JOC*Note*

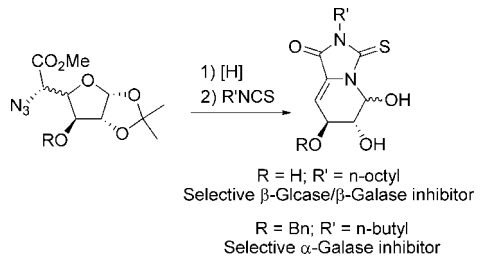
Synthesis of Thiohydantoin-Castanospermine Glycomimetics as Glycosidase Inhibitors

Matilde Aguilar-Moncayo,[†] Carmen Ortiz Mellet,[†] José M. García Fernández,[‡] and M. Isabel García-Moreno*,[†]

Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Profesor García González 1, E-41012 Sevilla, Spain, and Instituto de Investigaciones Químicas, CSIC−Universidad de Sevilla, Américo Vespucio 49, Isla de la Cartuja, E-41092 Sevilla, Spain

isagar@us.es

Received February 3, 2009



The preparation of bicyclic carbohydrate mimics related to (+)-castanospermine incorporating a thiohydantoin moiety is reported. The synthetic approach is compatible with molecular diversity-oriented strategies and involves α-azidoesters, built at the C-5/C-6 segment in gluco- or galactofuranose scaffolds, as the key precursors. Reduction to the corresponding α-amino ester and in situ coupling with isothiocyanates afford thioureidoester intermediates that undergo spontaneous cyclization to the corresponding hydantoins, β-elimination, and furanose → indolizidine rearrangement in a tandem manner. Biological evaluation of the new sp^2-iminosugar-type glycomimetics evidenced a strong influence of the nature of the substituents at the nitrogen or oxygen atoms on the glycosidase inhibitory properties.

(+)-Castanospermine (**1**) is one of a number of plant-derived polyhydroxyindolizidine alkaloids (iminosugars) that behave as competitive inhibitors of glycosidases,[1] bearing strong therapeutic potential for the treatment of diseases such as diabetes,[2] cancer,[3] and lysosomal storage disorders.[4] Analogously to the related piperidine iminocyclitol 1-deoxynojirimycin (**2**), the hydroxylation pattern of **1** matches that of D-glucose, which is translated into a high configurational specificity toward glucosidases. However, neither **1** nor **2** nor most of the analogues reported so far possess a defined configuration at the pseudoanomeric center (C-5).[5] It is therefore not surprising that they can inhibit α- and β-glucosidases simultaneously, which represents a serious drawback for clinical applications.

The selectivity among glucosidase isoenzymes is higher for **1** as compared with **2**, which has been ascribed to the rigid conformation imposed by the bicyclic skeleton at the bond analogous to C-5—C-6 in hexoses (C-8a—C-1 in the indolizidine nomenclature). Recently, we have reported a new family of castanospermine analogues that incorporates a pseudoanomeric oxygen substituent anchored in the axial orientation, as in α-glucopyranosides.[6] Interestingly, the reducing oxacastanospermine derivative **3**, in which the tertiary amine-type bridgehead nitrogen has been replaced by a neutral thiocarbamate-type nitrogen, with substantial sp^2 character (sp^2-iminosugar), was a competitive, α-selective glucosidase inhibitor.[6b] Moreover the selectivity toward different α-glucosidases was distinctly different as compared with the natural compound **1**. The endocyclic oxygen was found to be critical for the inhibitory activity, since the corresponding 2-azacastanospermine glucomimetic **4** was a 100-fold less potent inhibitor (Figure 1).[6b]

The above results allow the conclusion that the orientation of substituents at the positions neighboring the bridgehead carbon atom in indolizidine glycomimetics plays an important role in their biological activity. Introducing structural changes at this region of the molecule in a controlled manner appears, then, as a very attractive strategy to tailor the glycosidase inhibitory properties. Here we report the synthesis of a new family of castanospermine analogues in which the five-membered pyrrolidine ring has been replaced by a thiohydantoin motif (**I**) and their evaluation as glycosidase inhibitors. Formally, this structure can be considered as a hybrid of compounds **1**, **3**, and **4**. As in **1** and **3**, C-1 is linked to an oxygen substituent, which in this case exhibits an orientation close to that of OH-1 in castanospermine. The bridgehead sp^2-nitrogen is compatible with the presence of an axially anchored pseudoanomeric OH

[†] Departamento de Química Orgánica.
[‡] Instituto de Investigaciones Químicas.

(1) (a) Tyler, P. C.; Winchester, B. G. Synthesis and Biological Activity of Castanospermine and Close Analogues In *Iminosugars as Glycosidase Inhibitors*; Stütz, A., Ed.; Wiley-VCH: Weinheim, Germany, 1999; p 125. (b) Asano, N. In *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R. , Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 7. (c) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625.

(2) (a) Compain, P.; Desvergnes, V.; Liautard, V.; Pillard, C.; Toumieux, S. In *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 327. (b) Somsak, L.; Nagy, V.; Hadazy, Z.; Docsa, T.; Gergely, P. *Curr. Pharm. Design.* **2003**, *9*, 1177.

(3) Wrodnigg, T. M.; Steiner, A. J.; Ueberbacher, B. J. *Anticancer Agents Med. Chem.* **2008**, *8*, 77.

(4) (a) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683. (b) Fan, J.-Q. In *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 225.

(5) A notable exception corresponds to compounds having the exocyclic pseudoglycosidic oxygen replaced by carbon (iminosugar C-glycosides). For recent reviews, see: (a) Compain, P. In *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 65. (b) Vogel, P., Gerber-Lemaire, S., Juillerat-Jeanneret, L. In *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 87. (c) Zou, W. *Curr. Top. Med. Chem.* **2005**, *5*, 1363.

(6) (a) García-Moreno, M. I.; Díaz-Pérez, P.; Ortiz Mellet, C.; García Fernández, J. M. *Eur. J. Org. Chem.* **2005**, 2903. (b) Díaz Pérez, V. M.; García-Moreno, M. I.; Ortiz Mellet, C.; Fuentes, J.; Díaz Arribas, J. C.; Cañada, F. J.; García Fernández, J. M. *J. Org. Chem.* **2000**, *65*, 136. (c) Jiménez Blanco, J. L.; Díaz Pérez, V. M.; Ortiz Mellet, C.; Fuentes, J.; García Fernández, J. M.; Díaz Arribas, J. C.; Cañada, F. J. *Chem. Commun.* **1997**, 1969.

10.1021/jo900231b CCC: $40.75
Published on Web 03/31/2009

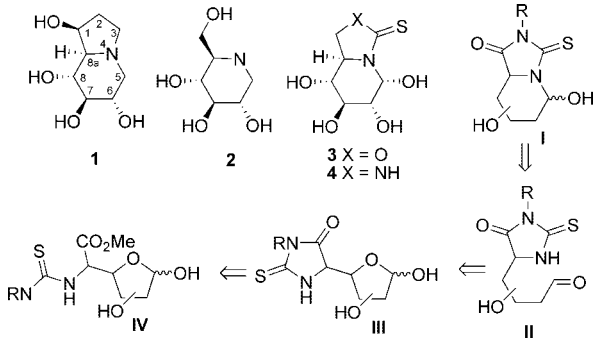


FIGURE 1. Structure of (+)-castanospermine (**1**), 1-deoxynojirimycin (**2**) and sp^2-iminosugar-type castanospermine analogues (**3** and **4**). General structure of the target thiohydantoin-castanospermine glycomimetics (I) and the corresponding retrosynthetic analysis is included.

substituent, as in the sp^2-iminosugars **3** and **4**. Moreover, the presence of a second endocyclic nitrogen offers the possibility to generate molecular diversity at this point.

(Thio)hydantoins and their bi- and tricyclic derivatives represent an important class of biologically active molecules with broad medical[7] (anticancer, anticonvulsant, antimuscarinic, antiulcer, and antiarrhythmic), agrochemical[8] (herbicidal and fungicidal), and synthetic applications.[9] Their preparation has been broadly studied,[10−12] with special attention to the synthesis of C-glycosylated derivatives because of their resemblance to natural nucleosides.[13] According to the retrosynthetic scheme depicted in Figure 1, the target thiohydantoin-piperidine fused bicyclic core could be assembled by the intramolecular nucleophilic addition of the nitrogen atom of the preformed five-membered heterocycle to the aldehyde group of a monosaccharide precursor in the open-chain form (**II**). The key synthetic intermediate would be the pseudo-*C*-nucleoside derivative **III**, which at its turn can be constructed from the corresponding furanose thioureidoester **IV**. A hydroxylation profile of stereochemical complementarity with (+)-castanospermine in the final bicyclic compounds implies the D-gluco configuration in the furanose precursors.

In a first approach, 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose **5**[14] was considered as a suitable starting material. Attempts to oxidize the primary hydroxyl into a carboxylate group resulted, however, in concomitant 6,3-lactone formation. To avoid this unwanted side reaction, the known 6-*O*-tetrahydropyranyl derivative **6**[14] was transformed into the corresponding 3-*O*-acetyl derivative **7**, which through a reaction sequence involving acid hydrolysis of the tetrahydropyranyl group, TEMPO oxidation of alcohol **8**,[15] and in situ esterification of the resulting carboxylic acid with methanol and 2,6-dichlorobenzoyl chloride (DCBzCl)[16] afforded the α-azido methyl ester **9**. Catalytic hydrogenation of **9** to give the corresponding α-amino ester intermediate proved to be troublesome due to O → N acetyl migration and 6,3-lactone formation, as seen from a mass spectrum of the reaction mixture. To minimize this problem the crude reduction mixture was reacted with butyl isothiocyanate in pyridine in the presence of triethylamine. The resulting thiourea derivative (**10**) underwent spontaneous Edman's-like reaction with formation of the thiohydantoin heterocycle (→ **11**), followed by fast elimination to the corresponding α,β-unsaturated carbonyl derivative (**12**), cleavage of the acetonide group, and rearrangement of the furanose pseudo-*C*-nucleoside intermediate into the target indolizidine **13** (Scheme 1).

This tandem transformation is remarkable: although formation of exocyclic double bonds in thiohydantoins bearing hydroxyalkyl substituents is well-documented,[17] acetal cleavage under basic conditions was unexpected. Most probably, the anomeric position is activated intramolecularly by the thiohydantoin moiety, thereby promoting hydrolysis of the isopropylidene group in the presence of water, which is liberated during the elimination reaction. The NH nitrogen atom then undergoes intramolecular attack to the masked aldehyde group of the reducing monosaccharide to zip up the bicyclic skeleton. Deceivingly, the global yield was very low, mainly due to the penalty associated with the formation of *N*-acyl byproduct during reduction of **9**.

Because configuration at the position equivalent to C-4 in glucose (C-8 in the final compound) is lost during the synthesis, starting from D-glucose or D-galactose precursors becomes irrelevant. Previous work had shown that 5-amino-5-deoxy galactofuranose derivatives bearing an acetyl group at C-3 do not experience acetyl migration,[6a] the main handicap in the glucose route. Accordingly, the D-galactofuranose-derived α-azidoester **16**, obtained from the known 5-azido-3-*O*-acetyl-5-deoxy derivative[16] **15** by oxidation and esterification as above, afforded the thiohydantoin-castanospermine bicycle **13** in a more satisfactory 70% yield after reduction and coupling with butyl isothiocyanate (→ **17** and **18**). Conventional sodium methoxide deacetylation of **13** afforded the fully unprotected derivative **14** (Scheme 1).

Although the galactose route allowed proof of the synthetic concept, the accessibility of the requested azidoalcohol **15** is more costly as compared with the D-gluco precursor **6**. To fully exploit the potential of the general approach to introduce molecular diversity in the new sp^2-iminosugar structure, an

(7) (a) Spinks, A.; Waring, W. S. *Prog. Med. Chem.* **1963**, *3*, 313. (b) Struck, R. F.; Kirk, M. C.; Rice, L. S.; Suling, W. J. *J. Med. Chem.* **1986**, *29*, 1319. (c) Matsukura, M.; Daiku, Y.; Ueda, K.; Tanaka, S.; Igarashi, T.; Minami, N. *Chem. Pharm. Bull.* **1992**, *40*, 1823. (d) Brouillete, W. J.; Brown, G. B. *J. Med. Chem.* **1994**, *37*, 3289. (e) Ahmed, I. K.; Philippe, B. *Tetrahedron* **1998**, *54*, 4859. (f) Paquette, L. A.; Brand, S.; Behrens, C. *J. Org. Chem.* **1999**, *64*, 2010. (g) Somsák, L.; Kovács, L.; Tóth, M.; Ösz, E.; Szilágyi, L.; Györgydeák, Z.; Dinya, Z.; Docsa, T.; Tóth, B.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 2843.

(8) (a) Mizuno, T.; Kino, T.; Ito, T.; Miato, T. *Synth. Commun.* **2000**, *30*, 1675. (b) Mappes, C. J.; Pommer, E. H.; Rentzea, C.; Zeeh, B. *U.S. Patent 4,198,423*, 1980; *Chem. Abstr. 93*, 71784. (c) Mio, S.; Ichinose, R.; Goto, K.; Sugai, S.; Sato, S. *Tetrahedron* **1991**, *47*, 2111. (d) Garribba, E.; Micera, G.; Chruscinska, E. *J. Chem. Res., Synop.* **2001**, *10*, 408. (e) Nakajima, N.; Matsumoto, M.; Kirihara, M.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1996**, *52*, 117. (f) Gerwick, B. C.; Crouse, G. D.; Murdoch, M. G.; Green, S. B.; Heim, D. R. *Pestic. Biochem. Physiol.* **1996**, *55*, 210.

(9) (a) Blériot, Y.; Simone, M. I.; Wormald, M. R.; Dwek, R. A.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2006**, *17*, 2276. (b) Ulgheri, F.; Orrù, G.; Crisma, M.; Spanu, P. *Tetrahedron Lett.* **2004**, *45*, 1047. (c) Koós, M.; Steiner, B.; Langer, V.; Gyepesová, D.; Durík, M. *Carbohydr. Res.* **2000**, *328*, 115. (d) Bodanszky, M. In *Principles of Peptide Synthesis*; Springer-Verlag: Berlin, 1993; p 95.

(10) De Oliveira, S. M.; Paraíso da Silva, J. B.; Hernandes, M. Z.; Alves de Lima, M. C.; Galdino, S. L.; da Rocha Pitta, I. *Quím. Nova* **2008**, *31*, 614.

(11) (a) Klason, P. *Chem. Ztg.* **1890**, *14*, 543. (b) Holan, G.; Samuel, E. *J. Chem. Soc.* **1961**, 4660.

(12) (a) Ware, E. *Chem. Rev.* **1950**, *46*, 403. (b) Edward, J. T. *Chem. Org. Sulfur Comp.* **1966**, *2*, 287. (c) Li, J.-P.; Ma, C.-M.; Qu, G.-R. *Synth. Commun.* **2005**, *35*, 1203.

(13) Khodair, A. I. A.; El Ashry, E. S. H.; Al-Masoudi, N. A. L. *Monatsh. Chem.* **2004**, *135*, 1061.

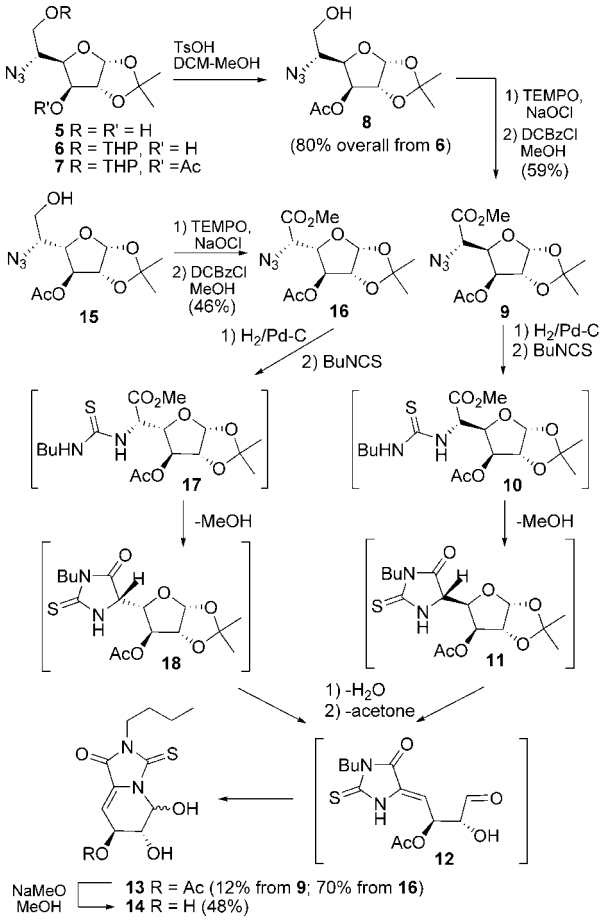
(14) Dax, K.; Gaigg, B.; Grassberger, V.; Kölblinger, B.; Stütz, A. E. *J. Carbohydr. Chem.* **1990**, *9*, 479.

(15) Hadwiger, P.; Mayr, P.; Tauss, A.; Stütz, A. E.; Nidetzky, B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1683.

(16) Brown, J. M.; Christodoulou, C.; Reese, C. B.; Sindona, G. *J. Chem. Soc, Perkin Trans. 1* **1984**, 1785.

(17) Winterfeld, G. A.; Khodair, A. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2003**, 1009.

SCHEME 1. Synthesis of Thiohydantoin-Castanospermine sp²-Iminosugars from D-Gluco and D-Galacto Precursors



alternative protecting group strategy was explored. Thus, compound **6** was transformed into the *p*-methoxybenzyl ether azidoalcohol **19**, which was subjected to the oxidation-esterification transformation to give the corresponding azidoester **20**. Subsequent reduction of the azido group and reaction of the intermediate aminoester with butyl and octyl isothiocyanates initiated the reaction cascade involving thiourea formation, cyclization to the thiohydantoin pseudo-*C*-nucleoside, β-elimination and furanose → indolizidine rearrangement, to give the thiohydantoin-castanospermine glycomimetics **21** and **22** in one pot (60% yield). Removal of the *p*-methoxybenzyl ether group under neutral conditions using DDQ in CH_2Cl_2/water mixtures afforded the fully unprotected ring-modified castanospermine analogues **14** and **23** in reasonable yields (Scheme 2). The disclosed reaction sequence allows access to the target sp²-iminosugars in just four separate steps from the readily available glucofuranose starting material **6**. The strategy is compatible with the introduction of different substituents not only at N-2 in the thiohydantoin ring, by selecting different isothiocyanates reagents, but also at C-7 in the indolizidine skeleton. To illustrate this aspect, the 3-*O*-benzyl derivative **24** was synthesized and transformed into the 7-*O*-benzyl indolizidine derivative **26** via the corresponding azidoester **25**.

The ^{1}H NMR spectra of compounds **13**, **14**, **21**−**23**, and **26** evidenced the occurrence of both the α and β diastereomers at the hemiaminal center (α:β ratio ca. 1:0.3; see Supporting Information), which strongly contrasts with that encountered for the thiocarbamate and thiourea analogues **3** and **4** where

SCHEME 2. Synthesis of Thiohydantoin-Castanospermine sp²-Iminosugars from D-Gluco Precursors

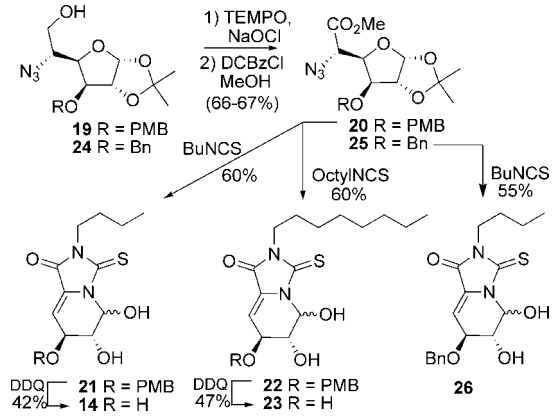


TABLE 1. Inhibition Constants (K_i, μM) for Thiohydantoin-Castanospermine Glycomimetics 14, 23, and 26; Data for Castanospermine (1) and sp²-Castanospermine Analogues 3 and 4 Included for Comparison[a]

enzyme	1	3	4	14	23	26
α-glucosidase (yeast)	1500	40	4200	n.i.	n.i.	n.i.[b]
β-glucosidase (almonds)	1.5	n.i.	n.i.	n.i.	59	n.i.
β-glucosidase/β-galactosidase (bovine liver)	n.d.	n.i.	n.d.	359	67	n.i.
β-galactosidase (*E. coli*)	n.d.	n.d.	n.d.	528	426	n.i.
α-galactosidase (green coffee)	n.d.	n.i.	n.d.	n.i.	n.i.	111

[a] The inhibition was of the competitive type in all cases. [b] No inhibition detected at 1 mM concentration.

exclusively the α anomer was observed in solution.[6] Most probably, the presence of the C-8═C-8a double bond endows the six-membered heterocycle with a much higher flexibility, allowing conformations that fulfill the anomeric effect for both possible orientations of the pseudoanomeric hydroxyl group with relatively small differences in stability and low interconversion barriers. Actually, the H−H coupling constants around the piperidine ring support the ^6E and ^5E envelope conformations for the α and β series, respectively, with the pseudoanomeric OH in axial disposition. The observation of long-range coupling constants in the later case is consistent with this assignment and further underlines the utmost importance of the anomeric effect in the conformational properties of sp²-iminosugars.

The inhibitory activities of the thiohydantoin-type indolizidine glucomimetics **14**, **23**, and **26** for α-glucosidase (yeast), β-glucosidase (almonds), β-glucosidase/β-galactosidase (bovine liver, cytosolic), β-galactosidase (*E. coli*), and α-galactosidase (green coffee beans), in comparison with data for (+)-castanospermine and the related sp²-iminosugar analogues **3** and **4**, are summarized in Table 1. None of the new compounds inhibited α-mannosidase (jack bean) or β-mannosidase (*Helix pomatia*), in agreement with the configurational pattern at the positions equivalent to C-2 and C-3 in the glycopyranoside substrates. Compound **14** behaved as a moderate inhibitor of β-glucosidase/β-galactosidase (bovine liver, cytosolic) and β-galactosidase (*E. coli*), in stark contrast with the potent and very selective inhibition of yeast α-glucosidase by the reducing cyclic thiocarbamate glucomimetic **3**. Replacement of the *n*-butyl substituent into an *n*-octyl chain significantly increases the inhibition potency toward the β-glucosidases. Remarkably, incorporation of the benzyl substituent at O-7 results in a sharp shift of the selectivity toward α-galactosidase.

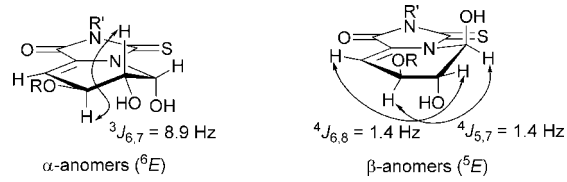


FIGURE 2. Conformations of the α and β diastereomers in thiohydantoin-castanospermine glycomimetics with indication of diagnostic ^{1}H coupling constants.

The presence of the double bond in **14** and **23**−**26** prevents a direct comparison of structure−activity relationships with compounds **1**, **3**, and **4**. The triol system at positions equivalent to C-2, C-3, and C-4 in monosaccharides is involved in hydrogen bond networks with amino acids at the active site of glycosidases, contributing to the binding, stability, and selectivity. However, β-glucosidases and galactosidases are generally not exigent considering configuration at C-4. On the other hand, incorporation of long alkyl chains at the vicinity of the endocyclic nitrogen has been shown to strongly stabilize the β-glucosidase-inhibitor complex for classical as well as sp^2-iminosugars.[18] The present results further underline the importance of these nonglyconic interactions and provide new clues to attain anomeric selectivity.

In summary, we have described an efficient synthetic route for the preparation of ring-modified castanospermine analogues incorporating a thiohydantoin ring in their structures. The method is based on the ability of the carbonyl group of a monosaccharide precursor to act as the electrophilic target for the nitrogen atom of the preformed five-membered heterocycle. The synthetic route involves α-azido esters as the key intermediates and implies only two steps, namely, reduction to the corresponding α-aminoesters and coupling with an isothiocyanate, with no need for purification of the reaction intermediates. The procedure is very well suited for the introduction of molecular diversity at both the five-membered and the six-membered ring in the bicyclic skeleton. The glycosidase inhibition results evidence the dramatic impact of such structural modifications in the biological activity and illustrate the importance of developing versatile synthetic methodologies for structure−activity studies and inhibitor optimization.

(18) Aguilar, M.; Gloster, T. M.; García-Moreno, I.; Ortiz Mellet, C.; Davies, G. J.; Llebaria, A.; Casas, J.; Egido-Gabás, M.; García Fernández, J. M. *ChemBioChem* **2008**, *9*, 2612, and references therein.

Experimental Section

General Procedure for the Preparation of (5*RS*,6*R*,7*S*)-7-*O*-Acyl(alkyl)-2-aza-8,8a-dehydro-5,6-dihydroxy-1-oxo-3-thioxoindolizidine (13, 21, 22, and 26). A solution of azidoester **9**, **16**, **20**, or **25** (0.59 mmol) in MeOH (4 mL) was hydrogenated at atmospheric pressure for 1 h using 10% Pd/C (78 mg) as catalyst. The suspension was filtered through Celite and concentrated. To a solution of the resulting aminoester in pyridine (3.0 mL) were added Et_3N (0.5 mL) and the corresponding alkyl isothiocyanate (0.71 mmol), and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the resulting residue was coevaporated several times with toluene and purified by column chromatography.

Data for (5*RS*,6*R*,7*S*)-7-*O*-Acetyl-2-aza-2-butyl-8,8a-dehydro-5,6-dihydroxy-1-oxo-3-thioxoindolizidine (13) as an Example. Yield (70%); α:β ratio 1:0.3 (H-4 integration); $[\alpha]_D$ +164.6 (*c* 1.0, CH_3OH); IR (KBr) ν_{max} 3425, 2962, 2930, 1740, 1614, 1510, 1420, 1260, 1080 cm^{-1}. α anomer: R_f 0.30 (20:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (d, 1 H, $J_{5,6}$ = 3.6 Hz, H-5), 5.95 (d, 1 H, $J_{7,8}$ = 2.7 Hz, H-8), 5.73 (dd, 1 H, $J_{6,7}$ = 8.9 Hz, H-7), 3.94 (dd, 1 H, H-6α), 3.80 (m, 2 H, CH_2N), 2.15 (s, 3 H, MeCO), 1.61 (m, 2 H, CH_2), 1.32 (m, 2 H, CH_2CH_3), 0.90 (t, 3 H, $^3J_{H,H}$ = 7.3 Hz, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 177.1 (CS), 171.1 (*C*OMe), 160.7 (*C*O_2Me), 128.6 (C-8a), 109.4 (C-8), 75.1 (C-5), 70.0 (C-6), 69.6 (C-7), 41.5 (CH_2N), 29.7 (CH_2), 21.0 (*Me*CO), 20.0 (CH_2CH_3), 13.6 (CH_3). β anomer: R_f 0.32 (20:1 CH_2Cl_2/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (dd, 1 H, $J_{7,8}$ = 5.3 Hz, $J_{6,8}$ = 1.0 Hz, H-8), 5.92 (dd, 1 H, $J_{5,6}$ = 2.7 Hz, $J_{5,7}$ = 0.9 Hz, H-5), 5.41 (ddd, 1 H, $J_{6,7}$ = 3.0 Hz, H-7), 4.33 (m, 1 H, H-6), 3.80 (m, 2 H, CH_2N), 2.08 (s, 3 H, MeCO), 1.61 (m, 2 H, CH_2), 1.32 (m, 2 H, CH_2CH_3), 0.90 (t, 3 H, $^3J_{H,H}$ = 7.3 Hz, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 177.8 (CS), 170.3 (*C*OMe), 161.0 (*C*O_2Me), 130.5 (C-8a), 105.1 (C-8), 76.9 (C-5), 67.9 (C-6), 67.1 (C-7), 41.3 (CH_2N), 29.7 (CH_2), 20.9 (*Me*CO), 20.0 (CH_2CH_3), 13.6 (CH_3); FABMS: *m*/*z* 355 (20, $[M + Na]^+$). Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91; S, 10.20. Found: C, 49.29; H, 5.55; N, 8.54; S, 9.76.

Acknowledgment. We thank the Spanish Ministerio de Educación y Ciencia (contract numbers CTQ2007-61180/PPQ and CTQ2006-15515-C02-01/BQU) and the Junta de Andalucía for financial support. The MEC is also acknowledged for a doctoral fellowship (to M.A.-M.)

Supporting Information Available: General experimental details, full purification, characterization data and NMR spectra for the prepared compounds and experimental procedures for determination of glycosidase inhibition constants (K_i). This material is available free of charge via the Internet at http://pubs.acs.org.

JO900231B