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Synthesis of Highly Substituted and Enantiomerically Pure 2,3,4-Tris(hydroxyalkyl)pyrrolidines Using a 1,3-Dipolar Cycloaddition Reaction as Key Step

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The major *endo* cycloadducts with a basic structure of methyl 1-aryl-3-(benzyl or methyl)-6-menthyloxy-7-oxooctahydropyrano[4,3-*c*]pyrrole-3-carboxylate were subjected to simple chemical transformations (mostly reduction and hydrolysis reactions) to afford pyrrolidine bicyclic systems with varied patterns of substitution and configurations. The cycloadducts have been obtained by the 1,3-dipolar cycloaddition of (*S*)-2-menthyloxy-2*H*-pyran-3(6*H*)-one, derived from D-xylose, with azomethine ylides derived from imines of L-alanine or L-phenylalanine. The synthetic route led to enantiomerically pure 2,3,4-tris(hydroxyalkyl) pyrrolidines possessing a tetrasubstituted carbon stereocenter vicinal to the ring nitrogen atom and carrying a phenyl substituent on the other carbon adjacent to the nitrogen.

Introduction

Polyhydroxypyrrolidines are commonly seen as sugar mimetics (iminosugars or azasugars) with nitrogen replacing the oxygen atom of the furanose ring. This kind of alkaloids has been isolated from plants and microorganisms.[1] The interest in the synthesis of polyhydroxypyrrolidines has increased dramatically since the commercialization of the first iminosugar-based drug in 1996.[2] The therapeutic potential of these molecules relies on the fact that they usually display inhibitory activity against a number of enzymes, including glycosidases[1,3] and glycosyltransferases,[4] which are involved in important metabolic processes. Therefore, lead compounds have been employed or are currently investigated, as new therapeutic agents for the treatment of varied diseases,[5] including diabetes,[6] viral infections[7] and cancers.[8]

Among the varied structures shown by polyhydroxypyrrolidines, a rather unusual type was found, which carries an aryl moiety as substituent of the carbon adjacent to the ring nitrogen atom. Thus, in 2001, radicamines A and B were isolated from the herb *Lobelia chinensis* Lour,[9] used in traditional Chinese medicine as diuretic and carcinostatic. Radicamines have shown to be glycosidase inhibitors, and their absolute configurations have been revised.[10] From the herb *Codonopsis clematidea*, used in folk medicine to improve the hepatic function, three 2-aryl polyhydroxylated pyrrolidine alkaloids have been isolated.[11] Members of this class, codonopsine and codonopsinine, exhibited antibiotic and hypotensive activities. Synthetic related molecules, such as the immucillins, have been prepared. These aza-*C*-nucleosides act as powerful inhibitors of human and protozoan nucleoside enzymes[12] and are expected to control T-cell function disorders.

The interesting structures and potentially useful biological activities of polyhydroxypyrrolidines have inspired the development of procedures for the synthesis of these molecules, including those having a 2-aryl substituent. The synthetic procedures have been the subject of a number of reviews,[13] including those which uses enzymes (aldolases) in a key step.[14] Recent synthesis of analogues of radicamines[15] and pyrrolidines containing heterocylcles as aryl substituents have been reported.[16]

In connection with our work on the synthesis of polyhydroxypyrrolidines,[17,18] by chemical modifications of the cycloadducts obtained via the 1,3-dipolar cycloaddition of sugar derivatives with azomethine ylides,[19] we report here the synthesis of enantiomerically pure pyrrolidines containing hydroxyalkyl substituents in three adjacent positions of the ring and a tetrasubstituted stereocenter in one of the carbons vicinal to the ring nitrogen atom and a phenyl group on the other.

Results and Discussion

Bicyclic compounds with a general structure of methyl 1-aryl-3-(methyl or benzyl)-6-menthyloxy-7-oxooctahydropyrano[4,3-*c*] pyrrole-3-carboxylate (**4a–c**, **5a–c**) have been prepared by means of the 1,3-dipolar cycloaddition between the sugar enone (*S*)-2-menthyloxy-2*H*-pyran-3(6*H*)-one (**1**), derived from D-xylose, with the azomethine ylides generated in situ from the

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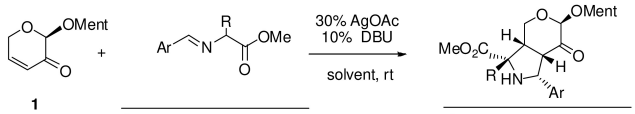


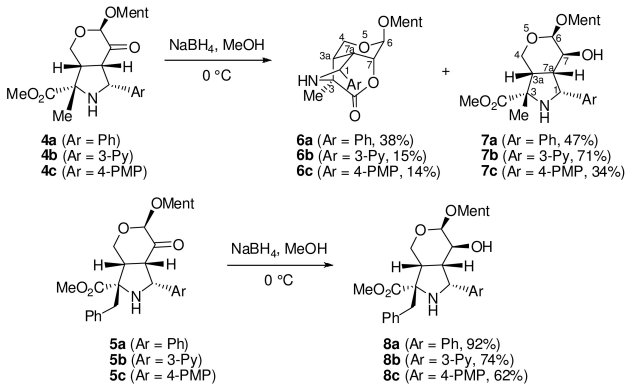
Compound	R	Ar
2a	Me	Ph
2b	Me	3-Py
2c	Me	4-PMP
3a	$PhCH_2$	Ph
3b	$PhCH_2$	3-Py
3c	$PhCH_2$	4-PMP

Compound	R	Ar
4a	Me	Ph
4b	Me	3-Py
4c	Me	4-PMP
5a	$PhCH_2$	Ph
5b	$PhCH_2$	3-Py
5c	$PhCH_2$	4-PMP

Scheme 1. Synthesis of *endo* isomers **4a–c**, **5a–c** via 1,3-dipolar cycloaddition of enone **1** with azomethine ylides derived from imines **2a-3c.**

imines **2a–c** and **3a–c**, obtained respectively from L-alanine or L-phenylalanine[17] (Scheme 1).

In first instance, the major stereoisomers of the cycloaddition reaction, the *endo* adducts **4a–c**, **5a–c**, were subjected to the reduction of the 7-oxo function in order to study the stereochemical course of the reaction and to generate an additional stereocenter in the molecules. The reduction of the carbonyl group of **4a–c**, **5a–c** was conducted with sodium borohydride in MeOH at 0 °C (Scheme 2). The reduction took



Scheme 2. Reduction of the carbonyl group of cycloadducts **4a-4c, 5a-5c.**

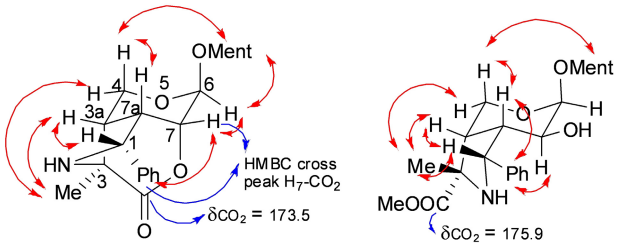


Figure 1. NMR data that confirm the structure of **6a** and **7a.**

The structure of compounds **7a–c** – **8a–c** was established by NMR spectroscopy, mostly according to diagnostic NOE interactions in their 2D-NOESY spectra (Figure 1).

Fortunately, nice crystals of **6a**, suitable for crystallography, could be obtained by keeping refrigerated a solution of the compound in acetonitrile at −20 °C for several weeks. The X-ray crystallography revealed that **6a** crystallized as a solvate accompanied with a molecule of acetonitrile (Figure 2). The

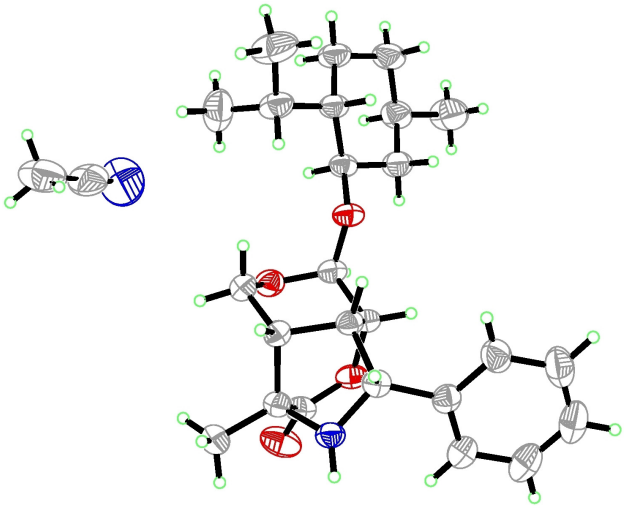


Figure 2. Crystal structure of compound **6a** (acetonitrile solvate) showing the displacement of ellipsoids of non-H atoms at 30% probability levels.

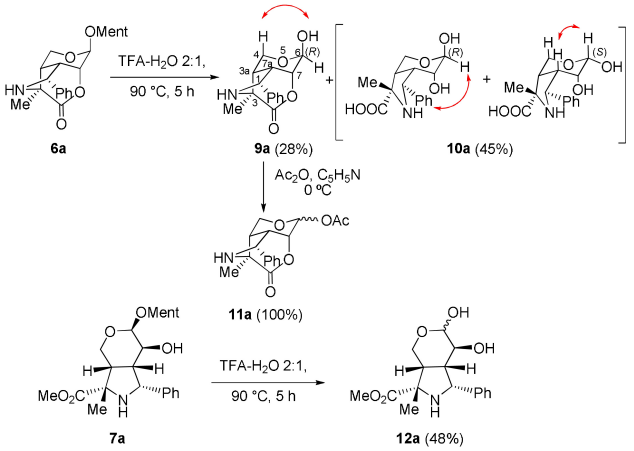
place rapidly (10 – 30 min) to afford two main products (**6a** and **7a**), which were isolated by column chromatography. The less polar and minor component of the mixture of reduction of **4a** was characterized as the lactone **6a.** The formation of **6a** was indicative that the attack of the hydride took place from the *Si* face of the carbonyl, to lead to the suitable disposition of the resulting hydroxyl group to lactonize with the methyl carboxylate substituent. As shown in Scheme 2, the alcohols **7a–c** (with *S*-configuration) were the main products in the reduction of all the respective adducts **4a–c**, following a tendency previously observed in analogous systems.[18] In fact, no lactone product was isolated in the reduction of **5a–c** and alcohols **8a–c** were the only products obtained.

crystal structure confirmed the absolute configuration not only of compound **6a**, but also the structure of the carbonyl precursor **4a** and the analogues prepared, by comparison of their spectral properties.

The diasteroselectivity observed in the reduction of the carbonyl group of pyranone derivatives may be mostly attributed to the axial orientation of the menthyloxy group due to the anomeric effect.[18] Such diastereoselectivity is probably reinforced by the substitution pattern of the pyrrolidine ring (i.e., the change of the methyl group in **4a–c** by a bulkier benzyl group in **5a–c**) that could modify its conformation. The conformational change may alter the relative orientation of the aryl group located near to the carbonyl, but in the face

opposite to that carrying the menthyloxy substituent. The selectivity in the reduction would result from the balance between the steric effects exerted by these two groups.

The next step of the synthetic sequence was the hydrolysis of the menthyl acetal. As the reduction of *endo*-**4a** gave **7a** and a considerable amount of lactone **6a**, both compounds were subjected to hydrolysis using trifluoroacetic acid (TFA)-water (2:1) at 90 °C for 5 h (Scheme 3). Thus, hydrolysis of **6a** led, after column chromatography, to the lactone hemiacetal **9a**, and the major product **10a**, which resulted from the hydrolysis of both the acetal and the lactone groups. Compound **10a** was obtained as an inseparable mixture of the hemiacetals of α (6*S*) and β (6*R*) configuration.

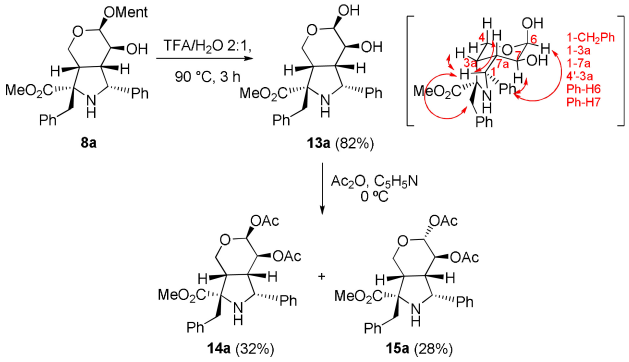


Scheme 3. Hydrolysis of the menthyloxy acetal of **6a** and **7a** (key NOE interactions for **9a** and **10a** are shown).

Interestingly, compound **9a** was isolated as a single diasteroisomer, which was assigned as 6*R* (β) as its ^{1}H NMR spectrum was very similar to that of the bicyclic moiety of its precursor **6a** (6*R*), particularly the similar values for $J_{3,4ax}$, $J_{3,4eq}$, $J_{6,7}$ and $J_{7,7a}$. Furthermore, the NOE interaction observed between the hemiacetal hydroxyl group (HO-6) and H-4ax, supported the assignment. The NMR spectra of **10a** were rather complex as we were dealing with a mixture of hemiacetals. In addition, the constrain to the chair conformation of the tetrahydropyran ring in **9a**, because of the lactone, is released and a conformational equilibrium is possible, with the consequent alteration in coupling constant values, which were already affected by the presence of the pyrrolidine ring fused to the tetrahydropyran. In spite of all these difficulties, we were able to identify the signals corresponding to each individual isomer using the NOESY and COSY spectra. Thus, the NOE contacts between the hemiacetal proton (H-6) with H-7a (shown in Scheme 3) was indicative of the 6*S* (α) configuration, as such interaction should be absent (and was not observed) for the other isomer (6*R*), which showed instead the expected H6 – Ph contact. Furthermore, the averaged values of the coupling constants for **10**-(6*S*) suggested conformational equilibrium between two chairs for the tetrahydropyran ring. The ratio of hemiacetals was established as α:β = 0.7:1, according to the ^{1}H NMR spectra.

Although conducted at 0 °C, the acetylation of **9a** led to partial isomerization of the hemiacetal group to afford **11a** as a mixture of 6*S* and 6*R* isomers in 3.5:1 ratio. The signals of the ^{1}H NMR spectrum of the mixture were fully assigned using 2D-NMR techniques, as explained above for **10a.** Interestingly, the integral of the spectrum was in agreement with the presence of just one acetyl group in the molecule of **11a**, in agreement with the HRMS, which showed the molecular ion corresponding to the monoacetylated product. Probably, because of the highly substituted environment of the pyrrolidine nitrogen atom, this amine function should be hindered to undergo acetylation. The selective acetylation of HO-6 was confirmed by the 2D-HMBC spectrum of **11a**, which showed for both stereisomers correlation between the acetyl carbonyl with H-6 and the lactone carbonyl with H-7. No correlations indicative of *N*-acetylation were observed.

Hydrolysis of **8a**, performed under the conditions employed for **6a** and **7a**, gave **13a** as a single product (82% yield), identified spectroscopically as the hemiacetal having 6*R* (β) configuration (Scheme 4). The signals of HO-6 and HO-7, which were observed in the ^{1}H-NMR spectrum of **13a** recorded in $CDCl_3$, were assigned on the basis of the 2D-COSY spectrum. The structure of **13a** was confirmed by the NOESY spectrum, which presented diagnostic NOE interactions shown in Scheme 4 for a given conformation of **13a.** However, averaged coupling constant values ($J_{7,7a}$ = 3.7, $J_{3a,4}$ = $J_{3a,4'}$ = 6.4 Hz) were indicative of conformational equilibrium for the tetrahydropyran ring (and probably also for the pyrrolidine ring).

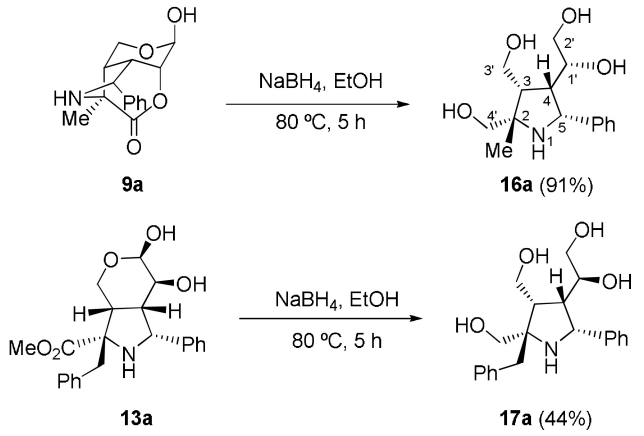


Scheme 4. Hydrolysis of the menthyloxy acetal of **8a** (key NOE interactions for **13a** are shown).

Acetylation of **13a** gave a mixture of the di-*O*-acetyl derivatives **14a** and **15a**, which were separated by column chromatography. Similar to the acetylation of **9a**, the pyrrolidine nitrogen was not acetylated. As already explained for related compounds (**11a**, **12a**) the absolute configuration of C-6 was established according to the 1D and 2D-NMR spectra. As the methyl signals of the two acetoxy groups at C-6 (AcO-6) and at C-7 (AcO-7) of **14a** appeared separated, they could be readily assigned by means of the HMBC spectrum according to

their respective correlation with C-6 and C-7 (the methyl signal at higher field corresponded to AcO-7). The conformer that satisfies the anomeric effect and shows coupling constants indicative of its presence in the conformational equilibrium, showed clear NOE interactions between H-4ax with H-7a, H–Ph with H-7 and H-6, and AcO-6 with H-4ax and H-7a. On the basis of all these evidences the configuration of C-6 in **14a** was assigned as *S* (β); hence, **15a** was the 6*R* (α) isomer.

The final step of the synthesis was the reduction of the hemiacetal and carboxylate groups of compounds **9a** and **13a.** The lactone derivative **9a** was readily reduced with $NaBH_4$ in anhydrous EtOH, under nitrogen atmosphere at 80 °C during 5 h, to afford **16a** in 91% yield (Scheme 5). The same procedure



Scheme 5. Synthesis of 2,3,4-tris-(hydroxyalkyl)-2-methyl-5-phenylpyrrolidine (**16a**) and its 2-benzyl analogue (**17a**).

applied to the methyl ester **13a** gave **17a**, although in a moderate yield (44%). The yields were even lower when the reaction was conducted at room temperature for longer times (24 h), due to partial reduction. Examples have been found on the $NaBH_4$ reduction of heterocyclic, aromatic and aliphatic esters with an excess of borohydride in MeOH,[20] or in a mixture of MeOH with THF or *t*-BuOH,[21] at the reflux temperature. The lower yield in the reduction of **13a** may be attributed to the steric hindrance of the ester function and the comparatively lower reactivity in the reduction of an ester with respect to a lactone (as **9a**). The structure of the 2,3,4-tris-(hydroxyalkyl)-2-methyl (or benzyl)-5-phenyl pyrrolidines were established by NMR spectroscopy and HRMS.

Conclusions

We report here the synthesis of enantiomerically pure 2,3,4-tris-(hydroxyalkyl) derivatives of pyrrolidines having a phenyl group in one of the positions vicinal to the ring nitrogen atom (C-5) and a tetrasubstituted carbon stereocenter on the other position (C-2), which also carries an additional methyl or benzyl substituent. The synthetic route involves simple reactions (such as reductions and hydrolysis) applied to the major adducts of the 1,3-dipolar cycloaddition of sugar enones and azomethine ylides, derived from the amino acids L-alanine and L-phenylalanine. Thus, the starting materials of the synthesis are basically natural products: a sugar (D-xylose) and the above mentioned amino acids. A number of intermediate products, with varied patterns of substitution and configurations have been prepared and fully characterized. The polyhydroxyalkyl alkaloids obtained (including some intermediate products) will be investigated as enzyme inhibitors and for other potential biological activities. They may additionally be explored as organocatalysts to induce asymmetry in synthesis.

Supporting Information Summary

The supporting information includes experimental details regarding sample preparation, the general procedures and synthetic procedures for new compounds. Copies of ^{1}H and ^{13}C NMR spectra and selected 2D NOESY spectra, as well as X ray data for compound **6a** are also provided.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: azomethine ylide · 1,3-dipolar-cycloaddition · polyhydroxyalkylpyrrolidine · pyrrolidine · sugar enone

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