Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 3897–3907

A short and highly stereoselective route to polyhydroxy-perhydroazaazulenes via a *C*-(D-*galacto*-pentopyranos-5-yl)isoxazolidine

M[a] Isabel Torres-Sánchez,[a] Pastora Borrachero,[a] Francisca Cabrera-Escribano,[a] Manuel Gómez-Guillén,[a,*] Manuel Angulo-Álvarez,[b] M[a] Jesús Diánez,[c] M[a] Dolores Estrada,[c] Amparo López-Castro[c] and Simeón Pérez-Garrido[c]

[a]*Departamento de Química Orgánica 'Profesor García González', Facultad de Química, Universidad de Sevilla, Apartado de Correos No. 553, E-41071 Seville, Spain*
[b]*Servicio de RMN, Centro de Investigación, Tecnología e Innovación de la Universidad de Sevilla (C.I.T.I.U.S.), Avda. Reina Mercedes, s/n, E-41012 Seville, Spain*
[c]*Instituto de Ciencias de Materiales de Sevilla and Departamento de Física de la Materia Condensada, C.S.I.C.-Universidad de Sevilla, Apartado de Correos No. 1065, E-41080 Seville, Spain*

Received 26 September 2005; accepted 14 October 2005
Available online 14 November 2005

Abstract—A short and efficient route to enantiomerically pure hexahydroxy- and pentahydroxy-perhydroazaazulenes, ring-homologues of castanospermine, starting from the sole isoxazolidine derivative obtained in the 1,3-dipolar cycloaddition of a D-galactose-derived nitrone and methyl acrylate, is established. The procedure allows both backbone and stereochemical modulation of the products by choice of the starting monosaccharide. Structural assignment was based on crystallographic analysis of the starting isoxazolidine and NMR techniques. The products were tested for inhibitory activity against several glycosidases.

1. Introduction

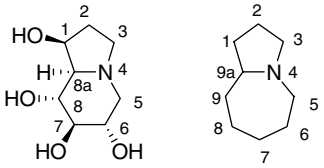
Polyhydroxy-indolizidines are a group of natural and synthetic compounds belonging to the wider class of the iminosugars (azasugars). Many of them show interesting biological activities, such as glycosidase inhibitory properties, and therefore therapeutic applications, such as immunosuppressive, anti-malarial, anti-viral, anti-cancer, and anti-diabetic agents.[1–3] Extensive efforts have been reported to obtain compounds of this kind, castanospermine **1** being one of the most representative, and a natural member of the series.[2] Analogues of **1** have also been synthesized in order to study their biological properties. The topic has been extensively reviewed in the last few years.[4–7] Diverse synthetic routes start from monosaccharide derivatives,[8] taking advantage of the configurational variety of sugars and their ability to exert asymmetric induction in the formation of new stereogenic centers. A very useful type of reaction for the synthesis of higher-chain amino sugars is the 1,3-dipolar cycloaddition reaction of olefins with *C*-glycosyl nitrones, including cyclic nitrones, in which glycosyl-isoxazolidines are regio- and stereoselectively formed.[9,10] Opening the isoxazolidine ring of the cycloadducts affords diverse kinds of higher-chain sugars; thus, we have described[11] the synthesis of C_7 and C_8 aminodialdoses by opening the cycloadduct obtained from conveniently protected *C*-glycosyl nitrones and vinyl trimethylsilane.

The perhydroazaazulene system **2** is a higher-ring homologue of indolizidine. A possible general route to new potential glycosidase inhibitors derived from **2** starts from methyl acrylate **3** (as the dipolarophile) and hexose *N*-benzyl-nitrones (as the 1,3-dipoles). Compound **3** is known to add to nitrones with high regioselectivity, so that, with few exceptions, the sole (or at least the main) product is the 5-methoxycarbonyl regioisomer.[12,13] We have briefly reported[14,15] that the cycloaddition reaction of **3** with the nitrone **4**, derived from D-galactose, affords

* Corresponding author. Tel.: +34 95 4557151; fax: +34 95 4624960; e-mail: mguillen@us.es

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.10.023

only one of the possible diastereomeric *N*-benzyl-3-(*O*-protected pentosyl)-5-methoxycarbonyl-isoxazolidines, whose hydrogenolysis, followed by reduction of the resulting lactam, leads to a 5-(O-protected pentosyl)-3-hydroxypyrrolidine. The chain of the sugar moiety in these compounds is long enough to undergo annellation in a subsequent step of the synthesis, giving rise to a seven-membered ring. This methodology might allow modulating both the ring size and the stereochemistry of the products. The synthetic versatility of this strategy is shown in Figure 1. Hence, the designed pathway would also allow the synthesis of polyhydroxy-indolizidines analogous to **1**, as well as their 5-hydroxy precursors.



We now report in detail the synthesis of two polyhydroxy-perhydroazaazulenes. To our knowledge, only one indolizidine homologue of this type has been synthesized.[16] We also include here a thorough configurational study of these molecules and their precursors, as well as the results of their biological evaluation. The first selected hexose nitrone was the O-protected D-galactose derivative **4**, which we have used for [3+2] cycloaddition reactions with other dipolarophiles.[10,11]

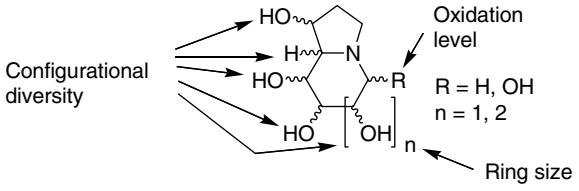
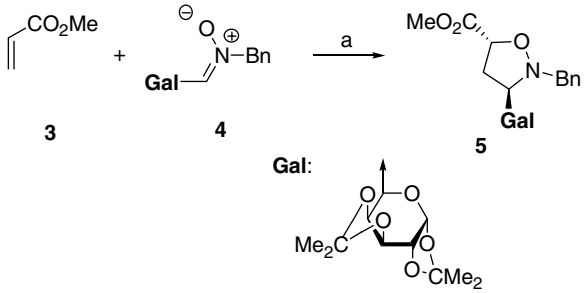


Figure 1. The synthetic versatility of the procedure, expressed on a general formula of the expected products.

2. Results

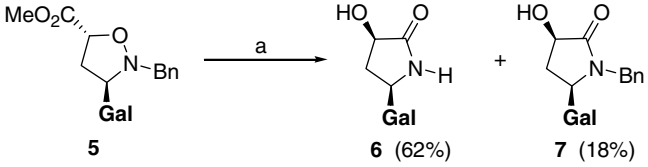
The reaction of **3** with the (*Z*)-*N*-benzyl-nitrone **4** (2:1 molar ratio) in toluene at 35 °C led with total regioselectivity to only one of the four possible diastereomeric cycloadducts—that coming from the *endo* attack of **3** to the *re* face of **4**—which was isolated as a crystalline compound **5** in 71% yield (Scheme 1). X-ray crystallographic analysis of **5** unambiguously showed, as discussed below, that it is the (2*R*) invertomer of the (3*R*,5*R*) configured diastereomer.[†]

[†] Compound **5** and the opening of its isoxazolidine ring under conditions different from those used by us have been described[17] after our first communication.[14]



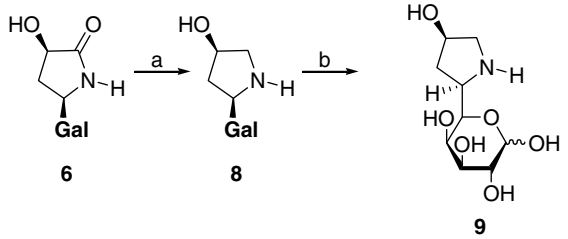
Scheme 1. Reagents and conditions: (a) Toluene, 35 °C, under Ar atmosphere (3 h), 71%.

Compound **5** was subjected to isoxazolidine-ring cleavage by treatment with hexacarbonylmolybdenum[18,19] to afford (3*R*,5*R*)-3-hydroxy-5-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)-2-oxopyrrolidine **6** and its *N*-benzyl derivative **7** in 62% and 18% yield, respectively, after column chromatography (Scheme 2). These nonopyranos-uronolactam derivatives should keep the (3*R*,5*R*) configuration coming from that of isoxazolidine C(5) and C(3) atoms, respectively. The (*R*) configuration assigned to C(5) for compounds **6** and **7** must be considered sure, since no epimerization of this center is to be expected. However, the C(3) of these compounds might have undergone epimerization. A correct assignment required the use of NMR techniques, as explained below.



Scheme 2. Reagents and conditions: (a) $Mo(CO)_6$, $MeCN/H_2O$, reflux (7 h), yields: 62% for **6**; 18% for **7**.

As we have previously reported,[14,15] the major product **6** of the foregoing reaction was reduced with lithium aluminum hydride in ether to afford 96%, after column chromatography, of (2*R*,4*R*)-4-hydroxy-2-(1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pentopyranos-5-yl)pyrrolidine **8**, whose treatment with trifluoroacetic acid (TFA), followed by cation-exchange chromatography, led to a product initially[14,15] formulated as the O-deprotected compound **9** (Scheme 3).



Scheme 3. Reagents and conditions: (a) $LiAlH_4$, ether, reflux (3 h), 96%; (b) 80% TFA, rt (24 h), 98%.