JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of Multibranched Australine Derivatives from Reducing Castanospermine Analogues through the Amadori Rearrangement of *gem*-Diamine Intermediates: Selective Inhibitors of *β*-Glucosidase

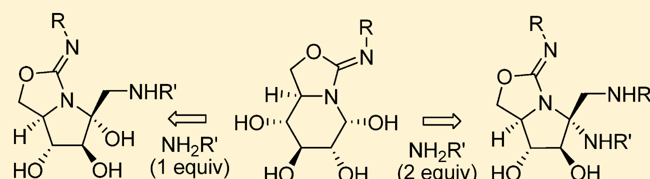
Elena M. Sánchez-Fernández,[†] Eleuterio Álvarez,[‡] Carmen Ortiz Mellet,*[,†] and José M. García Fernández*[,‡]

[†]Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, c/Profesor García González 1, E-41012 Sevilla, Spain

[‡]Instituto de Investigaciones Químicas, CSIC – Universidad de Sevilla, c/Américo Vespucio 49, Isla de la Cartuja, E-41092 Sevilla, Spain

Supporting Information

ABSTRACT: A practical one-pot synthesis of bi- and triantennated australine analogues from a pivotal sp^2-iminosugar-type reducing castanospermine precursor is reported. The transformation involves a *gem*-diamine intermediate that undergoes the indolizidine → pyrrolizidine Amadori-type rearrangement and proceeds under strict control of the generalized anomeric effect to afford a single diastereomer. The final compounds behave as selective competitive inhibitors of *β*-glucosidase and are promising candidates as pharmacological chaperones for Gaucher disease.



INTRODUCTION

Iminosugar-type glycomimetics have proven instrumental as modulators of biological processes involving carbohydrate processing enzymes, which has implications in the development of therapies against diabetes, infection, cancer, cystic fibrosis, or lysosomal storage disorders, among others.[1] Their broad range of potential medical applications has been a continuous motivation for synthetic chemists, and a plethora of analogues differing in the core structure, stereochemistry, and substitution profile has been reported.[2,3] In general, the configurational selectivity of iminosugars toward glycosidases can be predefined by matching the hydroxylation pattern of the sugar moiety that is split off by the action of the target enzyme in the putative enzyme substrate, the glycone moiety. Conversely, discrimination between glycosidases acting on glycoside anomers or between isoenzymes with different cell or organelle locations, whose substrates share the same glycone, remains very challenging and is the major bottleneck for the application of iminosugars in the clinic. Recent work has shown that the installation of nonglycone substituents in an iminosugar core capable of providing additional interactions with amino acids at the vicinity of the catalytic site significantly improves the glycosidase targeting abilities.[4] *N*-Substitution of the endocyclic nitrogen has been most often implemented toward this end, since modifications at this region of the molecule is well tolerated by several glycosidases. Polyhydroxylated indolizidine and pyrrolizidine iminosugars, which include some of the iminosugar representatives with the broadest range of biological activities such as castanospermine (**1**) or australine (**2**), are not amenable to this optimization approach due to the bridgehead location of the endocyclic nitrogen, however (Figure 1). Incorporation of aglycone-type substituents at the pseudoanomeric carbon, thereby emulating the structure of the natural glycosides, appears as an alternative biomimetic approach. Unfortunately, iminosugar derived *O*-, *S*-, or *N*-glycoside mimics suffer from the chemical lability of aminal, thioaminal, or *gem*-diamine functionalities.[5] Pseudo-*C*-glycoside structures have been proposed instead, but their preparation involves relatively long synthetic sequences that increase in complexity if

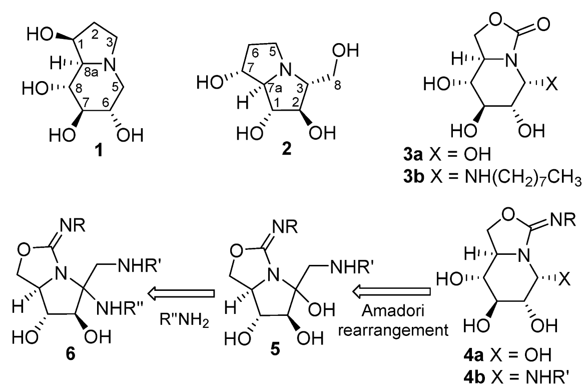


Figure 1. Structures of castanospermine (**1**), australine (**2**), and of the sp^2-iminosugar analogues **3a,b** and **4a,b**, with indication of the general strategy to access the title compounds **5** and **6**.

Received: November 5, 2014
Published: November 12, 2014

 © 2014 American Chemical Society

more than one substituent is to be attached.[6] The development of molecular diversity-oriented methodologies for the preparation of substituted multiantennated iminosugars is particularly appealing given that many medically relevant glycosidases, such as those that are dysfunctional in glycosphingolipid-related metabolic disorders, act on substrates with branched aglycone moieties.[7]

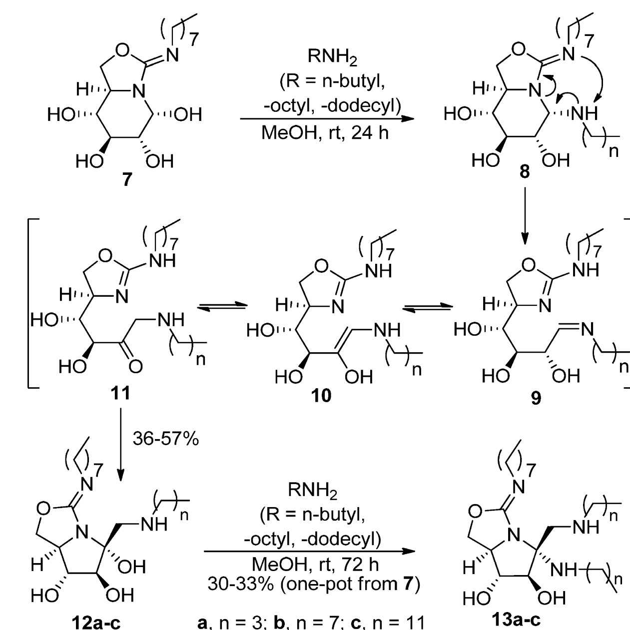
We have previously shown that replacement of the amine nitrogen of iminosugars into a pseudoamide-type nitrogen, with a high sp^2-hybridation character (sp^2-iminosugars, e.g., **3a**),[8] drastically modifies the stereoelectronic and chemical properties of the molecule, allowing access to unprecedented castanospermine-related *N*-glycosides (e.g., **3b**) exhibiting antiproliferative activity in breast cancer cells.[9] In these compounds the *gem*-diamine functionality is stabilized by a very efficient overlapping between the π-type orbital hosting the lone pair in the endocyclic nitrogen and the σ^*-antibonding orbital of the axially oriented paseudoanomeric carbon−nitrogen bond. We conceived that, under appropriate conditions, bicyclic isourea *gem*-diamine glycomimetics such as **4b**, generated by the reaction of amines with reducing precursors of general structure **4a**, might be susceptible to undergo an indolizidine → pyrrolizidine rearrangement reminiscent of the classical glycosylamine → 1-amino-1-deoxyketose Amadori rearrangement in the parent monosaccharide series,[10] providing a protecting group-free entry to *C*-substituted australine-related glycomimetics. Interestingly, the resulting Amadori-type product **5** still would possess a masked aldehyde group that is further susceptible to react with a second molecule of amine to give a pseudo-*N*-glycoside analogue **6** (Figure 1). Considering that the reported methodology for the preparation of isourea-type sp^2-iminosugars **4a** already allows the incorporation of a variety of R substituents,[11] up to three nonglycone groups can be introduced through this reaction sequence onto a pyrrolizidine scaffold, offering a versatile tool to finely control the affinity and selectivity toward glycosidases. As a proof of concept, here we report the one-pot preparation of multitail amphiphilic australine analogues behaving as selective inhibitors of β-glucosidase.

■ RESULTS AND DISCUSSION

The Amadori rearrangement can proceed in one pot following the reaction of a substrate bearing a masked 2-hydroxyaldehyde segment with an amine. For the purpose of this work, we selected the 3-(*N*-octylimino)-2-oxacastanospermine derivative **7**, a selective inhibitor of human lysosomal β-glucosidase,[12] as the pivotal aldehyde precursor and *n*-butyl, -octyl, and -dodecylamine as the amine partners to test the potential of the approach to generate molecular diversity. The transformation involves as the key step the ring opening of a *gem*-diamine intermediate (**8**; identified by NMR in the reaction mixture, but not isolated) to give a transient Schiff base (**9**). The presence of the basic isourea functionality in **7** was expected to facilitate this process by enabling a concerted mechanism involving intramolecular proton transfer from the amino to the closely located imino group. By analogy with the accepted mechanism for the Amadori rearrangement,[10a] the Schiff base **9** is assumed to be in equilibrium with the corresponding enol form (**10**; enamine−aldimine tautomerism) that further would proceed to give the more stable α-aminoketone derivative (**11**).

None of the species **9**−**11** were stable enough to be isolated. Subsequent nucleophilic addition of the isourea endocyclic nitrogen to the carbonyl group to zip up the pyrrolizidine skeleton is a fast and thermodynamically favored process under the reaction conditions, affording the reducing biantennated australine derivatives **12a**−**c**. These pseudo-*C*-nucleoside derivatives were the major species in the final reaction mixtures when using an equimolecular proportion of **7** and the corresponding amine reagent. If the proportion of the amine is doubled, formation of the corresponding australine *gem*-diamine derivatives takes place, affording the triantennary adducts **13a**−**c**. In all cases, conversions into the desired products ranged between 70% and 80% as assessed by NMR. Although purification of the amphiphilic polyamine compounds turned to be troublesome and handicapped the isolated yields (30−57%), the methodology still compares very favorably with the current multistep approaches for polyantennated iminosugars (Scheme 1).

Scheme 1. Synthesis of the Bi- and Triantennated Australine Analogues 12a−c and 13a−c from the Reducing Castanospermine Derivative 7 via Amadori Rearrangement



The six-to-five-membered azaheterocycle ring contraction on going from indolizidines **7** and **8** to pyrrolizidines **12a**−**c** and **13a**−**c**, consistent with the australine-type skeleton of the final products, was unequivocally confirmed by ^{1}H and ^{13}C NMR spectroscopy. Thus, the presence of the geminally coupled H-8a and H-8b system in the proton spectra and the carbon resonance at 55.2−51.0 ppm for the amine-linked methylene carbon C-8 (see the Experimental Section) are indicative of the 1-amino-1-deoxyketohexose-type structure characteristic of Amadori products. The high field shift of the pseudoanomeric carbon resonance C-3 in the *gem*-diamine derivatives **13a**−**c** (91.6−91.7 ppm) as compared with the reducing counterparts **12a**−**c** (100.9 ppm) additionally confirms the involvement of this position in ring closing.

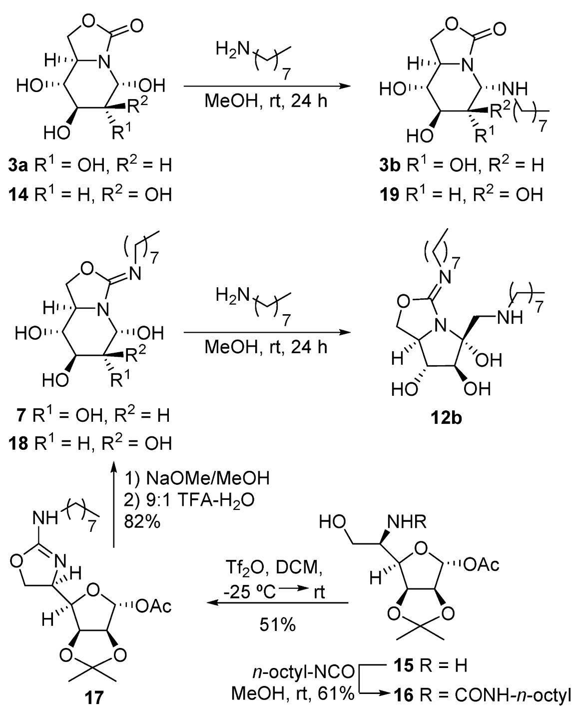
The efficiency of the Amadori transformation of isourea **7** upon reaction with amines is remarkable. It should be emphasized that *gem*-diamines derived from homologous carbamate-type indolizidines, such as **3b**, have been previously

reported to be highly stable.[8b,9] In order to rule out that this apparent discrepancy was the result of experimental divergences or structural misassignment, a control experiment was conducted by comparing the outcome of the reactions of the castanospermine-related carbamate- and isourea-type derivatives **3a**[13] and **7**[12] with *n*-octylamine with that of the corresponding C-6 epimers **14**[14] and **18** under identical conditions. Since the Amadori rearrangement involves the loss of chirality at the position vicinal to the pseudoanomeric carbon, C-6 epimeric indolizidine precursors should lead to identical pyrrolizidine products, according to the mechanistic pathway depicted in Scheme 1. On the contrary, if the reaction stops at the *gem*-diamine species, the chirality at C-6 must be retained.

The reducing isourea-type 6-*epi*-castanospermine derivative **18** had not been previously reported. Its synthesis was accomplished in three steps from the known 5-amino-5-deoxymannofuranose derivative **15** by reaction with *n*-octyl isocyanate, treatment of the resulting *vic*-hydroxyurea adduct **16** with trifluoromethanesulfonic anhydride (Tf_2O) to afford the 2-aminooxazoline derivative **17**, and subsequent removal of the acetate and isopropylidene protecting groups. The results fully corroborated the differences in reactivity for both series of compounds: the C-6 epimeric bicyclic carbamates **3a** and **14** afforded the C-6 epimeric α-configured *gem*-diamines **3b** and **19**, whereas the C-6 epimeric bicyclic isoureas **7** and **18** provided the same pyrrolizidine derivative **12b** as the major reaction product (Scheme 2).

The NMR spectroscopic data for **3b** were identical to those previously reported,[9b] with vicinal proton−proton coupling constants about the six-membered azaheterocyclic ring consistent with a chair conformation and with the α-configuration at the pseudoanomeric position. In the case of the C-6 epimer **19**, the *gauche* relative disposition of the H-5 and H-6 protons in the chair conformation for either of the two possible pseudoanomeric configurations, a scenario analogous to that encountered for H-1 and H-2 in mannopyranosyl glycosides, makes the configurational assignment more delicate. Fortunately, X-ray diffraction confirmed both the *gem*-diamine structure and the α-configuration, with the octylamino substituent in the axial orientation (Figure 2). Neither **3b** nor **19** underwent the Amadori rearrangement even when the reaction was conducted at 65 °C or after prolonging the reaction time for 3 days. The data supports our starting hypothesis about the key role of the exocyclic imino group in **8** to promote the Amadori rearrangement and is consistent with the intramolecular proton transfer indicated in Scheme 1 as the driving force for the indolizidine → pyrrolizidine isomerization.

Scheme 2. Comparative Analysis of the Reaction of C-6 Epimeric Carbamate- (3a and 14) and Isourea-type Castanospermine Derivatives (7 and 18) with Octylamine



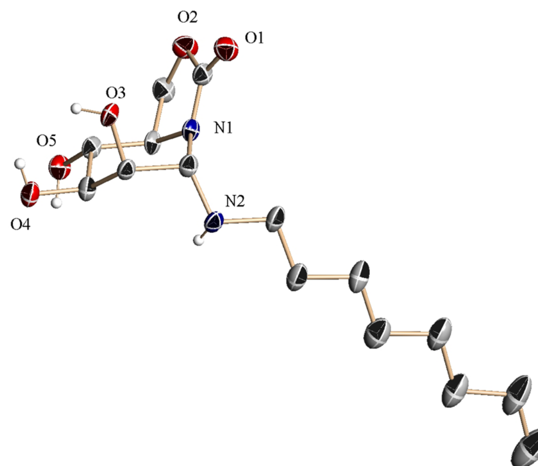


Figure 2. Ortep drawing of the crystal structure of compound **19** with 50% probability ellipsoids. The carbon atom labeling and their hydrogen atoms are omitted for clarity.

Both the bi- and triantennated australine analogues **12a−c** and **13a−c** existed as single diastereomers that kept their configurational integrity in solution. The hemiaminal and *gem*-diamine functionalities, respectively, in these systems are thus perfectly stable and do not undergo mutarotation with time to give a mixture of anomers, what is significantly different from that observed in the case of classical iminosugars. NOESY spectra evidenced an intense cross-peak between H-2 (see Figure 1 for atom notation) in the pyrrolidine ring and one of the methylene protons H-8 (H-8a), but not with the other (H-8b). This, together with the absence of an NOE cross-peak between H-7a and H-8a or H-8b, supports a *cis*-relationship between OH-2 and C-8, corresponding to a 3-*epi*-australine configurational pattern. The pyrrolidine ring adopts a conformation close to an envelope E_3 with the pseudoanomeric hydroxyl or alkylamino substituent in axial orientation, in agreement with the exacerbated anomeric effect typical of sp^2-iminosugars,[8,9,11−14] as supported by the intense NOE contacts H-1/H-7*A* and H-1/H-7*B*. The exocyclic C-3−C-8 bond, in equatorial orientation, adopts an alternate conformation in which the aminoalkyl substituent is in *anti* disposition to C-2, expected to be the most stable situation in *C*-glycosides,[15] in agreement with the above commented H-2/H-8a NOE contact. On the other hand, the intense NOESY cross-peaks between protons H-7*A*,*B* and the N=CH_2 protons points to the *Z*-configuration at the imino group, as already observed in the X-ray structure of related bicyclic isothioureas.[16] Such a scenario

places the imine lone pair and the amine proton in close proximity, enabling further stabilization through intramolecular hydrogen bonding (Figure 3).

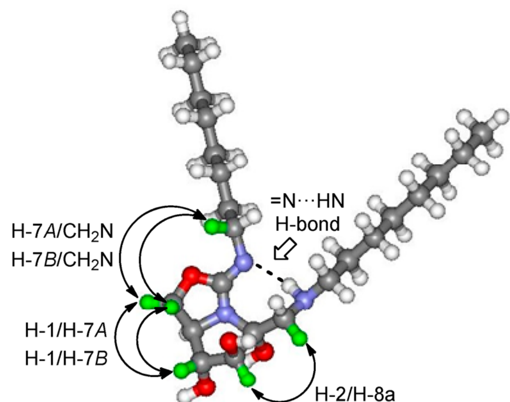


Figure 3. 3D molecular model of compound **12b** with indication of the protons involved in the diagnostic NOE contacts (in green). The favorable disposition of the imino group, in the *Z*-configuration, to form an intramolecular hydrogen bond with the amine proton is highlighted.

The new bi- and trianntenated asutraline derivatives **12a−c** and **13a−c** were first screened as inhibitors against a panel of commercial glycosidases, including *α*-glucosidase (*α*-Glcase; yeast), *β*-glucosidase (*β*-Glcase; almonds and bovine liver, cytosolic), *α*-mannosidase (Jack bean), *β*-mannosidase (*Helix pomatia*), trehalase (pig kidney), naringinase (*β*-glucosidase/*α*-L-rhamnosidase, *Penicillium decumbens*), *α*-galactosidase (green coffee beans), *β*-galactosidase (*β*-Galase; *E. coli*), and amyloglucosidase (*Aspergillus niger*). The corresponding inhibition constants (K_i) are summarized in Table 1.

The reference natural iminosugar australine is a *μ*M inhibitor of *α*-glucosidase, trehalase, and amyloglucosidase, whereas the epimer in C-3 is a rather modest inhibitor of the two later enzymes.[17] None of them inhibits *β*-glucosidase, however. In stark contrast, the substituted sp^2-iminosugar analogues prepared in this work behaved as potent and rather selective inhibitors of the mammalian *β*-glucosidase, with K_i values ranging from 2.9 to 58 *μ*M. The biantennated derivatives exhibited higher affinities as compared to the corresponding triantennated counterparts. The presence of the third, glycosylamine-type tail seems to have a more pronounced effect in the residual activity toward *α*-glucosidase, which eventually can be fully turned off. Selective inhibition of the bovine *β*-glucosidase has been previously used as a selection criterion to identify pharmacological chaperone candidates for human lysosomal *β*-glucosidase (*β*-glucocerebrosidase), the enzyme that is dysfunctional in patients suffering from Gaucher disease,[18] which warrants further biological evaluation.[19]

■ CONCLUSIONS

In summary, the ensemble of data illustrates the potential of the unprecedented Amadori rearrangement of *gem*-diamines as a protecting group-free strategy to access polyantennated pyrrolizidine glycomimetics with total control of the final stereochemistry. Two new types of sp^2-iminosugar structures, namely, reducing pseudo-*C*-nucleosides and dual pseudo-*C*- and *N*-nucleosides, can be accessed by simply acting on the reagents ratio. The methodology is compatible with molecular diversity-oriented approaches and can be successfully used to tailor the selectivity pattern in this family of glycomimetics.

■ EXPERIMENTAL METHODS

General Chemical Reagents and Methods. 1-Deoxy-(5*R*)-5-hydroxy-3-octylimino-2-oxacastanospermine (**7**),[12] 1-deoxy-(5*R*)-5-hydroxy-2-oxa-3-oxocastanospermine (**3a**),[13] 1-deoxy-6-*epi*-(5*R*)-5-hydroxy-2-oxa-3-oxocastanospermine (**14**),[14] and 1-*O*-acetyl-5-amino-5-deoxy-2,3-di-*O*-isopropylidene-*α*-D-mannofuranose (**15**)[14] were prepared according to literature procedures. Reagents and solvents were purchased from commercial sources and used without further purification. Optical rotations were measured using a sodium lamp (λ = 589 nm) at 22 °C in 1 cm or 1 dm tubes. NMR experiments were performed at 500 (125.7) MHz. 1-D TOCSY as well as 2-D COSY and HMQC experiments were carried out to assist on signal assignment. For ESI mass spectra, 0.1 pM sample concentrations were used, the mobile phase consisting of 50% aq MeCN at 0.1 mL min^{-1}. HRMS measurements were obtained using an ion trap mass analyzer. Thin-layer chromatography was performed on precoated TLC plates, silica gel 30F-245, with visualization by UV light and by charring with 10% H_2SO_4 or 0.2% w/v cerium(IV) sulfate−5% ammonium molybdate in 2 M H_2SO_4 or 0.1% ninhydrine in EtOH. Column chromatography was performed on Chromagel (silice 60 AC.C 70−200 *μ*m). The glycosidases *α*-glucosidase (from yeast), *β*-glucosidase (from almonds), *β*-glucosidase (from bovine liver, cytosolic), *α*-galactosidase (from green coffee beans), isomaltase (from yeast), trehalase (from pig kidney), amyloglucosidase (from *Aspergillus niger*), *α*-mannosidase (from jack bean), *β*-mannosidase (from *Helix pomatia*), *β*-galactosidase (from *E. coli*), and naringinase (from *Penicillium decumbes*) used in the inhibition studies, as well as the corresponding *o*- and *p*-nitrophenyl glycoside substrates, were purchased from Sigma Chemical Co.

Preparation of 1-Deoxy-(5*S*)-5-octylamino-3-octylimino-2-oxacastanospermine (8; *n* = 7 in Scheme 1). A solution of 1-deoxy-(5*R*)-5-hydroxy-3-octylimino-2-oxacastanospermine[12] (**7**, 23 mg, 0.07 mmol) and *n*-octylamine (9 *μ*L, 0.05 mmol, 0.75 equiv) in CD_3OD (0.6 mL) was placed in an NMR tube (proton NMR monitoring at RT every 20 min for 2 h). After 1 h, all the starting material had reacted to give **8** (*n* = 7). ^{1}H NMR (500 MHz, CD_3OD) δ 4.68 (d, 1 H, $J_{5,6}$ = 4.8 Hz, H-5), 4.36 (t, 1 H, $J_{1a,8a}$ = $J_{1a,1b}$ = 8.6 Hz, H-1a), 4.25 (dd, 1 H, $J_{1b,8a}$ = 4.0 Hz, H-1b), 3.74 (ddd, 1 H, $J_{8,8a}$ = 9.5 Hz, H-8a), 3.62 (t, 1 H, $J_{6,7}$ = $J_{7,8}$ = 9.5 Hz, H-7), 3.45 (dd, 1 H, H-6),

Table 1. Inhibition Constants (K_i, *μ*M) for the Bi- and Triantennated Australine Analogues 12a−c and 13a−c against Several Commercial Glycosidases[a]

enzyme	12a	13a	12b	13b	12c	13c
β-Glcase (bovine)	51 ± 4	58 ± 4	9.6 ± 0.5	12 ± 1	2.9 ± 0.1	25 ± 1
β-Glcase (almonds)	320 ± 15	223 ± 10	484 ± 20	441 ± 20	56 ± 3	367 ± 15
α-Glcase (yeast)	n.i.[b]	n.i.	434 ± 15	802 ± 30	66 ± 3	n.i.
β-Galase (*E. coli*)	n.i.	n.i.	176 ± 10	196 ± 10	261 ± 10	n.i.

[a]Inhibition was competitive in all cases. No inhibition was observed for any compound at 2 mM concentration on *α*-galactosidase (green coffee bean), *α*-mannosidase (Jack bean), *β*-mannosidase (*Helix pomatia*), amyloglucosidase (*Aspergillus niger*), and Trehalase (pig kidney). [b]n.i.: no inhibition observed at 2 mM concentration of the inhibitor.

3.16 (t, 1 H, H-8), 3.22–3.07 (m, 2 H, CH_2N), 2.65–2.58 (m, 2 H, $NHCH_2$).

General Procedure for the Formation of the Biantennated Australine Analogues (12a–c). A solution of 1-deoxy-(5*R*)-5-hydroxy-3-octylimino-2-oxacastanospermine (7, 0.30 mmol) and the corresponding *n*-alkylamine (0.30 mmol, 1.0 equiv) in MeOH (1 mL) was stirred at RT for 1 day (TLC monitoring). The solvent was eliminated under reduced pressure and the resulting residue was purified by column chromatography to afford **12a–c**.

8-Butylamino-7,8-dideoxy-3-hydroxy-5-octylimino-6-oxa-3-epi-australine (12a). Following the general procedure described above with 1.0 equiv of *n*-butylamine, the resulting residue was purified by column chromatography to afford **12a**. Column chromatography (15:1 CH_2Cl_2–MeOH). Yield: 60 mg (57%). R_f 0.60 (40:10:1 CH_2Cl_2-MeOH-H_2O). $[\alpha]_D$ +22.4 (*c* 0.9 in MeOH). ^1H NMR (500 MHz, CD_3OD) δ 4.35 (s, 1 H, H-1), 4.16 (d, 1 H, $J_{8a,8b}$ = 11.5 Hz, H-8a), 3.99–3.95 (m, 1 H, H-7a), 3.91 (d, 1 H, $J_{1,2}$ = 1.0 Hz, H-2), 3.79 (dd, 1 H, $J_{7A,7B}$ = 11.5 Hz, $J_{7a,7A}$ = 5.5 Hz, H-7*A*), 3.72 (dd, 1 H, $J_{7a,7B}$ = 2.5 Hz, H-7*B*), 3.50–3.33 (m, 4 H, NCH_2), 3.35 (d, 1 H, H-8b), 1.75–1.58 (m, 4 H, CH_2), 1.46–1.26 (m, 12 H, CH_2), 0.98 (t, 3 H, $^3J_{H,H}$ = 7.5 Hz, CH_3), 0.91 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH_3). ^{13}C NMR (125.7 MHz, CD_3OD) δ 157.9 (CN), 100.9 (C-3), 83.7 (C-1), 78.2 (C-2), 70.1 (C-7a), 59.8 (C-7), 55.2 (C-8), 46.5–46.0 (CH_2N), 32.9–20.7 (CH_2), 14.4–14.1 (CH_3). ESIMS: *m/z* 372.3 $[M + H]^+$. HRFABMS Calcd for $C_{19}H_{38}N_3O_4$ $[M + H]^+$ 372.2862, found 372.2873.

7,8-Dideoxy-3-hydroxy-8-octylamino-5-octylimino-6-oxa-3-epi-australine (12b). Following the general procedure described above with 1.0 equiv of *n*-octylamine, the resulting residue was purified by column chromatography to afford **12b**. Column chromatography (15:1 CH_2Cl_2–MeOH). Yield: 51 mg (40%). R_f 0.37 (70:10:1 CH_2Cl_2-MeOH-H_2O). $[\alpha]_D$ +17.1 (*c* 1.1 in MeOH). ^1H NMR (500 MHz, CD_3OD) δ 4.35 (s, 1 H, H-1), 4.15 (d, 1 H, $J_{8a,8b}$ = 11.5 Hz, H-8a), 3.99–3.95 (m, 1 H, H-7a), 3.91 (d, 1 H, $J_{1,2}$ = 1.5 Hz, H-2), 3.79 (dd, 1 H, $J_{7A,7B}$ = 11.5 Hz, $J_{7a,7A}$ = 6.0 Hz, H-7*A*), 3.72 (dd, 1 H, $J_{7a,7B}$ = 3.0 Hz, H-7*B*), 3.50–3.34 (m, 4 H, NCH_2), 3.35 (d, 1 H, H-8b), 1.78–1.58 (m, 4 H, CH_2), 1.48–1.23 (m, 20 H, CH_2), 0.93–0.88 (m, 6 H, CH_3). ^{13}C NMR (125.7 MHz, CD_3OD) δ 157.9 (CN), 100.9 (C-3), 83.6 (C-1), 78.2 (C-2), 70.1 (C-7a), 59.8 (C-7), 55.2 (C-8), 46.73–45.9 (CH_2N), 32.9–23.7 (CH_2), 14.4 (CH_3). ESIMS: *m/z* 428.0 $[M + H]^+$. HRFABMS Calcd for $C_{23}H_{46}N_3O_4$ $[M + H]^+$ 428.3488, found 428.3480.

7,8-Dideoxy-8-dodecylamino-3-hydroxy-5-octylimino-6-oxa-3-epi-australine (12c). Following the general procedure described above with 1.0 equiv of *n*-dodecylamine, the resulting residue was purified by column chromatography to afford **12c**. Column chromatography (15:1 CH_2Cl_2–MeOH). Yield: 55 mg (36%). R_f 0.67 (40:10:1 CH_2Cl_2-MeOH-H_2O). $[\alpha]_D$ +17.9 (*c* 1.3 in MeOH). ^1H NMR (500 MHz, CD_3OD) δ 4.35 (s, 1 H, H-1), 4.14 (d, 1 H, $J_{8a,8b}$ = 11.6 Hz, H-8a), 3.99–3.95 (m, 1 H, H-7a), 3.90 (d, 1 H, $J_{1,2}$ = 1.5 Hz, H-2), 3.79 (dd, 1 H, $J_{7A,7B}$ = 11.8 Hz, $J_{7a,7A}$ = 5.8 Hz, H-7*A*), 3.72 (dd, 1 H, $J_{7a,7B}$ = 2.7 Hz, H-7*B*), 3.51–3.33 (m, 4 H, NCH_2), 3.35 (d, 1 H, H-8b), 1.72–1.60 (m, 4 H, CH_2), 1.43–1.25 (m, 28 H, CH_2), 0.93–0.88 (m, 6 H, CH_3). ^{13}C NMR (125.7 MHz, CD_3OD) δ 157.9 (CN), 100.9 (C-3), 83.7 (C-1), 78.2 (C-2), 70.2 (C-7a), 59.8 (C-7), 55.2 (C-8), 46.6–46.0 (CH_2N), 33.1–23.7 (CH_2), 14.4 (CH_3). ESIMS: *m/z* 484.6 $[M + H]^+$. HRFABMS Calcd for $C_{27}H_{54}N_3O_4$ $[M + H]^+$ 484.4114, found 484.4129.

General Procedure for the Formation of the Triantennated Australine Analogues (13a–13c). A solution of 1-deoxy-(5*R*)-5-hydroxy-3-octylimino-2-oxacastanospermine (7) (0.43 mmol) and the corresponding *n*-alkylamine (0.86 mmol, 2.0 equiv) in MeOH (2 mL) was stirred at RT for 3 days (TLC monitoring). The solvent was eliminated under reduced pressure and the resulting residue was purified by column chromatography to afford **13a–c**.

3,8-Dibutylamino-7,8-dideoxy-5-octylimino-6-oxa-3-epi-australine (13a). Following the general procedure described above with 2.0 equiv of *n*-butylamine, the resulting residue was purified by column chromatography to afford 50 mg of **13a** (33%) and 8 mg of **12a** (6%). Column chromatography (15:1 CH_2Cl_2–MeOH). R_f 0.64 (40:10:1 CH_2Cl_2-MeOH-H_2O). $[\alpha]_D$ +8.2 (*c* 0.9 in MeOH). ^1H NMR (500 MHz, CD_3OD) δ 4.35 (s, 1 H, H-1), 4.14 (d, 1 H, $J_{8a,8b}$ = 11.5 Hz, H-8a), 3.93–3.90 (m, 1 H, H-7a), 3.82 (dd, 1 H, $J_{7A,7B}$ = 11.7 Hz, $J_{7a,7A}$ = 6.0 Hz, H-7*A*), 3.76 (dd, 1 H, $J_{7a,7B}$ = 2.6 Hz, H-7*B*), 3.76 (s, 1 H, H-2), 3.43–3.34 (m, 5 H, NCH_2, H-8b), 2.59–2.52 (m, 1 H, NCH_2), 2.47–2.41 (m, 1 H, NCH_2), 1.72–1.26 (m, 20 H, CH_2), 1.00–0.88 (m, 9 H, CH_3). ^{13}C NMR (125.7 MHz, CD_3OD) δ 158.2 (CN), 91.6 (C-3), 84.2 (C-1), 78.0 (C-2), 70.6 (C-7a), 59.9 (C-7), 51.2 (C-8), 46.1–41.8 (CH_2N), 33.0–20.9 (CH_2), 14.3–14.0 (CH_3). ESIMS: *m/z* 427.5 $[M + H]^+$. HRFABMS Calcd for $C_{23}H_{46}N_4O_3$ $[M + H]^+$ 427.3648, found 427.3656.

7,8-Dideoxy-3,8-dioctylamino-5-octylimino-6-oxa-3-epi-australine (13b). Following the general procedure described above with 2.0 equiv of *n*-octylamine, the resulting residue was purified by column chromatography to afford 70 mg of **13b** (30%) and 9 mg de **12b** (5%). Column chromatography (15:1 CH_2Cl_2–MeOH). R_f 0.54 (70:10:1 CH_2Cl_2-MeOH-H_2O). $[\alpha]_D$ +7.4 (*c* 0.7 in MeOH). ^1H NMR (500 MHz, CD_3OD) δ 4.35 (s, 1 H, H-1), 4.12 (d, 1 H, $J_{8a,8b}$ = 11.5 Hz, H-8a), 3.91 (dd, 1 H, $J_{7a,7A}$ = 6.0 Hz, $J_{7a,7B}$ = 3.0 Hz, H-7a), 3.81 (dd, 1 H, $J_{7A,7B}$ = 11.5 Hz, H-7*A*), 3.75 (dd, 1 H, H-7*B*), 3.75 (s, 1 H, H-2), 3.48–3.33 (m, 4 H, NCH_2), 3.41 (d, 1 H, H-8b), 2.57–2.40 (m, 2 H, NCH_2), 1.67–1.47 (m, 6 H, CH_2), 1.43–1.24 (m, 30 H, CH_2), 0.94–0.88 (m, 9 H, CH_3). ^{13}C NMR (125.7 MHz, CD_3OD) δ 158.2 (CN), 91.7 (C-3), 84.2 (C-1), 78.0 (C-2), 70.7 (C-7a), 59.9 (C-7), 51.0 (C-8), 46.3–42.2 (CH_2N), 33.0–23.7 (CH_2), 14.4 (CH_3). ESIMS: *m/z* 539.2 $[M + H]^+$. HRFABMS Calcd for $C_{31}H_{63}N_4O_3$ $[M + H]^+$ 539.4900, found 539.4890.

7,8-Dideoxy-3,8-didodecylamino-5-octylimino-6-oxa-3-epi-australine (13c). Following the general procedure described above with 2.0 equiv of *n*-dodecylamine, the resulting residue was purified by column chromatography to afford 62 mg of **13c** (31%) and 15 mg of **12c** (9%). Column chromatography (15:1 CH_2Cl_2–MeOH). R_f 0.29 (70:10:1 CH_2Cl_2-MeOH-H_2O). $[\alpha]_D$ +5.2 (*c* 1.0 in MeOH). ^1H NMR (500 MHz, CD_3OD) δ 4.35 (s, 1 H, H-1), 4.11 (d, 1 H, $J_{8a,8b}$ = 11.6 Hz, H-8a), 3.92 (dd, 1 H, $J_{7a,7A}$ = 5.8 Hz, $J_{7a,7B}$ = 2.2 Hz, H-7a), 3.82 (dd, 1 H, $J_{7A,7B}$ = 11.6 Hz, H-7*A*), 3.76 (s, 1 H, H-2), 3.76 (dd, 1 H, H-7*B*), 3.52–3.35 (m, 5 H, NCH_2, H-8b), 2.58–2.51 (m, 1 H, NCH_2), 2.48–2.41 (m, 1 H, NCH_2), 1.70–1.20 (m, 52 H, CH_2), 0.90 (t, 9 H, $^3J_{H,H}$ = 7.0 Hz, CH_3). ^{13}C NMR (125.7 MHz, CD_3OD) δ 158.3 (CN), 91.7 (C-3), 84.2 (C-1), 78.1 (C-2), 70.7 (C-7a), 59.9 (C-7), 51.0 (C-8), 46.1–42.2 (CH_2N), 33.1–23.8 (CH_2), 14.5–14.4 (CH_3). ESIMS: *m/z* 651.8 $[M + H]^+$. HRFABMS Calcd for $C_{39}H_{79}N_4O_3$ $[M + H]^+$ 651.6152, found 651.6176.

1-*O*-Acetyl-2,3-*O*-isopropylidene-5-deoxy-5-(*N*′-octylureido)-α-D-mannofuranose (16). Octyl isocyanate (43 μL, 1.0 equiv) was added to a solution of 1-*O*-acetyl-5-amino-5-deoxy-2,3-di-*O*-isopropylidene-α-D-mannofuranose[14] (**15**, 63 mg, 0.24 mmol) in MeOH (2.5 mL), and the reaction mixture was stirred at RT for 1 h (TLC monitoring). The solvent was removed under reduced pressure and purified by column chromatography (9:1 EtOAc–cyclohexane) to afford the urea adduct **16**. Yield: 61 mg (61%). R_f 0.33 (9:1 EtOAc–cyclohexane). $[\alpha]_D$ +15.5 (*c* 1.0 in DCM). ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (s, 1 H, H-1), 5.65 (d, 1 H, $J_{OH,6}$ = 6.6 Hz, OH), 5.35–5.23 (m, 1 H, NH), 4.83 (dd, 1 H, $J_{2,3}$ = 5.5 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 4.66 (d, 1 H, H-2), 4.30–4.23 (m, 1 H, H-4), 3.94–3.82 (m, 2 H, H-5, H-6a), 3.78–3.67 (m, 1 H, H-6b), 3.20–3.04 (m, 2 H, NCH_2), 2.04 (s, 3 H, MeCO), 1.48, 1.31 (2 s, 6 H, CMe_2), 1.30–1.20 (m, 12 H, CH_2), 0.86 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.6 (Me*C*O), 159.0 (CO urea), 113.1 (*C*Me$_2$), 100.5 (C-1), 85.0 (C-2), 81.0 (C-4), 79.8 (C-3), 63.0 (C-6), 51.8 (C-5), 40.7 (CH_2NH), 31.8–22.6 (CH_2, C*Me*$_2$), 21.0 (*Me*CO), 14.0 (CH_3). ESIMS: *m/z* 439.38 $[M + Na]^+$. HRESIMS Calcd for $C_{20}H_{36}N_2O_7Na$ $[M + Na]^+$ 439.2415, found 439.2400.

(4*R*)-4-[(4′*R*)-1′-*O*-Acetyl-2′,3′-*O*-isopropylidene-L-erythro-furanos-4′-yl]-2-octylamino-2-oxazoline (17). Pyridine (53 μL) and trifluoromethanesulfonic anhydride (36 μL, 0.22 mmol, 1.5 equiv) were added to a solution of the corresponding ureido derivative **16** (61 mg, 0.15 mmol) in DCM (0.5 mL) at −25 °C under an Ar atmosphere. The reaction mixture was stirred for 17 h and allowed to warm to RT (TLC monitoring), then, diluted with DCM and washed with saturated aq $NaHCO_3$ (10 mL), dried (Na_2SO_4), and

concentrated. Purification by column chromatography (20:1 → 15:1 EtOAc−MeOH) afforded **17**. Yield: 30 mg (51%). R_f 0.32 (15:1 EtOAc−MeOH). $[\alpha]_D$ +30.2 (*c* 0.7 in DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (s, 1 H, H-1), 4.82 (dd, 1 H, $J_{2,3}$ = 6.0 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 4.66 (d, 1 H, H-2), 4.41−4.32 (m, 3 H, H-5, H-6a, H-6b), 4.17−4.12 (m, 1 H, H-4), 3.17 (t, 2 H, $^3J_{H,H}$ = 7.0 Hz, $NHCH_2$), 2.05 (s, 3 H, MeCO), 1.48, 1.28 (2 s, 6 H, CMe_2), 1.56−1.20 (m, 12 H, CH_2), 0.86 (t, 3 H, $^3J_{H,H}$ = 6.5 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.5 (Me*C*O), 161.8 (C═N), 113.0 (*C*(Me)$_2$), 100.6 (C-1), 84.9 (C-2), 83.7 (C-4), 79.3 (C-3), 70.0 (C-6), 61.4 (C-5), 42.9 (CH_2NH), 31.7−21.0 (CH_2, C*Me*$_2$), 22.6 (*Me*CO), 14.0 (CH_3). ESIMS: *m*/*z* 399.35 [M + H]$^+$. HRESIMS Calcd for $C_{20}H_{35}N_2O_6$ [M + H]$^+$ 399.2490, found 399.2482.

1-Deoxy-6-*epi*-(5*R*)-5-hydroxy-3-octylimino-2-oxacastanospermine (18). To a solution of the 2-amino-2-oxazoline precursor **17** (46 mg, 0.12 mmol) in MeOH (1 mL), methanolic NaOMe (1 M, 0.1 equiv per mol of acetate) was added. The reaction mixture was stirred at rt for 2 h, then neutralized with solid CO_2 and concentrated. The residue was treated with TFA−H_2O (9:1, 0.54 mL) for 60 min, concentrated under reduced pressure, and coevaporated several times with water. Then, the residue was filtered through a pad of silica using (50:10:1 DCM−MeOH−H_2O) as eluent, concentrated, and freeze-dried to give **18**. Yield: 30 mg (82%). R_f 0.40 (50:10:1 DCM−MeOH−H_2O). $[\alpha]_D$ +15.5 (*c* 0.7 in MeOH). ^{1}H NMR (300 MHz, D_2O) δ 5.49 (d, 1 H, $J_{5,6}$ = 2.7 Hz, H-5), 5.05 (t, 1 H, $J_{1a,1b}$ = $J_{1a,8a}$ = 9.0 Hz, H-1a), 4.85−4.70 (m, 1 H, H-1b), 4.27 (bq, 1 H, $J_{8a,8}$ = 9.0 Hz, H-8a), 4.17 (t, 1 H, $J_{6,7}$ = 2.7 Hz, H-6), 3.95−3.82 (m, 2 H, H-7, H-8), 3.41 (t, 2 H, $^3J_{H,H}$ = 7.0 Hz, NCH_2), 1.68−1.55 (m, 2 H, NCH_2CH_2), 1.40−1.24 (m, 10 H, CH_2), 0.89 (t, 3 H, $^3J_{H,H}$ = 6.9 Hz, CH_3). ^{13}C NMR (75.5 MHz, D_2O) δ 159.4 (C═N), 77.7 (C-5), 73.7 (C-1), 70.7 (C-6), 69.7−69.5 (C-7, C-8), 56.8 (C-8a), 43.0 (CH_2N), 31.1−22.0 (CH_2), 13.4 (CH_3). ESIMS: *m*/*z* 317.3 [M + H]$^+$. HRESIMS Calcd for $C_{15}H_{29}N_2O_5$ [M + H]$^+$ 317.2071, found 317.2059.

1-Deoxy-6-*epi*-(5*R*)-5-octylamino-2-oxa-3-oxocastanospermine (19). A solution of 1-deoxy-6-*epi*-(5*R*)-5-hydroxy-2-oxa-3-oxocastanospermine[14] (78 mg, 0.38 mmol) and *n*-octylamine (63 μL, 0.38 mmol) in MeOH (2 mL) was stirred, under an Ar atmosphere, at 65 °C for 24 h. The solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography (20:1 → 10:1 CH_2Cl_2−MeOH) to give **19**. Yield: 74 mg (60%). R_f 0.15 (10:1 CH_2Cl_2−MeOH). $[\alpha]_D$ +20.6 (*c* 1.0, MeOH). ^{1}H NMR (500 MHz, CD_3OD, 313 K) δ 4.61 (d, 1 H, $J_{5,6}$ = 2.0 Hz, H-5), 4.50 (t, 1 H, $J_{1a,1b}$ = $J_{8a,1a}$ = 9.0 Hz, H-1a), 4.46 (dd, 1 H, $J_{8a,1b}$ = 4.5 Hz, H-1b), 3.97 (dd, 1 H, $J_{6,7}$ = 2.5 Hz, H-6), 3.75 (m, 1 H, H-8a), 3.70 (m, 2 H, H-7, H-8), 2.60 (m, 2 H, CH_2N), 1.53 (m, 2 H, CH_2CH_2N), 1.33 (m, 10 H, CH_2), 0.92 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH_3). ^{13}C NMR (125.7 MHz, CD_3OD) δ 158.9 (CO), 71.8 (C-6), 71.2 (C-7), 70.7 (C-5, C-8), 66.5 (C-1), 54.3 (C-8a), 45.8 (CH_2N), 31.6 (CH_2CH_2N), 29.1, 28.9, 27.0, 22.4 (CH_2), 12.9 (CH_3). FABMS: *m*/*z* 339 (40%, [M + Na]$^+$), 315 (15%, [M + H]$^+$). Anal. Calcd for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.61; H, 8.73; N, 8.50.

X-ray Structural Analysis of 19. One crystal of suitable size for X-ray diffraction analysis (colorless needle, 0.48 × 0.08 × 0.06 mm) was coated with dry perfluoropolyether and mounted on glass fiber and fixed in a cold nitrogen stream (T = 213 K) to the goniometer head. Data collection was performed using monochromatic radiation λ(Mo Kα) = 0.71073 Å, by means of ω and φ scans with a width of 0.50°. The data were reduced (SAINT)[20] and corrected for absorption effects by the multiscan method (SADABS).[21] The structures were solved by direct methods (SIR-2002)[22] and refined against all F^2 data by full-matrix least-squares techniques (SHELXTL-6.12)[23] minimizing $w[F_o^2 - F_c^2]^2$. All the non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were included in calculated positions and allowed to ride on the attached atoms with the isotropic temperature factors (U_{iso} values) fixed at 1.2 times (1.5 times for methyl groups) those U_{eq} values of the corresponding attached atoms. The absolute structure parameter (Flack parameter) for **19** is meaningless because this compound is a weak anomalous scatterer, so the Shelxl MERG4 command was used in the refinement to force Friedel pairs to be merged before use and the absolute structure parameter was removed from the CIF. Therefore, the absolute configuration of **19** has not been established by anomalous-dispersion effects in diffraction measurements on the crystal, but by reference to unchanging chiral centers in the synthetic procedure.

Crystal data for 19. $C_{15}H_{28}N_2O_5$, M = 316.39, monoclinic, a = 8.836(2) Å, b = 6.0632(19) Å, c = 16.037(5) Å, α = 90.00°, β = 100.167(7)°, γ = 90.00°, V = 845.7(4) Å^3, T = 100(2) K, space group $P2_1$, Z = 2, 13 814 reflections measured, 1861 independent reflections (R_{int} = 0.0669). The final R_1 values were 0.0513 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1319 ($I > 2\sigma(I)$). The final R_1 values were 0.0689 (all data). The final $wR(F^2)$ values were 0.1718 (all data). The goodness of fit on F^2 was 1.096.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds, representative NOESY spectra, protocol for determination of K_i values and representative Lineweaver−Burk and double reciprocal analysis plots against β-glucosidase, and selected X-ray data for **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: mellet@us.es (C.O.M.).
*E-mail: jogarcia@iiq.csic.es (J.M.G.F.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the European Union Seventh Framework Programme (FP7-People-2012-CIG) [grant agreement number 333594 (to E.M.S.-F., Marie Curie Reintegration Grant)]. This study was also financially supported by the Spanish Ministerio de Economía y Competitividad (contract numbers SAF2013-44021-R and CTQ2010-15848), the Junta de Andalucía, the Mehuer Foundation, and the European Regional Development Funds (FEDER and FSE). Technical assistance from the research support services of the University of Seville (CITIUS) is also acknowledged.

■ REFERENCES

(1) For selected reviews, see: (a) Nash, R. J.; Kato, A.; Yu, C.-Y.; Fleet, G. W. J. *Future Med. Chem.* **2011**, *3*, 1531−1521. (b) Home, G.; Francis, X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug Discovery Today* **2011**, *16*, 107−118. (c) Wrodnigg, T. M.; Steiner, A. J.; Ueberbacher, B. J. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 77−85.

(2) For recent reviews, see: (a) Bhat, C.; Tilve, S. G. *RSC Adv.* **2014**, *4*, 5405−5452. (b) Compain, P. *Synlett* **2014**, 1215−1240. (c) Lahiri, R.; Ansari, A. A.; Vankar, Y. D. *Chem. Soc. Rev.* **2013**, *42*, 5102−5118. (d) Dragutan, I.; Dragutan, V.; Demonceau, A. *RSC Adv.* **2012**, *2*, 719−736. (e) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, 1615−1637.

(3) For selected examples, see: (a) Laborda, P.; Sayago, F. J.; Cativiela, C.; Parella, T.; Joglar, J.; Clapés, P. *Org. Lett.* **2014**, *16*, 1422−1425. (b) Du-a-man, S.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakort, M. *Eur. J. Org. Chem.* **2014**, 1708−1715. (c) Abels, F.; Lindemann, C.; Schneider, C. *Chem.—Eur. J.* **2014**, *20*, 1964−1979. (d) Crabtree, E. V.; Martinez, R. F.; Nakagawa, S.; Adachi, I.; Kato, A.; Fleet, G. W. J.; Glawar, A. F. G. *Org. Biomol. Chem.* **2014**, *12*, 3932−3943. (e) Malik, G.; Ferry, A.; Guinchard, X.; Crestell, T.; Crich, D. *Chem.—Eur. J.* **2013**, *19*, 2168−2179. (f) Malik, M.; Witkowski, G.; Ceborska, M.; Jarosz, S. *Org. Lett.* **2013**, *15*, 6214−6217. (g) Dahnd, V.; Draper, J. A.; Moore, J.; Britton, R. *Org. Lett.* **2013**, *15*, 1914−1917. (h) Davies, S. G.; Figuccia, A. L. A.;

Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, *15*, 2042−2045. (i) Parmeggiani, C.; Cardona, F.; Giusti, L.; Reissig, H.-J; Goti, A. *Chem.—Eur. J.* **2013**, *19*, 10595−10604.

(4) (a) Yu, Y.; Mena-Barragán, T.; Higaki, K.; Johnson, J. L.; Drury, J. E.; Lieberman, R. L.; Nakasone, N.; Ninomiya, H.; Tsukimura, T.; Sakuraba, H.; Suzuki, Y.; Namba, E.; Ortiz Mellet, C.; García Fernández, C.; Ohno, K. *ACS Chem. Biol.* **2014**, *9*, 1460−1469. (b) Aguilar-Moncayo, M.; Takai, T.; Higaki, K.; Mena-Barragán, T.; Hirano, Y.; Yura, K.; Li, L.; Yu, Y.; Ninomiya, H.; García-Moreno, M. I.; Ishii, S.; Sakakibara, Y.; Ohno, K.; Namba, E.; Ortiz Mellet, C.; García Fernández, J. M.; Suzuki, Y. *Chem. Commun.* **2011**, *48*, 6514−6516.

(5) (a) Andrews, J. S.; Weimar, T.; Frandsen, T. P.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 10799−10804. (b) Kavlekar, L. M.; Kuntz, D. A.; Wen, X.; Johnston, B. D.; Svensson, B.; Rose, D. R.; Pinto, B. M. *Tetrahedron: Asymmetry* **2005**, *16*, 1035−1046. (c) Cumpstey, I.; Ramstadius, C.; Borbas, K. E.; Alonzi, D. S.; Butters, T. D. *Bioorg. Med. Chem.* **2011**, *19*, 5219−5223. (d) Shing, T. K. M.; Cheng, H. M.; Wong, W. F.; Kwong, C. S. K.; Li, J.; Lau, C. B. S.; Leung, P. S.; Cheng, C. H. K. *Org. Lett.* **2008**, *10*, 3145−3149.

(6) (a) Siriwardena, A.; Sonawane, D. P.; Bande, O. P.; Markad, P. R.; Yonekawa, S.; Tropak, M. B.; Ghosh, S.; Chopade, B. A.; Mahuran, D. J.; Dhavale, D. D. *J. Org. Chem.* **2014**, *79*, 4398−4404. (b) Senthilkumar, S.; Prasad, S. S.; Kumar, P. S.; Baskaran, S. *Chem. Commun.* **2014**, *50*, 1549−1551. (c) Biela-Banas, A.; Gallienne, E.; Front, S.; Martin, O. R. *Tetrahedron Lett.* **2014**, *55*, 838−841. (d) Zoidi, M.; Muller, B.; Torvisco, A.; Tysoe, C.; Benazza, M.; Siriwardena, A.; Withers, S. G.; Wrodnigg, T. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2777−2780. (e) Santana, A. G.; Paz, N. R.; Francisco, C. G.; Suárez, E.; González, C. *J. Org. Chem.* **2013**, *78*, 7527−7543. (f) Mondon, M.; Fontelle, N.; Désiré, J.; Lecornue, F.; Guillard, J.; Marrot, J.; Blériot, Y. *Org. Lett.* **2012**, *14*, 870−873. (g) Wennekes, T.; van den Berg, R. J. H. N.; Boltje, T. J.; Donker-Koopman, W. E.; Kuijper, B.; van der Marel, G. A.; Strijland, A.; Verhagen, C. P.; Aerts, J. M. F. G.; Overkleeeft, H. S. *Eur. J. Org. Chem.* **2010**, 1258−1283. (h) Compain, P.; Chagnault, V.; Martin, O. R. *Tetrahedron: Asymmetry* **2009**, *20*, 672−711.

(7) Wennekes, T.; van der Berg, R. J. B. H. N.; Boot, R. G.; van der Marel, G. A.; Overkleeft, H. S.; Aerts, J. M. F. G. *Angew. Chem., Int. Ed.* **2009**, *48*, 8848−8869.

(8) (a) Jiménez Blanco, J. L.; Díaz Pérez, V. M.; Ortiz Mellet, C.; Fuentes, J.; García Fernández, J. M. *Chem. Commun.* **1997**, 1969−1970. (b) Rísquez-Cuadro, R.; García Fernández, J. M.; Nierengarten, J.-F.; Ortiz Mellet, C. *Chem.—Eur. J.* **2013**, *19*, 16791−16803.

(9) (a) Sánchez-Fernández, E. M.; Rísquez-Cuadro, R.; Chasseraud, M.; Ahidouch, A.; Ortiz Mellet, C.; Ouadid-Ahidouch, H.; García Fernández, J. M. *Chem. Commun.* **2010**, *46*, 5328−5330. (b) Allan, G.; Ahidouch, A.; Sánchez-Fernández, E. M.; Rísquez-Cuadro, R.; García Fernandez, J. M.; Ortiz Mellet, C.; Ouadid-Ahidouch, H. *PLoS One* **2013**, *8*, e76411.

(10) For a review, see: (a) Wrodnigg, T. M.; Eder, B. *Top. Curr. Chem.* **2001**, *215*, 115−152. For selected synthetic applications, see: (b) Frongia, A.; Secci, F.; Capitta, F.; Piras, P. P.; Sanna, M. L. *Chem. Commun.* **2013**, *49*, 8812−8814. (c) Gallas, K.; Pototschnig, G.; Adanitsch, F.; Stütz, A. E.; Wrodnigg, T. M. *Beilstein J. Org. Chem.* **2012**, *8*, 1619−1629. (d) Hricovíniová, Z. *Tetrahedron: Asymmetry* **2010**, 2238−2243. (e) Wrodnigg, T. M.; Kartusch, C.; Illaszewicz, C. *Carbohydr. Res.* **2008**, *343*, 2057−2066. (f) Hotchkiss, D. J.; Soengas, R.; Booth, K. V.; Weymouth-Wilson, A. C.; Eastwick-Field, V.; Fleet, G. W. J. *Tetrahedron Lett.* **2007**, *48*, 517−520.

(11) García-Moreno, M. I.; Díaz-Pérez, P.; Ortiz Mellet, C.; García Fernández, J. M. *Chem. Commun.* **2002**, 848−849.

(12) Luan, Z.; Higaki, K.; Aguilar-Moncayo, M.; Ninomiya, H.; Ohno, K.; García-Moreno, M. I.; Ortiz Mellet, C.; García Fernández, J. M.; Suzuki, Y. *ChemBioChem* **2009**, *10*, 2780−2792.

(13) Díaz Pérez, V. M.; García-Moreno, M. I.; Ortiz Mellet, C.; Fuentes, J.; García Fernández, J. M.; Díaz Arribas, J. C.; Cañada, F. J. *J. Org. Chem.* **2000**, *65*, 136−143.

(14) Díaz Pérez, P.; García-Moreno, M. I.; Ortiz Mellet, C.; García Fernández, J. M. *Eur. J. Org. Chem.* **2005**, 2903−2913.

(15) Asensio, J. L.; Cañada, F. J.; García-Herrero, A.; Murillo, M. T.; Fernández-Mayoralas, A.; Johns, B. A.; Kozak, J.; Zhu, Z. Z.; Johnson, C. R.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1999**, *121*, 11318−11329.

(16) Suzuki, H.; Ohto, U.; Higaki, K.; Mena-Barragán, T.; Aguilar-Moncayo, M.; Ortiz Mellet, C.; Namba, E.; García Fernández, J. M.; Suzuki, Y.; Shimizu, T. *J. Biol. Chem.* **2014**, *289*, 14560−14568.

(17) Kato, A.; Kano, E.; Adachi, I.; Molineux, R. J.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Wormald, M. J.; Kizu, H.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2003**, *14*, 325−331.

(18) Castilla, J.; Rísquez, R.; Cruz, D.; Higaki, K.; Namba, E.; Ohno, K.; Suzuki, Y.; Díaz, Y.; Ortiz Mellet, C.; García Fernández, J. M.; Castillón, S. *J. Med. Chem.* **2012**, *58*, 6857−6865.

(19) In a preliminary test, compounds **12b**, **12c**, **13a**, and **13b** exhibited inhibition curves toward human β-glucocerebrosidase that matched that obtained for Ambroxol, a non-iminosugar type inhibitor in preclinical studies for chaperone therapy. See: Suzuki, Y. *Brain Dev.* **2013**, *6*, 515−518.

(20) *APEX2*; Bruker AXS Inc.: Madison, WI, 2007.

(21) *SADABS*; Bruker AXS Inc.: Madison, WI, 2001.

(22) Burla, M. C.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Giacovazzo, C.; Poliori, G.; Spagna, R. *J. Appl. Crystallogr.* **2003**, *36*, 1103.

(23) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112−122.