Desymmetrization of 7-dimethylphenylsilylcycloheptatriene. Towards the synthesis of new aminocycloheptitols†

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Desymmetrization of 7-silylcycloheptatriene through consecutive dihydroxylation and acyl-nitroso cycloaddition of the resulting diene moiety is described. Dihydroxylation occurred *anti* relative to the resident silicon group in line with previous observations made in the cyclohexadiene series. In contrast, the subsequent acyl-nitroso cycloaddition occurred with poor regiocontrol but good level of diastereocontrol *syn* to the bulky silyl substituent. The resulting cycloadducts were then elaborated further to provide a straightforward entry toward aminocycloheptitols in ten steps from commercially available tropylium salts.

Introduction

Aminoheptitols are seven membered-ring aminocyclitols, a class of significantly relevant natural products in medicinal chemistry.[1] Structurally, aminocyclitols are regarded as amino-substituted carbasugars.[2] Among these compounds, 1,3-diaminocyclitols are units of various aminoglycosides (*e.g.* streptomycin), which are particularly well known as antibacterial agents.[3] Aminocyclitols exhibit a wide structural diversity and consequently display various biological activities. In particular, many of them are glycosidase inhibitors due to their ability to act as carbohydrate mimics.[4] As glycosidases are involved in various fundamental biological pathways, glycosidase inhibitors are potent targets in the context of research of new therapeutic agents against miscellaneous affections (including viral infections, cancer, lysosomal diseases, diabetes, inflammatory processes *etc.*) extending the interest for such structures. Very recently, promising results have been reported concerning the role of aminocyclitols **1** and **2** as chaperone on glucocerebrosidases responsible for lysosomic Gaucher disease (Fig. 1).[5] C_7N-aminocyclitol derivatives, bearing a characteristic hydroxymethyl side chain[6] represent an important family of aminocarbasugars. For instance, the α-glycosidase inhibitor voglibose **3** has been shown to lower blood glucose level and is used in type 2 diabetes treatments.

The natural aminoheptitol **4** (Fig. 2) was isolated from the roots of *P. alkekengi var. francheti* in 1996 and was assumed to be a precursor or a degradation product of Calystegine A_5,[7] a bicyclic natural iminosugar. Similarly to many aminocarbasugars, aminoheptitols were quite recently reported to possess glycosidase inhibitory activities.[8]

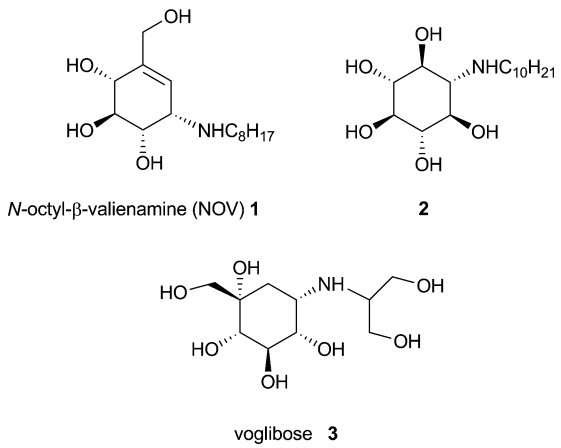

Fig. 1 Aminocyclitols of biological interest.

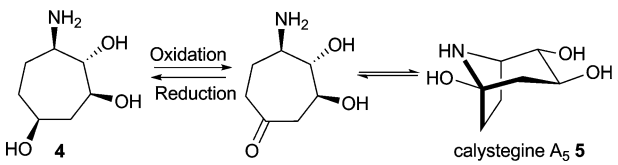

Fig. 2 Natural aminoheptitol **4** as potential calystegine A_5 **5** intermediate.

Several natural 5- and 6-membered ring aminocyclitols of therapeutic interest are known and the synthesis of such carbohydrates analogues has been broadly illustrated.[9] Surprisingly, if the synthesis of 7-membered ring analogues of these aminocarbasugars was initially reported in 1973,[10] it has attracted much less attention. To our knowledge, all the reported syntheses of aminocycloheptitols use the carbohydrate chiral pool as starting material, with the introduction of most hydroxyl substituents at the very beginning of the synthesis.[11] Three of them were based on an intramolecular nitrone-alkene cycloaddition of sugars.[11b–d]

In the course of our continuing interest in desymmetrization processes and its application to the synthesis of natural products,[12] we have explored the desymmetrization of cyclohexadienylsilanes and its use in the synthesis of cyclitols and aminopolyols.[13] We recently extended these investigations, by devising a novel approach to carbohydrate analogues relying on the desymmetrization

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of silyl-cycloheptatrienes, available from commercial tropylium salts.[14]

We report here the extension of the above approach to prepare original aminocycloheptitols of type **II**, using consecutive dihydroxylation and acyl-nitroso cycloaddition onto the silylcycloheptatriene **6** to introduce OH and NH_2 substituents (Fig. 3).

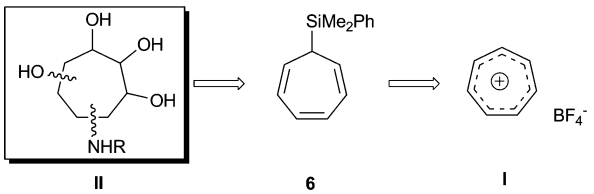
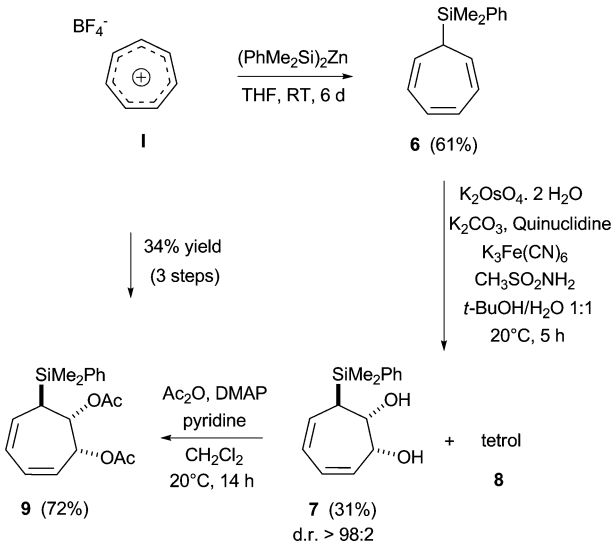


Fig. 3 Aminoheptitol disconnection from tropylium salt.

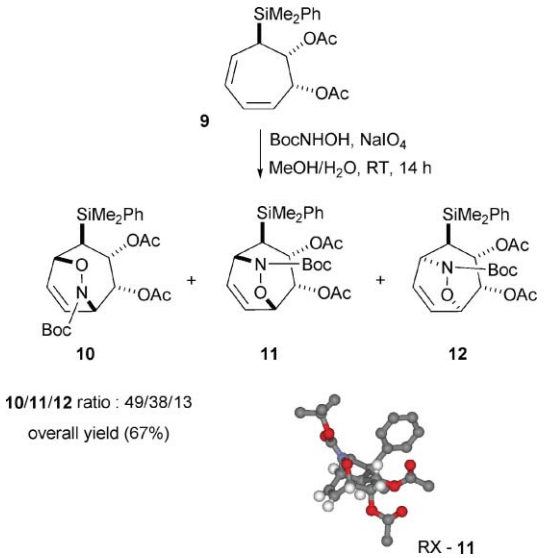
Results and discussion

We started our study with the gram-scale synthesis of phenyldimethylsilylcycloheptatriene **6**, obtained in satisfying yield, as a single isomer, through treatment of the tropylium tetrafluoroborate with the suitable zinc reagent (Scheme 1).[15] Dihydroxylation of **6** was then performed following standard Sharpless conditions,[16] affording the diol **7** and some tetrol **8** depending on the amount of potassium ferricyanide reoxidant used in excess. When the reaction was performed with only 2 equivalents of reoxidant, instead of three equivalents as usually indicated in standard protocols, tetrol **8** formation was limited.



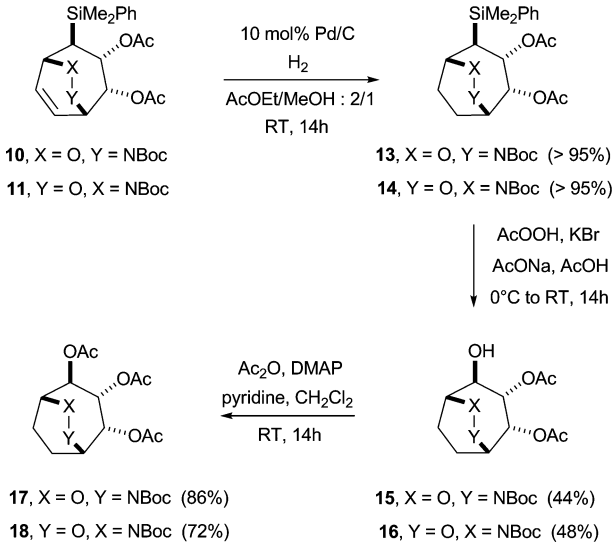
Scheme 1 Synthesis and dihydroxylation of 7-silylcycloheptatriene **6**.

The diol intermediate **7** is over-oxidised in the medium, as it likely reacts faster than the triene substrate for conformational reasons. It is worth noticing that tetrol **8**, not identified, was only recovered after the protection step as the tetraacetate derivative, **8** being partly soluble in the aqueous layer and difficult to extract from this medium. The overall yield of the sequence affording the bis-acetate compound **9** was found to be better when reactions were performed following a three-step one-pot sequential procedure (34% over three steps *versus* 13% if purification is performed at each step). We effectively observed that compound **6** is quite sensitive and tends to degrade even if stored at low temperature. Concerning the dihydroxylation step, the silicon group was found to be efficient at differentiating the two diastereotopic faces, leading to a complete diastereocontrol. As previously observed in the 6-membered ring series,[17] the osmium reagent approached *anti* relative to the silyl group mainly for steric reasons. Attempts were also made to protect the hydroxyl groups as benzyl ethers, but all the reaction conditions (acidic, basic or neutral using Dudley's reagent[18]), led to the degradation of the substrate, especially to the loss of the silyl group. Having in hand the bisacetate compound **9**, the other amino and hydroxyl groups were introduced through a cycloaddition process involving the diene moiety and an acyl-nitroso reagent, generated *in situ* from the corresponding hydroxylamine.[19] While the level of diastereocontrol was found to be high, the observed regioselectivity was low, as three of the four possible isomers were obtained, which could be separated by column chromatography (Scheme 2). When acetamide was used as a protective group, the four possible stereoisomers were obtained with very low diastereo- and regiocontrol and were found to be very difficult to separate.



Scheme 2 Acyl-nitroso cycloaddition onto the silylcycloheptadiene **9**.

The relative configuration of each isomer was determined unambiguously through X-ray diffraction studies of compound **11** and of derivatives for **10** and **12** (*vide infra*). Interestingly, the approach of the acyl-nitroso reagent mainly occurred *syn* to the silyl substituent, in contrast with what is usually observed in the 6-silylcyclohexa-1,4-diene series,[17b,c,20] where approach of reagents on both double bonds occurs *anti* relative to the silicon group for steric reasons (for instance when osmylation is followed by cyclopropanation). Structural diversity was then obtained by elaborating further the two major isomers (Scheme 3). We first performed the C–Si oxidation, under classical Fleming conditions,[21] after hydrogenation of the double bond. The resulting alcohols **15** and **16** were then protected as acetate to provide the compounds **17** and **18** in good yields. A three-step sequence without further purification from compounds **10** and **11** was found to be very efficient, providing compounds **17** and **18** in respectively 56% and 40% overall yield.



Scheme 3 Oxidation of the C–Si bond.

Among standard conditions, $Mo(CO)_6$ proved to be the most reliable reagent to perform the N–O bond reductive cleavage.[19b] Compounds **19** and **20** were thus obtained in 80% and 95% yield respectively, both as isomeric mixtures due to the ability of acetate groups to migrate onto the neighboring free hydroxyl group. Such migrations were unambiguously established through X-ray crystallographic studies of isomers in both series (Fig. 4). Final deprotection of the acetate protective groups to get aminoheptitols then proved to be troublesome. After extensive efforts, mild and efficient conditions were eventually found, using a basic carbonate resin (DOWEX) to deprotect acetate groups, and an acidic resin to remove the carbamate moiety.[22] The original aminoheptitols **22** and **24** (Scheme 4) were finally obtained cleanly in moderate, but non optimized yields, eluting the acidic resin with a 15% ammonia solution. It is worth noticing that the use of standard conditions, *i.e.* a large excess of TFA, was not efficient in our case, leading to incomplete deprotection of the carbamate. Moreover, when the deprotection was performed on a substrate bearing a free amino group, acetate migrations occurred onto nitrogen. In our hands, the resulting amide was then found impossible to cleave.

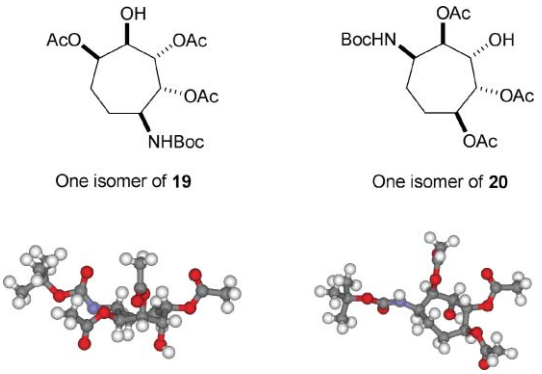
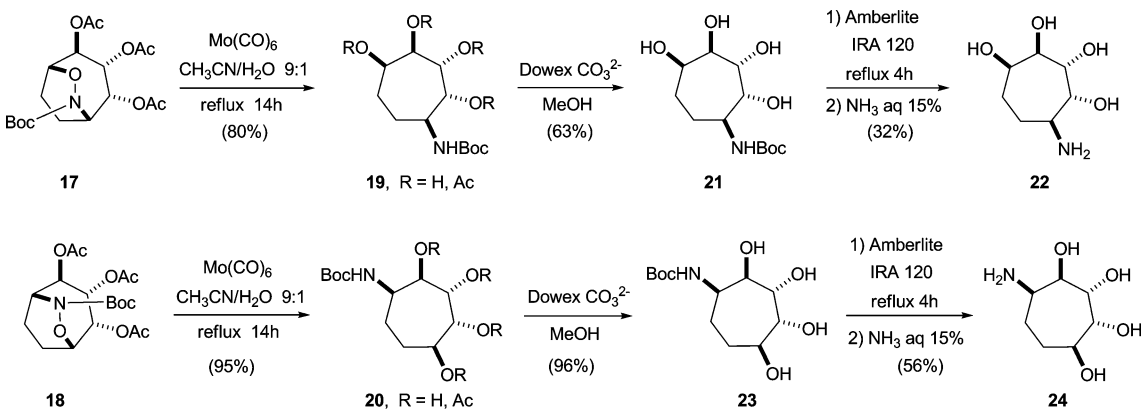


Fig. 4 Acetate migration structural probe.

The inhibitory activity of compounds **22** and **24** against a range of commercially available glycosidases (α-glucosidase, β-glucosidase, α-galactosidase, β-galactosidase, α-mannosidase, β-mannosidase, α-L-fucosidase, β-xylosidase) was then evaluated.[23] Unfortunately, in both cases, no inhibition was observed at 100 μM.

Conclusions

As a conclusion, we have described along these lines a short and efficient access to aminocycloheptitols, through desymmetrization and functionalization of 7-silylcycloheptatrienes. These aminocyclitols are obtained in 10 steps and only four purification operations from a commercially available tropylium salt. Complete diastereocontrol was observed during the dihydroxylation (desymmetrization). Interestingly, while the former functionalization occurred *anti* relative to the silicon substituent, the acyl-nitroso reagent approached *syn* to the silicon, in contrast with previous studies with analogous silyl-cyclohexadiene precursors. This study thus provides further insight into the reactivity of silylated polyenes toward electrophilic and dienophile reagents.[13,17,20] The functionalization of these 7-silylcycloheptatrienes has been performed in racemic series but might be rapidly extended into an enantioselective series following recent reports by Schreiner *et al.*[24] on organocatalytic desymmetrization and enantioselective kinetic resolution of 1,2-diols.



Scheme 4 Elaboration of original aminocycloheptitols **22** and **24**.

Experimental part

7-(Dimethyl(phenyl)silyl)cyclohepta-3,5-diene-1,2-diyl diacetate (9)

A three step sequence from the tropylium tetrafluoroborate can be carried out without purification. Each step was considered as complete and a yield of 34% was obtained over three steps.

Hammered lithium wire (1 g, 146 mmol, 13 eq) was added to THF (50 mL). The mixture was cooled to 0 °C and chlorodimethyl(phenyl)silane (5 mL, 30 mmol, 2.7 eq) was added. The mixture turned dark red within 30 min. The reaction was allowed to warm to room temperature overnight and the resulting lithiated species was titrated using phenolphthalein as color indicator and a 0.120 M solution of HCl. The concentration was found to be 0.52 M (27 mmol, 2.4 eq)). In parallel, $ZnCl_2$ (1.8 g, 13.49 mmol, 1.2 eq) was gun-heated under vacuum until complete melting. After complete cooling the flask was placed under argon and THF (37.5 mL) was added, sonication helped the dissolution of $ZnCl_2$. The mixture was cooled to 0 °C and the lithiated species was transferred *via* a cannula, the reaction mixture turned immediately green. The mixture was stirred during half an hour and a suspension of tropylium tetrafluoroborate **I** (ALFA AESAR 2 g, 11.2 mmol, 1 eq) in THF (37.5 mL) was prepared. It was stirred during half an hour more and then the zinc reagent was transferred into it *via* a cannula. The resulting solution was dark green and was left stirring until the coloration turned bright yellow (from 4 to 14 days).

The reaction was quenched using saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 50 mL). Combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to provide an orange oily product which could be purified by chromatography on silica gel (petroleum ether). See ref. 14 for description.

"AD-mix like" mixture was prepared by dry mixing K_2CO_3 (2.9 g, 22.5 mmol, 2 eq), $K_2OsO_4{\cdot}2H_2O$ (ALDRICH, 166 mg, 0.45 mmol, 0.04 eq), $K_3Fe(CN)_6$ (7.4 g, 22.5 mmol, 3 eq), quinuclidine (50 mg, 0.45 mmol, 0.04 eq) in a round bottomed flask for 10 min. A mixture of *t*-BuOH/H_2O (1 : 1, 56 mL/56 mL) and methanesulfonamide (1 g, 11.2 mmol, 1 eq) were added. After 10 min the resulting orange mixture was added in one portion onto the cycloheptatriene **6** (11.2 mmol, 1 eq). The reaction mixture quickly thickened and turned brown. After 3 h, no starting material remained and the reaction was quenched with solid sodium sulfite (Na_2SO_3). Extraction was carried out with EtOAc (3 × 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure (*t*BuOH was co-evaporated with hexane) to provide a brown pasty residue mixture of **7** and **8**.

The crude product (11.2 mmol, 1 eq) was dissolved CH_2Cl_2 (112 mL). Pyridine (7.3 mL, 90 mmol, 8 eq), acetic anhydride (6.5 mL, 90 mmol, 8 eq) and DMAP (catalytic amount) were then added. No starting material remained in the orange solution after 9 h (TLC control), and quench was performed using saturated aqueous NH_4Cl solution. Extraction was carried out using CH_2Cl_2 (3 × 50 mL), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure (pyridine and acetic anhydride were co-evaporated with toluene) to provide a yellow oil. The residue was then purified by column chromatography on silica gel (90 : 10, Petroleum ether/EtOAc) to provide the acetylated product **9** (1.3 g, 34%) as a yellow oil. **Rf** 0.61 (80 : 20 Petroleum ether/EtOAc). **FTIR** (film, NaCl): 3070, 3022, 2960, 1737, 1607, 1428, 1372, 1248, 1028 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 7.59–7.51 (m, 2H, CH_{ar}), 7.39–7.30 (m, 3H, CH_{ar}), 5.92–5.82 (m, 1H, $CH_{olefinic}$), 5.81–5.72 (m, 1H, $CH_{olefinic}$), 5.65–5.52 (m, 2H, $1CH_{olefinic}$ + 1CH-O), 5.45–5.40 (m, 1H, CH–O), 5.36–5.28 (m, 1H, $CH_{olefinic}$), 2.68 (t, J = 5.3 Hz, 1H, CH–Si), 2.03 (s, 3H, CH_3 of acetate), 1.98 (s, 3H, CH_3 of acetate), 0.45 (s, 6H, CH_3–Si). **^{13}C NMR** ($CDCl_3$, 75.5 MHz_f): δ (ppm) = 170.8 (Cq, C═O of acetate), 170.2 (Cq, C═O of acetate), 135.9 (Cq, ar), 134.2 (CH, ar), 131.0 (CH, olefinic), 129.6 (CH, ar), 128.0 (CH, ar), 126.4 (CH, olefinic), 125.4 (CH, olefinic), 122.2 (CH, olefinic), 72.9 (CH, CH–O), 70.3 (CH, CH–O), 37.3 (CH, CH–Si), 21.3 (CH_3, acetate), 21.1 (CH_3, acetate), –4.2 (CH_3, CH_3–Si), –4.4 (CH_3, CH_3–Si). **HRMS** (ESI): calc. for $C_{19}H_{24}O_4SiNa$ $[M+Na]^+$: 367.1342, found: 367.1339.

General procedure for cycloaddition

$NaIO_4$ (4.2 g, 31.3 mmol, 10 eq) was added to a solution of the diacetate **9** (1 g, 3.13 mmol, 1 eq) in a mixture of methanol–water (100 mL/39 mL). A solution of hydroxamic acid (6.7 g, 31.3 mmol, 10 eq) in methanol (17 mL) was then added slowly over 6 h using a syringe pump leading to a very thick orange mixture. The medium was stirred overnight and then the reaction was buffered using a saturated aqueous solution of $NaHCO_3$ (40 mL) and quenched using a saturated aqueous Na_2SO_3 solution (40 mL). Extraction was carried out using EtOAc (3 × 40 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the organic solvents led to a biphasic mixture, insoluble salts were removed by a quick filtration over silica gel pad using EtOAc as eluent. After evaporation, ^{1}H NMR spectra of the resulting residue was performed in C_2D_6CO to split the signals and allowed the ratio measurement by integration of the relevant signals. The crude products were then purified by column chromatography on silica gel (85 : 15 Petroleum ether/EtOAc) and 3 compounds (**10**/**11**/**12**) were isolated.

7-(*tert*-Butoxycarbonyl)-4-(dimethyl(phenyl)silyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-2,3-diyl diacetate (10)

Major cycloadduct. The product was obtained as a yellow powder (431 mg, 29%). **Rf** 0.29 (80 : 20 Petroleum ether/EtOAc) **mp**: 92–93 °C. **FTIR** (film, NaCl): 3068, 2977, 1744, 1427, 1368, 1248, 1029 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 250 MHz): δ (ppm) = 7.66–7.53 (m, 2H, CH_{ar}), 7.42–7.30 (m, 3H, CH_{ar}), 6.44–6.23 (m, 2H, $CH_{olefinic}$), 5.52 (t, J = 4.2 Hz, 1H, CH–O), 5.25 ($t_{appearing}$, J_1 = 3.8 Hz, J_2 = 3.6 Hz, 1H, CH–O), 4.84–4.73 (m, 1H, CH–N), 4.70–4.59 (m, 1H, CH–O), 2.02 (s, 3H, CH_3 of acetate), 1.86 (s, 3H, CH_3 of acetate), 1.72–1.61 (m, 1H, CH–Si), 1.48 (s, 9H, CH_3 of Boc), 0.50 (s, 3H, CH_3–Si), 0.47 (s, 3H, CH_3–Si). **^{13}C NMR** ($CDCl_3$, 75.5 MHz_f): δ (ppm) = 169.9 (C_q, C═O of acetate), 169.3 (C_q, C═O of acetate), 155.5 (C_q, C═O of Boc), 136.5 (C_q, ar), 134.2 (CH, ar), 132.2 (CH, olefinic), 129.5 (CH, ar), 128.0 (CH, ar or olefinic), 127.9 (CH, ar or olefinic), 82.2 (C_q, Boc), 73.6 (CH, CH–O), 72.7 (CH, CH–O), 69.4 (CH, CH–O), 55.4 (CH, CH–N), 36.5 (CH, CH–Si), 28.3 (CH_3, Boc), 21.0 (CH_3, acetate), 20.8 (CH_3,

acetate), –3.2 (CH_3, CH_3–Si), –3.6 (CH_3, CH_3–Si). **HRMS** (ESI): calc. for $C_{24}H_{33}NO_7SiNa$ $[M+Na]^+$ = 498.1924, found: 498.1923.

7-(*tert*-Butoxycarbonyl)-2-(dimethyl(phenyl)silyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-3,4-diyl diacetate (11)

Second major cycloadduct. The product was obtained as a white solid (312 mg, 21%). **Rf** 0.22 (80 : 20 Petroleum ether/EtOAc) **Anal**. **calcd**. for $C_{24}H_{33}NO_7Si$, C, 60.61; H, 6.99; N, 2.94 found C, 60.35; H, 6.92; N, 2.88. **mp**: 118–119 °C. **FTIR** (film, NaCl): 2978, 1742, 1428, 1368, 1248, 1051 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 7.64–7.48 (m, 2H, CH_{ar}), 7.41–7.30 (m, 3H, CH_{ar}), 6.52 (t, J = 7.9 Hz, 1H, $CH_{olefinic}$), 6.16 ($t_{appearing}$, J_1 = 8.7 Hz, J_2 = 7.0 Hz, 1H, $CH_{olefinic}$), 5.58 ($t_{appearing}$, J_1 = 4.7, J_2 = 4.5 Hz, 1H, CH–O), 5.20 ($t_{appearing}$, J_1 = 4.3 Hz, J_2 = 4.1 Hz, 1H, CH–O), 4.83–4.67 (m, 2H, CH–O and CH–N), 2.00 (s, 3H, CH_3 of acetate), 1.82 (s, 3H, CH_3 of acetate), 1.76 ($t_{appearing}$, J = 4.5 Hz, 1H, CH–Si), 1.38 (s, 9H, CH_3 of Boc), 0.49 (s, 3H, CH_3–Si), 0.44 (s, 3H, CH_3–Si). **^{13}C NMR** ($CDCl_3$, 75.5 $MHz_,$): δ (ppm) = 169.8 (Cq, C═O of acetate), 169.6 (Cq, C═O of acetate), 157.2 (Cq, C═O of Boc), 136.9 (Cq, ar), 135.0 (CH, ar), 134.1 (CH, olefinic), 129.4 (CH, ar), 128.0 (CH, olefinic), 125.7 (CH, ar), 82.2 (Cq, Boc), 72.9 (CH, CH–O), 72.8 (CH, CH–O), 69.3 (CH, CH–O), 54.2 (CH, CH–N), 32.1 (CH, CH–Si), 28.2 (CH_3, Boc), 21.0 (CH_3, acetate), 20.8 (CH_3, acetate), –3.2 (CH_3, CH_3–Si), –3.6 (CH_3, CH_3–Si). **HRMS** (ESI): calc. for $C_{24}H_{33}NO_7SiNa$ $[M+Na]^+$ = 498.1924, found: 498.1927.

7-(*tert*-Butoxycarbonyl)-2-(dimethyl(phenyl)silyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-3,4-diyl diacetate (12)

Minor cycloadduct. The product was obtained as a white powder (119 mg, 8%). **Rf** 0.16 (80 : 20 Petroleum ether/EtOAc) **mp**: 99–102 °C. **FTIR** (film, NaCl): 2977, 1744, 1427, 1368, 1246, 1056 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 250 MHz): δ (ppm) = 7.58–7.41 (m, 2H, CH_{ar}), 7.41–7.29 (m, 3H, CH_{ar}), 6.24 ($t_{appearing}$, J_1 = 8.7 Hz, J_2 = 6.5 Hz, 1H, $CH_{olefinic}$), 6.01 ($t_{appearing}$, J_1 = 7.5 Hz, J_2 = 8.5 Hz, 1H, $CH_{olefinic}$), 5.22 ($t_{appearing}$, J_1 = 4.8 Hz, J_2 = 5.0 Hz, 1H, CH–O), 5.04 (dd, J_1 = 4.3 Hz, J_2 = 11.9 Hz, 1H, CH–O), 4.90–4.74 (m, 2H, CH–O and CH–N), 2.13 (s, 3H, CH_3 of acetate), 1.71 (s, 3H, CH_3 of acetate), 1.41 (s, 9H, CH_3 of Boc), 1.26–1.10 (m, 1H, CH–Si), 0.38 (s, 3H, CH_3–Si), 0.34 (s, 3H, CH_3–Si). **^{13}C NMR** ($CDCl_3$, 100.6 $MHz_,$): δ (ppm) = 170.9 (Cq, C═O of acetate), 169.9 (Cq, C═O of acetate), 155.0 (Cq, C═O of Boc), 136.5 (Cq, ar), 133.8 (CH, ar), 131.1 (CH, olefinic), 129.7 (CH, ar), 128.2 (CH, ar), 127.6 (CH, olefinic), 81.8 (Cq, Boc), 71.6 (CH, CH–O), 70.4 (CH, CH–O), 70.0 (CH, CH–O), 53.6 (CH, CH–N), 29.1 (CH, CH–Si), 28.4 (CH_3, CH_3 of Boc), 21.0 (CH_3, acetate), 20.8 (CH_3, acetate), –3.2 (CH_3, CH_3–Si), –3.5 (CH_3, CH_3–Si). **HRMS** (ESI): calc. for $C_{24}H_{33}NO_7SiNa$ $[M+Na]^+$ = 498.1924, found: 498.1928.

7-(*tert*-Butoxycarbonyl)-6-oxa-7-azabicyclo[3.2.2]nonane-2,3,4-triyl triacetate (17)

To a solution of the olefinic compound **10** (1281 mg, 2.69 mmol, 1 eq) in a 2 : 1 mixture of EtOAc–MeOH (0.12 M, 15 mL+7.5 mL), 10% Pd/C (287 mg of the mixture, 0.27 mmol of palladium, 0.1 eq) was added. Vacuum followed by nitrogen refill was performed 3 times. Then vacuum followed by dihydrogen refill was performed twice and the mixture was stirred overnight under dihydrogen atmosphere. Palladium was removed by filtration on celite pad, using EtOAc as eluent. **13** was obtained as a white sticky foam.

KBr (640 mg, 5.38 mmol, 2 eq) and NaOAc (927 mg, 11.3 mmol, 4.2 eq) at 0 °C, acetic acid (6.1 mL, 0.44 M) was added to **13** (2.69 mmol, 1 eq). The mixture solidified and peracetic acid (9.78 mL, 0.275 M, 32 wt% in acetic acid) was added over 10 min, the liquid mixture then bubbled and turned orange. 5 min after the addition, the ice bath was removed, and the mixture was stirred overnight. The reaction was quenched using a 25% aqueous solution of $Na_2S_2O_3$ at 0 °C, followed by saturation of the aqueous phase with $Na_2S_2O_3$. The two phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed first with a saturated aqueous solution of $NaHCO_3$, secondly with brine and were then dried over sodium sulfate. An orange crude mixture containing **15** was obtained.

To a solution of this residue (2.69 mmol, 1 eq) in dichloromethane (27 mL, 0.1 M), pyridine (0.9 mL, 10.76 mmol, 4 eq), acetic anhydride (0.8 mL, 10.76 mmol, 4 eq) and DMAP (catalytic amount) were added. The reaction mixture was stirred overnight. It was then quenched using NH_4Cl saturated aqueous solution and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed successively with H_2O and brine and were dried over Na_2SO_4. Solvents were evaporated under reduced pressure (pyridine and acetic anhydride were co-evaporated with toluene). The crude was purified on silica gel column chromatography (60 : 40 Pentane/EtOAc) providing **17** as a vitrified colorless oil (604 mg, 56%).

FTIR (film, NaCl): 2979, 1751, 1460, 1370, 1228, 1048 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 250 MHz): δ (ppm) = 5.57–5.40 (m, 2H, CH–O or/and CH–N), 4.95 (d, J = 8.1 Hz, 1H, CH–O or CH–N), 4.52 ($t_{appearing}$, J_1 = 5.3 Hz, J_2 = 5.8 Hz, 1H, CH–O or CH–N), 4.33 ($d_{appearing}$, J = 5.2 Hz, 1H, CH–O or CH–N), 2.14–1.86 (m, 13H, $2CH_2$ + CH_3 of 3 acetate$_,$), 1.43 (s, 9H, CH_3 of Boc). **^{13}C NMR** ($CDCl_3$, 62.9 $MHz_,$): δ (ppm) = 170.3 (Cq, C═O of acetate), 169.3 (Cq, C═O of acetate), 154.2 (Cq, C═O of Boc), 82.3 (Cq, Boc), 76.8 (CH, CH–O), 76.2 (CH, CH–O), 69.3 (CH, CH–O), 68.3 (CH, CH–O), 51.5 (CH, CH–N), 28.2 (CH_3, Boc), 20.8 (CH_3 or CH_2), 20.71 (CH_3 or CH_2), 20.68 (CH_3 or CH_2), 20.6 (CH_3 or CH_2), 16.2 (CH_2). **HRMS** (ESI): calc. for $C_{18}H_{27}NO_9Na$ $[M+Na]^+$ = 424.15835 found: 424.1582.

7-(*tert*-Butoxycarbonyl)-6-oxa-7-azabicyclo[3.2.2]nonane-2,3,4-triyl triacetate (18)

Following the same experimental protocol as described above for **17** synthesis, **11** (581 mg, 1.22 mmol, 1 eq) was used as starting material providing **18** as a white crystalline solid (196 mg, 40%) after purification on silica gel chromatography (80 : 20 Pentane/EtOAc).

Rf 0.08 (60 : 40, Petroleum ether/EtOAc) **Anal**. **calcd**. for $C_{18}H_{27}NO_9$, C, 53.86; H, 6.78; N, 3.49, found C, 53.81; H, 6.81; N, 3.30. **mp**: 133–134 °C. **FTIR** (film, NaCl): 2979, 1746, 1699, 1430, 1370, 1226, 1047, 918 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 250 MHz): δ (ppm) = 5.66–5.51 (m, 2H, 2 CH–O), 5.07–4.97 (m, 1H, CH–O), 4.64–4.50 (m, 2H, CH–O and CH–N), 2.27–2.12 (m, 1H, 1H of CH_2), 2.05 (s, 1.5H, CH_3 of acetate), 2.04 (s, 1.5H, CH_3 of acetate), 2.00 (s, 1.5H, CH_3 of acetate), 1.99 (s, 1.5H, CH_3 of acetate), 1.96 (s, 1.5H, CH_3 of acetate), 1.95 (s, 1.5H, CH_3 of acetate), 1.92–1.79

(m, 3H,CH_2), 1.43 (s, 4.5H, CH_3 of Boc), 1.42 (s, 4.5H, CH_3 of Boc). **^{13}C NMR** ($CDCl_3$, 75.5 MHz_J: δ (ppm) = 170.3 (Cq, C═O of acetate), 169.6 (Cq, C═O of acetate), 169.5 (Cq, C═O of acetate), 155.1 (Cq, C═O of Boc), 82.0 (Cq, Boc), 76.6 (CH, CH–O), 73.4 (CH, CH–O), 70.9 (CH, CH–O), 70.6 (CH, CH–O), 53.7 (CH, CH–N), 28.2 (CH_3, Boc), 20.9 (CH_3, acetate), 20.7 (CH_3, acetate), 19.9 (CH_2), 19.3 (CH_2). **HRMS** (ESI): calc. for $C_{18}H_{27}NO_9Na$ $[M+Na]^+$ = 424.15835 found: 424.1577.

4-(*tert*-Butoxycarbonylamino)-7-hydroxycycloheptane-1,2,3-triyl triacetate and regioisomers (19)

To a solution of hydroxylamine **17** (199 mg, 0.5 mmol, 1 eq) in a 9 : 1 CH_3CN–H_2O (0.1 M, 4.5/0.5 mL) mixture, $Mo(CO)_6$ (ALDRICH-98%, 162 mg, 0.6 mmol, 1.3 eq) was added. The white mixture was refluxed overnight and rapidly turned black when temperature increased. Reflux was then stopped and silica was used to quench the reaction. The mixture was then filtered and the products were eluted with EtOAc. Solvent was evaporated under reduced pressure. The residue was purified on silica gel column chromatography (60 : 40 Pentane/EtOAc) affording a mixture of **19** and regioisomers as a white solid (161 mg, 80%). Spectra of the isomers mixture are available in ESI.†

tert-Butyl-2,3,4,5-tetrahydroxycycloheptylcarbamate (21)

To a solution of the acetate compounds mixture (**19 and regioisomers**) (482 mg, 1.2 mmol) in methanol, DOWEX CO_3^{2-} (2 spoons) was added. The mixture was stirred overnight. It was then filtered and the resin was rinsed thoroughly with methanol. The clean material **21** was obtained after evaporation as a white solid (320 mg, 96%). No further purification was performed.

Rf 0.23 (90 : 10 CH_2Cl_2–MeOH). **mp**: 149–151 °C. **FTIR** (neat) : 3334, 1725, 1519, 1455, 1366, 1157 cm^{-1}.**^{1}H NMR** (CD_3OD, 300 MHz): δ (ppm) = 4.05–3.91 (m, 3H, 3 CH–O), 3.82–3.78 (m, 1H, CH–O), 3.78–3.65 (m, 1H, CH–N), 1.96–1.79 (m, 2H, CH_2), 1.79–1.61 (m, 2H, CH_2), 1.47 (s, 9H, CH_3 of Boc). **^{13}C NMR** (CD_3OD, 75.5 MHz_J: δ (ppm) = 158.0 (Cq, C═O of Boc), 80.0 (Cq, Boc), 74.7 (CH, CH–O), 73.9 (CH, CH–O), 73.2 (CH, CH–O), 71.8 (CH, CH–O), 54.1 (CH, CH–N), 28.8 (CH_3, CH_3 of Boc), 28.4 (CH_2), 27.2 (CH_2). **HRMS** (ESI): calc. for $C_{12}H_{23}NO_6Na$ $[M+Na]^+$ = 300.14231 found: 300.1419

5-Aminocycloheptane-1,2,3,4-tetrol (22)

To a solution of carbamate **21** (180 mg, 0.65 mmol) in methanol (8 mL) Amberlite IRA 120 (1 spoon) was added. The mixture was refluxed during 2 h, stirred overnight at room temperature and refluxed again for additional 2 h. The resin was then separated by filtration and placed in a round bottomed flask. The flask was cooled to 0 °C and a 15% NH_3 aqueous solution was added. After 15 h of stirring, the resin was eliminated by filtration and the solution was evaporated under reduced pressure providing the colorless oil (63 mg, 56%).

^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 4.15–3.91 (m, 2H, 2 CH–O), 3.91–3.76 (m, 2H, 2 CH–O), 3.14–2.96 (m, 1H, CH–N), 2.05–1.77 (m, 2H, CH_2), 1.77–1.55 (m, 2H, CH_2). **^{13}C NMR** (CD_3OD, 75.5 MHz_J: δ (ppm) = 74.9 (CH, CH–O), 74.8 (CH, CH–O), 74.4 (CH, CH–O), 71.7 (CH, CH–O), 53.2 (CH, CH–N), 28.4 (CH_2), 28.3 (CH_2). **HRMS** (ESI): calc. for $C_7H_{16}NO_4$ $[M+H]^+$ = 178.10793 found: 178.1076.

4-(*tert*-Butoxycarbonylamino)-7-hydroxycycloheptane-1,2,3-triyl triacetate (20) and regioisomers

Following the same experimental protocol as described above for **19** synthesis, **18** (152 mg, 0.38 mmol, 1 eq) was used as starting material providing **20** as a white solid (152 mg, 99%) purified by silica gel column chromatography (60 : 40 Pentane/EtOAc). Spectra of the isomers mixture are available in the ESI.

tert-Butyl 2,3,4,5-tetrahydroxycycloheptylcarbamate (23)

Following the same experimental protocol as described above for **21** synthesis, **20** (98 mg, 0.24 mmol) was used as starting material providing **23** as a vitrified colorless solid (42 mg, 63%) after evaporation. No further purification was required.

Rf 0.14 (90 : 10 CH_2Cl_2–MeOH) **mp**: 154–155 °C. **FTIR** (film, NaCl): 3351, 3003, 2920, 1686, 1507, 1452, 1363, 1172, 1087 cm^{-1}.**^{1}H NMR** (CD_3OD, 400 MHz): δ (ppm) = 3.99–3.90 (m, 2H, CH–O), 3.88–3.77 (m, 3H, CH–O and CH–N), 2.11–1.95 (m, 1H, 1H of CH_2), 1.95–1.83 (m, 1H, 1H of CH_2), 1.83–1.68 (m, 1H, 1H of CH_2), 1.45 (s, 10H, 9H of Boc + 1H of CH_2)**^{13}C NMR** (CD_3OD, 100.6 MHz_J: δ (ppm) = 157.5 (Cq, C═O of Boc), 80.1 (Cq, Boc), 76.2 (CH, CH–O), 75.7 (CH, CH–O), 73.8 (CH, CH–O), 72.6 (CH, CH–O), 53.0 (CH, CH–N), 32.0 (CH_2), 28.7 (CH_3, CH_3 of Boc), 25.2 (CH_2). **HRMS** (ESI): calc. for $C_{12}H_{23}NO_6Na$ $[M+Na]^+$ = 300.14231 found: 300.1420.

5-Aminocycloheptane-1,2,3,4-tetrol (24)

Following the same experimental protocol as described above for **22** synthesis, **23** (40 mg, 0.14 mmol) was used as starting material providing **24** (8 mg, 32%) as a colorless oil.

^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) = 4.01–3.90 (m, 2H, 2 CH–O), 3.86–3.76 (m, 2H, 2 CH–O), 3.13 (dt, J_1 = 9.5 Hz, J_2 = 3.2 Hz, 1H, CH–N), 2.05–1.68 (m, 3H, CH_2), 1.58–1.47 (m, 1H, 1H of CH_2). **^{13}C NMR** (CD_3OD, 75.5 MHz_J: δ (ppm) = 75.6 (CH, CH–O), 74.8 (CH, CH–O), 73.9 (CH, CH–O), 72.1 (CH, CH–O), 52.9 (CH, CH–N), 30.7 (CH_2), 26.3 (CH_2). **HRMS** (ESI): calc. for $C_7H_{16}NO_4$ $[M+H]^+$ = 178.10793 found: 178.1082.

Enzyme inhibitions

Glycosidase activities were determined at 25 °C at the optimal pH of each enzyme[25] with the corresponding *p*-nitrophenyl glycopyranoside as substrate against α-D glucosidase (EC 3.2.1.20) from baker's yeast (9 units per mg of protein, *K*m 0.3 mM, pH 7), β-D-glucosidase (EC3.2.1.21) from almonds (20–40 units per mg of protein, *K*m 1.3 mM, pH 4.5), α-D galactosidase (EC 3.2.1.22) from green coffee beans (*K*m 0.25 mM, pH 6.5), β-D galactosidase (EC 3.2.1.23) from Escherichia coli (*K*m 0.4 mM, pH 7), α-D-mannosidase (EC 3.2.1.24) from Jack beans (*ca.* 20 units per mg of proteins, *K*m 2 mM, pH 4.5), β-D-mannosidase (EC 3.2.1.25) from Helix pomatia (*K*m 0.5 mM, pH 4.5), α-L-fucosidase (EC 3.2.1.51) from bovine kidney (5–15 units per mg, *K*m 0.3 mM, pH 5.8) and β-D-xylosidase (EC 3.2.1.37) from *Aspergilus niger* (*K*m 0.2 mM, pH 4.5).

Glycosidases and corresponding *p*-nitrophenyl glycopyranosides were obtained from Sigma Chemical Co. The release of *p*-nitrophenol was measured continuously at 400 nm to determine initial velocities.[26] All kinetics were started by enzyme addition in a 1 mL assay medium using substrate concentrations around the *K*m value of each enzyme. IC_{50} values were determined for weak inhibitions (at a substrate concentration equal to *K*m value) and correspond to the inhibitor concentration required for 50% inhibition of the enzyme in our experimental conditions.

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