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Stereodivergent Access to Polyhydroxylated 10-Azabicyclo[4.3.1]decanes as New Calystegine Analogues

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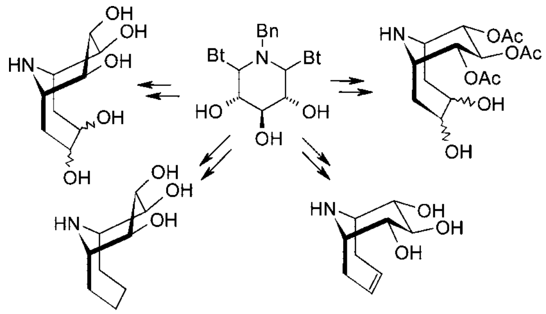

A rapid and stereodivergent access to polyhydroxylated 10-azabicyclo[4.3.1]decanes as new calystegine analogues by way of a double benzotriazolyl/carbon nucleophile exchange followed by a ring-closing metathesis was achieved. Preliminary evaluation of the new compounds as glucocerebrosidase inhibitors was also performed.

Over the past decade, the pace of discoveries in the field of iminosugars has been breathtaking.[1] Historically known as glycosidase inhibitors,[2] the scope of their biological activity has been extended to the inhibition of numerous enzymes such as glycosyltransferases,[3] glycogen phosphorylases,[4] nucleoside-processing enzymes,[5] UDP-Gal*p* mutase,[6] and more recently metalloproteinases.[7] As a consequence, iminosugars are now lead compounds for the treatment of an impressive variety of diseases including diabetes,[8] cancers,[9] viral infections,[10] psoriasis,[7] and rare genetic diseases (lysosomal storage disorders[11] and cystic fibrosis[12]).[1] The recent approval of Zavesca as the first oral treatment for Gaucher disease, a rare genetic disease, is a spectacular demonstration of the importance of iminosugars as medicines for unmet medical needs.[11] In this context, the development of rapid and general access to original iminosugars is more than ever highly needed.

In connection with our studies on pharmacological chaperone therapy for Gaucher disease,[13,14] we became interested in bicyclic structures related to calystegines,[15] a new class of iminosugars discovered in the 1990s. Our first aim was the preparation of constrained analogues of α-1-*C*-nonyl-DIX (**1**),[13] a potent and highly selective inhibitor of β-glucocerebrosidase, the enzyme involved in Gaucher disease (Figure 1).[16] In addition to that specific objective, our aim was to access rapidly a diversity of original non-natural calystegine analogues such as **2**[17] in order to evaluate their biological activities (Figure 1). Azabicyclo[*n*.3.1]alkanes containing a nitrogen atom in the one-atom bridge are indeed an important class of alkaloids with useful biological properties.[18]

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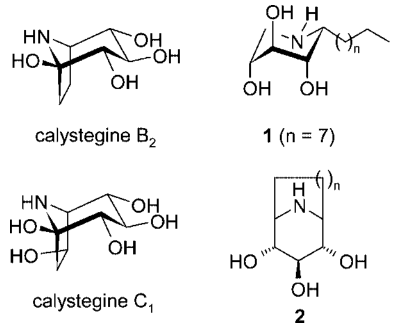
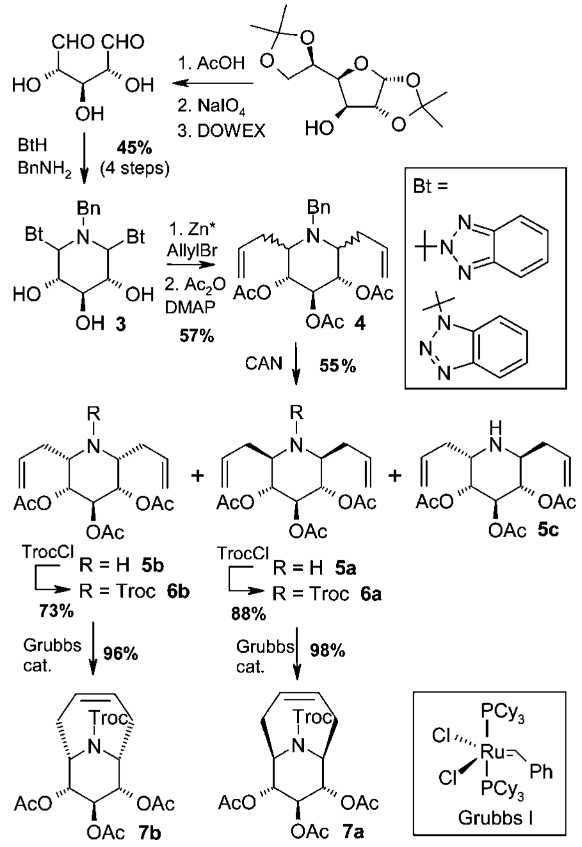


FIGURE 1. Some iminosugars and calystegine derivatives.

Our stereodivergent strategy hinges on the polyhydroxylated 2,6-bis(benzotriazolyl)piperidine **3** as a key substrate for double benzotriazolyl/carbon nucleophile exchange[19] allowing the one-step introduction of two alkenyl chains at C-2 and C-6. The next key step is then the formation of the desired bicyclic framework by way of a ring-closing metathesis (RCM). One of the main challenges in this straightforward approach was to find a strategy to separate the three possible stereoisomers obtained from the nucleophilic displacement reaction (i.e., the *trans* isomer, and the two *meso* compounds, the 2,3-*trans*-2,6-*cis*- and the 2,3-*cis*-2,6-*cis*-isomers). Bis(benzotriazolyl)piperidine **3** was synthesized in four steps from inexpensive diacetone-D-glucose according to the procedure reported by Shankar (Scheme 1).[20] In our hands, compounds **3** could be obtained on a multigram scale (up to 10 g) in 45% overall yield from diacetone-D-glucose after optimization.[21] Only one purification is required in this four-step process, **3** being purified by crystallization in AcOEt. The double benzotriazolyl/carbon nucleophile exchange was first investigated with alkyl-,[22] allyl-, or vinylmagnesium bromide with little success. With or without additives, such as $ZnBr_2$ or $MgBr_2$, the expected 2,6-dialkyl piperidines **4** were obtained in poor and unreproducible yields. The best results were finally obtained with 5 equiv of allyl zinc bromide, generated by treatment of allylbromide with activated Zn dust according to Knochel's procedure.[23] Following these conditions, 2,6-diallyl piperidines **4** were obtained as a mixture of stereoisomers in 57% yield after protection of the hydroxyl groups. Subsequent acetylation of the crude product was necessary for the next step of the synthesis and for the separation of the desired products from benzotriazole. The purification of the two RCM substrate precursors (i.e., the 2,6-*cis*-isomers **5a** and **5b**) and the chemoselective removal of the *N*-benzyl group[24] were performed in the single step (Scheme 1).

SCHEME 1. Access to the 10-Azabicyclo[4.3.1]decane Ring System



In addition to stereoisomer separation, one of the issues associated with our strategy was indeed the presence of an endocyclic amino function that could potentially chelate the RCM catalyst metal center and thus form unproductive complexes. The replacement of the endocyclic amine by a less coordinating function thus required the deprotection of the amino group. Even though an increasing number of examples of sterically crowded amines that are substrates for metathesis are reported in the literature,[25] reaction with Grubbs catalyst (I or II) using *N*-benzyl-2,6-diallyl piperidines **4** failed under various experimental conditions. As a prelude to RCM, the *N*-benzyl group in **4** was selectively removed by using 4 equiv of CAN[24] in a cosolvent system (THF/H_2O) to obtain a mixture of the three secondary amine stereoisomers **5a**,**b**,**c** (Scheme 1). Careful purification by flash chromatography on silica gel afforded the pure 2,3-*trans*-2,6-*cis*-isomer **5a** and 2,3-*cis*-2,6-*cis*-isomer **5b** in 29 and 13% yield, respectively. The chiral *trans*-isomer **5c** was obtained in a 1:1 mixture with the 2,3-*trans*-2,6-*cis*-isomer **5a** in 13% yield (**5a**:**5b**:**5c** = 23:17:10 determined by ^1H NMR on the crude reaction mixture). The relative configurations of the substituents in the piperidine rings were unambiguously established by NMR spectra (COSY and NOESY). These configurations were further confirmed by X-ray crystallography of compound **11b** at a later stage in the synthesis (Figure 2). Unfortunately, the same synthetic sequence could not be reproduced to obtain the divinyl analogues of **5**, as precursors of the 8-azabicyclo[3.2.1] ring system, because the alkylation step led to low yields and the deprotection step to degradation products. Having in hand the two diastereomerically pure 2,6-*cis*-diallyl piperidines **6a** and **6b** obtained after protection with

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[21] The following modifications were found to increase significantly the overall yield of the process; no $NaHCO_3$ is needed during the second step, and the reaction time in steps 2 and 3 has to be increased to 16 h (see Supporting Information for more details). In our hands, additional crystallization from the mother liquor, as reported by Shankar, afforded **3** polluted by unreacted benzotriazole. Compound **3** was found to decompose under purification by flash chromatography on silica gel.

[22] In our hands, the reaction performed with EtMgBr gave the desired pure product in only 20% yield.

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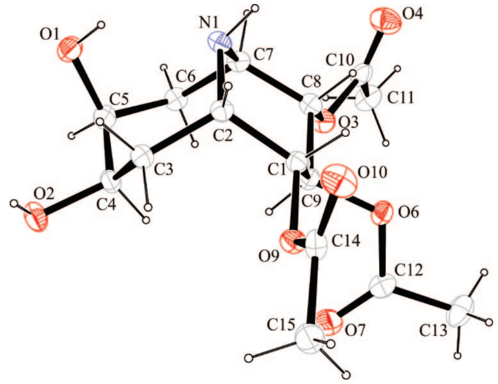
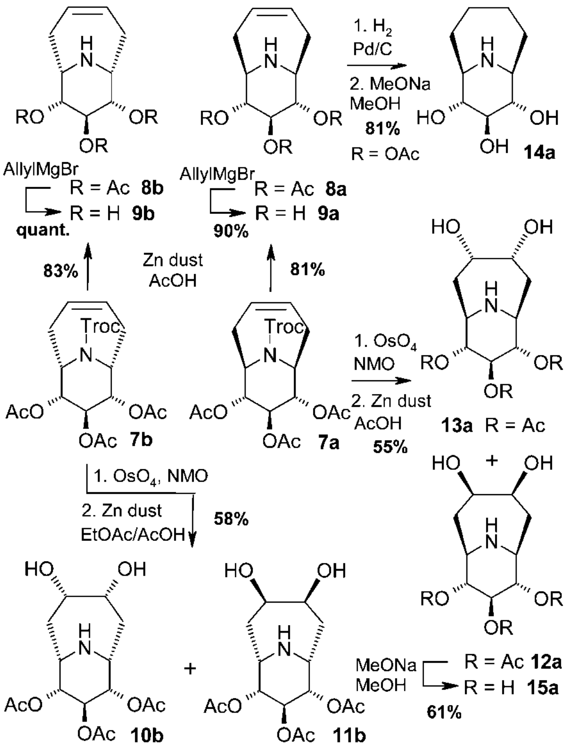


FIGURE 2. Perspective ORTEP view of compounds **11b**.[29]

SCHEME 2. Access to Polyhydroxylated 10-Azabicyclo[4.3.1]decane Derivatives



a Troc group, we submitted them to 10 mol % of Grubbs I in refluxing dichloromethane.[26] We were pleased to find that the RCM reaction performed on each of the two *cis* stereoisomers afforded the expected 10-azabicyclo[4.3.1]decane derivatives **7** in almost quantitative yields (Scheme 1).

A diversity of calystegine analogues was then obtained from advanced precursors **7**. The *N*-Troc protecting group of stereoisomers **7** was selectively removed using Zn in AcOH/AcOEt to yield the secondary endocyclic amines **8** (Scheme 2).[27] Subsequent deprotection of the acetyl groups using allylmagnesium bromide[28] provided the fully deprotected 10-azabicyclo[4.3.1]dec-3-ene derivatives **9** in high yields. Compound **14a**, the more flexible saturated analogue of **9a**, was also obtained from **8a** by way of hydrogenation. Homocalystegines analogues were then synthesized by dihydroxylation of the endocyclic double bond of **7** under Upjohn conditions. The reaction performed with the 2,3-*cis*-2,6-*cis*-isomer **7b** provided the *exo*-diol **11b** and the *endo*-diol **10b** in 43 and 15% yield, respectively, after deprotection of the *N*-Troc group and purification on silica gel (de 48%). Structural evidence for compounds **10b** and **11b** was obtained unambiguously by NMR spectra (COSY and NOESY) and X-ray crystallographic analysis (Figure 2).[29] Interestingly, **11b** adopts a chair−twist chair conformation. The twist chair conformation of the azepane moiety is favored by a hydrogen bond between one OH and the nitrogen atom and is known to be generally preferred in seven-membered rings.[30]

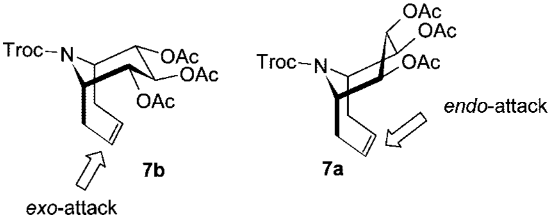


FIGURE 3. Rationale for observed selectivity in the dihydroxylation reaction.

The *exo*-attack observed is in agreement with dihydroxylation reactions performed on related bicyclic systems such as 8-azabicyclo[3.2.1]octenes[31] and 9-azabicyclo[4.2.1]nonenes.[17a] We assume that the 10-azabicyclo[4.3.1]decene ring system of **7b** adopts a chair−chair conformation in which all the acetate groups are in an equatorial position as indicated by ^{1}H NMR and suggested by the X-ray crystallographic analysis of **11b** (Figure 2). In such a system, the *exo*-attack is much more favored than the *endo* one because of steric hindrance (Figure 3). In sharp contrast, dihydroxylation of **7a**, the 2,3-*trans*-2,6-*cis*-isomer of **7b**, afforded the *endo*-diol **12a** as the major diastereoisomer after deprotection of the *N*-Troc group (de 34%). The reversal of facial selectivity may be explained by a conformational change of the azabicyclo[4.3.1]decene ring system from a chair−chair to a chair−boat conformation. The piperidine ring moiety adopts a boat conformation in which all the acetoxy groups are in a pseudoequatorial position, as indicated by ^{1}H NMR (Figure 3). The *endo* face of the double bond is then much more accessible than in a chair−chair conformation. The greater flexibility of the 10-azabicyclo[4.3.1]decene ring system compared to that of the 8-azabicyclo[3.2.1]octene[31] and 9-azabicyclo[4.2.1]nonene[17a] ring systems may explain the modest diastereoselectivity observed.

Preliminary biological evaluation of azabicyclo derivatives as inhibitors of β-glucocerebrosidase gave very promising results (Table 1). The best inhibition was observed for the pentahydroxy compound **15a** with an IC_{50} value in the micromolar range similar to the one observed for a reference compound, 1,5-dideoxy-1,5-iminoxylitol.[13] Comparison of the IC_{50} values between **9a**, **9b**, and **14a** indicated that best inhibitions were obtained for 2,3-*trans*-2,6-*cis*-isomers with an endocyclic double bond. In addition, compound **15a** was found to be a quite potent inhibitor of almond β-glucosidase.[2]

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TABLE 1. IC_{50} Values for 9, 14a, and 15a toward β-Glucosidase Almond

	DIX[a,13]	**9a**	**9b**	**14a**	**15a**
β-glucosidases almonds	180	240	NI[b]	NI	2.0
β-glucocerebrosidase	2.3	77	NI	750	1.2

[a] 1,5-Dideoxy-1,5-iminoxylitol. [b] Less than 50% inhibition at 1 mM.

In conclusion, we have reported a rapid and stereodivergent access to polyhydroxylated azabicyclo[4.3.1]decenes by way of a double benzotriazolyl/carbon nucleophile exchange followed by a RCM. Preliminary investigations on the activity of these original non-natural calystegine analogues as glucocerebrosidase inhibitors indicated that these compounds constitute a new, promising class of iminosugars of therapeutic interest.

Experimental Section

Preparation of Allyl Derivatives 4. Allyl bromide (2.8 mL, 32.8 mmol) in anhydrous THF (30 mL) was added slowly to a THF suspension of activated Zn* (cf. Supporting Information), and the reaction was stirred for 15−30 min. Compounds **3** (mixture of regio- and stereoisomers, 3 g, 6.56 mmol) in anhydrous THF (450 mL) were then added slowly at room temperature, and the reaction mixture was stirred overnight (20 h). Water was then added, and the solids were removed by filtration over Celite. Saturated aqueous Na_2CO_3 (100 mL) was added, and filtration over Celite was carried out. The filtrate was extracted with AcOEt (3×), and the organic phases were dried and concentrated under vacuum. DMAP (0.401 g, 3.28 mmol) was added to a solution of this crude mixture (1.99 g, 6.56 mmol) in CH_2Cl_2 (100 mL). Then acetic anhydride (6.19 mL, 65.6 mmol) was added dropwise, and the reaction mixture was stirred overnight at room temperature. Water (20 mL) was added while keeping stirring for 30 min. Na_2CO_3 was added until a basic pH was reached. The aqueous phase was extracted using CH_2Cl_2 (3×), and the organic phases were combined, dried, and concentrated under vacuum. The desired products were obtained by purification on silica gel chromatography using EtOAc/PE (20/80) to afford compounds **4** (1.611 g, 3.75 mmol, 57% yield).

N-Deprotection. To compounds **4** (1.446 g, 3.37 mmol), dissolved in a 5:1 mixture of THF (190 mL) and water (37 mL), was added CAN (7.38 g, 13.47 mmol) in portions. When the reaction was complete (5 h), the mixture was treated with saturated aqueous $NaHCO_3$ until a basic pH was reached and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The different products were isolated by flash chromatography using EtOAc/PE (20/80): **5a** (29%, 331 mg, $R_f = 0.25$), **5b** (13%, 149 mg, $R_f = 0.05$). **5a**: IR (cm^{-1}) (NaCl, FTIR) 1749.0, 1247.6, 1225.7, 1030.0; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.71 (tdd, J = 6.0, 8.4, 14.5 Hz, 2H, H-8, H-11), 5.15−5.08 (m, 4H, H-9, H-12), 5.04 (t, J = 9.4 Hz, 1H, H-4), 4.78 (t, J = 9.6 Hz, 2H, H-3, H-5), 2.71 (td, J = 3.4, 9.2 Hz, 2H, H-2, H-6), 2.32 (dd, J = 5.2, 10.0 Hz, 2H, H-10, H-7), 2.07−2.00 (m, 2H, H-10, H-7), 2.02 (s, 6H, CH_3CO), 1.99 (s, 3H, CH_3CO), 1.68 (s, NH); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.7 (CO), 170.1 (CO), 134.0 (C-11, C-8), 119.0 (C-12, C-9), 75.7 (C-4), 74.0 (C-3, C-5), 56.5 (C-2, C-6), 36.3 (C-10, C-7), 21.0 (2 × CH_3CO), 20.9 (CH_3CO); HRMS $[M + H]^+$ 340.1753 (calcd for $C_{17}H_{26}NO_6$ 340.1760).

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Supporting Information Available: Additional procedures and characterization data for new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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