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A convenient synthesis of new enantiomerically pure trihydroxypyrrolizidines using L-erythrose glycosylhydroxylamine as a masked acyclic chiral nitrone

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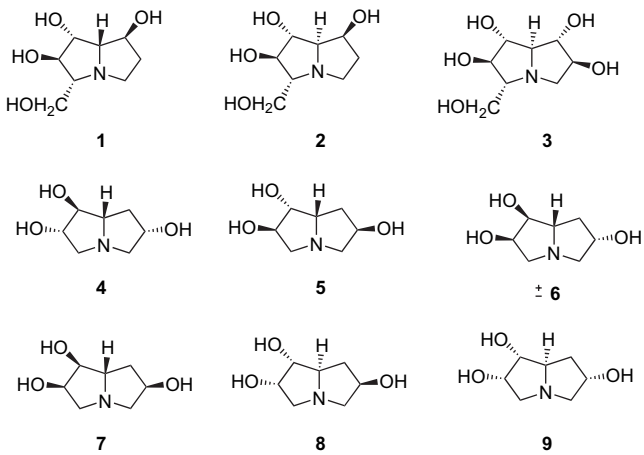
ABSTRACT

A route has been developed for the synthesis of enantiomerically pure trihydroxylated pyrrolizidines starting from L-erythrose glycosylhydroxylamine. The latter acts as a masked acyclic nitrone and reacts diastereoselectively from its *Re*-face with methyl acrylate to give the corresponding isoxazolidines, which after reductive N–O cleavage are recyclized to trihydroxypyrrolizidines via a Mitsunobu condensation.

1. Introduction

Polyhydroxylated pyrrolizidines belong to an important class of alkaloids that display a wide range of biological activities due mainly to their action as specific glycosidase inhibitors.[1] In particular, the naturally occurring compounds alexine (**1**), australine (**2**) and casuarine (**3**) have generated considerable interest as antiviral and anticancer agents.[2] Since the biological activity varies substantially with the number, the position and the stereochemistry of the hydroxy groups on the pyrrolizidine skeleton, the synthesis of both naturally occurring compounds as well as of their stereoisomers and analogues has received much attention.[3] A large part of the synthetic work in this area involves 1,3-dipolar cycloadditions of chiral nitrones derived from sugars. The synthetic strategy of these reaction schemes relies on the reductive cleavage of the N–O bond of the isoxazolidine cycloadduct and subsequent cyclization to carbon–nitrogen heterocycles. Using cycloadditions of cyclic nitrones derived from D or L-arabinopyranose, Wightman and coworkers have described the synthesis of the two enantiomeric 1,2,6-trihydroxypyrrolizidines **4**, **5** and the racemate of structure **6**.[4] Fišera, following a different procedure and using an open chain nitrone derived from D-glucose, has synthesized another chiral stereoisomer of 1,2,6-trihydroxypyrrolizidine for which he has proposed structure **7**.[5]

In connection with our previous studies devoted to the synthesis of pyrrolidine and pyrrolizidine derivatives via chiral nitrone cycloadditions,[6] we present herein a short and convenient synthesis of two new enantiopure trihydroxypyrrolizidines **8** and **9**, which to the best of our knowledge have not yet been described. Our synthetic scheme uses as a key intermediate the *N*-benzyl substituted glycosylhydroxylamine **10a**, which reacts as a hidden nitrone. *N*-Substituted *N*-glycosylhydroxylamines are a relatively new class of compounds and they have been the subject of rather few reports.[7] They have been recently prepared by three independent groups of researchers.[7a,b,e] They exist in equilibrium with the open chain



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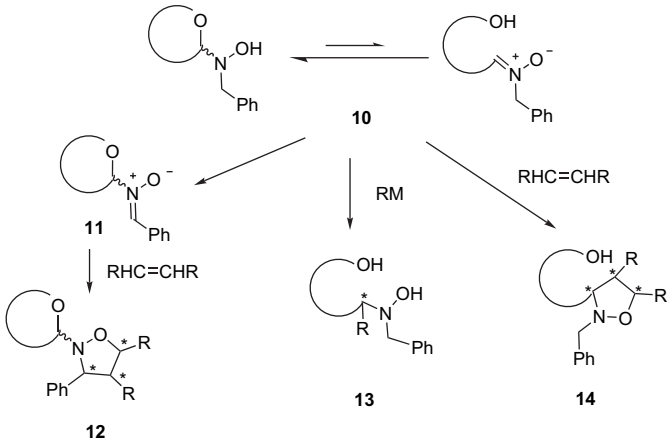


Scheme 1.

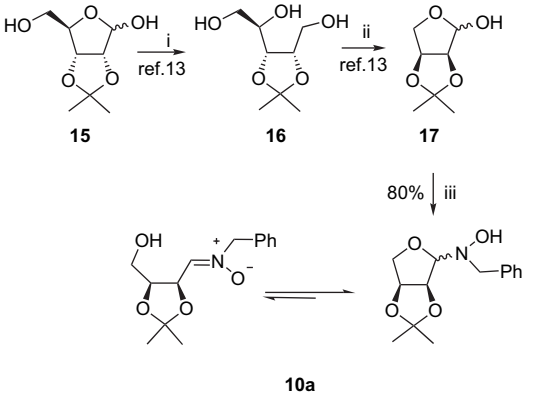
nitrones and are promising synthetic intermediates. They can be oxidized to the nitrones **11** with the sugar moiety acting as a removable chiral auxiliary or they themselves react as masked chiral nitrones in both additions with organometallic reagents and 1,3-dipolar cycloadditions, where the sugar framework remains embodied in the final adducts (Scheme 1).

Despite their apparent versatility for synthetic purposes they have received rather restricted attention mainly focused on their use as precursors of nitrones **11**[7c,e] and on organometallic additions as a synthetic path to pyrrolizidine homoazasugars.[7b,d,f,g] Regarding their participation as 1,3-dipoles by themselves in 1,3-dipolar cycloaddition reactions only one reaction with dimethyl maleate is referred[7c] to the best of our knowledge. The involvement of compounds **10** in synthetic reaction schemes leading to the synthesis of pyrrolizidines and other azasugars offers the advantage of the creation of a hydroxymethyl group useful for further manipulations simultaneously with the cycloaddition step avoiding the protection and deprotection of a preexisting hydroxymethyl group and reducing the reaction steps.

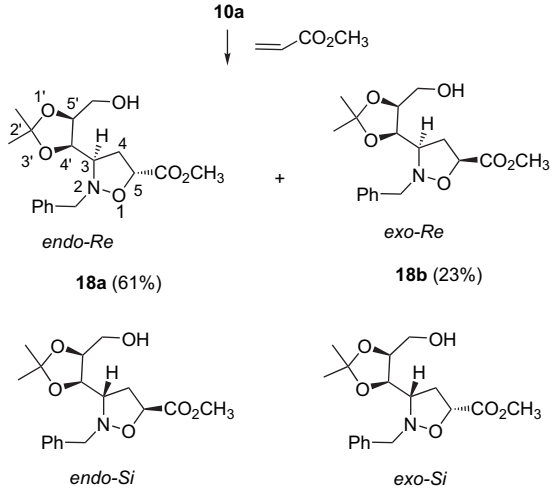
2. Results and discussion

Compound **10a** was prepared starting from D-ribose as shown in Scheme 2. Thus, the acetonide of D-ribose **15** was transformed to the acetonide of L-erythrose **17** applying typical sugar manipulations. The *N*-benzyl-*N*-glycosylhydroxylamine **10a** was obtained by reaction of the lactol **17** with benzylhydroxylamine hydrochloride in dry methylene chloride in the presence of triethylamine at room temperature following a slightly modified procedure than that described by Goti and co-workers.[7e] It was identified on the basis of its spectroscopic data, which showed a close similarity with those given in the literature for its antipode.[7e,f] As shown by its ^{1}H NMR spectrum the equilibrium is predominantly shifted towards the β-anomeric cyclic form. There is one series of main peaks corresponding to the cyclic form where the anomeric proton signal at δ 4.73 shows a zero coupling constant with 3-H consistent with their trans disposition. The existence of some low intensity additional peaks and especially a doublet at δ 6.80 (CH=N) are indicative of the open chain nitrone in less than 10%.

Nitrone **10a** reacted with methyl acrylate to give the two cycloadducts **18a** and **18b** in a ratio 2.6:1 and 84% total yield. Among the four possible 5-carboxymethyl stereoisomers from the reaction of **10a** with methyl acrylate (Scheme 3), structures **18a** and **18b** were proposed for the obtained cycloadducts assuming that they come from transition states on the less sterically hindered *Re*-face of the nitrone as predicted from molecular models. Some evidence for the stereochemistry of the obtained cyclodducts comes from ^{1}H NMR spectra. The $J_{3,4'}$=10.0 Hz of **18a** is almost equal to that of **18b** ($J_{3,4'}$=10.3 Hz) indicating that 3-H has the same geometry in both compounds as if they come from the same face of the nitrone. The discrimination between the two possible *endo* and *exo* isomers resulting from the *Re*-face of the nitrone was further made on the basis of the characteristic multiplicities and coupling constants of the two 4-H protons. In the major isomer **18a** the one of 4-H, which appears at δ 2.97 as dd (J_{gem}=13.1 Hz, $J_{4,5}$=8.7 Hz) exhibits a zero coupling constant with 3-H indicating that it is trans to that. Upon saturation of 5-H the same proton shows a large intensity increment (10%), whereas the other 4-H at δ 2.77 shows no measurable increment. Thus, it follows that the proton at δ 2.97 is cis to 5-H and trans to 3-H and consequently 3-H and 5-H are trans to each other. This trans arrangement results from an *endo* transition state assuming that nitrone **10a** reacts via its *Z*-form as it is generally accepted for acyclic nitrones.[8] In the minor isomer **18b** the two 4-H appear at δ 2.75 as ddd (J_{gem}=13.4 Hz, $J_{4,5}$=5.8 Hz, $J_{3,4}$=1.5 Hz) and δ 2.85 as ddd (J_{gem}=13.4 Hz, $J_{4,5}$=10.3 Hz, $J_{3,4}$=8.4 Hz). Thus, the 4-H at δ 2.85 with the larger coupling constants with both 3-H and 5-H should be cis to both of them, whereas the other one at δ 2.75 with the smaller coupling constants should be trans to both 3-H and 5-H, meaning that 3-H and 5-H are cis to each other, as it holds in the *exo*-cycloadducts. The overlapping of some crucial peaks as 3-H in both **18a** and **18b** along with



Scheme 2. Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C to rt, 1 h; (ii) $NaIO_4$, *t*-BuOH, H_2O, rt, 2 days; (iii) BnNHOH, CH_2Cl_2, Et_3N, rt, 2 days.



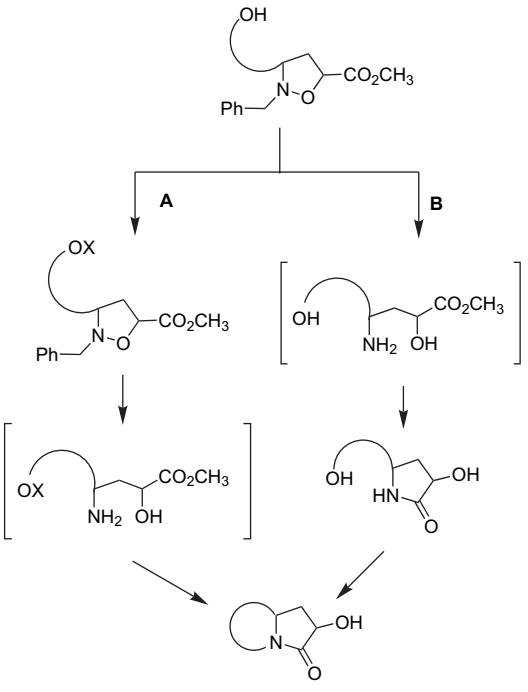
Scheme 3.

the conformational freedom of the C_3–$C_{4'}$ bond have not permitted more evidence from NOE measurements. However, the proposed stereochemistry was further supported by the transformation products of the initial cycloadducts as described below.

Isoxazolidines **18a** and **18b** bearing two functional groups (a CH_2OH and a $COOCH_3$) are suitable candidates for further transformation to pyrrolizidine derivatives via reductive cleavage of the N–O bond, which generates an NHR and an OH group.[9] The construction of the pyrrolizidine bicyclic system requires two ring closures between the amino group and the preexisting functional groups. The reaction between the NHR and the $COOCH_3$ groups leading to 3-hydroxypyrrolidones with retention of the stereochemistry is a well documented procedure.[10] For the formation of the second ring the preexisting hydroxymethyl group can be transformed to a good leaving group prior to the reduction step, so the bicyclic skeleton is formed in one step as depicted in path A (Scheme 4). Otherwise, the second cyclization via NHR, CH_2OH groups can be done after the reduction step and the formation of the pyrrolidine ring (path B, Scheme 4).

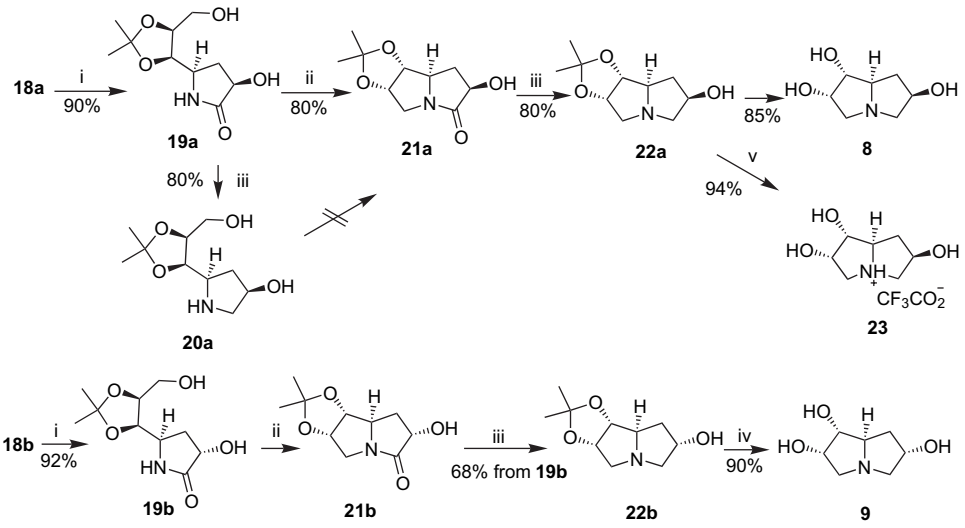
Although path A seems to be reasonable, it did not work in our hands. Several transformations of the hydroxyl to good leaving groups such as mesyl, tosyl or iodo along with several reduction conditions, that were tried on isoxazolidine **18a**, were unsuccessful. In particular the mesylation carried out by a typical procedure (MsCl, pyridine, DMAP) afforded a polar crude product, which was further subjected to hydrogenolysis over Pd/C or Raney Ni, but without definite results. In small scale experiments there were some indications for the formation of the targeted molecules but we had not obtained any repeatable and reliable results upon scaling up of the reaction. The attempts for transformation of hydroxyl group to a tosyl (TsCl, pyridine) or a iodo one (I_2, Ph_3P, imidazole) were also unsuccessful, resulted in unidentified products in both cases.

After that, we focused our experiments on the second path. Thus, direct hydrogenolysis of isoxazolidines **18a** and **18b** in methanol in the presence of palladium on carbon catalyst afforded pyrrolidinones **19a** and **19b**, respectively, in high yields via a reaction sequence involving isoxazolidine N–O bond cleavage, N-debenzylation and spontaneous cyclization. The amides **19** could be further selectively reduced to the amines **20** using $BH_3\cdot Me_2S$. For the condensation of the hydroxymethyl and NH moieties we have chosen to apply the Mitsunobu reaction.[11] However, typical Mitsunobu conditions using Ph_3P and DEAD as reagents did not work neither on the amide nor on its reduction product. After some experimentation on both **19a** and **20a** we found cyclodehydration of the amide **19a** to the pyrrolizidinone **21a** to proceed in high yield using 1,1′-(azodicarbonyl)dipiperidine (ADDP) and tri-*n*-butylphosphine as Mitsunobu reagents. Analogous modifications for the Mitsunobu reaction have been adapted in cases of nucleophiles with low basicity.[12] The same reaction sequence was successfully applied to the pyrrolidinone **19b** resulting from the isoxazolidine **18b**. Amides **21a** and **21b** were readily reduced to the corresponding methylene compounds **22a** and **22b** using $BH_3\cdot Me_2S$. It should be mentioned that it was not possible to obtain amide **21b** in pure form. Even after repeated chromatographies it was contaminated with the hydrazide derived from ADDP during the Mitsunobu reaction. This crude product was used for the next reduction step and fortunately the reduction product **22b** having a different Rf was eventually separated in pure form. Acid deprotection of **21a** and **21b** gave the trihydroxylated pyrrolizidines **8** and **9** (Scheme 5).



Scheme 4.

The structural elucidation of the obtained pyrrolizidines was based on their spectroscopic and elemental data. For the compounds coming from the major isomer of the cycloaddition reaction **18a** the stereochemistry was supported by NOE measurements carried out on compound **21a**. The ^1H NMR spectrum of this compound was well resolved and proton assignments and connectivities could be established by double resonance experiments. NOE data are fully in accordance with the structure **21a** as depicted in Figure 1. In particular, the significant NOE enhancements observed between 8-H^1 and 8b-H show the close proximity of these protons in a ladle arrangement of the three rings as a result of the initial approach of the dipolarophile to the *Re*-face of the nitrone. This is further supported by NOE enhancement induced on 8a-H upon saturation of one of the methyl groups of the dioxolane ring. Also significant mutual NOE increments were observed between 8-H^2 and both 7-H and 8a-H indicating that these three protons are in a cis arrangement as a result of an *endo* attack of the dipolarophile for the formation of the starting **18a** cycloadduct. The proposed stereo structures for the major cycloadduct and its transformation products were further corroborated by the identification of the ^1H NMR and ^{13}C NMR spectra of the final deprotected trihydroxypyrrolizidine trifluoroacetate salt **23** with those given by Wightman for its racemate.[4b] Compound **23** was obtained from deprotection of **22a** with TFA for purposes of comparison with the data of Wightman. For the compounds coming from the minor isomer **18b**, that is, **19b**, **21b**, **22b**, **9** our evidence for their stereochemistry is weaker since none of them exhibited a fully resolved spectrum suitable for extensive NOE measurements. Notwithstanding, in the proton NMR spectrum of compound **22b** it could be observed a remarkable enhancement of 8a-H (8%) upon saturation of one of the methyl groups of the dioxolane ring. This is indicative of a ladle arrangement of the three rings corresponding to a *Re*-approach to the nitrone in the initial cycloaddition step. Since the major isomer **18a** of the cycloaddition reaction has assigned as the *endo-Re* product, the other possible product from the *Re*-approach should be the *exo-Re*, that is, **18b**. As it has been already mentioned, this structure is also supported by the values of proton coupling constants in the initial minor cycloadduct. On the other hand, the final trihydroxypyrrolizidine **9** of this reaction sequence, as an antipode of compound **7**, described by Fišera and co-workers[5] should give the same ^1H NMR and ^{13}C NMR data. In fact these data are different. Unfortunately, attempts to assign undoubtedly the



Scheme 5. Reagents and conditions: (i) Pd/C, H_2, CH_3OH, rt, 2 days; (ii) PBu_3, ADDP, THF, 1 day; (iii) $BH_3{\cdot}Me_2S$, THF, rt, 1 day; (iv) $CH_3C_6H_4SO_3H$, CH_3OH, rt, 1 day; (v) TFA, H_2O, rt, 1 day.

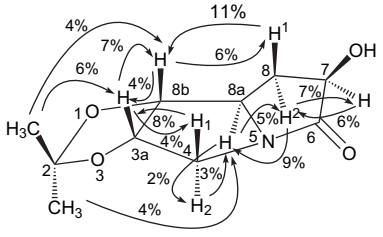


Figure 1. NOE enhancements measured on compound **21a**.

proposed stereochemistry by X-ray crystal structure analysis were unsuccessful, since despite our efforts none of the compounds of the above reaction sequence gave crystals suitable for this purpose. Thus, on the basis of the data we had in hand and following up the two newly formed stereogenic centres in the cycloaddition step through the whole reaction sequence, we tentatively assigned the proposed stereochemistry despite the above mentioned discrepancy with Fišera's data.

In conclusion, an efficient synthetic pathway to trihydroxypyrrolizidines **8** and **9** has been established from L-erythrosehydroxylamine in five steps with yields bigger than 80% for each step. Given the convenience of the synthesis of glycosyl hydroxylamines from sugars this process can be extended to the synthesis of diverse pyrrolizidines by choice of the suitable starting sugar.

3. Experimental

3.1. General

Mps were determined on a Kofler hot-stage microscope. IR spectra were recorded on a Perkin–Elmer 297 spectrometer. ^1H NMR spectra were recorded at 300 MHz on a Bruker 300 AM spectrometer and ^{13}C NMR spectra at 75.5 MHz on the same spectrometer, and are quoted relative to tetramethylsilane as internal reference, in deuteriochloroform solutions, unless otherwise stated. Mass spectra (EI) were performed on a VG-250 spectrometer with ionization energy maintained at 70 eV. High resolution mass spectra (HRESI) were obtained with a 7T APEX II spectrometer. Microanalyses were performed on a Perkin–Elmer 2400-II element analyser. Column chromatography was carried out on Merck Kieselgel (particle size 0.063–0.200 mm) and solvents were distilled before use.

3.2. Synthesis of compound 10a

Lactol **17** (844 mg, 5.2 mmol) prepared from D-ribose according to the conditions described in the literature[13] was dissolved in dry CH_2Cl_2 (20 mL) and dry triethylamine (0.72 mL, 5.1 mmol) was added. The solution was cooled to 0 °C and *N*-benzylhydroxylamine hydrochloride (1.25 g, 7.8 mmol) was gradually added. After that, the reaction mixture was stirred at room temperature for 2 days. Then a saturated solution of NH_4Cl (20 mL) was added, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were concentrated after drying with Na_2SO_4. The residue was purified by column chromatography (silica gel, hexane/EtOAc, 4:1) to give compound **10a** (1150 mg, 83% yield).

*3.2.1. (2S,3S,4S)-N-Benzyl-N-hydroxy-3,4-O-isopropylidene dioxytetrahydrofuran-2-amine (**10a**)*

This compound was obtained as a white solid, mp 83–88 °C; $[\alpha]_D^{25}$ +63.5 (*c* 5.1, $CHCl_3$); IR (KBr): ν_{max} 3418 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.88 (d, *J*=13.1 Hz, 1H, $CH_2C_6H_5$), 4.07 (d, *J*=8.7 Hz, 1H, 5-H), 4.09 (d, *J*=13.1 Hz, 1H, $CH_2C_6H_5$), 4.27 (dd, *J*=8.7, 4.3 Hz, 1H, 5-H), 4.67 (s, 1H, OH), 4.73 (s, 1H, 2-H), 4.88 (dd, *J*=6.1, 4.3 Hz, 1H, 4-H), 4.92 (d, *J*=6.1 Hz, 1H, 3-H), 7.25–7.40 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.7 (CH_3), 26.3 (CH_3), 59.2 (C-5), 76.1 ($CH_2C_6H_5$), 81.0 (C-4), 83.5 (C-3), 99.3 (C-2), 111.9 ($C(CH_3)_2$), 127.3, 128.3, 129.6 and 136.8 (C_6H_5). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.24; H, 6.95; N, 4.99.

3.3. Cycloaddition reaction of compound 10a with methyl acrylate

A solution of **10a** (1.325 g, 5 mmol) and methyl acrylate (18 mL) was heated under reflux and the consumption of the starting material was monitored with TLC. After 2 days the reaction has finished and the crude product obtained after evaporating the excess of methyl acrylate was purified by column chromatography (silica gel, hexane/EtOAc, 4:1) to give in order of elution 985 mg of **18a**, 120 mg of a mixture of **18a** and **18b** in a ratio 2:1 and 370 mg of **18b**.

*3.3.1. Methyl (3R,5R)-2-benzyl-3-[(4′R,5′S)-5′-(hydroxymethyl)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]isoxazolidine-5-carboxylate (**18a**)*

This compound was obtained as an oil in 61% total yield; $[\alpha]_D^{25}$ +53.2 (*c* 12.7, $CHCl_3$); IR (film): ν_{max} 3446 (OH), 1750 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.77 (ddd, *J*=13.1, 8.7, 7.1 Hz, 1H, 4-H), 2.97 (dd, *J*=13.1, 8.7 Hz, 1H, 4-H), 3.35 (ddd, *J*=12.3, 7.0, 4.3 Hz, 1H, C*H*$_2$OH), 3.59–3.72 (m, 2H, C*H*$_2$OH and 3-H), 3.66–3.83 (m, 5H, C*H*$_2$C$_6$H$_5$, OCH_3, OH), 3.97 (dd, *J*=10.0, 5.4 Hz, 1H, 4′-H), 4.20 (d, 1H, *J*=12.2 Hz, 1H, C*H*$_2$C$_6$H$_5$), 4.32 (ddd, *J*=10.0, 5.0, 4.3 Hz, 1H, 5′-H), 4.63 (t, *J*=8.7 Hz, 1H, 5-H), 7.29–7.37 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.3 (CH_3), 27.9 (CH_3), 33.3 (C-4), 52.4 (OCH_3), 59.3, 61.9, 64.6, 75.2, 77.2 and 77.4 (CH_2OH, *C*H$_2$C$_6$H$_5$, C-3, C-5, C-4′, C-5′), 108.6 (*C*(CH_3)$_2$), 127.9, 128.5, 129.7 and 135.7 (C_6H_5), 172.8 (CO); MS (EI): *m*/*z* (%) 352 (M^+, 40). Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.37; H, 7.16; N, 4.08.

*3.3.2. Methyl (3R,5S)-2-benzyl-3-[(4′R,5′S)-5′-(hydroxymethyl)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]isoxazolidine-5-carboxylate (**18b**)*

This compound was obtained in 23% total yield as a white solid, mp 87–89 °C; $[\alpha]_D^{25}$ +64.9 (*c* 7.1, $CHCl_3$); IR (KBr): ν_{max} 3490 (OH), 1738 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.75 (ddd, *J*=13.4, 5.8, 1.5 Hz, 1H, 4-H), 2.85 (ddd, *J*=13.4, 10.3, 8.4 Hz, 1H, 4-H), 3.41 (ddd, *J*=10.7, 7.8, 3.7 Hz, 1H, C*H*$_2$OH), 3.52–3.72 (m, 3H, C*H*$_2$OH, 3-H, OH), 3.78 (s, 3H, OCH_3), 3.83 (d, *J*=12.9 Hz, 1H, C*H*$_2$C$_6$H$_5$), 3.96 (d, *J*=12.9 Hz, 1H, C*H*$_2$C$_6$H$_5$), 4.18 (dd, *J*=10.3, 5.7 Hz, 1H, 4′-H), 4.35 (dt, *J*=7.8, 5.7 Hz, 1H, 5′-H), 4.79 (dd, *J*=10.3, 5.8 Hz, 1H, 5-H), 7.29–7.37 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.3 (CH_3), 27.9 (CH_3), 33.3 (C-4), 52.4 (OCH_3), 59.3, 61.9, 64.6, 75.2, 77.2 and 77.4 (CH_2OH, *C*H$_2$C$_6$H$_5$, C-3, C-5, C-4′, C-5′), 108.6 (*C*(CH_3)$_2$), 127.9, 128.5, 129.7 and 135.7 (C_6H_5), 172.8 (CO); MS (EI): *m*/*z* (%) 352 (M^+, 40). Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.71; H, 7.08; N, 3.86.

3.4. Reductive cleavage of isoxazolidines 18 to pyrrolidinones 19

General procedure. A catalytic amount of Pd/C (10% w/w (about 30 mg)) was added to a previously degassed solution of isoxazolidine (1.2 mmol) in MeOH (10 mL) under a hydrogen atmosphere (balloon). The mixture was stirred for about 2 days and then the crude reaction mixture was passed through Celite, concentrated and purified by column chromatography (silica gel, EtOAc/CH_3OH 20:1).

*3.4.1. (3R,5R)-3-Hydroxy-5-[(4′R,5′S)-5′-(hydroxymethyl)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-2-pyrrolidone (**19a**)*

This compound was obtained from **18a** in 90% yield as a white solid, mp 141–143 °C; $[\alpha]_D^{25}$ +18.1 (*c* 3.4, $CHCl_3$); IR (KBr): ν_{max} 3435 (OH), 1695 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.95 (dt, *J*=13.5, 7.7 Hz, 1H, 4-H), 2.71 (ddd, *J*=13.5, 8.2, 5.9 Hz, 1H, 4-H), 3.66–3.78 (m, 2H, 5-H and C*H*$_2$OH), 3.82 (dd, *J*=10.1, 5.2 Hz, 1H, C*H*$_2$OH), 4.05 (dd, *J*=9.0, 5.8 Hz, 1H, 4′-H), 4.25–4.38 (m, 4H, 5′-H and 3-H), 7.36 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.6 (CH_3), 28.2(CH_3), 35.1 (C-4), 50.3 (C-5), 60.7, 69.6, 77.8, 81.6 (C-3, C-4′, C-5′and CH_2OH), 109.0 (*C*(CH_3)$_2$), 178.4 (CO); HRESIMS for $C_{10}H_{17}NaNO_5$ $(M+Na)^+$: calcd 254.1004, found 254.1001.

*3.4.2. (3S,5R)-3-Hydroxy-5-[(4′R,5′S)-5′-(hydroxymethyl)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-2-pyrrolidone (**19b**)*

This compound was obtained from **18b** in 92% yield as a white solid, mp 102–104 °C; $[\alpha]_D^{25}$ −47.5 (*c* 4.4, $CHCl_3$); IR (KBr): ν_{max} 3437 (OH), 1695 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.18 (dt, *J*=14.0, 7.9, 6.8 Hz, 1H, 4-H), 2.50 (dd, *J*=14.0, 7.4 Hz, 1H, 4-H), 3.60–3.78 (m, 2H, 5-H and C*H*$_2$OH), 3.85 (t, *J*=8.0 Hz, 1H, 3-H), 3.95 (dd, *J*=7.9, 6.1 Hz, 1H, 4′-H), 4.23 (dd, *J*=12.5, 5.8 Hz, 1H, C*H*$_2$OH), 4.42 (t, *J*=7.9 Hz, 5′-H), 4.60 (br s, 2H, OH), 7.58 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.2 (CH_3), 27.6 (CH_3), 33.2 (C-4), 50.7 (C-5), 60.0, 68.4, 76.8 and 79.2 (C-3, C-4′, C-5′ and CH_2OH), 108.5 (*C*(CH_3)$_2$), 178.5 (CO); HRESIMS for $C_{10}H_{17}NaNO_5$ $(M+Na)^+$: calcd 254.1004, found 254.1000.

3.5. Mitsunobu condensation of pyrrolidinones 19 to pyrrolizinones 21

A solution of pyrrolidinone **19** (1 mmol) in dry THF (5 mL) was cooled to 0 °C under an argon atmosphere and then were added tri-*n*-butylphosphine (0.37 mL, 1.5 mmol) and ADDP (378 mg, 1.5 mmol). The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 1 day. After that, the solvent was evaporated in vacuo and the crude product was purified by column chromatography (silica gel, EtOAc).

*3.5.1. (3aS,7R,8aR,8bR)-7-Hydroxy-2,2-dimethylhexahydro-6H-[1,3]dioxolo[4,5-a]pyrrolizin-6-one (**21a**)*

This compound was obtained from **19a** in 80% yield as a white solid, mp 165–167 °C; $[\alpha]_D^{25}$ +58.02 (*c* 0.4, $CHCl_3$); IR (KBr): ν_{max} 3468 (OH), 1682 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.74 (ddd, *J*=12.9, 10.3, 8.6 Hz, 1H, 8-H), 2.89 (ddd, *J*=12.9, 7.4, 6.6 Hz, 1H, 8-H), 3.13 (dd, *J*=13.1, 3.4 Hz, 1H, 4-H), 3.73 (ddd, *J*=8.6, 6.6, 4.3 Hz, 1H, 8a-H), 4.13 (dd, *J*=13.1, 6.4 Hz, 1H, 4-H), 4.29 (br s, 1H, OH), 4.35 (dd, *J*=6.7, 4.3 Hz, 1H, 8b-H), 4.54 (dd, *J*=10.3, 7.4 Hz, 1H, 7-H), 4.84 (ddd, *J*=6.7, 6.4, 3.4, 1H, 3a-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 26.4 (CH_3), 28.5 (CH_3), 37.2 (C-8), 48.4 (C-4), 62.6 and 73.0 (C-8a and C-7), 81.2 and 85.8 (C-3a and C-8b), 115.2 (*C*(CH_3)$_2$), 175.6 (CO); HRESIMS for $C_{10}H_{16}NO_4$ $(M+H)^+$: calcd 214.1079, found 214.1075; for $C_{10}H_{15}NaNO_4$ $(M+Na)^+$: calcd 236.0899, found 236.0894.

*3.5.2. (3aS,7S,8aR,8bR)-7-Hydroxy-2,2-dimethylhexahydro-6H-[1,3]dioxolo[4,5-a]pyrrolizin-6-one (**21b**)*

This compound was obtained from **19b** after the described work up and repeated column chromatographies as a crude oil contaminated with byproducts of the Mitsunobu reaction and it was used for the next step in crude form. Its formation was certified by its MS spectrum; HRESIMS for $C_{10}H_{15}NaNO_4$ $(M+Na)^+$: calcd 236.0899, found 236.0896.

3.6. Reduction of pyrrolidinone 19a and pyrrolizinones 21

Borane–dimethylsulfide complex (2 M in BH_3, 2 mL, 4 mmol) was added with stirring to a cool (0 °C) solution of the lactam **19** or **20** (0.8 mmol) in THF (10 mL) under an argon atmosphere. The reaction mixture was allowed to stirred at room temperature for 1 day and the reaction was quenched by addition of satd Na_2SO_4 and the solvent was concentrated in vacuo. The residue was dissolved in water and was extracted with CH_2Cl_2 (3×15 mL). After drying and evaporation of the combined organic extracts the crude product was purified by column chromatography (silica gel, EtOAc).

*3.6.1. (3R,5R)-5-[(4′R,5′S)-5-(Hydroxymethyl)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]pyrrolidin-3-ol (**20a**)*

This compound was obtained from **19a** in 80% yield as a white solid, mp 129–133 °C; IR: ν_{max} 3469 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.43 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.80 (br, 2H, OH or NH), 1.97 (ddd, *J*=14.3, 4.7, 2.8 Hz, 1H, 4-H), 2.29 (ddd, *J*=14.3, 9.7, 4.7 Hz, 1H, 4-H), 2.73 (td, *J*=12.0, 3.0 Hz, 1H, 2-H), 3.20–3.30 (m, 2H, 2-H, 5-H), 3.68 (m as d, 2H, C*H*$_2$OH), 4.30 (br, 1H, OH or NH), 4.38

(dd, *J*=5.8, 2.7 Hz, 1H, 4′-H), 4.42–4.50 (m, 1H, 3-H), 4.78 (m, 1H, 5′-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.3 (CH_3), 26.2 (CH_3), 35.8 (C-4), 60.9, 63.1, 65.4, 70.4, 73.8 and 76.9 (CH_2OH, C-2, C-3, C-5, C-4′ and C-5′), 109.4 ($C(CH_3)_2$); HRESIMS for $C_{10}H_{20}NO_4$ $(M+H)^+$: calcd 254.1004, found 254.1000.

*3.6.2. (3aS,7R,8aR,8bR)-2,2-Dimethylhexahydro-4H-[1,3]dioxolo[4,5-a]pyrrolizin-7-ol (**22a**)*

This compound was obtained from **21a** in 80% yield as an oil; $[\alpha]_D^{25}$ +24.8 (*c* 0.9, $CHCl_3$); IR (KBr): ν_{max} 3468 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.05 (dd, *J*=13.5, 1.2 Hz, 1H, 8-H), 2.23 (br s, 1H, OH), 2.55 (ddd, *J*=13.5, 9.1, 5.5 Hz, 1H, 8-H), 2.98 (d, *J*=12.8 Hz, 1H, 6-H), 3.43–3.54 (m, 2H, 4-H and 6-H), 3.60–3.69 (m, 1H, 8a-H), 3.92 (dd, *J*=11.4, 1.2 Hz, 1H, 4-H), 4.52–4.59 (m, 1H, 7-H), 4.78 (dd, *J*=6.1, 3.1 Hz, 1H, 8b-H), 4.93–5.01 (m, 1H, 3a-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.4 (CH_3), 27.3 (CH_3), 38.7 (C-8), 69.2, 72.2, 72.6, 77.9, 78.8 and 86.9 (C-3a, C-4, C-6, C-7, C-8a and C-8b), 113.8 ($C(CH_3)_2$); HRESIMS for $C_{10}H_{18}NO_3$ $(M+H)^+$: calcd 200.1287, found 200.1282.

*3.6.3. (3aS,7S,8aR,8bR)-2,2-Dimethylhexahydro-4H-[1,3]dioxolo[4,5-a]pyrrolizin-7-ol (**22b**)*

This compound was obtained from crude **21b** in 68% yield (for two steps, calculated on **19b**) as a white solid, mp 103–105 °C; $[\alpha]_D^{25}$ +11 (*c* 0.41, $CHCl_3$); IR: ν_{max} 3468 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.34–2.59 (m, 2H, 8-H), 2.23 (br s, 1H, OH), 2.98 (dd, *J*=10.1, 6.1 Hz, 1H, 6-H), 3.36–3.59 (m, 2H, 4-H and 6-H), 3.96–4.09 (m, 1H, 8a-H), 4.36–4.58 (m, 2H, 7-H and 8b-H), 4.82 (dd, *J*=10.1, 6.1 Hz, 1H, 3a-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.2 (CH_3), 27.0 (CH_3), 39.6 (C-8), 67.9, 70.9, 71.2, 76.7, 78.3 and 86.1 (C-3a, C-4, C-6, C-7, C-8a and C-8b), 114.6 ($C(CH_3)_2$); HRESIMS for $C_{10}H_{18}NO_3$ $(M+H)^+$: calcd 200.1287, found 200.1282.

3.7. Hydrolysis of acetonides 22 to pyrrolizidines 8 and 9

To a solution of **22** (57 mg, 0.28 mmol) in 6 ml of methanol, *p*-toluenesulfonic acid (108 mg, 0.57 mmol) was added and the mixture was stirred overnight. The solution was neutralized by addition of K_2CO_3, the resulting solids were removed by filtration and the filtrates were concentrated in vacuo. After that, the crude product was purified by column chromatography (silica gel, CH_2Cl_2/CH_3OH 4:1).

*3.7.1. (1R,2S,6R,7aR)-Hexahydro-1H-pyrrolizine-1,2,6-triol (**8**)*

This compound was obtained from **22a** in 85% yield as an oil; $[\alpha]_D^{25}$ +28.8 (*c* 0.46, CH_3OH); IR (film): ν_{max} 3460 (OH) cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz): δ 1.94 (br d, *J*=13.6 Hz, 1H, 7-H), 2.17 (ddd, *J*=13.6, 9.7, 4.5 Hz, 1H, 7-H), 2.78 (br d, *J*=11.2 Hz, 1H, 5-H), 3.01–3.25 (m, 3H, 3-H and 5-H), 3.55 (br, 1H, 7a-H), 4.16 (m, 1H, 2-H), 4.24 (br m, 1H, 1-H), 4.40 (br m, 1H, 6-H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 39.4 (C-7), 62.5 and 63.7 (C-3 and C-5), 70.1 (C-7a), 74.5, 74.7 and 80.1 (C-1, C-2 and C-6); HRESIMS for $C_7H_{14}NO_3$ $(M+H)^+$: calcd 160.0973, found 160.0970.

*3.7.2. (1R,2S,6S,7aR)-Hexahydro-1H-pyrrolizine-1,2,6-triol (**9**)*

This compound was obtained from **22b** in 90% yield as an oil; $[\alpha]_D^{25}$ +21.2 (*c* 0.30, CH_3OH); IR (film): ν_{max} 3470 (OH) cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz): δ 1.78 (dt, *J*=12.6, 6.5 Hz, 1H, 7-H), 2.01 (ddd, *J*=12.6, 7.6, 3.7 Hz, 1H, 7-H), 2.58–2.74 (m, 2H, 3-H and 5-H), 2.94 (br d, *J*=10.9 Hz, 1H, 5-H), 3.07 (dd, *J*=11.4, 4.5 Hz, 1H, 3-H), 3.51–3.63 (br m, 1H, 7a-H), 3.76 (dd, *J*=8.7, 4.0 Hz, 1H, 2-H), 4.11–4.19 (br m, 1H, 1-H), 4.35–4.42 (br m, 1H, 6-H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 40.2 (C-7), 60.9 and 64.9 (C-3 and C-5), 69.6 (C-7a), 74.2, 74.3 and 79.6 (C-1, C-2 and C-6); HRESIMS for $C_7H_{14}NO_3$ $(M+H)^+$: calcd 160.0973, found 160.0969.

3.8. Hydrolysis of acetonide 22a to pyrrolizidine salt 23

A solution of **22a** (0.6 mmol) in TFA (2 mL) and water (2 mL) was allowed to stay at room temperature for 1 day and then evaporated. The residue was redissolved in water and reevaporated.

*3.8.1. (1R,2S,6R,7aR)-Hexahydro-1H-pyrrolizine-1,2,6-triol trifluoroacetate (**23a**)*

This compound was obtained from **22a** in 94% yield as a white solid, mp 160–162 °C; $[\alpha]_D^{25}$ +22.7 (*c* 0.42, H_2O); ^{1}H NMR (D_2O, 300 MHz): δ 2.17 (br d, *J*=14.6 Hz, 1H, 7-H), 2.34 (ddd, *J*=14.6, 9.4, 5.2 Hz, 1H, 7-H), 3.34 (d, *J*=12.8 Hz, 1H, 5-H), 3.46 (dd, *J*=12.8, 3.6 Hz, 1H, 5-H), 3.54 (dd, *J*=12.9, 2.6 Hz, 1H, 3-H), 3.76 (d, *J*=12.9 Hz, 1H, 3-H), 4.09 (dt, *J*≈8.6, 2.6 Hz, 1H, 7a-H), 4.40 (br m 1H, 2-H), 4.47 (dd, *J*=7.6, 3.4 Hz, 1H, 1-H), 4.66 (m, 1H, 6-H); ^{13}C NMR (D_2O, 75.5 MHz): δ 35.3 (C-7), 59.9 and 60.3 (C-3 and C-5), 68.3 (C-7a), 71.1, 71.6 and 76.6 (C-1, C-2 and C-6); HRESIMS for $C_7H_{14}NO_3$ $(M+H)^+$: calcd 160.0974, found 160.0968.

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