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Synthesis and evaluation of *galacto*-noeurostegine and its 2-deoxy analogue as glycosidase inhibitors

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An epimer of the known glycosidase inhibitor noeurostegine, *galacto*-noeurostegine, was synthesised in 21 steps from levoglucosan and found to be a potent, competitive and highly selective galactosidase inhibitor of *Aspergillus oryzae* β-galactosidase. *Galacto*-noeurostegine was not found to be an inhibitor of green coffee bean α-galactosidase, yeast α-glucosidase and *E. coli* β-galactosidase, whereas potent but non-competitive inhibition against sweet almond β-glucosidase was established. The 2-deoxy-*galacto*-noeurostegine analogue was also prepared and found to be a less potent inhibitor of the same enzymes.

Introduction

The combined family of imino- and azasugars represent the most important class of carbohydrate mimics, owing to their remarkable biological activities.[1] Initially studied for their properties as glycosidase inhibitors,[2] they have also been found to be potent inhibitors of glycosyl transferases,[3] metalloproteinases[4] and nucleoside-processing enzymes,[5] making them valuable bio-active compounds against a wide range of diseases.

A few years ago, our group designed a new nor-tropane carbohydrate mimetic named noeurostegine (**3**), as a hybrid between naturally occurring calystegine B_2 (**1**) and the synthetic noeuromycin (**2**) (Figure 1).[6] As a result of the ethylene bridge, both noeurostegine and calystegine B_2 are stable hemiaminals contrary to noeuromycin, which over time will undergo Amadori rearrangement. The increased inhibitory potency of noeuromycin compared to calystegine B_2 against a series of glycosidases, however, is partially a result of the presence of a hydroxymethyl substituent absent from calystegine B_2. We were able to demonstrate that for enzymes that tolerate the ethylene bridge, increased inhibitory power, to the level of noeuromycin, was obtained with the hybrid compound noeurostegine compared to calystegine B_2.[6] We have furthermore shown that noeurostegine is a potent inhibitor of glucocerebrosidase, making it a potentially valuable compound against Gaucher's disease.[7] In addition, a uronic acid analogue (**4**) of noeurostegine has been prepared, which has been found to exhibit very powerful and selective inhibition of *E. coli* β-glucuronidase, making it a potentially useful candidate in cancer therapy in combination with irinotecan.[8,9] Given the successful results achieved so far with the noeurostegines, we decided to embark on the synthesis of the *galacto*-configured congener, *galacto*-noeurostegine (**5**).

Several calystegines are known,[10,11] but none of the naturally occuring nortropane hemiaminals have a substitution pattern which has 1,3-diaxial interactions with the ethylene bridge. Boyer *et al.*[12] as well as Skaanderup and Madsen[13] have attempted to make synthetic calystegines with this 1,3-diaxial interaction and found these to be unable to cyclise into the bicyclic form or exist in an equilibrium between nortropane and aminocyoheptanone. Accordingly, it was unclear whether the

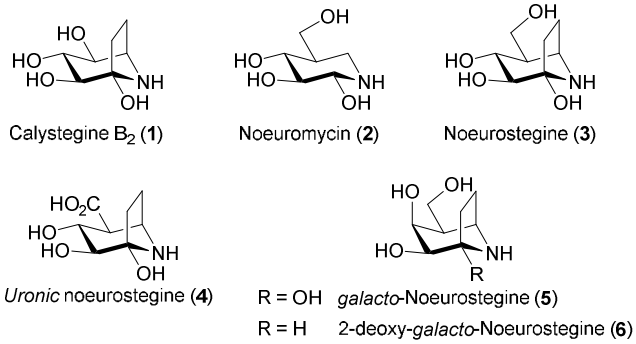


Figure 1. Structures of various known 1-azasugars (**1**-**4**) and of the two targets of this study (**5**-**6**).

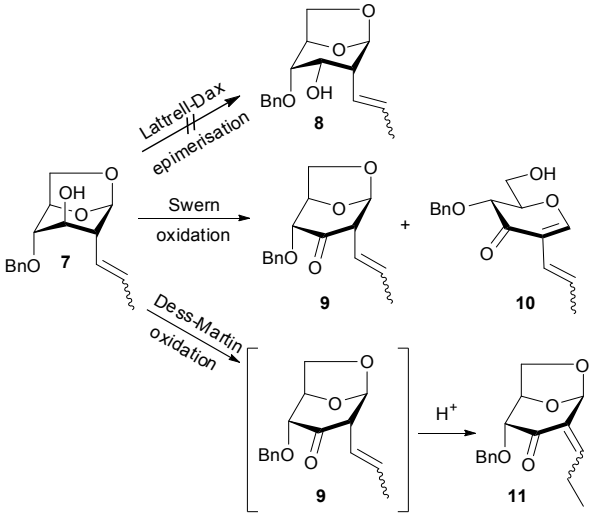
bicyclic synthetic target **5** could be destabilised to such an extent by unfavourable diaxial interaction to cause it to only exist in its monocyclic cycloheptanone structure.

In addition to making *galacto*-noeurostegine (**5**) and testing it for inhibition of a panel of glycosidases, we furthermore planned to synthesise the 2-deoxy analogue (**6**) to explore the importance of this OH-group for binding.[14] Previously, a hydroxyl group in this particular position has been found to contribute greatly to inhibitor-glycosidase binding.[15,16]

Results and discussion

For the preparation of the target azasugars we chose a strategy previously successful to us.[6-8,17] The starting point of our synthesis was the known alcohol **7**,[6] which is easily accessible from commercially available levoglucosan. To eventually reach the *galacto*-configuration, an early epimerisation at the 3-

position was envisaged. Hence the inverted alcohol **8** was the first target (Scheme 1). Triflation of alcohol **7** followed by nitrite-mediated substitution according to the Lattrell-Dax method was attempted,[18] unfortunately leading to full recovery of the starting material. This lack of reactivity can be explained by the absence of a neighbouring ester group in an equatorial position, as described by Ramström *et al.*[19] Furthermore, it was



Scheme 1. First attempts at epimerising alcohol **7**.

hypothesised that the steric hindrance of the bottom face resulted in a nitrite ion attack on the sulfur atom of the triflate rather than on C-3, giving rise to the initial alcohol with liberation of nitrosyl triflate. Consequently, it was decided to use the steric hindrance to our advantage and invert the stereochemistry in a two-step oxidation-hydride reduction process. Initially, Swern conditions were attempted to prepare ketone **9**. However, the yields were not reproducible and the by-product **10**, resulting from β-H elimination, was always isolated, albeit in lesser amount when Et_3N was replaced with DIPEA. Dess-Martin oxidation was also attempted but the *in situ* liberation of acetic acid led to isomerisation of the double bond (**11**, not described).

Finally, the use of PCC prevented any undesired rearrangements and gave ketone **9**, the hydride reduction of which furnished the inverted alcohol **8** (Scheme 2). Ozonolysis of the alkene followed by reductive work-up gave the diol **12** which was benzylated to give the protected anhydro-allopyranoside **13** (31% yield from **7**). Noteworthy, this synthetic sequence could be carried out on multigram scale without any purification of the different intermediates, only a single column chromatography was performed after the last step to give a clean compound **13**.

This anhydrosugar (**13**) then underwent acid-promoted methanolysis, giving alcohol **14** (85%) as a 3:1 α/β mixture of anomers. Both anomers were isolated once for full characterisation, otherwise they were iodinated together under Garegg's conditions,[20,21] affording halides **15** in 94% yield (α/β 3:1). Similarly, the anomeric mixture was used in the following zinc-mediated fragmentation, under sonication,[22] to give a unique hexenal **16** which was subsequently allylated in a Barbier-type reaction, affording a separable 3:2 diastereoisomeric mixture of homoallylic alcohols **17*R***/**17*S***.[23] Our previous experience in the synthesis of *gluco*-configured noeurostegine (**3**) encouraged us to protect the homoallylic alcohol before performing the metathesis reaction, however, all of our attempts to form a PMB ether were unfruitful, once more probably because of steric hindrance. Gratifyingly, unlike their *gluco* counterparts,[6] the ring closing metathesis could be performed without the need for protection of the homoallylic alcohol moieties and each diastereomer gave its corresponding cycloheptene in 78% yield. The undesired diastereomer (**18*R***) was then efficiently converted to its epimer (**18*S***) after PCC oxidation (**19**) and lithium tri-*tert*-butoxyaluminium hydride reduction (82% over two steps).

The hydroboration-oxidation sequence of cycloheptene **18*S*** gave a 3:1 mixture of regioisomers in favour of the desired one, as expected from previous work.[6,24] Both regioisomers were found as single diastereomers and their configurations were determined by X-ray analysis, either directly for diol **21**, which crystallised spontaneously after prolonged standing at -20 °C, or by formation of the bis-(3,5-dinitrobenzoate) derivative **22** for diol **20** (Figure 2).

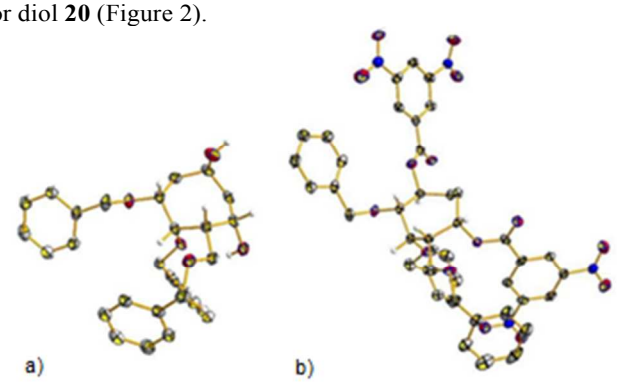


Figure 2. a) Crystal structure of diol **21**. b) Crystal structure of diester **22**. For clarity only polar and methine hydrogen atoms are shown.

Taking advantage of the lack of reactivity of the C-5 alcohol observed previously, we were able to regioselectively benzoylate the C-1 alcohol in a good 85% yield, as confirmed by COSY correlations of H-1 and H-2 (**23**) (Scheme 3). Unfortunately, substitution of the free alcohol by an azide under Mitsunobu conditions resulted in only 35% yield of the expected azide **25**, the elimination side reaction was predominant and cycloheptene **24** was obtained in 57% yield. Displacement of an activated alcohol under the form of a mesylate or a triflate was also largely in favour of the elimination process (not shown). Debenzoylation (**26**) and subsequent Dess-Martin oxidation uneventfully lead to the key intermediate **27**. In order to observe whether the 1,3-diaxial interactions are detrimental for cyclisation, it was decided to perform a sequential deprotection. To this end, the azide moiety of **27** was first reduced in the presence of pyridine so as to inhibit any benzyl ether hydrogenolysis.[25] Pleasantly, a single compound was observed by TLC analysis and **28** was obtained in good yield (89%). Proton NMR in deuterated chloroform showed only broad signals (not shown) and while the spectrum was much better resolved in deuterated methanol, some signals were still unusually broad. These first observations were clearly in favour of a cyclised form and definitive evidence was obtained from carbon NMR. Indeed, while an experiment performed at 303 K showed no remaining trace of ketone (δ_C 205.1 ppm), the hemiaminal signal (δ_C 92.2 ppm) could eventually be observed with a cold experiment performed at 253 K (Figure 3). The final deprotection was performed using Degussa type Pd/C and *galacto*-noeurostegine (**5**) was isolated in quantitative yield.

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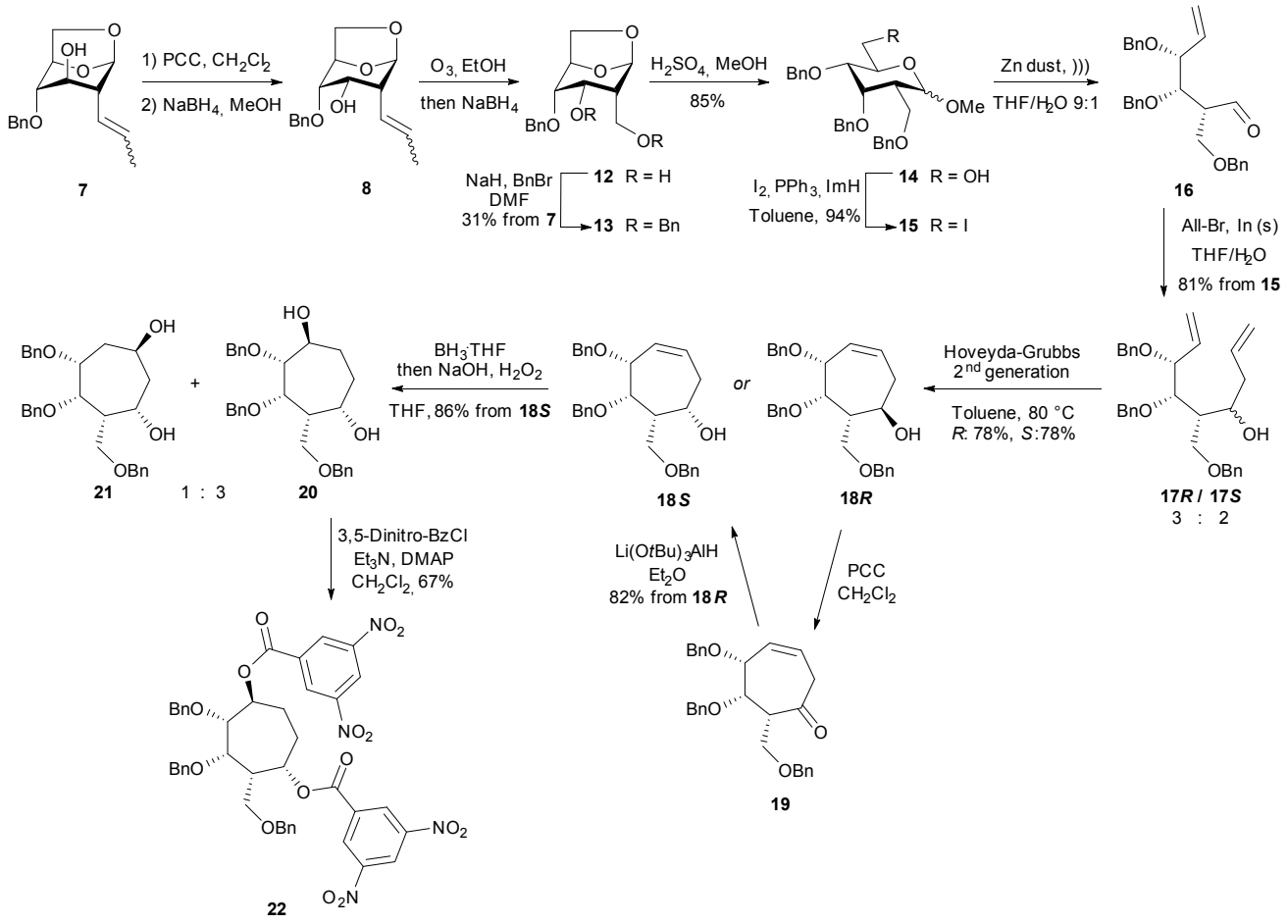

Scheme 2. Synthesis of diol **20** and bis-(3,5-dinitrobenzoate) **22** from anhydrosugar **7**.

Unexpectedly, NMR experiments showed that unlike its protected analogue **28** or its *gluco* epimer (**3**), *galacto*-noeurostegine (**5**) existed as a mixture of monocyclic (**5m**) and bicyclic forms (**5b**) (ca. 2:3). Intrigued by this phenomenon we performed MP2/aug'-cc-pVDZ//wb97xd/pcseg-1[26-29] quantum mechanical optimisations of both structures of benzylated and unprotected *gluco*- and *galacto*-noeurostegines using the IEFPCM[30] solvent models of chloroform and water for the protected and unprotected analogues, respectively. Consistently with what was observed experimentally, the bicyclic structures of protected *gluco*- and *galacto*-noeurostegines were more stable than the open structures by 27 and 23 kJ/mol, respectively. These energy differences were attributed to more favourable π-π interactions between the phenyl rings in the closed forms. As for the lower stability of *galacto*- compared to *gluco*-noeurostegine, it was attributed to 1,3-diaxial interactions. Regarding the deprotected compounds, once again, the bicyclic structures were more stable than the monocyclic ones; however the energy difference was lower for *galacto*-noeurostegine (6 kJ/mol) than for

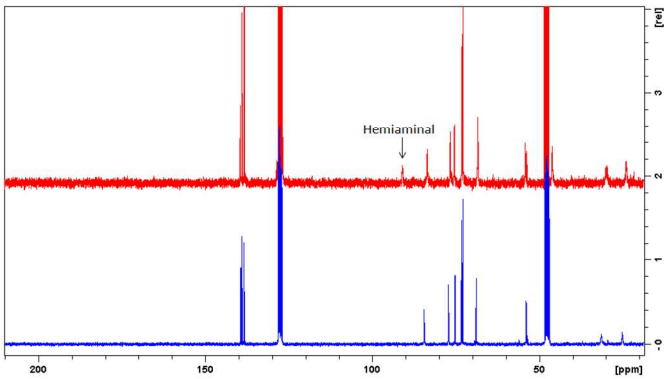

Figure 3. ^{13}C NMR spectra recorded in CD_3OD of compound **28** at 303K (blue) and 253K (red).

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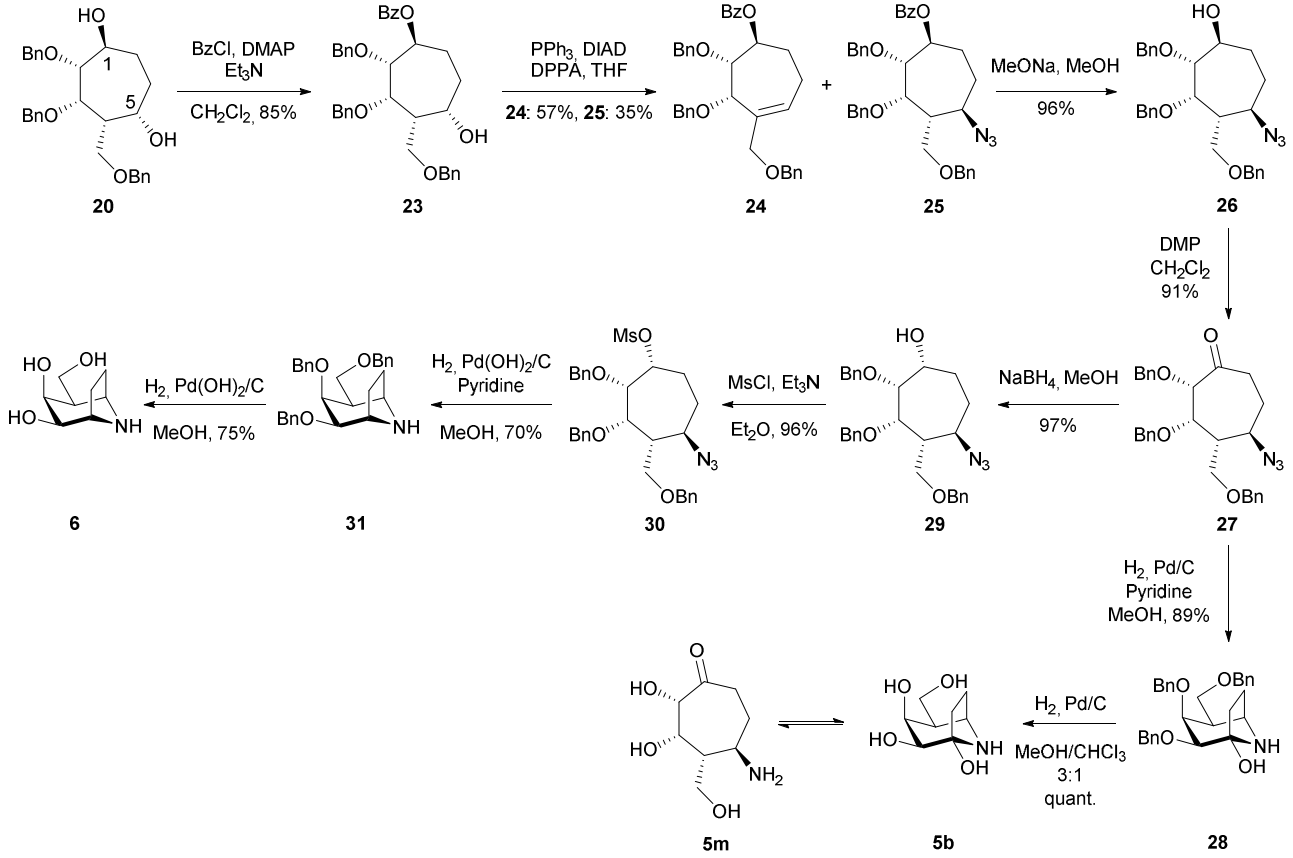


Scheme 3. Synthesis of *galacto*-noeurostegine **5** and 2-deoxy-*galacto*-noeurostegine **6** from diol **20**.

noeurostegine (**3**) (12 kJ/mol), also probably due to the diaxial interactions, which could account for the existence of an equilibrium in the case of *galacto*-noeurostegine (**5**).

Finally, we turned our attention to the synthesis of the 2-deoxy analogue of **5** (**6**) (Scheme 3). Ketone **27** was stereospecifically reduced to provide the 1,4-*trans* azido alcohol **29** (97%), which was in turn submitted to mesylation conditions to afford compound **30** (96%). Once more, the final deprotection was performed sequentially and gave first the protected derivative **31** in 70% yield, then the deprotected target **6** (75%), which unlike **5** cannot undergo ring opening to a monocyclic form.

Inhibition studies

Compounds **5** and **6** were evaluated as inhibitors against commercially available glycoside hydrolases (Table 1). The ability of compound **5** to bind in both its monocyclic (**5m**) and bicyclic (**5b**) forms was expected to make precise analysis of the binding difficult. To the best of our knowledge only very few amino-cycloheptanes have been evaluated as glycosidase inhibitors and only weak or no inhibition has been found,[31] but several azepanes[32] have been shown to inhibit these enzymes, which demonstrates that it is possible to accommodate the enlarged ring structure of **5m**.

Galacto-noeurostegine (**5**) was found to be an extremely potent inhibitor (K_i 18 nM) of sweet almond β-glucosidase but contrary to the *gluco*-configured congener (**3**), inhibition was established to be non-competitive. This particular enzyme is indeed known to be potently inhibited by azasugars otherwise designed to target galactosidases (iso-*galacto*-fagomine K_i 0.097 μM; aza-*galacto*-fagomine K_i 0.13 μM)[33] but inhibition for these was competitive as opposed to that found for **5**. In this case, as is often found for sweet almond β-glucosidase, inhibition was found to have a slow onset and required pre-incubating conditions (30 min) for tight binding. Measuring without pre-incubating conditions did not show micromolar inhibition.

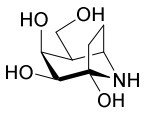
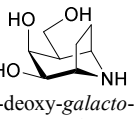
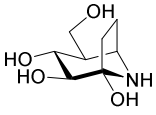
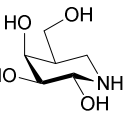
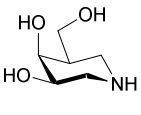
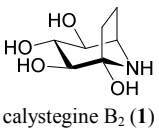
2-Deoxy *galacto*-noeurostegine (**6**) was, contrary to **5**, found to be a competitive inhibitor, but 100-fold weaker against almond β-glucosidase compared to iso-*galacto*-fagomine with the only structural difference being the ethylene bridge. This structural motif is otherwise tolerated for noeurostegine (**3**, K_i 50 nM),[6] which is equipotent to noeuromycin (K_i 69 nM).[34]

Yeast α-glucosidase was also tested for inhibition but neither **5** nor **6** were found to bind to this enzyme, in accordance with data for other azasugars designed to target galactosidases (Table 1).

Galacto-noeurostegine (**5**) was found to be a highly potent inhibitor of β-galactosidase from *Aspergillus oryzae,* with a K_i value of 31 nM, being of equal inhibitory potency as *galacto*-noeuromycin. Also, the 2-deoxy analogue (**6**) inhibited this enzyme in the sub-micromolar range albeit 33-fold less than iso-*galacto*-fagomine. Interestingly, amine iso-*galacto*-fagomine is 9-fold more potent against this enzyme compared to hemiaminal *galacto*-noeuromycin, while hemi-aminal **5** was 4-fold more potent against this enzyme than amine **6**.

Both *galacto*-noeurostegine (**5**) and its 2-deoxy analogue (**6**) were also tested as inhibitors of *E. coli* β-galactosidase and coffee bean α-galactosidase, but found to be inactive. In the case of the latter galactosidase this is particularly interesting since both calystegine B_2 (**1**) and noeurostegine (**3**) are reasonable competitive inhibitors of this enzyme (K_i 0.86 μM and 2.5 μM, respectively). This means that a binding mode exists where the ethylene bridge for both **1** and **3** can be accommodated. If this binding mode places the *N*-atom of these compounds in the place of the anomeric carbon of the enzyme substrate, then **5** and **6** would also be expected to be inhibitors of this α-galactosidase, which is not the case. This could suggest that **1** and **3** then bind in a deoxynojirimycin binding mode with the *N*-atom in place of the endocyclic *O*-atom of the substrate, with the ethylene bridge on the other face of the ring. One would then expect 1-deoxy-nojirimycin to be an inhibitor of this enzyme, which indeed has been found to be the case (K_i 23 μM).[35] In many cases, α-glycosidases are more potently inhibited by iminosugars bearing an *N*-atom in place of the endocyclic *O*-atom of the substrate,[36] while calystegine B_2 (**1**) binds with its *N*-atom in place of the anomeric carbon in *Thermotoga maritima* β-glucosidase.[37]

Table 1: K_i values in μM of *galacto*-noeurostegine (**5**) and 2-deoxy-*galacto*-noeurostegine (**6**) as well as similar azasugars.

K_i (μM)	 *galacto*-noeurostegine (**5**)	 2-deoxy-*galacto*-noeurostegine (**6**)	 noeurostegine (**3**)	 *galacto*-noeuromycin	 iso-*galacto*-fagomine	 calystegine B_2 (**1**)
β-Glucosidase (almonds)	0.018[a,b]	120	0.05[a,6]	n.d.	0.097[38]	1.2[a,41]
α-Glucosidase (yeast)	>1000	>1000	>1000[6]	n.d.	>2000[c,39]	>1000[41]
β-Galactosidase (*Asp. oryzae*)	0.031	0.13	23[6]	0.035[34]	0.004[40]	n.d.
β-Galactosidase (*E. coli*)	>1000	>1000	>1000[6]	0.397[34]	0.200[d,33]	n.d.
α-Galactosidase (green coffee beans)	>1000	>1000	2.5[6]	0.742[34]	50[33]	0.86[a,41]

[a]Preincubated 30 min; [b]Non-competitive; [c]IC_{50} value; [d]measured on racemic compound; n.d.: not determined

Conclusions

Inspired by the structure of calystegine B_2 (**1**) and noeurostegine (**3**), we have prepared *galacto*-noeurostegine (**5**) in 21 steps from levoglucosan. This compound is a stable nor-tropane hemiaminal, which has unfavourable 1,3-diaxial interactions between the ethylene bridge and a ring substituent. As a consequence of this steric repulsion an equilibrium mixture of monocyclic (**5m**) and bicyclic (**5b**) structures were obtained.

We have also presented the synthesis of the 2-deoxy version of *galacto*-noeurostegine (**6**) to investigate the influence of the 2-OH group on glycosidase inhibition.

Both compounds, **5** and **6**, were evaluated as glycosidase inhibitors and found to only inhibit *Aspergillus oryzae* of the three galactosidases tested. Inhibition of this enzyme, however, was in the low nanomolar region for both compounds. Potent inhibition of sweet almond β-glucosidase was also established and found both to be slow and non-competitive for *galacto*-noeurostegine (**5**). Generally, hemiaminal **5** was found to be more potent than amine **6**, emphasising the importance of a hydroxyl group in the 2-position.

Acknowledgements

The authors would like to thank Jacob Overgaard for the X-ray structural determinations.

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Experimental section

Abbreviations

Aq.: aqueous; DCM: dichloromethane; DIAD: diisopropyl azodicarboxylate; DIPEA: *N*,*N*-diisopropylethylamine; DMAP: 4-(dimethylamino)pyridine; DMF: dimethylformamide; DMP: Dess-Martin periodinane; DPPA: diphenyl phosphoryl azide; Hept: heptanes; HRMS: high resolution mass spectrometry; ImH: imidazole; PCC: pyridinium chlorochromate; Pent: pentane; PMB: *para*-methoxybenzyl; r.t.: room temperature; THF: tetrahydrofuran;))): sonication.

General information

Commercially available chemicals were purchased from Sigma-Aldrich and used without further purification. All reactions with air- and moisture sensitive compounds were conducted in oven (ca. 120 °C) or flame-dried glassware under an argon atmosphere. DCM, THF and toluene were dried over aluminum oxide via a Braun solvent purification system. Methanol and pyridine were dried over molecular sieves (4 Å). Et_2O was dried over a sodium wire. DMF was purchased as dry on molecular sieves (4 Å). Triethylamine was stored over KOH. TLC analysis was carried out on silica-coated aluminum foil plates (Merck Kieselgel 60 F_{254}). The TLC plates were first observed in UV-light (254 nm) and then visualised with a 10% H_2SO_4 aq. solution with charring or a ninhydrin solution (0.3 g ninhydrin in 100 mL of 1-butanol and 3 mL of glacial acetic acid) followed by heating to dryness. Flash column chromatography was carried out with Merck silica gel 60 (63–200 μm or 5–40 μm) as stationary phase. NMR spectra were recorded on a Varian Mercury 400 spectrometer at 303 K (or otherwise stated) at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), br s (broad singlet), br d (broad doublet) and coupling constants are reported in Hertz (Hz). Chemical shifts (δ) are reported in ppm relative to the residual solvent peak (*Organometallics* **2010**, *29*, 2176–2179). Elucidations of chemical structures were based on ^{1}H, COSY, DEPT-135, HMQC, ^{13}C and HMBC experiments. MS spectra were recorded on a Micromass LC-TOF instrument by using electrospray ionisation (ESI). Optical rotations were measured on a PE-241 polarimeter and are reported in units of deg·cm·g^{-1}. Concentrations are reported in g/100 mL. Sonication was conducted by use of a Branson 1510 ultrasonic bath. Melting point was measured on a Büchi B-450 and is not corrected.

Inhibition studies

Inhibition constants (K_i) were determined by measuring initial rates (<10% substrate conversion) using nitrophenyl glycosides (*p*-nitrophenyl β-D-galactopyranoside for β-galactosidase from *Asp. oryzae*, *o*-nitrophenyl β-D-galactopyranoside for β-galactosidase from *E. coli*, *p*-nitrophenyl β-D-glucopyranoside for almond β-glucosidase, *p*-nitrophenyl α-D-glucopyranoside for yeast α-glucosidase and *p*-nitrophenyl α-D-galactopyranoside for green coffee beans α-galactosidase) at six concentrations ranging from $\frac{1}{4}$ K_m up to 4 K_m monitoring at 400 nm with A < 1 using a Varian Cary 100 Bio UV-vis spectrophotometer. Measurements were conducted in 50 mM sodium phosphate buffer (pH 6.9) at 25 °C for 2 min. For experiments with pre-incubation, enzyme and inhibitor were mixed 30 min prior addition of substrate. K_m and K_m' values were obtained by fitting to the equation $v = (V_{max}\cdot[S])/(K_m+[S])$ using the program GraphPad Prism 6. Competitive inhibition was established from Hanes plots. K_i values were calculated as $K_i = [I]/((K_m'/K_m)-1)$ having $[I] \approx K_i$.

Synthetic procedures

1,6-Anhydro-4-*O*-benzyl-2-deoxy-2-(*E*/*Z*)-prop-1'-enyl-β-D-ribo-hexopyranos-3-ulose (9). To a solution of the known compound **7**[6] (14.49 g, 52.0 mmol) in dry DCM (200 mL) and under an argon atmosphere, was added silica gel (63–200 μm, 25 g) then PCC (22.42 g, 104 mmol, 2.0 eq.) at r.t. After 3 hours of stirring, additional PCC (5.61 g, 26.0 mmol, 0.5 eq.) was added. The reaction was left to stir for 30 min before it was filtered on Celite then transferred to cold Et_2O (150 mL). The organic phase was washed with water (1 × 100 mL), dried over $MgSO_4$, filtered and concentrated to give the crude ketone **9** as a yellow oil, which was used directly for the next step without further purification. R_f (Pent/EtOAc 5:1) 0.47. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.38-7.28 (m, 5H, Ar*H*), 5.81-5.70 (m, 1H, *H*C=CH), 5.67-5.58 (m, 1H, HC=C*H*), 5.53 (br s, 1H, H1 major), 5.50 (br s, 1H, H1 minor), 4.79 (d, 1H, *J* 4.6 Hz, H5) 4.60 (d, 1H, J_{gem} 11.8 Hz, OCH_aH$_b$Ph major), 4.57 (d, 1H, J_{gem} 10.9 Hz, OCH_aH$_b$Ph minor), 4.40 (d, 1H, J_{gem} 11.8, OCH$_a$$H_b$Ph major), 4.35 (d, 1H, J_{gem} 10.9 Hz, OCH$_a$$H_b$Ph minor), 3.86-3.79 (m, 1H, H6a), 3.73 (dd, 1H, $J_{6b,6a}$ 8.1 Hz, $J_{6b,5}$ 1.1 Hz, H6b minor), 3.70 (dd, 1H, $J_{6b,6a}$ 8.1 Hz, $J_{6b,5}$ 1.1 Hz, H6b major), 3.60 (d, 1H, $J_{2,HC=CH}$ 9.4 Hz, H2 minor), 3.52 (s, 1H, H4), 3.19 (d, 1H, $J_{2,HC=CH}$ 8.6 Hz, H2 major), 1.75 (dd, 3H, $J_{9,8}$ 8.5 Hz, $J_{9,7}$ 1.7 Hz, CH_3 minor) 1.70 (dd, 3H, $J_{9,8}$ 6.3 Hz, $J_{9,7}$ 1.4 Hz, CH_3 major). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 202.6 (*C*=O major), 202.3 (*C*=O minor), 136.8 (Ar), 131.3 (C=*C* major), 129.8 (C=*C* minor), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 123.8 (*C*=C major), 122.4 (*C*=C minor), 104.1 (C1 major), 103.8 (C1 minor), 81.2 (C4 minor), 81.0 (C4 major), 76.3 (C5 minor), 76.2 (C5 major), 71.4 (O*C*H$_2$Ph major), 71.3 (O*C*H$_2$Ph minor), 65.4 (C6 minor), 65.3 (C6 major), 62.0 (C2 major), 57.0 (C2 minor), 18.1 (CH$_3$ major), 13.6 (CH$_3$ minor). HRMS (ES$^+$): Calcd. for $C_{16}H_{18}O_4Na$: 297.1103; found 297.1101.

1,6-Anhydro-4-*O*-benzyl-2-deoxy-2-(*E*/*Z*)-prop-1'-enyl-β-D-allopyranoside (8). To a solution of crude ketone **9** in dry MeOH (500 mL), cooled to -15 °C and under an argon atmosphere, $NaBH_4$ (3.93 g, 104 mmol, 2.0 eq.) was added in a portionwise manner. The reaction mixture was stirred for 10 min before it was diluted with DCM (500 mL) and quenched with hydrochloric acid (1 M, 150 mL). The organic phase was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give the crude alcohol **8** (8.88 g) as a colourless oil which was pure enough to be used in the next step without purification. R_f (DCM/EtOAc 5:1) 0.53. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.41-7.27 (m, 5H, Ar*H*), 5.86-5.76 and 5.70-5.58 (m, 2H, *H*C=C*H*), 5.37 (d, 1H, $J_{1,2}$ 2.3 Hz, H1 major), 5.34 (d, 1H, $J_{1,2}$ 2.2 Hz, H1 minor), 4.81 (d, 1H, J_{gem} 12.1 Hz, OCH_aH$_b$Ph major), 4.79 (d, 1H, J_{gem} 11.9 Hz, OCH_aH$_b$Ph minor), 4.67-4.60 (m, 2H, OCH$_a$$H_b$Ph and H5), 4.04 (bs, 1H, H3 minor), 3.96 (bs, 1H, H3 major), 3.70-3.75 (m, 2H, H6a and H6b), 3.60-3.57 (m, 1H, H4), 3.20-3.13 (m, 1H, H2 minor), 2.75-2.69 (m, 1H, H2 major), 2.41 (bs, 1H, O*H* minor), 2.33 (bs, 1H, O*H* major), 1.74-1.71 (m, 3H, CH_3 major), 1.66 (dd, 3H, $J_{9,8}$ 6.8 Hz, $J_{9,7}$ 1.8 Hz, CH_3 minor). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.1 (Ar), 132.1 (*C*=C major), 130.4 (*C*=C minor), 128.6 (Ar), 127.9 (Ar), 127.6 (Ar), 127.5 (Ar), 126.2 (C=*C* major), 124.9 (C=*C*, minor), 103.9 (C1 major), 103.3 (C1 minor), 77.6 (C4 minor), 77.5 (C4 major), 73.4 (C5 major), 73.3 (C5 minor), 72.3 (O*C*H$_2$Ph minor), 72.2 (O*C*H$_2$Ph major),

65.5 (C6), 64.2 (C3 minor), 63.9 (C3 major), 52.0 (C2 major), 45.6 (C2 minor), 18.4 (*C*H$_3$ major), 13.5 (*C*H$_3$ minor). HRMS (ES$^+$): Calcd. for $C_{16}H_{20}O_4Na$: 299.1259; found 299.1254.

1,6-Anhydro-4-*O*-benzyl-1,2-dideoxy-2-(*E*/*Z*)-prop-1'-enyl-D-*erythro*-hex-1-enopyranos-3-ulose (10). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.43-7.29 (m, 6H, H-1, Ar*H*), 6.24-6.15 (m, 1H, C*H*-CH$_3$ major), 6.01-5.91 (m, C=C*H*), 5.83-5.75 (m, 1H, C*H*-CH$_3$ minor), 5.13 (d, 1H, J_{gem} 11.3 Hz, OC*H*$_a$H$_b$Ph minor), 5.12 (d, 1H, J_{gem} 11.3 Hz, OC*H*$_a$H$_b$Ph major), 4.72 (d, 1H, J_{gem} 11.3 Hz, OCH$_a$*H*$_b$Ph minor), 4.69 (d, 1H, J_{gem} 11.3 Hz, OCH$_a$*H*$_b$Ph major), 4.36 (dt, $J_{4,5}$ 12.0 Hz, $J_{5,6}$ 3.2 Hz, 1H, H5 minor), 4.30 (dt, $J_{4,5}$ 12.2 Hz, $J_{5,6}$ 3.2 Hz, 1H, H5 major), 4.23 (d, $J_{5,4}$ 12.2 Hz, 1H, H-4 minor), 4.19 (d, $J_{5,4}$ 12.2 Hz, 1H, H-4 major), 3.98-3.85 (m, 2H, H6a, H6b), 2.17 (br s, 1H, OH), 1.80 (dd, 3H, $J_{9,8}$ 6.6 Hz, $J_{9,7}$ 1.4 Hz, C*H*$_3$ major), 1.74 (dd, 3H, $J_{9,8}$ 6.9 Hz, $J_{9,7}$ 1.6 Hz, C*H*$_3$ minor). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 193.5 (*C*=O minor), 193.1 (*C*=O major), 160.3 (C1 minor), 158.6 (C1 major), 137.4 (Ar), 128.6 (Ar), 128.5 (Ar), 128.3 (Ar), 128.1 (C8 minor), 126.8 (C8 major), 120.6 (C7 major), 119.0 (C7 minor), 115.5 (C2 major), 113.9 (C2 minor), 81.7 (C5 minor), 81.6 (C5 major), 74.6 (O*C*H$_2$Ph), 73.6 (C4), 61.2 (C6), 18.9 (CH$_3$ major), 14.8 (CH$_3$ minor). HRMS (ES$^+$): Calcd. for $C_{16}H_{18}O_4H$: 275.1283; found 275.1281.

1,6-Anhydro-4-*O*-benzyl-2-deoxy-2-hydroxymethyl-β-D-allopyranoside (12). Ozone was bubbled through a solution of crude alcohol **8** (8.88 g, 32.1 mmol) in EtOH (96%, 140 mL) at 0 °C. After 2 hours of bubbling at 0 °C a stream of oxygen, followed by a stream of nitrogen was passed through the solution. $NaBH_4$ (9.72 g, 257 mmol, 8.0 eq.) was then slowly added to the reaction mixture at 0 °C which was then stirred for 2 hours at r.t. before it was quenched by slow addition of Amberlite IR 120 H$^+$ (620 mL) followed by stirring for 30 min. The reaction mixture was filtered and the Amberlite was washed with methanol. The resulting filtrate was concentrated to give the crude product diol **12** as a yellow oil (7.34 g), which was used directly in the next step without further purification. R_f (Pent/EtOAc 4:1) 0.22. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.42-7.30 (m, 5H, Ar*H*), 5.56 (d, 1H, $J_{1,2}$ 1.8 Hz, H1), 4.85 (d, 1H, J_{gem} 11.7 Hz, OC*H*$_a$H$_b$Ph), 4.71-4.68 (m, 1H, H5), 4.63 (d, 1H, J_{gem} 11.7 Hz, OCH$_a$*H*$_b$Ph), 4.21-4.16 (m, 1H, H3), 3.97 (dd, 1H, J_{gem} 11.2 Hz, $J_{7a,2}$ 5.8 Hz, H7a), 3.86 (dd, 1H, J_{gem} 11.2 Hz, $J_{7b,2}$ 5.7 Hz, H7b), 3.77-3.68 (m, 2H, H6), 3.65-3.62 (m, 1H, H4), 2.87 (bs, 1H, O*H*), 2.41-2.30 (m, 1H, H2), 1.62 (bs, OH). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 128.9 (2C, Ar), 128.4 (Ar), 127.9 (2C, Ar), 102.6 (C1), 76.7 (C4), 73.1 (C5), 72.3 (O*C*H$_2$Ph), 65.1 (C6), 64.7 (C3), 60.3 (C7), 48.0 (C2). HRMS (ES$^+$): Calcd. for $C_{14}H_{18}O_5Na$: 289.1052; found 289.1051.

1,6-Anhydro-3,4-di-*O*-benzyl-2-benzyloxymethyl-2-deoxy-β-D-allopyranoside (13). NaH (60%, 4.41 g, 110 mmol, 4.0 eq.) was added in a portionwise manner to a cooled (0 °C) solution of crude diol **12** (7.34 g) in dry DMF (110 mL) under an argon atmosphere. After 10 min of stirring, BnBr (13.2 mL, 110 mmol, 4.0 eq.) was slowly added and the reaction mixture was left to stir overnight at r.t.. The reaction mixture was then cooled to 0 °C and methanol (30 mL) was slowly added. The solution was diluted with EtOAc and successively washed with water and brine. The organic phase was then dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography (Pent/EtOAc 88:12→82:18) to give the fully protected compound **13** as a colourless oil (7.10 g, 15.9 mmol, 31% over 5 steps from **7**). R_f (Pent/EtOAc 2:1) 0.65. $[\alpha]_D^{21}$ +61 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.41-7.27 (m, 15H, ArH), 5.77 (s, 1H, H1), 4.81 (d, 1H, J_{gem} 12.4 Hz, OC*H*$_a$H$_b$Ph), 4.74 (d, 1H, J_{gem} 12.4 Hz, OCH$_a$*H*$_b$Ph), 4.64-4.45 (m, 5H, 2×OC*H*$_2$Ph, H5), 4.05 (dt, 1H, J_{gem} 10.2 Hz, $J_{7a,2}$ 2.9 Hz, H7a), 3.90-3.84 (m, 2H, H7b, H3), 3.68 (t, 1H, *J* 6.7 Hz, H6a), 3.61 (m, 2H, H6b, H4), 2.62 (br s, 1H, H2). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.8 (Ar), 138.6 (Ar), 138.2 (Ar), 128.5-127.5 (m, 15C, Ar), 102.1 (C1), 74.9 (C5), 74.8 (C4), 73.4 (O*C*H$_2$Ph), 72.4 (O*C*H$_2$Ph), 71.8 (C3), 70.4 (O*C*H$_2$Ph), 67.4 (C7), 65.5 (C6), 44.8 (C2). HRMS (ES$^+$): Calcd. for $C_{28}H_{30}O_5Na$: 469.1991; found 469.1988.

Methyl 3,4-di-*O*-benzyl-2-benzyloxymethyl-2-deoxy-α/β-D-allopyranoside (14). A solution of compound **13** (4.91 g, 11.0 mmol) dissolved in 10% H_2SO_4 in dry MeOH (140 mL), under an argon atmosphere and stirred at 40 °C overnight. The solution was then slowly transferred to a saturated $NaHCO_3$ aq. solution (300 mL) and extracted with DCM (3 × 200 mL). The combined organics were dried ($MgSO_4$) filtered and concentrated. The crude product was purified by flash column chromatography (Pent/EtOAc 80:20→60:40) to afford alcohol **14** (4.47 g, 9.34 mmol, 85%, α/β 3:1) as a colourless oil. HRMS (ES$^+$): Calcd. for $C_{29}H_{34}O_6Na$: 501.2253; found 501.2253. An analytical sample of each pure anomer was put aside during column chromatography for NMR characterisation. α anomer: R_f (Pent/EtOAc 2:1) 0.43. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.37-7.23 (m, 15H, Ar*H*), 4.91 (d, 1H, J_{gem} 12.2 Hz, OC*H*$_a$H$_b$Ph), 4.68 (d, 1H, J_{gem} 11.7 Hz, OC*H*$_a$H$_b$Ph), 4.64 (d, 1H, $J_{1,2}$ 4.2 Hz, H1), 4.60 (d, 1H, J_{gem} 12.2 Hz, OCH$_a$*H*$_b$Ph), 4.52 (d, 1H, J_{gem} 11.7 Hz, OCH$_a$*H*$_b$Ph), 4.42 (d, 1H, J_{gem} 11.8 Hz, OC*H*$_a$H$_b$Ph), 4.38 (d, 1H, J_{gem} 11.8 Hz, OCH$_a$*H*$_b$Ph), 4.19 (dt, 1H, $J_{5,4}$ 9.8 Hz, $J_{5,6a}$=$J_{5,6b}$ 3.6 Hz, H5), 4.14 (t, 1H, *J* 2.9 Hz, H3), 3.87-3.77 (m, 2H, H6a, H6b), 3.54 (d, 2H, $J_{7,2}$ 7.0 Hz, H7), 3.49 (dd, 1H, $J_{4,5}$ 9.9 Hz, $J_{4,3}$ 2.7 Hz, H4), 3.33 (s, 3H, OCH$_3$), 2.11-2.06 (m, 1H, H2). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 139.3, 138.3, 138.1 (3×ArC), 128.5-127.2 (m, 15C, Ar), 98.9 (C1), 74.5 (C4), 73.3 (O*C*H$_2$Ph), 72.1 (O*C*H$_2$Ph), 71.6 (C3), 67.7 (O*C*H$_2$Ph), 66.6 (C7), 62.5 (C6), 55.8 (OCH$_3$), 44.4 (C2). β anomer: R_f (Pent/EtOAc 2:1) 0.29. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.37-7.26 (m, 15H, Ar*H*), 4.91 (d, 1H, J_{gem} 11.0 Hz, OC*H*$_a$H$_b$Ph), 4.73 (d, 1H, J_{gem} 11.5 Hz, OC*H*$_a$H$_b$Ph), 4.55-4.50 (m, 4H, H1, OCH$_a$*H*$_b$Ph, OC*H*$_2$Ph), 4.45 (d, 1H, J_{gem} 11.7 Hz, OCH$_a$*H*$_b$Ph), 4.34 (t, 1H, *J* 2.3 Hz, H3), 4.00 (ddd, 1H, $J_{5,4}$ 9.6 Hz, $J_{5,6b}$ 4.5 Hz, $J_{5,6a}$ 3.2 Hz, H5), 3.89 (dd, 1H, $J_{6a,6b}$ 11.7 Hz, $J_{6a,5}$ 3.2 Hz, H6a), 3.76 (d, 1H, $J_{6a,6b}$ 11.7 Hz, $J_{6b,5}$ 4.6 Hz, H6b), 3.64-3.57 (m, 2H, H7a, H7b), 3.53 (dd, 1H, $J_{4,5}$ 9.6 Hz, $J_{4,3}$ 2.3Hz, H4), 3.43 (s, 3H, OCH$_3$), 2.02-1.95 (m, 1H, H2). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 139.2 (Ar), 138.3 (Ar), 138.0 (Ar), 128.6-127.5 (m, 15C, Ar), 100.5 (C1), 77.7 (C4), 75.0 (O*C*H$_2$Ph), 73.5 (O*C*H$_2$Ph), 72.8 (C5), 72.6 (C3), 71.9 (O*C*H$_2$Ph), 66.2 (C7), 62.7 (C6), 56.7 (OCH$_3$), 46.4 (C2).

Methyl 3,4-di-*O*-benzyl-2-benzyloxymethyl-2,6-dideoxy-6-iodo-α/β-D-allopyranoside (15). To a solution of alcohol **14** (11.93 g, 24.9 mmol) in dry toluene (400 mL), under an argon atmosphere, were successively added imidazole (4.24 g, 62.3 mmol, 2.5 eq.), iodine (9.48 g, 37.4 mmol, 1.5 eq.) and PPh_3 (16.36 g, 62.4 mmol, 2.5 eq.). The reaction mixture was heated under reflux for 1 h 40 min then cooled down to r.t. before an aq. solution of sodium thiosulfate (10%, 120 mL) was added. The reaction mixture was diluted with toluene (500 mL) before the two layers were separated and the organic layer washed with water (100 mL) and brine (100 mL) then dried ($MgSO_4$)

and concentrated. The residue was purified by flash column chromatography (Pent/EtOAc 94:6→88:12) to give the iodinated compound **15** (13.8 g, 23.5 mmol, 94%, α/β 3:1) as a colourless oil. HRMS (ES^+): Calcd. for $C_{29}H_{33}IO_5Na$: 611.1270; found 611.1271. An analytical sample of each pure anomer was put aside during column chromatography for NMR characterisation. α anomer: R_f (Pent/EtOAc 90:10) 0.50. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.37-7.23 (m, 15H, Ar*H*), 4.87 (d, 1H, J_{gem} 12.1 Hz, OC*H*$_a$H$_b$Ph), 4.71 (d, 1H, J_{gem} 11.3 Hz, OC*H*$_a$H$_b$Ph), 4.67 (d, 1H, $J_{1,2}$ 4.3 Hz, H1), 4.57 (d, 1H, J_{gem} 12.1 Hz, OCH$_a$*H*$_b$Ph), 4.53 (d, 1H, J_{gem} 11.3 Hz, OCH$_a$*H*$_b$Ph), 4.42 (d, 1H, J_{gem} 11.7 Hz, OC*H*$_a$H$_b$Ph), 4.38 (d, 1H, J_{gem} 11.7 Hz, OCH$_a$*H*$_b$Ph), 4.15 (pt, 1H, *J* 2.8 Hz, H3), 3.95 (ddd, 1H, $J_{5,4}$ 9.0 Hz, $J_{5,6b}$ 6.4 Hz, $J_{5,6a}$ 2.6 Hz, H5), 3.60-3.51 (m, 3H, H6a, H7a, H7b), 3.41 (dd, 1H, $J_{6b,6a}$ 10.4 Hz, $J_{6b,5}$ 6.3 Hz, H6b), 3.39 (s, 3H, OCH_3), 3.33 (dd, 1H, $J_{4,5}$ 9.0 Hz, $J_{3,4}$ 2.7 Hz, H4), 2.17-2.11 (m, 1H, H2). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 139.2 (Ar), 138.2 (Ar), 137.7 (Ar), 128.5-127.2 (m, 15C, Ar), 99.1 (C1), 80.9 (C4), 74.5 (O*C*H$_2$Ph), 73.2 (O*C*H$_2$Ph), 71.7 (C3), 71.6 (O*C*H$_2$Ph), 67.4 (C7), 65.4 (C5), 56.0 (OCH_3), 44.4 (C2), 9.8 (C6). β anomer: R_f (Pent/EtOAc 90:10) 0.35. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.34-7.23 (m, 15H, Ar*H*), 4.83 (d, 1H, J_{gem} 11.0 Hz, OC*H*$_a$H$_b$Ph), 4.70 (d, 1H, J_{gem} 11.3 Hz, OC*H*$_a$H$_b$Ph), 4.51-4.46 (m, 4H, H1, OCH$_a$*H*$_b$Ph, OC*H*$_2$Ph), 4.40 (d, 1H, J_{gem} 11.7 Hz, OCH$_a$*H*$_b$Ph), 4.29 (t, 1H, *J* 2.2 Hz, H3), 3.76 (ddd, 1H, $J_{5,4}$ 9.7 Hz, $J_{5,6b}$ 7.6 Hz, $J_{5,6a}$ 2.4 Hz, H5), 3.61-3.53 (m, 3H, H6a, H7a, H7b), 3.42 (s, 3H, OCH_3), 3.30-3.23 (m, 2H, H4, H6b), 2.04-1.98 (m, 1H, H2). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 139.0 (Ar), 138.2 (Ar), 137.7 (Ar), 128.6-127.6 (m, 15C, Ar), 100.2 (C1), 81.4 (C4), 75.1 (O*C*H$_2$Ph), 73.4 (O*C*H$_2$Ph), 72.2 (C3), 72.0 (O*C*H$_2$Ph), 71.6 (C5), 66.0 (C7), 56.6 (OCH_3), 46.5 (C2), 8.6 (C6).

(2*R*,3*S*,4*R*)-3,4-Di-*O*-benzyl-2-benzyloxymethyl-hex-5-enal (16). To a solution of iodinated compound **15** (17.0 g, 28.9 mmol) in THF/H_2O (9:1 v/v, 600 mL) was added pre-activated Zn-dust[42] (20.8 g, 318 mmol, 11 eq.). The reaction mixture was sonicated at 40 °C for 4 hours then filtered through Celite and diluted with EtOAc (800 mL). The organic phase was washed with water (250 mL) and brine (250 mL) before the aq. phase was extracted with DCM (100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated to give the crude aldehyde **16** (12.67 g) as a colourless oil, which was used without further purification in the next reaction. R_f (Pent/EtOAc 9:1) 0.44. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 9.83 (d, 1H, $J_{1,2}$ 2.1 Hz, H1), 7.44-7.22 (m, 15H, Ar*H*), 5.93-5.80 (m, 1H, H5), 5.45-5.33 (m, 2H, H6a, H6b), 4.69 (d, 1H, J_{gem} 11.4 Hz, OC*H*$_a$H$_b$Ph), 4.68 (d, 1H, J_{gem} 11.9 Hz, OC*H*$_a$H$_b$Ph), 4.55 (d, 1H, J_{gem} 11.4 Hz, OCH$_a$*H*$_b$Ph), 4.49-4.44 (m, 2H, OC*H*$_2$Ph), 4.41 (d, 1H, J_{gem} 11.9 Hz, OCH$_a$*H*$_b$Ph), 4.07-3.97 (m, 2H, H3, H4), 3.78 (dd, 1H, J_{gem} 9.3 Hz, $J_{7a,2}$ 6.8 Hz, H7a), 3.70 (dd, 1H, J_{gem} 9.3 Hz, $J_{7b,2}$ 5.8 Hz, H7b), 3.02- 2.93 (m, 1H, H2). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 202.3 (C1), 138.0 (3C, Ar), 135.4 (C5), 128.5-127.7 (m, 15C, Ar), 119.9 (C6), 80.3 (C3 or C4), 80.0 (C3 or C4), 73.4 (O*C*H$_2$Ph), 73.4 (O*C*H$_2$Ph), 70.6 (O*C*H$_2$Ph), 66.3 (C7), 53.0 (C2). HRMS (ES^+): Calcd. for $C_{28}H_{30}O_4Na$: 453.2042; found 453.2040.

(4*R/S*,5*S*,6*S*,7*R*)-6,7-Di-*O*-benzyl-5-*C*-benzyloxymethyl-nona-1,8-dien-4-ol (17). To a solution of crude aldehyde **16** (12.67 g) in THF/H_2O (1:1 v/v, 290 mL) was added allyl bromide (6.3 mL, 73.1 mmol, 2.5 eq.) and indium dust (4.65 g, 40.5 mmol, 1.4 eq.). The reaction mixture was stirred overnight at r.t. before a saturated NH_4Cl aq. solution (150 mL) was added. After 5 minutes of stirring a saturated $NaHCO_3$ aq. solution (150 mL) was added before the resulting mixture was extracted with DCM (4 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated and the residue purified by flash chromatography (Pent/EtOAc 95:5→88:12) to afford the diene **17** (11.03 g, 23.3 mmol, 81% over two steps, *R*/*S* 3:2) as a colourless oil. A second column chromatography (Pent/EtOAc 9:1) was necessary to fully separate both diastereomers. **17*R***: R_f (Hept/EtOAc 4:1) 0.35. $[\alpha]_D^{22}$ –45.1 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.37-7.21 (m, 15H, Ar*H*), 5.97-5.88 (m, 1H, H8), 5.78-5.68 (m, 1H, H2), 5.42-5.30 (m, 2H, H9a, H9b), 5.06-5.00 (m, 2H, H1a, H1b), 4.71 (d, 1H, J_{gem} 10.8 Hz, OC*H*$_a$H$_b$Ph), 4.64 (d, 1H, J_{gem} 12.0 Hz, OC*H*$_a$H$_b$Ph), 4.48 (d, 1H, J_{gem} 11.9 Hz, OC*H*$_a$H$_b$Ph), 4.42-4.38 (m, 2H, OC*H*$_2$Ph), 4.34 (d, 1H, J_{gem} 11.9 Hz, OCH$_a$*H*$_b$Ph), 4.11-4.08 (m, 1H, H4), 4.03 (dd, 1H, $J_{6,7}$ 6.1 Hz, $J_{5,6}$ 3.8 Hz, H6), 3.98-3.95 (m, 1H, H7), 3.68-3.61 (m, 2H, H10a, H10b), 3.38 (d, 1H, $J_{OH,4}$ 2.3 Hz, O*H*), 2.35-2.28 (m, 1H, H3a), 2.14-2.08 (m, 2H, H3b, H5). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.3 (Ar), 138.2 (Ar), 138.1 (Ar), 136.1 (C8), 135.7 (C2), 128.5-127.7 (m, 15C, Ar), 120.0 (C9), 116.8 (C1), 81.6 (C6), 80.8 (C7), 74.9 (O*C*H$_2$Ph), 73.3 (O*C*H$_2$Ph), 70.2 (O*C*H$_2$Ph), 70.0 (C4), 66.8 (C10), 42.9 (C5), 39.7 (C3). HRMS (ES^+): Calcd. for $C_{31}H_{36}O_4Na$: 495.2511; found 495.2515. **17*S***: R_f (Hept/EtOAc 4:1) 0.28. $[\alpha]_D^{22}$ –33.1 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.35-7.26 (m, 15H, Ar*H*), 5.95-5.82 (m, 2H, H2, H8), 5.38-5.27 (m, 2H, H1 or H9), 5.06-5.02 (m, 2H, H1 or H9), 4.76 (d, 1H, J_{gem} 11.2 Hz, OC*H*$_a$H$_b$Ph), 4.63 (d, 1H, J_{gem} 11.9 Hz, OC*H*$_a$H$_b$Ph), 4.54 (d, 1H, J_{gem} 11.2 Hz, OCH$_a$*H*$_b$Ph), 4.43 (d, 1H, J_{gem} 12.0 Hz, OC*H*$_a$H$_b$Ph), 4.39 (d, 1H, J_{gem} 12.0 Hz, OCH$_a$*H*$_b$Ph), 4.35 (d, 1H, J_{gem} 11.9 Hz, OCH$_a$*H*$_b$Ph), 4.02-3.97 (m, 2H, H4, H7), 3.92 (bt, 1H, *J* 5.4 Hz, H6), 3.52-3.45 (m, 2H, H10a, H10b), 3.41 (br s, 1H, O*H*), 2.39-2.33 (m, 1H, H3a), 2.21-2.13 (m, 1H, H3b), 2.12-2.05 (m, 1H, H5). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.4 (Ar), 138.2 (Ar), 138.1 (Ar), 136.1 (C8), 135.4 (C2), 128.5-127.7 (m, 15C, Ar), 119.8 (C9), 116.8 (C1), 82.0 (C6), 81.1 (C7), 74.0 (O*C*H$_2$Ph), 73.3 (O*C*H$_2$Ph), 70.5 (O*C*H$_2$Ph), 70.3 (C4), 68.9 (C10), 45.6 (C5), 39.2 (C3). HRMS (ES^+): Calcd. for $C_{31}H_{36}O_4Na$: 495.2511; found 495.2513.

(1*R*,5*R*,6*S*,7*S*)-5,6-Di-*O*-benzyl-7-*C*-benzyloxymethyl-cyclohept-3-en-1-ol (18*R*). To a solution of diene **17*R*** (6.12 g, 12.95 mmol) in dry toluene (220 mL), under an argon atmosphere, was added Hoveyda-Grubbs 2nd generation catalyst (330 mg, 0.53 mmol, 0.04 eq.) before the reaction mixture was heated to 80 °C. After 2 h 30 min of stirring the reaction mixture was cooled down to r.t. and then concentrated. The residue was purified by flash chromatography (Pent/EtOAc 85:15) to give the alkene **18*R*** (4.48 g, 10.07 mmol, 78%) as a colourless oil. R_f (Hept/EtOAc 4:1) 0.18. $[\alpha]_D^{24}$ –54.5 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.38-7.26 (m, 15H, Ar*H*), 5.91-5.82 (m, 2H, H3, H4), 4.80 (d, 1H, J_{gem} 12.0 Hz, OC*H*$_a$H$_b$Ph), 4.67 (d, 1H, J_{gem} 12.1 Hz, OC*H*$_a$H$_b$Ph), 4.53-4.49 (m, 3H, OC*H*$_2$Ph, OCH$_a$*H*$_b$Ph), 4.46 (d, 1H, J_{gem} 11.7 Hz, OCH$_a$*H*$_b$Ph), 4.34 (br s, 1H, H5), 3.94-3.90 (m, 2H, H6, H8a), 3.84 (dt, 1H, $J_{1,2a}$=$J_{1,7}$ 10.7 Hz, $J_{1,2b}$ 2.5 Hz, H1), 3.74 (br s, 1H, O*H*), 3.58 (dd, 1H, $J_{8b,8a}$ 9.6 Hz, $J_{8b,7}$ 4.2 Hz, H8b), 2.44-2.38 (m, 1H, H2a), 2.28-2.21 (m, 1H, H2b), 2.06-1.99 (m, 1H, H7). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 139.0 (Ar), 138.4 (Ar), 137.6 (Ar), 133.2 (C4), 128.6-127.4 (m, 15C, Ar), 126.4 (C3), 81.8 (C5), 78.9 (C6), 74.6 (O*C*H$_2$Ph), 73.6 (O*C*H$_2$Ph), 72.6 (O*C*H$_2$Ph), 71.5 (C8), 68.1 (C1), 50.8 (C7), 36.7 (C2). HRMS (ES^+): Calcd. for $C_{29}H_{32}O_4Na$: 467.2198; found 467.2200.

(1*S*,5*R*,6*S*,7*S*)-5,6-Di-*O*-benzyl-7-*C*-benzyloxymethyl-cyclohept-3-en-1-ol (18*S*). From **17*S***: To a solution of diene **17*S*** (2.32 g, 4.91 mmol) in dry toluene (75 mL), under an argon atmosphere and heated to 80 °C, was added Hoveyda-Grubbs 2nd generation catalyst (31 mg, 49 µmol, 0.01 eq.). After 90 min of stirring the reaction mixture was cooled down to r.t. and then concentrated. The residue was purified by flash chromatography (Pent/EtOAc 86:14) to give the alkene **18*S*** (1.70 g, 3.82 mmol, 78%) as a colourless oil. R_f (Hept/EtOAc 4:1) 0.23. $[\alpha]_D^{24}$ –15.4 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.36-7.24 (m, 15H, Ar*H*), 6.03-6.00 (m, 1H, H4), 5.86-5.80 (m, 1H, H3), 4.90 (d, 1H, J_{gem} 11.7 Hz, OC*H*$_a$H$_b$Ph), 4.68 (d, 1H, J_{gem} 12.0 Hz, OC*H*$_a$H$_b$Ph), 4.54-4.48 (m, 3H, OCH$_a$*H*$_b$Ph, OC*H*$_2$Ph), 4.43 (d, 1H, J_{gem} 11.8 Hz, OCH$_a$*H*$_b$Ph), 4.28-4.26 (m, 2H, H5, H6), 3.94-3.90 (m, 1H, H1), 3.77-3.73 (m, 1H, H8a), 3.68 (dd, 1H, $J_{8b,8a}$ 9.2 Hz, $J_{8b,7}$ 5.8 Hz, H8b), 3.47 (d, 1H, $J_{OH,1}$ 10.7 Hz, O*H*), 2.72-2.64 (m, 1H, H2a), 2.17-2.12 (m, 1H, H2b), 1.91-1.88 (m, 1H, H7). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.6 (Ar), 138.4 (Ar), 138.3 (Ar), 134.4 (C4), 128.5-127.5 (m, 15C, Ar), 126.0 (C3), 82.8 (C5), 78.8 (C6), 73.6 (O*C*H$_2$Ph), 73.4 (O*C*H$_2$Ph), 71.4 (2C, O*C*H$_2$Ph, C8), 68.1 (C1), 48.4 (C7), 35.1 (C2). HRMS (ES$^+$): Calcd. for $C_{29}H_{32}O_4Na$: 467.2198; found 467.2199. From **19***:* Lithium tri-*tert*-butoxyaluminum hydride (7.09 g, 27.85 mmol, 5.0 eq.) was added to a solution of ketone **19** (2.46 g, 5.57 mmol) in dry Et_2O (23 mL) at -78 °C under an argon atmosphere. After 1 h of stirring the cold bath was removed and the reaction was stirred for another 2 h at r.t. The reaction mixture was diluted with Et_2O (230 mL), washed successively with HCl (1 M, 2 × 30 mL), a saturated $NaHCO_3$ aq. solution (30 mL) and brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated before the residue was purified by flash chromatography (Pent/EtOAc 85:15) to give alcohol **18*S*** (2.04 g, 4.59 mmol, 82%) as a yellow oil.

(5*R*,6*S*,7*R*)-5,6-Di-*O*-benzyl-7-*C*-benzyloxymethyl-cyclohept-3-en-1-one (19). To a solution of alcohol **18*R*** (2.92 g, 6.57 mmol) in dry DCM (25 mL) and under an argon atmosphere, was added silica gel (63–200 µm, 4 g) then PCC (22.42 g, 104 mmol, 2.5 eq.) at r.t. After 4 hours of stirring the reaction mixture was filtered through Celite and then transferred to cold Et_2O (100 mL). The organic phase was washed with water (50 mL), dried over $MgSO_4$, filtered and concentrated to give the crude ketone **19** (2.46 g) as a yellow oil. This was used directly for the next step without further purification. An aliquot was purified by column chromatography to serve as an analytical sample (Pent/EtOAc 85:15). R_f (Hept/EtOAc 4:1) 0.25. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.38-7.25 (m, 15H, Ar*H*), 5.94-5.90 (m, 1H, H4), 5.82-5.75 (m, 1H, H3), 4.85 (d, 1H, J_{gem} 12.1 Hz, OC*H*$_a$H$_b$Ph), 4.70 (d, 1H, J_{gem} 11.9 Hz, OC*H*$_a$H$_b$Ph), 4.62 (d, 1H, J_{gem} 12.1 Hz, OCH$_a$*H*$_b$Ph), 4.58 (d, 1H, J_{gem} 12.0 Hz, OCH$_a$*H*$_b$Ph), 4.46-4.37 (m, 4H, OC*H*$_2$Ph, H5, H6), 3.81 (dd, 1H, J_{gem} 9.5 Hz, $J_{8a,7}$ 5.1 Hz, H8a), 3.63 (t, 1H, *J* 9.3 Hz, H8b), 3.25 (dd, 1H, J_{gem} 15.2 Hz, $J_{2a,3}$ 6.5 Hz, H2a), 3.15 (dd, 1H, J_{gem} 15.2 Hz, $J_{2b,3}$ 5.7 Hz, H2b), 2.97-2.93 (m, 1H, H7). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 203.8 (C1), 138.8 (Ar), 138.3 (Ar), 138.2 (Ar), 132.0 (C4), 128.6-127.5 (m, 15C, Ar), 122.8 (C3), 81.6 (C5), 77.3 (C6), 73.6 (O*C*H$_2$Ph), 73.4 (O*C*H$_2$Ph), 71.5 (O*C*H$_2$Ph), 67.6 (C8), 56.2 (C7), 44.7 (C2). HRMS (ES$^+$): Calcd. for $C_{29}H_{30}O_4Na$: 465.2042; found 465.2039.

(1*S*,2*R*,3*S*,4*S*,5*S*)-2,3-Di-*O*-benzyl-4-*C*-benzyloxymethyl-cycloheptan-1,5-diol (20) and (1*S*,3*S*,4*S*,5*S*,6*R*)-5,6-Di-*O*-benzyl-4-*C*-benzyloxymethyl-cycloheptan-1,3-diol (21). To a cooled solution (-10 °C) of alcohol **18*S*** (1.72 g, 3.64 mmol) in dry THF, under an argon atmosphere was added BH_3·THF (1M, 14.6 mL, 14.6 mmol, 4 eq.) in a dropwise manner. After 2 h of stirring at -10 °C, aq. NaOH (2 M, 8 mL) was added followed by H_2O_2 (35%, 16 mL) before the solution was allowed to warm up to r.t. After 2 h 30 min the reaction mixture was diluted with Et_2O (150 mL) and washed with water (2 × 30 mL) and brine (30 mL). The aq. phase was extracted with DCM (40 mL) before the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography (Pent/EtOAc 1:1, then EtOAc 100%) to give first the diol **20** (1.06 g, 2.29 mmol, 63%) as a colourless oil, then diol **21** (0.39 g, 0.84 mmol, 23%) as a colourless oil. **20**: R_f (Hept/EtOAc 2:3) 0.30. $[\alpha]_D^{22}$ +7.3 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.38-7.21 (m, 15H, Ar*H*), 4.91 (d, 1H, J_{gem} 11.3 Hz, OC*H*$_a$H$_b$Ph), 4.81 (d, 1H, J_{gem} 11.4 Hz, OC*H*$_a$H$_b$Ph), 4.54-4.49 (m, 2H, OC*H*$_2$Ph), 4.41 (br s, 1H, H3), 4.40-4.36 (m, 2H, OC*H*$_2$Ph), 4.05-4.00 (m, 1H, H1), 3.90 (br s, 1H, H5), 3.66 (dd, 1H, J_{gem} 9.5 Hz, $J_{8a,4}$ 4.5 Hz, H8a), 3.59 (t, 1H, *J* 9.5 Hz, H8b), 3.27 (dd, 1H, $J_{2,1}$ 8.5 Hz, $J_{2,3}$ 1.0 Hz, H2), 2.70 (d, 1H, $J_{OH,5}$ 11.1 Hz, O*H*(5)), 2.44 (br s, 1H, O*H*(1)), 2.15-2.05 (m, 2H, H6a, H7a), 1.80-1.76 (m, 1H, H4), 1.74-1.67 (m, 1H, H6b), 1.51-1.44 (m, 1H, H7b). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.5 (Ar), 138.2 (Ar), 137.9 (Ar), 128.8-127.9 (m, 15C, Ar), 89.8 (C2), 77.4 (C3), 74.9 (O*C*H$_2$Ph), 73.3 (O*C*H$_2$Ph), 73.2 (C1), 72.4 (O*C*H$_2$Ph), 70.9 (C8), 70.5 (C5), 45.0 (C4), 31.6 (C6), 26.2 (C7). HRMS (ES$^+$): Calcd. for $C_{29}H_{34}O_5Na$: 485.2304; found 485.2307. **21**: R_f (Hept/EtOAc 2:3) 0.15. $[\alpha]_D^{23}$ –29.2 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.36-7.24 (m, 15H, Ar*H*), 4.93 (d, 1H, J_{gem} 11.4 Hz, OC*H*$_a$H$_b$Ph), 4.61 (d, 1H, J_{gem} 11.9 Hz, OC*H*$_a$H$_b$Ph), 4.57 (d, 1H, J_{gem} 11.9 Hz, OCH$_a$*H*$_b$Ph), 4.50-4.46 (m, 3H, OC*H*$_2$Ph, H1), 4.39 (d, 1H, J_{gem} 11.9 Hz, OCH$_a$*H*$_b$Ph), 4.35 (br s, 1H, H5), 4.02-3.96 (m, 1H, H3), 3.75 (dd, 1H, $J_{6,7a}$ 9.9 Hz, $J_{6,7b}$=$J_{6,5}$ 6.0 Hz, H6), 3.68-3.61 (m, 2H, H8), 3.28 (d, 1H, $J_{OH,3}$ 10.0 Hz, O*H*(3)), 2.48-2.39 (m, 1H, H7a), 2.18-2.11 (m, 2H, H7b, H2a), 1.90-1.83 (m, 2H, H4, H2b). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.6 (Ar), 138.4 (Ar), 138.3 (Ar), 128.6-127.5 (m, 15C, Ar), 81.5 (C5), 80.2 (C6), 74.6 (O*C*H$_2$Ph), 73.3 (O*C*H$_2$Ph), 71.2 (O*C*H$_2$Ph), 70.7 (C8), 70.0 (C3), 63.6 (C1), 46.6 (C4), 43.5 (C2), 38.1 (C7). HRMS (ES$^+$): Calcd. for $C_{29}H_{34}O_5Na$: 485.2304; found 485.2302.

(1*S*,2*R*,3*S*,4*S*,5*S*)-2,3-Di-*O*-benzyl-4-*C*-benzyloxymethyl-1,5-di-*O*-[3',5'-dinitro]benzoate-cycloheptane (22). To a solution of diol **20** (275 mg, 0.59 mmol) in dry DCM (5 mL), under an argon atmosphere, were successively added Et_3N (0.41 mL, 2.94 mmol, 5.0 eq.), DMAP (15 mg, 0.12 mmol, 0.2 eq.) and 3,5-dinitrobenzoyl chloride (544 mg, 2.36 mmol, 4.0 eq.). The reaction mixture was stirred at r.t. overnight before water (2 mL) was added and the DCM was removed under vacuum. The residue was taken up in EtOAc (30 mL) and washed with a saturated $NaHCO_3$ aq. solution (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated before the residue was purified by flash column chromatography (Pent/EtOAc 80:20→60:40) to afford diester **22** (337 mg, 0.40 mmol, 67%) as a pale yellow solid. Recrystallisation from toluene/hexane afforded suitable crystals for X-ray diffraction analysis. M.p. 67.2-69.4°C. R_f (Hept/EtOAc 4:1) 0.17. $[\alpha]_D^{25}$ +69.3 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 9.20-9.18 (m, 2H, Ar*H*), 9.01 (d, 2H, *J*

2.1 Hz, Ar*H*), 8.95 (d, 2H, *J* 2.2 Hz, Ar*H*), 7.38-7.36 (m, 2H, Ar*H*), 7.31-7.26 (m, 3H, Ar*H*), 7.22-7.10 (m, 10H, Ar*H*), 5.71 (dt, 1H, $J_{1,2}$ 8.3 Hz, $J_{1,7}$ 5.0 Hz, H1), 5.58-5.55 (m, 1H, H5), 5.07 (d, 1H, J_{gem} 11.8 Hz, OCH_aH$_b$Ph), 4.79 (d, 1H, J_{gem} 11.8 Hz, OCH$_a$$H_b$Ph), 4.78 (d, 1H, J_{gem} 12.3 Hz, OCH_aH$_b$Ph), 4.44 (d, 1H, J_{gem} 12.3 Hz, OCH$_a$$H_b$Ph), 4.35 (d, 1H, J_{gem} 11.9 Hz, OCH_aH$_b$Ph), 4.32 (br s, 1H, H3), 4.23 (d, 1H, J_{gem} 11.9 Hz, OCH$_a$$H_b$Ph), 3.80 (d, 1H, $J_{2,1}$=$J_{2,3}$ 8.3 Hz, H2), 3.59 (dd, 1H, $J_{8a,8b}$ 8.9 Hz, $J_{8a,4}$ 7.1 Hz, H8a), 3.36 (dd, 1H, $J_{8a,8b}$ 8.9 Hz, $J_{8b,4}$ 7.5 Hz, H8a), 2.55-2.47 (m, 1H, H7a), 2.30-2.09 (m, 3H, H4, H6a, H6b), 1.77-1.69 (m, 1H, H7b). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 161.9 (2C, *C*=O), 148.7 (2C, Ar), 138.1 (Ar), 137.7 (Ar), 137.5 (Ar), 134.2 (Ar), 134.1 (Ar), 129.4-127.8 (m, 22 C, Ar), 122.4 (Ar), 85.6 (C2), 78.4 (C1), 75.4 (C3), 74.3 (O*C*H$_2$Ph), 74.1 (C5), 73.3 (O*C*H$_2$Ph), 72.5 (O*C*H$_2$Ph), 69.1 (C8), 45.4 (C4), 26.0 (C6), 24.6 (C7). HRMS (ES$^+$): Calcd. for $C_{43}H_{38}N_4O_{15}NH_4$: 868.2677; found 868.2688.

(1*S*,2*R*,3*S*,4*S*,5*S*)-1-*O*-Benzoyl-2,3-di-*O*-benzyl-4-*C*-benzyloxymethyl-cycloheptan-5-ol (23). To a solution of diol **20** (1.43 g, 3.09 mmol) in dry DCM, under an argon atmosphere, were added Et_3N (0.86 mL, 6.17 mmol, 2.0 eq.) and DMAP (78 mg, 0.64 mmol, 0.2 eq.). The reaction mixture was cooled to 0 °C before benzoyl chloride was added (0.50 mL, 4.31 mmol, 1.4 eq.) and the ice-bath was removed. After 21 h of stirring at r.t. water was added (5 mL) and the mixture was partially evaporated to remove the DCM. EtOAc was added (150 mL) and the organic layer was washed with hydrochloric acid (1M, 2 × 20 mL), a saturated $NaHCO_3$ aq. solution (2 × 20 mL) and brine (2 × 20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated before the residue was purified by flash column chromatography (Pent/EtOAc 80:20) to afford the ester **23** (1.52 g, 2.68 mmol, 86%) as a yellow oil. R_f (Hept/EtOAc 7:3) 0.32. $[\alpha]_D^{22}$ +56.3 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 8.00-7.98 (m, 2H, Ar*H*), 7.57 (t, 1H, J_o 7.4 Hz, Ar*H*), 7.46-7.42 (m, 2H, Ar*H*), 7.39-7.25 (m, 10H, Ar*H*), 7.22-7.16 (m, 5H, Ar*H*), 5.60 (dt, 1H, $J_{1,2}$=$J_{1,6a}$ 8.0 Hz, $J_{1,6b}$ 4.9 Hz, H1), 4.99 (d, 1H, J_{gem} 11.4 Hz, OCH_aH$_b$Ph), 4.67 (d, 1H, J_{gem} 12.0 Hz, OCH_aH$_b$Ph), 4.56 (d, 1H, J_{gem} 12.0 Hz, OCH$_a$$H_b$Ph), 4.49 (d, 1H, J_{gem} 11.4 Hz, OCH$_a$$H_b$Ph), 4.47 (d, 1H, J_{gem} 11.9 Hz, OCH_aH$_b$Ph), 4.43 (s, 1H, H3), 4.36 (d, 1H, J_{gem} 11.9 Hz, OCH$_a$$H_b$Ph), 3.99-3.92 (m, 1H, H5), 3.72-3.66 (m, 2H, H2, H8a), 3.60 (t, 1H, *J* 9.3 Hz, H8b), 3.06 (d, 1H, $J_{OH,5}$ 11.0 Hz, O*H*), 2.42-2.35 (m, 1H, H7a), 1.99-1.81 (m, 3H, H4, H6a, H6b), 1.71-1.64 (m, 1H, H7b). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 165.9 (C=O), 138.5 (Ar), 138.0 (Ar), 137.9 (Ar), 133.0 (Ar), 130.8 (Ar), 129.8 (Ar), 128.7-127.8 (m, 18C, Ar), 86.1 (C2), 79.0 (C3), 77.2 (C1), 75.0 (O*C*H$_2$Ph), 73.3 (O*C*H$_2$Ph), 72.6 (O*C*H$_2$Ph), 70.7 (C8), 70.6 (C5), 46.0 (C4), 30.5 (C6), 24.5 (C7).

(1*S*,2*R*,3*S*,4*R*,5*R*)-5-Azido-1-*O*-benzoyl-2,3-di-*O*-benzyl-4-*C*-benzyloxymethyl-cycloheptane (25) and (1*S*,2*R*,3*S*)-1-*O*-Benzoyl-2,3-di-*O*-benzyl-4-*C*-benzyloxymethyl-cyclohept-4-ene (24). To a cooled solution (0° C) of alcohol **23** (3.61 g, 6.37 mmol) in dry THF under an argon atmosphere was added PPh_3 (5.01 g, 19.10 mmol, 3.0 eq.) followed by DIAD (3.1 mL, 15.74 mmol, 2.5 eq.) and DPPA (4.0 mL, 18.56 mmol, 2.9 eq.). The reaction mixture was warmed up to r.t., stirred for 2 h 30 min then concentrated. The residue was purified by flash column chromatography (Pent/EtOAc 95:5→90:10) to give first the azide **25** (1.34 g, 2.25 mmol, 35%) as a colourless oil and then the eliminated by-product **24** (1.98 g, 3.61 mmol, 57%) as a colourless oil. **25**: R_f (Hept/EtOAc 80:20) 0.51. $[\alpha]_D^{22}$ –15.2 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 8.03-8.01 (m, 2H, Ar*H*), 7.60 (t, 1H, J_o 7.4 Hz, Ar*H*), 7.49-7.45 (m, 2H, Ar*H*), 7.42-7.21 (m, 15H, Ar*H*), 5.53-5.48 (m, 1H, H1), 4.99 (d, 1H, J_{gem} 11.5 Hz, OCH_aH$_b$Ph), 4.71 (d, 1H, J_{gem} 12.0 Hz, OCH_aH$_b$Ph), 4.59 (d, 1H, J_{gem} 12.0 Hz, OCH$_a$$H_b$Ph), 4.52 (d, 1H, J_{gem} 11.8 Hz, OCH_aH$_b$Ph), 4.51 (d, 1H, J_{gem} 11.5 Hz, OCH$_a$$H_b$Ph), 4.44 (s, 1H, H3), 4.40 (d, 1H, J_{gem} 11.8 Hz, OCH$_a$$H_b$Ph), 3.71-3.66 (m, 2H, H2, H8a), 3.48 (t, 1H, *J* 9.4 Hz, H8b), 3.35-3.30 (m, 1H, H5), 2.24-2.14 (m, 2H, H6a, H7a), 1.96-1.86 (m, 2H, H6b, H7b), 1.80 (dt, 1H, $J_{4,5}$ 10.0 Hz, $J_{4,3}$ 3.1 Hz, H4). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 166.0 (C=O), 138.8 (Ar), 138.3 (Ar), 138.0 (Ar), 133.0 (Ar), 130.7 (Ar), 129.8 (Ar), 128.6-127.7 (m, 18C, Ar), 85.9 (C2), 76.6 (C1), 75.6 (C3), 74.8 (O*C*H$_2$Ph), 73.2 (O*C*H$_2$Ph), 72.6 (O*C*H$_2$Ph), 70.0 (C8), 61.3 (C5), 46.7 (C4), 27.5 (C7), 26.7 (C6). HRMS (ES$^+$): Calcd. for $C_{36}H_{37}N_3O_5Na$: 614.2631; found 614.2629. **24**: R_f (Hept/EtOAc 80:20) 0.43. $[\alpha]_D^{24}$ +118.9 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 8.00-7.98 (m, 2H, Ar*H*), 7.58-7.54 (m, 1H, Ar*H*), 7.45-7.41 (m, 2H, Ar*H*), 7.36-7.27 (m, 10H, Ar*H*), 7.20-7.16 (m, 5H, Ar*H*), 6.08-6.05 (m, 1H, H5), 5.80-5.76 (m, 1H, H1), 4.77 (d, 1H, J_{gem} 12.0 Hz, OCH_aH$_b$Ph), 4.68 (d, 1H, J_{gem} 12.0 Hz, OCH$_a$$H_b$Ph), 4.63 (d, 1H, J_{gem} 12.1 Hz, OCH_aH$_b$Ph), 4.52 (d, 1H, J_{gem} 12.1 Hz, OCH$_a$$H_b$Ph), 4.47 (d, 1H, J_{gem} 11.8 Hz, OCH_aH$_b$Ph), 4.46 (br s, 1H, H3), 4.40 (d, 1H, J_{gem} 11.8 Hz, OCH$_a$$H_b$Ph), 3.99 (d, 1H, J_{gem} 11.5 Hz, H8a), 3.85 (d, 1H, J_{gem} 11.5 Hz, H8b), 3.75 (d, 1H, $J_{1,2}$ 8.2 Hz, H2), 2.41-2.19 (m, 3H, H6a, H6b, H7a), 1.87-1.80 (m, 1H, H7b). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 165.8 (C=O), 138.8 (ArC), 138.4 (Ar), 138.3 (Ar), 136.7 (C4), 134.1 (br s, C5), 132.9 (Ar), 130.8 (Ar), 129.8 (Ar), 128.5-127.5 (m, 18C, Ar), 82.0 (br s, C2), 75.8 (br s, C1), 75.6 (C3), 74.2 (br s, C8), 72.6 (O*C*H$_2$Ph), 72.3 (O*C*H$_2$Ph), 72.2 (O*C*H$_2$Ph), 30.4 (C7), 22.6 (C6). HRMS (ES$^+$): Calcd. for $C_{36}H_{36}O_5Na$: 571.2460; found 571.2458.

(1*S*,2*R*,3*S*,4*R*,5*R*)-5-Azido-2,3-di-*O*-benzyl-4-*C*-benzyloxymethyl-cycloheptan-1-ol (26). To a solution of ester **25** (1.33 g, 2.25 mmol) in MeOH (15mL) was added sodium methoxide (181 mg, 3.35 mmol, 1.5 eq.). The reaction mixture was stirred overnight at 50 °C before being cooled to r.t.. Dowex®50WX8 was then added until pH 7. The reaction mixture was filtered through Celite and concentrated. The residue was purified by flash column chromatography (Pent/EtOAc 90:10→80:20) to give the alcohol **26** (1.05 g, 2.15 mmol, 96%) as a colourless oil. R_f (Hept/EtOAc 80:20) 0.29. $[\alpha]_D^{24}$ –24.4 (*c* 1.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.40-7.22 (m, 15H, Ar*H*), 4.90 (d, 1H, J_{gem} 11.4 Hz, OCH_aH$_b$Ph), 4.82 (d, 1H, J_{gem} 11.4 Hz, OCH_aH$_b$Ph), 4.55 (d, 1H, J_{gem} 11.4 Hz, OCH$_a$$H_b$Ph), 4.54 (d, 1H, J_{gem} 12.0 Hz, OCH_aH$_b$Ph), 4.44-4.40 (m, 3H, OCH_2Ph, H3), 3.96-3.91 (m, 1H, H1), 3.64 (dd, 1H, $J_{8a,8b}$ 9.1 Hz, $J_{8a,4}$ 3.7 Hz, H8a), 3.46 (pt, 1H, *J* 9.4 Hz, H8b), 3.33-3.29 (m, 1H, H5), 3.26 (d, 1H, $J_{1,2}$=$J_{1,7}$ 8.4 Hz, H2), 2.42 (br s, 1H, OH), 2.20-2.11 (m, 1H, H6a), 2.03-1.91 (m, 2H, H6b, H7a), 1.77-1.66 (m, 2H, H4, H7b). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.9 (Ar), 138.3 (Ar), 137.9 (Ar), 128.8-127.6 (m, 15C, Ar), 89.8 (C2), 74.6 (O*C*H$_2$Ph), 74.3 (C3), 73.1 (O*C*H$_2$Ph), 72.5 (C1), 72.3 (O*C*H$_2$Ph), 70.3 (C8), 61.0 (C5), 45.8 (C4), 27.5 (C7), 27.0 (C6). HRMS (ES$^+$): Calcd. for $C_{29}H_{33}N_3O_4Na$: 510.2369; found 510.2370.

(2*S*,3*S*,4*R*,5*R*)-5-Azido-2,3-di-*O*-benzyl-4-*C*-benzyloxymethyl-cycloheptan-1-one (27). To a solution of alcohol **26** (1.30 g, 2.67 mmol) in DCM (13 mL) was added DMP (1.58 g, 3.73 mmol, 1.4 eq.). After 2 h 30 min of stirring

the reaction mixture was diluted with Et_2O (100 mL) before a saturated aq. solution of $NaHCO_3$ (20 mL) followed by a saturated $Na_2S_2O_3$ aq. solution (20 mL) were added and the reaction mixture was stirred for an additional 15 min. The phases were separated and the organic phase washed with brine (20 mL), the aq. phase back extracted with DCM (10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (Pent/EtOAc 86:14) to give the ketone **27** (1.18 g, 2.43 mmol, 91%) as a colourless oil. R_f (Hept/EtOAc 80:20) 0.35. $[\alpha]_D^{24}$ –17.8 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.41-7.24 (m, 13H, Ar*H*), 7.19-7.16 (m, 2H, Ar*H*), 4.87 (d, 1H, J_{gem} 11.8 Hz, OCH_aH$_b$Ph), 4.77 (d, 1H, J_{gem} 11.1 Hz, OCH_aH$_b$Ph), 4.48-4.42 (m, 3H, OCH_2Ph, H2), 4.37-4.32 (m, 3H, OCH_2Ph, H3), 3.71 (dd, 1H, $J_{8a,8b}$ 9.0 Hz, $J_{8a,4}$ 3.7 Hz, H8a), 3.48 (pt, 1H, *J* 9.5 Hz, H8b), 3.42 (dt, 1H, $J_{5,4=5,6a}$ 10.8 Hz, $J_{5,6b}$ 2.5 Hz, H5), 2.67-2.60 (m, 1H, H7a), 2.55-2.47 (m, 1H, H7b), 2.21-2.14 (m, 1H, H6a), 2.06-1.96 (m, 2H, H4, H6b). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 205.1 (C1), 137.0 (2C, Ar), 136.9 (Ar), 127.6-126.8 (m, 15C, Ar), 86.7 (C2), 76.8 (C3), 72.8 (O*C*H$_2$Ph), 72.3 (O*C*H$_2$Ph), 71.6 (O*C*H$_2$Ph), 68.1 (C8), 59.9 (C5), 48.4 (C4), 37.1 (C7), 27.3 (C6). HRMS (ES$^+$): Calcd. for $C_{29}H_{31}N_3O_4Na$: 508.2212; found 508.2210.

(1*R*,2*S*,3*S*,4*R*,5*R*)-2,3-Di-*O*-benzyl-4-*C*-benzyloxymethyl-8-azabicyclo[3.2.1]octan-1-ol (28). A solution of ketone **27** (299 mg, 0.62 mmol) and pyridine (25 µL, 0.31 mmol, 0.5 eq.) in MeOH (3 mL) was degassed then flushed with nitrogen. Pd/C (10%, 149 mg) was added and the reaction mixture stirred 4 h under a hydrogen atmosphere (balloon). The reaction mixture was filtered through Celite, concentrated then co-evaporated twice with toluene. The residue was purified by flash column chromatography (DCM/MeOH 96:4→95:5) to afford protected *galacto*-noeurostegine **28** (253 mg, 0.55 mmol, 89%) as a colourless oil. R_f (DCM/MeOH 95:5) 0.39. $[\alpha]_D^{25}$ +15.2 (*c* 1.0, $CHCl_3$). ^{1}H-NMR (CD_3OD, 400 MHz): δ_H 7.46-7.20 (m, 15H, Ar*H*), 4.90 (d, 1H, J_{gem} 11.7 Hz, OCH_aH$_b$Ph), 4.84 (d, 1H, J_{gem} 11.2 Hz, OCH_aH$_b$Ph), 4.73 (d, 1H, J_{gem} 11.7 Hz, OCH$_a$H$_b$Ph), 4.44 (br s, 2H, OCH_2Ph), 4.36 (d, 1H, J_{gem} 11.2 Hz, OCH$_a$H$_b$Ph), 4.10 (t, 1H, *J* 3.8 Hz, H3), 3.78 (br s, 1H, H2), 3.56-3.48 (m, 2H, H8a, H8b), 3.26 (dd, 1H, *J* 7.3 Hz, *J* 3.9 Hz, H5), 2.66-2.60 (m, 1H, H7a), 2.17-2.11 (m, 1H, H4), 2.03-1.95 (m, 1H, H6a), 1.92-1.81 (m, 1H, H6b), 1.67-1.60 (m, 1H, H7b). ^{13}C-NMR (CD_3OD, 100 MHz): δ_C 140.6 (Ar), 140.3 (Ar), 139.7 (Ar), 129.4-128.2 (m, 15C, Ar), 85.8 (C2), 78.5 (C3), 76.5 (O*C*H$_2$Ph), 74.5 (O*C*H$_2$Ph), 74.1 (O*C*H$_2$Ph), 70.2 (C8), 55.2 (C5), 48.3 (C4), 32.8 (br s, C7), 26.5 (br s, C6). ^{13}C-NMR (253 K, CD_3OD, 100 MHz): δ_C 140.8 (Ar), 140.3 (Ar), 139.6 (Ar), 129.4-128.2 (m, 15C, Ar), 92.2 (br s, C1), 84.7 (br s, C2), 77.9 (br s, C3), 76.7 (br s, O*C*H$_2$Ph), 74.5 (O*C*H$_2$Ph), 74.1 (O*C*H$_2$Ph), 69.7 (br s, C8), 55.4 (br s, C5), 47.3 (br s, C4), 31.3 (br s, C7), 25.2 (br s, C6).

(1*R*,2*S*,3*S*,4*R*,5*R*)-4-(Hydroxymethyl)-8-azabicyclo[3.2.1]octane-1,2,3-triol (5). A solution of protected *galacto*-noeurostegine **28** (40.7 mg, 85.6 µmol) in MeOH/$CHCl_3$ (3:1 v/v, 1 mL) was degassed then flushed with nitrogen. Degussa type Pd/C (10%, 19.6 mg) was added and the reaction mixture stirred overnight under a hydrogen atmosphere (balloon). The reaction mixture was filtered through Celite, concentrated then started all over again. This sequence was performed one more time before the reaction mixture was filtered through Celite and concentrated to give *galacto*-noeurostegine **5** (17.0 mg, 89.9 µmol, quantitative) as a white solid. R_f (EtOH/NH_4OH 25% 66:34) 0.47. ^{1}H-NMR (CD_3OD, 400 MHz): δ_H 4.72 (s, 0.4H, H2-**5m**), 4.10 (t, 0.6H, *J* 4.1 Hz, H3-**5b**), 4.00 (s, 0.4 H, H3-**5m**), 3.94-3.65 (m, 3.2H, H8a, H8b, H2-**5b**, H5-**5b**), 3.53-3.48 (m, 0.6H, H5-**5m**), 2.76-2.62 (m, 1H, H7a), 2.54-2.01 (m, 3.4H, H4, H6a, H6b, H7b-**5m**), 1.72 (br t, 0.6H, *J* 12.4 Hz, H7b-**5b**). ^{13}C-NMR (CD_3OD, 100 MHz): δ_C 211.8 (C1-**5m**), 95.3 (C1-**5b**), 81.8 (C2-**5m**), 75.4 (C3-**5m**), 73.2 (C2-**5b**), 69.0 (C3-**5b**), 66.4 (C8-**5m**), 60.3 (C8-**5b**), 55.7 (C5-**5b**), 54.6 (C5-**5m**), 45.4 (C4-**5b**), 37.9 (C7-**5m**), 28.3 (C6-**5m**), 28.2 (C7-**5b**), 23.3 (C6-**5b**). HRMS (ES$^+$): Calcd. for $C_8H_{15}NO_4H$: 190.1074; found 190.1075.

(1*R*,2*R*,3*S*,4*R*,5*R*)-5-Azido-2,3-di-*O*-benzyl-4-*C*-benzyloxymethyl-cycloheptan-1-ol (29). To a solution of ketone **27** (413 mg, 0.85 mmol) at -20 °C in dry MeOH (8.5 mL) was added $NaBH_4$ (49 mg, 1.30 mmol, 1.5 eq.). The reaction mixture was stirred for 1 h before it was diluted with DCM (30 mL) and quenched with hydrochloric acid (1 M, 10 mL). The organic phase was washed with water (10 mL) and brine (10 mL) before the aq. phase was back extracted with DCM (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude alcohol **29** (401 mg, 0.82 mmol, 97%) as a colourless oil which was used in the next step without purification. R_f (Hept/EtOAc 80:20) 0.29. $[\alpha]_D^{25}$ +48.5 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.40-7.17 (m, 15H, Ar*H*), 4.89 (d, 1H, J_{gem} 11.4 Hz, OCH_aH$_b$Ph), 4.76 (d, 1H, J_{gem} 11.9 Hz, OCH_aH$_b$Ph), 4.63 (d, 1H, J_{gem} 11.9 Hz, OCH$_a$H$_b$Ph), 4.47 (br d, 2H, OCH_aH$_b$Ph, OCH$_a$H$_b$Ph), 4.38-4.35 (m, 2H, OCH$_a$H$_b$Ph, H3), 4.25 (br s, 1H, H1), 3.58 (dd, 1H, $J_{8a,8b}$ 9.1 Hz, $J_{8a,4}$ 3.8 Hz, H8a), 3.42-3.37 (m, 2H, H8b, H5), 3.33 (br d, 1H, $J_{OH,1}$ 5.5 Hz, O*H*), 3.29 (dd, 1H, $J_{2,1}$ 4.3 Hz, $J_{2,3}$ 1.4 Hz, H2), 2.55-2.47 (m, 1H, H6a), 2.00-1.93 (m, 1H, H7a), 1.78-1.65 (m, 3H, H4, H6b, H7b). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.5 (Ar), 138.2 (2C, Ar), 129.2-127.8 (m, 15C, Ar), 83.5 (C2), 80.1 (C3), 75.7 (O*C*H$_2$Ph), 73.2 (O*C*H$_2$Ph), 71.0 (O*C*H$_2$Ph), 70.3 (C8), 68.9 (C1), 61.2 (C5), 45.6 (C4), 26.2 (C7), 24.2 (C6). HRMS (ES$^+$): Calcd. for $C_{29}H_{33}N_3O_4Na$: 510.2369; found 510.2371.

(1*R*,2*S*,3*S*,4*R*,5*R*)-5-Azido-2,3-di-*O*-benzyl-4-*C*-benzyloxymethyl-cycloheptyl methanesulfonate (30). To a solution of alcohol **29** (511 mg, 1.05 mmol) at 0 °C in dry Et_2O (6.3 mL) under an argon atmosphere, was added Et_3N (0.29 mL, 2.08 mmol, 2.0 eq.) followed by methanesulfonyl chloride (0.12 mL, 1.55 mmol, 1.5 eq.). The reaction mixture was stirred at r.t. for 50 min before it was diluted with DCM (30 mL) and washed with a 5% $NaHCO_3$ aq. solution (10 mL) and brine (10 mL). The aq. phase was back extracted with DCM (5 mL) before the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (Pent/EtOAc 80:20) to give the mesylate **30** as a colourless oil (572 mg, 1.01 mmol, 96%). R_f (Hept/EtOAc 80:20) 0.25. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.38-7.29 (m, 15H, Ar*H*), 5.24-5.20 (m, 1H, H1), 4.96 (d, 1H, J_{gem} 11.4 Hz, OCH_aH$_b$Ph), 4.70 (s, 2H, OCH_2Ph), 4.50 (d, 1H, J_{gem} 12.0 Hz, OCH_aH$_b$Ph), 4.46 (d, 1H, J_{gem} 11.4 Hz, OCH$_a$H$_b$Ph), 4.38 (d, 1H, J_{gem} 12.0 Hz, OCH$_a$H$_b$Ph), 4.34 (br s, 1H, H3), 3.63 (dd, 1H, $J_{8a,8b}$ 9.1 Hz, $J_{8a,4}$ 4.1 Hz, H8a), 3.54-3.49 (m, 2H, H8b, H2), 3.47-3.42 (m, 1H, H5), 2.90 (s, 3H, SO_2CH_3), 2.65-2.57 (m, 1H, H6a), 2.23-2.16 (m, 1H, H7a), 1.99-1.92 (m, 1H, H7b), 1.80-1.70 (m, 2H, H6b, H4). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 138.8 (Ar), 138.2 (Ar), 137.4 (Ar), 128.7-127.6 (m, 15C, Ar), 83.6 (C2), 79.9 (C1), 76.5 (C3), 73.9

(O*C*H$_2$Ph), 73.1 (O*C*H$_2$Ph), 72.3 (O*C*H$_2$Ph), 69.9 (C8), 61.2 (C5), 46.1 (C4), 38.7 (SO$_2$*C*H$_3$), 25.7 (C7), 24.8 (C6).

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3-Di-*O*-benzyl-4-*C*-benzyloxymethyl-8-azabicyclo[3.2.1]octane (31). A solution of mesylate **30** (355 mg, 0.73 mmol) and pyridine (30 µL, 0.37 mmol, 0.5 eq.) in MeOH (4 mL) was degassed and then flushed with nitrogen. Pearlman's catalyst (20% Pd(OH)$_2$/C, 186 mg) was added and the reaction mixture was stirred overnight under a hydrogen atmosphere (balloon). The reaction mixture was filtered through Celite, concentrated and then co-evaporated with toluene. The residue was taken up in EtOAc (20 mL) and washed with a 5% NaHCO$_3$ aq. solution (2 × 5 mL) and brine (5 mL). The organic phase was dried over MgSO$_4$, filtered and concentrated before the residue was purified by flash column chromatography (DCM/MeOH 95:5→94:6) to afford protected 2-deoxy-*galacto*-noeurostegine **31** (228 mg, 0.51 mmol, 70%) as a colourless oil. R_f (DCM/MeOH 94:6) 0.28. $[\alpha]_D^{25}$ –5.9 (*c* 1.0, CHCl$_3$). ^{1}H-NMR (CD$_3$OD, 400 MHz): δ_H 7.38-7.20 (m, 15H, Ar*H*), 4.87 (d, under DHO signal, 1H, OC*H*$_a$H$_b$Ph), 4.68 (d, 1H, J_{gem} 12.0 Hz, OC*H*$_a$H$_b$Ph), 4.62 (d, 1H, J_{gem} 12.0 Hz, OCH$_a$*H*$_b$Ph), 4.44-4.34 (m, 3H, OC*H*$_2$Ph, OCH$_a$*H*$_b$Ph), 3.98 (t, 1H, *J* 3.9 Hz, H3), 3.65-3.63 (m, 1H, H2), 3.60-3.58 (m, 1H, H1), 3.52-3.44 (m, 2H, H8a, H8b), 3.40-3.38 (m, 1H, H5), 2.55-2.49 (m, 1H, H7a), 2.18-2.08 (m, 2H, H4, H6a), 1.66-1.53 (m, 2H, H6b, H7b). ^{13}C-NMR (CD$_3$OD, 100 MHz): δ_C 140.8 (Ar), 140.0 (Ar), 139.7 (Ar), 129.4-128.2 (m, 15C, Ar), 80.6 (C2), 77.3 (C3), 76.8 (O*C*H$_2$Ph), 74.2 (O*C*H$_2$Ph), 72.2 (O*C*H$_2$Ph), 70.1 (C8), 57.3 (C1), 56.2 (C5), 46.1 (C4), 25.8 (C7), 25.1 (C6). HRMS (ES$^+$): Calcd. for $C_{29}H_{33}NO_3H$: 444.2539; found 444.2548.

(1*S*,2*R*,3*S*,4*R*,5*R*)-4-(Hydroxymethyl)-8-azabicyclo[3.2.1]octane-2,3-diol (6). A solution of protected 2-deoxy-*galacto*-noeurostegine **31** (228 mg, 514 µmol) in MeOH (5 mL) was degassed then flushed with nitrogen. Pearlman's catalyst (20% Pd(OH)$_2$/C, 118 mg) was added followed by one drop of concentrated HCl then the reaction mixture was stirred overnight under a hydrogen atmosphere (balloon). The reaction mixture was filtered through Celite, concentrated and the residue purified by flash column chromatography (EtOH/NH$_4$OH 25% 90:10) to give 2-deoxy-*galacto*-noeurostegine **6** (67 mg, 387 µmol, 75%) as a white solid. R_f (EtOH/NH$_4$OH 25% 2:1) 0.52. $[\alpha]_D^{25}$ –11.2 (*c* 0.8, H$_2$O). ^{1}H-NMR (D$_2$O, 400 MHz): δ_H 4.03 (t, 1H, *J* 4.3 Hz, H3), 3.79 (t, 1H, *J* 4.2 Hz, H2), 3.71 (dd, 1H, J_{gem} 11.3 Hz, $J_{8a,4}$ 6.4 Hz, H8a), 3.65 (dd, 1H, J_{gem} 11.3 Hz, $J_{8b,4}$ 8.2 Hz, H8b), 3.49-3.44 (m, 2H, H1, H5), 2.17-2.12 (m, 1H, H6a), 2.04-1.97 (m, 2H, H4, H7a), 1.68-1.64 (m, 2H, H6b, H7b). ^{13}C-NMR (D$_2$O, 100 MHz): δ_C 69.7 (C2), 67.6 (C3), 60.3 (C8), 57.2 (C1), 53.4 (C5), 45.4 (C4), 23.5 (C7), 22.7 (C6). HRMS (ES$^+$): Calcd. for $C_8H_{15}NO_3H$: 174.1130; found 174.1126.

Notes and references

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Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR for spectra for all new compounds. X-ray crystal data for compounds **22** and **23**. Quantum mechanical calculation setups. Michaelis-Menten and Hanes plots for compounds **5** and **6**. Details See DOI: 10.1039/b000000x/

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