Article

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Synthesis of enantiomeric polyhydroxyalkylpyrrolidines from 1,3-dipolar cycloadducts. Evaluation as inhibitors of a β-galactofuranosidase

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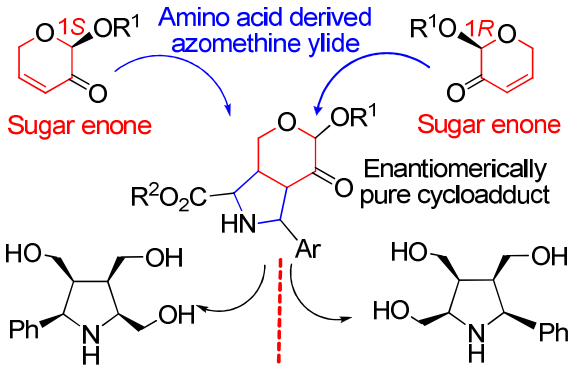
Abstract



Enantiomeric 2,3,4-tris(hydroxyalkyl)-5-phenylpyrrolidines have been synthesized from the major cycloadducts obtained by the 1,3-dipolar cycloaddition of sugar enones with azomethine ylides derived from natural amino acids. Reduction of the ketone carbonyl group of the cycloadducts, which possess a basic structure of bicyclic 6-menthyloxyhexahydropyrano[4,3-*c*]pyrrol-7(6*H*)one, afforded a number of pyrrolidine-based bicyclic systems. A sequence of reactions, which involved hydrolysis of the menthyloxy substituent, reduction, *N*-protection and degradative oxidation, afforded varied pyrrolidine structures having diverse configurations and patterns of substitution, particularly polyhydroxylated derivatives have been obtained. The unprotected products were isolated as pyrrolidinium trifluoroacetates. Because of the furanose-like nature of the target trihydroxyalkyl pyrrolidines, these molecules have been evaluated as inhibitors of the β-galactofuranosidase from *Penicillium fellutanum*. The compounds showed practically no inhibitory activity for concentration of pyrrolidines in the range of 0.1 to 1.6 mM.

Introduction

The increasing interest in polyhydroxypyrrolidines relies on their potential in the treatment of diseases. Polyhydroxypyrrolidines are also known as azasugars or iminosugars as they are mimics of sugars in which the ring oxygen atom has been replaced by a nitrogen atom. The most valuable properties of these compounds is their ability to inhibit glycosidases. These enzymes catalyze the cleavage of glycosidic linkages and are involved in a wide range of important biological events, including the processing of oligosaccharide chains of oligosaccharides, bacterial and viral infections and tumor metastasis.[1] The glycosidase inhibitors have shown to be effective for the treatment of varied pathologies,[2] and the scope is constantly increased.[3] Thus, alkaloidal sugar mimics are currently employed or are potential drugs for the treatment of type II diabetes, for the modulation of the immune response, in cancer therapy, as anti-infective and antiviral agents, in the development of novel therapeutics for lysosomal storage diseases, in the chaperone-mediated therapy, etc.[4]

The inhibitory activity of glycosidases and glycosyltransferases by azasugars is attributed to the fact that, at physiological pH, the nitrogen atom is protonated and this charged species mimics the oxacarbenium transition state formed during glycosidase hydrolysis and glycosyl transfer.[5] Moreover, azasugar transition state analogues proved to be useful tools for the study of the mechanism of action of carbohydrate-processing enzymes.[6]

Alkaloids mimicking the structure of monosaccharides are believed to be widespread in plants and microorganisms.[7] Particularly, polyhydroxylated pyrrolidines with varied arrangements of at least two hydroalkyl groups as substituent of the five-membered heterocyclic ring have been isolated first from *Derris elliptica*,[8] and later from many

disparate species of plants and microorganisms,[9] indicating that they are rather common metabolites. These type of pyrrolidines have also been isolated from seeds of *Angylocalyx pinaerty*[8] and from the leaves or bulbs of different species of *Hyacintus*[10,11] and *Hyacinthaceae*.[10,12]

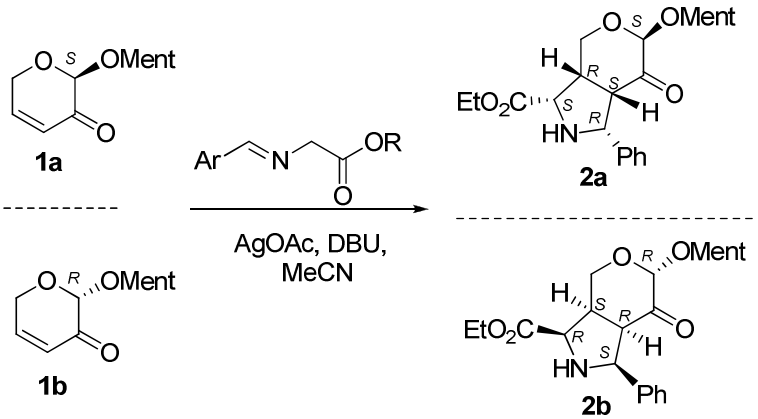
The synthesis of pyrrolidines, including those with hydroxyalkyl substituents in the ring, has been recently reviewed.[13] Some recent syntheses of this type of molecules have been reported.[14]

As continuation of our project on the synthesis of sugar mimetics as inhibitors of glycosidases,[15] we report here the synthesis of enantiomeric pyrrolidines substituted in three adjacent positions of the ring with hydroxyalkyl groups. These compounds were obtained by chemical transformations performed on cycloadducts generated by 1,3-dipolar cycloaddition of azomethine ylides and sugar enones.[16] Some representative compounds were evaluated as inhibitors of the β-galactofuranosidase from *Penicillium fellutanum*. We are seeking for inhibitors of this enzyme as some pathogenic microorganisms, including mycobacteria, fungus (*Aspergillus* and *Penicillium* species) and protozoa (*Trypanosoma* and *Leishmania*), display β-galactofuranosidase activity.[17] The inhibition of enzymes involved in the metabolism of galactofuranose, which is absent in higher eukaryotes, is expected to prevent the proliferation of pathogens such as *Mycobacterium tuberculosis* or *Trypanosoma cruzi*, the respective agents of tuberculosis or Chagas disease. Furthermore, as the structure and interactions in the catalytic site of the enzyme remain unknown, the development of new inhibitors can contribute to the understanding of the processes triggered by galactofuranose processing enzymes.

Results and discussion

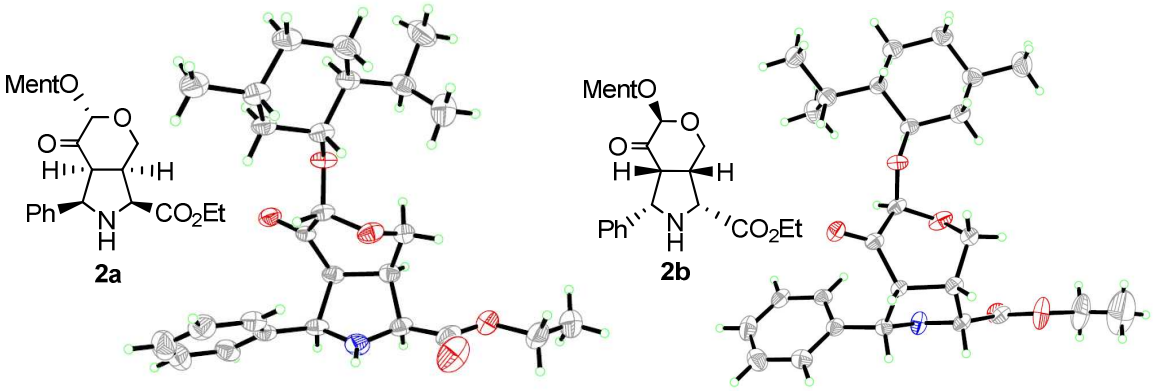
The 1,3-dipolar cycloaddition is one of the most powerful tools for the synthesis of heterocyclic scaffolds and the reaction has been applied in diverse fields like drug discovery, polymers and materials.[18] We have employed the 1,3-dipolar cycloaddition reaction of stabilized azomethine ylides and sugar-derived enones (**1a** and **1b**) to afford cycloadducts of the type of **2a** or **2b**, as shown in Scheme 1.[16] The stereogenic center (*S*) or (*R*) of the sugar pyranone (**1a** or **1b**, respectively) exerts a strict diastereocontrol during the [3+2]-cycloaddition. Thus, the menthyloxy substituent of such a stereocenter is axially-oriented because of the anomeric effect, and induces the approach of the dipole from the opposite face of the pyranone ring. This remarkable selectivity was also observed for Diels-Alder cycloadditions and other additions to the double bond of enones of the type of **1a** or **1b**.[19] Therefore, the pyrrolidine ring of the major product *endo*-**2a**, obtained from (*S*)-**1a**, had the opposite configuration for the four stereocenters generated during the cycloaddition than those of *endo*-**2b**, obtained from (*R*)-**1b**.

Scheme 1: Enantiomeric pyrrolidines (*endo* isomers) obtained from enones **1a** (*S*) or **1b** (*R*) via 1,3-dipolar cycloaddition.



Now, we were able to confirm by X ray crystallography the structure of compounds **2a** and **2b**, which had been previously assigned on the basis of NMR data.[16] Suitable crystals of **2a** and **2b** could be obtained using acetonitrile as recrystallization solvent, and the X-ray diffraction analysis confirmed the absolute configuration assigned to these two key cycloadducts (Figure 1). In fact, the crystallographic data (fully described in the Supporting Information) reveals that compound **2a** crystalizes as a solvate with one molecule of acetonitrile, while two independent molecules of **2b** occupy the asymmetric unit (Z = Z' = 2).

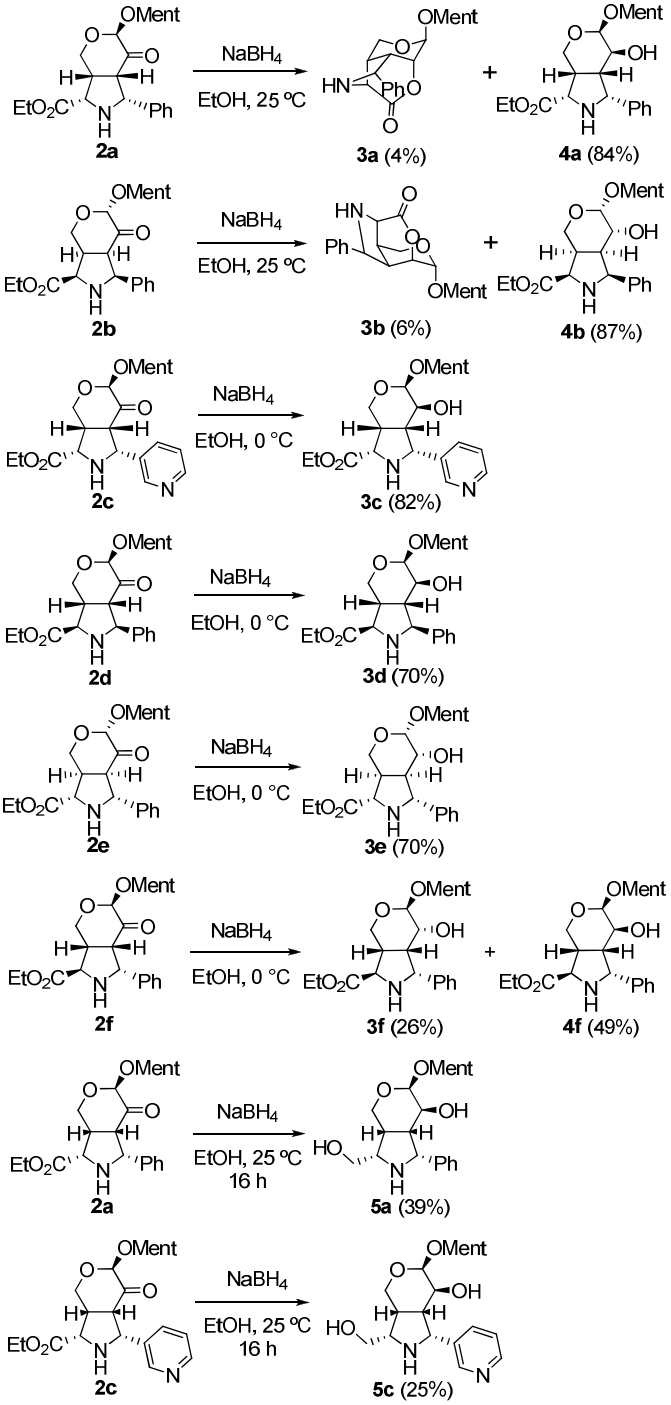
Figure 1: Drawing of molecules **2a** and **2b** showing the displacement ellipsoids of non-H atoms at 50% probability levels.



Starting from **1a** or **1b** a number of cycloadducts (**2a**−**2f**) have been prepared and they were subjected to a sequence of reduction and hydrolysis reactions in order to obtain enantiomerically pure polyhydroxypyrrolidines of varied configurations. In first instance, the reduction of the carbonyl group of **2a**−**2f** was studied (Scheme 2). The reaction was conducted with sodium borohydride in ethanol at 0 °C, except when the dissolution of the starting compound requires a slightly higher temperature (25 °C). Anyway, the reduction of **2a** was completed after 10−30 min to afford two main products, which were separated by column chromatography. The minor component of

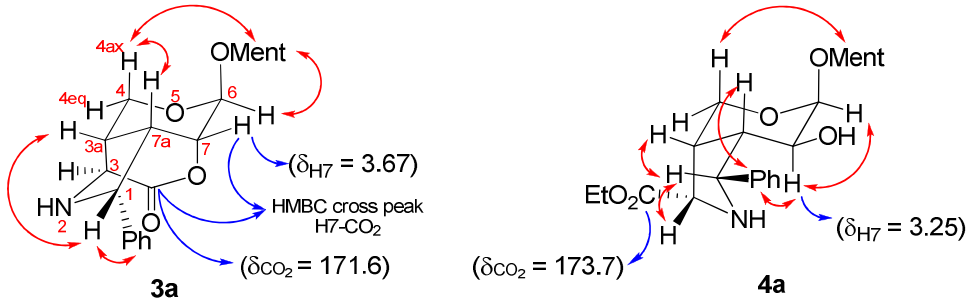
the mixture was identified as **3a**, which resulted from the attack of the hydride from the *Si* face of the carbonyl. The resulting alcohol underwent spontaneous lactonization by nucleophilic attack to the ethyl carboxylate conveniently located, to give **3a**. The major product of the reduction was the epimeric alcohol **4a** (84%), having 7*S* configuration.

Scheme 2: Reduction of ketone carbonyl for cycloadducts **2a**-**2f**.



The structure of **3a** and **4a** was established on the basis of the NMR data, including the NOE interactions observed. Some relevant NMR information is shown in Figure 2. For example, the formation of the lactone ring induces a downfield shifting of the H-7 signal in **3a**, compared with that of **4a**, and H-7 correlates with the carboxylate carbon in the HMBC spectrum of **3a**.

Figure 2: Significant NMR data for assignment of the structure of compounds **3a** and **4a**. NOE contacts are shown in red.



Reduction of *endo*-**2b**, under the conditions employed for the diasteroisomer *endo*-**2a**, led also to the lactone **3b** and the alcohol **4b** (major product). Other adducts having diverse structures, were also reduced under similar conditions (0 to 25 °C for 10-30 min) to give alcohols with 7*S* configuration. Thus, *endo*-**2c** that carries at C-1 a 3'-pyridyl group instead of a phenyl group as **2a**, was reduced to the alcohol **3c** as the only isolated product (82% yield). Similarly, the *exo* adducts **2d** and **2e** led to, although in somewhat lower yield compared to *endo*-compounds, the respective **3d** and **3e**, without isolation of the epimeric alcohols of configuration 7*R*.

The diasteroselectivity observed for the reduction of **2a**–**2e** could be attributed to the axial orientation of the bulky menthyloxy substituent because of the anomeric effect, as

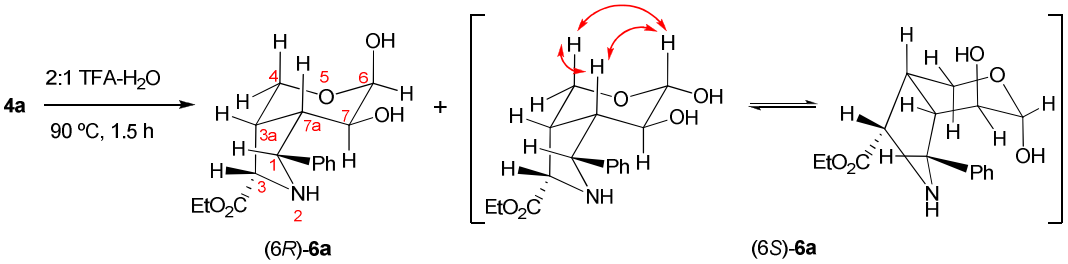
clearly shown for **2a** and **2b** in the crystalline state (Figure 1). This group induces the approach of the hydride from the opposite face, to give the product with a *syn* relationship for the substituents of C-6 and C-7. However, the configuration of stereocenters of the pyrrolidine ring seems to affect the stereochemical course of the reaction, as the reduction of **2f** was less diasteroselective. A distinctive structural fact between **2a**−**2e** and **2f** is the relative orientation of the substituents at C-1 and C-3 vicinal to the nitrogen atom, which are *trans* in **2f** and *cis* in the other precursors **2a**−**2e**. The C-1 and C-3 substituents of the pyrrolidine ring in **2f** are not able to be simultaneously quasi-equatorially oriented. A preliminary modeling of the structure of **2f**, using the AM1 semiempirical method, showed a tendency of the phenyl group at C-3 to adopt a quasi-axial disposition. In this case, such a group should hinder the approach of hydride from this side. Therefore, the hindrance of both faces of the carbonyl group leads to the formation of a diasteroisomeric mixture of alcohols **3f** and **4f**.

The $NaBH_4$ reduction of the *endo* cycloadducts **2a** and **2c** was conducted at room temperature for 16 h. As expected, in addition to the reduction of the carbonyl group the ethyl carboxylate was partially reduced to afford the diol compounds **5a** and **5c**. Although **5a** and **5c** were obtained in a rather low yield (39% and 25%, respectively) the reaction conditions were not optimized.

The next step was the hydrolysis of the menthyl acetal of compounds **4a** or **4b**, which was performed with 2:1 trifluoroacetic acid (TFA)-water at 90 °C for ~1.5 h. Thus, hydrolysis of **4a** afforded the hemiacetal **6a**, being initially the isomer β (6*R*) the major product, which on standing in pyridine solution rapidly equilibrates to an inseparable ~1:1 α:β anomeric mixture (Scheme 3). However, the individual signals of the ^{1}H and ^{13}C NMR spectra (recorded in pyridine-d_5) could be assigned using 2D NMR

experiments (see Experimental Section). The assignment of the configuration of the C-6 stereocenter was rather difficult because of the distortion of the conformation of the tetrahydropyran ring fused to the pyrrolidine ring, with the resulting alteration in the coupling constant values. In addition, these values appeared averaged because of the conformational equilibrium of the tetrahydropyran ring, which is able to adopt two chair forms ($^{6}C_{3a}$ and $^{3a}C_{6}$), illustrated for the 6*S* stereoisomer. Fortunately, the detection of specific NOE contacts (H-6 with H-7a and H-6 with H-4), allowed us to assign as *S* the C-6 configuration of one of the isomers, since the *R*-counterpart did not show such NOE interactions. The equilibrium between the two chair forms $^{6}C_{3a}$ and $^{3a}C_{6}$ for the pyran ring of 6(*S*)-**6a**, justifies the small values measured for $J_{6,7}$ and $J_{7,7a}$ (both ~ 3.1 Hz) and the relatively large one for $J_{3a,4}$ (7.1 Hz).

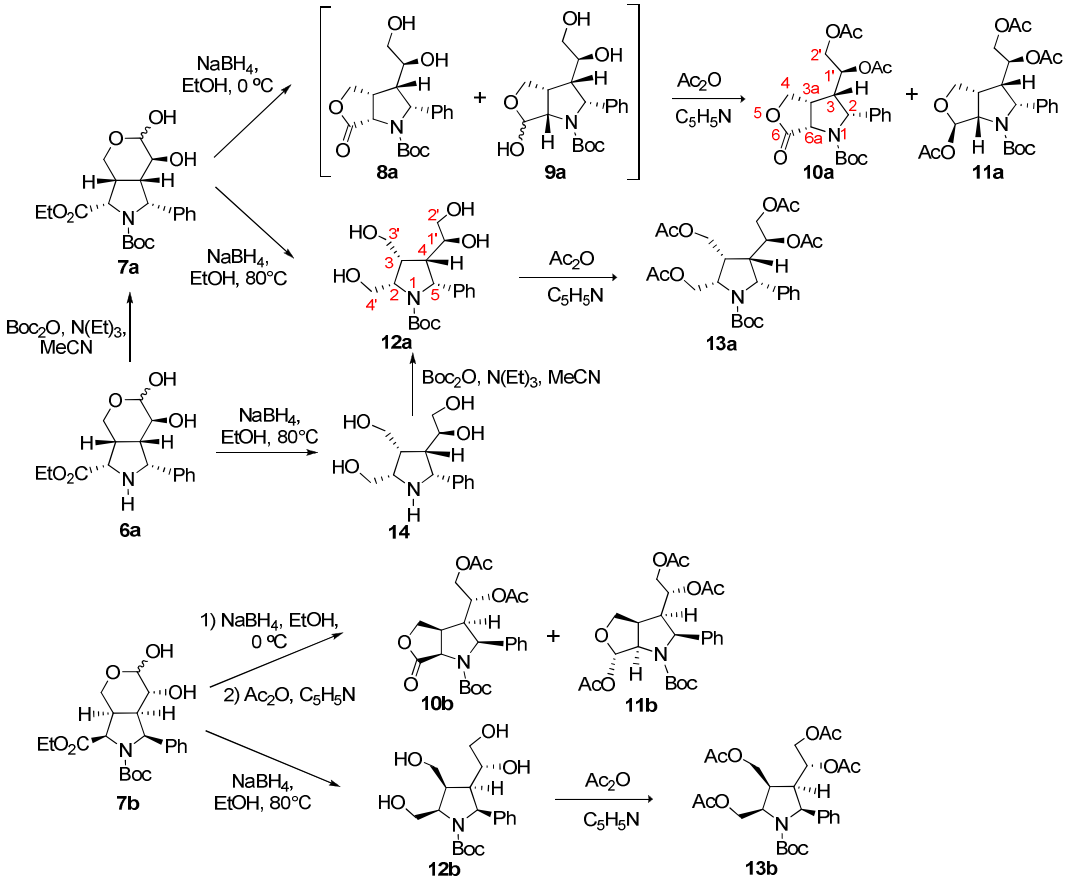
Scheme 3: Hydrolysis of the acetal group of **4a** and conformational equilibrium for (6S)-**6a**.



The same hydrolysis procedure applied to **4b** gave **6b**. The purification of the polar compounds **6a** and **6b** by column chromatography on silica gel was rather difficult, therefore the less polar *N*-Boc derivatives of **7a** and **7b** were prepared (Scheme 4). The protection of the amino group was also required for further reactions applied to **7a** or **7b**. The NMR spectra revealed that **7a** was a 4:1 mixture of 6*R*:6*S* isomers (6*S*:6*R* for **7b)**. In fact, the spectra of **7a** and **7b** are identical, as they are enantiomeric compounds. Such spectra, similar to those of other related *N*-Boc derivatives, exhibited the signal of

the *tert*-butyl group of *N*-Boc as a broad singlet, indicating restriction in the rotation of this group due to the hindrance caused by the substituents of the carbons vicinal to the pyrrolidine nitrogen atom.

Scheme 4: Intermediate and final products obtained by reduction of **6a**, **7a** and **7b**



The bicyclic compound **7a** was treated with $NaBH_4$ in EtOH at 0 °C for 1 h. The reduction product was isolated by column chromatography as a homogenous syrup, which was shown to be a mixture by NMR analysis. The spectra revealed the absence of the ethyl group of the ester of **7a**, but a carboxylate carbon (174.4 ppm) suggested the formation of a lactone (**8a**). The lactonization of a methyl ester with a conveniently located vicinal hydroxymethyl group in a pyrrolidine ring has been described.[20] In the case of **7a**, the reduction of the hemiacetal should release a hydroxymethyl group,

conveniently located for the lactonization with the ethyl ester to give **8a**. Separation of the mixture was achieved upon acetylation, which led to the per-*O*-acetyl derivatives of the lactone (**10a**) and the lactol (**11a**). The correlation in the HMBC spectrum of **10a** between the lactone carbonyl (172.6 ppm) and one of the C-4 methylene protons confirmed the formation of the lactone ring. The ^{1}H NMR spectrum of **10a** showed a broadening of the signals of the *tert*-butyl group of the *N*-Boc and those of the protons vicinal to the *N*-Boc, H-2 and H-6a. The signal broadening is typical due to a slow exchange regime in the conformational equilibrium of the urethane group.

The location of the lactol function of **11a** was confirmed on the basis of the HMBC spectrum, which showed correlation of the acetal proton H-6 with C-3a and C-4. The presence of two anomeric protons (H-6) in the ^{1}H NMR spectrum of **11a** suggested a diastereomeric mixture of hemiacetals. However, the fact that each H-6 appeared as a singlet, in spite of the presence of a proton in the adjacent carbon (C-6a), and the duplicated signals of the *N*-Boc *tert*-butyl group, H-2 and H-6a led us to suspect that the molecule was populating two conformations.[21] Beyond the signal broadening in the lactone **10a**, in the case of **11a** the signals of the same protons, which corresponded to each rotamer, were clearly separated. Probably, the crowded environment of the nitrogen in the bicyclic system of **11a** prevents the free rotation of the Boc substituent, giving rise to two detected conformers in ~1.6 : 1 ratio. This fact was confirmed by the NOESY spectrum of **11a**, which clearly showed exchange peaks between the corresponding pairs of H-2, H-6a and *tert*-butyl signals from each rotamer. As observed for slow exchange systems, the pair of peaks were of the same sign as the diagonal peaks, while the NOE cross-peaks are of opposite sign compared to the diagonal peaks.[22] As an additional confirmation of equilibrium between rotamers, the selective

irradiation at the resonance frequency of each *tert*-butyl signal led to the disappearance of the other one (See Supporting information).

The configuration of the C-6 stereocenter was assigned as *R*, since a NOE contact between H-6 and phenyl protons was detected. This should be the favored configuration as the acetoxy group is attached to the less hindered face of the oxacyclopentane, opposite to the fused pyrrolidine ring.

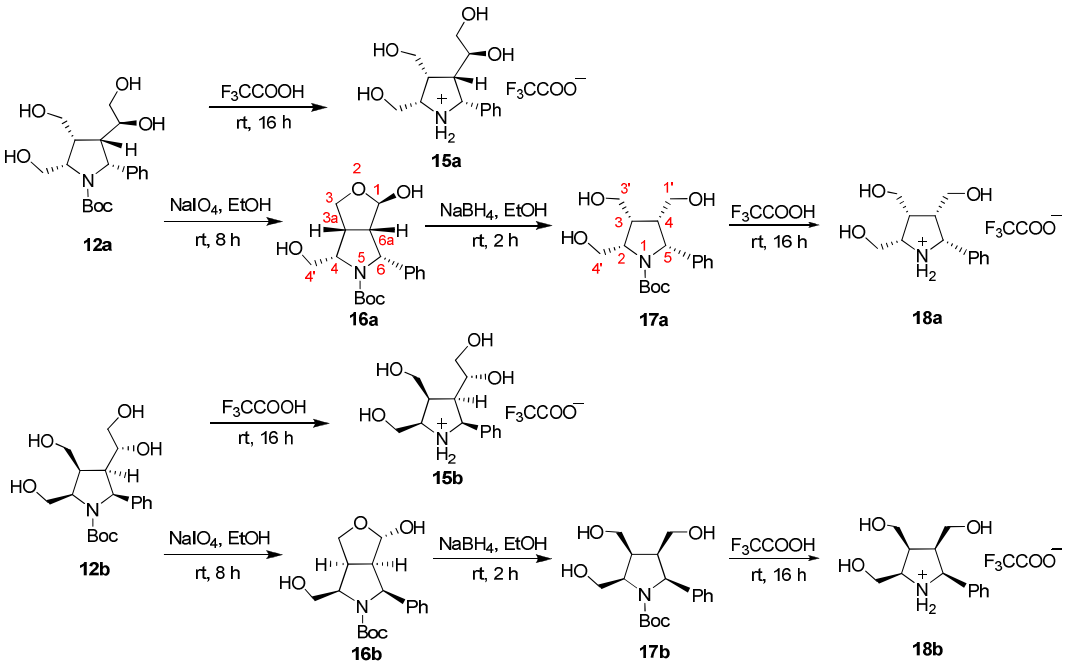
Reduction of **7b** under the same conditions, followed by acetylation, afforded the lactone **10b** and lactol **11b**, the enantiomeric counterparts of **10a** and **11a**, respectively. The ratio of lactone/lactol formed was rather difficult to control. The product distribution proved to be particularly sensitive to the reaction time. For example, $NaBH_4$ reduction of **7b** at 0 °C for 30 min led, after acetylation, to lactone **10b** as a major product.

On the other hand, the reduction of both the hemiacetal and the ester functionalities of **7a** could be performed on treatment with $NaBH_4$ (3mol/mol **7a**) in anhydrous EtOH at 80 °C, to afford the polyhydroxyalkylpyrrolidine **12a** in 82% yield. Acetylation of crude **12a** led to the per-*O*-acetyl derivative **13a**. The same reactions applied to **7b** afforded **12b**, which was per-*O*-acetylated to **13b**. The absolute value of the optical rotation and the opposite sign of **12a** and **12b**, as well as their identical ^{1}H and ^{13}C NMR spectra, confirmed that these pairs of compounds are enantiomeric. In order to obtain the unprotected pyrrolidine **14**, the adduct **6a** was reduced at 80 °C, as already described for **7a** and **7b**, to afford the pyrrolidine **14**. The ^{1}H NMR spectrum of **14** admitted a first order analysis. Therefore, many NOE interactions could be observed; those between H-5 and H-2, H-3 and H-4, and H-2 with H-4 were in agreement with the all-*cis* disposition of the protons of the pyrrolidine ring. As an additional confirmation, NOE contacts between the protons of the phenyl group with H-1' and with the CH_2-3' were

detected. Furthermore, protection of the amino group of **14** as the *N*-Boc derivative led to **12a**.

Treatment of **12a** with TFA led to the removal of the *tert*-butyloxycarbonyl (Boc) group to afford the corresponding pyrrolidinium trifluoroacetate (**15a**). The same reaction applied to **12b** afforded the corresponding salt **15b**, the enantiomer of **15a** (Scheme 5). Compounds **15a** and **15b** are fully unprotected phenyl substituted pyrrolidines which possess a hydroxyalkyl group on each of the other three adjacent stereocenters of the ring.

Scheme 5: Synthesis of tri(hydroxyalkyl)pyrrolidines **15a**, **15b**, **18a** and **18b**.



The 1,2-ethanediol moiety linked at C-4 of **12a** was subjected to degradative oxidation with sodium periodate. The resulting aldehyde function spontaneously reacts with the vicinal hydroxymethyl group to give the furanoid hemiacetal **16a**. The HMBC spectrum of **16a** showed the correlation of the hemiacetal carbon (C-1) with the CH_2-3, H-3a, 6,

and 6a; while C-3 correlates with H-1 and H-4, confirming the formation of the furan ring. The absolute configuration of C-1 was established on the basis of the small value for the coupling constant $J_{1,6a}$ (2.1 Hz), Characteristic of 1,2-*trans* furanoses, and also the observed NOE interactions of H-1 with H-6, 6a and protons of the phenyl group, in agreement with the *R* configuration for C-1. Other NOE contacts (H-4 with H-6 and H-6a, H-3x with H-6a, H-3a with H-6) confirmed the structure proposed.

Reduction of the hemiacetal derivatives **16a** or **16b** with $NaBH_4$ afforded the respective tris(hydroxymethyl) pyrrolidines **17a** or **17b**. The ^{1}H NMR spectra of **17a** and **17b** showed a broad signal for the *N*-Boc *tert*-butyl group, but the signal of the vicinal protons to the *N*-Boc (H-2 and H-5) appeared well resolved. The relatively large values for the coupling constant between the protons of the pyrrolidine ring ($J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ ~ 7.8−7.9 Hz) suggested an envelope conformation with the N atom below the plane formed by the ring carbon atoms. The NOESY spectrum of **17a** showed NOE interactions of the phenyl group with all the protons of the hydroxymethyl groups (CH_2-1', 3' and 4').

Removal of the *N*-Boc group of **17a** with TFA led to the pyrrolidinium trifluoroacetate **18a**. The NMR spectra of this compound showed a similar behavior to that of **17a**. Hence, a similar conformation could be expected. Interestingly, the trifluoroacetate anion showed two quartets due to the carboxylate (162.4 ppm, J = 36.0 Hz) and trifluoromethyl (116.0 ppm, J = 291.0 Hz).

Evaluation of the inhibitory activity of selected pyrrolidines against a β-galactofuranosidase.

Because of the furanoid nature of the pyrrolidines, a furanosidase (the β-D-galactofuranosidase from *P. fellutanum*) was selected as model enzyme for the inhibition studies. The natural substrate for the *exo* β-D-galactofuranosidase is the extracellular peptide phosphogalactomannan from *P. fellutanum*. This glycopeptide contains terminal (1→5)-linked β-D-galactofuranose units, attached to a α-mannose core.[23] The enzyme, which is not commercially available, has been isolated from the culture growth of the fungus.[24]

The pyrrolidines **14**, **15a**, **15b**, **18a** and **18b** were evaluated as inhibitors of the enzyme. To determine the inhibitory activity of the compounds we employed 4-nitrophenyl β-D-galactofuranoside as substrate of the enzyme and the protocol previously established was followed.[15b] The inhibitory profile was compared with those of the known inhibitor galactono-1,4-lactone (*K*i = 0.10 mM).[15b] Compounds **14**, **15a**, **15b**, **18a** and **18b** were subjected to the enzymatic reaction, in concentrations ranging from 0.1 to 1.6 mM. Releasing of 4-nitrophenol was employed as a measurement of galactofuranosidase activity. Unfortunately, none of the compounds revealed a noticeable inhibitory activity even at high concentrations (1.6 mM). The activity of the enzyme was reported to be highly sensitive to steric factors (size of substituents of the furanose ring) in the inhibitor.[25] Probably the presence of the phenyl group and the additional carbon atoms of pyrrolidines **14**, **15a**, **15b**, **18a** and **18b**, compared to galactofuranosides, could introduce steric hindrance hampering their accommodation within the active site of the enzyme. The configurations of the stereocenters of the evaluated molecules may also play a decisive role on the activity.

Conclusions

The cycloadducts obtained by the 1,3-dipolar cycloaddition reaction of sugar enones with azomethine ylides have been converted, via simple reactions, into a number of pyrrolidines with varied configurations and patterns of substitution. Enantiomeric pyrrolidines having four stereocenters of defined configuration have been prepared. The formation of enantiomers was defined by the stereochemistry of the acetal function of the starting sugar-derived enone. Thus, reduction of the carbonyl of the bicyclic 6-menthyloxyhexahydropyrano[4,3-c]pyrrol-7(6*H*)-ones followed by hydrolysis of the menthyl acetal afforded hemiacetal-ester derivatives, which were reduced with $NaBH_4$. The reaction conditions were adjusted for selective reduction of the hemiacetal function or both, the hemiacetal and ester groups, to afford a variety of polyhydroxyalkylpyrrolidines. Selective protection of the amino function of such compounds, followed by oxidative degradation of a 1,2-diol (glycol) system and reduction led to polyhydroxymethylpyrrolidines via an effective and simple methodology. The resulting 2,3,4-tris(hydroxymethyl)-5-phenylpyrrolidines were not active as inhibitors of the β-galactofuranosidase from *P. fellutanum*. However, these compounds may well serve as example for the systematic drug design. Further studies on the inhibitory activity of the compounds will be conducted with other enzymes (glycosidases or glycosyltransferases) which proved to be inhibited by pyrrolidines structurally related to those described here.[2e,14a] Furthermore, other possible biological activities[2-4] for the new compounds will be explored as well as their potential use in asymmetric organocatalysis,[26] since enantiomeric pairs of pyrrolidines are available.

Experimental Section

General procedure for the reduction of adducts 2a−2e.

The cycloadduct **2a**−**2e**[16] (1.00 mmol) was dissolved in anhydrous EtOH (15 mL). In some cases, smooth heating was necessary to achieve complete dissolution. The resulting solution was allowed to reach room temperature and placed in a bath at 0 °C or 25 °C. Upon addition of $NaBH_4$ (1.50 mmol) the mixture was stirred at 0 °C or 25 °C for 10−30 min, when TLC (hexane:EtOAc, 1:1) showed disappearance of the starting material, and formation of lower moving products. The reaction was neutralized with AcOH and concentrated. The residue was redissolved in EtOH (20 mL) followed by evaporation of the solvent. After the same treatment with toluene (20 mL), the residue was purified by column chromatography, with solvent indicated in each particular case. As the by-products were obtained in small amounts, the yields reported are approximate.

Reduction of Ethyl (1*R*,3*S*,3a*R*,6*S*,7a*S*)-7-oxo-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (2a).

The general procedure applied to the reduction (at 25 °C) of cycloadduct **2a** (247 mg, 0.56 mmol) afforded compounds **3a** and **4a**, which were separated by column chromatography (hexane:EtOAc, 85:15).

(1*R*,3*S*,3a*R*,6*S*,7*R*,7a*S*)-7-hydroxy-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylic acid 3,7-lactone (3a): white solid (9.4 mg, 4%), mp = 134−136 °C (from EtOH); R_f = 0.64 (hexane:EtOAc, 1:1), $[\alpha]_D^{25}$ −52.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR

(CDCl$_3$, 500 MHz) δ 7.45−7.25 (5H, H-aromatic), 4.87 (d, 1H, $J_{6,7}$ = 2.7 Hz, H-6), 4.83 (d, 1H, $J_{1,7a}$ = 5.4 Hz, H-1), 4.19 (dd, 1H, $J_{3a,4ax}$ = 3.1, $J_{4ax,4eq}$ = 12.2 Hz, H-4ax), 3.94 (d, 1H, $J_{4ax,4eq}$ = 12.2 Hz, H-4eq), 3.87 (d, 1H, $J_{3,3a}$ = 4.2 Hz, H-3), 3.67 (dd, 1H, $J_{6,7}$ = 3.8, $J_{7,7a}$ = 2.7 Hz, H-7), 3.47 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.89 (m, 1H, $J_{1,7a}$ = 5.4, $J_{3a,7a}$ = 1.8, $J_{7,7a}$ = 3.8 Hz, H-7a), 2.50 (m, 1H, H-3a), 2.24 (ddd, 1H, H menthyl), 1.94 (m, 1H, H menthyl), 1.66−1.61 (m, 2H, H menthyl), 1.32−1.22 (m, 2H, H menthyl), 0.97−0.80 (m, 12H, H menthyl); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 171.6 (CO_2-lactone), 139.2−127.1 (C-aromatic), 93.0 (C-6), 75.7 (C-1 menthyl), 74.4 (C-7), 63.7 (C-1), 60.7 (C-3), 57.9 (C-4), 48.1 (C-menthyl), 42.2 (C-3a), 39.8 (C-menthyl), 38.1 (C-7a), 34.5, 31.4, 25.6, 22.9, 22.3, 21.4, 15.6 (C-menthyl); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{24}H_{33}NNaO_4$ 422.2302, found 422.2326.

Ethyl (1*R*,3*S*,3a*R*,6*S*,7*S*,7a*S*)-7-hydroxy-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (4a): colorless syrup (208 mg, 84%); R_f = 0.56 (hexane:EtOAc, 1:1), $[\alpha]_D^{25}$ −57.6 (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.49−7.23 (5H, H-aromatic), 4.87 (brs, 1H, O*H*), 4.68 (d, 1H, $J_{6,7}$ = 1.4 Hz, H-6), 4.47 (d, 1H, $J_{1,7a}$ = 5.1 Hz, H-1), 4.31 (m, 2H, OCH_2CH$_3$), 4.10 (d, 1H, $J_{3,3a}$ = 11.3 Hz, H-3), 4.09 (dd, 1H, $J_{3a,4ax}$ = 4.7, $J_{4ax,4eq}$ = 12.5 Hz, H-4ax), 3.89 (dd, 1H, $J_{3a,4eq}$ = 1.7, $J_{4ax,4eq}$ = 12.5 Hz, H-4eq), 3.38 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 3.25 (br s, 1H, H-7), 2.76 (m, 1H, $J_{3,3a}$ = 11.3, $J_{3a,4ax}$ = 4.7, $J_{3a,4eq}$ = 1.7, $J_{3a,7a}$ = 7.0 Hz, H-3a), 2.69 (dddd, 1H, $J_{1,7a}$ = 5.1, $J_{3a,7a}$ = 7.0, $J_{7,7a}$ = 4.5 Hz, H-7a), 2.26 (m, 1H, H menthyl), 1.99 (m, 1H, H menthyl), 1.64−1.59 (m, 2H, H menthyl), 1.35 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3), 1.27−1.18 (m, 2H, H menthyl), 0.96−0.76 (m, 12H, H menthyl); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 173.7 (*C*O$_2$Et), 138.2−126.8 (C-aromatic), 96.0 (C-6), 74.7 (C-1 menthyl), 65.7 (C-7), 64.6 (C-1), 61.6 (O*C*H$_2$CH$_3$), 59.2 (C-3), 56.1 (C-4), 48.2, 39.8 (C-menthyl), 39.3 (C-3a), 39.0 (C-7a), 34.5, 31.4, 25.4, 23.0, 22.4, 21.4, 15.8 (C-

menthyl), 14.4 (OCH_2CH_3); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{40}NO_5$ 446.2901, found 446.2922.

Reduction of Ethyl (1*S*,3*R*,3a*S*,6*R*,7a*R*)-7-oxo-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (2b).

The general reduction procedure (at 25 °C) applied to cycloadduct **2b** (100 mg, 0.23 mmol) afforded compounds **3b** and **4b**.

(1*S*,3*R*,3a*S*,6*R*,7*S*,7a*R*)-7-hydroxy-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylic acid 3,7-lactone (3b): colorless syrup (6 mg, 6 %); R_f = 0.64 (hexane:EtOAc, 1:1); $[\alpha]_D^{25}$ −37.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43−7.26 (5H, H-aromatic), 4.81 (d, 1H, $J_{1,7a}$ = 5.5 Hz, H-1), 4.71 (d, 1H, $J_{6,7}$ = 2.7 Hz, H-6), 4.27 (dd, 1H, $J_{3a,4ax}$ = 3.0, $J_{4ax,4eq}$ = 12.2 Hz, H-4ax), 3.92 (d, 1H, $J_{4ax,4eq}$ = 12.2 Hz, H-4eq), 3.86 (d, 1H, $J_{3,3a}$ = 4.5 Hz, H-3), 3.71 (dd, 1H, $J_{6,7}$ = 2.7, $J_{7,7a}$ = 3.8 Hz, H-7), 3.29 (ddd, 1H, *J* = 4.1, *J* = 10.7 Hz, H-1 menthyl), 2.94 (dt, 1H, $J_{1,7a}$ = 5.5, $J_{3a,7a}$ ~ 2.0, $J_{7,7a}$ = 3.8 Hz, H-7a), 2.48 (dddd, 1H, $J_{3,3a}$ = 4.5, $J_{3a,4ax}$ = 3.0, $J_{3a,7a}$ ~ 2.0 Hz, H-3a), 2.12 (m, 1H, H menthyl), 1.81 (m, 1H, H menthyl), 1.65−1.55 (m, 2H, H menthyl), 1.36 (m, 1H, H menthyl), 1.18 (m, 1H, H menthyl), 0.93−0.60 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 171.7 (CO_2-lactone), 139.2−127.0 (C-aromatic), 98.5 (C-6), 81.2 (C-1 menthyl), 73.7 (C-7), 63.5 (C-1), 60.7 (C-3), 57.9 (C-4), 48.7, 43.1 (C-menthyl), 42.3 (C-3a), 38.1 (C-7a), 34.3, 31.7, 26.0, 23.5, 22.3, 21.0, 16.5 (C-menthyl); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{34}NO_4$ 400.2482, found 400.2473.

Ethyl (1*S*,3*R*,3a*S*,6*R*,7*R*,7a*R*)-7-hydroxy-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (4b): white solid (87 mg, 87%); mp = 163−164 °C (from EtOH:H_2O); R_f = 0.56, hexane:EtOAc, 1:1; $[\alpha]_D^{25}$ −19.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48−7.24 (5H, H-aromatic), 4.53 (s, 1H, H-6),

4.46 (d, 1H, $J_{1,7a}$ = 5.0 Hz, H-1), 4.31 (m, 2H, OC*H*$_2$CH$_3$), 4.20 (dd, 1H, $J_{3a,4ax}$ = 5.0, $J_{4ax,4eq}$ = 12.5 Hz, H-4ax), 4.10 (d, 1H, $J_{3,3a}$ = 11.3 Hz, H-3), 3.87 (d, 1H, $J_{4ax,4eq}$ = 12.5 Hz, H-4eq), 3.33 (d, 1H, $J_{7,7a}$ = 3.5 Hz, H-7), 3.23 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.76 (dddd, 1H, $J_{3,3a}$ = 11.3, $J_{3a,4ax}$ = 5.0, $J_{3a,7a}$ = 5.7 Hz, H-3a), 2.68 (m, 1H, $J_{1,7a}$ = 5.0, $J_{3a,7a}$ = 5.7, $J_{7,7a}$ = 3,5 Hz, H-7a), 2.11 (m, 1H, H menthyl), 1.95 (m, 1H, H menthyl), 1.64−1.54 (m, 2H, H menthyl), 1.34 (t, 4H, H menthyl, OCH$_2$C*H*$_3$), 1.16 (m, 1H, H menthyl), 0.90−0.62 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 173.8 (*C*O$_2$Et), 138.2−126.8 (C-aromatic), 102.2 (C-6), 80.6 (C-1 menthyl), 65.3 (C-7), 64.6 (C-1), 61.6 (O*C*H$_2$CH$_3$), 59.2 (C-3), 56.3 (C-4), 48.9, 43.0 (C-menthyl), 39.2 (C-3a), 39.0 (C-7a), 34.4, 31.8, 25.5, 23.3, 22.4, 21.2, 16.3 (C-menthyl), 14.4 (OCH$_2$*C*H$_3$); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{40}NO_5$ 446.2901, found 446.2900.

Reduction of Ethyl (1*R*,3*S*,3a*R*,6*S*,7a*S*)-7-oxo-6-(-)-menthyloxy-1-(pyridine-3-yl)octahydropyrano[4,3-*c*]pyrrole-3-carboxylate (2c).

The general procedure applied to the reduction (at 0 °C) of cycloadduct **2c** (100 mg, 0.22 mmol) led, after column chromatography (hexane:EtOAc, 3:7), to compound **3c** (82 mg, 82%).

Ethyl (1*R*,3*S*,3a*R*,6*S*,7*S*,7a*S*)-7-hydroxy-6-(-)-menthyloxy-1-(pyridine-3-yl)octahydropyrano[4,3-*c*]pyrrole-3-carboxylate (3c): colorless syrup; R_f = 0.19 (EtOAc); $[\alpha]_D^{25}$ −52.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.62 (d, 1H, J = 1.5 Hz, H-2'Py), 8.46 (dd, 1H, J = 1.1, 4.8 Hz, H-6'Py), 7.92 (dt, 1H, J = 1.1, 7.9 Hz, H-4'Py), 7.26 (dd, 1H, J = 4.8, 7.9 Hz, H-5'Py), 4.66 (d, 1H, $J_{6,7}$ < 1.0 Hz, H-6), 4.47 (d, 1H, $J_{1,7a}$ = 4.9 Hz, H-1), 4.31 (m, 2H, OC*H*$_2$CH$_3$), 4.11 (d, 1H, $J_{3,3a}$ = 10.8 Hz, H-3), 4.09 (dd, 1H, $J_{3a,4ax}$ = 4.8, $J_{4ax,4eq}$ = 12.6 Hz, H-4ax), 3.84 (d, 1H, $J_{4ax,4eq}$ = 12.6 Hz, H-4eq), 3.35 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 3.19 (dd, 1H, $J_{6,7}$ < 1.0, $J_{7,7a}$ =

2.9 Hz, H-7), 2.74 (m, 2H, H3a, H-7a), 2.22 (m, 1H, H menthyl), 1.97 (m, 1H, H menthyl), 1.63−1.57 (m, 2H, H menthyl), 1.34 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.29−1.16 (m, 2H, H menthyl), 0.88−0.69 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 174.3 (CO_2Et), 148.9−123.2 (C-aromatic), 96.0 (C-6), 74.9 (C-1 menthyl), 65.6 (C-7), 62.7 (C-1), 61.9 (OCH_2CH_3), 59.3 (C-3), 55.8 (C-4), 48.2 (C-menthyl), 39.8, 39.5, 39.1 (C-3a, 7a, menthyl), 34.5, 31.4, 25.4, 23.0, 22.3, 21.4, 15.8 (C-menthyl), 14.4 (OCH_2CH_3). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{39}N_2O_5$ 447.2853, found 447.2873.

Reduction of Ethyl (1*S*,3*R*,3a*R*,6*S*,7a*S*)-7-oxo-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (2d).

The cycloadduct **2d** (100 mg, 0.23 mmol) was reduced (at 0 °C) according to the general procedure to afford **3d**, which was isolated by column chromatography (hexane:EtOAc, 92:8).

Ethyl (1*S*,3*R*,3a*R*,6*S*,7*S*,7a*S*)-7-hydroxy-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (3d): colorless syrup (70 mg, 70%); R_f = 0.28 (hexane:EtOAc, 8:2), $[\alpha]_D^{28}$ −153.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50−7.21 (5H, H-aromatic), 5.01 (d, 1H, $J_{6,7}$ = 3.9 Hz, H-6), 4.59 (d, 1H, $J_{1,7a}$ = 1.0 Hz, H-1), 4.26 (m, 2H, OCH_2CH_3), 4.05 (d, 1H, $J_{3,3a}$ = 10.2 Hz, H-3), 3.96 (dd, 1H, $J_{3a,4ax}$ = 3.6, $J_{4ax,4eq}$ = 12.2 Hz, H-4ax), 3.77 (dd, 1H, $J_{3a,4eq}$ = 1.3, $J_{4ax,4eq}$ = 12.2 Hz, H-4eq), 3.66 (dd, 1H, $J_{6,7}$ = 3.9, $J_{7,7a}$ = 9.4 Hz, H-7), 3.50 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.40 (m, 1H, $J_{3,3a}$ = 10.2, $J_{3a,4ax}$ = 3.6, $J_{3a,4eq}$ = 1.3, $J_{3a,7a}$ = 4.1 Hz, H-3a), 2.18−2.12 (m, 3H, H menthyl, H-7a), 1.69−1.63 (m, 2H, H menthyl), 1.38 (m, 1H, H menthyl), 1.32 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.26 (m, 1H, H menthyl), 0.94−0.74 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 174.6 (CO_2Et), 145.3−126.5 (C-

aromatic), 93.5 (C-6), 75.7 (C-1 menthyl), 67.8 (C-7), 64.5 (C-1), 61.3 (OCH_2CH_3), 60.7 (C-3), 57.7 (C-4), 51.2 (C-7a), 48.3 (C-menthyl), 40.8 (C-3a), 40.4, 34.5, 31.6, 25.4, 22.9, 22.4, 21.3, 15.4 (C-menthyl), 14.4 (OCH_2CH_3). HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{39}NNaO_5$ 468.2720, found 468.2718.

Reduction of Ethyl (1*R*,3*S*,3a*S*,6*R*,7a*R*)-7-oxo-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (2e).

Reduction (at 0 °C) of **2e** (100 mg, 0.23 mmol) led to **3e**, which was purified by column chromatography (hexane:EtOAc, 85:15).

Ethyl (1*R*,3*S*,3a*S*,6*R*,7*R*,7a*R*)-7-hydroxy-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (3e): colorless syrup (70 mg, 70%); R_f = 0.40 (hexane:EtOAc, 7:3); $[\alpha]_D^{25}$ +92.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49−7.21 (5H, H-aromatic), 4.90 (d, 1H, $J_{6,7}$ = 3.3 Hz, H-6), 4.58 (br s, 1H, $J_{1,7a}$ ~ 0 Hz, H-1), 4.26 (m, 2H, OCH_2CH_3), 4.03 (d, 1H, $J_{3,3a}$ = 10.0 Hz, H-3), 4.01 (dd, 1H, $J_{3a,4ax}$ = 3.6, $J_{4ax,4eq}$ = 12.2 Hz, H-4ax), 3.78 (dd, 1H, $J_{3a,4eq}$ = 1.4, $J_{4ax,4eq}$ = 12.2 Hz, H-4eq), 3.64 (dd, 1H, $J_{6,7}$ = 3.3, $J_{7,7a}$ = 9.4 Hz, H-7), 3.39 (ddd, 1H, *J* = 4.1, *J* = 10.7 Hz, H-1 menthyl), 2.39 (m, 1H, $J_{3,3a}$ = 10.0, $J_{3a,4ax}$ = 3.6, $J_{3a,4eq}$ = 1.4, $J_{3a,7a}$ = 3.5 Hz, H-3a), 2.21−2.16 (m, 2H, H menthyl, H-7a), 2.12 (m, 1H, H menthyl), 1.66−1.60 (m, 2H, H menthyl), 1.40 (m, 1H, H menthyl), 1.26 (m, 1H, H menthyl), 1.31 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 0.94−0.76 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 174.7 (CO_2Et), 145.3−126.4 (C-aromatic), 99.4 (C-6), 81.2 (C-1 menthyl), 68.7 (C-7), 64.6 (C-1), 61.3 (OCH_2CH_3), 60.8 (C-3), 57.8 (C-4), 51.5 (C-7a), 48.8, 43.1 (C-menthyl), 41.0 (C-3a), 34.3, 31.8, 25.8, 22.9, 22.4, 21.3, 15.6 (C-menthyl), 14.4 (OCH_2CH_3). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{40}NO_5$ 446.2901, found 446.2902.

Reduction of Ethyl (1*R*,3*R*,3a*R*,6*S*,7a*S*)-7-oxo-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (2f).

Reduction of **2f**[16] (100 mg, 0.23 mmol) according to the general procedure (at 0 °C) afforded compounds **3f** and **4f**, which were separated by column chromatography (hexane:EtOAc, 92:8).

Ethyl (1*R*,3*R*,3a*R*,6*S*,7*R*,7a*S*)-7-hydroxy-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (3f): colorless syrup (26 mg, 26%); R_f = 0.54 (hexane:EtOAc, 8:2); $[\alpha]_D^{25}$ −70.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55−7.23 (5H, H-aromatic), 4.87 (d, 1H, $J_{6,7}$ = 4.3 Hz, H-6), 4.68 (d, 1H, $J_{1,7a}$ = 4.0 Hz, H-1), 4.23 (m, 2H, OCH_2CH$_3$), 4.11 (dd, 1H, $J_{3a,4ax}$ = 3.0, $J_{4ax,4eq}$ = 12.0 Hz, H-4ax), 4.00 (d, 1H, $J_{3,3a}$ = 8.6 Hz, H-3), 3.94 (dddd, 1H, $J_{6,7}$ = 4.3, $J_{7,7a}$ = 9.1, $J_{7,OH}$ = 7.6 Hz, H-7), 3.78 (d, 1H, $J_{4ax,4eq}$ = 12.0 Hz, H-4eq), 3.43 (ddd, 1H, *J* = 4.1, *J* = 10.7 Hz, H-1 menthyl), 2.46 (dddd, 1H, $J_{3,3a}$ = 8.6, $J_{3a,4ax}$ = 3.0, $J_{3a,7a}$ = 6.4 Hz, H-3a), 2.44 (dddd, 1H, $J_{1,7a}$ = 4.0, $J_{3a,7a}$ = 6.4, $J_{7,7a}$ = 9.1 Hz, H-7a), 2.29 (m, 1H, H menthyl), 2.02 (m, 1H, H menthyl), 1.66−1.61 (m, 2H, H menthyl), 1.31 (t, 3H, *J* = 7.1 Hz, OCH$_2$CH_3), 1.26−1.24 (m, 2H, H menthyl), 1.03 (d, 1H, $J_{2,OH}$ = 7.6 Hz, O*H*), 0.93−0.79 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 176.0 (*C*O$_2$Et), 141.0−127.0 (C-aromatic), 93.5 (C-6), 75.9 (C-1 menthyl), 65.0 (C-1), 64.0 (C-7), 61.4 (O*C*H$_2$CH$_3$), 59.6 (C-3), 58.0 (C-4), 48.1 (C-menthyl), 46.9 (C-7a), 44.3 (C-3a), 40.2, 34.5, 31.5, 25.5, 22.9, 22.3, 21.3, 15.5 (C-menthyl), 14.4 (OCH$_2$*C*H$_3$). HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{39}NNaO_5$ 468.2720, found 468.2721.

Ethyl (1*R*,3*R*,3a*R*,6*S*,7*S*,7a*S*)-7-hydroxy-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (4f): colorless syrup (49 mg, 49%); R_f = 0.25 (hexane:EtOAc, 8:2); $[\alpha]_D^{25}$ −55.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44−7.24 (5H, H-aromatic), 4.76 (d, 1H, $J_{6,7}$ = 1.6 Hz, H-6), 4.71 (d, 1H, $J_{1,7a}$

= 4.6 Hz, H-1), 4.26 (m, 2H, OCH_2CH$_3$), 4.14 (dd, 1H, $J_{3a,4ax}$ = 4.2, $J_{4ax,4eq}$ = 12.3 Hz, H-4ax), 4.11 (d, 1H, $J_{3,3a}$ = 8.8 Hz, H-3), 3.94 (d, 1H, $J_{4ax,4eq}$ = 12.3 Hz, H-4eq), 3.46 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 3.29 (dd, 1H, $J_{6,7}$ = 1.6, $J_{7,7a}$ = 4.1 Hz, H-7), 2.71 (dt, 1H, $J_{1,7a}$ = 4.6, $J_{3a,7a}$ = 6.0, $J_{7,7a}$ = 4.1, Hz, H-7a), 2.36 (m, 1H, $J_{3,3a}$ = 8.8, $J_{3a,4ax}$ = 4.2, $J_{3a,7a}$ = 6.0 Hz, H-3a), 2.27 (m, 1H, H menthyl), 2.03 (m, 1H, H menthyl), 1.66−1.60 (m, 2H, H menthyl), 1.34−1.21 (m, 2H, H menthyl), 1.33 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3), 0.96−0.80 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 175.2 (CO_2Et), 138.2−126.5 (C-aromatic), 95.0 (C-6), 75.0 (C-1 menthyl), 66.0 (C-7), 64.9 (C-1), 61.6 (OCH_2CH$_3$), 60.4 (C-3), 57.9 (C-4), 48.2 (C-menthyl), 41.2 (C-3a), 40.4 (C-7a), 39.9, 34.6, 31.4, 25.5, 23.0, 22.4, 21.4, 15.8 (C-menthyl), 14.4 (OCH$_2$$CH_3$). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{40}NO_5$ 446.2901, found 446.2914.

Reduction of Ethyl (1*R*,3*S*,3a*R*,6*S*,7a*S*)-7-oxo-6-(-)-menthyloxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (2a) or Ethyl (1*R*,3*S*,3a*R*,6*S*,7a*S*)-7-oxo-6-(-)-menthyloxy-1-(pyridine-3-yl)octahydropyrano[4,3-*c*]pyrrole-3-carboxylate (2c) with $NaBH_4$/EtOH (25 °C, 16 h).

The cycloadduct **2a** (100 mg, 0.23 mmol) was dissolved in anhydrous EtOH (4 mL) and $NaBH_4$ (12 mg, 0.33 mmol) was added. The reaction was stirred at 25 °C for 16 h and stopped upon addition of AcOH. Monitoring by TLC (EtOAc) showed the formation of a polar product (R_f = 0.23), which after the usual work up, was isolated by column chromatography (EtOAc).

The same procedure applied to **2c** (100 mg, 0.22 mmol) led to **5c**, which was purified by column chromatography using CH_2Cl_2:MeOH, 95:5 as solvent.

(1*R*,3*S*,3a*R*,6*S*,7*S*,7a*S*)-7-hydroxy-6-(-)-menthyloxy-3-hydroxymethyl-1-phenyloctahydropyrano[4,3-*c*]pyrrolidine (5a): colorless syrup (36 mg, 39%); $[\alpha]_D^{25}$ −53.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.24 (5H, H-aromatic), 4.67 (d, 1H, $J_{6,7}$ = 1.8 Hz, H-6), 4.47 (d, 1H, $J_{1,7a}$ = 4.8 Hz, H-1), 4.13 (dd, 1H, $J_{3,3'a}$ = 7.4, $J_{3'a,3'b}$ = 11.5 Hz, H-3'a), 4.07 (dd, 1H, $J_{3a,4ax}$ = 5.1, $J_{4ax,4eq}$ = 12.7 Hz, H-4ax), 3.97 (dd, 1H, $J_{3,3'b}$ = 4.7, $J_{3'a,3'b}$ = 11.5 Hz, H-3'b), 3.77 (d, 1H, $J_{4ax,4eq}$ = 12.7 Hz, H-4eq), 3.73 (dddd, 1H, $J_{3,3a}$ = 11.1, $J_{3,3'a}$ = 7.4, $J_{3,3'b}$ = 4.7 Hz, H-3), 3.37 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 3.27 (dd, 1H, $J_{6,7}$ = 1.8, $J_{7,7a}$ = 4.2 Hz, H-7), 2.73 (dddd, 1H, $J_{1,7a}$ = 4.8, $J_{3a,7a}$ = 7.4, $J_{7,7a}$ = 4.2 Hz, H-7a), 2.52 (m, 1H, $J_{3,3a}$ = 11.1, $J_{3a,4ax}$ = 5.1, $J_{3a,7a}$ = 7.4 Hz, H-3a), 2.24 (m, 1H, H menthyl), 1.96 (m, 1H, H menthyl), 1.64−1.59 (m, 2H, H menthyl), 1.31−1.19 (m, 2H, H menthyl), 0.93−0.77 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 136.8−126.5 (C-aromatic), 95.3 (C-6), 75.0 (C-1 menthyl), 65.2 (C-7), 63.5 (C-1), 62.2 (C-3'), 58.9 (C-3), 56.0 (C-4), 48.2, 39.8 (C-menthyl), 38.7 (C-7a), 35.5 (C-3a), 34.5, 31.4, 25.4, 23.0, 22.3, 21.4, 15.7 (C-menthyl). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{38}NO_4$ 404.2795, found 404.2814.

(1*R*,3*S*,3a*R*,6*S*,7*S*,7a*S*)-7-hydroxy-6-(-)-menthyloxy-3-hydroxymethyl-1-(pyridine-3-yl)octahydropyrano[4,3-*c*]pyrrolidine (5c): colorless syrup (22 mg, 25%), R_f = 0.44 (CH_2Cl_2:MeOH, 9:1); $[\alpha]_D^{25}$ −38.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.63 (br s, 1H, H-2'Py), 8.46 (d, 1H, J = 4.8 Hz, H-6'Py), 7.81 (d, 1H, J = 7.9 Hz, H-4'Py), 7.29 (dd, 1H, J = 4.8, 7.9 Hz, H-5'Py), 4.71 (s, 1H, H-6), 4.49 (d, 1H, $J_{1,7a}$ = 4.7 Hz, H-1), 4.13 (dd, 1H, $J_{3,3'a}$ = 7.0, $J_{3'a,3'b}$ = 11.7 Hz, H-3'a), 4.09 (dd, 1H, $J_{3a,4ax}$ = 5.0, $J_{4ax,4eq}$ = 12.8 Hz, H-4ax), 3.97 (dd, 1H, $J_{3,3'b}$ = 4.2, $J_{3'a,3'b}$ = 11.7 Hz, H-3'b), 3.79 (d, 1H, $J_{4ax,4eq}$ = 12.8 Hz, H-4eq), 3.73 (m, 1H, $J_{3,3a}$ = 10.0, $J_{3,3'a}$ = 7.0, $J_{3,3'b}$ = 4.2 Hz, H-3), 3.38 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 3.23 (d, 1H, $J_{7,7a}$ = 3.5 Hz, H-7), 2.77 (dddd, 1H, $J_{1,7a}$ = 4.7, $J_{3a,7a}$ = 8.1, $J_{7,7a}$ = 3.5 Hz, H-7a), 2.56 (dddd, 1H, $J_{3,3a}$ = 10.0, $J_{3a,4ax}$ =

5.0, $J_{3a,7a}$ = 8.1 Hz, H-3a), 2.24 (m, 1H, H menthyl), 1.98 (m, 1H, H menthyl), 1.65−1.60 (m, 2H, H menthyl), 1.32−1.20 (m, 2H, H menthyl), 0.94−0.75 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 148.3−123.5 (C-aromatic), 95.4 (C-6), 75.2 (C-1 menthyl), 65.2 (C-7), 62.5 (C-3'), 61.5 (C-1), 58.9 (C-3), 56.0 (C-4), 48.2, 39.8 (C-menthyl), 38.8 (C-7a), 35.6 (C-3a), 34.5, 31.5, 25.5, 23.0, 22.4, 21.4, 15.7 (C-menthyl). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{37}N_2O_4$ 405.2748, found 405.2758.

Hydrolysis of the menthyloxy acetal of 4a and 4b.

A solution of **4a** or **4b** (1 mmol) in 2:1 TFA:H_2O (12 mL) was heated at 90 °C in a sealed vial under static Ar atmosphere. When monitoring by TLC (hexane:EtOAc, 1:1) showed conversion of the starting material into a more polar product (~1.5 h), the solution was concentrated in vacuum. The residue was dissolved in water (20 mL) and the mixture concentrated to eliminate TFA and menthol. Then, toluene (20 mL) was added and removed by evaporation. The resulting syrup was purified by column chromatography (EtOAc:hexane, 9:1) to afford compound **6a** or **6b** (from **4a** or **4b**, respectively).

Ethyl (1*R*,3*S*,3a*R*,7*S*,7a*S*)-6,7-dihydroxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (6a): was obtained from **4a** (114 mg, 0.26 mmol) as a colorless syrup (51 mg, 65%); R_f = 0.30 (EtOAc). On standing in solution **6a** equilibrates to a 1:1 anomeric mixture (α = 6*S*; β = 6*R*). ^{1}H NMR (pyridine-d_5, 500 MHz) δ 7.72−7.26 (10H, H-aromatic), 5.45 (d, 1H, $J_{6,7}$ = 1.6 Hz, H-6β), 5.02 (d, 1H, $J_{6,7}$ = 3.1 Hz, H-6α), 4.64 (dd, 1H, $J_{3a,4}$ = 5.5, $J_{4,4'}$ = 12.0 Hz, H-4β), 4.61 (d, 1H, $J_{1,7a}$ = 5.4 Hz, H-1β), 4.49 (d, 1H, $J_{1,7a}$ = 5.8 Hz, H-1α), 4.38 (d, 1H, $J_{3,3a}$ = 11.1 Hz, H-3β), 4.35 (dd, 1H, $J_{3a,4}$ = 8.7, $J_{4,4'}$ = 11.3 Hz, H-4α), 4.30 (dd, 1H, $J_{3a,4'}$ = 3.6, $J_{4,4'}$ = 12.0 Hz, H-4'β), 4.29 (d, 1H, $J_{3,3a}$ = 10.5 Hz, H-3α), 4.34−4.14 (m, 4H, OCH_2CH$_3$), 4.05 (dd, 1H, $J_{3a,4'}$ = 7.1, $J_{4,4'}$ = 11.3 Hz, H-

4'α), 3.92 (t, 1H, $J_{6,7} = J_{7,7a} = 3.1$ Hz, H-7α), 3.89 (dd, 1H, $J_{6,7} = 1.6$, $J_{7,7a} = 4.2$ Hz, H-7β), 3.19−3.14 (m, 2H, H-3aα, H-7aβ), 3.01 (m, 1H, H-3aβ), 2.62 (dddd, 1H, $J_{1,7a} = 5.8$, $J_{3a,7a} = 8.3$, $J_{7,7a} = 3.1$ Hz, H-7aα), 1.21, 1.12 (2 t, 3H, $J = 7.1$ Hz, OCH_2CH_3),; ^{13}C NMR (pyridine-d_5, 125.7 MHz) δ 173.9, 172.8 (CO_2Et), 140.6−124.3 (C-aromatic), 96.1 (C-6β), 94.1 (C-6α), 67.5 (C-7β), 66.7 (C-7α), 64.8 (×2) (C-1α, 1β), 62.3 (C-4α), 61.5, 61.3 (OCH_2CH_3), 61.0 (C-3α), 60.4 (C-3β), 57.3 (C-4β), 44.1 (C-7aα), 41.2, 39.9 (C-3aα, 7aβ), 40.4 (C-3aβ), 14.8, 14.7 (OCH_2CH_3). HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{21}NNaO_5$ 330.1312, found 330.1311.

Ethyl (1*S*,3*R*,3a*S*,7*R*,7a*R*)-6,7-dihydroxy-1-phenyloctahydropyrano[4,3-*c*]pyrrole-3-carboxylate (6b): The same procedure described for the preparation of **6a** was applied starting from **4b** (18 mg, 0.04 mmol). Compound **6b** was obtained as a 1:1 anomeric mixture (8 mg, 64%); $R_f = 0.30$ (EtOAc) identical ^{1}H and ^{13}C spectra as **6a**; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{22}NO_5$ 308.1492, found 308.1485.

Ethyl (1*R*,3*S*,3a*R*,6,7*S*,7a*S*)-2-(*tert*-butyloxycarbonyl)-6,7-dihydroxy-1-phenyloctahydropyrano[3,4-*c*]pyrrole-3-carboxylate (7a): The crude compound **6a**, obtained by hydrolysis of **4a** (53 mg, 0.12 mmol), was dried in vacuum (2 h) and then dissolved in anhydrous MeCN (2 mL) and Boc_2O (26 mg, 0.12 mmol) and $N(Et)_3$ (12 mg, 0.12 mmol) were added. The mixture was stirred at room temperature overnight, when TLC showed a main product of $R_f = 0.60$ (EtOAc), which was isolated by column chromatography (hexane:EtOAc, 3:2) to afford foamy compound **7a** (36 mg, 74%) as a 4:1 mixture of 6*R*:6*S* isomers; $[\alpha]_D^{25}$ +16.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) (6*R* isomer) δ 7.35−7.20 (5H, H-aromatic), 5.09 (d, 1H, $J_{1,7a} = 6.8$ Hz, H-1), 4.55 (d, 1H, $J_{3,3a} = 10.7$ Hz, H-3), 4.37 (d, 1H, $J_{6,7} = 1.6$ Hz, H-6), 4.32 (m, 2H, OCH_2CH_3), 4.17 (dd, 1H, $J_{3a,4'} = 1.0$, $J_{4,4'} = 13.0$ Hz, H-4'), 3.78 (dd, 1H, $J_{3a,4} = 4.7$, $J_{4,4'} = 13.0$ Hz, H-4),

3.15 (dd, 1H, $J_{6,7}$ = 1.6, $J_{7,7a}$ = 4.4 Hz, H-7), 2.82 (m, 1H, $J_{1,7a}$ = 6.8, $J_{3a,7a}$ = 8.0, $J_{7,7a}$ = 4.4 Hz, H-7a), 2.77 (m, 1H, $J_{3,3a}$ = 10.7, $J_{3a,4}$ = 4.7, $J_{3a,4'}$ = 1.0, $J_{3a,7a}$ = 8.0 Hz, H-3a), 1.35 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.20 (br s, 9H, $(CH_3)_3CO$); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 174.4 (CO_2Et), 155.1 (NCO_2), 127.5−127.0 (C-aromatic), 95.2 (C-6), 81.1 ($C(CH_3)$), 65.9 (C-7), 65.1 (C-1), 62.5, 62.2, 61.9 (C-3, 4, OCH_2CH_3), 46.2 (C-7a), 37.9 (C-3a), 28.0 ($C(CH_3)_3$), 14.3 (OCH_2CH_3); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{29}NNaO_7$ 430.1836, found 430.1835.

Ethyl (1*S*,3*R*,3a*S*,6,7*R*,7a*R*)-2-(*tert*-butyloxycarbonyl)-6,7-dihydroxy-1-phenyloctahydropyrano[3,4-*c*]pyrrole-3-carboxylate (7b): The same procedure described for the preparation of **7a** was applied starting from **4b** (84 mg, 0.19 mmol). Compound **7b** (61 mg, 79%) was obtained as a 4:1 mixture of 6*S*:6*R* isomers; $[\alpha]_D^{25}$ −17.9 (*c* 0.9, $CHCl_3$); identical ^{1}H and ^{13}C spectra as **7a**; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{29}NNaO_7$ 430.1836, found 430.1832.

(2*R*,3*S*,3a*R*,6a*S*)-1-(*tert*-butyloxycarbonyl)-3-(1'(*S*),2'-diacetoxyethyl)-6-oxo-2-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole (10a) and (2*R*,3*S*,3a*R*,6a*S*)-1-(*tert*-butyloxycarbonyl)-3-(1'(*S*),2'-diacetoxyethyl)-6-acetoxy-2-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole (11a)

Compound **7a** (34 mg, 0.08 mmol) was dissolved in anhydrous EtOH (1 mL) and $NaBH_4$ (5 mg, 0.12 mmol) was added. The mixture was stirred at 0 °C for 1 h, when TLC (EtOAc) showed complete conversion of the starting material (R_f = 0.60) into a lower moving product (R_f = 0.20). The mixture was neutralized with AcOH and concentrated. The residue was redissolved in EtOH (10 mL) and the solvent evaporated. The resulting syrup was purified by column chromatography (hexane:EtOAc, 3:7) to afford an inseparable mixture of **8a** and **9a** (25 mg) isolated as a foam. The mixture was

acetylated by addition of anhydrous pyridine (2 mL) and acetic anhydride (2 mL) at 0 °C. The solution was stirred for 16 h, when TLC (toluene: EtOAc, 7:3) showed complete conversion of the starting material into two new spots of R_f = 0.30 and 0.18. Upon addition of MeOH (10 mL), concentration and co-evaporation with toluene (20 mL), the resulting mixture was subjected to column chromatography (toluene:EtOAc, 95:5) to afford first the faster moving lactol **11a** (13 mg, 32%, two steps) and then the lactone **10a** (13 mg, 35%, two steps).

Compound **10a**: $[\alpha]_D^{25}$ −42.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.14 (5H, H-aromatic), 5.22 (d, 1H, $J_{2,3}$ = 9.1 Hz, H-2), 5.11 (dt, 1H, $J_{1',2'x}$ = 4.1, $J_{1',2'y}$ = 4.6, $J_{1',3}$ = 6.2 Hz, H-1'), 4.66 (d, 1xH, $J_{3a,6a}$ = 8.5 Hz, H-6a), 4.38 (dd, 1H, $J_{1',2'x}$ = 4.1, $J_{2'x,2'y}$ = 12.1 Hz, H-2'x), 4.36 (dd, 1H, $J_{3a,4x}$ = 8.1, $J_{4x,4y}$ = 9.9 Hz, H-4x), 4.17 (t, 1H, $J_{3a,4y}$ = $J_{4x,4y}$ = 9.9 Hz, H-4y), 4.07 (dd, 1H, $J_{1',2'y}$ = 4.6, $J_{2'x,2'y}$ = 12.1 Hz, H-2'y), 3.53 (dddd, 1H, $J_{3,3a}$ = 7.2, $J_{3a,4x}$ = 8.1, $J_{3a,4y}$ = 9.9, $J_{3a,6a}$ = 8.5 Hz, H-3a), 3.02 (ddd, $J_{1',3}$ = 6.2, $J_{2,3}$ = 9.1, $J_{3,3a}$ = 7.2 Hz, H-3), 2.09, 1.65 (2s, 6H, CH_3CO), 1.40 (br s, 9H, (CH_3)$_3$CO); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 172.6 (CO_2-lactone), 170.5, 169.3 (Me*C*O), 153.8 (N*C*O_2), 129.2−126.3 (C-aromatic), 81.7 (*C*(CH_3)), 68.5 (C-1'), 67.2 (C-4), 64.0 (×2) (C-2, 2'), 59.4 (C-6a), 44.2 (C-3), 41.6 (C-3a), 28.2 (C(*C*H_3)$_3$), 20.9, 20.5 (*C*H_3CO); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{29}NNaO_8$ 470.1785, found 470.1770.

Compound **11a**: $[\alpha]_D^{25}$ −15.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) major conformer: δ 7.38−7.24 (5H, H-aromatic), 6.67 (s, 1H, H-6), 4.91 (d, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 4.80 (m, 1H, H-1'), 4.37 (d, 1H, $J_{3a,6a}$ = 7.0 Hz, H-6a), 4.27 (dd, 1H, $J_{1',2'x}$ = 2.8, $J_{2'x,2'y}$ = 12.3 Hz, H-2'x), 4.17 (dd, 1H, $J_{3a,4x}$ = 5.6, $J_{4x,4y}$ = 9.6 Hz, H-4x), 4.05 (dd, 1H, $J_{1',2'y}$ = 4.2, $J_{2'x,2'y}$ = 12.3 Hz, H-2'y), 3.99 (t, 1H, $J_{3a,4y}$ = $J_{4x,4y}$ = 9.6 Hz, H-4y), 3.31 (m, 1H, $J_{3,3a}$ ~ 8.0, $J_{3a,4x}$ = 5.6, $J_{3a,4y}$ = 9.6, $J_{3a,6a}$ = 7.0 Hz, H-3a), 3.11 (dt, $J_{2,3}$ = 9.7, $J_{3,3a}$ ~ $J_{1',3}$ ~ 8.0 Hz, H-3), 2.10 (×2), 1.80 (3s, 9H, CH_3CO), 1.12 (br s, 9H, (CH_3)$_3$CO); minor

conformer (selected signals): 6.65 (s, H-6), 5.06 (d, $J_{2,3}$ = 9.7 Hz, H-2), 4.28 (overlapped with H-2'x major, H-6a), 1.40 (br s, $(CH_3)_3CO$) ; δ ^{13}C NMR ($CDCl_3$, 125.7 MHz) major conformer: δ 170.7, 169.9, 169.5 (Me*C*O), 154.3 (N*C*O_2), 139.6−127.3 (C-aromatic), 100.1 (C-6), 80.8 (*C*(CH_3)), 69.9 (C-1'), 68.5 (C-4), 68.3 (C-6a), 64.2 (C-2), 63.6 (C-2'), 44.0 (C-3), 42.2 (C-3a), 28.0 (C(*C*H_3)$_3$), 20.9, 20.7 (×2) (*C*H_3CO); minor conformer (selected signals): 100.7 (C-6), 68.8 (C-6a), 64.0 (C-2), 28.4 (C(*C*H_3)$_3$). HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{33}NNaO_9$ 514.2047, found 514.2031.

(2*S*,3*R*,3a*S*,6a*R*)-1-(*tert*-butyloxycarbonyl)-3-(1'(*R*),2'-diacetoxyethyl)-6-oxo-2-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole (10b) and (2*S*,3*R*,3a*S*,6a*R*)-1-(*tert*-butyloxycarbonyl)-3-(1'(*R*),2'-diacetoxyethyl)-6-acetoxy-2-phenylhexahydro-1*H*-furo[3,4-*b*]pyrrole (11b)

Compound **7b** (90 mg; 0.22 mmol) was dissolved in anhydrous EtOH and $NaBH_4$ was added, as described before for compound **7a**. In this case, the mixture was stirred at 0 °C for 30 min, neutralized with AcOH and concentrated. The residue was redissolved in EtOH (10 mL) and the solvent evaporated. The crude mixture was acetylated by addition of anhydrous pyridine (2 mL) and acetic anhydride (2 mL) at 0 °C. The solution was stirred for 16 h, when TLC (toluene: EtOAc, 7:3) showed two spots of R_f = 0.30 and 0.18 corresponding respectively to **11b** and **10b**. This mixture was subjected to the usual work up.

Compound **10b** (44 mg, 45%, two steps); $[\alpha]_D^{25}$ +44.1 (*c* 0.7, $CHCl_3$); identical ^{1}H and ^{13}C NMR spectra as **10a**; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{29}NNaO_8$ 470.1785, found 470.1789.

Compound **11b** (6 mg, 6%, two steps); $[\alpha]_D^{25}$ +15.0 (*c* 0.9, $CHCl_3$); identical ^1H and ^{13}C NMR spectra as **11a**; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{33}NNaO_9$ 514.2047, found 514.2038.

(2*S*,3*R*,4*S*,5*R*)-1-(*tert*-butyloxycarbonyl)-4-(1'(*S*),2'-dihydroxyethyl)-2,3-bis(hydroxymethyl)-5-phenylpyrrolidine (12a): Compound **7a** (50 mg, 0.12 mmol) and $NaBH_4$ (14 mg, 0.36 mmol) were dissolved in anhydrous EtOH (2 mL) and the mixture was heated under stirring in a sealed vial under N_2, at 80 °C for 5 h. The mixture was neutralized with AcOH and concentrated. The residue was dissolved in EtOH (10 mL), followed by evaporation of the solvent. The same procedure was conducted using toluene (10 mL). The resulting residue was purified by column chromatography (EtOAc) to give **12a** (37 mg, 82%) as a colorless syrup; R_f = 0.10 (EtOAc); $[\alpha]_D^{25}$ −32.7 (*c* 1.4, EtOH); ^1H NMR (DMSO, 500 MHz) δ 7.30−7.18 (5H, H-aromatic), 4.89 (dd, 1H, $J_{4,5}$ = 8.2 Hz, H-5), 4.15 (dd, 1H, $J_{2,4'x}$ = 4.3, $J_{4'x,4'y}$ = 10.7 Hz, H-4'x), 3.91 (ddd, 1H, $J_{2,3}$ = 7.3, $J_{2,4'x}$ = 4.3, $J_{2,4'y}$ = 8.6 Hz, H-2), 3.79 (dd, 1H, $J_{2,4'y}$ = 8.6, $J_{4'x,4'y}$ = 10.7 Hz, H-4'y), 3.67−3.60 (m, 2H, H-2'x, H-3'x), 3.46 (m, 1H, H-3'y), 3.41 (dd, 1H, $J_{1',2'y}$ = 4.2, $J_{2'x,2'y}$ = 10.6 Hz, H-2'y), 3.28 (m, 1H, H-1'), 2.62 (m, 1H, $J_{2,3}$ ~ $J_{3,3'x}$ ~ $J_{3,3'y}$ ~ $J_{3,4}$ ~ 7.0 Hz, H-3), 2.49 (m, 1H, H-4), 1.15 (s, 9H, $(CH_3)_3CO$); ^{13}C NMR (DMSO, 125.7 MHz) δ 154.7 (NCO_2), 140.9−126.5 (C-aromatic), 79.2 ($C(CH_3)$), 68.7 (C-1'), 65.5 (C-2'), 63.2 (C-5), 62.0 (C-2), 60.0 (C-4'), 57.6 (C-3'), 47.0 (C-4), 44.9 (C-3), 27.9 ($C(CH_3)_3$); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{29}NNaO_6$ 390.1887, found 390.1881.

(2*R*,3*S*,4*R*,5*S*)-1-(*tert*-butyloxycarbonyl)-4-(1'(*R*),2'-dihydroxyethyl)-2,3-bis(hydroxymethyl)-5-phenylpyrrolidine (12b): The procedure described for the

reduction of **7a** ($NaBH_4$, 80 °C, 5 h) was applied to **7b** (50 mg, 0.12 mmol) to afford compound **12b** (31 mg, 69%); $[\alpha]_D^{25}$ +30.0 (*c* 1.4, EtOH); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{29}NNaO_6$ 390.1887, found 390.1881.

(2*S*,3*R*,4*S*,5*R*)-4-(1'(*S*),2'-diacetoxyethyl)-2,3-bis(acetoxymethyl)-1-(*tert*-butyloxycarbonyl)-5-phenylpyrrolidine (13a): Compound **7a** (50 mg, 0.12 mmol) was reduced with $NaBH_4$, as indicated in the previous item. The crude product was dissolved in anhydrous pyridine (1 mL) and Ac_2O (1 mL) was added. The mixture was stirred at rt for 16 h, cooled to 0 °C and MeOH (10 mL) was added. The residue obtained upon concentration was purified by column chromatography (hexane:EtOAc, 7:3) to give compound **13a** as a white solid (53 mg, 81%), mp = 136−137 °C (from EtOH:H_2O); R_f = 0.10 (hexane:EtOAc, 7:3); $[\alpha]_D^{25}$ −11.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30−7.21 (5H, H-aromatic), 5.04 (d, 1H, $J_{4,5}$ = 6.9 Hz, H-5), 5.02 (m, 1H, $J_{2,3}$ = 7.4, $J_{2,4'x}$ = 3.5, $J_{2,4'y}$ = 5.2 Hz, H-2), 4.68 (dd, 1H, $J_{1',2'x}$ = 3.3, $J_{2'x,2'y}$ = 11.3 Hz, H-2'x), 4.60 (dd, 1H, $J_{1',2'y}$ = 7.3, $J_{2'x,2'y}$ = 11.3 Hz, H-2'y), 4.27 (dd, 1H, $J_{2,4'x}$ = 3.5, $J_{4'x,4'y}$ = 12.0 Hz, H-4'x), 4.26−4.20 (m, 3H, H-3'x, H-3'y, H-1'), 3.81 (dd, 1H, $J_{2,4'y}$ = 5.2, $J_{4'x,4'y}$ = 12.0 Hz, H-4'y), 2.93 (m, 1H, $J_{3,4}$ = 7.5, $J_{4,5}$ = 6.9, $J_{1',4}$ = 7.8 Hz, H-4), 2.90 (m, 1H, $J_{2,3}$ = 7.4, $J_{3,4}$ = 7.5 Hz, H-3), 2.10, 2.03, 1.97, 1.80 (4s, 12H, C*H*$_3$CO), 1.21 (s, 9H, (C*H*$_3$)$_3$CO); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 170.5 (×2), 169.7 (Me*C*O), 155.0 (N*C*O_2), 139.7−126.7 (C-aromatic), 80.7 (*C*(CH_3)), 68.9, 64.1 (C-2, 5), 64.0 (C-4'), 62.7 (C-2'), 61.4, 58.7 (C-1', 3'), 44.4 (C-4), 42.4 (C-3), 28.1 (C(*C*H$_3$)$_3$), 21.0, 20.9 (×2), 20.8 (*C*H$_3$CO); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{27}H_{37}NNaO_{10}$ 558.2310, found 558.2299.

(2*R*,3*S*,4*R*,5*S*)-4-(1'(*R*),2'-diacetoxyethyl)-2,3-bis(acetoxymethyl)-1-(*tert*-butyloxycarbonyl)-5-phenylpyrrolidine (13b): The reduction and acetylation conditions reported for **7a** were employed starting from **7b** (50 mg, 0.12 mmol) to afford compound **13b** as a white solid (50 mg, 76%), mp = 136 °C (from EtOH:H_2O); $[\alpha]_D^{25}$ +10.8 (*c* 1.1, $CHCl_3$); identical ^1H and ^{13}C NMR spectra as **13a**; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{27}H_{37}NNaO_{10}$ 558.2310, found 558.2305.

(2*S*,3*R*,4*S*,5*R*)-4-(1'(*S*),2'-dihydroxyethyl)-2,3-bis(hydroxymethyl)-5-phenylpyrrolidine (14): Compound **6a** (41 mg, 0.13 mmol) and $NaBH_4$ (14 mg, 0.38 mmol) were dissolved in anhydrous EtOH (2 mL) and the mixture was heated under stirring in a sealed vial under N_2, at 80 °C for 5 h, as described before for **12a**. After the same work up, the residue was purified by column chromatography (EtOAc:MeOH, 4:1) to give **14** (19 mg, 53%) as a colorless syrup; R_f = 0.17 (MeOH:EtOAc, 6:4); $[\alpha]_D^{25}$ +39.7 (*c* 0.9, MeOH); ^1H NMR (MeOD, 500 MHz) δ 7.52−7.34 (5H, H-aromatic), 4.61 (d, 1H, $J_{4,5}$ = 8.1 Hz, H-5), 4.06 (dd, 1H, $J_{3,3'x}$ = 6.1, $J_{3'x,3'y}$ = 10.7 Hz, H-3'x), 4.02 (dd, 1H, $J_{2,4'x}$ = 5.6, $J_{4'x,4'y}$ = 11.5 Hz, H-4'x), 3.98 (dd, 1H, $J_{2,4'y}$ = 7.9, $J_{4'x,4'y}$ = 11.5 Hz, H-4'y), 3.91 (dd, 1H, $J_{3,3'y}$ = 4.8, $J_{3'x,3'y}$ = 10.7 Hz, H-3'y), 3.69 (dt, 1H, $J_{2,3}$ = 7.3, $J_{2,4'x}$ = 5.6, $J_{2,4'y}$ = 7.9 Hz, H-2), 3.58 (dt, 1H, $J_{1,2'x}$ = 4.1, $J_{1,2'y}$ = $J_{1',4}$ = 6.5 Hz, H-1'), 3.20 (dd, 1H, $J_{1',2'x}$ = 4.1, $J_{2'x,2'y}$ = 11.4 Hz, H-2'x), 3.11 (dd, 1H, $J_{1',2'y}$ = 6.5, $J_{2'x,2'y}$ = 11.4 Hz, H-2'y), 2.85−2.78 (m, 2H, H-3, H-4); ^{13}C NMR (MeOD, 125.7 MHz) δ 137.5−127.3 (C-aromatic), 71.5 (C-1'), 65.7 (C-2'), 65.2 (C-5), 63.5 (C-2), 61.0 (C-4'), 59.6 (C-3'), 46.6, 45.5 (C-3, 4); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{22}NO_4$ 268.1543, found 268.1540.

Hydrolysis of the *N*-Boc protecting group of 12a and 12b.

A solution of **12a** or **12b** (0.08 mmol) in TFA (2 mL) was stirred at rt for 16 h. Monitoring by TLC (EtOAc) showed conversion of the starting material into a more polar product (R_f = 0). The solution was concentrated in vacuum and residue was dissolved in toluene (10 mL) followed by evaporation of the solvent. After the same treatment with methanol (10 mL), compounds **15a** or **15b** (from **12a** or **12b**, respectively) were obtained.

(2*S*,3*R*,4*S*,5*R*)-4-(1'(*S*),2'-dihydroxyethyl)-2,3-bis(hydroxymethyl)-5-phenylpyrrolidinium trifluoroacetate (15a): colorless syrup (27 mg, 93%), $[\alpha]_D^{25}$ +56.0 (*c* 1.4, MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 7.58−7.49 (5H, H-aromatic), 4.88 (d, 1H, $J_{4,5}$ = 10.0 Hz, H-5), 4.16 (dd, 1H, $J_{2,4'x}$ = 4.9, $J_{4'x,4'y}$ = 12.2 Hz, H-4'x), 4.12 (dd, 1H, $J_{3,3'x}$ = 5.5, $J_{3'x,3'y}$ = 11.3 Hz, H-3'x), 4.11 (dd, 1H, $J_{2,4'y}$ = 8.9, $J_{4'x,4'y}$ = 12.2 Hz, H-4'y), 3.97 (dd, 1H, $J_{3,3'y}$ = 4.3, $J_{3'x,3'y}$ = 11.3 Hz, H-3'y), 3.94 (m, 1H, $J_{2,3}$ = 7.3, $J_{2,4'x}$ = 4.9, $J_{2,4'y}$ = 8.9 Hz, H-2), 3.78 (m, 1H, $J_{1',2'x}$ = 3.1, $J_{1',2'y}$ = 6.8, $J_{1',4}$ = 8.5 Hz, H-1'), 3.15 (dd, 1H, $J_{1',2'x}$ = 3.1, $J_{2'x,2'y}$ = 12.0 Hz, H-2'x), 3.05 (dd, 1H, $J_{1',2'y}$ = 6.8, $J_{2'x,2'y}$ = 12.0 Hz, H-2'y), 3.04 (dt, 1H, $J_{1',4}$ = 8.5, $J_{3,4}$ = 7.6, $J_{4,5}$ = 10.0 Hz, H-4), 2.90 (m, 1H, $J_{2,3}$ = 7.3, $J_{3,3'x}$ = 5.5, $J_{3,3'y}$ = 4.3, $J_{3,4}$ = 7.6, Hz, H-3); ^{13}C NMR (D_2O, 125.7 MHz) δ 132.4−128.5 (C-aromatic), 69.7 (C-1'), 64.0 (C-2'), 63.1 (C-5), 62.8 (C-2), 58.4 (C-4'), 57.6 (C-3'), 43.6 (C-4), 42.4 (C-3); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{22}NO_4$ 268.1543, found 268.1548.

(2*R*,3*S*,4*R*,5*S*)-4-(1'(*R*),2'-dihydroxyethyl)-2,3-bis(hydroxymethyl)-5-phenylpyrrolidinium trifluoroacetate (15b): colorless syrup (29 mg, 99%), $[\alpha]_D^{25}$ −54.1 (*c* 1.4, MeOH); identical ^{1}H and ^{13}C NMR spectra as **15a**; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{22}NO_4$ 268.1543, found 268.1544.

Degradative oxidation of the 1,2-ethanediol moiety of 12a and 12b.

(1*R*,3a*R*,4*S*,6*R*,6a*S*)-5-(*tert*-butyloxycarbonyl)-4-(hydroxymethyl)-6-phenylhexahydro-1*H*-furo[3,4-c]pyrrol-1-ol (16a): To a solution of **12a** (28 mg, 0.08 mmol) in anhydrous EtOH (2 mL) was added $NaIO_4$ (50 mg, 0.22 mmol). The mixture was stirred at rt for 8 h, when TLC showed a main spot of R_f = 0.40 (toluene:EtOH, 4:1). The mixture was diluted with EtOAc (10 mL), filtered and concentrated. Column chromatography with hexane:EtOAc 3:7 gave **16a** white solid, (23 mg, 90%), mp = 147−148 °C (from EtOH:H_2O); $[\alpha]_D^{25}$ +10.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33−7.19 (5H, H-aromatic), 5.18 (d, 1H, $J_{6,6a}$ = 10.0 Hz, H-6), 4.77 (d, 1H, $J_{1,6a}$ = 2.1 Hz, H-1), 4.23 (ddd, 1H, $J_{3a,4}$ = 8.8, $J_{4,4'x}$ = 4.5, $J_{4,4'y}$ = 6.5 Hz, H-4), 4.05 (dd, 1H, $J_{3a,3x}$ = 6.2, $J_{3x,3y}$ = 9.7 Hz, H-3x), 3.97 (dd, 1H, $J_{3a,3y}$ = 2.8, $J_{3x,3y}$ = 9.7 Hz, H-3y), 3.89−3.86 (m, 2H, H-4'x, H-4'y), 3.26 (m, 1H, $J_{3a,3x}$ = 6.2, $J_{3a,3y}$ = 2.8, $J_{3a,4}$ = 8.8, $J_{3a,6a}$ = 8.4 Hz, H-3a), 3.15 (m, 1H, $J_{1,6a}$ = 2.1, $J_{3a,6a}$ = 8.4, $J_{6,6a}$ = 10.0 Hz, H-6a), 1.15 (s, 9H, (CH_3)$_3$CO); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 156.7 (N*C*O$_2$), 140.7−126.1 (C-aromatic), 99.9 (C-1), 81.2 (*C*(CH_3)), 67.6 (C-3), 64.7 (C-4'), 63.6 (C-6), 62.5 (C-4), 56.1 (C-6a), 45.3 (C-3a), 28.0 (C(*C*H_3)$_3$); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{25}NNaO_5$ 358.1625, found 358.1614.

(1*S*,3a*S*,4*R*,6*S*,6a*R*)-5-(*tert*-butyloxycarbonyl)-4-(hydroxymethyl)-6-phenylhexahydro-1*H*-furo[3,4-c]pyrrol-1-ol (16b): The periodate oxidation of **12b** (15 mg, 0.04 mmol) was conducted as described above to give **16b** as a white solid (13 mg, 95%), mp = 146−147 °C (from EtOH:H_2O); $[\alpha]_D^{25}$ −9.5 (*c* 1.0, $CHCl_3$); identical ^{1}H and ^{13}C NMR spectra as **16a**; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{25}NNaO_5$ 358.1625, found 358.1616.

(2*S*,3*R*,4*S*,5*R*)-1-(*tert*-butyloxycarbonyl)-2,3,4-tris(hydroxymethyl)-5-phenylpyrrolidine (17a): The crude hemiacetal **16a**, obtained from **12a** (22 mg, 0.06 mmol) was dissolved in anhydrous EtOH (2 mL) and $NaBH_4$ (6.7 mg, 0.17 mmol) was added. The solution was stirred at rt for 2 h and then neutralized with AcOH and concentrated. The residue was dissolved in EtOH (10 mL) followed by evaporation of the solvent. After the same treatment with toluene (10 mL), the residue was subjected to column chromatography with EtOAc to give compound **17a** (19 mg, 94%) as a colorless syrup; R_f = 0.20 (toluene:EtOH, 4:1); $[\alpha]_D^{25}$ +12.9 (*c* 1.0, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28−7.08 (5H, H-aromatic), 4.94 (d, 1H, $J_{4,5}$ = 7.9 Hz, H-5), 4.13 (ddd, 1H, $J_{2,3}$ = 7.8, $J_{2,4'x}$ = 7.1, $J_{2,4'y}$ = 6.1 Hz, H-2), 3.94 (dd, 1H, $J_{2,4'x}$ = 7.1, $J_{4'x,4'y}$ = 11.0 Hz, H-4'x), 3.82 (dd, 1H, $J_{2,4'y}$ = 6.1, $J_{4'x,4'y}$ = 11.0 Hz, H-4'y), 3.79−3.76 (d, 2H, $J_{3,3'x}$ = $J_{3,3'y}$ = 6.0 Hz, H-3'x, H-3'y), 3.37 (dd, 1H, $J_{1'x,4}$ = 10.1, $J_{1'x,1'y}$ = 11.3 Hz, H-1'x), 3.05 (dd, 1H, $J_{1'y,4}$ = 4.6, $J_{1'x,1'y}$ = 11.3 Hz, H-1'y), 2.72 (m, 1H, $J_{2,3}$ = $J_{3,4}$ = 7.8, $J_{3,3'x}$ = $J_{3,3'y}$ = 6.0 Hz, H-3), 2.68 (m, 1H, $J_{1'x,4}$ = 10.1, $J_{1'y,4}$ = 4.6, $J_{3,4}$ = 7.8, $J_{4,5}$ = 7.9 Hz, H-4), 1.05 (s, 9H, $(CH_3)_3CO$); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 156.9 (NCO_2), 140.2−126.0 (C-aromatic), 80.9 ($C(CH_3)$), 64.8 (C-5), 64.0 (C-2), 62.3 (C-4'), 61.7 (C-1'), 59.1 (C-3'), 46.6 (C-4), 45.5 (C-3), 27.9 ($C(CH_3)_3$); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{27}NNaO_5$ 360.1781, found 360.1789.

(2*R*,3*S*,4*R*,5*S*)-1-(*tert*-butyloxycarbonyl)-2,3,4-tris(hydroxymethyl)-5-phenylpyrrolidine (17b): The $NaBH_4$ reduction of **16b**, obtained from **12b** (78 mg, 0.21 mmol) was conducted as already described for the analogue **16a**. Column chromatography with EtOAc gave compound **17b** (59 mg, 82%); $[\alpha]_D^{25}$ −14.1 (*c* 1.0,

EtOH); identical ^{1}H and ^{13}C NMR spectra as **17a**; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{27}NNaO_5$ 360.1781, found 360.1768.

Hydrolysis of the *N*-Boc protecting group of 17a and 17b

Hydrolysis of compounds **17a** or **17b** (34 mg, 0.10 mmol) with TFA (2 mL) at rt for 16 h afforded, after the usual work-up, the respective trifluoroacetates **18a** or **18b**.

(2*S*,3*R*,4*S*,5*R*)-2,3,4-tris(hydroxymethyl)-5-phenylpyrrolidinium trifluoroacetate (18a): colorless syrup (34 mg, 96%), $[\alpha]_D^{25}$ +66.3 (*c* 1.0, MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 7.41−7.34 (5H, H-aromatic), 4.81 (d, 1H, $J_{4,5}$ = 7.2 Hz, H-5), 4.03−3.98 (m, 3H, H-2, H-4'x, H-4'y), 3.82 (dd, 1H, $J_{3,3'x}$ = 6.5, $J_{3'x,3'y}$ = 11.3 Hz, H-3'x), 3.79 (dd, 1H, $J_{3,3'y}$ = 6.6, $J_{3'x,3'y}$ = 11.3 Hz, H-3'y), 3.47 (dd, 1H, $J_{1'x,4}$ = 3.0, $J_{1'x,1'y}$ = 11.6 Hz, H-1'x), 3.36 (dd, 1H, $J_{1'y,4}$ = 4.2, $J_{1'x,1'y}$ = 11.6 Hz, H-1'y), 2.98 (m, 1H, $J_{2,3}$ = 9.4, $J_{3,4}$ = 8.1, $J_{3,3'x}$ = 6.5, $J_{3,3'y}$ = 6.6 Hz, H-3), 2.82 (m, 1H, $J_{3,4}$ = 8.1, $J_{4,5}$ = 7.2, $J_{1'x,4}$ = 3.0, $J_{1'y,4}$ = 4.2 Hz, H-4); ^{13}C NMR (D_2O, 125.7 MHz) δ 162.4 (q, *J* = 36.0 Hz, F_3CCO), 131.7−126.7 (C-aromatic), 116.0 (q, *J* = 291.0 Hz, F_3CCO), 64.2 (C-5), 61.7, 58.0 (C-2, 4'), 57.4 (C-3'), 57.1 (C-1'), 43.6 (C-4), 41.1 (C-3); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{20}NO_3$ 238.1438, found 238.1430.

(2*R*,3*S*,4*R*,5*S*)-2,3,4-tris(hydroxymethyl)-5-phenylpyrrolidinium trifluoroacetate (18b): colorless syrup (34 mg, 96%), $[\alpha]_D^{25}$ −68.2 (*c* 1.0, MeOH); the ^{1}H and ^{13}C NMR spectra were identical to those of **18a**; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{20}NO_3$ 238.1438, found 238.1431.

Enzymatic assays

The inhibition studies were performed by Professor Carla Marino, who had isolated the enzyme.[24,25] The enzymatic activity was assayed using the filtered medium of a stationary culture of *P. fellutanum* as source of *exo* β-D-galactofuranosidase and 4-nitrophenyl β-D-galactofuranoside as substrate. The standard assay was conducted with 50 μL of 66 mM NaOAc buffer (pH4.6), 20 μL of a 5 mM solution of 4-nitrophenyl β-D-galactofuranoside and 20 μL (4 μg protein) of the enzyme medium, in a final volume of 250 μL. Compounds **14, 15a, 15b, 18a** and **18b** were incorporated in the amounts required to obtain a final concentration of 0.1 to 1.6 mM. The enzymatic reaction was stopped after 1.5 h of incubation at 37 ºC by addition of 1mL of 0.1 M Na_2CO_3 buffer (pH 9.0). The 4-nitrophenol released was measured spectrophotometrically at 410 nm.

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Supporting Information: Details on general experimental methods; copies of ^{1}H and ^{13}C NMR and selected 2D-COSY, 2D-NOESY, and 2D-HMBC spectra; X-ray data for compounds **2a** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org/

References

(1) (a) D'Alessio, C.; Dahms, N.M. *Curr. Protein Pept. Sci.* **2015**, *16*, 31-48. (b) Jacobs, P.P.; Callewaert, N. *Curr Mol Med.* **2009**, *9*, 774-800. (c) Kato, K.; Kamiya, Y. *Glycobiology.* **2007**, *17*,1031-1044. (d) Sjögren, J.; Collin, M. *Future Microbiol*. **2014**, *9*, 1039-1051. (e) Gorelik, E.; Galili, U.; Raz, A. *Cancer Metastasis Rev.* **2001**, *20*, 245-277.

(2) (a) Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *Mini-Rev. Med. Chem.* **2006**, *6*, 1043−1052. (b) Asano, N. *Cell. Mol. Life Sci.* **2009**, *66*, 1479−1492. (c) Kajimoto, T; Node, M. *Curr. Top. Med. Chem.* **2009**, *9*, 13−33. (d) Moorthy, N. S. H. N.; Ramos, M. J.; Fernandes, P. A. *Mini-Rev. Med. Chem.* **2012**, *12*, 713−720. (e) Wang, J-T.; Lin, T-C.; Chen, Y-H.; Lin, C-H.; Fang, J-M. *Med. Chem. Commun.* **2013**, *4*, 783−791.

(3) Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug. Discov. Today* **2011**, *16*, 107−118.

(4) (a) *Iminosugars as Glycosidase Inhibitors*; Stütz, A. E.; *Ed.: Wiley-VCH: Weinheim, Germany,* **1999**. (b) Scott, L. J.; Spencer, C. M. *Drugs,* **2000**, *59*, 521–549. (c) Winchester, B. *The Development of Iminosugars as Drugs in Glycobiology*; Sansom, C.; Markman, O.; *Eds.; Scion Publishing Limited, Bloxham:Oxfordshire, UK*, **2006**, 308−324. (d) Zitzmann, N.; Block, T.; Methta, A.; Rudd, P.; Burton, D.; Wilson, I.; Platt, F.; Butters, T.; Dwek, R. A. *Adv. Exp. Med. Biol.* **2005**, *564*, 1–2. (e) Butters, T. D.; Dwek, R. A. Platt, F. M. *Glycobiology,* **2005**, *15*, 43R–52R. (f) Cox, T. M. *Acta Paedtr.* **2005**, *94*, 69–75. (g) Durantel, D. *Curr. Opin. Invest. Drugs,* **2009**, *10*, 860–870. (h) Winchester, B. G. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 2829–2834 *Tetrahedrom: Asymmetry,* **2009**, *20*, 645–651.

(5) (a) Vasella, A.; Davies, G. J.; Böhm, M. *Curr. Opin. Chem. Biol.* **2002**, *6*, 619−629. (b) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem.-Eur. J.* **2006**, *12*, 6607–6620.

(6) (a) Sinnot, M. L. *Chem. Rev.* **1990**, *90*, 1171–1202. (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319–384. (c) Stütz, A. E. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1926–1928. (d) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed*. **1999**, *38*, 750–770. (e) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553.

(7) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron:Asymmetry* **2000**, *11*, 1645–1680.

(8) Molyneux, R. J.; Pan, Y. T.; Tropea, J. E.; Elbein, A. D.; Lawyer, C. H. Hughes, D. J.; Fleet, G. W. J. *J. Nat. Prod.* **1993**, *56*, 1356–1364.

(9) Nash, R. J.; Asano, N.; Watson, A. A. In *Alkaloids: Chemical and Biological Perspectives; Pelletier, S. W. Ed.; Elsevier Science: Oxford,* **1996**, Vol II, 345−376.

(10) Watson, A. A.; Nash, R. J.; Wormald, M. R.; Harvey, D. J.; Dealler, S.; Lees, E.; Asano, N.; Kizu, H.; Kato, A.; Griffiths, R. C.; Cairns, A. J.; Fleet, G. W. J. *Phytochemistry* **1997**, *46*, 255−259.

(11) Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *J. Nat. Prod.* **1998**, *61*, 625−628.

(12) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95−103.

(13) (a) Compain, P.; Chagnault, V.; Martin, O. R. *Tetrahedron : Asymmetry* **2009**, *20*, 672−711. (b) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, *9*, 1615−1637.

(14) (a) Doddi, V. R.; Vankar, Y. D. *Eur. J. Org. Chem.* **2007**, *33*, 5583−5589. (b) Rodriguez-Borges, J. E.; Vale, M. L. C.; Rizzo Aguiar, F.; Alves, M. J.; García-Mera,

X. *Synthesis* **2008**, *1*, 1−7. (c) Petakamsetty, R.; Jain, V. K.; Majhi, P. K.; Ramapanicker, R. *Org. Biomol. Chem.* **2015**, *13*, 8512−8523.

(15) (a) Lo Fiego, M. J.; Marino, C.; Varela, O. *RSC Adv.* **2015**, *5*, 45631−45640. (b) Repetto, E.; Marino, C.; Varela, O. *Bioorg. Med. Chem.* **2013**, *21*, 3327−3333. (c) Repetto, E.; Manzano, V. M.; Uhrig, M. L.; Varela, O. *J. Org. Chem.* **2012**, *77*, 253−265, and references therein.

(16) Oliveira Udry, G. A.; Repetto, E.; Varela, O. *J. Org. Chem.* **2014**, *79*, 4992−5006.

(17) (a) Richards, M. R.; Lowary, T. L. *ChemBioChem,* **2009**, *10*, 1920−1938. (b) Peltier, P.; Euzen, R.; Daniellou, R.; Nugier-Chauvin, C. Ferrières, V. *Carbohydr. Res.* **2008**, *343*, 1897−1923. (c) Miletti, L. C.; Mariño, K.; Marino, C.; Colli, W.; Alves, M. J. M.; Lederkremer, R. M. *Mol. Biochem. Parasitol.* **2003**, *127*, 85−88. (d) Wallis, G. L. F.; Hemming, F. W.; Peberdy, J. F. *BBA-Gen. Subjects* **2001**, *1525*, 19−28.

(18) (a) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev.* **2010**, *39*, 845-883. (b) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 12434-12446. (c) Narayan, R.; Potowski, M.; Jia, Z.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296-1310. (d) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115,* 5366-5412. (e) Singh, M. S.; Chowdhury, S.; Koley, S. *Tetrahedron* **2016**, *72*, 1603-1644.

(19) (a) Iriarte Capaccio, C. A.; Varela, O. *J. Org. Chem*. **2001**, *66*, 8859−8866. (b) Iriarte Capaccio, C. A.; Varela, O. *J. Org. Chem*. **2002**, *67*, 7839−7846. (c) Iriarte Capaccio, C. A.; Varela, O. *Tetrahedron Lett.* **2003**, *44*, 4023−4026. (d) Cagnoni, A. J.; Uhrig, M. L.; Varela, O. *Bioorg. Med. Chem.* **2009**, *17*, 6203-6212. (e) Colomer, J. P.; Manzano, V. E.; Varela, O. *Eur J. Org. Chem.* **2013**, 7343-7353.

(20) Sousa, C. A. D.; Rizzo-Aguiar, F.; Vale, M. L C.; García-Mera, X.; Caamaño, O.; Rodríguez-Borges, J. E. *Tetrahedron Lett*. **2012**, *53*, 1029-1032.

(21) Deetz, M. J.; Jonas, M.; Malerich, J. P.; Smith, B. D. *Supramol. Chem*. **2002**, *14*, 487-489.

(22) (a) Bleich, H.; Wilde, J. *J. Magn. Reson*. **1984**, *56*, 149-150. (b) Hennig, J.; Limbach, H. H. *J. Magn. Reson*. **1982**, *49*, 322-328. (c) Davis, D. G.; Bax, A. *J. Magn. Reson.* **1985**, *64*, 533-535.

(23) Rietschel-Berst, M.; Jentoft, N. H.; Rick, P. D.; Pletcher, C.; Fang, F.; Gander, J. E. *J. Biol. Chem.* **1977**, *252*, 3219−3226.

(24) (a) Marino, C.; Mariño, K.; Miletti, L.; Manso Alves, M. J.; Colli, W.; Lederkremer, R. M. *Glycobiology* **1998**, *8*, 901-904; (b) Marino, C.; Baldoni, L. *ChemBioChem*. **2014**, *15*, 188−204. (c) Imamura, A.; Lowary, T. *Trends Glycosci. Glyc.* **2011**, *23*, 134−152.

(25) Bordoni, A.; Lederkremer, R. M.; Marino, C. *Bioorg. Med. Chem.* **2010**, *18*, 5339-5345.

(26) (a) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G.; Echeverría, G. A.; Piro, O. E. *Org. Lett*. **2012,** *14*, 2556−2559. (b) Brazier, J. B.; Tomkinson, N. C. O. *Top. Curr. Chem.* **2010**, *291*, 281−347. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471−5569. (d) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123-3135.