salt **17** which was transformed further into the *trans*-fused piperidine acetonides **4-8** in six steps and 23-32% overall yield. In the final step, ring closure was effected *via* cleavage of the *N*-Boc group of intermediates **27-29** with trimethylsilyl iodide: this enabled internal, face selective 1,4-addition of the free amino group to the (5,6)-α,β-unsaturated carbonyl moiety. Further modification and (or) deprotection of compounds **4-8** afforded the piperidine and indolizidine imino sugars **9-12** and **14-15**.
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INTRODUCTION

Glucosidase inhibitors have attracted considerable attention as potential chemotherapeutic agents for treatment of some viral diseases[1] or carbohydrate-dependent metabolic disorders such as diabetes[2] and cancer[3]. The polyhydroxylated alkaloids 1-deoxynojirimycin[4] **1** and castanospermine[5] **2** (Figure 1) are selective inhibitors of several glucosidases. They further exhibit antiviral (including anti-HIV) and antidiabetic activities.[6] The high potential of these alkaloids in a wide range of biological applications makes them and their structural analogues inviting targets in organic synthesis.[7,8] To accomplish structural modification, for example the introduction of lipophilic (fluoro,[9] alkyl,[10] and acyl[11]), amino,[12] and glucosyl[13] groups at specific positions of the piperidine and indolizidine ring systems of compounds **1** and **2**, new selectively protected chiral synthons must be created. In this respect the *trans*-fused piperidine acetonides **4-8** and the β-ketoester **13** can play a key role since they represent advanced intermediates showing the desired variety of protected and non protected functional groups. When further modified and (or) deprotected, they may therefore provide access to a large number of variously substituted analogues of 1-deoxynojirimycin and castanospermine.

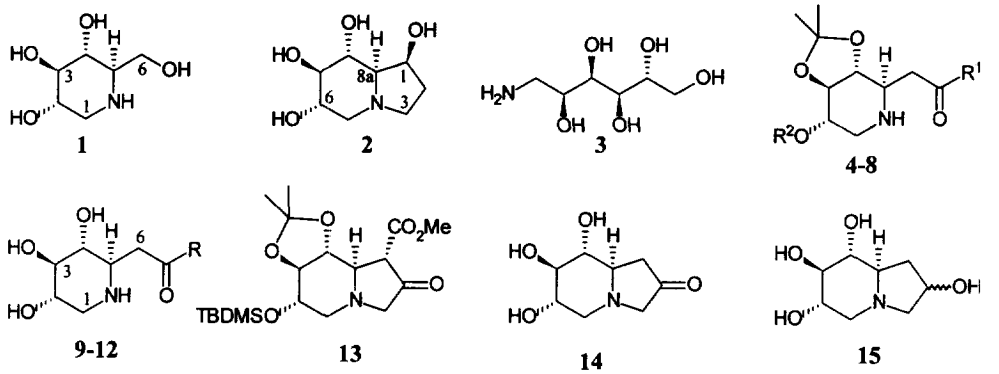


Figure 1 (For substituents R, R^1, and R^2: see schemes 4 and 5)

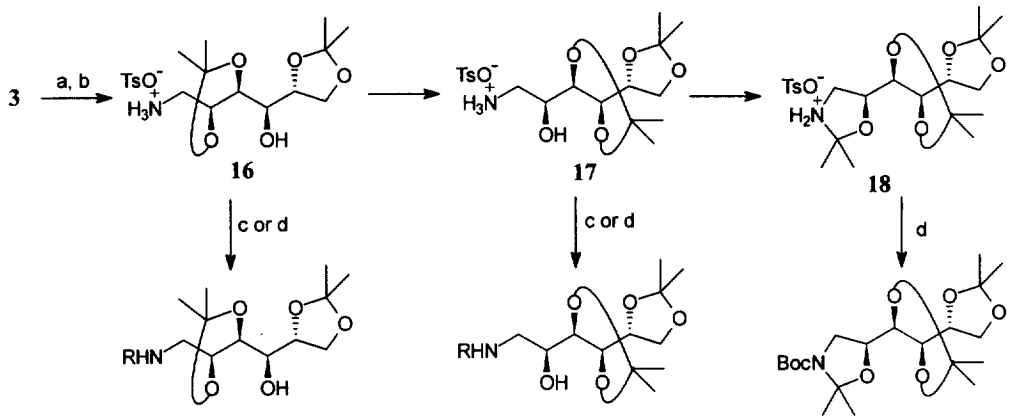
A brief account of the synthesis of the keto imino sugars **9-12** has appeared recently.[14] Starting from 1-amino-1-deoxy-D-glucitol **3**, our synthetic sequence proceeded through acid deprotection of the *trans*-fused acetonides **4-8** to afford the piperidine products **9-12**, 7-carbonyl homologues of 1-deoxynojirimycin. We now report full details of the scope and limitations of these transformations. The potential of **4-8** as synthetic intermediates was confirmed by conversion of the ester compound **6** (R^1 = OMe, R^2 = *t*-$BuMe_2Si$) into the β-ketoester **13** which in turn served as a key intermediate in the synthesis of the 2-substituted castanospermine analogues **14** and **15**.

RESULTS AND DISCUSSION

At the outset of this work our aim was to transform 1-amino-1-deoxy-D-glucitol (**3**)[15] into various chiral synthons,[16,17,18] e.g. selectively protected piperidine imino sugars suited for conversion into analogues of **1** and **2**. Initial protection of **3** as a diacetonide has been accomplished in two different regioselective ways. When starting from an *N*-acyl compound, e.g. the *N*-Boc derivative of **3**, the 2,3;5,6-di-*O*-isopropylidene derivative was produced as the major diacetonide; this product can be transformed into analogues of 1-deoxynojirimycin modified at C-4 and C-6.[16] In the alternative conversion of the *N*-unprotected aminoalditol **3** described below, a crystalline 3,4;5,6-di-*O*-isopropylidene ammonium salt derivative **17** was isolated which in turn may serve as a precursor of analogues modified at C-2 and C-6.

On treatment of the *p*-toluenesulfonate salt of **3** with acetone, 2,2-dimethoxypropane (DMP), and additional *p*-toluenesulfonic acid (*p*-TsOH) (0.5 equivalents), the diacetonide ammonium salt **17** was produced in 71 % yield by spontaneous crystallisation from the reaction medium (Scheme 1). However, t.l.c. analysis revealed that the proportion of salt products, *i.e.* the regioisomeric diacetonides **16** and **17** and triacetonide **18**, was highly time-dependent. After reaction for 30 min **16** was detected as the predominant kinetic product in the homogeneous reaction mixture. Subsequent acid catalysed equilibration led to transformation of **16** into the crystalline regioisomer **17** that was collected by filtration. After 24 hours, compound **16** was no longer chromatographically detectable in the filtrate which contained **17** along with the triacetonide **18** originating

from a slow further reaction of **17**. To analyse the proportion of acetonides **16**, **17** and **18** the ammonium salts were converted into the less polar *N*-acylvinyl or *N*-Boc derivatives by treating samples of the reaction mixture with Na_2CO_3 and diethyl ethoxymethylenemalonate or di-*tert*-butyl dicarbonate. A clean t.l.c. separation of the diacetonide regioisomers was achieved for the *N*-acylvinyl derivatives **19** and **20** but not for the corresponding *N*-Boc compounds **21** and **22** (hexanes-EtOAc 7:3). For the triacetonide salt a complementary t.l.c. analysis as the apolar *N*-Boc compound **23** was required since the secondary amine derived from **18** failed to react with the acylvinyl reagent.



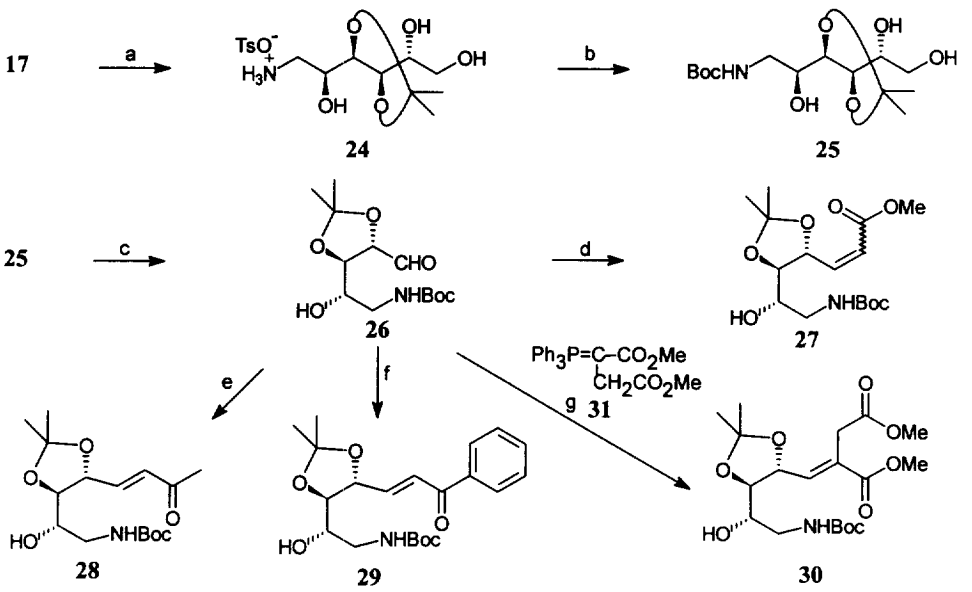
Reagents: (a) MeOH, *p*-TsOH.H_2O (1 eq); (b) Acetone-DMP (1:3), *p*-TsOH.H_2O (0.5 eq); (c) Na_2CO_3, MeOH-H_2O, $EtOCH=C(CO_2Et)_2$; (d) Na_2CO_3, MeOH-H_2O, $(t\text{-}BuOCO)_2O$.

Scheme 1

The free amino function of compound **17** can be derivatised also with other *N*-protecting groups (e.g. formyl, trityl, benzyloxycarbonyl) thus allowing for a general preparation of *N*-protected 3,4;5,6-*O*-diacetonides that cannot be obtained in pure form when subjecting the corresponding *N*-derivatives of **3** to acetal formation.

Our plan for conversion of **17** into the piperidine synthons **4-8** involved deprotection and oxidative cleavage of the 5,6-diol group, chain elongation of the resulting C-5 aldehyde to form the (5,6)-α,β-unsaturated 7-carbonyl compounds **27-30**, and final ring closure through internal 1,4-addition of the free amino group (see Schemes 2 and 4). Of crucial importance in our synthetic strategy was the choice of a suitable *N*-protecting group allowing both for manipulation of the functional groups and for retention of the 3,4-*O*-isopropylidene group during the final *N*-deprotection step. The synthesis of the α,β-unsaturated carbonyl compounds **27-30** is depicted in Scheme 2. The 5,6-*O*-isopropylidene group of the diacetonide salt **17** could be hydrolysed without affecting the 3,4-*O*-isopropylidene group by heating the salt with 1 equivalent of pyridinium *p*-toluenesulfonate (PPTS) in aqueous methanol at 60°C for 1 hour. The resulting monoacetonide salt **24** and non hydrolysed **17** were converted *in situ* to the corresponding *N*-Boc derivatives and the apolar diacetonide **22** was separated from the desired triol **25** by successive extraction of an aqueous solution with toluene and ethyl acetate. Additional

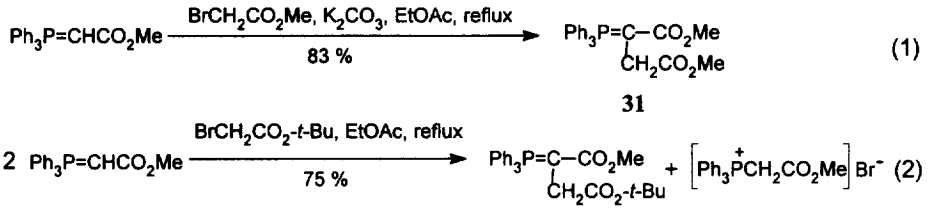
triol was obtained by subjecting the recovered (28 %) diacetonide **22** to the same hydrolysis and extraction procedure. Following crystallisation of the combined triol fractions in ethyl acetate-hexanes compound **25** was isolated in 81 % overall yield based on **17**.



Reagents: (a) PPTS (1 eq), MeOH-H_2O (9:1), 60 °C, 1 h; (b) Na_2CO_3, (*t*-BuOCO)$_2O$, 0.5 h; (c) $NaIO_4$, H_2O, 5 min; (d) $Ph_3P{=}CHCO_2Me$, MeOH, 0.5 h; (e) $Ph_3P{=}CHCOMe$, MeOH or CH_2Cl_2, 0.5 h; (f) $PhCOCH_2Ph_3P^+Br^-$, MeONa, MeOH, 0.5 h; (g) **31**, MeOH, 0.5 h.

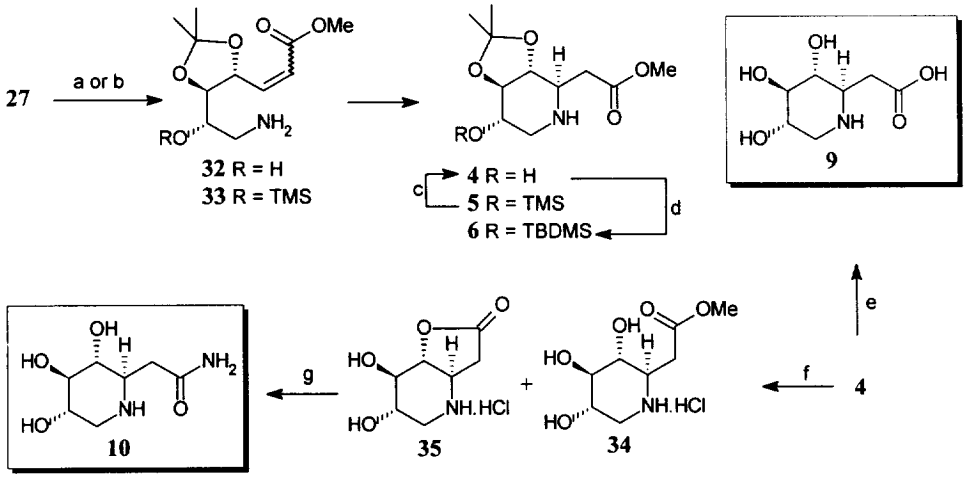
Scheme 2

The oxidative cleavage of the 5,6-diol group of triol **25** was effected with $NaIO_4$ in water to produce the unstable L-xylose derivative **26**. This was subjected directly to various Wittig reactions using the appropriate triphenylphosphoranylidene reagents in methanol or dichloromethane. Following chromatographic purification the α,β-unsaturated carbonyl compounds **27-30** were isolated in 57-75 % yield based on the triol precursor **25**. Analysis of the ^1H and ^{13}C NMR spectra of the ester compound **27** revealed a 85:15 mixture of the (*Z*)- and (*E*)-isomers. For the α,β-unsaturated ketones **28** and **29** the (*E*)-geometry was established by the olefinic coupling constant $J_{5,6}$ = 16 Hz. The analogous diester **30** was prepared in 70 % yield by reaction of L-xylose **26** with methyl 2-(triphenylphosphoranylidene)succinate **31** in dichloromethane. The (*E*)-geometry of **30** was inferred by comparing the δ-value for the olefinic proton H-4 (δ = 6.85) to the values observed for the analogous proton H-3 in the spectrum of the (*E*)- and (*Z*)-isomers **27** (δ = 6.85 and 6.20, respectively). The required Wittig reagent **31** was prepared (Scheme 3, eq. 1) by reaction of methyl (triphenylphosphoranylidene)acetate with methyl bromoacetate and K_2CO_3 in ethyl acetate. In this modification of the reported method (eq. 2),[19] K_2CO_3 was used instead of the expensive methyl (triphenylphosphoranylidene)acetate to abstract the α-proton of the phosphonium intermediate.



Scheme 3

The key step in our synthetic sequence involved *N*-deprotection of the enone compounds **27-30** which enabled the internal 1,4-addition of the free amino group. Cleavage of the *N*-Boc group of ester **27** was attempted first with formic acid at 0°C for 10 min (Scheme 4). On neutralisation with aqueous Na_2CO_3 cyclisation of the intermediate primary amine **32** occurred producing the desired piperidine ester **4** in 36 % yield. The low yield was due to incomplete deprotection of the amino group and, presumably, partial deprotection of the isopropylidene group resulting in unidentified polar side products. A more selective deprotection of the amino group was achieved by reaction of ester **27** with Me_3SiI in dry dichloromethane for 10 min. Addition of methanol and triethylamine to the reaction mixture led to rapid cyclisation of the intermediate *O*-silylated amine **33** to give piperidine compound **5** and the corresponding *O*-desilylated product **4**. No cyclisation was observed in the absence of methanol. In view of these results complete *O*-desilylation was carried out on the ether/alcohol mixture **5** and **4**, using K_2CO_3 in methanol, to afford the alcohol product **4** in 53 % yield based on **27**.



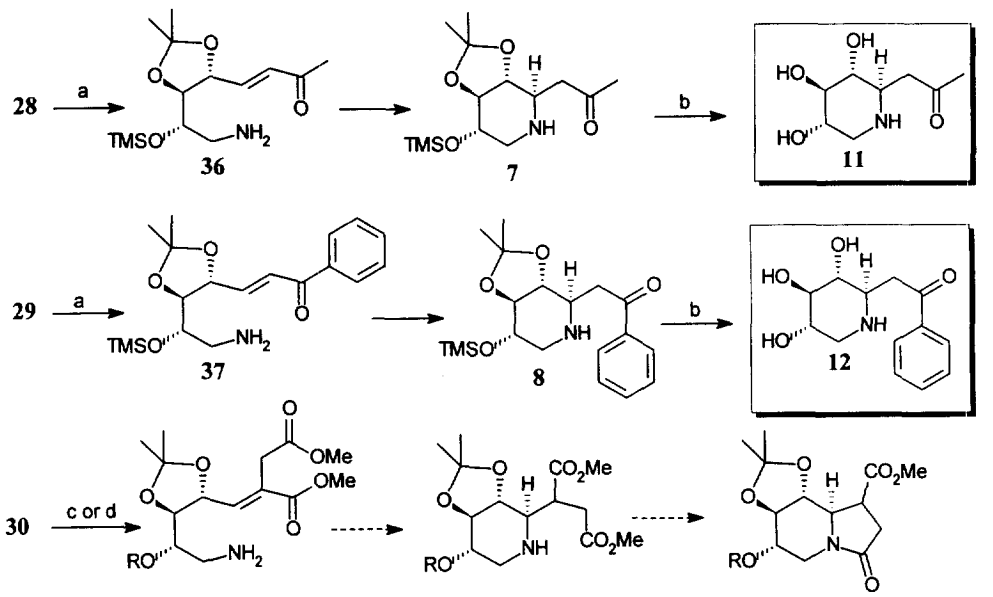
Reagents: (a) HCO_2H, r.t. 10 min; aq. Na_2CO_3; (b) Me_3SiI, CH_2Cl_2, r.t., 10 min; MeOH-Et_3N; (c) MeOH-K_2CO_3; (d) *t*-$BuMe_2SiCl$, DBU, CH_2Cl_2, 2.5 h; (e) 6M HCl; Dowex 50W-X8 (0.2M NH_4OH); (f) HCl-MeOH; (g) NH_3-MeOH, NaCN, reflux; Dowex 50W-X8 (0.2M NH_4OH).

Scheme 4

A more effective protection of the OH group was achieved as the *tert*-butyldimethylsilylether **6** which was prepared by further reaction of **4** with *t*-BuMe$_2$SiCl and DBU in dichloromethane (43 % yield from **27**). Compound **6** was used as an intermediate in the synthesis of castanospermine analogues (see Scheme 6 below).

Further modification and subsequent deprotection of ester **4** furnished the acid and amide target compounds **9** and **10** (Scheme 4). The acid was produced by treatment with aqueous 6M HCl for 48 hours and was isolated in 88 % yield by using ion exchange chromatography. A mixture of deprotected methyl ester **34** and lactone **35** was formed when **4** was subjected to treatment with methanolic HCl followed by complete evaporation of the acidic solution. Ammonolysis of this mixture provided amide **10**: the conversion was effected by prolonged heating with methanolic ammonia using NaCN as a catalyst.[20] Following ion exchange chromatography the amide was isolated in 61 % yield from ester **4**.

The conversion of the α,β-unsaturated ketones **28** and **29** into the piperidine acetonides **7** and **8** also was achieved *via* cleavage of the *N*-Boc protecting group with trimethylsilyl iodide in dichloromethane (Scheme 5). Quenching of the reaction with triethylamine generated the primary amines **36** and **37** which, in contrast to the aminoester **33**, underwent smooth cyclisation without further addition of methanol. Piperidines **7** and **8** were isolated in 57 % and 51 % yield. Deprotection of diester **30** with formic acid or Me$_3$SiI gave the free amine **38**. However, none of the expected monocyclic or bicyclic compound (**39** or **40**) was formed, even on heating the free amine **38** in methanol or 2-butanol.

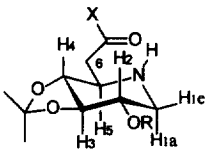


Reagents: (a) Me$_3$SiI, CH_2Cl_2, r.t., 5 min; Et_3N; (b) 6M HCl; NH_4OH; (c) HCO_2H; aqueous Na_2CO_3; MeOH or *sec*-BuOH, reflux; (d) Me$_3$SiI, CH_2Cl_2, r.t., 10 min; Et_3N-MeOH; MeOH or *sec*-BuOH, reflux.

Scheme 5

From a conformational study it appears that both unsaturated amino esters **32** and **38** can adopt a similar low energy conformation which favours *Re*-face addition of the amino group to C-5. For the piperidine products **4-8**, this *Re*-attack results in the observed equatorial orientation of the C-5 substituent. Hence, the failure of diester **38** to undergo 1,4-addition would not be due to a restricted access of the amino group to the *Re*-face, but rather must be accounted for by the inherently low reactivity of the trisubstituted double bond. The structure of compounds **4-8** was secured by spectral data which support the D-configuration of the imino sugars. In the ^{1}H NMR spectra (Table 1), the newly created stereogenic center at C-5 was assigned on basis of the coupling constant values, $J_{4,5} = J_{3,4} = 9$ Hz. These *J*-values clearly show the *trans*-diaxial relationship for H-4 and H-5 and hence the equatorial orientation of the side chain.

Table 1. Chemical Shifts (δ) and *J*-values for compounds 4, 7 and 8

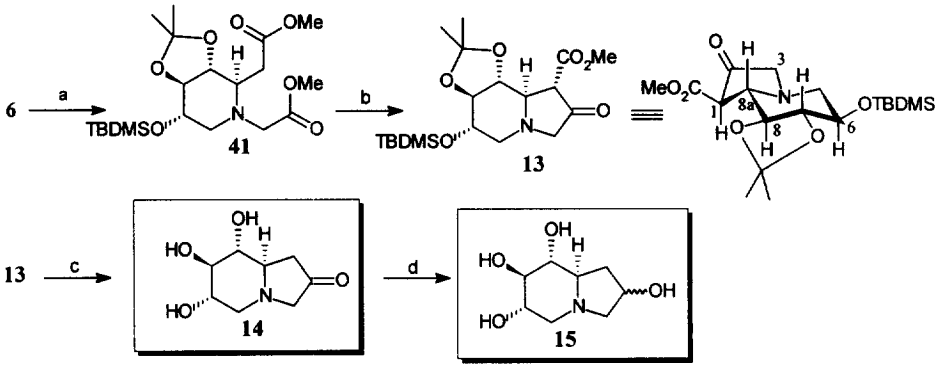


	[a]Compound 4 X= OMe, R = H			[a]Compound 7 X = Me, R = TMS			[b]Compound 8 X = Ph, R = TMS		
proton	d, ppm, $CDCl_3$	multi-plicity	*J*, Hz	d, ppm, C_6D_6	m.	*J*, Hz	d, ppm, $CDCl_3$	m.	*J*, Hz
H1a	2.49	dd	$J_{1a,1e}$ = 12.5 $J_{1a,2}$ = 9.0	2.35	dd	$J_{1a,1e}$ = 13.0 $J_{1a,2}$ = 9.0	2.57	dd	$J_{1a,1e}$ = 13.0 $J_{1a,2}$ = 9.0
H1e	3.21	dd	$J_{1a,1e}$ = 12.5 $J_{1e,2}$ = 5.0	2.85	m		3.09	dd	$J_{1a,1e}$ = 13.0 $J_{1e,2}$ = 5.0
H2	3.81	td	$J_{1e,2}$ = 5.0 $J_{1a,2}$ = 9.0 $J_{2,3}$ = 9.0	3.65	td	$J_{1e,2}$ = 5.0 $J_{1a,2}$ = 9.0 $J_{2,3}$ = 9.0	3.80	td	$J_{1e,2}$ = 5.0 $J_{1a,2}$ = 9.0 $J_{2,3}$ = 9.0
H3	3.34	t	$J_{2,3}$ = 9.0 $J_{3,4}$ = 9.0	3.28	t	$J_{2,3}$ = 9.0 $J_{3,4}$ = 9.0	3.37	t	$J_{2,3}$ = 9.0 $J_{3,4}$ = 9.0
H4	3.08	t	$J_{3,4}$ = 9.0 $J_{4,5}$ = 9.0	2.92	t	$J_{3,4}$ = 9.0 $J_{4,5}$ = 9.0	3.18-3.28	m	*J* = 9
H5	3.07	m		2.85	m		3.18-3.28	m	*J* = 2.5, 9
H6	2.39	dd	$J_{5,6}$ = 8.5 $J_{6,6'}$ = 16.5	2.02	dd	$J_{5,6}$ = 9.0 $J_{6,6'}$ = 17.0	2.95	dd	$J_{5,6}$ = 9.0 $J_{6,6'}$ = 17.0
H6'	2.79	dd	$J_{5,6'}$ = 2.5 $J_{6,6'}$ = 16.5	2.50	dd	$J_{5,6'}$ = 2.5 $J_{6,6'}$ = 17.0	3.47		$J_{5,6'}$ = 2.5 $J_{6,6'}$ = 17.0
CH_3O	3.69	s							
CH_3CO				1.50	s				
$(CH_3)_2C$	1.41	s		1.25 1.28	s s		1.50	s	
Ph							7.50-7.95	m	

[a] 400 MHz; [b] 250 MHz

Acidic cleavage of the isopropylidene group of compounds **7** and **8** with 6M HCl as described for ester **4** provided the ketone target compounds **11** and **12** (Scheme 5). These were isolated in 91 % and 85 % yield, respectively, by using column chromatography on silica gel. In the ^{1}H NMR specta of ketones **11** and **12**, recorded in D_2O and CD_3OD, deuterium exchange was observed for the protons α to the carbonyl group.

The conversion of amine **6** into the indolizidine β-ketoester **13** was accomplished in good overall yield (73 %) *via* *N*-alkylation followed by regioselective Dieckmann cyclisation of the resulting diester **41** (Scheme 6). The structure of **13** was confirmed by the ^{1}H NMR spectrum which displayed an AB quartet for protons H-3. The axial position of protons H-6 to H-8a was shown by the coupling constant values $J_{6,7} = J_{7,8} = J_{8,8a} = 9$ Hz. The value $J_{1,8a} = 9$ Hz observed for H-1 is consistent with the quasi-equatorial equilibrium position expected for the β-ketoester group.



Reagents: (a) $BrCH_2CO_2Me$, K_2CO_3, acetone, r.t. 48h; (b) *t*-BuOK, toluene O°C, 15 min; (c) 6M HCl, 60 °C, 3 h; $NaBH_4$, MeOH, 0 °C, 0.5 h.

Scheme 6

The indolizidinone target compound **14** was prepared (75 %) by heating compound **13** with 6M HCl: this resulted in both the removal of the isopropylidene group and concomitant decarboxylation of the β-ketoester. On reduction of the 2-carbonyl function of **14** with $NaBH_4$ in methanol at 0 °C, a mixture of the epimeric alcohols **15** was produced in a ratio 9:11 as indicated by the relative abundance of signals in the ^{13}C NMR spectrum.

CONCLUSION

The target imino sugars **9-12** are 7-carbonyl homologues of 1-deoxynojirimycin. They can be used to examine the effect on the biological activity when replacing the C-6 hydroxyl group of 1-deoxynojirimycin with a carbonyl function. Ganem and co-workers have reported that removal of the C-6 hydroxymethyl group of 1-deoxynojirimycin had remarkably little effect on enzyme-substrate interactions.[21] In this respect, the carbonyl function could serve as an anchor for binding to solid supports or biomolecules, e.g. in affinity chromatography. The potential of the *trans*-fused piperidine acetonides **4-8** as synthetic intermediates was confirmed by conversion of the ester compound **6** into the selectively protected indolizidine β-ketoester **13** and further into the 2-substituted castanospermine analogues **14** and **15**.

EXPERIMENTAL SECTION

General methods: Melting points were uncorrected. The optical rotations were measured on a Propol polarimeter fitted with a 7 cm cell at a temperature of 20 °C. IR spectra were recorded as thin films between NaCl plates or as KBr pellets on a Perkin-Elmer 297 grating IR spectrophotometer. ^1H and ^{13}C NMR were recorded on Bruker AMX 400 and WM 250 instruments operating at 400 and 250 MHz for ^1H and 100 and 62.9 MHz for ^{13}C. ^1H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. *J* values are reported in Hz. Mass spectra were run on a Kratos MS50 instrument; the ion source temperature was 150 - 250 °C as required. Exact mass measurements were performed at a resolution of 10,000. Analytical and preparative thin layer chromatography was performed using Merck silica gel 60 PF-224. Column chromatography was carried out using 70-230 mesh silica gel 60 (Merck). Unless otherwise stated, the same eluent was used for t.l.c. and column chromatography. Solutions were dried over $MgSO_4$. All non aqueous reactions were performed under a nitrogen atmosphere. Dry solvents were freshly distilled before use. 1-Amino-1-deoxy-D-glucitol was supplied by Cerestar.

1-Amino-1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-glucitol *p*-toluenesulfonate (17). To a suspension of 1-amino-1-deoxy-D-glucitol **3** (purity 95 %, 14.20 g, 74.5 mmol) in MeOH (200 mL) was added *p*-TsOH.H_2O (21.26 g, 110.7 mmol). The mixture was stirred until it became clear. The solvent was removed and the residue was evaporated with toluene and CCl_4, respectively, to afford the *p*-toluenesulfonate salt of compound **3** as a white solid. To this salt was added a solution of acetone/DMP (1:3, 400 mL) and the mixture was stirred at room temperature. The course of the reaction was followed up by t.l.c. analysis (hexanes-EtOAc 7:3) of the *N*-acylvinyl and *N*-Boc derivatives **19-20** and **21-23** prepared by treatment of samples of the reaction mixture with Na_2CO_3 and diethyl ethoxymethylenemalonate or di-*tert*-butyl dicarbonate (compound **19** was more polar than **20**; R_f**21** = R_f**22** = 0.2; R_f**23** = 0.5). After being stirred for 30 min, the reaction mixture became homogeneous. Crystallisation of diacetonide **17** started after 45 min; after 4 h, 13.09 g of compound **17** was collected by filtration. On further stirring of the filtrate for 20 h, an additional amount of **17** was isolated (total yield after 24 h: 21.11 g, 71 %). This yield did not change significantly when compound **17** was filtered just once after 24 h (*e.g.* a 64 % yield was produced after 18 h). Compound **17** was a white solid, m.p. 108 °C, $[\alpha]_D$ -13.4 (*c* 0.67, MeOH).

1-(*N*-*tert*-Butoxycarbonyl)amino-1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-glucitol (22). To a solution of diacetonide salt **17** (3 g, 6.9 mmol) in water (20 ml) was added K_2CO_3 (1.02 g, 7.4 mmol), methanol (10 mL) and (t-BuOCO)$_2$O (1.70, 7.5 mmol). After 25 min at room temperature, t.l.c. (hexanes-EtOAc, 7:3) indicated complete consumption of starting material. The mixture was extracted with CH_2Cl_2 (30 mL, three times). The organic phase was dried ($MgSO_4$) and evaporated and the residue was purified by column chromatography on silica gel (hexanes-EtOAc, 7:3) to give 2.38 g (95 % yield) of *N*-Boc diacetonide **22** as a white solid: m.p. 84-85 °C; $[\alpha]_D$ - 4.69 (c 0.73, $CHCl_3$); IR ν_{max} (KBr) 3400, 2970, 2900, 2895, 2870, 1650, 1540, 1430, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (s, 3 H, Me_2C), 1.35 (s, 3 H, Me_2C), 1.40 (2 s, 6 H, Me_2C), 1.45 (s, 9 H, Me_3C), 2.75 (d, J = 7.5 Hz, 1 H, OH), 3.22 (m, 1 H, H-1), 3.43 (m, 1 H, H-1'), 3.80 (m, 1 H, H-2), 3.91 (m, 2 H, H-6), 4.05 (m, 1 H, H-5), 4.15 (dd, 1 H, J = 8, 7 Hz, H-4), 5.10 (*br* s, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm) 25.3, 26.6, 26.9, 27.2 (Me_2C), 28.4 (Me_3C), 44.7 (C-1), 67.9 (C-6), 69.8 (C-2), 77.3, 77.7 (C-4, C-5), 79.4 (Me_3C), 81.5 (C-3), 109.8, 109.9 (Me_2C) 156.4 HN-COO-); HRMS: calcd. for $C_{16}H_{28}NO_7$ [M^+ – CH_3] 346.1866, found 346.1879 (26%).

1-(*N*-*tert*-Butoxycarbonyl)amino-1-deoxy-3,4-*O*-isopropylidene-D-glucitol (25). PPTS (6.27g, 25 mmol) was added to a solution of diacetonide **17** (10.84 g, 25 mmol) in a 9:1 mixture of MeOH and water (125 mL). The reaction mixture was heated at 60 °C for 1 h, and was allowed to cool to room temperature. An aqueous solution (10 mL) of K_2CO_3 (6.9 g, 50 mmol) was added followed by (t-BuOCO)$_2$O (5.63 g, 25 mmol). After completion of the reaction (30 min), t.l.c. (EtOAc) revealed the presence of the *N*-Boc derivatives **22** and **25**.

The solvent was removed by evaporation and the residue was dissolved in water (50 mL); the aqueous solution was extracted successively with toluene (40 mL, twice) and EtOAc (40 mL, four times). In the EtOAc phase, the pure triol **25** was detected while the toluene extracts contained the diacetonide **22** contaminated with the monoacetonide **25**. Evaporation of the toluene solution afforded 2.53 g of an oily residue which in turn was treated with PPTS (2.52 g, 10 mmol) in a 9:1 mixture of MeOH and water (60 mL) for two more hours at 60 °C; this new mixture of compounds **22** and **25** was separated by extraction as described above. The EtOAc extracts were combined, dried ($MgSO_4$), and concentrated. Crystallization of triol **25** was effected by addition of an excess of hexanes. Thus, 6.48 g of crystalline **25** was collected by filtration (81 % yield based on the diacetonide salt **17**): m.p. 93-94 °C; $[\alpha]_D$ +8.57 (*c* 0.2, MeOH); ν_{max} (KBr) 3560, 3390, 3290, 3080, 2970, 2915, 2890, 2830, 1670, 1580, 1440, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.40 (s, 15 H, Me_2C, Me_3C), 3.25 (dd, 1 H, *J* = 14, 8 Hz, H-1), 3.39 (dd, 1 H, *J* = 14, 3 Hz, H-1'), 3.50 (*br* s, 1 H, OH), 3.68 (m, 2 H, H-5 + H-6), 3.76 (*br* s, 1 H, OH), 3.85 (m, 2 H, H-2 + H-6'), 3.95 (t, *J* = 8, 7 Hz, 1 H, H-4), 4.05 (dd, 1 H, *J* = 8, 4 Hz, H-3), 4.40 (*br* s, 1 H, OH), 5.4 (*br* s, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 27.1, 27.2 (Me_2C), 28.5 (Me_3CO), 43.8 (C-1), 64.0 (C-6), 70.4 (C-2), 13.4 (C-5), 76.7 (C-4), 80.0 (Me_3CO), 80.9 (C-3), 109.6 (Me_2C), 157.2 (N-COO); HRMS: calcd. for $C_{13}H_{24}NO_7$ [$M^+ - CH_3$] 306.1553, found 306.1556 (2.7 %); (**25**-tris-*O*-trimethylsilyl derivative) calcd. for $C_{22}H_{48}NO_7Si_3$ [$M^+ - CH_3$] 522.2739, found 522.2741 (0.8 %).

Methyl (2*EZ*)-7-(*N*-*tert*-Butoxycarbonyl)amino-2,3,7-trideoxy-4,5-*O*-isopropylidene-L-*xylo*-hept-2-enonate (27). Sodium periodate (3.30 g, 15.4 mmol) was added to a solution of the monoacetonide triol **25** (4.13 g, 12.8 mmol) in water (30 mL). After 5 min, t.l.c. (EtOAc) indicated complete consumption of **25** to give the unstable L-xylose compound **26**. The reaction mixture was extracted with EtOAc (20 mL, three times). The organic solution was dried ($MgSO_4$) and evaporated to furnish 3.70 g of an oily residue. This residue was dissolved in MeOH (85 mL) and treated with $Ph_3P{=}CHCO_2Me$ (6.60 g, 19.3 mmol) at 0 °C; complete conversion was observed after reaction for 30 min. The solution was evaporated and the residue was chromatographed on silica gel (hexanes-EtOAc, 1:1). The unsaturated ester **27** (85:15 *Z*/*E* mixture) was isolated as an oily residue: 3.31 g (75 % yield from **25**): IR ν_{max} 3550, 3380, 2985, 2940, 1710, 1690, 1530, 1455, 1370, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) *Z*-isomer: 1.40 (s, 15 H, Me_2C, Me_3C), 3.15 (m, 1 H, H-7), 3.35 (m, 1 H, H-7'), 3.45 (*br* d, 1 H, *J* = 5 Hz, OH), 3.61 (dd, 1 H, *J* = 8.5, 2.5 Hz, H-5), 3.67 (m, 1 H, H-6), 3.69 (s, 3 H, OMe), 5.1 (*br* s, 1 H, NH), 5.45 (td, 1 H, *J* = 8.5, 1.5 Hz, H-4), 5.95 (dd, 1 H, *J* = 12, 1.5 Hz, H-2), 6.2 (dd, 1 H, *J* = 12, 8.5 Hz, H-3); *E*-isomer 6.10 (dd, 1 H, *J* = 16, 1.5 Hz, H-2), 6.85 (dd, 1 H, *J* = 16, 8.5 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) *Z*-isomer 26.7, 27.0 (Me_2C), 28.3 (Me_3C), 43.8 (C-7), 51.9 (OMe), 67.5 (C-6), 72.9 (C-4), 79.8 (Me_3C), 81.1 (C-5), 109.9 (Me_2C), 122.4 (CH, CH=C, C-2), 146.2 (CH, CH=C, C-3), 156.2 (N-COO), 166.7 (CO_2Me, C-1); HRMS: calcd. for $C_{15}H_{24}NO_7$ [$M^+ - CH_3$] 330.1553, found 330.1554 (0.6 %).

(3*E*)-8-(*N*-*tert*-Butoxycarbonyl)amino-1,3,4,8-tetradeoxy-5,6-*O*-isopropylidene-L-*xylo*-oct-3-enulose (28). Sodium periodate (3.24 g, 15 mmol) was added to a solution of the monoacetonide triol **25** (4.85 g, 15 mmol) in water (70 mL). After 5 min, t.l.c. (EtOAc) indicated complete consumption of triol **25** to give **26**. The reaction mixture was extracted with EtOAc (40 mL, three times). The organic solution was dried ($MgSO_4$) and evaporated to furnish an oily residue. This residue was dissolved in MeOH (100 mL) and the solution was treated with $Ph_3P{=}CHCOMe$ (5.7 g, 17.9 mmol) at 0 °C for 30 min. The solution was evaporated and the residue was chromatographed on silica gel (hexanes-EtOAc, 2:3) to afford the unsaturated ketone **28** as an oily residue: 3.03 g (61 % yield from **25**); $[\alpha]_D$ - 3,86 (*c* 2.5; $CHCl_3$); IR ν_{max} 3380, 2985, 2935, 2360, 1700, 1520, 1455, 1370, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.45 (2 s, 15 H, Me_2C, Me_3C), 2.30 (s, 3 H, Me_3CO), 2.80 (br s, 1 H, OH), 3.20 (m, 1 H, H-8), 3.35 (m, 1 H, H-8'), 3.72 (m, 1 H, H-7), 3.75 (dd, 1 H, *J* = 8, 3 Hz, H-6), 4.63 (ddd, 1 H, *J* = 8, 6, 1 Hz, H-5), 5.05 (*br* s, 1 H, NH), 6.37 (dd, 1 H, *J* = 16, 1 Hz, H-3), 6.72 (dd, 1 H, *J* = 16, 6 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 26.8 (Me_2C), 27.7 (C-1), 28.3 (Me_3C), 44.1 (C-8), 68.8 (C-7), 76.4 (C-5 or C-6), 79.8 (Me_3C), 81.2 (C-6 or C-5), 110.4 (Me_2C), 131.7 (C-3), 142.2 (C-4), 156.3 (N-COO), 197.8 (C-2); HRMS: calcd. for $C_{15}H_{24}NO_6$ [$M^+ - CH_3$] 314.1604, found 314.1632 (0.4 %).

(2*E*)-7-(*N*-*tert*-Butoxycarbonyl)amino-2,3,7-trideoxy-4,5-*O*-isopropylidene-1-*C*-phenyl-D-*xylo*-hept-2-en-1-ulose (29). Sodium periodate (0.88 g, 4.1 mmol) was added to a solution of the monoacetonide triol **25** (1.09 g, 3.4 mmol) in water (10 mL). After 5 min, t.l.c. (EtOAc) indicated complete consumption of triol **25** to

26. The reaction mixture was extracted with EtOAc (7 mL, three times). The organic solution was dried ($MgSO_4$) and evaporated to furnish an oily residue. This residue was dissolved in MeOH (15 mL) and the solution was treated with $PhCOCH_2Ph_3P^+Br^-$ (2.35 g, 5.1 mmol) and MeONa (0.32 g, 6 mmol) at 0 °C for 30 min. The solution was diluted with water (15 mL) and extracted with CH_2Cl_2 (30 mL, three times). The organic phase was evaporated and the residue was chromatographed on silica gel (hexanes-EtOAc, 7:3) to afford the unsaturated ketone **29** as an oily residue: 0.755 g (57 % yield from **25**); $[\alpha]_D$ + 94,1 (*c* 0.48, $CHCl_3$); IR ν_{max} 3385, 2980, 2360, 1685, 1625, 1510, 1455, 1370, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.40 (s, 9 H, Me_3C), 1.45 (s, 3 H, Me_2C), 1.50 (s, 3 H, Me_2C), 3.23 (ddd, 1 H, *J* = 14, 8, 5 Hz, H-7), 3.37 (ddd, 1 H, *J* = 14, 6, 4 Hz, H-7'), 3.75 (m, 1 H, H-6), 3.81 (dd, 1 H, *J* = 8, 3 Hz, H-5), 4.73 (ddd, 1 H, *J* = 8, 6, 1.5 Hz, H-4), 4.98 (*br* t, 1 H, NH), 6.95 (dd, 1 H, *J* = 16, 6 Hz, H-3), 7.21 (dd, 1 H, *J* = 16, 1.5 Hz, H-2); 7.46 (t, 2 H, *J* = 7.5 Hz, H-3'arom + H-5'arom), 7.56 (m, 1 H, H-4'arom), 7.94 (m, H-2'arom + H-6'arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.8, 27.0 (*Me*$_2$C), 28.4 (*Me*$_3$C), 44.8 (C-7), 69.1 (C-6), 77.0 (C-4), 81.5 (Me_3*C*), 81.6 (C-5), 110.5 (Me_2*C*), 126.9 (C-2), 128.6, 128.8 (CH arom), 136.7 (C arom), 143.4 (C-3), 156.6 (N-COO), 189.9 (C-1); HRMS: calcd. for $C_{16}H_{18}NO_6$ [M^+ – CH_3 – isobutene] 320.1134, found 320.1133 (1 %).

Methyl (3*E*)-8-(*N-tert*-Butoxycarbonyl)amino-2,3,4,8-tetradeoxy-5,6-*O*-isopropylidene-3-*C*-methoxycarbonyl-D-*xylo*-oct-3-enonate (30). Sodium periodate (1.08 g, 4.9 mmol) was added to a solution of the monoacetonide triol **25** (1.45 g, 4.5 mmol) in water (20 mL). After 5 min, t.l.c. (EtOAc) indicated complete consumption of the triol **25** to give **26**. The reaction mixture was extracted with EtOAc (25 mL, five times). The organic solution was dried and evaporated to furnish 1.29 g of an oily residue. This residue was dissolved in CH_2Cl_2 (15 mL) and the solution was treated with dimethyl 2-(triphenylphosphoranylidene)succinate **31** (1.94 g, 4.7 mmol) at 0 °C for 30 min. The solution was evaporated and the residue was chromatographed on silica gel (hexanes-EtOAc, 1:4) to afford the unsaturated ester **30** as an oily residue: 1.31 g (70 % yield from **25**); ν_{max} 3390, 2985, 2950, 2930, 1730, 1530, 1455, 1440, 1370, 1320, 1275, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.35 (s, 15 H, Me_2C, Me_3C), 3.07 (*br* s, 1 H, OH), 3.20 (m, 1 H, H-8), 3.35 (m, 1 H, H-8'), 3.42 (d, 1 H, *J* = 16.5 Hz, H-2), 3.55 (d, 1 H, *J* = 16 Hz, H-2'), 3.65 (m, 1 H, H-7), 3.69 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.80 (dd, 1 H, *J* = 8, 2.5 Hz, H-6), 4.76 (t, 1 H, *J* = 8 Hz, H-5), 5.20 (*br* s, 1 H, NH), 6.85 (d, 1 H, *J* = 8 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.7, 26.9 (*Me*$_2$C), 28.3 (*Me*$_3$C), 32.7 (C-2), 44.6 (C-8), 52.1 (OMe), 52.2 (OMe), 68.0 (C-7), 73.4 (C-5), 79.5 (Me_3*C*O), 81.4 (C-6), 110.3 (Me_2*C*), 129.5 (C, CH=*C*, C-3), 139.8 (CH, *C*H=C, C-4), 156.6 (N-COO), 166.5 (*C*O$_2$Me), 171.0 (*C*O$_2$Me, C-1), HRMS calcd. for $C_{18}H_{28}NO_9$ [M^+ - Me] 402.1764, found 402.1760 (1 %).

Dimethyl 2-(triphenylphosphoranylidene)succinate (31). A solution of Ph_3P=$CHCO_2Me$ (1.71 g, 5 mmol) in EtOAc (50 ml) was heated under reflux with $BrCH_2CO_2Me$ (0.51 ml, 5.4 mmol) and K_2CO_3 (1.38 g, 10 mmol) for 4 h, the reaction mixture was cooled and filtered. Evaporation of the filtrate followed by crystallisation from hexanes-EtOAc afforded compound **31:** 1.69 g (83 % yield); m.p. : 150-151 °C; ^1H NMR : (90 MHz, $CDCl_3$) δ (ppm) 3.0 (d, 2 H, *J* = 17 Hz, CH_2), 3.20 (*br* s, 3 H, OMe), 3.60 (s, 3 H, OMe), 7.20-7.40 (m, 15 H, 3 Ph). EIMS m/z 406 (M^+, 8 %) 347 (M^+ - CO_2Me, 100 %); HRMS calcd. for $C_{24}H_{23}O_4P$ [M+] 406.1334, found 406.1329.

Methyl 2,3,7-trideoxy-3,7-imino-4,5-*O*-isopropylidene-D-*gluco*-heptonate (4). To a stirred solution of α,β-unsaturated ester **27** (2.76 g, 8 mmol) in dry CH_2Cl_2 (30 ml) was added Me_3SiI (3 mL, 20 mmol) at room temperature. After 10 min, MeOH (10 mL) and Et_3N (1 ml) were added. The mixture was stirred for 1 h and evaporated. T.l.c. analysis (MeOH-EtOAc, 3:47) of the residue revealed the presence of a mixture of piperidines **4** and **5**. The mixture was treated with K_2CO_3 (1.38 g) in MeOH (30 mL) for 4 h at room temperature. The solvent was removed, and the residue was dissolved in water (30 mL) and extracted with EtOAc (30 ml, five times). After evaporation of the organic phase and column chromatography (EtOAc-MeOH, 47:3), compound **4** (1.05 g, 53 % yield based on **27**) was isolated as a white solid: m.p *:* 138-140°C; $[\alpha]_D$ + 9,3 (*c* 0.2, $CHCl_3$); ν_{max} (KBr) 3350, 3100, 2980, 2890, 2850, 2830, 2370, 1730, 1450, 1430, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.41 (s, 6 H, Me_2C), 2.39 (dd, 1 H, *J* = 8.5, 16.5 Hz, H-2), 2.49 (dd, 1 H, *J* = 9, 12.5 Hz, H-7*ax*), 2.79 (dd, 1 H, *J* = 2.5, 16.5 Hz, H-2'), 3.07 (m, 1 H, H-3), 3.08 (t, 1 H, *J* = 9 Hz, H-4), 3.21 (dd, 1 H, *J* = 5, 12.5 Hz, H-7*eq*), 3.34 (t, 1 H, *J* = 9 Hz, H-5), 3.69 (s, 3 H, OMe), 3.81 (td, 1 H, *J* = 5, 9 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.6, 26.8 (*Me*$_2$C), 36.6 (C-2), 50.6 (C-7), 51.8 (OMe), 54.7 (C-3), 70.1 (C-6), 78.3

(C-4), 83.8 (C-5), 110.2 (Me_2C), 172.2 (C-1); HRMS: calcd. for $C_{11}H_{19}NO_5$ [M^+] 245.1263, found 245.1269 (1 %).

Methyl 6-*O*-*tert*-butyldimethylsilyl-2,3,7-trideoxy-3,7-imino-4,5-*O*-isopropylidene-D-*gluco*-heptonate (6). To a stirred solution of α,β-unsaturated ester **27** (1.845 g, 5.3 mmol) in dry CH_2Cl_2 (20 ml) was added Me_3SiI (3 mL, 13.4 mmol) at room temperature. After 10 min, MeOH (10 mL) and Et_3N (1 ml) were added. The mixture was stirred for 1 h and evaporated. T.l.c. analysis (MeOH-EtOAc, 3:47) revealed the presence of a mixture of piperidines **4** and **5**. The mixture was treated with K_2CO_3 (1.38 g) in MeOH (30 mL) for 4 h. The solvent was removed, and the residue was dissolved in water (30 mL) and extracted with EtOAc (30 ml, five times). The EtOAc extracts were dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2 and made to react with *t*-Bu_2Me_2SiCl (0.760 g, 5 mmol) and DBU (1.3 mL, 8.5 mmol). After 2.5 h, the organic solution was washed with water (10 mL, twice), dried, and evaporated. The residue was chromatographed on silica gel (hexanes-EtOAc, 7:3) to give compound **6** (0.830 g, 43 % yield based on ester **27**) as an oily residue: $[\alpha]_D$ + 5,07 (*c* 5.72, $CHCl_3$); IR ν_{max} 3360, 2985, 2955, 2930, 2890, 2860, 2365, 1740, 1475, 1465, 1440, 1410, 1370, 1300, 1250, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.09 (s, 3 H, MeSi), 0.10 (s, 3 H, MeSi), 0.89 (s, 9 H, Me_3CSi), 1.39 (s, 6 H, Me_2C), 2.14 (s, 1 H, NH), 2.34 (ddd, 1 H, *J* = 2.5, 9, 16.5 Hz, H-7), 2.47 (dd, 1 H, *J* = 9.5, 13 Hz, H-2*ax*), 2.79 (dd, 1 H, *J* = 2.5, 16.5 Hz, H-7'), 3.02 (m, 2 H, H-5 + H-6), 3.08 (dd, 1 H, *J* = 5, 13 Hz, H-2*eq*), 3.33 (m, 1 H, H-4), 3.69 (s, 3 H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) ; -4.9, -4.6 (MeSi), 18.2 (Me_3CSi), 25.8 (Me_3CSi), 26.5, 26.9 (Me_2C), 36.8 (C-7), 51.6 (C-2), 51.6 (OMe), 54.6 (C-6), 71.5 (C-3), 78.5 (C-5), 83.6 (C-4), 109.5 (Me_2C), 172.2 (CO_2Me); HRMS: calcd. for $C_{17}H_{33}NO_5Si$ [M^+] 359.2128, found 359.2140 (3 %).

1,3,4,8-Tetradeoxy-4,8-imino-5,6-*O*-isopropylidene-7-*O*-trimethylsilyl-D-*gluco*-octulose (7). To a stirred solution of α,β-unsaturated ketone **28** (1.51 g, 4.6 mmol) in dry CH_2Cl_2 (30 ml) was added Me_3SiI (1.73 mL, 11.5 mmol) at room temperature. After 5 min, Et_3N (3 ml) was added. The mixture was stirred for 20 min and evaporated. The residue was chromatographed on silica gel (hexanes-EtOAc, 3:2) to give compound **7** (0.786 g, 57 % yield) as an oily residue: $[\alpha]_D$ + 10,2 (*c* 1.22, $CHCl_3$); IR ν_{max} 3380, 2980, 2950, 2850, 2360, 1710, 1640, 1450, 1370, 1260, 1090 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ (ppm) 0.10 (s, 9 H, Me_3Si), 1.25 (s, 3 H, Me_2C), 1.28 (s, 3 H, Me_2C), 1.5 (s, 3 H, 3 H-1), 2.02 (dd, 1 H, *J* = 9, 17 Hz, H-3), 2.35 (dd, 1 H, *J* = 9, 13 Hz, H-8*ax*), 2.50 (dd, 1 H, *J* = 2.5, 17 Hz, H-6'), 2.85 (m, 2 H, H-8*eq* + H-4), 2.92 (t, 1 H, *J* = 9 Hz, H-5), 3.28 (t, 1 H, *J* = 9 Hz, H-6), 3.65 (td, 1 H, *J* = 5, 9 Hz, H-7); ^{13}C NMR (100 MHz, C_6D_6) δ (ppm) 0.15 (Me_3Si), 26.5, 26.8 (Me_2C), 30.4 (C-1), 45.5 (C-3), 51.5 (C-8), 53.9 (C-4), 70.9 (C-7), 78.2 (C-5), 83.4 (C-6), 109.5 (Me_2C), 207.9 (C-2); HRMS: calcd. for $C_{14}H_{27}NO_4Si$ [M^+] 301.1709, found 301.1722 (2 %).

2,3,7-Trideoxy-3,7-imino-4,5-*O*-isopropylidene-1-*C*-phenyl-6-*O*-trimethylsilyl-D-*gluco*-hept-1-ulose (8). To a stirred solution of α,β-unsaturated ketone **29** (0.529 g, 1.35 mmol) in dry CH_2Cl_2 (10 ml) was added Me_3SiI (0.50 mL, 3.4 mmol) at room temperature. After 5 min, Et_3N (0.5 ml) was added. The mixture was stirred for 20 min and evaporated. The residue was chromatographed on silica gel (hexanes-EtOAc, 3:2) to give compound **8** (0.251 g, 51 % yield) as an oily residue: $[\alpha]_D$ + 23.5 (*c* 0.6, $CHCl_3$); IR ν_{max} 3335, 2895, 2360, 1685, 1600, 1580, 1560, 1540, 1510, 1450, 1375, 1230 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.10 (s, 9 H, Me_3Si), 1.25 (s, 3H, Me_2C), 1.28 (s, 3H, Me_2C), 2.57 (dd, 1 H, *J*= 13, 9 Hz, H-7*ax*), 2.95 (dd, 1 H, *J* = 17, 9 Hz, H-2), 3.09 (dd, 1 H, *J* = 13, 5 Hz, H-7*eq*), 3.18-3.28 (m, 2 H, *J* = 2.5, 9 Hz, H-3 + H-4), 3.37 (t, 1 H, *J* = 9 Hz, H-5), 3.47 (dd, 1 H, *J* = 2.5, 17 Hz, H-1'), 3.80 (td, 1 H, *J* = 9, 5 Hz, H-6), 7.5 (m, 3 H, H-3', H-4', H-5' arom), 7.95 (d, 2 H, *J* = 8 Hz, H-2' + H-6' Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 0.15 (Me_3Si), 26.6, 26.9 (Me_2C), 40.7 (C-7), 51.7 (C-2), 54.2 (C-6), 70.9, 78.4, 83.6 (C-3,4,5), 109.7 (Me_2C), 128.0, 128.5, 133.3 (CH arom), 136.7 (C arom), 199.0 (C-8); HRMS: calcd. for $C_{19}H_{29}NO_4Si$ [M^+] 363.1866, found 363.1867 (2 %).

2,3,7-Trideoxy-3,7-imino-D-*gluco*-heptonic Acid (9). A solution of the protected iminoheptonate **4** (100.5 mg, 0.41 mmol) in aqueous 6M HCl (3 mL) was stirred at room temperature for 24 h. After removing the solvent and co-evaporation with toluene (2 x 5 mL), the residue was purified by ion exchange chromatography (Dowex 50W-X8, H^+ form, eluting with 0.2M NH_4OH) to give heptonic acid **9** (69 mg, 88 % yield) as a gummy solid, R_f 0.42 ($EtOH/H_2O/NH_4OH$, 80:20:1); IR ν_{max} 3410, 3010, 2920, 2800, 1725, 1595, 1365, 1090, 1045 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ (ppm) 2.11 (dd, 1 H, *J* = 9, 16 Hz, H-2), 2.47 (dd, 1 H, *J* = 11, 12 Hz, H-

7*ax*), 2.72 (dd, 1 H, *J* = 3, 16 Hz, H-2'),2.73 (m, 1 H, H-3), 3.06 (dd, 1 H, *J* = 5, 12 Hz, H-7*eq*), 3.08 (t, 1 H, *J* = 9 Hz, H-4), 3.28 (t, 1 H, *J* = 9 Hz, H-5), 3.48 (ddd, 1 H, *J* = 5, 9, 12 Hz, H-6); ^{13}C NMR (100 MHz, D_2O) δ (ppm) 39.7 (C-2), 48.9 (C-7), 57.5 (C-3), 70.6 (C-6), 74.4 (C-4), 78.3 (C-5), 180.2 (C-1); HRMS : (**9**-tetrakis-*O*-trimethylsilyl derivative) calcd. for $C_{16}H_{35}NO_4Si_3$ [M^+ – Me_3SiOH] 389.1874, found 389.1865 (5 %).

2,3,7-Trideoxy-3,7-imino-D-*gluco*-heptonamide (10). A solution of the protected iminoheptonate **4** (226 mg, 0.92 mmol) in saturated methanolic HCl (3 mL) was stirred at room temperature for 2 h. After removing the solvent, MeOH was added and the solution was evaporated. Mass spectral analysis of the residue revealed the presence of a mixture of iminoheptonate **34** and iminoheptonolactone **35** (R_f**34** = R_f**35** = 0.56, EtOH/H_2O/NH_4OH, 80:20:1). The residue was dissolved in a saturated methanolic solution of ammonia (5 mL), NaCN (20 mg, 0.41 mmol) was added, and the solution was heated in a sealed tube at 70 °C for 4 days. The solvent was removed and the residue was purified by using ion exchange chromatography (Dowex 50W-X8, H^+ form, eluting with 0.2M NH_4OH) to give heptonamide **10** (109 mg, 62 % yield based on compound **4**) as a gummy solid, R_f 0.43 (EtOH/H_2O/NH_4OH, 80:20:1); $[\alpha]_D$ + 27.4 (*c* 0.15, H_2O); IR ν_{max} 3500, 3410, 3280, 2920, 2800, 1705, 1595, 1365, 1090, 1045 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ(ppm) 2.18 (dd, 1 H, *J* = 9, 16 Hz, H-2), 2.40 (dd, 1 H, *J* = 11, 12 Hz, H-7*ax*), 2.71 (dd, 1 H, *J* = 3, 16 Hz, H-2'), 2.78 (td, 1 H, *J* = 3, 9 Hz, H-3), 3.02 (dd, 1 H, *J* = 5, 12 Hz, H-7*eq*), 3.05 (t, 1 H, *J* = 9 Hz, H-4), 3.25 (t, 1 H, *J* = 9 Hz, H-5), 3.43 (ddd, 1 H, *J* = 5, 9, 12 Hz, H-6); ^{13}C NMR (100 MHz, D_2O) δ (ppm) 37.3 (C-2), 48.6 (C-7), 56.8 (C-3), 70.5 (C-6), 74.2 (C-4), 77.8 (C-5), 176.6 (C-1); HRMS: calcd. for $C_7H_{12}N_2O_3$ [M^+ – H_2O] 172.0848, found 172.0860 (7 %).

1,3,4,8-Tetradeoxy-4,8-imino-D-*gluco*-2-octulose (11) A solution of the protected iminooctulose **7** (160 mg, 0.53 mmol) was stirred in aqueous 6M HCl (3 mL) at room temperature for 3 h. After removing the solvent and co-evaporation with toluene (2 x 5 mL), the residue was purified by column chromatography on silica gel (eluting with NH_4OH/H_2O/MeOH/$CHCl_3$, 1:1:28:70) to give after crystallisation from MeOH-Et_2O, iminooctulose **11** (91.5 mg, 91 % yield), a white solid, R_f 0.23 (NH_4OH/H_2O/MeOH/$CHCl_3$); m.p. 170 °C (dec); $[\alpha]_D$ + 40.3 (*c* 0.8, H_2O); IR ν_{max} 3410, 3280, 2920, 2800, 1705, 1595, 1365, 1090, 1045 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ (ppm) 2.15 (m, 1 H, H-3), 2.17 (s, 1 H, H-1), 2.42 (t, 1 H, *J* = 11, 12 Hz, H-8*ax*), 2.87 (m, 1 H, H-4), 3.01 (dd, 1 H, *J* = 5, 12 Hz, H-8*eq*), 3.07 (t, 1 H, *J* = 9 Hz, H-5), 3.24 (t, 1 H, *J* = 9 Hz, H-6), 3.44 (ddd, 1 H, *J* = 5, 9, 12 Hz, H-7); ^{13}C NMR (100 MHz, D_2O) 29.8 (C-1), 44.5 (C-3), 48.5 (C-8), 55.7 (C-4), 70.3 (C-7), 73.9 (C-5), 77.8 (C-6), 213.4 (C-2); HRMS: (**11**-tris-*O*-trimethylsilyl derivative) calcd. for $C_{14}H_{19}NO_3Si_2$ [M^+ – Me_3SiOH] 315.1686, found 315.1681 (4 %).

2,3,7-Trideoxy-3,7-imino-1-*C*-phenyl-D-*gluco*-1-heptulose (12). A solution of the protected iminooctulose **8** (80 mg, 0.22 mmol) was stirred in aqueous 6M HCl (3 mL) at room temperature for 3 h. After removing the solvent and co-evaporation with toluene (2 x 5 mL), the residue was purified by column chromatography on silica gel (eluting with NH_4OH/H_2O/MeOH/$CHCl_3$, 1:1:28:70) to give iminoheptulose **11** (47 mg, 85 % yield), an oily residue, R_f 0.40 (NH_4OH/H_2O/MeOH/$CHCl_3$); $[\alpha]_D$ + 35.0 (c 0.39, H_2O); IR ν_{max} 3390, 2920, 1680, 1505, 1225, 1100, 1055, 1005, 760, 695 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 2.60 (*br* t, 1 H, *J* = 12 Hz, H-7*ax*), 3.13 (m, 1 H, H-3), 3.16 (dd, 1 H, J = 5, 12 Hz, H-7*eq*), 3.22-3.33 (m, 2 H, H-5, H-4), 3.56 (m, 1 H, H-6); 7.50, 7.62, 8.01 (m, 5 H, CH arom); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 40.4 (C-2), 50.7 (C-7), 58.0 (C-3), 71.7 (C-6), 75.0 (C-4), 80.1 (C-5), 129.3, 129.8, 134.7, 138.1 (C arom), 201.0 (C-1); HRMS: calcd. for $C_{13}H_{15}NO_3$ [M^+ – H_2O] 233.1052, found 233.1053 (3 %).

Methyl 6-*O*-*tert*-butyldimethylsilyl-2,3,7-trideoxy-4,5-*O*-isopropylidene-3,7-[[(methoxycarbonyl)methyl] imino]-D-*gluco*-heptonate (41). To a solution of the protected iminoheptonate **6** (1.413 g, 3.93 mmol) in acetone (30 mL) were added methyl bromoacetate (1.1 mL, 11.81 mmol) and K_2CO_3 (1.1 g, 7.87 mmol). The mixture was stirred at room temperature for 48 h after which time water (30 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (30 mL, three times). The CH_2Cl_2 solution was evaporated, and the residue was purified by column chromatography on silica gel (eluting with hexanes/EtOAc, 7:3) to yield diester **41** (1.611g, 95 % yield), a white solid, R_f 0.48, m.p. 62-64 °C; $[\alpha]_D$ - 6.12 (*c* 1.4, $CHCl_3$); ν_{max} (KBr) 2990, 2950, 2915, 2880, 1735, 1460, 1370, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.08 (s, 3 H, MeSi), 0.10 (s, 3 H, MeSi), 0.88 (s, 9 H, Me_3CSi), 1.40 (s, 6 H, Me_2C), 2.54 (dd, 1 H, *J* = 5.5, 15.5 Hz, H-7), 2.71 (dd, 1 H, *J* = 9, 11.5 Hz, H-2*ax*), 2.74 (dd, 1 H, *J* = 3, 15.5 Hz, H-7'), 2.88 (dd, 1 H, *J* = 5, 11.5, H-2*eq*), 3.25 (m, 1 H, H-5), 3.27 (m, 1 H, H-6), 3.34 (tr, 1 H, *J* = 9.0 Hz, H-4), 3.39 (d, 1 H, *J* = 7.5 Hz, N-CH_2-CO), 3.61 (d, 1 H, *J* = 7.5

Hz, N-CH_2-CO), 3.67 (s, 3 H, OMe), 3.71 (s, 3 H, OMe), 3.85 (dtr, 1 H, J = 5, 9 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) -4.9, -4.6 (MeSi), 18.2 (Me_3C-Si), 25.8 (Me_3C-Si), 26.6, 26.9 (Me_2C), 35.4 (C-7), 51.4, 51.7 (OMe), 52.8 (C-8), 57.3 (C-6), 58.6 (C-2), 69.1 (C-3), 77.4 (C-5), 83.3 (C-4), 110.5 (Me_2C), 171.1, 171.7 (CO_2Me); HRMS: calcd. for $C_{20}H_{37}NO_7Si$ [M^+] 431.2339, found 431.2335 (6 %).

(1*S*,6*S*,7*R*,8*R*,8a*R*)-6-*O*-*tert*-Butyldimethylsilyl-6,7,8-trihydroxy-7,8-*O*-isopropylidene-1-methoxycarbonyl-2-indolizidinone (13). A solution of diester **41** (0.285 g, 0.66 mmol) in toluene (15 mL) was treated with *t*-BuOK (0.111 g, 0.99 mmol) at 0 °C for 1 h. The solution was treated with saturated aqueous NH_4Cl (5 ml), and the two layers were separated. The aqueous solution was extracted further with toluene (5 mL). The toluene extracts were combined, dried, and evaporated. The residue was purified by column chromatography on silica gel (eluting with hexanes/EtOAc, 7:3) to give the protected indolizidinone **13** (0.202 g, 77 % yield) , an oil, R_f 0.5; $[\alpha]_D$ + 23,8 (*c* 1.5, $CHCl_3$); IR: ν_{max} 2990, 2955, 2860, 1740, 1675, 1465, 1440, 1375, 1235 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.2 (2 s, 6 H, MeSi) 0.8 (s, 9 H, Me_3CSi), 1.34 (s, 6 H, Me_2C), 2.29 (*br* t, 1 H, J = 10 Hz, H-5*ax*), 3.03 (d, 1 H, J = 16.7 Hz, H-3), 3.13 (dd, 1 H, J = 5, 11.5 Hz, H-5*eq*), 3.17 (t, 1 H, J = 9 Hz, H-8a), 3.27(d, 1 H, J = 9 Hz, H-1), 3.30 (t, 1 H, J = 9 Hz, H-8), 3.37 (t, 1 H, J = 9 Hz, H-7), 3.45 (d, 1 H, J = 16.7 Hz, H-3'), 3.75 (s, OMe), 3.95 (td, 1 H, J = 5, 9 Hz , H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) -4.6, -5.0 (Me_2Si), 18.2 (Me_3C-Si), 25.7 (Me_3C-Si), 26.7, 26.8 (Me_2C), 52.7 (OMe), 55.5 (C-5), 58.8 (C-8a), 59.4 (C-3), 64.8 (C-1), 69.2 (C-6), 78.1 (C-8), 83.9 (C-7), 111.0 (Me_2C), 167.2 (COO), 205.0 (C-2). CIMS, m/z: 400 (5 %), [M+H]$^+$; EIMS: 399 (9 %), M^+, HRMS calcd. for $C_{19}H_{33}NO_6Si$ [M^+] 399.2077, found 399.2078.

(6*S*,7*R*,8*R*,8a*R*)-6,7,8-Trihydroxy-2-indolizidinone (14). A solution of diester **41** (0.285 g, 0.66 mmol) in toluene (15 mL) was treated with *t*-BuOK (0.111 g, 0.99 mmol) at 0 °C for 1 h. The solution was treated with saturated aqueous NH_4Cl (5 ml), and the two layers were separated. The aqueous solution was extracted further with toluene (5 mL). The toluene extracts were combined, dried ($MgSO_4$), and evaporated. The residue was dissolved in aqueous 6M HCl (5 mL). The solution was stirred at room temperature for 24 h, and then was heated at 80 °C for 3 h. After removing the solvent and co-evaporation with toluene (2 x 5 mL), the residue was purified by column chromatography on silica gel (eluting with $CHCl_3$/MeOH/H_2O, 80:19:1) to give indolizidinone **14** (88 mg, 83 % yield based on diester **41**) as an oil. R_f 0.28. The ^{1}H NMR spectrum of **14** run in d_5-pyridine using a sample that first had been dissolved in CD_3OD revealed deuterium exchange for one of the H-1 protons. $[\alpha]_D$ + 49.6 (*c* 0.36, MeOH); IR: ν_{max} 3420, 2990, 2955, 2855, 1735 cm^{-1}; ^{1}H NMR (400 MHz, pyridine-d_5) δ (ppm) 2.54 (m, 2 H, H-1 + H-5*ax*), 2.82 (m, 2 H, H-3 + H-8a), 3.48 (m, 2 H, H-3' + H-5*eq*), 3.96 (t, 1 H, J = 9 Hz, H-8), 4.01 (t, 1 H, J = 9 Hz, H-7), 4.33 (ddd, 1 H, J = 5, 9, 11 Hz, H-6); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 43.6 (C-1), 57.3 (C-5), 62.7 (C-3), 66.9 (C-8a), 72.0 (C-6), 76.7 (C-8), 80.7 (C-7), 214.0 (C-2); HRMS: calcd. for $C_8H_{13}O_4N$ [M^+] 187.0845, found 187.0851 (12%).

(2*RS*,6*S*,7*R*,8*R*,8a*R*)-2,6,7,8-Tetrahydroxyindolizidine (15). To a solution of indolizidinone **14** (49 mg, 0.26 mmol) in MeOH (5 mL) was added at 0 °C $NaBH_4$ (20.1 mg, 0.52 mmol). The mixture was stirred for 30 min, and then was evaporated. The residue was purified by column chromatography on silica gel (eluting with NH_4OH/H_2O/MeOH/$CHCl_3$, 1:5:45:50) to give the tetrahydroxyindolizidines **15** (39 mg, 79 % yield) as a 45/55 mixture of C-2 epimeric alcohols. Oil, R_f 0.33; ^{13}C NMR: major diastereoisomer, 38.5 (C-1), 54.5 (C-5), 63.3 (C-3), 68.5 (C-8a), 69.1, 69.7 (C-2, C-6), 73.3 (C-8), 78.8 (C-7); minor diastereoisomer 39.1 (C-1), 54.5 (C-5), 62.6 (C-3), 67.0 (C-8a), 69.9, 71.1 (C-2, C-6), 73.3 (C-8), 78.8 (C-7).

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