PAPER

Stable analogues of nojirimycin – synthesis and biological evaluation of nojiristegine and manno-nojiristegine†

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Two novel iminosugars called nojiristegines, being structural hybrids between nor-tropane alkaloid calystegine and nojirimycins, have been synthesised and found to be stable molecules despite the presence of a hemiaminal functionality. The synthesised iminosugars were evaluated against a panel of glycosidases and the best inhibition (IC_{50}), found against α-glucosidases, was in the micromolar region. The compounds were also evaluated as potential antibiotics but no useful level of activity was observed.

Introduction

In 1965, the first naturally occurring iminosugar 5-amino-5-deoxy-glucospyranose was found[1] and subsequently named nojirimycin, after its isolation from *Streptomyces nojiriensis*.[2] In 1984, the mannose derivative of nojirimycin (manno-nojirimycin or nojirimycin B), was discovered by Niwa *et al.*[3] who isolated it from *Streptomyces lavendulae* SF-425. One of the main reasons for the interest in these molecules was their potent glycosidase inhibition established in 1970 by Niwa *et al.* for nojirimycin[4] and by Legler and Jülich for manno-nojirimycin.[5] These two prominent alkaloids of the imino-sugar/azasugar family[6] have spawned a whole area of research mainly due to their potent inhibition of glycosidases. Several analogous molecules have been found in Nature or synthesised by creative chemists.[7–9]

In general, iminosugars/azasugars have been reported to have important therapeutic potential in diseases such as diabetes, cancer, lysosomal storage diseases, viral and bacterial diseases.[10–12] Recently Warren *et al.* published their work on the iminosugar BCX4430 which is a broad spectrum antiviral agent that inhibits infection with *e.g.* Ebola and other highly fatal viruses.[13]

Despite their potent glycosidase inhibition, both nojirimycin and manno-nojirimycin have little potential to be therapeutic candidates, due to their instability caused by their hemiaminal functionality, which eventually undergoes the Amadori rearrangement.[14,15] This inherent drawback of the nojirimycins has been addressed by Inouye *et al.* through chemical reduction of nojirimycin to arrive at 1-deoxynojirimycin (Fig. 1),[16] which was later found by Yagi *et al.* to be naturally present in mulberry trees.[17] The stability issue of nojirimycins has probably caused the scientific community to mainly focus on 1-deoxynojirimycin and its analogues at the expense of nojirimycins. However, one finding often cited in the literature is the antibiotic activity of the nojirimycins, which was recognised very shortly after their discovery. Ishida *et al.* reported nojirimycin to have antibiotic activity against bacterial strains from the otherwise dissimilar genera, *Shigella flexneri*, *Sarcina lutea* and *Xanthomonas oryzae*. Surprisingly, the compound had weak or no activity towards closely related bacteria such as *Escherichia coli* and even other strains of *Shigella*.[18] Manno-nojirimycin was found by their discoverers to have weak antibiotic activity against *Xanthomonas oryzae* but no activity against other bacteria tested.[19]

The hemi-aminal functionality of alkaloids is not always as unstable as that of nojirimycins. Among the naturally occurring iminosugars, the calystegines possess a bicyclic structure that prevents imine formation and thereby Amadori rearrangement. Calystegines are glycosidase inhibitors, but have a hydroxyl group in the place of the hydroxymethyl group of the natural substrate.[20] Inspired by the calystegine core structure and the unstable noeuromycins from the Bols laboratories[21] we previously reported on the synthesis of both glucose, galactose and glucuronic acid configured synthetic hybrids of

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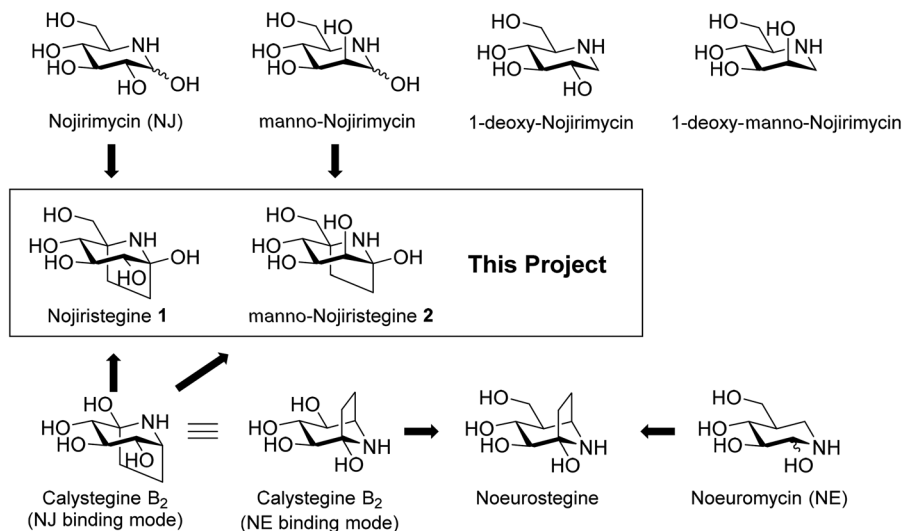[c]Department of Biomedicine, Aarhus University, Wilhelm Meyers allé 4, 8000 Aarhus C, Denmark

Fig. 1 Structure of known iminosugars/azasugars. Box shows the structural hybrid molecules synthesised and evaluated in this study.

calystegines and noeuromycins (Fig. 1). These compounds have been christened noeurostegines.[22–24]

In this report we describe the synthesis, initial inhibitory data and potential antibiotic activity of stable hybrids between nojirimycin/manno-nojirimycin and calystegines. We here refer to these molecules as nojiristegine (**1**) and manno-nojiristegine (**2**).
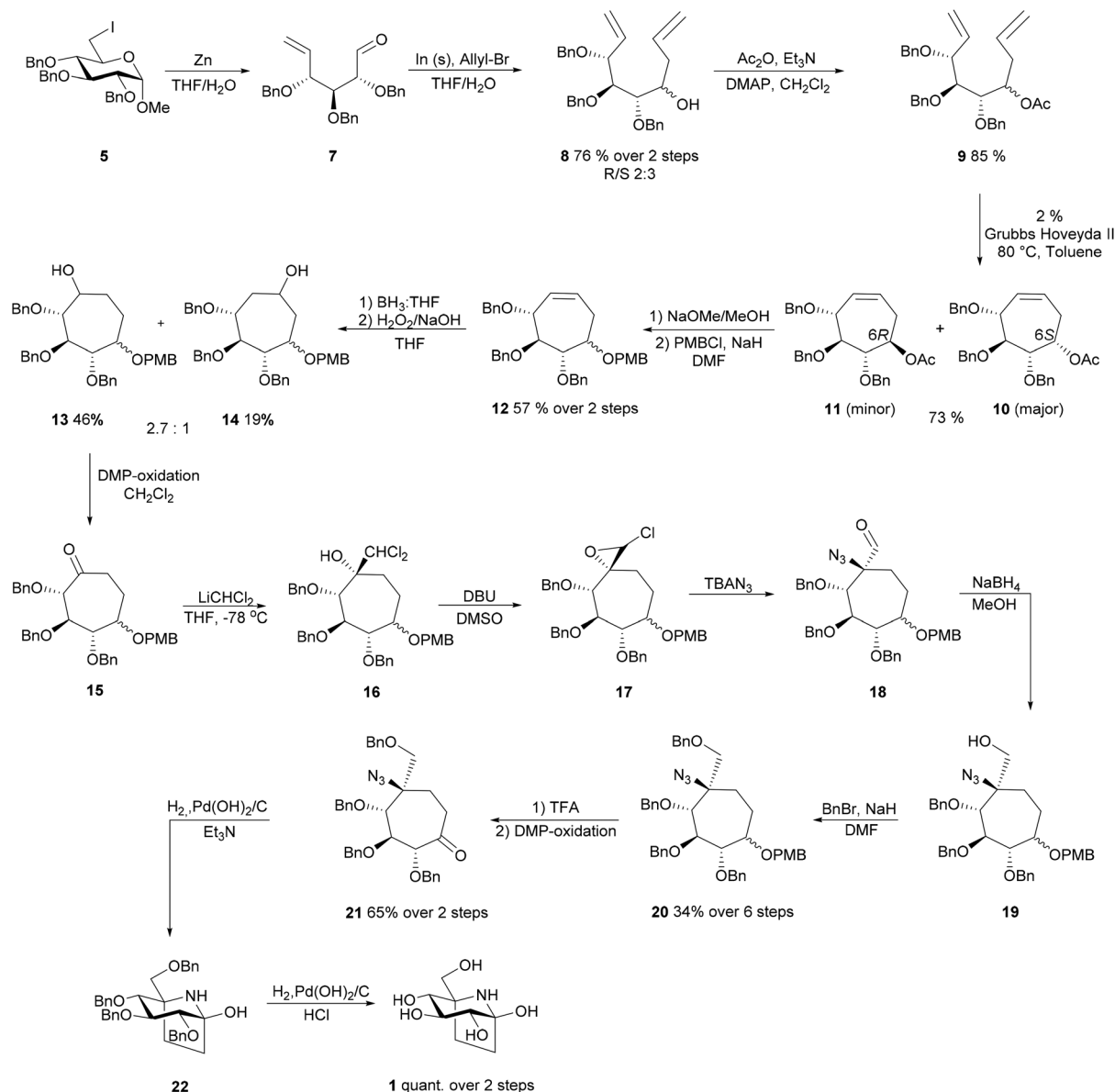
Synthesis

The strategy for the synthesis of the nojiristegines was largely inspired by our previously reported synthesis of noeurostegine[22] and calystegine A$_3$.[25] The synthesis of both target molecules (**1** and **2**) was performed from methyl α-D-glucopyranoside (**3**) and methyl α-D-mannopyranoside (**4**), respectively. In a series of known steps[26] these were separately converted into 2,3,4-tri-O-benzyl-6-iodo-6-deoxy pyranosides **5** and **6** (Scheme 1).

For the synthesis of glucose-configured nojiristegine (**1**), the 6-iodo-glucoside **5** was subjected to zinc-mediated fragmentation under sonication in THF–H$_2$O[27] giving an aldehyde, which was used directly in the following Barbier reaction, without further purification. This resulted in two diastereoisomeric allylic alcohols (**8R** and **8S**) as an inseparable 2 : 3 mixture in 76% yield over 2 steps (Scheme 2).
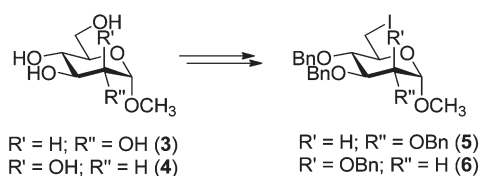
The mixture of dienes **8** possessing a free secondary alcohol proved incapable of undergoing ring-closing metathesis with the Grubbs–Hoveyda 2nd generation catalyst.[28] Subsequent to alcohol acetylation with acetic anhydride, triethyl amine and DMAP in 85% yield, the stereoisomers **9** could if needed be separated and ring closing metathesis promoted by Grubbs–Hoveyda 2nd generation catalyst went smoothly in 93% yield on the diastereoisomeric mixture from the previous reaction. When working with the single isomers, the C6 stereochemistry could be deduced by 1D and 2D ^{1}H-NMR experiments and assigned based on $^3J_{HH}$ coupling constants for **10** and **11**. This established the major product from the Barbier allylation to be **8S**, but since both allylic alcohols (**8R** and **8S**) eventually would be oxidised to the same ketone, the synthesis of nojiristegine (**1**) progressed with a mixture of isomers. The acetyl groups were then removed from a mixture of ring closed acetates **10** and **11** by Zemplén conditions and the resulting alcohol was next protected by the more robust p-methoxybenzyl (PMB) ether with PMB-Cl/NaH in 57% yield over 2 steps. The cycloheptene was next subjected to a hydroboration/oxidation sequence to give the two regioisomeric secondary alcohols **13** and **14**, of which each was found to be a single diastereoisomer. The ratio of the two secondary alcohols was found to be different depending on whether the reaction was conducted on the R or the S-isomer. The S-isomer gave 1 : 2.7 in favour of the desired alcohol, while the R-isomer gave 1.7 : 1 in favour of the undesired alcohol. Performing the reaction on the mixture of stereoisomers originating from the Barbier reaction gave the desired alcohol in a yield of 46%. The alcohol could now be oxidised using Dess–Martin periodinane (DMP)[29] to give the ketones **15**, which could be used as a precursor for the introduction of both an azide and a hydroxymethyl substituent. Accordingly, ketone **15** was first converted into the chloroepoxides[30] **17** by reaction with lithiated dichloromethane followed by treatment with DBU. These compounds (**17**) were

Scheme 1 Synthesis of known 6-deoxy-6-iodo glycosides.

Scheme 2 Synthesis of nojiristegine (**1**).

then reacted with tetrabutylammonium azide to give aldehydes **18**, which were reduced with NaBH$_4$ and the resulting alcohols protected as benzyl ethers to give the desired azides **20** in 34% over 6 steps. This sequence of known reactions was easily monitored by TLC analysis but intermediate structural assignment by NMR spectroscopy was highly challenging. Intermediates **16–18** were found to be unstable and chromatographic purification was therefore omitted. Identity was established by mass spectrometry alone and the yield reported is for the full sequence (**15–20**).

Given the nature of these reactions it cannot be ruled out, that other isomers than the one shown in Scheme 2 was formed but none could be isolated. The stereochemistry of the product could not be verified until the last step of the syn-

thesis, since it was not possible to obtain crystals of high enough quality for a crystal structure.

The PMB ether could now be deprotected using TFA and the resulting alcohol oxidised using DMP in 65% over two steps. Basic hydrogenation with triethylamine resulted in reduction of the azide and spontaneous cyclisation into the benzyl protected nojiristegine (**22**), as established by a hemi-aminal ^{13}C-NMR chemical shift of 92 ppm. Hydrogenolysis using Pearlman's catalyst was then used to remove the remaining benzyl groups in quantitative yield. The presence of exclusively large coupling constants as a result of axial–axial ^{1}H–^{1}H geometry verifies the stereochemistry of the quaternary centre originating from the introduction of the azido group.

Nojiristegine (**1**) was hence successfully synthesised in 21 linear steps and was found to be fully shelf stable and stable in solution over several weeks.

The synthesis of the epimeric manno-nojirimycin (**2**) followed a similar synthetic route. The iodide **6** (Scheme 1) was subjected to zinc-mediated fragmentation and subsequent Barbier reaction with allyl bromide.[27] This resulted in two inseparable diastereoisomers in a 2.2 : 1 mixture in 76% yield (Scheme 3). The stereochemical outcome was established *via* derivatisation at a later stage (*vide infra*). The diastereoisomeric mixture was then acetylated using acetic anhydride and DMAP in pyridine and subsequently subjected to ring-closing metathesis. It was possible to separate the two stereoisomers (**26** and **27**) as the ring-closed acetates in 19% and 50% over two steps, respectively (Scheme 3).

For structural assignment, the two acetates (**26** and **27**) were then individually deacylated by Zemplén conditions, *O*-benzylated by NaH/BnBr and the double bond reduced. This gave two isomers (**32** and **33**) where one could be established by ^{13}C-NMR to be symmetrical. Consequently, the major/minor isomer from the Barbier reaction was established as the 6*R*/6*S* isomer, respectively (Scheme 3). As for the synthesis of nojiristegine (**1**, Scheme 2) both diastereoisomers (**26** and **27**) could principally be used in the next steps but the synthesis was completed with **27** alone (Scheme 4).

The alcohol **29** was protected as a PMB ether in 84% over two steps to give cycloheptene **34**, which was subjected to hydroboration and oxidative work up to afford two regio-isomeric alcohols in a 2.1 : 1 ratio as sole diastereoisomers in a combined yield of 78%. The desired major alcohol isomer **36** was then oxidised using Dess–Martin periodinane (DMP). The

resulting ketone underwent the same sequence of reactions as in the nojiristegine synthesis (Scheme 2) to install benzyloxy-methyl and azide substituents. Hence, **37** was treated with lithiated dichloromethane and then DBU to give the chloro-epoxide **39**, which could be opened to compound **40** by treatment with tetrabutylammonium azide in DMSO. The aldehyde function was then reduced using sodium borohydride and the resulting alcohol protected as a benzyl ether. This gave the desired product **42** in a 1.7 : 1 mixture with its epimer **43** in a total yield of 38% over 5 steps from ketone **37**. The PMB ether of **42** could now be deprotected using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the resulting alcohol oxidised to the ketone (**44**) in 39% over two steps. Azide reduction first afforded the spontaneously cyclised **45** as shown by the presence of a hemiaminal C-atom (δ_C 91.2 ppm) and next hydrogenolysis to remove benzyl ether protection gave manno-nojiristegine (**2**) in quantitative yield. The stereochemistry originating from the azide introduction step could now be verified by analysis of coupling constants originating from the ^{1}H nuclei of the bicyclic molecule **2**. The ^{1}H-NMR spectrum showed one small (4.0 Hz) and one large coupling constant (9.2 Hz) as expected from an equatorial/axial (H2/H3) and axial/axial (H3/H4) arrangement, respectively. If the quaternary carbon atom bearing the nitrogen had been opposite (**46**), two small coupling constants would be expected upon cyclisation (Scheme 5).

The synthesis produced manno-nojiristegine in 21 steps from the unprotected methyl manno-pyranoside (**4**). The compound was stable and did not show any degradation after several weeks on the shelf.

Concerning the modest stereoselectivity in the Barbier reactions of aldehydes **7** and **23**, we found the two major products
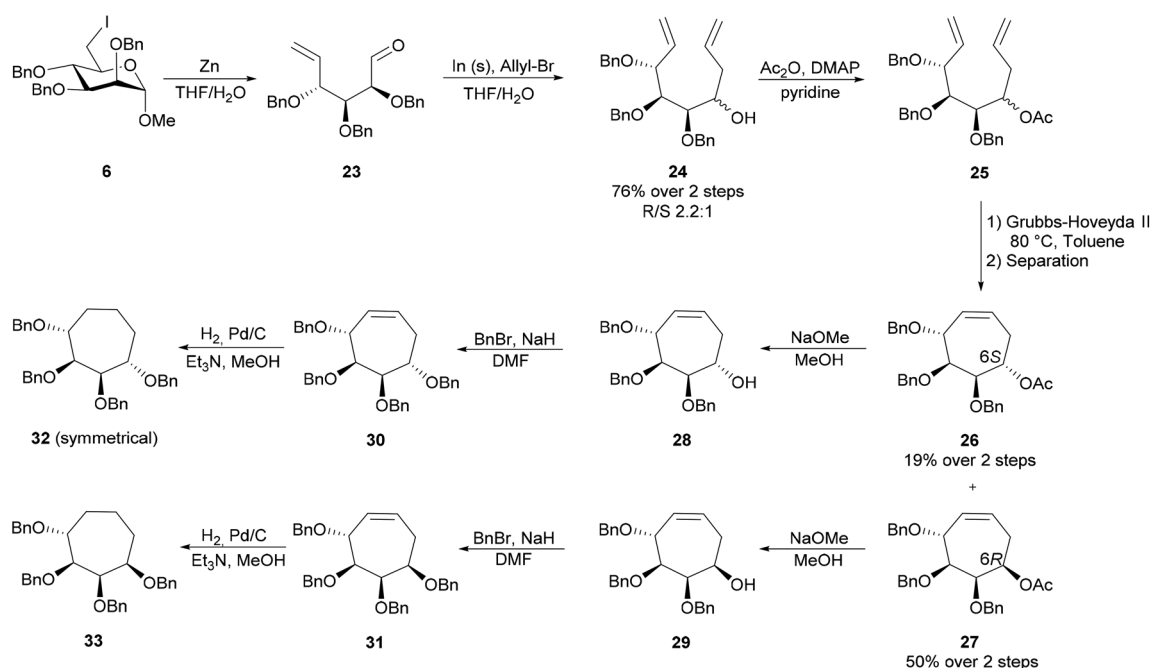
Scheme 3 Synthesis towards manno-nojiristegine (**2**) and establishing the stereochemical outcome of the Barbier reaction.
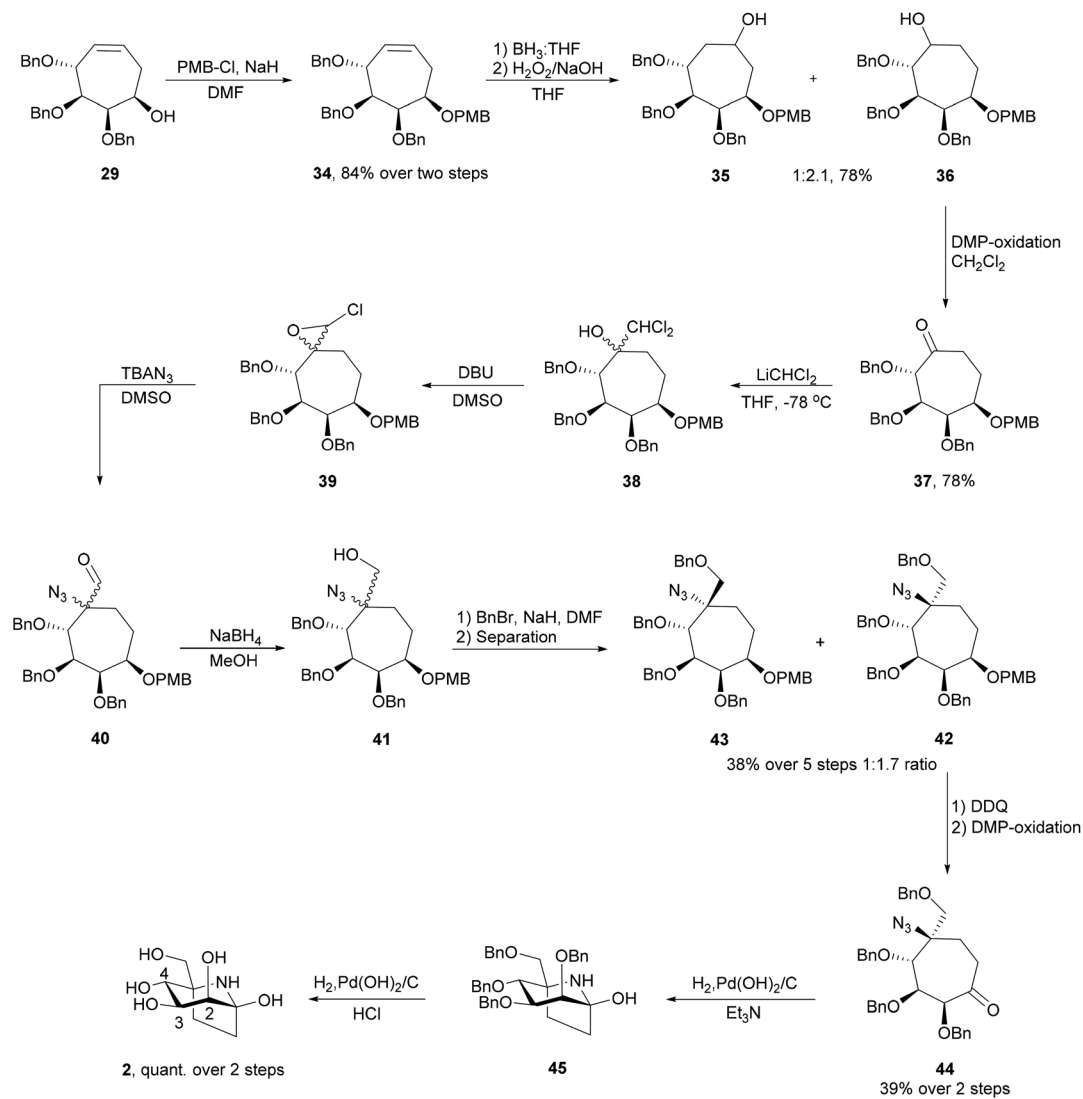
Scheme 4 Synthesis of manno-nojiristegine (**2**) from cycloheptenol **29**.
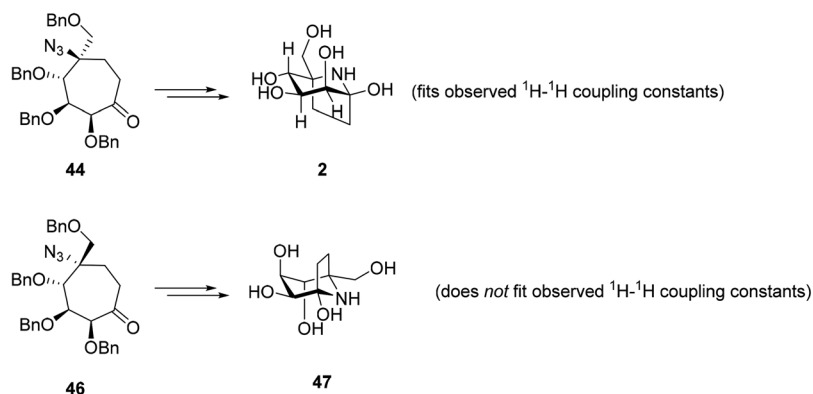
Scheme 5 The different products formed from the two possible azide isomers **44** and **46**.

(**8S** and **24R**) to possess opposite stereochemistry of the newly formed stereogenic centre (Table 1, entries 1 and 2). Interestingly, Skaanderup and Madsen found a more pronounced selectivity for both indium, magnesium and zinc in the analogous Barbier reaction with allyl bromide on the corresponding *N*-benzyl imines (entries 6–8).[31] Except for the metal zinc in reaction with the *N*-benzyl imine of **23**, the stereochemical outcome was reversed compared to the aldehyde substrates (**7** and **23**).

For a complete comparison, we also prepared the aldehyde analogous to **7** and **23** from D-galactose[26] (entry 3) and again found the reaction to be selective for the C6–S isomer as compound **7** originating from D-glucose demonstrating the depen-

dence on C-α stereochemistry. This was also opposite to the corresponding *N*-benzyl imine (entry 8).[31]

Interestingly, the indium mediated Barbier allylation was previously found to be dependent on the C-β stereochemistry in the synthesis of noeurostegine and *galacto*-noeurostegine (entries 4 and 5), where the aldehyde is flanked by a benzyloxy group (Table 1).[22,24] For these examples, the aldehyde leading to noeurostegine (entry 4) having the same stereochemistry as **7**, the *S*-product dominated, while the opposite was true for the aldehyde leading to *galacto*-noeurostegine (entry 5).

Inhibition studies

The compounds **1** and **2** were tested for inhibitory activity against a panel of glycosidases (Table 2), but in many cases no inhibition was found. Nojiristegine (**1**) was, however, found to be moderately active as an α-glucosidase inhibitor with an IC_{50} of 14 μM for rat intestinal sucrase, 27 μM for rice and 30 μM for recombinant α-glucosidase alglycosidase alpha of which the latter enzyme is used in enzyme replacement therapy for Pompe disease. In comparison, 1-deoxynojirimycin is a strong inhibitor of these enzymes (K_i 0.024 μM, K_i 0.01 μM, K_i 0.55 μM, respectively).[35–37] which indicates that the steric bulk of the ethylene bridge in nojiristegine (**1**) might interfere with binding to the enzymes. Yeast α-glucosidase and sweet almond β-glucosidase are both potently inhibited by nojirimycin,[5] whereas nojiristegine was largely inactive. Human glucocerebrosidase was modestly inhibited by nojiristegine (**1**, IC_{50} 440 μM) but much less than what has been found for noeurostegine (IC_{50} 0.4 μM).[38] Interstingly, nojiristegine (**1**) was not found to be an inhibitor of coffee beans α-galactosidase despite the fact that both calystegine B_2 (K_i 0.86 μM),[39] noeurostegine (K_i 2.5 μM)[22] and 1-deoxynojirimycin (K_i 23 μM)[40] are all potent inhibitors of this enzyme (Fig. 2). Since *galacto*-noeurostegine (4-*epi*-noeurostegine) is not an inihibitor of green coffee beans α-galactosidase, but calystegine and noeurostegine inhibit this enzyme potently, we have previously speculated that the two former azasugars would bind in a nojirimycin (NJ) binding mode[24] placing the ethylene bridge in the same position as nojiristegine (**1**). The observation, that nojiristegine is not an inhibitor of this enzyme, brings our previous suggestion into question.

Manno-nojiristegine (**2**) did not show any activity against tested mannosidases and most other glycosidases. Weak inhibition of β-glucoronidase from *E. coli* and α,α-trehalase from porcine kidney (IC_{50} of 810 μM and 400 μM, respectively) was obtained.

Antibiotic studies

Nojiristegines **1** and **2** and the close structural analogue 1-deoxynojirimycin were evaluated for potential antibiotic activity against a series of bacterial strains based on availability, clinical relevance and their close relation to original

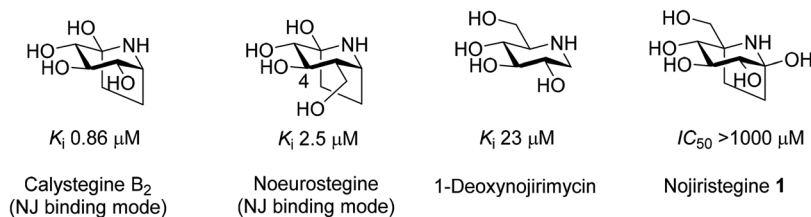**Table 1** The stereoselectivity of the Barbier allylation of aldehydes using different metals

Entry	Ref.	Starting material	Product	Metal	R/S
1	This work	**7**	**8**	In	2:3
2	This work	**23**	**24**	In	2.2:1
3	This work			In	1:2.1
4	22			In	1:1.7
5	24			In	3:2
6	31			In / Mg / Zn	1:0 / 16:1 / 5:1
7	31			In / Mg / Zn	0:1 / 1:8 / 8:1
8	31			In / Mg / Zn	1:0 / 8:1 / 2:1

Table 2 K_i and IC_{50} values of iminosugars against various glycosidases

Enzyme	Values in μM			
	Nojiristegine (1)	*manno*-Nojiristegine (2)	Nojirimycin	*manno*-Nojirimycin
α-Glucosidase				
Yeast	[a]NI [b](16%)	NI (20%)	K_i: 6.3[5]	85% at 100 μM[32]
Rice	IC_{50}: 27	NI (12%)		
Rat intestinal maltase	IC_{50}: 181	NI (11%)		
Rabbit small intestine maltase			IC_{50}: 4.6[33]	
Rat intestinal sucrase	IC_{50}: 14	NI (23%)		
Rabbit small intestine sucrase			K_i: 0.13[34]	
Amyloglucosidase				
Aspergillus niger	NI (0%)	NI (0%)		
Alglucosidase alfa				
Human lysosome	IC_{50}: 30	NI (2%)		
α-Amylase				
Porcine pancreas	NI (26%)	NI (9%)		
β-Glucosidase				
Sweet almond	NI (28%)	NI (21%)	K_i: 0.9[5]	K_i: 20[5]
Bovine liver	NI (44%)	NI (35%)		
β-Glucocerebrosidase				
Human lysosome	IC_{50}: 440	NI (20%)		
α-Galactosidase				
Green coffee beans	NI (23%)	NI (7%)		
α-Galactosidase A				
Human lysosome	NI (21%)	NI (0%)		
β-Galactosidase				
Bovine liver	NI (16%)	NI (19%)		
α-Mannosidase				
Jack bean	NI (24%)	NI (4%)	K_i: 500[5]	K_i: 6.5[5]
β-Mannosidase				
Snail	NI (17%)	NI (0%)		
Aspergillus wentii			K_i: 900[5]	K_i: 7.7[5]
α-ʟ-Rhamnosidase				
Penicillium decumbens	NI (33%)	NI (3%)		
α-ʟ-Fucosidase				
Bovine kidney	NI (43%)	NI (2%)		
β-Glucuronidase				
E. coli	IC_{50}: 620	IC_{50}: 810		
Bovine liver	NI (37%)	NI (4%)		
α,α-Trehalase				
Porcine kidney	NI (8%)	IC_{50}: 420		
β-*N*-Acetyl-hexosaminidase				
Human placenta	NI (8%)	NI (2%)		

[a] NI: No inhibition (less than 50% inhibition at 1000 μM). [b] ( ): Inhibition % at 1000 μM.

K_i 0.86 μM	K_i 2.5 μM	K_i 23 μM	IC_{50} >1000 μM
Calystegine B$_2$ (NJ binding mode)	Noeurostegine (NJ binding mode)	1-Deoxynojirimycin	Nojiristegine 1

Fig. 2 Inhibitory data for inhibition of α-galactosidase from green coffee beans.

strains tested with nojirimycin (*Pseudomonas aeruginosa* strain PAO1, *Escherichia coli* strains VK98 and VK144, and *Staphylococcus aureus* strain VK75). Nojirimycin has been found largely inactive against non-resistant *Shigella flexneri* 2a, *Shigella flexneri* 6 Mita, *Staphylococcus aureus* Terashima and 209 P and *E. coli* Umezawa, but highly active against *Xanthomonas oryzae*, resistant *Shigella flexneri* 2a and *Sarcina lutea* PCI 1001.[18]

Neither 1-deoxynojirimycin nor nojiristegine (**1**) showed any antibiotic activity against the tested strains of *Pseudomonas aeruginosa*, *Staphylococcus aureus* or *E. coli* up to concentrations of 500 μg mL^{-1}. Lack of activity against *E. coli* and *Staphylococcus aureus* was also seen in the original results for nojirimycin,[18] but activity against *E. coli* could have been expected due its close genetic relation to *Shigella flexneri*.

Niwa *et al.* reported manno-nojirimycin to be weakly active (50-fold less than nojirimycin) against *Xanthomonas oryzae* and also tested other unspecified bacterial strains but found no activity.[19] Assuming that Niwa *et al.* tested the activity against the same bacteria as Ishida *et al.*[18] there seems to be a noteworthy difference between the antibiotic activity of nojirimycin and its manno-epimer, but this cannot, to the best of our knowledge, be confirmed.

In our test, manno-nojiristegine (**2**) did not show any activity against the strains as investigated for **1**.

While glycosidase inhibition has been carefully investigated, our literature study has revealed that only little is known about the antibiotic activity of nojirimycin and manno-nojirimycin. In order to take advantages of this antibiotic activity, it is evident that further studies must be conducted in order to establish the mechanism for this activity.

Conclusion

Two new iminosugars of the hemiaminal nortropane type have been synthesised through 21 steps from methyl α-D-glucopyranoside and methyl α-D-mannopyranoside. The key transformation was the instalment of a nitrogen atom in form of an azide at a quarternary carbon atom, which was performed over several steps from a ketone functionality.

The synthesised highly functionalised iminosugars were named nojiristegine and manno-nojiristegine due to their resemblance with both calystegines and nojirimycin. As a result of the ethylene bridge inherited from calystegines, the synthesised molecules were found to be stable in aqueous medium for several days.

Nojiristegine (**1**) and its manno-configured isomer (**2**) were both evaluated as potential glycosidase inhibitors, but only weak inhibition was found. This shows that only limited space is available in the glycosidase binding pocket, which only in certain cases can accommodate the ethylene bridge. Glycosidase inhibition by calystegines and noeuromycins has in general been found to be more potent that what was found for the two nojiristegines investigated in this study.

The synthesised compounds (**1** and **2**) were also evaluated as a potential antibiotics against a few bacterial strains, result-

ing in no activity against any of the strains of *Pseudomonas aeruginosa*, *E. coli*, and *Staphylococcus aureus* for neither **1** nor **2**. A careful literature survey revealed that literature only holds very little information about the antibiotic activity of nojirimycin despite the fact that this compound is often referred to as an antibiotic. Given the current threat of resistant bacteria a modern study of the nojirimycins would be in order to confirm its activity and activity profile.

Experimental

Inhibition studies

The ability of the compounds to inhibit glycosidase activity was carried out as previously described.[23]

Antibiotic studies

The ability of the compounds to inhibit bacterial growth was tested on 5% blood agar plates (Statens Serum Institut, Copenhagen). The inoculum was a suspension of the respective bacterial strains in sterile 0.9% saline at a density of approximately 10^7 bacteria per ml. The suspension was added to the entire surface of the agar plate where upon excess fluid was removed with a pipette. After drying of the plate filter paper discs with a diameter of 5 mm were placed on the agar surface and 200 ul of the respective dilutions of the compounds were added. Potential inhibition zones were read after overnight incubation at 37 °C.

The bacterial strains used in the inhibition experiments were *Pseudomonas aeruginosa* strain PAO1, *Escherichia coli* strains VK98 and VK144, and *Staphylococcus aureus* strain VK75.

Organic synthesis

General methods. All reactions with air- and moisture sensitive compounds were conducted in an atmosphere of nitrogen or argon. Dichloromethane, toluene, acetonitrile and THF were dried over aluminum oxide *via* an MBraun SPS-800 solvent purification system, other dry solvents were dried over molecular sieves. Evaporation of solvents was done under reduced pressure at 40 °C. Flash column chromatography was carried out with a Merck silica gel (230–400 Mesh). TLC analysis was carried out on silica gel on aluminum foil (Merck Kieselgel 60 F254). TLC plates were visualized by using ceric sulfate/ammonium molybdate in 10% H_2SO_4 or ninhydrin in *n*-butanol/acetic acid and successive heating to dryness.

Apparatus. NMR spectra were recorded on a Varian Mercury 400 spectrometer. ^{1}H-, gCOSY-, and gHMQC-NMR were recorded at 400 MHz and ^{13}C-NMR and DEPT-135 at 100 MHz. Chemical shifts (δ) are given in ppm relative to the residual solvent signals (CDCl$_3$ (δ 7.26 ppm for proton and 77.16 ppm for carbon resonances) and D$_2$O (δ 4.79 ppm for proton). Assignment of NMR spectra is based on gCOSY, gHMQC and DEPT-135 experiments. Mass spectra were recorded on a Micromass LC-TOF spectrometer with positive electrospray ionization. Melting points were measured on a Büchi B-450,

and are not corrected. Optical rotations were measured on an ADP440+ polarimeter and reported in units of deg cm^2 g^{-1}. Concentrations are given in g per 100 mL. IR spectra were obtained as neat on a PerkinElmer FT-IR spectrometer (Spectrum TWO/UATR TWO) and the wavelengths (ν_{max}) are reported in cm^{-1}.

Synthesis

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (48). Methyl α-D-glucopyranoside (3) (5.11 g, 26.3 mmol) was dissolved in freshly distilled acetonitrile (100 mL) and the mixture was stirred vigorously under a nitrogen atmosphere. Benzaldehyde dimethyl acetal (7 mL, 46.6 mmol, 1.8 eq.) and 10-camphorsulfonic acid (298 mg, 1.28 mmol, 5%) were added, and the mixture was heated to reflux. After 45 min the reaction mixture was allowed to cool to r.t., neutralized by adding a few drops of triethylamine and concentrated under reduced pressure. The resulting white powder was dissolved in ethyl acetate (250 mL), washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The resulting crystals were mixed with diethyl ether and filtered to remove excess benzaldehyde dimethyl acetal. Methyl 4,6-O-benzylidene-α-D-glucopyranoside (48) was isolated as white crystals (7.43 g, 74%).

R_f (methanol/EtOAc 1:9) 0.55; ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.51–7.34 (5H, m, Ar*H*), 5.53 (1H, s, C*H*Ph), 4.79 (1H, d, $J_{1,2}$ 4.0 Hz, H1), 4.29 (1H, dd, $J_{6eq,5}$ 4.8 Hz, $J_{6eq,6ax}$ 9.8 Hz, H6eq), 3.92 (1H, t, $J_{3,2} = J_{3,4}$ 9.2 Hz, H3), 3.81 (1H, dt, $J_{5,6ax} = J_{5,4}$ 10.4 Hz, $J_{5,6eq}$ 4.5, H5), 3.74 (1H, t, $J_{6ax,6eq} = J_{6ax,5}$ 9.7 Hz, H6ax), 3.62 (1H, bred s, H2), 3.49 (1H, t, $J_{4,5} = J_{4,3}$ 9.2 Hz, H4), 3.44 (3H, s, C*H*$_3$), 2.82 (1H, bs, O*H*), 2.34 (1H, bs, O*H*). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 137.2 (Ar), 129.4, 128.5, 126.6 (Ar), 102.2 (*C*HPh), 100.0 (C1), 81.2 (C4), 73.0 (C2), 71.9 (C3), 69.2 (C6), 62.6 (C5), 55.8 (*C*H$_3$) LRMS (ESI): calcd for C$_{14}$H$_{18}$O$_6$Na 305.0996; found 304.9;

NMR data were in accordance with previously reported values.[41]

Methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (49). NaH (60%, 3.00 g 75.0 mmol, 3.9 eq.) was slowly added to a stirred solution of methyl 4,6-O-benzylidene-α-D-glucopyranoside **48** (5.35 g 19.0 mmol) in DMF (40 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and BnBr (7 mL, 58.9 mmol, 3.1 eq.) was added drop wise under formation of hydrogen gas. The mixture was allowed to slowly heat to r.t. and after 45 min the mixture was diluted with water and diethyl ether and extracted with diethyl ether. The combined organic phases were washed with water, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/ethyl acetate 8:1 → 6:1) to give the benzyl protected compound **49** as white crystals (7.63 g, 87%).

R_f (pentane/ethyl acetate 6:1) 0.39; M_p (uncorr.) 96.8–97.8 °C (lit. 94–95 °C crystalised from MeOH); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.51–7.26 (15H, Ar*H*), 5.55 (1H, s, C*H*Ph), 4.92 (1H, d, J 11.3 Hz, C*H*HPh), 4.86 (1H, d, J 12.1 Hz, C*H*HPh), 4.84 (1H, d, CH*H*Ph) 4.70 (1H, d, CH*H*Ph), 4.60 (1H, d, $J_{1,2}$ 3.6 Hz, H1), 4.27 (1H, dd, $J_{6eq,5}$ 4.8 Hz $J_{6eq,6ax}$ 9.6 Hz,

H6eq), 4.05 (1H, t, $J_{3,2} = J_{3,4}$ 9.4 Hz, H3), 3.82 (1H, dt, $J_{5,6eq}$ 4.6 Hz $J_{5,6ax} = J_{5,4}$ 9.7 Hz, H5), 3.71 (1H, t, $J_{6ax,5} = J_{6ax,6eq}$ 10.2 Hz, H6ax), 3.60 (1H, t, $J_{4,5} = J_{4,3}$ 10.2 Hz, H4), 3.56 (1H, dd, $J_{2,1}$ 3.6 Hz $J_{2,3}$ 10.0 Hz, H2), 3.41 (3H, s, C*H*$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 138.9 (Ar), 138.4 (Ar), 137.6 (Ar), 129.1 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.8 (Ar), 126.2 (Ar), 101.4 (*C*HPh), 99.4 (C1), 82.3 (C4), 79.4 (C2), 78.8 (C3), 75.5 (*C*H$_2$Ph), 73.9 (*C*H$_2$Ph), 69.3 (C6), 62.5 (C5), 55.5 (*C*H$_3$). LRMS (ESI): calcd for C$_{28}$H$_{30}$O$_6$Na 485.1935; found 484.9.

NMR data was in accordance with previously reported values.[41]

Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (50). BH$_3$·THF complex (1 M solution in THF, 80 mL, 80 mmol, 4.9 eq.) was mixed with methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (49) (7.54 g, 16.3 mmol) under a nitrogen atmosphere. The mixture was stirred for 10 min before Cu(OTf)$_2$ (294 mg 0.810 mmol, 5%) was added and the reaction was then allowed to stir overnight. The reaction was quenched by adding triethylamine (2.3 mL) and methanol (29 mL), concentrated under reduced pressure, added additional methanol (25 mL) and concentrated again. Toluene was added and the mixture was concentrated and purified by flash column chromatography (pentane/ethyl acetate 2:1). Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (50) was isolated as white crystals (6.48 g, 86%).

R_f (pentane/ethyl acetate 2:1) 0.29; ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.38–7.27 (15H, m, Ar*H*), 4.99 (1H, d, J 10.8 Hz, C*H*HPh), 4.89 (1H, d, CH*H*Ph), 4.84 (1H, d, J 11.2 Hz, C*H*HPh), 4.81 (1H, d, J 12.0 Hz, C*H*HPh), 4.67 (1H, d, CH*H*Ph), 4.65 (1H, d, CH*H*Ph), 4.58 (1H, d, $J_{1,2}$ 3.6 Hz, H1), 4.01 (1H, t, $J_{3,2} = J_{3,4}$ 9.4 Hz, H3), 3.77 (1H, dd, $J_{6a,5}$ 2.4 Hz, $J_{6a,6b}$ 11.7 Hz, H6a) 3.73–3.63 (2H, m, H6b, H5), 3.53 (1H, t, $J_{4,5} = J_{4,3}$ 9.2 Hz, H4), 3.51 (1H, dd, $J_{2,1}$ 3.6 Hz, $J_{2,3}$ 9.2 Hz, H2), 3.37 (3H, s, C*H*$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 138.8 (Ar), 138.2 (Ar), 138.2 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 128.0 (Ar), 127.9 (Ar), 127.7 (Ar), 98.2 (C1), 82.0 (C3), 80.0 (C2), 76.8 (C4), 75.8 (*C*H$_2$Ph), 75.1 (*C*H$_2$Ph), 73.4 (*C*H$_2$Ph), 70.7 (C5), 61.9 (C6), 55.2 (*C*H$_3$). LRMS (ESI): calcd for C$_{28}$H$_{32}$O$_6$Na 487.2091; found 487.0.

NMR data were in accordance with previously reported values.[41]

Methyl 2,3,4-tri-O-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside (5). Triphenylphosphine (8.88 g, 33.8 mmol, 2.5 eq.), imidazole (1.91 g, 28.0 mmol, 2.1 eq.) and iodine (3.78 g, 14.9 mmol, 1.1 eq.) were added to a solution of methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (50) (6.30 g, 13.6 mmol) in anhydrous toluene (150 mL) under a nitrogen atmosphere. The mixture was heated to reflux for 2 hours, then cooled to r.t. and added 5% aqueous sodium thiosulfate (130 ml). The organic phase was washed with brine, dried over MgSO$_4$ and concentrated. The crude product was purified by flash column chromatography (pentane/ethyl acetate 15:1) to yield the iodide **5** as a white solid (5.35 g, 69%).

R_f (pentane/ethyl acetate 15:1) 0.16; ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.37–7.23 (15H, m, Ar*H*), 4.98 (1H, d, J 10.8 Hz,

CHHPh) 4.93 (1H, d, J 10.9 Hz, CHHPh), 4.80 (1H, d, J 10.8 Hz, CHHPh) 4.79 (1H, d, J 12.2 Hz, CHHPh), 4.68 (1H, d, J 9.1 Hz, CHHPh), 4.65 (1H, d, J 10.2 Hz, CHHPh), 4.62 (1H, d, $J_{1,2}$ 2.6 Hz, H1), 4.02 (1H, t, $J_{3,2} = J_{3,4}$ 9.6 Hz, H3), 3.58 (1H, dd, $J_{2,1}$ 3.6 Hz $J_{2,3}$ 9.6 Hz, H2), 3.49–3.42 (2H, m, H5, H6a), 3.42 (3H, s, CH_3), 3.36–3.26 (2H, m, H4, H6b). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 138.7 (Ar), 138.2 (Ar), 138.1 (Ar), 128.7 (Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar), 128.2 (Ar), 128.1 (Ar), 127.9 (Ar), 98.3 (C1), 81.7 (C4), 81.6 (C3), 80.3 (C2), 75.9 (CH$_2$Ph), 75.5 (CH$_2$Ph), 73.6 (CH$_2$Ph), 69.5 (C5), 55.6 (CH$_3$), 7.9 (C6). LRMS (ESI): calcd for C$_{28}$H$_{31}$O$_5$INa 597.1108; found 596.6.

NMR data was in accordance with previously reported values.[42]

(2R,3S,4R)-2,3,4-Tri-O-benzylhex-5-enal (7). Pre-activated Zn dust‡ (6.42 g, 98.2 mmol, 11 eq.) and water (25 mL) were added to a solution of the iodide **5** (5.14 g, 8.95 mmol) in THF (230 mL). The mixture was sonicated at 40 °C for 1 h 35 min, then diluted with water and diethyl ether and filtered through a pad of Celite®. The organic phase was washed with water and brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to yield the aldehyde **7** (3.67 g) without further purification.

R_f (pentane/ethyl acetate 1:5) 0.74; ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 9.61 (1H, s, CHO), 7.33–7.18 (15H, m, ArH), 5.79 (1H, ddd, $J_{5,4}$ 7.61 Hz, $J_{5,6Z}$ 11.0 Hz, $J_{5,6E}$ 16.7 Hz, H5), 5.24 (1H, d, $J_{6Z,5}$ 11.0 Hz, H6Z), 5.23 (1H, d, $J_{6E,5}$ 16.6 Hz, H6E), 4.68 (1H, d, J 11.7 Hz, CHHPh), 4.67 (d, J 11.8 Hz, 1H, CHHPh) 4.54 (1H, d, CHHPh), 4.50 (1H, d, J 11.5 Hz, CHHPh), 4.45 (1H, d, CHHPh), 4.33 (1H, d, CHHPh), 4.11 (1H, dd, $J_{4,5}$ 7.6 Hz, $J_{4,3}$ 5.0 Hz, H4), 3.84 (1H, dd, $J_{2,3}$ 4.2 Hz, $J_{2,1}$ 0.6 Hz, H2), 3.76 (1H, t, $J_{3,2} = J_{3,4}$ 4.6 Hz, H3). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 201.7 (CHO), 137.9 (Ar), 137.8 (Ar), 137.3 (Ar), 134.9 (C5), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.7 (Ar), 119.5 (C6), 82.6 (C4), 82.0 (C3), 80.0 (C2), 74.7 (CH$_2$Ph), 73.4 (CH$_2$Ph), 71.1 (CH$_2$Ph). HRMS (ESI): calcd for C$_{27}$H$_{28}$O$_4$Na 439.1880; found 439.1885.

NMR data was in accordance with previously reported values.[43]

(3R,4S,5S,6R/S)-3,4,5-Tri-O-benzyl-6-hydroxy-1,8-nonadiene (8). Indium dust (1.96 g, 17.1 mmol, 1.9 eq.) and allyl bromide (2.3 mL, 27.1 mmol, 3 eq.) were added to a stirred solution of the crude aldehyde **7** (3.67 g, 8.81 mmol) in 50% aqueous THF (64 mL). The reaction was stirred overnight at r.t. after which sat. aq. NH$_4$Cl was added to the reaction mixture and the aqueous phase was neutralized with sat. aq. NaHCO$_3$. The resulting mixture was extracted with dichloromethane and the combined organic phases dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/ethyl acetate 11:1) to give the diene **8** as an oil (3.13 g, 76% over 2 steps).

According to NMR the product was a 2:3 mixture of *R*- and *S*-diastereoisomers.

R_f (pentane/ethyl acetate 11:1) 0.19, ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.43–7.21 (48.7H, m, ArH), 6.03–5.74 (3.9H, m), 5.67 (1.9H, ddt, J 17.4 Hz, J 10.6, J 7.0 Hz), 5.38–5.24 (6.1H, m), 5.10–4.99 (6.1H, m), 4.83 (3.2H, dd, J 11.3 Hz, J 15.3 Hz), 4.72 (3.2H, d, J 11.1 Hz), 4.68–4.51 (9.8H, m), 4.37 (3.1H, dd, J 23.1 Hz, J 11.8 Hz), 4.19 (1H, dd, J 7.6 Hz, J 5.5 Hz), 4.02 (2.3H, dd, J 3.6 Hz, J 7.4 Hz), 3.87 (1H, bs), 3.80–3.72 (3.2H, m), 3.65 (2.1H, dd, J 2.2 Hz, J 7.5 Hz), 3.60–3.49 (3.6H, m), 2.89 (0.8H, bs), 2.39–2.10 (7.7H, m); ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 138.7, 138.5, 138.4, 138.2, 138.1, 138.0, 135.5, 135.5, 135.3, 135.1, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.7, 119.1, 118.9, 117.4, 82.5, 81.4, 81.1, 80.9, 80.1, 79.6, 75.3, 75.1, 74.5, 73.0, 70.9, 70.6, 70.5, 70.4, 39.1, 38.2. HRMS (ESI): calcd for C$_{29}$H$_{32}$O$_4$Na 481.2346; found 481.2356.

(3R,4S,5S,6R)-6-O-Acetyl-3,4,5-tri-O-benzyl-1,8-nonadiene(9R) and (3R,4S,5S,6S)-3,4,5-tri-O-benzyl-6-O-acetyl-1,8-nonadiene (9S). The alcohol **8** (1.09 g, 2.39 mmol) was dissolved in anhydrous dichloromethane under a nitrogen atmosphere before Ac$_2$O (0.41 mL, 4.34 mmol, 1.8 eq.), Et$_3$N (0.66 mL, 4.74 mmol, 2 eq.) and DMAP (27.7 mg, 0.23 mmol, 0.09 eq.) were added. The mixture was allowed to stir overnight after which a small amount of DMAP was added. After stirring for additional 2 h the reaction was quenched by adding methanol and diluted with dichloromethane. The organic phase was washed with 1 M aq. HCl and sat. aq. NaHCO$_3$, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/ethyl acetate 25:1) yielding the *R* (**9R**) and *S* (**9S**) isomers of the product (1.02 g, 85%) which could be partly separated.

9S: colourless oil (0.550 g, 46%), R_f (pentane/ethyl acetate 11:1) 0.45; $[\alpha]_D^{293K}$ −14.4 (*c* 1, CHCl$_3$); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.34–7.26 (15H, m, ArH), 5.91 (1H, ddd, $J_{2,3}$ 7.7 Hz, $J_{2,1Z}$ 10.3 Hz, $J_{2,1E}$ 16.7 Hz, H2), 5.65 (1H, m, H8) 5.33 (1H, dd, $J_{1Z,1E}$ 1.1 Hz, H1Z), 5.30 (1H, dd, H1E), 5.21 (1H, dt, $J_{6,7a} = J_{6,5}$ 3.5 Hz, $J_{6,7b}$ 9.1 Hz, H6), 4.99 (1H, dt, $J_{9E,8}$ 16.1 Hz $J_{9E,7a} = J_{9E,7b}$ 1.6 Hz, H9E) 4.98 (1H, dt, $J_{9Z,8}$ 10.3 Hz $J_{9Z,7a} = J_{9Z,7b}$ 0.94 Hz, H9Z), 4.75 (1H, d, J 11.2 Hz, CHHPh), 4.71 (1H, d, J 11.4 Hz, CHHPh), 4.66 (1H, d, CHHPh), 4.61 (2H, d, J 12.2 Hz, CHHPh, CHHPh) 4.36 (1H, d, CHHPh), 4.06 (1H, dd, $J_{4,3}$ 5.6 Hz, H3), 3.76 (1H, dd, $J_{5,4}$ 5.6 Hz, H5), 3.62 (1H, t, H4), 2.48 (2H, m, H7), 1.98 (1H, s, CH_3). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_H 170.1 (C=O), 138.1 (Ar), 138.3 (Ar), 138.6 (Ar), 134.8 (C8/C2), 134.4 (C2/C8), 128.2 (Ar), 128.2 (Ar), 127.9 (Ar), 127.7 (Ar), 127.5 (Ar), 127.5 (Ar), 127.4 (Ar), 119.4 (C1), 117.1 (C9), 81.8 (C3), 81.1 (C5), 80.5 (C4), 74.7 (CH$_2$Ph), 74.1 (CH$_2$Ph), 73.9 (C6), 70.7 (CH$_2$Ph), 34.0 (C7), 21.0 (CH$_3$). HRMS (ESI): calcd for C$_{32}$H$_{36}$O$_5$Na 523.2455; found 523.2466.

9R: colourless oil (0.250 g, 21%), R_f (pentane/ethyl acetate 11:1) 0.31; $[\alpha]_D^{293K}$ −9.2 (*c* 1, CHCl$_3$); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.36–7.25 (15H, m, ArH), 5.97–5.83 (1H, m, H2), 5.58–5.42 (1H, m, H8), 5.28 (1H, bs, H1a), 5.27 (1H, ddd, J 6.8 Hz, J 1.8 Hz, J 0.9 Hz, H1b), 4.99–4.96 (1H, m, H9Z),

‡Zinc dust (1.01 g) was mixed with 1 M HCl (10 mL) and stirred at r.t for 30 min. The mixture was then filtered and the zinc dust was washed with water and diethyl ether. At last the zinc dust was dried under high vacuum with a heat gun.

4.96–4.92 (1H, m, H9E), 4.90 (1H, ddd, $J_{6,7b}$ 3.7 Hz, $J_{6,7a}$ 5.8 Hz, $J_{6,5}$ 7.4 Hz, H6), 4.82 (1H, d, J 11.5 Hz, CHHPh), 4.76 (1H, d, J 11.3 Hz, CHHPh), 4.69 (1H, d, CHHPh), 4.64 (1H, d, J 11.9 Hz, CHHPh), 4.63 (1H, d, CHHPh), 4.31 (1H, d, CHHPh), 3.97 (1H, dd, $J_{3,2}$ 4.1 Hz, $J_{3,4}$ 7.5 Hz, H3), 3.79 (1H, dd, $J_{5,4}$ 3.9 Hz, H5), 3.55 (1H, dd, H4), 2.29–2.19 (2H, m, H7), 1.98 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ_C 170.4 (C=O), 138.5 (Ar), 138.2 (Ar), 138.0 (Ar), 135.5 (C2/C8), 133.6 (C8/C2), 128.3 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.7 (Ar), 127.6 (Ar), 127.6 (Ar), 118.7 (C1), 117.7 (C9), 81.6 (C4), 79.8 (C3), 78.8 (C5), 74.9 (CH₂Ph), 74.8 (CH₂Ph), 72.6 (C6), 70.5 (CH₂Ph), 35.5 (C7), 21.0 (CH₃). HRMS (ESI): calcd for C₃₂H₃₆O₅Na 523.2455; found 523.2463.

(3R,4S,5S,6S)-6-O-Acetyl-3,4,5-tri-O-benzyl-cycloheptene **(10)** *and (3R,4S,5S,6R)-6-O-acetyl-3,4,5-tri-O-benzyl-cycloheptene* **(11)**. The diene **9** (2.98 g, 5.94 mmol) was dissolved in anhydrous toluene (21 mL) under a nitrogen atmosphere. Grubbs–Hoveyda 2ⁿᵈ generation catalyst (75 mg, 0.12 mmol, 2%) was added to the reaction flask, which was immediately put in a preheated 80 °C oil bath. The mixture was stirred for 1 h 30 min, cooled down to r.t. and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/ethyl acetate 15 : 1) to give the cycloheptenes **10** and **11** (2.04 g, 73%) as a slightly yellow oil.

(3R,4S,5S,6S)-6-O-Acetyl-3,4,5-tri-O-benzyl-cycloheptene **(10)**. R_f (pentane/ethyl acetate 5 : 1) 0.56; $[\alpha]_D^{293K}$ −6.4 (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃): δ_H 7.37–7.26 (15H, m, ArH), 5.70 (1H, dd, $J_{2,1}$ 11.8 Hz, $J_{2,3}$ 1.0 Hz, H2), 5.62 (1H, dt, $J_{1,7a} = J_{1,7b}$ 5.5 Hz, $J_{1,2}$ 11.8 Hz, H1), 5.33 (1H, ddd, $J_{6,7b/5}$ 1.6 Hz, $J_{6,7b/5}$ 3.0 Hz, $J_{6,7a}$ 9.8 Hz, H6), 4.77 (1H, d, J 11.1 Hz, CHHPh), 4.69 (2H, s, CH₂Ph), 4.66 (2H, s, CH₂Ph), 4.63 (1H, d, CHHPh), 4.30 (1H, d, $J_{5,4}$ 9.2 Hz, H5), 3.79 (1H, dd, $J_{3,4}$ 4.7 Hz, H3), 3.74 (1H, dd, H4), 2.62 (1H, ddd, $J_{7a,7b}$ 16.7 Hz, H7a), 2.35 (1H, d, $J_{7b,7a}$ 16.7 Hz, H7b), 2.04 (3H, s, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ_C 170.1 (C=O), 138.6 (Ar), 138.5 (Ar), 138.3 (Ar), 131.2 (C2), 128.3 (Ar), 128.3 (Ar), 128.0 (Ar), 127.9 (Ar), 127.6 (Ar), 127.5 (Ar), 126.0 (C1), 83.3 (C4), 82.6 (C3), 79.0 (C5), 74.2 (CH₂Ph), 72.8 (CH₂Ph), 73.1 (CH₂Ph), 71.2 (C6), 29.6 (C7), 21.2 (CH₃). HRMS (ESI): calcd for C₃₀H₃₂O₅Na 495.2142; found 495.2154.

(3R,4S,5S,6R)-6-O-Acetyl-3,4,5-tri-O-benzyl-cycloheptene **(11)**. R_f (pentane/ethyl acetate 11 : 1) 0.33; $[\alpha]_D^{293K}$ −2.9 (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃): δ_H 7.36–7.21 (m, 15H, ArH), 5.84 (ddd, $J_{2,1}$ 11.3 Hz, $J_{2,3}$ 3.6 Hz, J 1.6 Hz, 1H, H2), 5.76–5.66 (m, 1H, H1), 4.95 (ddd, $J_{6,7b}$ 10.0 Hz, $J_{6,5}$ 7.2 Hz, $J_{6,7a}$ 2.8 Hz, 1H, H6), 4.87 (d, J 10.6 Hz, 1H, CHHPh), 4.82 (d, J 11.3 Hz, 1H, CHHPh), 4.69 (d, J 10.7 Hz, 2H, 2 × CHHPh), 4.68 (d, J 11.5 Hz, 2H, 2 × CHHPh), 4.20 (m, 1H, H4), 3.70–3.58 (m, 2H, H5, H3), 2.37 (ddd, $J_{7a,7b}$ 15.6 Hz, $J_{7a,1}$ 6.6 Hz, 1H, H7a), 2.32–2.22 (m, 1H, H7b), 1.93 (s, 3H, CH₃). ¹³C-NMR (100 MHz, CDCl₃): δ_C 170.1 (C=O), 138.8 (Ar), 138.7 (Ar), 138.6 (Ar), 134.0 (C2), 128.4 (Ar), 128.4 (Ar), 128.2 (Ar), 127.8 (Ar), 127.6 (Ar), 127.6 (Ar), 127.6 (Ar), 125.3 (C1), 85.8 (C5/C3), 84.3 (C5/C3), 77.9 (C4), 75.8 (CH₂Ph), 75.3 (CH₂Ph), 73.0 (CH₂Ph), 72.7 (C6), 29.4 (C7), 21.3 (CH₃). HRMS (ESI): calcd for C₃₀H₃₂O₅Na 495.2142; found 495.2146.

(3R,4S,5S,6S/R)-3,4,5-Tri-O-benzyl-6-hydroxy-cycloheptene **(51)**. The acetyl protected compounds (**10** and **11**) (2.62 g, 5.54 mmol) was dissolved in anhydrous methanol (86 mL) under a nitrogen atmosphere. Sodium (52 mg) was added and the mixture was stirred for 6 h 20 min. The mixture was then concentrated under reduced pressure, added toluene and concentrated again. The crude product (**51**) was used directly in the next step without further purification.

(3R,4S,5S,6S)-3,4,5-Tri-O-benzyl-6-hydroxy-cycloheptene **(51S)**. R_f (pentane/ethyl acetate 5 : 1) 0.25; $[\alpha]_D^{293K}$ +2.1 (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃): δ_H 7.37–7.25 (15H, m, ArH), 5.81 (1H, ddd, $J_{2,3}$ 1.5 Hz, $J_{2,7}$ 3.2 Hz, $J_{2,1}$ 11.5 Hz, H2), 5.72 (1H, ddt, $J_{1,7a}$ 1.9 Hz, $J_{1,7b}$ = $J_{1,3}$ 5.7 Hz, H1), 4.92 (1H, d, J 10.8 Hz, CHHPh), 4.85 (1H, d, J 11.5 Hz, CHHPh), 4.70 (1H, d, CHHPh), 4.70 (2H, s, CH₂Ph), 4.66 (1H, d, CHHPh), 4.16 (1H, ddd, $J_{3,4}$ 9.1 Hz, H3), 4.06 (1H, d, $J_{6,7a}$ 8.4 Hz, H6), 3.78 (1H, dd, $J_{4,5}$ 7.2 Hz, H4), 3.67 (1H, dd, $J_{5,6}$ 3.2 Hz, H5), 2. 63 (1H, bs, OH), 2.52 (1H, ddt, $J_{7a,7b}$ 16.5 Hz, H7a), 2.19 (1H, dd, H7b). ¹³C-NMR (100 MHz, CDCl₃): δ_C 138.8 (Ar), 138.5 (Ar), 138.5 (Ar), 132.3 (C2), 128.6 (Ar), 128.5 (Ar), 128.2 (Ar), 128.0 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.0 (C1), 85.2 (C5), 82.6 (C4), 75.3 (CH₂Ph), 78.6 (C3), 74.1 (CH₂Ph), 72.9 (CH₂Ph), 69.0 (C6), 31.4 (C7). HRMS (ESI): calcd for C₂₈H₃₀O₄Na 453.2036; found 453.2044.

(3R,4S,5S,6R)-3,4,5-Tri-O-benzyl-6-hydroxy-cycloheptene **(51R)**. R_f (pentane/ethyl acetate 5 : 1) 0.36; ¹H-NMR (400 MHz, CDCl₃): δ_H 7.45–7.29 (m, 15H, ArH), 5.91–5.82 (m, 2H, H1, H2), 5.08 (d, J 11.3 Hz, 1H, CHHPh), 4.99 (d, J 10.7 Hz, 1H, CHHPh), 4.78 (d, 1H, CHHPh), 4.74 (s, 2H, CH₂Ph), 4.69 (d, 1H, CHHPh), 4.23 (d, J 8.8 Hz, 1H, H3), 3.67–3.56 (m, 2H, H4 + H6), 3.48 (dd, J 18.1 Hz, J 9.8 Hz, 1H, H5), 2.50–2.37 (m, 1H, H7a), 2.29–2.11 (m, 1H, H7b). ¹³C-NMR (100 MHz, CDCl₃): δ_C 138.6 (Ar), 138.4 (Ar), 138.4 (Ar), 133.7 (C2), 128.6 (Ar), 128.3 (Ar), 128.0 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.5 (Ar), 127.5 (Ar), 126.8 (C1), 89.3 (C5), 83.4 (C4/C6), 78.4 (C3), 75.9 (CH₂Ph), 75.4 (CH₂Ph), 72.7 (CH₂Ph), 70.6 (C4/C6), 31.1 (C7). HRMS (ESI): calcd for C₂₈H₃₀O₄Na 453.2036; found 453.2044.

(3R,4S,5S,6S/R)-3,4,5-Tri-O-benzyl-6-O-p-methoxybenzyl-cyclo-heptene **(12)**. NaH (60%, 0.454 g, 18.92 mmol, 2 eq.) and PMBCl (1.5 mL, 11.05 mmol, 2 eq.) were added to a cooled (0 °C) and stirred solution of the crude alcohol (**51**) (5.54 mmol) in anhydrous DMF (27 mL) under a nitrogen atmosphere. The reaction mixture was heated to r.t. and stirred overnight. The next day more NaH was added. After 20 min the reaction mixture was quenched by addition of *n*-butylamine, diluted with EtOAc, washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/ethyl acetate 14 : 1) yielding the PMB ether (**12**) (1.75 g, 57% over 2 steps).

(3R,4S,5S,6S)-3,4,5-Tri-O-benzyl-6-O-p-methoxybenzyl-cyclohep-tene **(12S)**. R_f (pentane/ethyl acetate 14 : 1) 0.23; $[\alpha]_D^{293K}$ −6.8 (c 1, CHCl₃); ¹H-NMR (400 MHz, CDCl₃): δ_H 7.38–7.25 (15H, m, ArH), 7.24–7.20 (2H, m, ArH from PMB), 6.87–6.82 (2H, m, ArH from PMB), 5.69–5.56 (2H, m, H1, H2), 4.76–4.59 (5H, m, CHHAr), 4.54 (1H, d, J 11.2, CHHAr), 4.45 (2H, s, CH₂Ar), 4.21

(1H, d, $J_{3,4}$ 9.2 Hz, H3), 3.94 (1H, ddd, $J_{6,5}$ 1.0 Hz, $J_{6,7}$ 3.8 Hz, $J_{6,7}$ 10.0 Hz, H6), 3.88 (1H, dd, $J_{5,4}$ 3.8 Hz, H5), 3.8 (3H, s, CH_3), 3.74 (1H, dd, H4), 2.61–2.51 (1H, m, H7a), 2.37 (1H, d, $J_{7b,7a}$ 18.0, H7b). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 159.1 (Ar), 158.4 (Ar from PMB), 128.9 (Ar), 128.7 (Ar), 132.0 (Ar), 130.6 (C1/C2), 129.9 (Ar), 129.8 (Ar), 129.1 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 127.4 (C1/C2), 127.0 (Ar), 113.7 (Ar from PMB), 113.5 (Ar from PMB), 84.1 (C4), 82.0 (C5), 79.3 (C3), 76.0 (C6), 73.7 (CH_2Ar), 73.2 (CH_2Ar), 72.5 (CH_2Ar), 70.6 (CH_2Ar), 57.4 (C7), 55.2 (CH_3). HRMS (ESI): calcd for C$_{36}$H$_{38}$O$_5$Na 573.2611; found 573.2619.

(3R,4S,5S,6R)-3,4,5-Tri-O-benzyl-6-O-p-methoxybenzyl-cyclohept-ene (12R). R_f (pentane/ethyl acetate 13 : 1) 0.33; $[\alpha]_D^{293K}$ −4.1 (*c* 1, CHCl$_3$); M_p (uncorr.) 73.8–78.4 °C; ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.31–7.19 (15H, m, Ar*H*), 7.19–7.14 (2H, m, Ar*H* from PMB), 6.85–6.76 (2H, m, Ar*H* from PMB), 5.79 (1H, ddd, $J_{2,1}$ 11.4 Hz, $J_{2,7}$ 3.5 Hz, $J_{2,3}$ 1.0 Hz, H2), 5.65 (1H, dtd, $J_{1,7}$ 6.1 Hz, *J* 2.0 Hz, H1), 4.85 (1H, d, *J* 10.8 Hz, C*H*HAr), 4.76 (1H, d, *J* 11.0 Hz, C*H*HAr), 4.73 (1H, d, CH*H*Ar), 4.70 (1H, d, CH*H*Ar), 4.70 (1H, d, *J* 12.1 Hz, C*H*HAr), 4.63 (1H, d, CH*H*Ar), 4.48 (2H, s, C*H$_2$*Ar), 4.26 (1H, dd, $J_{3,4}$ 8.9 Hz, H3), 3.76 (3H, s, CH_3), 3.72–3.60 (2H, m, H4, H5), 3.55 (1H, ddd, *J* 8.7 Hz, *J* 6.4 Hz, *J* 2.4 Hz, H6), 2.39 (1H, dd, $J_{7a,7b}$ 15.9 Hz, $J_{7a,1}$ 6.2 Hz, H7a), 2.32–2.21 (1H, m, H7b). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 159.2 (Ar from PMB), 139.1 (Ar), 138.8 (Ar), 133.4 (C2), 130.7 (Ar), 129.4 (Ar), 128.4 (Ar), 128.4 (Ar), 128.1 (Ar), 127.9 (Ar), 127.9 (Ar), 127.6 (Ar), 125.9 (C1), 113.9 (Ar from PMB), 87.0 (C4/C5), 84.6 (C4/C5), 78.7 (C6), 78.2 (C3), 75.6 (CH_2Ar), 75.2 (CH_2Ar), 73.1 (CH_2Ar), 71.7 (CH_2Ar), 55.4 (CH_3), 29.3 (C7). HRMS (ESI): calcd for C$_{36}$H$_{38}$O$_5$Na 573.2611; found 573.2617.

(2R,3S,4S,5S/R)-2,3,4-tri-O-benzyl-5-O-p-methoxybenzyl-cyclo-heptane-1-ol (13) and *(3R,4S,5S,6S/R)-3,4,5-tri-O-benzyl-6-O-p-methoxybenzyl-cycloheptane-1-ol (14).* The alkene 12 (1.75 g, 3.17 mmol) was dissolved in anhydrous THF (61 mL) and BH$_3$·THF complex (1 M solution in THF, 12.7 mL, 12.7 mmol, 4 eq.) was added drop wise at 0 °C under a nitrogen atmosphere. After stirring for 1 h 10 min more BH$_3$·THF complex (2 mL) was added. After additional 1 h 45 min the reaction was added 2 M NaOH (6.5 mL) and 35% aqueous H$_2$O$_2$ (13 mL) and the reaction was allowed to stir at r.t. for additional 3 h 15 min. The mixture was then diluted with diethyl ether and the organic phase was washed with water and brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/ethyl acetate 4 : 1) to give the two regioisomers 13 (830 mg, 46%) and 14 (340 mg, 19%) which were easily separated.

(2R,3S,4S,5S)-2,3,4-Tri-O-benzyl-5-O-p-methoxybenzyl-cyclohep-tane-1-ol (13S). Oil; R_f (pentane/ethyl acetate 4 : 1) 0.17; $[\alpha]_D^{293K}$ +12.8 (*c* 1, CHCl$_3$); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.38–7.22 (15H, m, Ar*H*), 7.22–7.18 (2H, m, Ar*H* from PMB), 6.87–6.82 (2H, m, Ar*H* from PMB), 4.77 (1H, d, *J* 12.2 Hz, C*H*HAr), 4.75 (1H, d, *J* 11.2 Hz, C*H*HAr), 4.63 (1H, d, CH*H*Ar), 4.54 (1H, d, CH*H*Ar), 4.47 (2H, s, C*H$_2$*Ar), 4.44 (1H, d, *J* 11.8 Hz, C*H*HAr), 4.38 (1H, d, CH*H*Ar), 3.98 (1H, dd, *J* 2.3 Hz, *J* 9.6 Hz, H1/H5), 3.96 (1H, dd, *J* 8.3 Hz, *J* 4.2 Hz, H4/H2), 3.82 (1H,

dd, *J* 4.8 Hz, *J* 4.1 Hz, H3), 3.79 (3H, s, CH_3) 3.62 (1H, dd, *J* 10.8 Hz, *J* 3.3 Hz, H5/H1), 3.32 (1H, dd, *J* 9.5 Hz, *J* 4.9 Hz, H2/H4), 2.82 (1H, bs, O*H*), 2.13–1.99 (2H, m, H6a, H7a), 1.86–1.77 (1H, m, H6b/H7b), 1.50–1.37 (1H, m, H6b/H7b). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 159.14 (Ar from PMB), 138.7 (Ar), 138.2 (Ar), 138.0 (Ar), 130.8 (Ar), 129.1 (Ar), 128.6 (Ar), 128.6 (Ar), 128.4 (Ar), 127.9 (Ar), 127.8 (Ar), 127.6 (Ar), 113.8 (Ar from PMB), 89.3 (C2/C4), 82.8 (C3), 78.7 (C1/C5), 78.03 (C2/C4), 74.22 (CH_2Ar), 72.84 (CH_2Ar), 72.32 (CH_2Ar), 70.72 (CH_2Ar), 69.44 (C1/C5), 53.3 (CH_3), 31.0 (C6/C7), 24.8 (C6/C7). HRMS (ESI): calcd for C$_{36}$H$_{40}$O$_6$Na 591.2717; found 591.2715.

(2R,3S,4S,5R)-2,3,4-Tri-O-benzyl-5-O-p-methoxybenzyl-cyclohep-tane-1-ol (13R). Colourless oil; R_f (pentane/ethyl acetate 4 : 1) 0.42; $[\alpha]_D^{293K}$ +20.4 (*c* 1, CHCl$_3$); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.30–7.18 (m, 15H, Ar*H*), 7.14 (d, *J* 8.3, 2H, Ar*H* from PMB), 6.79–6.73 (m, 2H, Ar*H* from PMB), 4.69–4.52 (m, 5H, C*H$_2$*Ar), 4.51–4.42 (m, 2H, C*H$_2$*Ar), 4.37 (d, *J* 10.9 Hz, 1H, C*H$_2$*Ar), 4.11–4.01 (m, 1H, H1/H5), 3.99 (dt, *J* 6.7 Hz, *J* 3.3 Hz, 1H, H1/H5), 3.95–3.89 (m, 1H, H2/H4), 3.82 (dd, *J* 6.8 Hz, *J* 2.6 Hz, 1H, H3), 3.77 (dd, *J* 7.4 Hz, *J* 2.5 Hz, 1H, H2/H4), 3.74 (s, 3H, CH_3), 2.12–1.94 (m, 4H, H6/H7). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 159.3 (Ar from PMB), 138.8 (Ar), 138.7 (Ar), 138.5 (Ar), 130.3 (Ar), 129.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.0 (Ar), 127.9 (Ar), 127.9 (Ar), 127.7 (Ar), 127.7 (Ar), 127.5 (Ar), 113.9 (Ar from PMB), 84.2 (C2/C4), 81.6 (C3), 78.8 (C2/C4), 77.0 (C1/C5), 73.3 (CH_2Ar), 72.7 (CH_2Ar), 72.0 (CH_2Ar), 71.7 (CH_2Ar), 67.0 (C1/C5), 55.4 (CH_3), 36.6 (C6/C7), 35.8 (C6/C7). HRMS (ESI): calcd for C$_{36}$H$_{40}$O$_6$Na 591.2717; found 591.2710.

(3R,4S,5S,6S)-3,4,5-Tri-O-benzyl-6-O-p-methoxybenzyl-cyclo-heptane-1-ol (14S). Oil; R_f (pentane/ethyl acetate 4 : 1) 0.06; $[\alpha]_D^{293K}$ −0.9 (*c* 1, CHCl$_3$); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.37–7.25 (15H, m, Ar*H*), 7.23–7.19 (2H, m, Ar*H* from PMB), 6.87–6.82 (2H, m, Ar*H* from PMB), 4.68 (1H, d, *J* 12.2 Hz, C*H*HAr), 4.61 (1H, d, *J* 11.6 Hz, C*H*HAr), 4.61 (1H, d, CH*H*Ar) 4.61 (2H, s, C*H$_2$*Ar), 4.55 (1H, d, CH*H*Ar), 4.42 (2H, s, C*H$_2$*Ar), 4.18 (1H, bd, *J* 4.1 Hz, H1), 3.94 (1H, dd, *J* 7.3 Hz, *J* 9.5 Hz, H3/H6) 3.90 (1H, d, *J* 2.5 Hz, H5/H4), 3.85 (1H, dd, *J* 2.7 Hz, *J* 11.5 Hz, H6/H3), 3.80 (3H, s, CH_3), 3.73 (1H, dd, *J* 7.1 Hz, *J* 2.7 Hz, H4/H5), 2.38 (1H, ddd, *J* 14.8 Hz, *J* 11.6 Hz, *J* 4.0 Hz, H7a/H2a), 2.17 (1H, ddd, *J* 1.3 Hz, *J* 11.0 Hz, *J* 14.3 Hz, H2a/H7a), 1.94 (1H, dd, *J* 14.3 Hz, *J* 6.0 Hz, H2b/H7b), 1.84 (1H, d, *J* 14.2 Hz, H7b/H2b). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 159.1 (Ar from PMB), 138.9 (Ar), 138.7 (Ar), 138.6 (Ar), 130.8 (Ar), 129.2 (Ar), 128.4 (Ar), 128.4 (Ar), 128.3 (Ar), 127.9 (Ar), 127.9 (Ar), 127.7 (Ar), 127.5 (Ar), 113.8 (Ar from PMB), 83.5 (C4/C5), 79.8 (C5/C4), 77.4 (C6/C3), 74.5 (C3/C6), 72.7 (CH_2Ar), 72.4 (CH_2Ar), 71.9 (CH_2Ar), 70.9 (CH_2Ar), 65.1 (C1), 55.3 (CH_3), 37.2 (C2/C7), 35.6 (C7/C2). HRMS (ESI): calcd for C$_{36}$H$_{40}$O$_6$Na 591.2717; found 591.2726.

(3R,4S,5S,6R)-3,4,5-Tri-O-benzyl-6-O-p-methoxybenzyl-cyclohep-tane-1-ol (14R). Colourless oil; R_f (pentane/ethyl acetate 4 : 1) 0.14; $[\alpha]_D^{293K}$ +1.0 (*c* 1, CHCl$_3$); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.35–7.15 (m, 18H, Ar*H*), 6.82 (2H, m, Ar*H* from PMB), 4.92 (1H, d, *J* 11.1 Hz, C*H*HAr), 4.72 (1H, d, *J* 11.2 Hz, C*H*HAr), 4.65 (1H, d, CH*H*Ar), 4.59 (1H, d, *J* 11.5 Hz, C*H*HAr), 4.54 (1H, d, CH*H*Ar), 4.53 (1H, d, CH*H*Ar) 4.48 (1H, d, *J* 11.5 Hz, C*H*HAr),

4.44 (1H, d, CH*H*Ar), 3.76 (3H, s, C*H₃*), 3.76–3.72 (2H, m), 3.70 (1H, d, *J* 8.3 Hz) 3.65 (1H, dd, *J* 8.4 Hz, *J* 4.4 Hz), 3.63–3.58 (1H, m), 1.92–1.81 (2H, m, H2/H7), 1.81–1.71 (2H, m, H2/H7). ^{13}C-NMR (100 MHz, CDCl₃): δ_C 159.2 (Ar from PMB), 138.6 (Ar), 138.5 (Ar), 138.5 (Ar), 130.7 (Ar), 129.2 (Ar), 128.6 (Ar), 128.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.7 (Ar), 113.8 (Ar from PMB), 84.8, 83.9, 83.0, 77.4, 75.5 (*CH₂*Ar), 74.5 (*CH₂*Ar), 73.1 (*CH₂*Ar), 71.7, 70.8 (*CH₂*Ar), 55.4 (*CH₂*Ar), 27.3 (C2/C7), 22.8 (C2/C7). HRMS (ESI): calcd for C₃₆H₄₀O₆Na 591.2717; found 591.2718.

(2S,3R,4S,5S/R)-2,3,4-Tri-O-benzyl-5-p-methoxybenzyl-cyclohep-tanon (15). The alcohol **13** (830 mg, 1.46 mmol) was dissolved in dichloromethane (45 mL) and Dess–Martin periodinane (1.24 g, 2.93 mmol, 2 eq.) was added. The mixture was stirred for 40 min after which it was quenched by adding Na₂S₂O₃ (s) and sat. aq. NaHCO₃. The mixture was allowed to stir for 35 min and was then extracted with dichloromethane, dried over MgSO₄, filtered and concentrated under reduced pressure giving the ketone **15** (919 mg). The crude product was used directly in the next step without further purification.

(2S,3R,4S,5S)-2,3,4-Tri-O-benzyl-5-p-methoxybenzyl-cycloheptanon (15S). R_f (pentane/ethyl acetate 4 : 1) 0.26; $[\alpha]_D^{293K}$ −15.3 (*c* 1, CHCl₃); ^{1}H-NMR (400 MHz, CDCl₃): δ_H 7.36–7.20 (13H, m, Ar*H*), 7.18–7.12 (4H, m, Ar*H*), 6.83–6.78 (2H, m, Ar*H* from PMB), 4.77 (1H, d, *J* 11.9 Hz, C*H*HAr), 4.65 (1H, d, *J* 12.3 Hz, C*H*HAr), 4.57 (1H, d, *J* 11.9 Hz, CH*H*Ar), 4.51 (1H, d, CH*H*Ar), 4.44–4.37 (4H, m, C*H₂*Ar), 4.08 (1H, d, $J_{2,3}$ 3.7 Hz, H2) 3.92–3.84 (3H, m, H3, H4, H5), 3.76 (3H, s, C*H₃*), 2.54 (1H, ddd, $J_{7a,6a}$ 4.5 Hz, $J_{7a,6b}$ 7.3 Hz, $J_{7a,7b}$ 13.2 Hz, H7a), 2.31 (1H, ddd, $J_{7b,6b}$ 4.9 Hz, $J_{7b,6a}$ 10.4 Hz, H7b), 2.08 (1H, ddt, $J_{6a,5}$ 10.4 Hz, $J_{6a,6b}$ 14.0 Hz, H6a), 1.84 (1H, ddt, $J_{6b,5}$ 7.3 Hz, H6b). ^{13}C-NMR (100 MHz, CDCl₃): δ_C 206.7 (*C*=O), 159.3 (Ar from PMB), 138.4 (Ar), 137.9 (Ar), 129.3 (Ar), 128.5 (Ar), 128.3 (Ar), 128.3 (Ar), 127.9 (Ar), 127.9 (Ar), 127.7 (Ar), 127.5 (Ar), 113.9 (Ar), 86.5 (C2), 80.4 (2 × C, C3/C4/C5), 76.2 (C3/C4/C5), 73.2 (*CH₂*Ar), 72.7 (*CH₂*Ar), 72.5 (*CH₂*Ar), 70.8 (*CH₂*Ar), 55.4 (*CH₃*), 37.0 (C7), 24.2 (C6). HRMS (ESI): calcd for C₃₆H₃₈O₆Na 589.2561; found 589.2563.

(2S,3R,4S,5R)-2,3,4-Tri-O-benzyl-5-p-methoxybenzylcycloheptanon (15R). R_f (pentane/ethyl acetate 3 : 1) 0.63; $[\alpha]_D^{293K}$ −1.8 (*c* 1, CHCl₃); ^{1}H-NMR (400 MHz, CDCl₃): δ_H 7.35–7.18 (m, 15H, Ar*H*), 7.18–7.13 (m, 2H, Ar*H* from PMB), 6.83–6.77 (m, 2H Ar*H* from PMB), 4.66 (1H, d, *J* 11.8 Hz, C*H*HAr), 4.66 (1H, d, CH*H*Ar), 4.58 (1H, d, *J* 10.5 Hz, C*H*HAr), 4.56 (1H, d, CH*H*Ar), 4.49 (1H, d, *J* 11.3, CH*H*Ar), 4.47–4.40 (4H, m), 3.86 (1H, dd, *J* 7.2 Hz, *J* 3.4 Hz), 3.81 (1H, t, *J* 4.8 Hz), 3.80–3.76 (1H, m) 3.77 (3H, s, C*H₃*), 2.58–2.39 (2H, m, H7), 2.12–1.95 (2H, m, H6). ^{13}C-NMR (100 MHz, CDCl₃): δ_C 207.3 (*C*=O), 159.3 (Ar from PMB), 138.2 (Ar), 138.1 (Ar), 137.7 (Ar), 130.5 (Ar), 129.4 (Ar), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 113.8 (Ar from PMB), 86.1, 81.3, 81.0, 78.8, 73.6 (*CH₂*Ar), 73.1 (*CH₂*Ar), 72.5 (*CH₂*Ar), 71.4 (*CH₂*Ar), 55.4 (*CH₃*), 37.4 (C7), 24.5 (C6). HRMS (ESI): calcd for C₃₆H₃₈O₆Na 589.2561; found 589.2569.

(1R,2R,3S,4S,5R/S)-1-Azido-2,3,4-tri-O-benzyl-1-(benzyloxy)methyl-5-O-p-methoxybenzyl-cycloheptane (20). Anhydrous dichloromethane (0.23 mL, 3.60 mmol, 9.8 eq.) was added to a solution

of freshly prepared LDA in THF (∼0.37 M, 2.0 mL, 0.740 mmol, 2 eq.) at −78 °C. The mixture was stirred for 10 min and then a solution of the ketone **15** (208 mg, 0.367 mmol) in THF (1.8 mL) was added. After stirring for 8 h more LDA was added (2 mL) at −78 °C and the reaction was left to stir overnight. The next morning more LDA (2 mL) and dichloromethane (0.2 mL) was added and the reaction heated to 0 °C. After 2 h the reaction was quenched with sat. aq. NH₄Cl, diluted with ethyl acetate, washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude alcohol (**16**).

Crude alcohol **16** was dissolved in anhydrous DMSO (2 mL) and added DBU (90 μL, 0.602 mmol, 1.7 eq.) and stirred for 1 h 40 min. The mixture was then diluted with ethyl acetate and washed with water and brine. The combined aqueous phases were extracted with ethyl acetate and the combined organic phases were now dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude chloro-epoxide (**17**).

Crude **17** was dissolved in anhydrous DMF (2.4 mL) and added TBAN₃ (322 mg, 1.13 mmol, 3.1 eq.) under a nitrogen atmosphere. The mixture was heated to 50 °C and after 10 min cooled to r.t., diluted with ethyl acetate, washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure.

The resulting aldehyde **18** was then dissolved in methanol (3.5 mL) and NaBH₄ (98.6 mg, 2.60 mmol, 7 eq.) was added and the mixture stirred at 0 °C for 2 h. More NaBH₄ was then added and after another 10 min at 0 °C and 15 min at room temperature the mixture was quenched with water, concentrated under reduced pressure, redissolved in ethyl acetate, washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude alcohol (**19**).

19 was then dissolved in anhydrous DMF (1.9 mL) and cooled to 0 °C. NaH (60%, 53.7 mg, 1.34 mmol, 3.7 eq.) and then benzyl bromide (65 μL, 0.547 mmol, 1.5 eq.) was added under a nitrogen atmosphere. The reaction was stirred overnight and then quenched with water, diluted with ethyl acetate, washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/ethyl acetate 20 : 1) to give the product (**20**) (81 mg, 34% over 6 steps).

(1R,2R,3S,4S,5R)-1-Azido-2,3,4-tri-O-benzyl-1-(benzyloxy)methyl-5-O-p-methoxybenzyl-cycloheptane (20R). R_f (pentane/ethyl acetate 20 : 1) 0.23; $[\alpha]_D^{293K}$ +6.0 (*c* 1, CHCl₃); ^{1}H-NMR (400 MHz, CDCl₃): δ_H 7.39–7.19 (m, 20H, Ar*H*), 7.19–7.12 (m, 2H, Ar*H* from PMB), 6.86–6.78 (m, 2H, Ar*H* from PMB), 4.84 (d, *J* 10.7 Hz, 1H, C*H*HAr), 4.73 (d, *J* 11.5 Hz, 1H, C*H*HAr)), 4.72 (d, 1H, CH*H*Ar), 4.69 (d, *J* 12.0 Hz, 1H, C*H*HAr), 4.61 (d, 1H, CH*H*Ar), 4.57 (d, *J* 11.1 Hz, 1H, C*H*HAr), 4.52 (d, *J* 11.9 Hz, 2H, C*H*HAr, CH*H*Ar), 4.47 (d, 1H, CH*H*Ar), 4.28 (d, 1H, CH*H*Ar), 3.94 (d, *J* 4.4 Hz, 1H, H2/H3), 3.87 (dd, *J* 8.4 Hz, *J* 6.9 Hz, 1H, H2/H3), 3.81–3.76 (m, 4H, C*H₃*, H4), 3.63 (d, $J_{8a,8b}$ 9.6 Hz, 1H, H8a), 3.60 (d, 1H, H8b), 3.57 (td, *J* 8.6 Hz, *J* 2.7 Hz, 1H, H5), 1.93–1.71 (m, 3H, H6/H7), 1.55 (dd, *J* 11.3 Hz, *J* 6.7 Hz, 1H, H6/H7). ^{13}C-NMR (100 MHz, CDCl₃): δ_C 159.2

(Ar from PMB), 139.1 (Ar), 138.6 (Ar), 138.1 (Ar), 138.0 (Ar), 131.1 (Ar), 129.4 (Ar), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.4 (Ar), 128.2 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.7 (Ar), 127.6 (Ar), 113.8 (Ar from PMB), 87.7 (C2/C3), 82.9 (C4), 80.4 (C2/C3), 78.8 (C5), 75.5 (CH_2Ar), 74.5 (CH_2Ar), 73.8 (CH_2Ar), 73.8 (C8), 73.4 (CH_2Ar), 72.5 (CH_2Ar), 67.1 (C1), 55.4 (CH_3), 26.9 (C6/C7), 26.7 (C6/C7). HRMS (ESI): calcd for $C_{44}H_{47}N_3O_6Na$ 736.3357; found 736.3363.

(1R,2R,3S,4S,5S)-1-Azido-2,3,4-tri-O-benzyl-1-(benzyloxy)methyl-5-O-p-methoxybenzyl-cycloheptane **(20S)**. R_f (pentane/ethyl acetate 20 : 1) 0.10; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.46–7.20 (m, 23H, Ar*H*), 6.82–6.71 (m, 2H, Ar*H* from PMB), 4.73–4.52 (m, 9H), 4.48 (d, *J* 11.1 Hz, 1H), 4.07–3.95 (m, 4H), 3.81 (s, 3H, C*H*$_3$), 3.83–3.78 (m, 1H) 3.73 (d, *J* 9.8 Hz, 1H), 2.31 (ddd, *J* 14.7 Hz, *J* 11.0 Hz, *J* 4.1 Hz, 1H, H6a/H7), 2.04–1.90 (m, 1H, H6a/H7), 1.79 (ddt, *J* 14.7 Hz, *J* 11.2 Hz, *J* 3.9 Hz, 1H, H6b), 1.40–1.27 (m, 1H, H6a/H7). HRMS (ESI): calcd for $C_{44}H_{47}N_3O_6Na$ 736.3357; found 736.3385.

(2R,3S,4R,5R)-5-Azido-2,3,4-tri-O-benzyl-5-(benzyloxy)methyl-cycloheptanon **(21)**. The PMB ether **(20)** (69.6 mg, 97.6 µmol) was mixed with trifluoroacetic acid/dichloromethane 1 : 1 (7.6 mL) at 0 °C. After 1 h 10 min the mixture had turned dark purple and was concentrated under reduced pressure. The crude alcohol was redissolved in dichloromethane (4.4 mL) and added Dess–Martin periodinate (109 mg, 0.255 mmol, 2.6 eq.). After 30 min the reaction was quenched with sat. aq. $NaHCO_3$ and $Na_2S_2O_3$. The mixture was left to stir for 1 h and then extracted with dichloromethane, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was combined with another batch (18 µmol) and purified by flash column chromatography (pentane/ethyl acetate 8 : 1) to give the ketone **(21)** (43.2 mg, 65% over 2 steps).

R_f (pentane/ethyl acetate 6 : 1) 0.36; $[\alpha]_D^{293K}$ +33.0 (*c* 1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.45–7.21 (m, 18H, Ar*H*), 7.08 (dd, *J* 6.6 Hz, *J* 2.9 Hz, 2H, Ar*H*), 4.78 (d, *J* 11.8 Hz, 1H, C*H*HPh), 4.71 (d, *J* 11.6 Hz, 2H, 2 × C*H*HPh), 4.69 (d, $J_{2,3}$ 5.6 Hz, 1H, H2), 4.48 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.45 (d, *J* 11.3 Hz, 2H, 2 × C*H*HPh), 4.42 (d, *J* 10.3 Hz, 1H, C*H*HPh), 4.11 (d, *J* 11.4 Hz, 1H, C*H*HPh), 4.01 (d, $J_{3,4}$ 3.7 Hz, 1H, H4), 3.89 (dd, 1H, H3), 3.61 (d, $J_{8a,8b}$ 9.6 Hz, 1H, H8a), 3.47 (d, H8b), 2.60–2.38 (m, 2H, H6/H7), 1.99 (ddd, *J* 14.1 Hz, *J* 9.1 Hz, *J* 4.7 Hz, 1H, H6/H7), 1.75 (ddd, *J* 14.5 Hz, *J* 7.9 Hz, *J* 5.3 Hz, 1H, H6/H7). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 205.9 (*C*=O), 137.9 (Ar), 137.7 (Ar), 137.7 (Ar), 137.3 (Ar), 128.5 (Ar), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.2 (Ar), 128.2 (Ar), 128.0 (Ar), 128.0 (Ar), 127.9 (Ar), 127.9 (Ar), 127.6 (Ar), 87.3 (C2), 80.0 (C3), 78.4 (C4), 74.4 (C8), 74.0 (CH_2Ar), 73.4 (CH_2Ar), 73.2 (CH_2Ar), 72.5 (CH_2Ar), 66.1 (C5), 37.6 (C6/C7), 26.0 (C6/C7). HRMS (ESI): calcd for $C_{36}H_{37}N_3O_5Na$ 614.2625; found 614.2623.

(1S,2R,3S,4R,5R)-2,3,4-Tris(benzyloxy)-5-((benzyloxy)methyl)-8-azabicyclo[3.2.1]octan-1-ol **(22)**. The ketone **(21)** (42.2 mg, 71.3 µmol) was dissolved in methanol/ethyl acetate 1 : 1 (2.6 mL). Three drops of triethylamine and then 20% Pearlmans catalyst (12.5 mg, 0.0178 mmol, 20%) were added. The mixture was bubbled through with hydrogen and stirred under a hydrogen atmosphere for 15 min. The catalyst was then

filtered of through a syringe filter and the filtrate concentrated under reduced pressure to give the crude hemiaminal **(22)** (38.8 mg).

R_f (pentane/ethyl acetate 1 : 1) 0.36; $[\alpha]_D^{293K}$ +15.4 (*c* 1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.43–7.16 (m, 20H, Ar*H*), 5.04 (d, *J* 11.4 Hz, 1H, C*H*Ph), 4.92 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.81 (d, *J* 11.1 Hz, 1H, C*H*HPh), 4.79 (d, *J* 10.8 Hz, 2H, CH*H*Ph, C*H*HPh), 4.60 (d, 1H, CH*H*Ph), 4.53 (d, *J* 11.7 Hz, 1H, C*H*HPh), 4.43 (d, 1H, CH*H*Ph), 3.75 (d, $J_{6a,6b}$ 9.0 Hz, 1H, H6a), 3.74 (d, $J_{2,3}$ 8.2 Hz, 1H, H2), 3.65 (t, $J_{3,4}$ 8.3 Hz, 1H, H3), 3.53 (d, 1H, H4), 3.36 (d, 1H, H6b), 2.34 (ddd, $J_{8a,8b}$ 12.0 Hz, $J_{8a,7a}$ 9.9 Hz, $J_{8a,7b}$ 4.0 Hz, 1H, H8a), 1.90 (ddd, $J_{7a,7b}$ 12.6 Hz, $J_{7a,8b}$ 4.5 Hz, 1H, H7a), 1.66 (td, $J_{8b,7b}$ 12.2 Hz, 1H, H8b), 1.56 (td, 1H, H7b). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 139.1 (Ar), 138.9 (Ar), 138.9 (Ar), 138.1 (Ar), 128.5 (Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.6 (Ar), 91.7 (C1), 87.2 (C2), 84.9 (C3), 82.8 (C4), 77.4 (CH_2Ph), 75.7 (CH_2Ph), 74.7 (CH_2Ph), 73.5 (CH_2Ph), 73.2 (CH_2Ph), 62.9 (C5), 31.7 (C8), 25.5 (C7). HRMS (ESI): calcd for $C_{36}H_{39}NO_5H$ 566.2901; found 566.2910.

(1S,2R,3S,4R,5R)-5-(Hydroxymethyl)-8-azabicyclo[3.2.1]octane-1,2,3,4-tetraol – nojiristegine **(1)**.

1
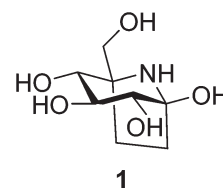
The crude benzyl protected compound **(21)** (66.8 µmol) was dissolved in methanol/ethyl acetate 1 : 1 (2.6 mL) and added 20% Pearlmans catalyst (10.2 mg, 14.5 µmol, 22%). The mixture was bubbled through with hydrogen and stirred under a hydrogen atmosphere for 3 h 50 min. 2 drops of concentrated hydrochloric acid was then added and the reaction left overnight. The next morning the catalyst was filtered of through a syringe filter and the filtrate concentrated under reduced pressure. The crude compound was purified by flash column chromatography (5% NH_4OH in ethanol) to give nojiristegine **(1)** (16.5 mg, quant.).

R_f (5% NH_4OH in ethanol) 0.31; $[\alpha]_D^{293K}$ −2.4 (*c* 1, H_2O); ^{1}H-NMR (400 MHz, D_2O): δ_H 3.78 (d, $J_{6a,6b}$ 12.2 Hz, 1H, H6a), 3.68 (d, *J* 8.7 Hz, 1H, H2), 3.58 (d, *J* 8.7 Hz, 1H, H4), 3.56 (d, 1H, H6b), 3.46 (t, $J_{2,3}$ 8.7 Hz, 1H, H3), 2.28–2.14 (m, 1H, H8a), 1.88–1.73 (m, 2H, H7a + H8b), 1.73–1.62 (m, 1H, H7b). ^{13}C-NMR (100 MHz, D_2O): δ_C 91.5 (C1), 75.9 (C2), 74.9 (C3), 72.1 (C4), 65.3 (C5), 62.3 (C6), 28.3 (C8), 23.2 (C7). HRMS (ESI): calcd for $C_8H_{15}NO_5H$ 206.1023; found 206.1023.

Methyl 6-O-trityl-α-D-mannopyranoside **(52)**. Commercially available methyl α-D-mannopyranoside **(4)** (4.96 g, 25.5 mmol) was dissolved in anhydrous pyridine (40 mL). Trityl chloride (10.8 g, 38.7 mol, 1.5 eq.) and DMAP (634 mg, 5.15 mmol, 0.2%) were added and the reaction mixture was stirred at room temperature overnight under a nitrogen atmosphere. The pyridine was then removed under reduced pressure and the residue was diluted with dichloromethane. The organic phase

was washed with 1 M aq. HCl, sat. aq. $NaHCO_3$ and brine and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure giving the tritylated crude compound (**52**) (18.1 g) as a white solid.

R_f (ethyl acetate/pentane 1 : 1) 0.39. HRMS (ESI): calcd for $C_{26}H_{28}O_6Na$ 459.1778; found 459.1782.

Methyl 2,3,4-Tri-O-benzyl-6-O-trityl-α-D-mannopyranoside (53). The crude compound **52** was dissolved in anhydrous DMF (110 mL) under a nitrogen atmosphere. The mixture was cooled to 0 °C and 60% sodium hydride in mineral oil (6.20 g, 156 mmol, 6 eq.) was slowly added, followed by dropwise addition of benzyl bromide (13.9 mL, 117 mmol, 4.5 eq.) under formation of hydrogen gas. The reaction mixture was then allowed slowly to warm to room temperature and react overnight. The mixture was quenched by addition of methanol (30 mL) and then evaporated under reduced pressure. The residue was diluted with diethyl ether and washed with water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure yielding the crude compound (**53**) (32.6 g) as a brown oil.

R_f (ethyl acetate/pentane 1 : 1) 0.39. HRMS (ESI): calcd for $C_{47}H_{50}O_6NH_4$ 724.3633; found 724.3640.

Methyl 2,3,4-tri-O-benzyl-6-hydroxy-α-D-mannopyranoside (54). The crude compound (**53**) was dissolved in methanol/dichloromethane 2 : 1 and then *p*-toluenesulfonic acid was added until pH < 4. The reaction was stirred overnight. The mixture was then neutralised with triethylamine and evaporated under reduced pressure. The residue was diluted with ethyl acetate and washed with water. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1 : 10 → 1 : 1) to give **54** as a yellow oil (7.86 g, 65% over 3 steps).

R_f (ethyl acetate/pentane 1 : 3) 0.27; ^{1}H-NMR (400 MHz, $CDCl_3$): $δ_H$ 7.40–7.27 (15H, m, Ar*H*), 4.97 (1H, d, *J* 10.9 Hz, C*H*HPh), 4.81 (1H, d, *J* 12.3 Hz, C*H*HPh), 4.72 (1H, s, H1), 4.71 (1H, d, CH*H*Ph), 4.68 (1H, d, CH*H*Ph), 4.66 (2H, s, C*H_2*Ph), 4.00 (1H, t, $J_{4,3} = J_{4,5}$ 9.5 Hz, H4), 3.93 (1H, dd, $J_{3,2}$ 2.9 Hz, H3), 3.87 (1H, dd, $J_{2,1}$ 9.2 Hz, H2), 3.83–3.78 (1H, m, H6), 3.65 (1H, ddd, $J_{5,6a}$ 4.4 Hz, $J_{5,6b}$ 3.1 Hz, H5), 3.22 (3H, s, C*H_3*), 2.16 (1H, bs, O*H*). ^{13}C-NMR (100 MHz, $CDCl_3$): $δ_C$ 138.6 (Ar), 138.5 (Ar), 138.3 (Ar), 128.5 (Ar), 128.5 (Ar), 128.5 (Ar), 128.3 (Ar), 128.1 (Ar), 128.0 (Ar), 127.8 (Ar), 127.7 (Ar), 99.4 (C1), 80.3 (C3), 75.3 (*C*H_2Ph), 75.0 (C4), 74.8 (C2), 73.0 (*C*H_2Ph), 72.3 (*C*H_2Ph), 72.2 (C6), 62.5 (C6), 54.9 (*C*H_3). HRMS (ESI): calcd for $C_{28}H_{32}O_6NH_4$ 482.2537; found 482.2546.

NMR data was in accordance with previously reported values.[44]

Methyl 2,3,4-tri-O-benzyl-6-deoxy-6-iodo-α-D-mannopyranoside (6). Methyl 2,3,4-tri-O-benzyl-α-D-mannopyranoside (**54**) (24.3 g, 52.5 mmol) was dissolved in anhydrous toluene (300 mL) under a nitrogen atmosphere. Triphenylphosphine (34.5 g, 131 mmol, 2.5 eq.), imidazole (8.59 g, 126 mmol, 2.4 eq.) and iodine (14.7 g, 57.8 mmol, 1.1 eq.) were added and the reaction

mixture was heated to reflux. The reaction was stirred for 1 h 30 min., and then cooled to room temperature. $Na_2S_2O_3$ (aq) (300 mL) was added and the mixture was washed with water and brine, dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1 : 20 → 1 : 2) to give the iodide (**6**) as a yellow oil (28.1 g, 93%).

R_f (ethyl acetate/pentane 1 : 19) 0.32; ^{1}H-NMR (400 MHz, $CDCl_3$): $δ_H$ 7.44–7.28 (15H, m, Ar*H*), 5.01 (1H, d, *J* 11.0 Hz, C*H*HPh), 4.78 (d, *J* 12.5 Hz, 1H, C*H*HPh), 4.77 (1H, d, *J* 1.8 Hz, H1). 4.73 (1H, d, CH*H*Ph), 4.70 (1H, d, CH*H*Ph), 4.62 (2H, s, C*H_2*Ph) 3.91 (1H, dd, $J_{3,4}$ 9.3 Hz, $J_{3,2}$ 3.0 Hz, H3), 3.84–3.77 (2H, m, H4, H2), 3.63–3.51 (2H, m, H6a, H5) 3.39 (3H, s, C*H_3*) 3.35 (1H, dd, $J_{6a,6b}$ 10.2 Hz, $J_{5,6b}$ 2.4 Hz, H6b). ^{13}C-NMR (100 MHz, $CDCl_3$): $δ_C$ 138.4 (Ar), 138.3 (Ar), 138.3 (Ar), 128.6 (Ar), 128.5 (Ar), 128.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 99.1 (C1), 80.0 (C3), 78.7 (C4), 75.5 (*C*H_2Ph), 74.6 (C2), 72.8 (*C*H_2Ph), 72.2 (*C*H_2Ph), 71.5 (C5), 55.2 (*C*H_3), 7.2 (C6). HRMS (ESI): calcd for $C_{28}H_{31}O_5INH_4$ 592.1554; found 592.1554.

NMR data was in accordance with previously reported values.[42]

(2S,3S,4R)-2,3,4-Tri-O-benzylhex-5-enal (23). A solution of iodide **6** (541 mg, 0.934 mmol) in anhydrous THF (20 mL) and water (5 mL) was degassed in a sonication bath. Then preactivated zinc dust (625 mg, 10.3 mmol, 11 eq.)§ was added and the mixture sonicated at 40 °C for 1 h 30 min. The reaction mixture was diluted with water and diethyl ether and filtered through a pad of Celite®. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the aldehyde (**23**) (394 mg) as a clear oil without further purification.

R_f (ethyl acetate/pentane 1 : 11) 0.34; ^{1}H-NMR (400 MHz, $CDCl_3$): $δ_H$ 9.66 (1H, s, C*H*O), 7.35–7.26 (15H, m, Ar*H*), 5.87 (1H, ddd, $J_{5,4}$ 8.0 Hz, $J_{5,6Z}$ 10.4 Hz, $J_{5,6E}$ 17.6 Hz, H5), 5.37 (1H, d, $J_{6E,5}$ 17.3 Hz, H6*E*), 5.35 (1H, d, $J_{6Z,5}$ 10.3 Hz, H6*Z*) 4.72–4.61 (4H, m, 2 × C*H*HPh), 4.49 (1H, d, *J* 11.7 Hz, CH*H*Ph), 4.37 (1H, d, *J* 11.8 Hz, CH*H*Ph), 4.11 (1H, m, H4) 4.07 (1H, dd, $J_{2,3}$ 3.7 Hz, $J_{2,1}$ 1.2 Hz, H2), 3.89 (1H, dd, $J_{3,4}$ 5.6 Hz, H3). ^{13}C-NMR (100 MHz, $CDCl_3$): $δ_C$ 201.8 (*C*HO), 138.2 (Ar), 138.0 (Ar), 137.5 (Ar), 135.3 (C5), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 127.7 (Ar), 120.0 (C6), 83.8 (C4), 83.0 (C3), 80.7 (C2), 74.3 (*C*H_2Ph), 73.0 (*C*H_2Ph), 70.9 (*C*H_2Ph). HRMS (ESI): calcd for $C_{27}H_{28}O_4Na$ 439.1880; found 439.1880.

NMR data was in accordance with previously reported values.[43]

(4R/S,5R,6S,7R)-5,6,7-Tri-O-benzyl-1,8-nonadiene-4-ol (24). To a stirred solution of the crude aldehyde (**23**) (0.934 mmol) in 50% aqueous THF (14 mL) was added indium dust (227 mg, 1.98 mmol, 2 eq.) and allyl bromide (0.30 mL, 3.47 mmol,

4 eq.). The mixture was stirred overnight at room temperature. Sat. aq. NaHCO$_3$ (5 mL) was added to neutralise the reaction mixture, which was then extracted with chloroform and the combined organic phases dried over MgSO$_4$, filtered and concentrated. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1:20) to give the product (**24**) as a colourless oil (310 mg, 76% over 2 steps). According to NMR the product was a 1:2.2 mixture of *S*- and *R*-diastereoisomers.

R_f (ethyl acetate/pentane 1:9) 0.40; ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.27–7.09 (30H, m, Ar*H*), 5.87–5.58 (4H, m), 5.28–5.19 (4H, m), 5.01–4.87 (4H, m), 4.66 (4H, dt, *J* 18.6 Hz, *J* 11.5 Hz), 4.55 (2H, d, *J* 11.8 Hz), 4.39–4.34 (4H, m), 4.28 (q, *J* 11.0 Hz), 4.04 (1H, dd, *J* 7.4 Hz, *J* 5.8 Hz), 3.97 (1H, dd, *J* 7.9 Hz, *J* 5.0 Hz), 3.85 (2H, dd, *J* 10.2 Hz, *J* 7.4 Hz), 3.74–3.69 (2H, m), 3.53–3.47 (2H, m), 2.96 (1H, s), 2.57 (1H, s), 2.43–2.36 (1H, m), 2.27–2.11 (3H, m). Major isomer: ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 138.3 (Ar), 138.3 (Ar), 138.3 (Ar), 136.0 (*C*H=CH$_2$), 135.5 (*C*H=CH$_2$), 119.1 (CH=*C*H$_2$), 117.4 (CH=*C*H$_2$), 82.9, 81.5, 81.5, 74.7, 72.9, 71.1, 70.6, 37.7 (C3). Minor isomer: ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 138.2 (Ar), 138.1 (Ar), 138.0 (Ar), 135.7 (*C*H=CH$_2$), 135.2 (*C*H=CH$_2$), 119.3 (CH=*C*H$_2$), 117.2 (CH=*C*H$_2$), 82.1, 81.0, 78.1, 75.3, 73.0, 70.7, 70.3, 38.7 (C3). Major isomer + minor isomer: ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 128.4 (Ar), 128.4 (Ar), 128.3 (Ar), 128.3 (Ar), 128.1 (Ar), 128.0 (Ar), 128.0 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.6 (Ar). HRMS (ESI): calcd for C$_{30}$H$_{34}$O$_4$Na 481.2349; found 481.2350.

(4R/S,5R,6S,7R)-5,6,7-Tri-*O*-benzyl-1,8-nonadiene-4-acetate *(25)*. The alcohol (**24**) (2.67 g, 5.81 mmol) was dissolved in anhydrous pyridine (20 mL) under an atmosphere of nitrogen. Acetic anhydride (20 mL) and DMAP (35.2 mg, 0.293 mmol, 5 mol%) were added and stirred at room temperature for 3 h 30 min. The reaction was cooled on a water bath and quenched by slow addition of water (20 mL) and then diluted with ethyl acetate. The organic phase was washed with 1 M aq. HCl and sat. aq. NaHCO$_3$, dried over MgSO$_4$, filtered and concentrated under reduce pressure to yield the acetylated compound (**25**) (2.93 g) without further purification.

R_f (ethyl acetate/pentane 1:15) 0.32; ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.33–7.13 (m, 20.4H), 5.86 (tdd, *J* 17.7 Hz, *J* 10.3 Hz, *J* 7.7 Hz, 1.3H), 5.61 (ddt, *J* 17.3 Hz, *J* 10.6 Hz, *J* 7.1 Hz, 1.3H), 5.36–5.17 (m, 3.7H), 4.96–4.89 (m, 2.4H), 4.71 (d, *J* 11.4 Hz, 0.9H), 4.64 (d, *J* 11.4 Hz, 1H), 4.63–4.47 (m, 3.1H), 4.48 (s, 0.5H), 4.31 (d, *J* 11.3 Hz, 1H), 4.27 (d, *J* 11.9 Hz, 1.1H), 4.09 (dd, *J* 7.9 Hz, *J* 4.0 Hz, 0.3H), 4.04 (dd, *J* 7.7 Hz, *J* 4.9 Hz, 0.9H), 3.77 (dd, *J* 6.0 Hz, *J* 3.3 Hz, 1H), 3.69 (dd, *J* 6.8 Hz, *J* 2.8 Hz, 0.3H), 3.62–3.58 (m, 0.2H), 3.56 (dd, *J* 6.0 Hz, *J* 4.9 Hz, 1H), 2.39 (t, *J* 6.7 Hz, 0.9H), 2.34 (t, *J* 7.0 Hz, 0.4H), 1.89 (s, 1.1H), 1.89 (s, 2.7H). Major isomer: ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 170.1 (*C*=O), 138.6 (Ar), 138,5 (Ar), 138.4 (Ar), 136.0 (CH$_2$=*C*H), 134.6 (CH$_2$=*C*H), 119.0 (*C*H$_2$=CH), 117.4 (*C*H$_2$=CH), 81.9, 81.1, 79.6, 74.5 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 73.0, 70.6 (*C*H$_2$Ph), 34.6 (C3), 21.2 (*C*H$_3$). Minor isomer: ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 170.7 (*C*=O), 138.5 (Ar), 138.4 (Ar), 138.3 (Ar), 136.3 (CH$_2$=*C*H), 134.0 (CH$_2$=*C*H), 119.1 (*C*H$_2$=CH),

117.9 (*C*H$_2$=CH), 81.7, 80.8, 78.1, 74.9 (*C*H$_2$Ph), 73.8, 72.4 (*C*H$_2$Ph), 70.5 (*C*H$_2$Ph), 36.3 (C3), 21.4 (*C*H$_3$). Major isomer + minor isomer: ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 128.5 (Ar), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 128.1 (Ar), 128.1 (Ar), 127.9 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.7 (Ar), 127.6 (Ar). HRMS (ESI): calcd for C$_{32}$H$_{36}$O$_5$NH$_4$ 518.2901; found 518.2903.

(3R,4S,5R,6S)-6-*O*-Acetyl-3,4,5-tri-*O*-benzyl-cycloheptene *(26)* and *(3R,4S,5R,6R)*-6-*O*-acetyl-3,4,5-tri-*O*-benzyl-cycloheptene *(27)*. The crude acetate (**25**) (5.81 mmol)) was dissolved in anhydrous toluene (30 mL) under an atmosphere of nitrogen. Grubbs–Hoveyda 2nd generation catalyst (35.7 mg, 54.8 µmol, 1 mol%) was added to the mixture which was immediately put on a pre-heated 80 °C oil bath. The mixture stirred for 2 h before more catalyst was added. After additional 1 h 30 min the reaction was concentrated under reduced pressure and the crude product was purified by flash column chromatography (diethyl ether/chloroform 0:1 → 1:40) yielding **27** and **26** (1.96 g, 71% over 2 steps) which were partly separated.

(3R,4S,5R,6S)-6-*O*-Acetyl-3,4,5-tri-*O*-benzyl-cycloheptene *(26)*. Colourless oil (53.7 mg, 19% over 2 steps); R_f (ethyl acetate/pentane 1:13) 0.38; $[\alpha]_D^{298K}$ −1.2 (*c* 1.0, CHCl$_3$). ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.38–7.23 (m, 15H, Ar*H*), 5.81 (1H, dd, $J_{2,1}$ 11.7 Hz, $J_{2,3}$ 4.1 Hz, H2), 5.72 (1H, ddd, $J_{1,7b}$ 6.9 Hz, $J_{1,7a}$ 1.2 Hz, H1), 5.15 (1H, td, $J_{6,5} = J_{6,7b}$ 6.9 Hz, $J_{6,7a}$ 3.2 Hz, H6), 4.78 (1H, d, *J* 9.7 Hz, C*H*HPh), 4.75 (1H, d, CH*H*Ph), 4.73 (1H, d, *J* 12.2 Hz, C*H*HPh), 4.66 (1H, d, CH*H*Ph), 4.62 (1H, d, *J* 11.8 Hz, C*H*HPh), 4.55 (1H, d, CH*H*Ph), 4.35 (1H, dd, $J_{3,4}$ 7.2 Hz, H3), 3.96 (1H, dd, $J_{5,4}$ 1.8 Hz, H5), 3.91 (1H, dd, H4), 2.56 (1H, dddt, $J_{7a,7b}$ 15.6 Hz, H7a), 2.33 (1H, dt, H7b), 1.96 (3H, s, C*H*$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 169.9 (*C*=O), 138.6 (Ar), 138.6 (Ar), 138.5 (Ar), 132.2 (*C*H=CH), 128.2 (Ar), 128.2 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 126.2 (CH=*C*H), 80.5 (C5), 78.3 (C4), 75.9 (C3), 73.4 (*C*H$_2$Ph), 73.3 (*C*H$_2$Ph), 71.8 (*C*H$_2$Ph/C6), 71.8 (*C*H$_2$Ph/C6), 28.2 (C7), 21.1 (*C*H$_3$). HRMS (ESI): calcd for C$_{30}$H$_{32}$O$_5$Na 495.2142; found 495.2147.

(3R,4S,5R,6R)-6-*O*-Acetyl-3,4,5-tri-*O*-benzyl-cycloheptene *(27)*. Colourless oil (1.37 g, 50% over 2 steps); R_f (ethyl acetate/pentane 1:13) 0.38; $[\alpha]_D^{298K}$ −4.0 (*c* 1.0, CHCl$_3$); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.42–7.23 (15H, m, Ar*H*), 5.76 (1H, dt, $J_{2,1}$ 12.4 Hz, $J_{2,3}$ 2.7 Hz, H2), 5.62 (1H, m, H1), 4.92 (1H, d, *J* 11.9 Hz, C*H*HPh), 4.84 (1H, d, *J* 11.7 Hz, C*H*HPh), 4.79 (1H, d, CH*H*Ph), 4.76 (1H, d, *J* 11.4 Hz, C*H*HPh), 4.75 (1H, dt, $J_{6,7a}$ 11.4 Hz, $J_{6,7b} = J_{6,5}$ 1.3 Hz, H6), 4.68 (1H, d, CH*H*Ph) 4.68 (1H, d, CH*H*Ph), 4.60 (1H, dq, $J_{3,4}$ 9.2 Hz, H3), 4.14 (1H, s, H5), 3.56 (1H, dd, $J_{4,5}$ 1.4 Hz H4), 2.78 (1H, ddq, $J_{7a,7b}$ 14.6 Hz, $J_{7a,1}$ 2.9 Hz, H7a), 2.05 (1H, dddd, $J_{7b,1}$ 8.8 Hz, $J_{7b,1}$ 3.5 Hz, H7b), 1.99 (3H, s, C*H*$_3$). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 170.4 (*C*=O), 139.0 (Ar), 138.9 (Ar), 134.5 (*C*H=CH), 128.4 (Ar), 128.4 (Ar), 128.3 (Ar), 128.0 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 124.1 (CH=*C*H), 83.1 (C4), 80.1 (C5), 77.1 (C3), 74.7 (*C*H$_2$Ph), 73.7 (*C*H$_2$Ph), 73.4 (*C*H$_2$Ph), 73.2 (C6), 26.9 (C7), 21.4 (*C*H$_3$). HRMS (ESI): calcd for C$_{30}$H$_{32}$O$_5$Na 495.2142; found 495.2143.

(3R,4S,5R,6R)-3,4,5-Tri-*O*-benzyl-6-hydroxy-cycloheptene *(29)*. Sodium (70.2 mg, 2.96 mmol, 1 eq.) was dissolved in

anhydrous methanol (10 mL). The sodium methoxide solution (10 mL) was added to the acetylated compound (**27**) (1.36 g, 2.88 mmol) under an atmosphere of nitrogen. The reaction mixture was stirred overnight at room temperature. The mixture was concentrated under reduced pressure, diluted with dichloromethane and washed with water, dried with $MgSO_4$, filtered and concentrated. The deacetylated crude product (**29**) (1.22 g) was used without further purification.

R_f (diethyl ether/chloroform 1 : 40) 0.23; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.39–7.27 (15H, m, Ar*H*), 5.87–5.75 (2H, m, C*H*=C*H*), 4.92 (1H, d, *J* 11.9 Hz, C*H*HPh), 4.84 (1H, d, *J* 11.9 Hz, C*H*HPh), 4.78 (1H, d, CH*H*Ph), 4.73 (1H, d, CH*H*Ph), 4.65 (1H, d, *J* 11.8 Hz, C*H*HPh), 4.58 (1H, d, CH*H*Ph), 4.42 (1H, dd, $J_{3,4}$ 8.0 Hz, $J_{3,2}$ 3.7 Hz, H3), 4.04 (1H, t, $J_{5,4}$ = $J_{5,6}$ 1.8 Hz, H5), 3.86 (1H, ddt, $J_{6,OH}$ 9.6 Hz, $J_{6,7b}$ 7.2 Hz, $J_{6,5}$ 2.4 Hz, H6), 3.80 (1H, dd, H4), 2.89 (1H, d, $J_{OH,6}$ 9.7 Hz, O*H*), 2.64–2.55 (1H, m, H7a), 2.19 (1H, ddd, $J_{7b,7a}$ 14.3 Hz, $J_{7b,1}$ 2.6 Hz, H7b). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 139.0 (Ar), 138.7 (Ar), 138.7 (Ar), 132.8 (*C*H=CH), 128.5 (Ar), 128.5 (*C*H=CH), 128.4 (Ar), 128.2 (Ar), 128.0 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.7 (Ar), 127.6 (Ar), 81.9 (C4, C5), 75.1 (C3), 74.2 (*C*H$_2$Ph), 73.6 (*C*H$_2$Ph), 72.2 (*C*H$_2$Ph), 70.8 (C6), 31.3 (C7). HRMS (ESI): calcd for $C_{28}H_{30}O_4Na$ 453.2036; found 453.2040.

(3R,4S,5R,6R)-3,4,5-Tri-O-benzyl-6-O-p-methoxybenzyl-cyclohep-tene (34). The crude alcohol (**29**) (2.88 mmol) was dissolved in anhydrous DMF (20 mL) under an atmosphere of nitrogen and cooled to 0 °C. Sodium hydride (234 mg, 5.74 mmol, 2 eq.) and *p*-methoxybenzyl chloride (0.77 mL, 5.71 mmol, 2 eq.) were added to the reaction mixture which was heated to room temperature. The mixture was stirred for 4 h 30 min and was quenched by addition of *n*-butylamine (5 mL), diluted with ethyl acetate, washed with 1 M aq. HCl and sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1 : 25 → 1 : 15) yielding the PMB-ether (**34**) (1.33 g, 84% over 2 steps) as a clear oil.

R_f (ethyl acetate/pentane 1 : 12) 0.28; $[\alpha]_D^{298K}$ +7.6 (*c* 1.0, CHCl$_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.35–7.15 (15H, m, Ar*H*), 7.09 (2H, d, *J* 8.6 Hz, Ar*H* from PMB), 6.77 (2H, d, *J* 8.6 Hz, Ar*H* from PMB), 5.60 (1H, dt, *J* 12.5 Hz, *J* 2.5 Hz, H2), 5.50 (1H, m, H1), 4.81 (2H, s, C*H*$_2$Ph), 4.72 (1H, d, *J* 11.9 Hz, C*H*HPh) 4.68 (1H, d, *J* 11.6 Hz, C*H*HPh), 4.59 (1H, d, CH*H*Ph), 4.53–4.46 (2H, m, H3, CH*H*Ph), 4.30 (1H, d, *J* 11.7 Hz, C*H*HPh), 4.26 (1H, d, CH*H*Ph), 4.08 (1H, s, H5), 3.71 (3H, s, C*H*$_3$), 3.29 (1H, dd, *J* 9.3 Hz, *J* 1.0 Hz, H4), 3.21 (1H, dd, *J* 10.7 Hz, *J* 3.2, H6), 2.67–2.57 (1H, m, H7a), 2.07 (1H, ddd, *J* 15.1 Hz, *J* 8.6 Hz, *J* 2.9 Hz, H7b). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.3 (Ar from PMB), 139.5 (Ar), 139.1 (Ar), 139.0 (Ar), 133.4 (C2), 130.6 (Ar), 129.2 (Ar), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.2 (Ar), 127.9 (Ar), 127.9 (Ar), 127.9 (Ar), 127.6 (Ar), 127.5 (Ar), 127.3 (Ar), 125.0 (C1), 113.9 (Ar from PMB), 83.3 (C4), 80.1 (C5), 78.5 (C6), 74.2 (C3), 73.6 (*C*H$_2$Ph), 73.4 (*C*H$_2$Ph), 70.5 (*C*H$_2$Ph), 55.4 (*C*H$_3$), 27.7 (C7). HRMS (ESI): calcd for $C_{36}H_{38}O_5Na$ 573.2611; found 573.2613.

(3R,4S,5R,6R)-3,4,5-Tri-O-benzyl-6-O-p-methoxybenzyl-cyclo-heptane-1-ol (35) and (2R,3S,4R,5R)-2,3,4-tri-O-benzyl-5-O-

p-methoxybenzyl-cycloheptane-1-ol (36). The alkene (**34**) (1.33 g, 2.42 mmol, 1 eq.) was dissolved in anhydrous THF (50 mL) under an atmosphere of nitrogen. The stirred reaction mixture was cooled to 0 °C and then BH$_3$·THF (1 M in THF, 7.3 mL, 7.3 mmol, 3 eq.) was added drop wise. The reaction was left at 0 °C for 2 hours 30 min, then 35% H_2O_2 (11 mL) and 2 M NaOH (6.6 mL) were added drop wise at 0 °C and the mixture was stirred at room temperature overnight. The mixture was then diluted with diethyl ether (50 mL) and washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1 : 3 → 1 : 1) to yield the two regio-isomeres **35** and **36** (1.07 g, 78%) as a 1 : 2.1 mixture which were partly separated.

(3R,4S,5R,6R)-3,4,5-Tri-O-benzyl-6-O-p-methoxybenzyl-cyclohep-tane-1-ol (35). Colourless oil (61.4 mg, 4%); R_f (ethyl acetate/pentane 1 : 3) 0.24; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.48–7.26 (15H, m, Ar*H*), 7.26–7.20 (2H, m, Ar*H* from PMB), 6.92–6.86 (2H, m, Ar*H* from PMB), 4.87 (1H, d, *J* 12.2 Hz, C*H*HPh), 4.82 (d, CH*H*Ph), 4.69 (d, *J* 11.4 Hz, C*H*HPh), 4.64 (d, CH*H*Ph), 4.60 (d, *J* 11.8 Hz, C*H*HPh), 4.52 (d, CH*H*Ph), 4.42 (d, *J* 11.6 Hz, C*H*HPh), 4.36 (d, CH*H*Ph), 4.29 (1H, m, H1), 4.14 (1H, bs, H4/H5), 3.99–3.91 (1H, m, H3/H6), 3.81 (3H, s, C*H*$_3$), 3.74 (1H, dd, *J* 10.8 Hz, *J* 5.5 Hz, H3/H6), 3.70 (dd, *J* 6.9 Hz, *J* 1.1 Hz, H4/H5), 2.54 (1H, bs, O*H*), 2.29 (1H, dd, *J* 14.7 Hz, *J* 4.3 Hz, H2/H7), 2.21–2.07 (2H, m, H2/H7), 2.03–1.95 (1H, m, H2/H7). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.2 (Ar from PMB), 139.2 (Ar), 138.7 (Ar), 138.6 (Ar), 130.7 (Ar), 129.3 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.7 (Ar), 127.6 (Ar), 127.3 (Ar), 113.9 (Ar PMB), 85.5 (C4/C5), 81.5 (C4/C5), 79.5 (C1), 77.0 (*C*H$_2$Ph), 73.4 (*C*H$_2$Ph), 72.7 (*C*H$_2$Ph), 72.6 (*C*H$_2$Ph), 71.0 (C3/C6), 66.7 (C3/C6), 55.4 (O*C*H$_3$), 37.3 (C2/C7), 36.1 (C2/C7). HRMS (ESI): calcd for $C_{36}H_{40}O_6Na$ 591.2717; found 591.2724.

(2R,3S,4R,5R)-2,3,4-Tri-O-benzyl-5-O-p-methoxybenzyl-cyclohep-tane-1-ol (36). Colourless oil (0.181 g, 13%); R_f (ethyl acetate : pentane 1 : 5) 0.28; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.45–7.24 (15H, m, Ar*H*), 7.16 (2H, d, *J* 8.6 Hz, Ar*H* from PMB), 6.88–6.82 (2H, m, Ar*H* from PMB), 4.90 (1H, d, *J* 11.8 Hz, C*H*HPh), 4.86 (1H, d, CH*H*Ph), 4.69 (2H, s, C*H*$_2$Ph), 4.57 (1H, d, *J* 11.8 Hz, C*H*HPh), 4.46 (1H, d, CH*H*Ph), 4.34 (1H, d, $J_{OH,1}$ 10.1 Hz, O*H*), 4.32 (1H, d, *J* 11.7 Hz, C*H*HPh), 4.26 (1H, d, CH*H*Ph), 4.11 (1H, s, H2), 3.89 (1H, ddd, $J_{1,7a}$ 7.2 Hz, $J_{1,7b}$ 2.8 Hz, H1), 3.83 (1H, dd, $J_{4,3}$ 7.3 Hz, $J_{4,5}$ 2.4 Hz, H4), 3.75 (3H, s, C*H*$_3$), 3.42 (1H, d, H3), 3.27 (1H, dd, $J_{5,6a}$ 11.2 Hz, $J_{5,6b}$ 5.0 Hz, H5), 2.04 (1H, dtd, $J_{6a,6b}$ 14.3 Hz, $J_{6a,5}$ = $J_{6a,7b}$ 11.8 Hz, $J_{6a,7a}$ 3.0 Hz, H6a), 1.93 (1H, dtd, $J_{7a,7b}$ 14.5 Hz, $J_{7a,1}$ = $J_{7a,6b}$ 7.1 Hz, H7a), 1.86–1.73 (1H, m, H6b), 1.61 (1H, ddd, H7b). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 159.2 (Ar from PMB), 138.5 (Ar), 138.4 (Ar), 137.7 (Ar), 130.4 (Ar), 129.1 (Ar), 129.0 (Ar), 128.4 (Ar), 128.4 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 113.8 (Ar from PMB), 87.5 (C4), 84.4 (C3), 80.1 (C2), 79.8 (C5), 73.8 (*C*H$_2$Ph), 73.3 (*C*H$_2$Ph), 73.0 (*C*H$_2$Ph), 70.5 (*C*H$_2$Ph), 68.8 (C1), 55.2 (*C*H$_3$) 25.8 (C7), 22.3 (C6). HRMS (ESI): calcd for $C_{36}H_{40}O_6Na$ 591.2717; found 591.2720.

(2S,3R,4R,5R)-2,3,4-Tri-O-benzyl-5-p-methoxybenzyl-cycloheptanone (37). The alcohol (**36**) (177 mg, 0.311 mmol) was dissolved in dichloromethane (9.4 mL) and stirred at room temperature. Freshly prepared Dess–Martin periodinane (269 mg 0.634 mmol, 2 eq.) was added and after 20 min the reaction was quenched by addition of $Na_2S_2O_3$(aq) and sat. aq. $NaHCO_3$, stirred for 10 min and then extracted with dichloromethane, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1 : 10) yielding the product (**37**) (0.152 g, 87%) as a colourless oil.

R_f (ethyl acetate/pentane 1 : 6) 0.48; $[\alpha]_D^{298K}$ +0.6 (*c* 1.0, $CHCl_3$); ¹H-NMR (400 MHz, $CDCl_3$): δ_H 7.40–7.29 (15H, m, Ar*H*), 7.18 (2H, d, *J* 8.6 Hz, Ar*H* from PMB), 6.88 (2H, d, *J* 8.6 Hz, Ar*H* from PMB), 4.84 (2H, s, C*H*₂Ph), 4.68 (1H, d, *J* 12.0 Hz, C*H*HPh), 4.63 (1H, d, *J* 11.4 Hz, C*H*HPh), 4.58 (1H, d, CH*H*Ph), 4.54 (1H, d, CH*H*Ph), 4.34 (2H, s, C*H*₂Ph), 4.12 (1H, s, H4), 4.09 (1H, d, *J* 7.2 Hz, H2), 3.82 (3H, s, C*H*₃), 3.69 (1H, d, $J_{3,2}$ 7.3 Hz, H3), 3.47 (1H, dd, $J_{5,6}$ 10.6 Hz, $J_{5,6}$ 5.0 Hz, H5), 2.55 (td, $J_{7a,7b} = J_{7a,6a}$ 11.8, $J_{7a,6b}$ 4.2 Hz, H7a), 2.47 (1H, ddd, $J_{7b,6b}$ 6.9 Hz, $J_{7b,6a}$ 3.8 Hz, H7b), 2.13 (1H, ddd, $J_{6a,6b}$ 14.4 Hz, H6a), 2.09–1.98 (1H, d, H6b). ¹³C-NMR (100 MHz, $CDCl_3$): δ_C 206.0 (C1), 159.3 (Ar from PMB), 138.6 (Ar), 138.3 (Ar), 137.7 (Ar), 130.2 (Ar), 129.2 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.4 (Ar), 113.9 (Ar from PMB), 86.3 (C2), 82.6 (C3), 79.8 (C5), 79.5 (C4), 73.1 (*C*H₂Ph), 73.1 (*C*H₂Ph), 72.7 (*C*H₂Ph), 70.8 (*C*H₂Ph), 55.3 (*C*H₃), 35.5 (C7), 26.8 (C6). HRMS (ESI): calcd for $C_{28}H_{32}O_6NH_4$ 589.2561; found 589.2565.

(1R,2R,3S,4R,5R)-1-Azido-2,3,4-tri-O-benzyl-1-(benzyloxy)methyl-5-p-methoxybenzyl-cycloheptane (42) and *(1S,2R,3S,4R,5R)-1-azido-2,3,4-tri-O-benzyl-1-(benzyloxy)methyl-5-p-methoxybenzyl-cycloheptane (43).* Anhydrous dichloromethane (1.02 mL, 15.9 mmol, 9.6 eq.) was slowly added to a solution of freshly prepared LDA (~0.37 M in THF, 8.6 mL, 3.18 mmol, 1.9 eq.) at −78 °C under nitrogen atmosphere. The mixture was stirred for 10 min and then a solution of the ketone (**37**) (936 mg, 1.65 mmol) in THF (7.8 mL) was added. After 50 min at −78 °C the reaction was removed from cooling, quenched with sat. aq. NH_4Cl and diluted with ethyl acetate. The mixture was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude alcohol (**38**).

R_f (ethyl acetate/pentane 1 : 10) 0.23; HRMS (ESI): calcd. for $C_{37}H_{40}O_6Cl_2Na$ 673.2094; found 673.2099.

The crude alcohol (**38**) (1.65 mmol) was dissolved in anhydrous DMSO (11 mL) and stirred at room temperature under nitrogen atmosphere. DBU (0.40 mL, 2.69 mmol, 1.6 eq.) was added and the reaction stirred until TLC analysis showed full consumption of starting material. The reaction was then quenched by addition of water and diluted with ethyl acetate. The organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude epoxide (**39**).

R_f (ethyl acetate/pentane 1 : 4) 0.25.

The crude epoxide (**39**) (1.65 mmol) was dissolved in anhydrous DMSO (33 mL) and tetra-butylammonium azide (2.23 g, 7.9 mmol, 4.8 eq.) was added. The reaction was stirred at 50 °C under an atmosphere of nitrogen. After $3\frac{1}{2}$ h the reaction was quenched by addition of water and diluted with ethyl acetate. The organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated to give the crude aldehyde (**40**).

R_f (ethyl acetate/pentane 1 : 7) 0.34; HRMS (ESI): calcd for $C_{37}H_{39}N_3O_6Na$ 644.2731; found 644.2727.

The crude aldehyde (**40**) (1.65 mmol) was dissolved in anhydrous methanol (40 mL) and stirred under an atmosphere of nitrogen at 0 °C. The mixture was added $NaBH_4$ (555 mg, 15.0 mmol, 9.1 eq.) and stirred for 1 h 15 min before it was quenched by addtion of water and diluted with dichloromethane. The mixture was extracted with dichloromethane, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude alcohol (**41**) (0.873 g).

R_f (ethyl acetate : pentane 1 : 6) 0.23; ¹H-NMR (400 MHz, $CDCl_3$): δ_H 7.38 (1H, d, *J* 6.8 Hz, Ar*H*), 7.28–7.18 (14H, m, Ar*H*), 7.12 (2H, d, *J* 8.6 Hz, Ar*H* from PMB), 6.79 (2H, d, *J* 8.6 Hz, Ar*H* from PMB), 4.91–4.79 (3H, m, C*H*₂Ar), 4.65 (1H, d, *J* 12.0 Hz, C*H*HAr), 4.58 (1H, d, *J* 10.2 Hz, C*H*HAr), 4.47 (1H, d, CH*H*Ar), 4.37–4.24 (3H, m), 4.05 (1H, s, *J* 14.0 Hz), 3.74 (3H, s, C*H*₃), 3.71 (1H, d, *J* 5.2 Hz), 3.57 (1H, d, *J* 11.6 Hz), 3.40 (1H, d, *J* 9.2 Hz), 3.15 (1H, ddd, *J* 10.5 Hz, *J* 4.2 Hz, *J* 2.7 Hz), 1.95–1.65 (4H, m), 1.26 (1H, ddd, *J* 15.3 Hz, *J* 9.3 Hz, *J* 2.2 Hz), 0 0.84–0.72 (1H, m). HRMS (ESI): calcd for $C_{37}H_{41}N_3O_6NH_4$ 641.3334; found 641.3334.

The crude alcohol (**41**) (1.65 mmol) was dissolved in anhydrous DMF and cooled to 0 °C. Sodium hydride (2.8 mmol, 1.7 eq.) was slowly added under a nitrogen atmosphere. Benzyl bromide (0.25 mL, 2.1 mmol, 1.3 eq.) was then slowly added and the mixture stirred overnight. The reaction was quenched with methanol and concentrated under reduced pressure. The residue was redissolved in diethyl ether and washed with water. The combined aqueous phases were extracted with ether and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20 : 1 → 10 : 1 pentane : ethyl acetate) to give an approximately 1 : 1.7 mixture of epimers (**42** and **43**), which was partly separated (444 mg, 38% over 5 steps).

(1R,2R,3S,4R,5R)-1-Azido-2,3,4-tri-O-benzyl-1-(benzyloxy)methyl-5-p-methoxybenzyl-cycloheptane (42). (154 mg, 13%), R_f (pentane/ethyl acetate 4 : 1) 0.5; ¹H-NMR (400 MHz, $CDCl_3$): δ_H 7.41 (d, *J* 7.1 Hz, 2H, Ar*H*), 7.37–7.09 (m, 20H, Ar*H*), 6.83 (d, *J* 8.5 Hz, 2H, Ar*H*), 4.87 (d, *J* 8.6 Hz, 1H, C*H*HAr) 4.86 (s, 2H, C*H*₂Ar), 4.69 (d, *J* 10.8 Hz, 1H, C*H*HAr), 4.66 (d, *J* 12.2 Hz, 1H, C*H*HAr), 4.58 (d, *J* 12.0 Hz, 1H, C*H*HAr), 4.42 (d, *J* 12.1 Hz, 1H, C*H*HAr), 4.41 (d, *J* 11.9 Hz, 1H, C*H*HAr) 4.32 (d, *J* 11.8 Hz, 1H, C*H*HAr), 4.26 (d, *J* 11.7 Hz, 1H, C*H*HAr), 4.15 (d, $J_{2,3}$ 9.1 Hz, 1H, H2), 4.04 (s, 1H, H4), 3.74 (s, 3H, C*H*₃), 3.70 (d, $J_{8a,8b}$ 10.1 Hz, 1H, H8a), 3.66 (d, 1H, H8b), 3.51 (d, $J_{2,3}$ 9.1 Hz, 1H, H3), 3.24 (bt, *J* 6.8 Hz, 1H, H5), 2.13–1.97 (m, 1H, H7a), 1.97–1.69 (m, 3H, H6, H7b). ¹³C-NMR (100 MHz, $CDCl_3$): δ_C 159.2 (Ar

from PMB), 139.2 (Ar), 138.8 (Ar), 138.7 (Ar), 137.9 (Ar), 130.6 (Ar), 129.1 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.2 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 113.8 (Ar form PMB), 82.1 (C2), 80.7 (C3), 79.4 (C4), 79.3 (C5), 75.9 (CH_2Ar), 74.2 (CH_2Ar), 73.8 (CH_2Ar), 73.7 (CH_2Ar), 71.6 (C8), 70.4 (CH_2Ar), 68.8 (C1), 55.3 (CH_3), 29.0 (C7), 24.1 (C6). HRMS (ESI): calcd for $C_{44}H_{47}N_3O_6NH_4$ 731.3803; found 731.3612.

(1S,2R,3S,4R,5R)-1-Azido-2,3,4-tri-O-benzyl-1-(benzyloxy)methyl-5-p-methoxybenzyl-cycloheptane (43). (54.9 mg, 5%), R_f (pentane/ ethyl acetate 4 : 1) 0.8; [^1]H-NMR (400 MHz, CDCl$_3$): δ_H 7.39 (d, *J* 6.5 Hz, 1H, Ar*H*), 7.36–7.12 (m, 20H, Ar*H*), 6.83 (d, *J* 8.5, 1H, Ar*H* from PMB), 4.91 (d, *J* 11.4 Hz, 1H, C*H*HAr), 4.84 (s, 2H, C*H*$_2$Ar), 4.63 (d, 1H, CH*H*Ar), 4.51 (d, *J* 11.2 Hz, 1H, C*H*HAr), 4.48 (d, 1H, CH*H*Ar), 4.45 (s, 2H, C*H*$_2$Ar), 4.34 (d, *J* 11.6 Hz, 1H, C*H*HAr), 4.28 (d, 1H, CH*H*Ar), 4.06 (s, 1H, H2), 3.82 (d, *J*$_{3,4}$ 8.9 Hz, 1H, H4), 3.77 (s, 3H, C*H*$_3$), 3.66–3.56 (m, 4H, H5 + H3 + H8), 2.24–2.14 (m, 1H, H7a), 2.06–1.86 (m, 2H, H6a, H7b), 1.82–1.70 (m, 1H, H6b). [^13]C-NMR (100 MHz, CDCl$_3$): δ_C 159.2 (Ar from PMB), 139.3 (Ar), 138.7 (Ar), 138.6 (Ar), 137.9 (Ar), 130.8 (Ar), 129.3 (Ar), 129.1 (Ar), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.2 (Ar), 128.2 (Ar), 128.0 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.6 (Ar), 127.5 (Ar), 127.3 (Ar), 113.9 (Ar from PMB), 83.5 (C5/C3), 82.2 (C4), 79.6 (C2), 78.2 (C5/C3), 75.8 (CH_2Ar), 73.9 (2C, C8, CH_2Ar), 73.7 (CH_2Ar), 73.5 (CH_2Ar), 70.8 (CH_2Ar), 67.1 (C1), 55.4 (CH_3), 28.1 (C7), 25.5 (C6). HRMS (ESI): calcd for $C_{44}H_{47}N_3O_6NH_4$ 731.3803; found 731.3611.

(1R,2R,3S,4R,5R)-1-Azido-2,3,4-tri-O-benzyl-1-(benzyloxy)methyl-cycloheptane (55). The PMB-ether (**42**) (154 mg, 0.216 mmol) was dissolved in dichloromethane (2.8 mL) and water (0.12 mL) and DDQ (69 mg, 0.302 mmol, 1.4 eq.) was added. The reaction was stirred vigorously for 4 h and then quenched with sat. aq. NaHCO$_3$, diluted with dichloromethane and washed with brine. The organic phase was dried over MgSO$_4$, filtered and concentrated to give the crude alcohol (**55**) which was used directly in the next step without further purification.

R_f (pentane/ethyl acetate 4 : 1) 0.32, [^1]H-NMR (400 MHz, CDCl$_3$): δ_H 7.89–7.78 (m, 2H, Ar*H*), 7.40–7.17 (m, 19H, Ar*H*), 7.08–6.94 (m, 2H, Ar*H*), 4.93 (d, *J* 11.8 Hz, 1H), 4.82 (t, *J* 10.8 Hz, 2H), 4.71 (d, *J* 11.7 Hz, 1H), 4.68–4.52 (m, 7H), 4.24 (d, *J* 8.0 Hz, 1H), 4.03–3.93 (m, 2H), 3.85 (s, 3H, C*H*$_3$), 3.78 (d, *J* 9.8 Hz, 1H), 3.72–3.63 (m, 1H), 1.97–1.80 (m, 2H), 1.73 (dddd, *J* 31.1 Hz, *J* 15.2 Hz, *J* 10.0 Hz, *J* 4.6 Hz, 2H). [^13]C-NMR (100 MHz, CDCl$_3$): δ_C 164.6, 138.4, 138.3, 138.2, 137.8, 134.4, 132.0, 129.9, 129.7, 129.0, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 114.3, 80.3, 79.6, 78.8, 75.2, 75.1, 74.2, 73.7, 73.6, 73.2, 71.5, 68.5, 55.5, 27.4, 26.4. HRMS (ESI): calcd for $C_{36}H_{39}N_3O_5Na$ 616.2782; found 616.2785.

(2R,3S,4R,5R)-5-Azido-2,3,4-tri-O-benzyl-1-(benzyloxy)methyl-cycloheptanone (44). The crude alcohol (**55**) (0.216 mmol) was dissolved in dichloromethane (9 mL) and added Dess–Martin

periodinane (146 mg, 0.345 mmol, 1.6 eq.). Stirred for 50 min and then quenched with Na$_2$S$_2$O$_3$ and sat. aq. NaHCO$_3$. Stirred for 10 min at r.t. and left at 4 °C for 2 weeks. The mixture was then extracted with dichloromethane, dried over MgSO$_4$, filtered and concentrated. The crude compound was purified by flash column chromatography to give the ketone (**44**) (50.3 mg, 39% over 2 steps).

R_f (pentane/ethyl acetate 8 : 1) 0.32; $[\alpha]_D^{298K}$ +19.2 (*c* 1, CHCl$_3$); [^1]H-NMR (400 MHz, CDCl$_3$): δ_H 7.37–7.13 (m, 18H, Ar*H*), 7.05–6.96 (m, 2H, Ar*H*), 4.76 (d, *J* 11.9 Hz, 1H, C*H*HAr), 4.67 (d, *J* 12.1 Hz, 1H, C*H*HAr), 4.67 (s, 1H, H2), 4.53 (d, 1H, CH*H*Ar), 4.50 (d, 1H, CH*H*Ar), 4.45 (d, *J* 11.9 Hz, 1H, C*H*HAr), 4.43 (d, *J* 11.0 Hz, 1H, C*H*HAr), 4.38 (d, 1H, CH*H*Ar), 4.27 (d, 1H, CH*H*Ar), 4.05 (d, *J* 5.0 Hz, 1H, H3/H4), 4.00 (d, *J* 5.1 Hz, 1H, H3/H4), 3.78 (d, *J* 9.1 Hz, 1H, H8a), 3.29 (d, *J* 9.1 Hz, 1H, H8b), 2.74 (ddd, *J*$_{6a,6b}$ 19.3 Hz, *J*$_{6a,7a}$ 12.6 Hz, *J*$_{6a,7b}$ 3.2 Hz, 1H, H7a), 2.21 (ddd, *J*$_{6b,7b}$ 5.5 Hz, *J*$_{6b,7a}$ 2.7 Hz, 1H, H7b), 1.88 (ddd, *J*$_{7a,7b}$ 15.2 Hz, 1H, H6a), 1.27 (bd, 1H, H6b). [^13]C-NMR (100 MHz, CDCl$_3$): δ_C 207.2 (*C*=O), 137.9 (Ar), 137.9 (Ar), 137.7 (Ar), 137.6 (Ar), 128.6 (Ar), 128.5 (Ar), 128.5 (Ar), 128.3 (Ar), 128.3 (Ar), 128.1 (Ar), 127.9 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 82.9 (C2), 79.2 (C3/C4), 76.4 (C8), 75.3 (C3/C4), 74.0 (CH_2Ar), 73.6 (CH_2Ar), 73.5 (CH_2Ar), 72.3 (CH_2Ar), 66.0 (C5), 35.6 (C7), 23.9 (C6). HRMS (ESI): calcd for $C_{36}H_{37}N_3O_5NH_4$ 609.3071; found 609.3078.

(1S,2S,3S,4R,5R)-2,3,4-Tris(benzyloxy)-5-((benzyloxy)methyl)-8-azabicyclo[3.2.1]octan-1-ol (45). The ketone (**44**) (50.3 mg, 85 μmol) was dissolved in methanol/ethyl acetate 1 : 1 (3 mL) and added 3 drops of triethyl amine and 20% Pearlman's catalyst (11.8 mg, 16.8 μmol, 20%). The atmosphere was exchanged for hydrogen and the reaction stirred for 5 h. The mixture was then filtered through Celite® and concentrated under reduced pressure, to give the crude product (**45**) (48.3 mg).

R_f (pentane/ethylacetat 1 : 1 + 1% triethyl amine) 0.27; $[\alpha]_D^{298K}$ −12 (*c* 1, CHCl$_3$); [^1]H-NMR (400 MHz, CDCl$_3$): δ_H 7.38–7.09 (m, 2H, Ar*H*), 4.96 (d, *J* 11.9, 1H, C*H*HAr), 4.83 (d, *J* 10.8 Hz, 1H, C*H*HAr), 4.81 (d, 1H, 11.7 CH*H*Ar), 4.60 (d, *J* 11.6 Hz, 1H, C*H*HAr), 4.56 (d, *J* 11.7 Hz, 2H, 2 × C*H*HAr), 4.51 (d, *J* 11.9 Hz, 1H, C*H*HAr), 4.41 (d, 1H, CH*H*Ar), 3.91 (d, *J*$_{2,3}$ 9.2 Hz, 1H, H2), 3.79 (d, *J*$_{3,4}$ 3.7 Hz, 1H, H4), 3.74 (d, *J*$_{6a,6b}$ 8.9 Hz, 1H, H6a), 3.62 (dd, 1H, H3), 3.27 (d, 1H, H6b), 1.83–1.72 (m, 2H, H7a, H8a), 1.70–1.59 (m, 1H, H7b/H8b), 1.48–1.30 (m, 1H, H7b/H8b). [^13]C-NMR (100 MHz, CDCl$_3$): δ_C 139.2 (Ar), 138.9 (Ar), 138.5 (Ar), 138.3 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.3 (Ar), 127.9 (Ar), 127.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.7 (Ar), 127.5 (Ar), 91.2 (C1), 80.9 (C3), 79.9 (C2), 79.8 (C4), 74.9 (CH_2Ar), 74.7 (CH_2Ar), 73.6 (CH_2Ar), 73.4 (C6), 72.5 (CH_2Ar), 63.3 (C5), 33.6 (C7/C8), 24.5 (C7/C8). HRMS (ESI): calcd for $C_{36}H_{39}NO_5H$ 566.2901; found 566.2907.

(1S,2S,3S,4R,5R)-5-(Hydroxymethyl)-8-azabicyclo[3.2.1]octane-1,2,3,4-tetraol – manno-nojiristegine (2). The crude benzyl protected compound (**45**) (85 μmol) was dissolved in 1 : 1 methanol : ethyl acetate (3 mL) and added 20% Pearlmans catalyst (12.1 mg, 17 μmol, 20%) and 1 drop of concentrated hydrochloric acid. The mixture was bubbled through with hydrogen and stirred under a hydrogen atmosphere. After 5 h

the reaction was concentrated under reduced pressure, re-dissolved in methanol and filtered through Celite®. The filtrate was concentrated under reduced pressure, dissolved in water and filtered through a syringe filter (VWR 0.2 μM cellulose acetate) to give the product hydrochloric salt with no further purification (**2**) (20.6 mg, quant.) as a yellow solid.

R_f (5% NH$_4$OH in ethanol) 0.22; $[\alpha]_D^{298K}$ −16.2 (*c* 1, H$_2$O); ^{1}H-NMR (400 MHz, D$_2$O): δ_H 4.00 (d, $J_{2,3}$ 4.0 Hz, 1H, H2), 3.86 (d, $J_{4,3}$ 9.2 Hz, 1H, H4), 3.84 (d, $J_{6a,6b}$ 12.5 Hz, 1H, H6a), 3.78 (dd, 1H, H3), 3.69 (d, 1H, H6b), 2.25–2.08 (m, 2H, H7/H8), 2.03–1.93 (m, 1H, H8/H7), 1.93–1.81 (m, 1H, H8/H7). ^{13}C-NMR (100 MHz, D$_2$O): δ_C 96.5 (C1), 75.4 (C2), 72.3 (C3), 71.8 (C4), 69.3 (C5), 63.2 (C6), 31.8 (C7/C8), 24.1 (C8/C7). HRMS (ESI): calcd for C$_8$H$_{15}$NO$_5$H 206.1023; found 206.1024.

(3R,4S,5R,6S)-3,4,5,6-Tetra-O-benzyl-cycloheptene **(30)**. The alcohol (**28**) (50.2 mg, 0.116 mmol) was dissolved in anhydrous DMF (4 mL) under a nitrogen atmosphere and stirred at 0 °C. 60% NaH in mineral oil (9.76 mg, 0.232 mmol, 2 eq.) was slowly added and then BnBr (29.1 mg, 0.170 mmol, 1.5 eq.) was under the formation of hydrogen gas. The mixture was stirred overnight. The reaction was quenched by addtion of methanol (2 mL) and the mixture was then diluted with diethyl ether and washed with water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with brine, dried with MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1 : 15) yielding the product (**30**) (28.1 mg, 47% over 2 steps) as a clear oil.

R_f (ethyl acetate/pentane 1 : 10) 0.41; $[\alpha]_D^{298K}$ +7.8 (*c* 1.0, CHCl$_3$); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.28–7.17 (20H, m, Ar*H*), 5.73 (1H, ddd, $J_{1,2}$ 11.7 Hz, $J_{2,3}$ 3.8 Hz, J 1.0 Hz, C*H*=CH), 5.65–5.58 (1H, m, CH=C*H*), 4.73 (2H, d, J 11.9 Hz, 2 × C*H*HPh), 4.63 (1H, d, CH*H*Ph), 4.61 (1H, d, CH*H*Ph), 4.55 (2H, s, C*H$_2$*Ph), 4.43 (1H, d, J 11.9 Hz, C*H*HPh), 4.38 (1H, d, CH*H*Ph), 4.42–4.32 (m, 1H, H3), 3.90 (2H, ddd, $J_{4,3}$ 9.8 Hz, $J_{5,6}$ 7.1 Hz, $J_{4,5}$ 1.8 Hz, H4, H5), 3.62 (1H, td, $J_{6,7}$ 2.8 Hz, 1H), 2.50–2.37 (1H, m, H7a), 2.34–2.18 (1H, m, H7b). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 139.3 (Ar), 139.2 (Ar), 139.0 (Ar), 138.8 (Ar), 132.8 (Ar), 128.4 (Ar), 128.4 (Ar), 128.4 (Ar), 128.4 (Ar), 127.9 (Ar), 127.9 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.5 (Ar), 126.3 (Ar), 81.7 (C4/C5), 79.7 (C4/C5), 77.8 (C6), 76.9 (C*H$_2$*Ph), 73.9 (C3), 73.8 (C*H$_2$*Ph), 72.3 (C*H$_2$*Ph), 71.6 (C*H$_2$*Ph), 28.1 (C7). HRMS (ESI): calcd for C$_{28}$H$_{32}$O$_6$NH$_4$ 543.2506; found 543.2506.

(3R,4S,5R,6R)-3,4,5,6-Tetra-O-benzyl-cycloheptene **(31)**. The alcohol (**29**) (39.4 mg, 91.1 mmol) was dissolved in anhydrous DMF (4 mL) under a nitrogen atmosphere and stirred at 0 °C. 60% NaH in mineral oil (7.53 mg, 0.181 mmol, 2 eq.) was slowly added and then BnBr (23.8 mg, 0.136 mmol, 1.5 eq.) was added under formation of hydrogen gas. The mixture was stirred overnight. The reaction was quenched by addtion of methanol (2 mL) and the mixture was then diluted with diethyl ether and washed with water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with brine, dried with MgSO$_4$, filtered and

concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1 : 25 → 1 : 15) yielding the product (**31**) (20.9 mg, 45% over 2 steps) as a clear oil.

R_f (ethyl acetate/pentane 1 : 10) 0.41; $[\alpha]_D^{298K}$ +4.0 (*c* 1.0, CHCl$_3$); ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.35–7.15 (20 H, m, Ar*H*), 5.60 (1H, dt, J 12.5 Hz, J 2.5 Hz, H2), 5.54–5.47 (1H, m, H1), 4.82 (2H, s, C*H$_2$*Ph), 4.73 (1H, d, J 11.9 Hz, C*H*HPh), 4.68 (1H, d, J 11.6 Hz, C*H*HPh), 4.60 (1H, d, CH*H*Ph), 4.52 (1H, CH*H*Ph) 4.54–4.46 (1H, m, H3), 4.37 (1H, d, J 12.1 Hz, C*H*HPh), 4.32 (1H, d, CH*H*Ph), 4.11 (1H, s, H5), 3.31 (1H, dd, J 9.3 Hz, J 1.0 Hz, H4), 3.23 (1H, dd, J 11.1 Hz, J 2.7 Hz, H6), 2.73–2.53 (1H, m, H7a), 2.10 (1H, ddd, J 15.1 Hz, J 8.6 Hz, J 2.8 Hz, H7b). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 139.5 (Ar), 139.1 (Ar), 139.1 (Ar), 138.7 (Ar), 133.6 (*C*H=CH), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.2 (Ar), 127.9 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.3 (Ar), 124.9 (CH=*C*H), 83.4 (C4), 80.3 (C5), 79.0 (C6), 77.4 (C*H$_2$*Ph) 74.3 (C*H$_2$*Ph), 73.7 (C3), 73.4 (C*H$_2$*Ph), 70.9 (C*H$_2$*Ph), 27.6 (C7). HRMS (ESI): calcd for C$_{35}$H$_{36}$O$_4$Na 543.2506; found 543.2506.

(1R,2S,3R,4S)-1,2,3,4-Tetra-O-benzl-cycloheptane **(32)**. The alkene (**30**) (25 mg, 48 μmol) was dissolved in anhydrous methanol (0.5 mL) and stirred under a nitrogen atmosphere at room temperature. Triethylamine (5 μL, 37 μmol, 0.77 eq.) and a catalytic amount of Pearlman's catalyst were added to the mixture. The atmosphere was exchanged for hydrogen gas and the reaction was stirred for 1 h 30 min hours before exchanging the atmosphere to nitrogen and diluting with methanol. The mixture was then filtrated through cotton wool and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1 : 30) yielding the product (**32**) (15.2 mg, 61%) as a colourless oil.

R_f (ethyl acetate/pentane 1 : 20) 0.35; ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.40–7.15 (10H, m, Ar*H*), 4.72 (1H, d, J 12.0 Hz, C*H*HPh), 4.67 (1H, d, CH*H*Ph), 4.58 (d, J 11.8 Hz, C*H*HPh), 4.50 (1H, d, CH*H*Ph), 4.09 (1H, d, J 6.4 Hz, H1/H2), 3.81 (1H, dd, J 6.3 Hz, J 3.8 Hz, H1/H2), 1.99–1.90/1H, m, H5/H6/H7) 1.87–1.68 (2H, m, H5/H6/H7). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 139.2 (Ar), 139.2 (Ar), 128.4 (Ar), 128.4 (Ar), 127.7 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 81.8 (C1/C2), 73.1 (C*H$_2$*Ph), 71.5 (C*H$_2$*Ph), 31.0 (C5/C6/C7), 17.4 (C5/C6/C7). HRMS (ESI): calcd for C$_{35}$H$_{38}$O$_4$Na 545.2662; found 545.2660.

(1R,2S,3R,4R)-1,2,3,4-Tetra-O-benzyl-cycloheptane **(33)**. The alkene (**31**) (20.9 mg, 40 μmol) was dissolved in anhydrous methanol (0.5 mL) and stirred under a nitrogen atmosphere at room temperature. Triethylamine (4 μL, 30 μmol, 0.77 eq.) and a catalytic amount of Pearlman's catalyst were added to the mixture. The atmosphere was exchanged for hydrogen gas and the reaction was stirred for 3 hours before exchanging the atmosphere to nitrogen and diluting with methanol. The mixture was then filtrated through cotton wool and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/pentane 1 : 30) yielding the (**33**) (9.52 mg, 45%) as a colourless oil.

R_f (ethyl acetate/pentane 1 : 20) 0.35. ^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 7.36–7.15 (20H, m, ArH), 4.79 (1H, d, J 12.3 Hz, CHHPh), 4.75 (1H, d, J 12.3 Hz, CHHPh), 4.55 (1H, d, J 11.8 Hz, CHHPh), 4.54 (1H, d, J 11.4 Hz, CHHPh) 4.48 (1H, d, J 11.4 Hz, CHHPh), 4.46 (1H, d, J 11.8 Hz, CHHPh), 4.31 (2H, s, CH_2Ph), 4.05 (1H, s, C2/C3), 3.78–3.71 (1H, m, C2/C3), 3.39 (1H, dd, J 7.2 Hz, J 0.8 Hz, C1/C4), 3.30–3.24 (1H, m, C1/C4), 2.00–1.50 (6H, m, C5, C6, C7). ^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 139.5 (Ar), 139.2 (Ar), 139.0 (Ar), 138.8 (Ar), 128.5 (Ar), 128.4 (Ar), 128.4 (Ar), 128.2 (Ar), 128.0 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 127.6 (Ar), 127.5 (Ar), 127.3 (Ar), 85.3 (C1/C4), 82.5 (C2/C3), 81.1 (C1/C4), 79.9 (C2/C3), 73.4 (CH_2Ph), 73.0 (CH_2Ph), 72.1 (CH_2Ph), 71.0 (CH_2Ph), 30.2 (C5/C6/C7), 29.8 (C5/C6/C7), 18.6 (C5/C6/C7). HRMS (ESI): calcd for C$_{35}$H$_{38}$O$_4$H 523.2843; found 523.2843.

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