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# Skeletal rearrangement of seven-membered iminosugars: Synthesis of (−)-adenophorine, (−)-1-epi-adenophorine and derivatives and evaluation as glycosidase inhibitors

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ABSTRACT

The mirror image of natural product (+)-adenophorine along with its 1-epi-, 1-homo-analogs and other derivatives have been synthesized and evaluated as glycosidase inhibitors. The synthetic strategy is based on the skeletal rearrangement of tetrahydroxylated *C*-alkyl azepanes obtained via a Staudinger/azaWittig/alkylation sequence starting from a sugar-derived azidolactol. Several organometallic species have been investigated for the alkylation step including organomagnesium, organolithium, organozinc, organoaluminum and organocerium reagents. While diallylzinc proved to be the most efficient to introduce an allyl substituent, disappointing results were obtained with the other organometallic species leading either to lower yields or no reaction. Enzymatic assays indicate that (−)-adenophorine is a moderate α-L-fucosidase inhibitor.



## 1. Introduction

Iminosugars, sugar analogs in which the endocyclic oxygen has been replaced by nitrogen, constitute a major class of sugar mimetics.[1] Their promising therapeutic potential is illustrated by the approval of Glyset®[2] and Zavesca®[3] (Fig. 1) for the treatment of type II diabetes and Gaucher disease, respectively. Many other pathologies are currently under investigation[4] including cystic fibrosis[5] and Fabry disease.[6] Glyset® and Zavesca® both exhibit an alkyl substituent on the nitrogen that improves the lipophilic balance of these polyhydroxylated molecules. Moving the alkyl chain from the endocyclic nitrogen to the pseudoanomeric carbon leads to another class of important iminosugars, the iminosugar C-glycosides that can be seen as glycoconjugates with a stable substituent at the C-1 position. Iminosugar C-glycosides are usually more potent and selective compared to the more synthetically accessible iminoalditols, an improved efficacy that can be attributed in part to a better location of the alkyl chain in order to favourably interact with the target glycoenzyme.[7] As a consequence, a vast array of pharmacophores has been introduced at this position yielding iminosugars with improved selectivity and/or potency towards glycosidases,[8] enabling the modulation of new therapeutically relevant pathways.[9]

Iminosugar C-glycosides have also been identified as natural products.[10] Among them, (+)-adenophorine was isolated by Asano in 2000 along with its glucoside from *Adenophorae radix*, a traditional Chinese crude drug named 'Sya-zin'.[11] It is a rare example of an α-D-HNJ homolog with a hydrophobic alkyl substituent at the pseudoanomeric position. It inhibits a selection of glycosidases in vitro including several α-glucosidases and coffee bean α-galactosidase. Its total synthesis has been achieved in 2007 by Lebreton[12] and its structure firmly established in 2003 by Davis[13] through the synthesis of its enantiomer (−)-adenophorine, a L-iminosugar C-glycoside (Fig. 1).

The absence of inhibition data for (−)-adenophorine combined with the recent biological potential of unnatural L-iminosugars[14] including their synergistic effect with D-iminosugars,[15] prompted us to explore an alternative chemical approach to (−)-adenophorine and analogs and evaluate them as glycohydrolase inactivators.

Synthesis of iminosugar C-glycosides has been extensively investigated.[16] Most of the reported synthetic strategies are based either on an intramolecular reductive amination or on the late alkylation of the iminosugar pseudoanomeric carbon through the use of an electrophilic iminosugar donor. This latter approach appears as the best strategy for late stage diversification but has been much less explored due to the difficult generation of stable electrophilic iminosugars. Piperidinose donors have been developed by Johnson,[17] Vasella[18] and Schmidt[19] and nucleophilic addition to the endocyclic C=N bond of a six-membered iminosugar-derived

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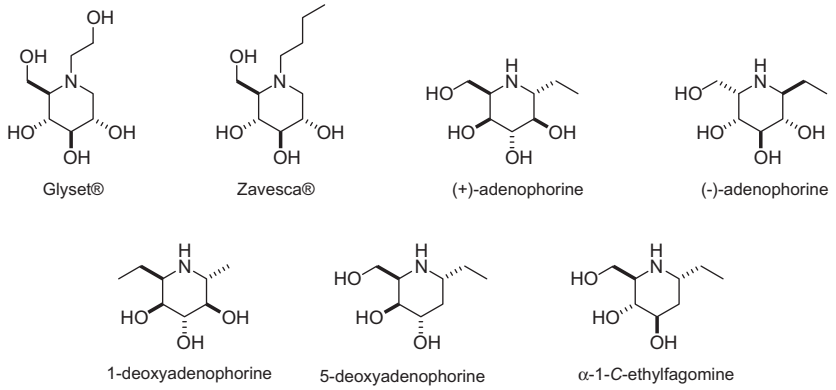



**Figure 1.** Structure of Glyset®, Zavesca®, (+)-adenophorine, (−)-adenophorine, 1-deoxy-adenophorine, 5-deoxy-adenophorine and α-1-*C*-ethylfagomine.

cyclic imine or nitrone has been reported by Davis[20] and Vasella,[21] respectively. Our interest in the synthesis[22] and skeletal rearrangement[23] of seven-membered iminosugars forced us to combine both aspects to develop a new strategy based on the C-alkylation of a seven-membered electrophilic iminosugar and its subsequent ring isomerisation. This route allowed the preparation of both L- and D-iminosugar C-glycosides from a common sugar-based azidolactol precursor exploiting a Staudinger/azaWittig ring expansion.[24] We would like to disclose herein the use of this methodology to access (−)-adenophorine and analogs in order to evaluate their potency towards a panel of glycosidases.

## 2. Results and discussion

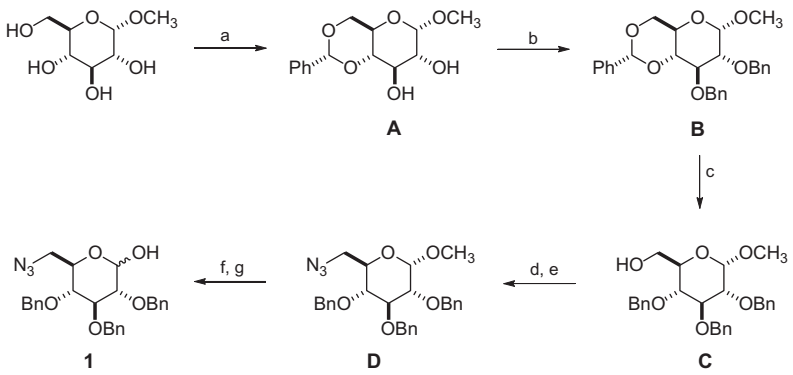
### 2.1. Synthesis

Azidolactol **1**[25] is well suited for the preparation of (−)-adenophorine that displays an α-L-ido-like configuration and was prepared as follows (Scheme 1). Methyl α-D-glucopyranoside was protected as its 4,6-O-benzylidene **A** followed by benzylation of the free alcohols to furnish the fully protected compound **B**. Regioselective benzylidene opening produced the primary alcohol **C** that was tosylated and further displaced with sodium azide to give azide **D**. Acetolysis of **D** and subsequent deacetylation furnished azidolactol **1** in seven steps and 39–46% overall yield.

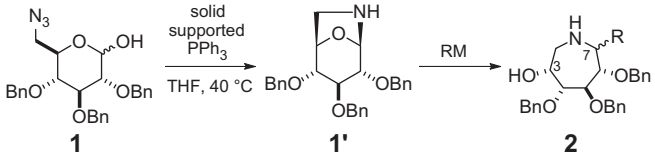
Introduction of the ethyl group at the pseudoanomeric position can be performed either through addition of a vinyl or ethyl-based organometallic reagent. Both types of nucleophiles were investigated and compared to the allyl-derived organometallics that previously gave the best conversion for this step. In our previous work, only organomagnesium reagents were explored leading to the expected *C*-alkyl azepanes **2**[24] in moderate to good yield (38–58% from azidolactol **1**) and good stereoselectivity (>95/5) except for the vinyl derivatives **2c** and **2d** (67:33 ratio). These results forced us to examine other metals for the introduction of an allyl or ethyl group including aluminum, lithium, cerium and zinc-based reagents (Scheme 2; Table 1).

Addition of organomagnesium, organolithium, organoaluminum, organozinc and organocerium reagents to imine and related N,O-acetals is well-documented.[26] In the field of iminosugars, RMgX and RLi have been widely used to introduce aryl and alkyl chains.[27] Allyl zinc bromide has been successfully employed to generate diallyl trihydroxypiperidines.[28]

In a typical procedure, azidolactol **1** was converted into the crude bicyclic N,O acetal **1'** which was directly reacted at 0 °C with 3 equiv of the organometallic species. After 2 h, the reaction was quenched, worked up and purified by flash chromatography. We observed that the allyl-derived organozinc and organoaluminum reagents proved almost as efficient as AllMgBr (entry 1) to perform C-allylation furnishing the C-7 *S*-configured allyl azepane **2a** in 62% and 51% yield, respectively (entries 3 and 4) while the organocerium reagent provided only traces of **2a** (5%, entry 2). Unfortunately, switching to the required ethyl organometallic species failed to give the corresponding azepanes (entries 5 and 6). Use of ethyl lithium proved inefficient generating the C-7 *R*-configured ethyl azepane **2b** in only 17% yield (entry 7) compared to EtMgBr (49%, entry 4). In all cases only one diastereomer was isolated except for $CH_2$=CHMgBr (entry 8). This lack of diastereomeric control




**Scheme 1.** Synthesis of azidolactol **1**. Reagents and conditions: (a) benzylidene dimethyl acetal, $CH_3CN$, CSA, 85 °C, 6 h, 76% yield; (b) BnBr, NaH, DMF, rt, overnight, 83% yield; (c) $LiAlH_4$ (4.7 equiv) $AlCl_3$ (4 equiv), $CH_2Cl_2/Et_2O$, reflux, 2 h, 86% yield; (d) TsCl, pyridine, rt, overnight, 91% yield; (e) $NaN_3$, DMF, 90 °C, 2 h; (f) $Ac_2O$ (7 equiv), conc. $H_2SO_4$ (0.5 equiv), $CH_2Cl_2$, rt, 30 min.; (g) NaOMe, MeOH, rt, 30 min, 80–94% yield over 3 steps.




**Scheme 2.** Synthesis of azepanes **2**.

**Table 1**
Synthesis of *C*-allyl, *C*-ethyl and *C*-vinyl azepanes **2a–d** from azidolactol **1** using various organometallic reagents

| Entry | R | Metal | Azepane | Yield (%) | C-7 configuration | d.r. |
|---|---|---|---|---|---|---|
| 1 | All | Mg | **2a** | 58 | S | <5:95 |
| 2 | All | Ce | **2a** | 5 | S | <5:95 |
| 3 | All | Zn | **2a** | 62 | S | <5:95 |
| 4 | All | Al | **2a** | 51 | S | <5:95 |
| 4 | Et | Mg | **2b** | 49 | R | >95:5 |
| 5 | Et | Ce | **2b** | No reaction | | |
| 6 | Et | Zn | **2b** | No reaction | | |
| 7 | Et | Li | **2b** | 17 | R | >95:5 |
| 8 | $CH=CH_2$ | Mg | **2c**/**2d** | 38 | R/S | 67:33 |

was further exploited as it produces the minor vinyl azepane **2d** displaying the required C-7 *S* configuration that should be easily amenable to the target (−)-adenophorine.

The stereochemical outcome of this ring opening reaction can be tentatively explained as follows (Scheme 3). Treatment of hemiaminal **1**′ with the organomagnesium reagent leads to a seven-membered imine **1**″ than can be attacked from both *Re* and *Si* faces. With aromatic and conjugated species such as AllMgBr (or PhMgBr[24]), a π–stacking interaction could take place with the sugar benzyl groups to favour the attack on the *Si* face of the imine yielding the 3,7-*trans* C-allyl azepane **2a**. A similar interaction has been invoked in the case of related 6,8-diazabicyclo[3.2.1]oct-6-ene scaffold.[29] With alkyl species such as EtMgBr (or MeMgBr[24]), an intramolecular delivery of the nucleophile guided by the 3-OH could operate yielding to the attack on the *Re* face of the imine generating the 3,7-*cis* C-ethyl azepane **2b**. Such hypothesis is supported by the formation of the 3,7-*cis* *C*-allyl azepane using homoallyl magnesium bromide (unpublished results) and the formation of both 3,7-*cis* and 3,7-*trans* *C*-vinyl azepanes **2c** and **2d** respectively using vinyl magnesium bromide that can be considered to behave both as an alkyl and conjugated nucleophile.

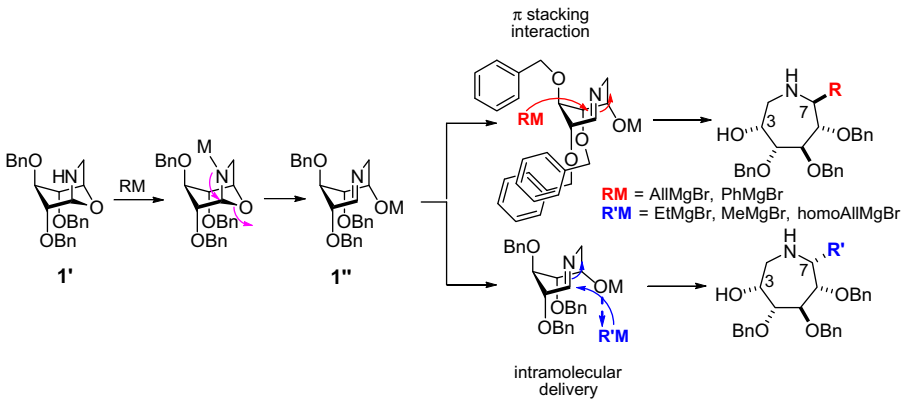
Overall, as no significant yield improvement was observed by varying the nature of the organometallic reagent, organomagnesium reagents were used for the alkylation step in the synthetic sequence. Noteworthy flash chromatography purification of the resulting polar *C*-alkyl hydroxyaminoazepanes **2a–d** proved tedious leading to loss of material. This problem was solved by applying a three steps sequence starting from azidolactol **1** including the N-benzylation of the crude *C*-alkyl azepane. This sequence allowed the introduction of an allyl, an ethyl or a vinyl group affording the corresponding azepanes **3a**, **3b**, **3c** and **3d** in 53%, 38% and 29% (**3c** + **3d**), respectively. With the N-protected alkyl azepanes **3a–d** in hands, the skeletal rearrangement under Mitsunobu conditions was performed and yielded the corresponding piperidines **4a–d** (34–67%) and the fully protected azepanes **5a–d** (10–30%) with overall retention of configuration. Formation of the piperidines results from a nucleophilic attack at the aziridinium methylene carbon of the fused-piperidine-aziridinium intermediate while the azepanes are obtained through a nucleophilic attack at the aziridinium methine carbon (Scheme 4).

Ester hydrolysis in piperidines **4a–d** under mild basic conditions ($K_2CO_3$, MeOH) afforded the corresponding hydroxymethyl piperidines **6a–d** that were uneventfully hydrogenolyzed to furnish the target tetrahydroxylated piperidines **7a–c** including (−)-adenophorine **7c** which spectroscopic data were in good agreement with the literature. We were also interested in the biological evaluation of the corresponding alkyl azepanes **8a–c** that were quantitatively obtained as their hydrochloride salt by hydrogenolysis of azepanes **3a–d** under mild acidic conditions (Scheme 5).

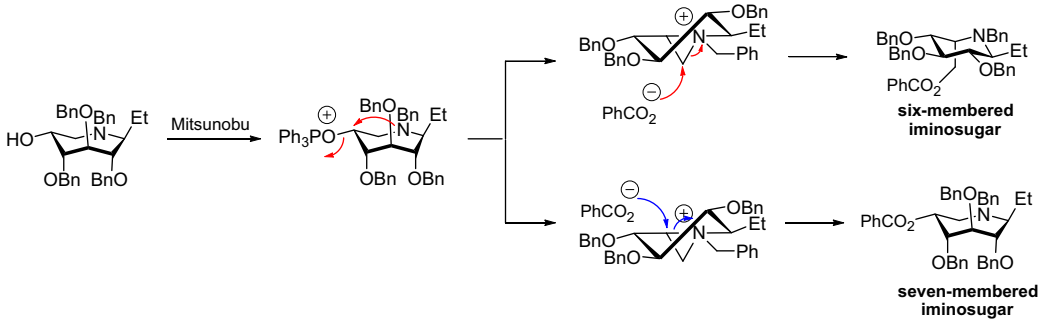
Hydrophobic homonojirimycin analogs displaying fewer hydroxyl groups have also been isolated from *Adenophora* spp. including 1-deoxy-adenophorine, 5-deoxy-adenophorine and α-1-*C*-ethyl-fagomine (Fig. 1) that demonstrated potent glycosidase inhibition.[11] Hydrophobically modified analogues of adenophorine have also been reported to improve their metabolic stability.[30] In this context, the Staudinger/azaWittig/alkylation approach allows the functionalization of both C-2 and C-6 positions of the piperidine ring and the introduction of hydrophobic chains at these positions. The access to a new hydrophobic 2,6-diethyl-3,4,5-trihydroxypiperidine starting from the advanced precursor **6c** was explored. Oxidation of hydroxymethylpiperidine **6c** under Swern conditions followed by olefination with a Wittig reaction generated the *bis* vinyl derivative **9** (46% yield over two steps). The C-2 symmetry of **9** was confirmed by the simplification of its NMR spectra. Final hydrogenolysis furnished the target trihydroxypiperidine **10** (Scheme 6).

## 2.2. Biological activity

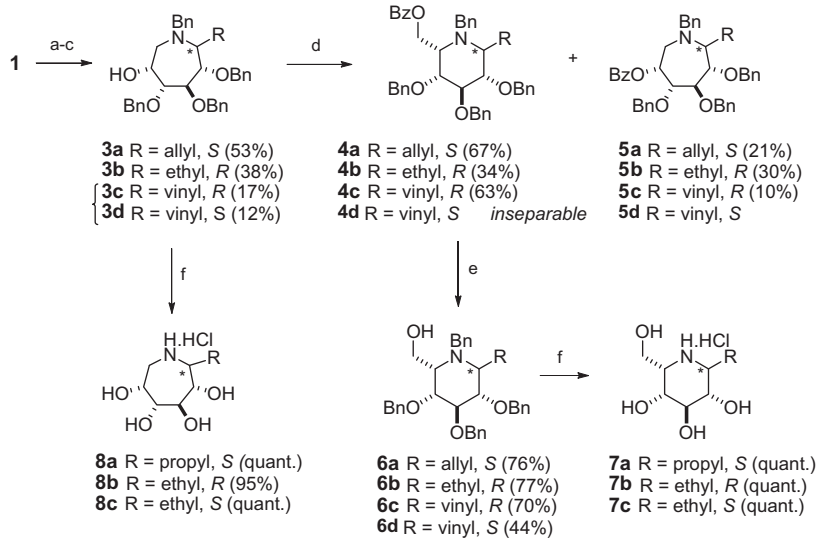
Inhibition by the tri- and tetrahydroxylated piperidines **7a–c**, **10** and tetrahydroxylated azepanes **8a–c** of the following glycosidases was studied (Fig. 2): α-glucosidases (rice, yeast, rat intestinal maltase, *A. niger*), β-glucosidases (almond, bovine liver, *A. niger*),



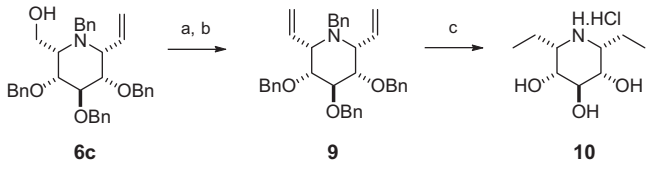

**Scheme 3.** Proposed mechanism to rationalize the stereochemical outcome of the bicycle 1′ ring opening reaction.




**Scheme 4.** Mechanism of the azepane skeletal rearrangement under Mitsunobu conditions.




**Scheme 5.** Synthesis of *C*-alkyl piperidines **7a–c** and *C*-alkyl azepanes **8a–c**. Reagents and conditions: (a) $PPh_3$ polymer bound, THF, 40 °C, overnight; (b) AllMgBr or EtMgBr or $CH_2$=CHMgBr, THF, 1 h, rt; (c) BnBr, $K_2CO_3$, DMF; (d) $PPh_3$, DIAD, *p*-nitrobenzoic acid, THF; (e) $K_2CO_3$, MeOH, THF; (f) $H_2$, 10% Pd/C, Pd black, MeOH, 1 M HCl. Bz = *p*-nitrobenzoate.




**Scheme 6.** Synthesis of trihydroxypiperidine **10**. Reagents and conditions: (a) oxalyl chloride, DMSO, $Et_3N$, $CH_2Cl_2$, −78 °C; (b) $PPh_3CH_3^+Br^-$, BuLi, $CH_2Cl_2$, 46% over two steps; (c) $H_2$, 10% Pd/C, Pd black, MeOH, 1M HCl, quant.

α-galactosidase (coffee beans), β-galactosidase (bovine liver), α-mannosidase (Jack beans), β-mannosidase (snail), α-L-rhamnosidase (*P. decumbens*), α-L-fucosidase (bovine kidney), β-glucuronidases (*E. coli*, bovine liver), trehalase (porcine kidney), and amyloglucosidases (*A. niger*, *Rhizopus* sp).

This study (Table 2) revealed that (−)-adenophorine **7c** is a moderate α-L-fucosidase inhibitor ($IC_{50}$ 72 μM). The epimer at the pseudoanomeric position **7b** is also a α-L-fucosidase inhibitor ($IC_{50}$ 208 μM). The one carbon elongated analog **7a** yields also a weak fucosidase inactivator ($IC_{50}$ 713 μM) and a weak β-glucuronidase

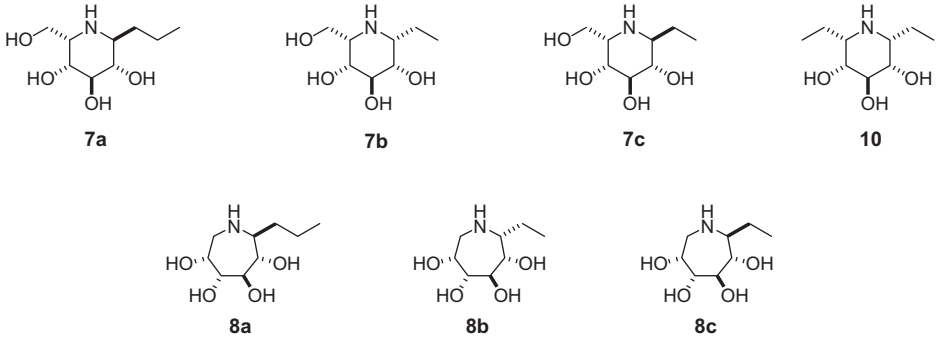
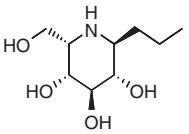
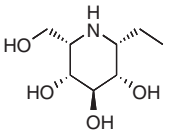
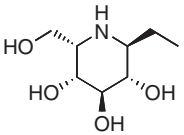
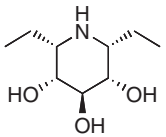
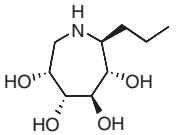
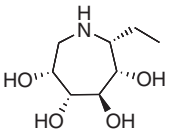
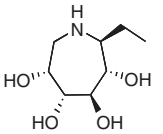



**Figure 2.** Structure of iminosugar C-glycosides assayed in this work.

**Table 2**
Concentration of iminosugars and its derivatives giving 50% inhibition of various glycosidases (in bold)

| Enzyme | | $IC_{50}$ (μM) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | |  |  |  |  |  |  |  |
| | | **7a** | **7b** | **7c** | **10** | **8a** | **8b** | **8c** |
| α-Glucosidase | Rice | NI[a] (0%)[b] | NI (0%) | NI (0%) | NI (1.7%) | 839 | NI (1.0%) | NI (0%) |
| | Yeast | NI (40.0%) | NI (9.0%) | NI (0%) | NI (2.0%) | NI (0%) | NI (0%) | NI (23.5%) |
| | Rat intestinal maltase | NI (0%) | NI (3.3%) | NI (0%) | NI (0%) | NI (0%) | NI (0%) | NI (13.7%) |
| | *Aspergillus niger* | NI (1.4%) | NI (0%) | NI (6.1%) | NI (0%) | ND[c] | NI (0%) | NI (0.2%) |
| β-Glucosidase | Almond | NI (42.6%) | NI (16.9%) | NI (33.5%) | NI (21.4%) | NI (0%) | NI (5.1%) | NI (48.7%) |
| | Bovine liver | NI (13.2%) | NI (32.8%) | NI (12.6%) | NI (21.6%) | NI (6.0%) | NI (24.6%) | **487** |
| | *Aspergillus niger* | NI (0%) | NI (0%) | NI (0%) | NI (0%) | NI (9.1%) | NI (0%) | NI (0%) |
| α-Galactosidase | Coffee beans | NI (10.4%) | NI (8.7%) | NI (0.6%) | NI (3.7%) | NI (46.0%) | NI (1.2%) | NI (7.5%) |
| β-Galactosidase | Bovine liver | NI (26.8%) | NI (20.3%) | NI (6.5%) | NI (9.7%) | 541 | NI (12.1%) | **526** |
| α-Mannosidase | Jack beans | NI (5.1%) | NI (5.1%) | NI (0%) | NI (0.4%) | NI (1.6%) | NI (0%) | NI (11.0%) |
| β-Mannosidase | Snail | NI (1.3%) | NI (0%) | NI (0%) | NI (0.3%) | NI (3.6%) | NI (0%) | NI (0%) |
| α-L-Rhamnosidase | *Penicillium decumbens* | NI (13.0%) | NI (2.4%) | NI (37.7%) | NI (0%) | NI (14.8%) | NI (5.3%) | **231** |
| α-L-Fucosidase | Bovine kidney | **713** | **208** | **72** | NI (0%) | NI (0%) | NI (36.7%) | NI (37.2%) |
| β-Glucuronidase | E.coli | **586** | NI (11.0%) | NI (7.2%) | NI (12.9%) | ND | NI (3.1%) | NI (18.1%) |
| | Bovine liver | NI (0%) | NI (0%) | NI (0.8%) | NI (0.5%) | ND | NI (0.1%) | NI (0.1%) |
| α,α-Trehalase | Porcine kidney | NI (0%) | NI (0%) | NI (6.0%) | NI (4.9%) | NI (0%) | NI (3.9%) | NI (0%) |
| Amyloglucosidase | *Aspergillus niger* | NI (0%) | NI (1.9%) | NI (0%) | NI (4.1%) | NI (0%) | NI (0.8%) | NI (0%) |
| | *Rhizopus* sp | NI (0%) | NI (0%) | NI (0%) | NI (3.4%) | ND | NI (0%) | NI 0%) |

[a] NI: no inhibition (less than 50% inhibition at 1000 μM).
[b] (): inhibition% at 1000 μM.
[c] ND: not determined.

inhibitor ($IC_{50}$ 586 μM). The more hydrophobic 2,6-diethyl derivative **10** demonstrated no effect as glycosidase inhibitor. The azepane derivatives display a very different glycosidase inhibition profile compared to their piperidine counterparts. The ring homolog of (−)-adenophorine **8c** is a weak inhibitor of bovine liver β-glucosidase ($IC_{50}$ 487 μM), bovine liver β-galactosidase ($IC_{50}$ 526 μM) and α-L-rhamnosidase ($IC_{50}$ 231 μM). Its epimer at C-2 **8b** does not inhibit glycosidases significantly while the propyl derivative **8a** is a weak inhibitor of yeast α-glucosidase ($IC_{50}$ 839 μM) and bovine liver β-galactosidase ($IC_{50}$ 541 μM).

## 3. Conclusion

In summary, a new route to (−)-adenophorine **7c** based on the skeletal rearrangement of a *C*-alkyl azepane has been deviced. Compound **7c** is a moderate α-L-fucosidase inhibitor and exhibits a very distinctive inhibitory profile compared to (+)-adenophorine, a potent and selective α-glucosidase inactivator.[11] The structurally related azepanes **8a**–**c** proved to be weak glycosidase inhibitors. This suggests that introduction of an ethyl or a propyl group at C-1 on the azepane ring is detrimental to their glycosidase inhibitory potential as the known *3R*, *4R*, *5R*, *6S* tetrahydroxyazepane[31] is a potent inhibitor of coffee bean α-galactosidase ($K_i$ 54 μM) and bovine kidney α-fucosidase (4.6 μM).

## 4. Experimental

### 4.1. Material and methods

All reagents were used as purchased from commercial suppliers without further purification. THF was distilled under anhydrous conditions. TLC plates (Macherey-Nagel, ALUGRAM® SIL G/$UV_{254}$, 0.2 mm silica gel 60 Å) were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of 3 g of phosphomolybdic acid in 100 mL of ethanol followed by heating with a heat gun. Flash column chromatography was performed using Macherey-Nagel silica gel 60 (15–40 μm). NMR experiments were recorded with a Bruker Avance 400 spectrometer at 400 MHz for $^1$H nuclei and at 100 MHz for $^{13}$C nuclei. The chemical shifts are expressed in part per million (ppm) relative to TMS ($\delta$ = 0 ppm) and the coupling constant *J* in Hertz (Hz). NMR multiplicities are reported using the following abbreviations: br = broad, s = singulet, d = doublet, t = triplet, q = quadruplet, m = multiplet. HRMS were obtained from the Mass Spectrometry Service, ICOA, at Orleans, France, using a MICROMASS ZABSPEC-TOF spectrometer and a VARIAN MAT311 spectrometer.

### 4.2. General procedure for the synthesis of azepanes 2a–d

Triphenylphosphine polymer bound (250 mg, 0.78 mmol, 3.2 mmol/g) was added to a solution of azidolactol **1** (250 mg, 0.53 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred at 40 °C for 17 h, then filtered through a Celite plug eluted with THF, and the solvent removed under reduced pressure. The crude product was taken in $Et_2O$ (5 mL), filtered again through a Celite plug, and the filtrate concentrated to give the crude bicyclic N,O-acetal as a pale yellow oil. The organometallic reagent (3 equiv, allylmagnesium chloride 2 M solution in THF, ethylmagnesium bromide 3 M solution in $Et_2O$, vinylmagnesium bromide 1 M solution in THF) was added to a solution of crude bicyclic N,O-acetal in THF (5 mL) at 0 °C except for ethyl lithium for which reaction was performed at −78 °C. The reaction was stirred at room temperature for 2 h with Grignard and organozinc reagents,[32] and at 0 °C for 2 h with organocerium reagents.[33] The reaction was quenched with saturated aqueous $NH_4Cl$ (10 mL), diluted with EtOAc (10 mL) at 0 °C and extracted with EtOAc (3 × 15 mL). The organic layer was washed with water (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure after filtration. The residue was purified by flash chromatography (EtOAc/MeOH 95/5).

### 4.3. General procedure for the synthesis of azepanes 3a–d

Starting from azidolactol **1** (4 g, 8.42 mmol), the crude azepane **2a** was obtained in 2 steps as described before and engaged, without purification, in the next benzylation step. To a cooled solution (0 °C) of crude **2a** and benzyl bromide (1.6 mL, 12.8 mmol) in DMF (80 mL), was added $K_2CO_3$ (3.5 g, 25.2 mmol). The mixture was stirred at room temperature for 14 h, quenched with saturated aqueous $NH_4Cl$, and extracted with EtOAc/toluene (2:1). The organic layer was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure, after filtration. The residue was purified by flash chromatography (EtOAc/petroleum ether 10:90) to afford azepane **3a** as colorless syrup (2.53 g, 53%, 3 steps).

#### 4.3.1. (3*R*,4*R*,5*R*,6*S*,7*S*) 7-Allyl-1-benzyl-4,5,6-tris(benzyloxy)azepan-3-ol (3a)

$[\alpha]_D$ = −14 (*c* 0.94, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.37–7.20 (m, 20H, ArH), 5.86–5.76 (m, 1H, –C*H*═), 5.05–4.98 (m, 2H, $H_2$C═), 4.71 (d, *J* = 11.7 Hz, 1H, OCH*H*Ph), 4.63 (d, *J* = 11.7 Hz, 1H, OCH*H*Ph), 4.58 (s, 2H, $OCH_2$Ph), 4.39 (qAB, 2H, $OCH_2$Ph), 4.10 (dd, *J* = 7 and 2.5 Hz, 1H, H-5), 4.02 (m, 1H, H-3), 3.86–3.76 (m, 3H, H-4, $NCH_2$), 3.54 (dd, *J* = 6.5 and 2.5 Hz, 1H, H-6), 3.49 (brd, *J* = 10.8 Hz, OH), 3.20 (q, *J* = 7-6.5 Hz, 1H, H-7), 2.90–2.80 (m, 2H, 2H-2), 2.39 (m, 2H, $CH_2$ allyl); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 139.7, 138.6, 138.4, 137.9 (4 ArC), 136.7 (–*C*H═), 128.9, 128.5, 128.41, 128.39, 128.0, 127.98, 127.88, 127.82, 127.77, 127.6, 127.1 (Ar*C*H), 116.7 (*C*$H_2$═), 86.2 (C-4), 83.9 (C-5), 80.1 (C-6), 73.3, 72.7, 71.6 (3 *C*$H_2$Ph), 69.2 (C-3), 62.6 (C-7), 58.6 (N*C*$H_2$), 53.0 (C-2), 30.2 (*C*$H_2$ allyl); HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_{37}H_{41}NO_4Na$: 586.2933; found: 586.2933.

#### 4.3.2. (3*R*,4*R*,5*R*,6*S*,7*R*)-1-Benzyl-4,5,6-tris(benzyloxy)-7-ethylazepan-3-ol (3b)

Starting from azidolactol **1** (2 g, 4.21 mmol), azepane **3b** was obtained as described above as colorless syrup (870 mg, 38% over 3 steps).

$[\alpha]_D$ = 22 (*c* 0.9, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.33–7.19 (m, 20H, ArH), 4.71–4.45 (m, 6H, 3$CH_2$Ph), 3.97–3.83 (m, 5H, H-3, H-4, H-5, $NCH_2$), 3.73 (dd, *J* = 7.5, 2.4 Hz, 1H, H-6), 3.22 (dd, *J* = 14.4, 8.5 Hz, 1H, 1H-2), 2.78 (m, 1H, H-7), 2.57 (dd, *J* = 14.4, 2.2 Hz, 1H, 1H-2), 1.84 (m, 1H, CH*H* ethyl), 1.64 (m, 1H, CH*H* ethyl), 0.92 (t, *J* = 14.4, 2.2 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 140.9, 138.5, 138.4, 138.1 (4 ArC), 128.5–126.9 (ArCH), 84.4 (C-5 or C-4), 82.6 (C-6), 82.2 (C-4 or C-5) 73.7, 73.4, 72.5 (3 *C*$H_2$Ph), 68.7 (C-3), 63.0 (C7), 57.5 ($NCH_2$), 50.2 (C-2), 19.9 (*C*$H_2$ ethyl), 12.11 ($CH_3$); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{36}H_{42}NO_4$: 552.3113; found: 552.3107.

#### 4.3.3. (3*R*,4*R*,5*R*,6*S*,7*R*)-1-Benzyl-4,5,6-tris(benzyloxy)-7-vinylazepan-3-ol (3c) and (3*R*,4*R*,5*R*,6*S*,7*S*)-1-benzyl-4,5,6-tris(benzyloxy)-7-vinylazepan-3-ol (3d)

Starting from azidolactol **1** (2 g, 4.21 mmol), azepanes **3c** and **3d** were obtained as described above as colorless oils with the more polar compound **3c** (393 mg, 17%, over 3 steps) and the less polar compound **3d** (277 mg, 12%, over 3 steps).

Compound **3c**: $[\alpha]_D$ = 29 (*c* 1.26, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.31–7.25 (m, 20H, ArH), 6.24 (ddd, *J* = 17.1, 10.2, 8.9 Hz, 1H, –C*H*═), 5.30 (dd, *J* = 10.2, 2.0 Hz, 1H, ═CH*H*), 5.17 (dd, *J* = 17.1, 1.5 Hz, 1H, ═CH*H*), 4.71–4.42 (3 O$CH_2$Ph), 3.97 (m, 1H, H-3), 3.86 (dd, *J* = 7.6, 4.0 Hz, 1H, H-5), 3.80 (dd, *J* = 4.0, 2.5 Hz, 1H, H-4), 3.71 (d, *J* = 13.8 Hz, 1H, NCH*H*Ph), 3.68 (dd, *J* = 7.6, 3.1 Hz, 1H, H-6), 3.59 (d, *J* = 13.8 Hz, 1H, NCH*H*Ph), 3.42 (dd,

$J$ = 8.9, 3.1 Hz, 1H, H-7), 3.06 (dd, $J$ = 13.2, 8.2 Hz, 1H, H-2), 2.66-2.61 (m, 2H, OH, H-2); NMR (100 MHz, $CDCl_3$): $\delta$ 139.3, 138.5, 138.2, 138.1 (4 ArC), 133.9 (–*C*H=), 128.6–127.0 (ArCH), 119.6 (=$CH_2$), 84.16, 84.12 (C-4, C-6), 81.3 (C-5), 73.8, 73.1, 72.5 (3 $CH_2$Ph), 69.2 (C-3), 64.7 (C-7), 59.6 (N$CH_2$), 52.0 (C-2); HRMS (ESI) $m/z$: $[M+H]^+$ calcd for $C_{36}H_{40}NO_4$: 550.2957; found: 550.2953.

Compound **3d**: $[\alpha]_D$ = −22 ($c$ 1.08, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.31–7.20 (m, 20H, ArH), 5.97 (ddd, $J$ = 16.9, 10.2, 8.2 Hz, 1H, –C*H*=), 5.34 (dd, $J$ = 10.2, 1.5 Hz, 1H, =CH*H*), 5.22 (dd, $J$ = 16.9, 1.5 Hz, 1H, =CH*H*), 4.73 (d, $J$ = 11.6 Hz, 1H, OCH*H*Ph), 4.66 (d, $J$ = 11.6 Hz, 1H, OCH*H*Ph), 4.66 (s, 2H, O$CH_2$Ph), 4.47 (d, $J$ = 11.4 Hz, 1H, OCH*H*Ph), 4.40 (d, $J$ = 11.4 Hz, 1H, OCH*H*Ph), 4.11 (dd, $J$ = 7.2, 4.2 Hz, 1H, H-5), 3.97 (m, 1H, H-3), 3.75 (dd, $J$ = 7.2, 2.2 Hz, 1H, H-4), 3.72 (d, $J$ = 13.6 Hz, 1H, NCH*H*Ph), 3.67 (d, $J$ = 13.6 Hz, 1H, NCH*H*Ph), 3.54–3.49 (m, 2H, H-6, H-7), 2.90–2.81 (m, 2H, 2 H-2); NMR (100 MHz, $CDCl_3$): $\delta$ 139.2, 138.6, 138.5, 137.7 (4 ArC), 132.6 (–*C*H=), 128.9–126.9 (ArCH), 119.8 (=$CH_2$), 86.1 (C-4), 83.8 (C-5), 80.8 (C-6), 73.6, 72.8, 72.4 (3 $CH_2$Ph), 69.2 (C-3), 65.1 (C-7), 59.3 (N$CH_2$), 53.0 (C-2); HRMS (ESI) $m/z$: $[M+H]^+$ calcd for $C_{36}H_{40}NO_4$: 550.2957; found: 550.2956.

### 4.4. General procedure for the synthesis of piperidines 4a–d

Diisopropyl azodicarboxylate (DIAD) (0.16 mL, 0.80 mmol,) was added to a solution of azepane **3a** (230 mg, 0.408 mmol), triphenylphosphine (214 mg, 0.80 mmol) and *p*-nitrobenzoic acid (103 mg, 0.60 mmol) in THF (4 mL) at 0 °C. The resulting solution was stirred for 30 min at room temperature and concentrated in vacuo. Separation by flash column chromatography (EtOAc/petroleum ether, 5:95) gave the piperidine **4a** as a pale yellow oil (195 mg, 67%) and a less polar azepane **5a** as a pale yellow oil (61 mg, 21%).

#### 4.4.1. (2*S*,3*R*,4*R*,5*S*,6*S*)-6-Allyl-1-benzyl-3,4,5-tris(benzyloxy)piperidin-2-yl)methyl 4-nitrobenzoate (4a) and (3*R*,4*R*,5*R*,6*S*,7*S*)-7-allyl-1-benzyl-4,5,6-tris(benzyloxy)azepan-3-yl 4-nitrobenzoate (5a)

Compound **4a**: $[\alpha]_D$ = 22 ($c$ 1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.25 (d, $J$ = 8 Hz, 2H, ArH), 8.10 (d, $J$ = 8 Hz, 2H, ArH), 7.39–7.07 (m, 20H, ArH), 5.89–5.79 (m, 1H, –C*H*=), 5.07–5.03 (m, 2H, =$CH_2$), 4.96 (d, $J$ = 10.7 Hz, 1H, OCH*H*Ph), 4.94 (d, $J$ = 10.7 Hz, 1H, OCH*H*Ph), 4.82 (d, $J$ = 10.7 Hz, 1H, OCH*H*Ph), 4.80 (dd, $J$ = 11.9, 8.6 Hz, 1H, CH*H*OCO), 4.66–4.55 (m, 3H, OCH*H* Ph), 4.52 (dd, $J$ = 11.9, 3.5 Hz, 1H, CH*H*OCO), 3.90 (dd, $J$ = 9.9, 5.9 Hz, 1H, H-3), 3.84 (d, $J$ = 13.4 Hz, 1H, CH*H*N), 3.78 (t, $J$ = 9.9, 8.7 Hz, 1H, H-4), 3.64 (d, $J$ = 13.4 Hz, 1H, CH*H*N), 3.50 (dd, $J$ = 10.1, 8.7, Hz, 1H, H-5), 3.32 (ddd, $J$ = 8.6, 5.9, 3.5 Hz, 1H, H-2), 3.27 (ddd, $J$ = 10.1, 8.5, 4.5 Hz, 1H, H-6), 2.78 (m, 1H, CH*H* allyl), 2.35 (m, 1H, CH*H* allyl); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.4 (CO), 150.6, 139.2, 138.7, 138.4, 138.0, 135.7 (6 ArC), 135.3 (–*C*H=), 130.9 (ArCH), 128.63, 128.58, 128.54, 128.52, 128.3, 128.1, 127.97, 127.91, 127.7, 127.2 (ArCH), 123.5 (ArCH), 116.7 ($CH_2$=), 84.5 (C-4), 80.5 (C-5), 77.4 (C-3), 75.7, 75.3, 72.8 (3 $CH_2$Ph), 60.6 ($CH_2$OCO), 57.3 (C-6), 55.1 (C-2), 50.1 (N$CH_2$), 32.8 ($CH_2$ allyl); HRMS (ESI) $m/z$: $[M+H]^+$ calcd for $C_{44}H_{45}N_2O_7$: 713.3221; found: 713.3221.

Compound **5a**: $[\alpha]_D$ = −34.7 ($c$ 0.7, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.20 (d, $J$ = 8 Hz, 2H, ArH), 8.04 (d, $J$ = 8 Hz, 2H, ArH), 7.39–7.19 (m, 20H, ArH), 6.04–5.94 (m, 1H, –C*H*=), 5.70 (ddd, $J$ = 10.8, 4.7, 1.5 Hz, 1H, H-3), 5.11–5.05 (m, 2H, =$CH_2$), 4.72 (d, $J$ = 11.7 Hz, 1H, OCH*H*Ph), 4.69 (d, $J$ = 12.2 Hz, 1H, OCH*H*Ph), 4.65 (d, $J$ = 11.7 Hz, 1H, OCH*H*Ph), 4.57 (d, $J$ = 11.2 Hz, 1H, OCH*H*Ph), 4.54 (d, $J$ = 12.2 Hz, 1H, OCH*H*Ph), 4.48 (d, $J$ = 11.2 Hz, 1H, OCH*H*Ph), 4.17 (brd, $J$ = 6.2 Hz, 1H, H-4), 4.10 (dd, $J$ = 6.2, 2 Hz, 1H, H-5), 3.90 (m, 2H, $NCH_2$), 3.60 (dd, $J$ = 8.9, 2 Hz, 1H, H-6), 3.53 (td, $J$ = 8.9, 4.3 Hz, 1H, H-7), 3.22 (dd, $J$ = 13.7, 10.8 Hz, 1H, H-2), 2.91 (dd, $J$ = 13.7, 4.7 Hz, 1H, H-2), 2.60 (m, 1H, CH*H* allyl), 2.34 (m, 1H, CH*H* allyl); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 163.9 (CO), 150.5, 140.0, 138.3, 138.2, 139.0, 137.6 (6 ArC), 135.8 (–*C*H=), 130.9 (ArCH), 128.7, 128.6, 128.5, 128.4, 128.3, 128.08, 128.06, 128.0, 127.93, 127.86, 127.77, 126.9 (ArCH), 123.5 (ArCH), 115.8 ($CH_2$=), 85.7 (C-6), 79.3, 79.0 (C-4, C-5), 72.9, 72.8, 72.6 (3 $OCH_2$Ph), 70.5 (C-3), 64.3 (C-7), 50.6 (N$CH_2$), 49.3 (C-2), 35.0 ($CH_2$ allyl); HRMS (ESI) $m/z$: $[M+H]^+$ calcd for $C_{44}H_{45}N_2O_7$: 713.3221; found: 713.3220.

#### 4.4.2. (2*S*,3*R*,4*R*,5*S*,6*R*)-1-Benzyl-3,4,5-tris(benzyloxy)-6-ethylpiperidin-2-yl)methyl 4-nitrobenzoate (4b) and (3*R*,4*R*,5*R*,6*S*,7*R*)-1-benzyl-4,5,6-tris(benzyloxy)-7-ethylazepan-3-yl 4-nitrobenzoate (5b)

Piperidine **4b** (132 mg, 34%) and azepane **5b** (116 mg, 30%) were obtained from azepane **3b** (210 mg, 0.382 mmol) as described above.

Compound **4b** $[\alpha]_D$ = 13 ($c$ 1.2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.21 (d, $J$ = 8.9 Hz, 2H, ArH), 8.01 (d, $J$ = 8.9 Hz, 2H, ArH), 7.33–7.21 (m, 20H, ArH), 4.84 (m, 2H, C$H_2$Ph), 4.74 (dd, $J$ = 11.5, 5.4 Hz, 1H, CH*H*OBz), 1H, 4.70–4.51 (m, 5H, 2C$H_2$Ph, CH*H*OBz), 3.98 (qAB, $J$ = 14.5 Hz, 2H, C$H_2$N), 3.84–3.77 (m, 2H, H-3, H-4), 3.70 (dd, $J$ = 7.8, 5.7 Hz, 1H, H-5), 3.54 (q, $J$ = 7.0–5.4 Hz, 1H, H-2), 2.98 (q, $J$ = 7.3–6.0 Hz, 1H, H-6), 1.82 (m, 1H, CH*H* ethyl), 1.57 (m, 1H, CH*H* ethyl), 0.98 (t, $J$ = 7.4 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.5 (CO), 150.4, 140.2, 138.8, 138.5, 138.2, 135.6 (6 ArC), 130.7 (ArCH), 128.4–127.1 (ArCH), 123.4 (ArCH), 80.0 (C-5), 78.9 and 78.7 (C-3 and C-4), 75.1, 72.9, 72.8 (3 $CH_2$Ph), 65.4 ($CH_2$O-CO), 61.6 (C-6), 59.1 ($NCH_2$), 58.0 (C-2), 22.4 ($CH_2$ ethyl), 16.0 ($CH_3$); HRMS (ESI) $m/z$: $[M+H]^+$ calcd for $C_{43}H_{45}N_2O_7$: 701.3221; found: 701.3218.

Compound **5b**: $[\alpha]_D$ = 33.4 ($c$ 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.21 (d, $J$ = 8.9 Hz, 2H, ArH), 8.05 (d, $J$ = 8.5 Hz, 2H, ArH), 7.31–7.18 (m, 20H, ArH), 5.41 (brd, $J$ = 8.8 Hz, 1H, H-3), 4.70 (d, $J$ = 12 Hz, 1H, CH*H*Ph), 4.69 (d, $J$ = 11.4 Hz, 1H, CH*H*Ph), 4.65 (s, 2H, C$H_2$Bn), 4.58 (d, $J$ = 12 Hz, 1H, CH*H*Ph), 4.53 (d, $J$ = 11.4 Hz, 1H, CH*H*Ph), 4.12 (d, $J$ = 14.2 Hz, 1H, CH*H*N), 3.97 (brs, 1H, H-4), 3.88–3.83 (m, 3H, CH*H*N, H-5, H-6), 3.59 (dd, $J$ = 14.5, 9.0 Hz, 1H, H-2), 2.85 (dm, $J$ = 7 Hz, 1H, H-7), 2.63 (d, $J$ = 14.3 Hz, 1H, H-2), 1.96 (m, 1H, CH*H* ethyl), 1.70 (m, 1H, CH*H* ethyl), 0.96 (t, $J$ = 7.3 Hz, 3H, C$H_3$ ethyl); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 163.6 (CO), 150.5, 140.1, 138.6, 138.2, 138.0, 135.7 (6 *C*arom), 130.7-123.4 (*C*Harom), 83.0 and 82.7 (C-5, C-6), 81.1 (C-4), 73.6, 73.5, 72.4 (3 $CH_2$Ph), 71.7 (C-3), 63.8 (C-7), 57.5 (N$CH_2$), 46.3 (C-2), 19.3 ($CH_2$), 12.0 ($CH_3$); HRMS (ESI) $m/z$: $[M+H]^+$ calcd for $C_{43}H_{45}N_2O_7$: 701.3221; found: 701.3222.

#### 4.4.3. (2*S*,3*R*,4*R*,5*S*,6*R*)-1-Benzyl-3,4,5-tris(benzyloxy)-6-vinylpiperidin-2-yl)methyl 4-nitrobenzoate (4c) and (3*R*,4*R*,5*R*,6*S*,7*R*)-1-benzyl-4,5,6-tris(benzyloxy)-7-vinylazepan-3-yl 4-nitrobenzoate (5c)

Piperidine **4c** (168 mg, 63%) and less polar azepane **5c** (26.7 mg, 10%) were obtained from azepane **3c** (210 mg, 0.382 mmol) as described above.

Compound **4c**: $[\alpha]_D$ = 35 ($c$ 1.36, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.17 (d, $J$ = 8.9 Hz, 2H, ArH), 8.01 (d, $J$ = 8.9 Hz, 2H, ArH), 7.34–7.21 (m, 20H, ArH), 5.85 (dt, $J$ = 16.9, 10.0 Hz, 1H, –C*H*=), 5.38 (dd, $J$ = 10.0, 1.6 Hz, 1H, =CH*H*), 5.14 (dd, $J$ = 16.9, 1.4 Hz, 1H, =CH*H*), 4.87 (qAB, $J$ = 10.7 Hz, 2H, C$H_2$Ph), 4.68 (qAB, $J$ = 11.7 Hz, 2H, C$H_2$Ph), 4.60 (m, 2H, C$H_2$OCO), 4.50 (qAB, $J$ = 11.5 Hz, 2H, C$H_2$Ph), 3.93 (s, 2H, NC$H_2$), 3.84 (m, 2H, H-3, H-4), 3.67 (m, 2H, H-2, H-5), 3.54 (dd, $J$ = 10.0, 6.1 Hz, 1H, H-6); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.4 (CO), 150.4 (ArC), 138.8, 138.7, 138.2, 138.0 (4 ArC), 135.5 (ArC), 133.7 (–*C*H=), 130.6 (ArCH), 128.5-127.2 (ArCH), 123.4 (ArCH), 120.7 ($CH_2$=), 80.2, 80.1, 79.1 (C-3, C-4, C-5), 75.6, 72.8, 71.9 (3 $CH_2$Ph), 64.4 ($CH_2$OCO), 61.0

(C-6), 58.9 (C-2), 56.4 ($NCH_2$); HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_{43}H_{42}N_2O_7Na$: 721.2889; found: 721.2889.

Compound **5c**: $[\alpha]_D = 48$ (*c* 0.26, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.24 (d, *J* = 8 Hz, 2H, ArH), 8.05 (d, *J* = 8 Hz, 2H, ArH), 7.33–7.19 (m, 20H, ArH), 6.36 (ddd, *J* = 17.0, 10.2, 9.1 Hz, 1H, –CH=), 5.45 (brd, *J* = 7.7 Hz, 1H, H-3), 5.32 (dd, *J* = 10.2, 1.9 Hz, 1H, =CH*H*), 5.17 (dd, *J* = 17.0, 1.5 Hz, 1H, =CH*H*), 4.68-4.42 (m, 6H, 3 $CH_2$Ph), 3.99 and 3.85 (2s, 1H and 2H, H-4, H-5, H-6), 3.72 (qAB, *J* = 13.8, 2H, $NCH_2$), 3.50 (hidden in part, 1H, 1H-2), 3.48 (dd, *J* = 9.1, 2.9 Hz, 1H, H-7), 2.72 (dd, *J* = 13.0, 2.8 Hz, 1H, 1H-2); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 163.5 (CO), 150.5, 139.1, 138.3, 137.9, 135.6 (Ar*C*), 132.8 (–*C*H=), 130.7 (Ar*C*H), 128.5–127.1 (Ar*C*H), 123.5 (Ar*C*H), 120.4 ($CH_2$=), 85.1, 81.7, 80.6 (C-4, C-5, C-6), 73.6 (C-3), 73.5, 72.9, 72.4 (3 $CH_2$Ph), 64.0 (C-7), 59.4 ($NCH_2$), 48.5 (C-2); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{43}H_{43}N_2O_7$: 699.3070; found: 699.3065.

#### 4.4.4. (2*S*,3*R*,4*R*,5*S*,6*S*)-1-Benzyl-3,4,5-tris(benzyloxy)-6-vinylpiperidin-2-yl)methyl 4-nitrobenzoate (4d) and (3*R*,4*R*,5*R*,6*S*,7*S*)-1-benzyl-4,5,6-tris(benzyloxy)-7-vinylazepan-3-yl 4-nitrobenzoate (5d)

Piperidine **4d** and azepane **5d** were obtained as an inseparable mixture (301 mg, 67%), from azepane **3d** (353 mg, 0.643 mmol) as described above.

### 4.5. General procedure for the synthesis of piperidines 6a–d

Potassium carbonate (378 mg, 2.7 mmol) was added to a solution of piperidine **4a** (190 mg, 0.266 mmol) in MeOH/THF (12 mL, 10:2). The mixture was stirred at room temperature for 4 h, quenched with saturated aqueous $NH_4Cl$, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure after filtration. The residue was purified by flash chromatography (EtOAc/petroleum ether 10:90) to afford piperidine **6a** as colorless oil (114 mg, 76% yield).

#### 4.5.1. (2*S*,3*R*,4*R*,5*S*,6*S*)-6-Allyl-1-benzyl-3,4,5-tris(benzyloxy)piperidin-2-yl)methanol (6a)

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.35–7.10 (m, 20H, ArH)), 5.86 (m, 1H, –C*H*=), 5.17–5.13 (m, 2H, =$CH_2$), 4.93 (d, *J* = 10.7 Hz, 2H, 2CH*H*Ph), 4.83 (d, *J* = 10.7 Hz, 1H, CH*H*Ph), 4.62 (d, *J* = 10.7 Hz, 1H, CH*H*Ph), 4.55 (qAB, 2H, $CH_2$Ph), 4.02 (d, *J* = 12.7 Hz, 1H, CH*H*N), 3.98 (dd, *J* = 9.6, 6.2 Hz, 1H, H-3), 3.76 (like t, *J* = 9.6, 9.0 Hz, 1H, H-4), 3.68–3.58 (m, 2H, $CH_2$OH), 3.52 (dd, *J* = 10.6, 9.0 Hz, 1H, H-5), 3.40 (d, *J* = 12.7 Hz, 1H, CH*H*N), 3.11–3.01 (m, 2H, H-2, H-6), 2.86 (m, 1H, H-7), 2.67 (d, *J* = 8.2 Hz, 1H, OH), 2.31 (m, 1H, H-7); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 138.6, 138.4, 138.1, 137.8 (4 Ar*C*), 135.4 (–*C*H=), 128.9–127.5 (Ar*C*H), 117.6 ($CH_2$=), 84.8 (C-4), 79.9 (C-5), 77.2 (C-3), 75.8, 75.5, 72.8 (3 $CH_2$Ph), 56.3 (C-2), 56.2 ($CH_2$OH), 55.5 (C-6), 49.7 ($NCH_2$), 32.4 ($CH_2$ allyl); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{37}H_{42}NO_4$: 564.3113; found: 564.3111.

#### 4.5.2. (2*S*,3*R*,4*R*,5*S*,6*R*)-1-Benzyl-3,4,5-tris(benzyloxy)-6-ethylpiperidin-2-yl)methanol (6b)

Piperidine **6b** was obtained as a colorless oil (161 mg, 77%) from piperidine **4b** (265 mg, 0.378 mmol) as described above.

$[\alpha]_D = 4.1$ (*c* 1.2, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.35–7.13 (m, 20H, ArH), 4.87 (d, *J* = 10.8 Hz, 1H, CH*H*Ph), 4.81 (d, *J* = 10.8 Hz, 1H, CH*H*Ph), 4.74 (d, *J* = 11.4 Hz, 1H, CH*H*Ph), 4.65 (d, *J* = 11.7 Hz, 1H, CH*H*Ph), 4.61 (d, *J* = 11.7 Hz, 1H, CH*H*Ph), 4.54 (d, *J* = 11.4 Hz, 1H, CH*H*Ph), 3.85 (m, 5H, H-3, H-4 and 3H $CH_2N$ or $CH_2OH$), 3.64 (m, 2H, H-5, CH*H*O or CH*H*N), 3.27 (m, 1H, H-2), 2.93 (br s, 1H, OH), 2.83 (m, 1H, H-6), 1.80 (m, 1H, CH*H* ethyl), 1.30 (m, 1H, CH*H* ethyl), 0.86 (t, *J* = 7.4 Hz, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 139.7, 138.8, 138.4, 138.0 (4 Ar*C*), 128.5–127.4 (Ar*C*H), 79.7, 79.4, 79.3 (C-3, C-4, C-5), 75.4, 73.8, 72.9 (3 $CH_2$Ph), 61.2 (C-2, C-6), 60.9, 60.5 ($NCH_2$, $CH_2OH$), 21.8 ($CH_2$ ethyl), 13.0 ($CH_3$ ethyl); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{36}H_{42}NO_4$: 552.3113; found: 552.3111.

#### 4.5.3. (2*S*,3*R*,4*R*,5*S*,6*R*)-1-Benzyl-3,4,5-tris(benzyloxy)-6-vinylpiperidin-2-yl)methanol (6c)

Piperidine **6c** was obtained as a colorless oil (69 mg, 70%) from piperidine **4c** (124 mg, 0.177 mmol) as described above.

$[\alpha]_D = 35$ (*c* 1.3, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.35–7.24 (m, 20H, ArH), 5.76 (ddd, *J* = 17.0, 10.2, 9.2 Hz, 1H, –C*H*=), 5.31 (d, *J* = 10.2 Hz, 1H, =CH*H*), 5.06 (d, *J* = 17.0 Hz, 1H, =CH*H*), 4.93 (d, *J* = 10.8 Hz, 1H, CH*H*Ph), 4.81 (d, *J* = 10.8 Hz, 1H, CH*H*Ph), 4.80 (d, *J* = 11.3 Hz, 1H, CH*H*Ph), 4.65 (d, *J* = 11.3 Hz, 1H, CH*H*Ph), 4.46 (qAB, *J* = 11.5 Hz, 2H, $CH_2$Ph), 3.91 (t, *J* = 9.2, 8.9 Hz, 1H, H-4), 3.84 (dd, *J* = 9.2, 5.96 Hz, 1H, H-3), 3.79 (m, 3H, $CH_2N$, CH*H*O), 3.64 (dd, *J* = 8.9, 6.2 Hz, 1H, H-5), 3.65 (m, 1H, CH*H*O), 3.46 (dd, *J* = 9.2, 6.2 Hz, 1H, H-6), 3.33 (ddd, *J* = 7.9, 5.96, 4.2 Hz, 1H, H-2), 2.82 (br s, 1H, OH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 138.9, 138.8, 138.1, 137.9 (4 Ar*C*), 134.4 (–*C*H=), 128.5–126.6 (Ar*C*H), 120.2 ($CH_2$=), 81.2 (C-3), 80.2 (C-5), 79.7 (C-4), 75.5, 74.2, 71.8 (3 $CH_2$Ph), 61.9 (C-2), 60.8 ($CH_2OH$), 60.6 (C-6), 56.4 ($NCH_2$); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{36}H_{40}NO_4$: 550.2957; found: 550.2951.

#### 4.5.4. (2*S*,3*R*,4*R*,5*S*,6*S*)-1-Benzyl-3,4,5-tris(benzyloxy)-6-vinylpiperidin-2-yl)methanol (6d)

Piperidine **6d** (155 mg, 44% yield over 2 steps) and azepane **3d** (78 mg, 22% over 2 steps) were obtained from mixture of compounds **4d** and **5d** (265 mg, 0.378 mmol) as described above after separation by flash chromatography.

$[\alpha]_D = 31.3$ (*c* 1.44, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.29–7.23 (m, 20H, ArH), 5.72 (ddd, *J* = 17.2, 10.2, 7.8 Hz, 1H, –C*H*=), 5.42 (dd, *J* = 17.2, 1.2 Hz, 1H, =CH*H*), 5.32 (dd, *J* = 10.2, 1.5 Hz, 1H, =CH*H*), 4.92 (d, *J* = 10.8 Hz, 1H, CH*H*Ph), 4.85 (d, *J* = 10.8 Hz, 1H, CH*H*Ph), 4.77 (d, *J* = 10.3 Hz, 1H, CH*H*Ph), 4.65 (d, *J* = 11.4 Hz, 1H, CH*H*Ph), 4.63 (d, *J* = 10.3 Hz, 1H, CH*H*Ph), 4.56 (d, *J* = 11.4 Hz, 1H, CH*H*Ph), 3.98–3.73 (m, 6H, H-3, H-4 ou H-5, $CH_2N$, $CH_2OH$), 3.43 (t, *J* = 9.4, 7.8 Hz, 1H, H-4 ou H-5), 3.38 (t, *J* = 9.4, 7.8 Hz, 1H, H-6), 3.11 (q, *J* = 6.8-5.6 Hz, 1H, H-2), 2.53 (dd, *J* = 6.8, 5.6 Hz, 1H, OH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 139.7, 138.8, 138.3, 137.8 (4 Ar*C*), 137.7 (–*C*H=), 128.5–127.1 (Ar*C*H), 120.3 ($CH_2$=), 83.4, 82.3, 80.2 (C-3, C-4, C-5), 75.7, 75.3, 73.5 (3 $CH_2$Ph), 63.8 (C-6), 57.08, 57.00 ($CH_2OH$, C-2), 52.8 ($NCH_2$); HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_{36}H_{39}NO_4Na$: 572.2776; found: 572.2777.

### 4.6. General procedure for the synthesis of piperidines 7a–d and azepanes 8a–c

To a solution of piperidine **6a** (43 mg, 0.076 mmol) in $CH_3OH$ (6 mL) was added 10% Pd/C (22 mg), Pd black (22 mg) and a 1 M HCl aqueous solution (0.15 mL, 0.15 mmol). The solution was purged with $N_2$ followed by $H_2$ then stirred under a $H_2$ atmosphere. After stirring overnight at room temperature, the reaction mixture was purged with $N_2$, filtered over a Celite pad eluted with $CH_3OH$. The filtrate was concentrated under reduced pressure to give piperidine **7a** (18 mg, quantitative yield) as its hydrochloride salt.

#### 4.6.1. (2*S*,3*R*,4*R*,5*S*,6*S*)-2-(hydroxymethyl)-6-propylpiperidine-3,4,5-triol (7a)

$[\alpha]_D = -34$ (*c* 0.2, MeOH); $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 3.95 (dd, *J* = 11.9, 4.8 Hz, 1H, CH*H*OH), 3.90–3.84 (m, 2H, H-3, CH*H*OH), 3.73 (t, *J* = 6.8 Hz, 1H, H-4), 3.66–3.61 (m, 1H, H-2), 3.59 (t, *J* = 7.1, 6.8 Hz, 1H, H-5), 3.37–3.33 (m, 1H, H-6), 2.12 (m, 1H, CH*H*), 1.67 (m, 1H, CH*H*), 1.54 (m, 2H, $CH_2$), 1.02 (t, *J* = 7.6 Hz, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta$ = 73.2 (C-4), 71.6 (C-5), 69.8 (C-3), 57.9 (C-6), 57.7 ($CH_2OH$), 56.6 (C-2), 31.9 ($CH_2$ propyl), 19.8 ($CH_2$ propyl), 14.1 ($CH_3$ propyl); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_9H_{20}NO_4$: 184.1687; found: 184.1685.

#### 4.6.2. (2*R*,3*S*,4*R*,5*R*,6*S*)-2-Ethyl-6-(hydroxymethyl)piperidine-3,4,5-triol (7b)

Piperidine **6b** (11 mg, 0.020 mmol) was deprotected as described for **7a** to give piperidine **7b** (4.5 mg, quantitative yield) as its hydrochloride salt.

$[\alpha]_D$ = 7.5 (*c* 0.08, $H_2O$); $^1$H NMR (400 MHz, $D_2O$): $\delta$ 4.13 (t, *J* = 3.4 Hz, 1H, H-4), 4.03 (m, 2H, H-3, H-5), 3.86 (m, 2H, C$H_2$OH), 3.57 (m, 1H, H-6), 3.40 (ddd, *J* = 6.4, 4.8, 1.4 Hz, H-2), 1.85–1.75 (m, 2H, $CH_2$ ethyl), 0.96 (t, *J* = 7.4 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $D_2O$): $\delta$ 66.85, 66.80, 66.3 (C-3, C-4, C-5), 59.0 (*C*$H_2$OH), 56.5 (C-2, C-6), 20.7 (*C*$H_2$ ethyl), 8.4 (*C*$H_3$ ethyl); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_8H_{18}NO_4$: 192.1236; found: 192.1237.

#### 4.6.3. (2*S*,3*S*,4*R*,5*R*,6*S*)-2-Ethyl-6-(hydroxymethyl)piperidine-3,4,5-triol (7c)

Piperidine **6d** (32 mg, 0.058 mmol) was deprotected as described for **7a** to give piperidine **7c** (13.3 mg, quantitative yield) as its hydrochloride salt.

$[\alpha]_D$ = −27 (*c* 0.28, $CH_3OH$); $^1$H NMR (400 MHz, $D_2O$): $\delta$ 3.94 (dd, *J* = 12.6, 4.6 Hz, 1H, CH*H*OH), 3.85–3.79 (m, 2H, H-5, CH*H*OH), 3.69 (m, 1H, H-6), 3.62 (t, *J* = 8.7 Hz, 1H, H-4), 3.44 (dd, *J* = 9.7, 8.7 Hz, 1H, 1H, H-3), 3.21 (ddd, *J* = 9.7, 6.5, 4.4 Hz, H-2), 1.95 (m, 1H, CH*H* ethyl), 1.66 (m, 1H, CH*H* ethyl), 0.95 (t, *J* = 7.6 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $D_2O$): $\delta$ = 72.3 (C-4), 70.3 (C-3), 68.1 (C-5), 56.1 (C-6), 55.6 (C-2), 55.0 (*C*$H_2$OH), 21.3 (*C*$H_2$ ethyl), 8.2 (*C*$H_3$ ethyl); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_8H_{18}NO_4$: 192.1236; found: 192.1235.

#### 4.6.4. (2*S*,3*S*,4*R*,5*R*,6*R*)-2-Propylazepan-3,4,5,6-tetraol (8a)

Azepane **3a** (30 mg, 0.053 mmol) was deprotected as described for **7a** to give **8a** as its hydrochloride salt (12.8 mg, quantitative yield).

$[\alpha]_D$ = −15 (*c* 0.24, $CH_3OH$); $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 4.20 (m, 1H, H-6), 3.82 (like t, 1H, *J* = 7.3, 7.0 Hz, H-4), 3.78 (dd, *J* = 7.3, 2.0 Hz, 1H, H-5), 3.62 (dd, *J* = 7.6, 7.0 Hz, 1H, H-3), 3.41 (m, 1H, H-2), 3.31 (m, 2H, 2H-7), 1.90 (m, 1H, CH*H*), 1.75 (m, 1H, CH*H*), 1.58 (m, 1H, CH*H*), 1.46 (m, 1H, CH*H*), 1.0 (t, *J* = 7.2 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 76.6(C-5), 74.7 (C-4), 73.4 (C-3), 67.5 (C-6), 61.4 (C-2), 46.2 (C-7), 33.7 (*C*$H_2$), 19.4 (*C*$H_2$), 14.2 (*C*$H_3$); $[M+H]^+$ calcd for $C_9H_{20}NO_4$: 206.1392; found: 206.1394.

#### 4.6.5. (2*R*,3*S*,4*R*,5*R*,6*R*)-2-Ethylazepan-3,4,5,6-tetraol (8b)

Azepane **3b** (41 mg, 0.074 mmol) was deprotected as described for **7a** to give azepane **8b** (16.2 mg, 95%) as its hydrochloride salt.

$[\alpha]_D$ = 4 (*c* 0.3, MeOH); $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 4.16 (dd, *J* = 8.3, 3.4 Hz, 1H, H-6), 3.85-3.86 and 3.80–3.79 (m, 2H and m, 1H, H-3, H-4, H-5), 3.33 (dd, *J* = 13.0, 8.3 Hz, 1H, H-7), 3.27 ((t, *J* = 6.7 Hz, 1H, H-2), 3.15 (dd, *J* = 13.0, 3.4 Hz, 1H, H-7), 1.71–1.63 (m, 2H, C$H_2$ ethyl), 0.93 (t, *J* = 7.4 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 79.1, 73.7, 72.6 (C-3, C-4, C-5), 67.5 (C-6), 58.7 (C-2), 47.8 (C-7), 25.7 (*C*$H_2$ ethyl), 10.4 (*C*$H_3$ ethyl); HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_8H_{17}NO_4$: 214.1055; found: 214.1055.

#### 4.6.6. (2*S*,3*S*,4*R*,5*R*,6*R*)-2-Ethylazepan-3,4,5,6-tetraol (8c)

Azepane **3c** (35 mg, 0.0637 mmol) was deprotected as described for **7a** to give **8c** (15 mg, quantitative yield) as its hydrochloride salt.

$[\alpha]_D$ = −16 (*c* 0.3, MeOH); $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 4.23–4.20 (m, 1H, H-6), 3.87–3.80 (m, 2H, H-4, H-5), 3.66 (dd, *J* = 7.8, 6.3 Hz, 1H, H-3), 3.42–3.36 (m, 1H, H-2), 3.34-3.25 (m, 2H, 2H-7), 2.04–1.94 (m, 1H, CH*H* ethyl), 1.94–1.81 (m, 1H, CH*H* ethyl), 1.10 (t, *J* = 7.4 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 76.5, 75.0 (C-4, C-5), 73.1 (C-3), 67.6 (C-6), 62.5 (C-2), 46.4 (C-7), 24.4 (*C*$H_2$ ethyl), 9.7 (*C*$H_3$ ethyl); $[M+Na]^+$ calcd for $C_8H_{17}NO_4$: 214.1055; found: 214.1055.

#### 4.6.7. (2*R*,3*R*,4*R*,5*S*,6*R*)-1-Benzyl-3,4,5-tris(benzyloxy)-2,6-divinylpiperidine (9)

Oxalyl chloride (0.13 mL, 1.45 mmol) was added to a stirred solution of DMSO (0.14 mL, 1.94 mmol) in dry $CH_2Cl_2$ (3.5 mL) at −78 °C and the resulting mixture was stirred at this temperature for 30 min. A solution of piperidine **6c** (266 mg, 0.484 mmol) in dry $CH_2Cl_2$ (1.5 mL) was added to the reaction mixture at −78 °C and stirred for 1 h at this temperature. Then, $Et_3N$ (0.4 mL, 2.87 mmol) was added at −78 °C and stirred for an additional 30 min at rt. The reaction mixture was diluted with water and extracted with $CH_2Cl_2$. The organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the crude aldehyde that was used for the next reaction without further purification. *n*-Butyllithium (0.8 mL of a 2.5 M solution in hexanes, 2.0 mmol) was added to a solution of methyltriphenylphosphonium bromide (692 mg, 1.94 mmol) in THF (3.5 mL) at 0 °C. After 30 min, the solution was cooled to −50 °C and a solution of the crude aldehyde in THF (3 mL) was added dropwise. The mixture was stirred between −30 and −20 °C for 1 h, quenched with water and extracted with EtOAc. Flash chromatography purification (EtOAc/petroleum ether 10:90) gave piperidine **9** (122 mg, 46% over 2 steps) as an oil.

#### 4.6.8. Aldehyde

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.91 d, *J* = 4.2 Hz, 1H, C*H*O), 7.32–7.21 (m, 20H, ArH), 5.74 (dt, *J* = 16.8, 9.5–10.1 Hz, 1H, –C*H*=), 5.35 (dd, *J* = 10.1, 1.5 Hz, 1H, =CH*H*), 5.12 (dd, *J* = 16.8, 1.2 Hz, 1H, =CH*H*), 4.86 (d, *J* = 10.9 Hz, 1H, CH*H*Ph), 4.78 (d, *J* = 10.9 Hz, 1H, CH*H*Ph), 4.64 (d, *J* = 11.6 Hz, 1H, CH*H*Ph), 4.58 (d, *J* = 11.6 Hz, 1H, CH*H*Ph), 4.51 (2H, C$H_2$Ph), 4.00 (t, *J* = 8.6 Hz, 1H, H-4), 3.84 (d, *J* = 14.3 Hz, 1H, CH*H*N), 3.80 (dd, *J* = 8.6, 6.4 Hz, 1H, H-3), 3.70 (d, *J* = 14.3 Hz, 1H, CH*H*N), 3.65 (dd, *J* = 8.6, 5.4 Hz, 1H, H-5), 3.54 (dd, *J* = 9.5, 5.4 Hz, 1H, H-6), 3.41 (dd, *J* = 6.4, 4.2 Hz, 1H, H-2); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 201.9 (*C*HO), 137.6 (ArC), 136.9 (ArC), 134.1 (ArC), 127.5–126.3 (12ArCH), 78.9 (C-5), 77.8 (C-4), 77.5 (C-3), 74.1, 72.1, 71.0 (3 *C*$H_2$Ph), 65.3 (C-2), 60.5 (C-6), 57.08, 54.9 (N*C*$H_2$).

Compound **9** $[\alpha]_D$ = 6.3 (*c* 0.7, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.37–7.25 (m, 20H, ArH), 5.88 (dt, *J* = 16.8, 10.1, 2H, –C*H*=), 5.30 (dd, *J* = 10.1, 1.8 Hz, 2H, =CH*H*), 5.04 (dd, *J* = 16.8, 1.6 Hz, 2H, =CH*H*), 4.86 (s, 2H, C$H_2$Ph), 4.56 (d, *J* = 11.5 Hz, 2H, 2CH*H*Ph), 4.50 (d, *J* = 11.5 Hz, 2H, 2CH*H*Ph), 3.89 (t, *J* = 9.4 Hz, 1H, H-4), 3.72 (dd, *J* = 9.4, 6.2 Hz, 2H, H-3, H-5), 3.66 (s, 2H, C$H_2$N), 3.59 (dd, *J* = 10.1, 6.2 Hz, 2H, H-2, H-6); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 139.2, 139.1, 138.3 (3 Ar*C*), 135.0 (–*C*H=), 123–126.9 (7ArCH), 119.6 (*C*$H_2$=), 80.4 (C-3, C-5), 79.2 (C-4), 75.6 (*C*$H_2$Ph), 71.9 (2*C*$H_2$Ph), 62.8 (C-2, C-6), 55.5 (N*C*$H_2$); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{37}H_{40}NO_3$: 546.3008; found: 546.3011.

#### 4.6.8. (2*S*,3*R*,4*R*,5*S*,6*R*)-2,6-Diethylpiperidine-3,4,5-triol (10)

Piperidine **9** (41 mg, 0.074 mmol) was deprotected as described for **7a** to give piperidine **10** (16.2 mg, 95%) as its hydrochloride salt.

$[\alpha]_D$ = 3 (*c* 0.4, MeOH); $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 4.08 (t, *J* = 3.6 Hz, 1H, H-4), 3.91 (m, 2H, H-3, H-5), 3.33 (m, 2H, H-2, H-6), 1.91 (m, 2H, 2CH*H*), 1.75 (m, 2H, 2CH*H*), 1.02 (t, *J* = 7.5 Hz, 6H, 2×$CH_3$); $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ = 68.39 (C-3, C-5), 68.25 (C-4), 58.37 (C-2, C-6), 22.37 (2*C*$H_2$), 9.67 (2*C*$H_3$); HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_9H_{20}NO_3$: 190.1443; found: 190.1440.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