Carbohydrate Research 346 (2011) 2855–2861

Contents lists available at SciVerse ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Chiral pool synthesis of calystegine A_3 from 2-deoxyglucose via a Brown allylation

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ARTICLE INFO

Article history:
Received 31 August 2011
Received in revised form 14 October 2011
Accepted 14 October 2011
Available online 22 October 2011

Keywords:
Calystegine
Benzylidene opening
Ring closing metathesis
Staudinger reduction

ABSTRACT

Calystegine A_3 is a naturally occurring nortropane iminosugar of which there previously have been three total syntheses. Inspired by our previous work we here report on a fourth approach using 17 steps from 2-deoxy-D-glucose applying a diastereoselective allylation protocol.

1. Introduction

Calystegines are naturally occurring polyhydroxylated nortropanes found in the underground organs and root exudates of plants belonging to the families *Convolvulaceae* and *Solanaceae*, for example, *Calystegia sepium*.[1] These compounds are classified into three groups based on the numbers of hydroxyl groups present on the bicyclic ring system: those carrying three hydroxyl groups are designated A, while calystegines containing four or five hydroxyl groups are designated B and C, respectively. More than 10 different calystegines have been isolated and some representative examples are shown in Figure 1, **1**–**4**. A typical feature of calystegines is the presence of a tertiary hydroxyl group at the bridge head as a part of a hemiaminal functionality. Due to the structural resemblance to monosaccharides, many calystegines show significant inhibition of glycoside hydrolases, in particular β-glucosidase and both α- and β-galactosidases.[2–4] Calystegine B_2 (**2**) is the most abundant of the calystegines and since the structural determination in the beginning of 1990s it has been a synthetically challenging target and several elegant total syntheses have been reported.[5–8] Recent crystallographic results have shown that calystegine B_2 binds to *Thermotoga maritima* of the glycosidase family 1 (*Tm*GH1) in a 'noeuromycin binding mode' rather than the opposite '1-deoxynojirimycin binding mode'.[9] The observed binding mode places the endocyclic nitrogen atom in the position taken up by C-1 of the substrate, which will allow for strong interactions between the hemiaminal OH and the protein.[10–13] This binding mode can also be expected to be in operation for other calystegines.

A stereochemically identical yet deoxygenated version of calystegine B_2 is calystegine A_3 (**1**), which is also widespread in occurrence. It was first isolated from *Calystegia sepium* in 1988[14] followed by structural determination in 1990.[15,16] There has to date been three total syntheses of calystegine A_3 (**1**).[17–19] The most recent of these uses a zinc-mediated tandem reaction in combination with ring-closing metathesis, which allows for the transformation of an iodo-glycoside into a cycloheptene in two steps.[19] Here we report a new total synthesis of calystegine A_3 (**1**) using a strategy inspired by our recent synthesis of the non-natural analogues noeurostegine (**5**)[20,21] and *uronic*-noeurostegine,[22] where the nitrogen atom is introduced as an azide instead of as a carbamate for easy structure elucidation by avoiding rotamers of several synthetic intermediates.

2. Results and discussion

Calystegine A_3 (**1**) is deoxygenated in the 4-position and contains two equatorial positioned secondary hydroxyl groups at C2 and C3. This substituent pattern can be found in commercially available 2-deoxy-D-glucose (**6**) and hence it was planned to transform this compound into calystegine A_3 (**1**) via a similar route as applied for noeurostegine (**5**).[20,21] By our earlier results we envisaged that calystegine A_3 (**1**) could be obtained in a series of steps from cycloheptene **8** via azido compound **7**. Formation of cycloheptene **8** was to be achieved by a ring-closing metathesis of diene **9**, which in turn was to originate from iodoglucoside **10** through a

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doi:10.1016/j.carres.2011.10.025

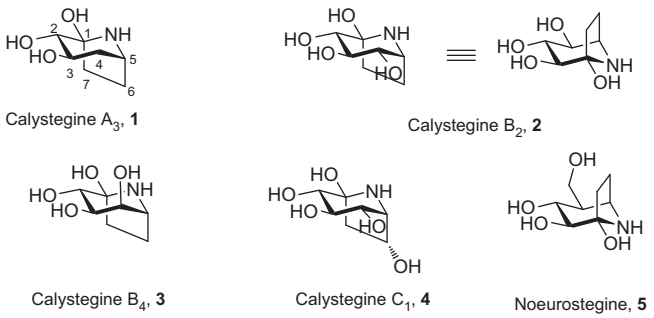
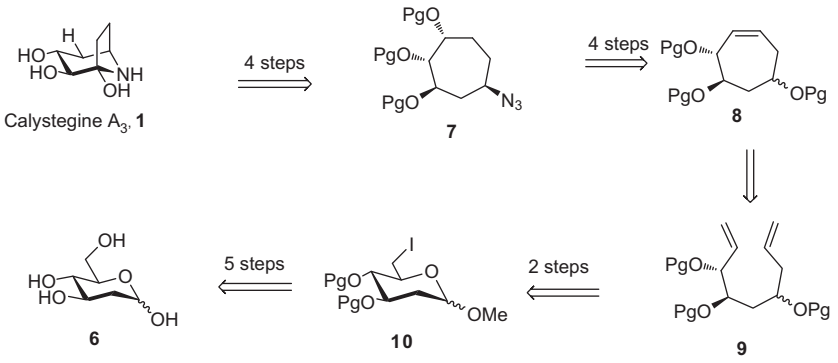


Figure 1. Examples of naturally occurring calystegines (**1**–**4**) and a synthetic analogue **5**.

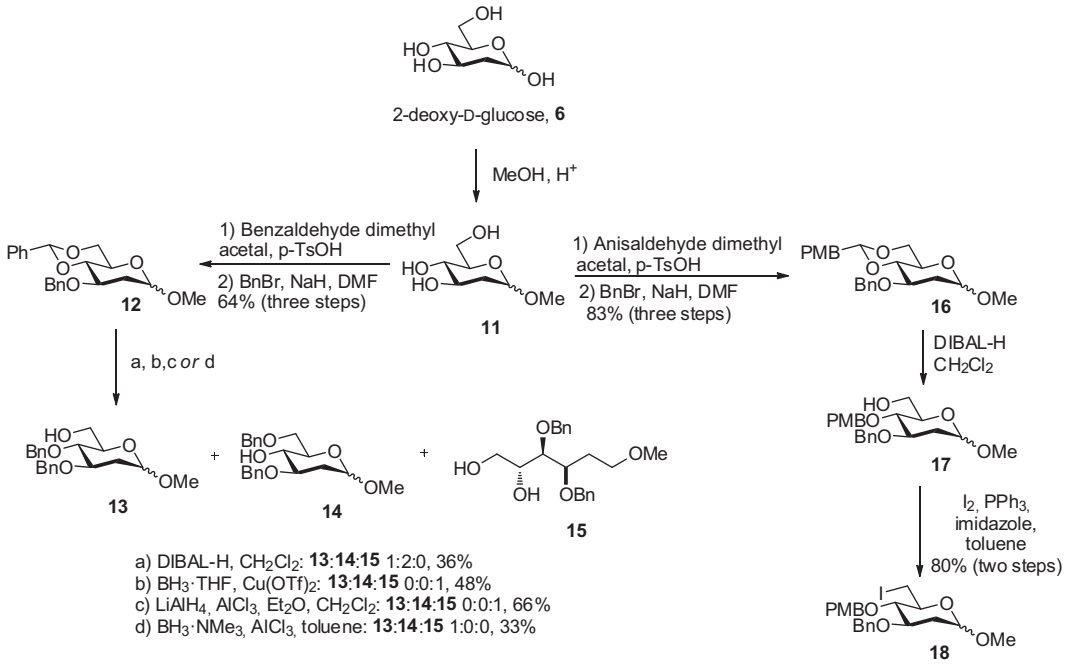
zinc-mediated fragmentation and subsequent diastereoselective allylation of the aldehyde. Methyl 6-iodoglucoside **10** is hence a key intermediate in our synthesis of calystegine A_3 (**1**), which we believe could be obtained from 2-deoxy-D-glucose (**6**) in a series of steps involving several protecting group manipulations (Scheme 1).

For the synthesis of **10**, 2-deoxyglucose (**6**) was first transformed into its methyl glucoside **11** by Fischer glycosylation and next 4,6-*O*-benzylidene formation using benzaldehyde dimethylacetal under acidic conditions and reduced pressure (Scheme 2).[23,24] Next, the free 3-OH was protected as a benzyl ether in one-pot to give **12** in a 64% yield over three steps. It was next attempted to regioselectively open the acetal function to liberate the 6-OH for later substitution with iodide. This, however, proved troublesome. Opening with DIBAL-H in toluene[25,26] gave a regioisomeric mixture in favour of the undesired 4-OH product (**14**) in contrast to the findings by Tanaka et al. for the regioselectivity in similar systems undergoing opening with DIBAL-H in toluene.[26] Reaction of **12** with borane–THF complex using $Cu(OTf)_2$ was found to reductively open the acetal with the desired selectively but was too reactive for this labile 2-deoxy glycoside resulting in methyl ether **15**. This was also the case for $LiAlH_4/AlCl_3$. Finally, borane-trimethylamine complex was tried in combination with $AlCl_3$. These conditions did provide the free 6-OH compound **13** as the main product, but the yield proved to be low (33%).

As an alternative approach resembling our initial strategy we were indeed capable of accessing the needed key iodo-intermediate **10** for the synthesis of calystegine A_3 (**1**) in five steps starting



Scheme 1. Retrosynthetic considerations.

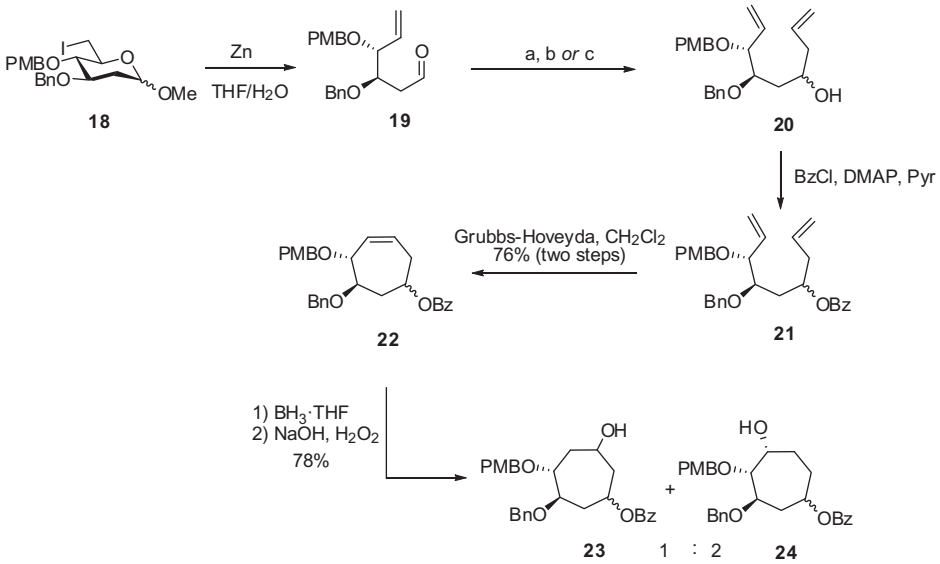


Scheme 2. Different strategies for formation of protected methyl 2-deoxy-6-hydroxyglucoside.

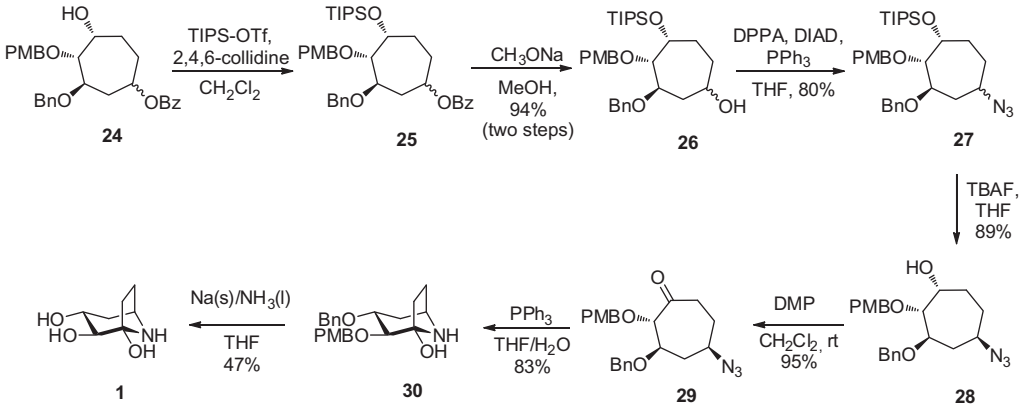
from 2-deoxy-D-glucose **6** (Scheme 2). Again starting from 2-deoxy-D-glucose (**6**) via the methyl glucoside (**11**) we formed the 4,6-*p*-methoxybenzylidene acetal by reaction with *p*-methoxybenzaldehyde dimethylacetal in the presence of PTSA followed by benzylation of the free 3-OH in one pot afforded the protected 2-deoxyglucoside **16** in 83% yield over three steps. Next, we found it to be possible to open the 4,6-acetal of **16** using DIBAL-H in toluene with complete regioselectivity, affording compound **17** bearing a free 6-OH. Opening of the *p*-methoxybenzylidene acetal was also attempted with DIBAL-H in THF, however, no reaction was observed under these conditions. This reaction was followed by iodination to give **18** in an 80% yield over two steps (Scheme 2).

Zinc-mediated fragmentation of iodide **18** under sonication in THF–H_2O as described by Madsen and co-workers[27] resulted in clean conversion into aldehyde **19**, which was used directly in the following Barbier reaction[28] without purification. This resulted in a non-separable diastereoisomeric 2:3 mixture of homoallylic alcohol **20*R*/20*S*** in an 80% yield (conditions a, Scheme 3). The stereochemistry at the new stereogenic centre was established after the ring-closing metathesis reaction. As a consequence of the reaction outcome and the fact that the isomers could not be separated we investigated an asymmetric allylation as an alternative. Two asymmetric allylation protocols were investigated. Diastereoselective addition of allyltin reagents[29,30] was first attempted, however, only degradation of the aldehyde was observed (conditions b, Scheme 3). Then, the Brown allylation was investigated, and this asymmetric protocol proved to be very efficient.[31–36] The Brown allylation gave hydroxydiene **20** as a diastereoisomeric 1:11 mixture of *R*- and *S*-isomers in a 79% yield (conditions c, Scheme 3). With this satisfactory result we continued with protection of the secondary alcohol as a benzoyl ester followed by a Hoveyda–Grubbs catalysed ring-closing metathesis to give the cycloheptene **22** in a 76% yield, still as a non-separable mixture of diastereoisomers (Scheme 3). Oxidation of the double bond by a standard hydroboration/oxidative workup protocol afforded an isomeric mixture of secondary alcohols in a 78% yield (Scheme 3). Both regioisomers **23** and **24** were obtained as a single isomer which corresponds to previous observations in the noeurostegine (**5**) synthesis.[20] The regioisomeric ratio was 2:1 in favour of the desired product **24** in accordance with Madsen and co-workers observation in a similar system.[19]

The secondary alcohol of **24** was protected as a silyl ether (**25**) with triisopropylsilyl triflate in dichloromethane followed by benzoyl ester removal by Zemplén deacylation[37] to give alcohol **26** in a 94% yield over two steps (Scheme 4). The free secondary alcohol **27** was then substituted for azide under Mitsunobu-type conditions[38]



Scheme 3. Synthesis of cycloheptane **23** and **24** from iodoglucoside **18**. Reagents and conditions for attempted allylations: (a) Allyl-Br, In(s), THF/H_2O, 80%, *dr* 3:2; (b) (*S*)-BINOL, Ti(OiPr)$_4$, allyl-Sn(Bu)$_3$, CH_2Cl_2, no product; (c) 1) (−)-Ipc-allylborane, Et_2O, then $NaBO_3{\cdot}4H_2O$, THF/H_2O, 79%, *dr* 11:1.



Scheme 4. Synthesis of calystegine A_3 from intermediate **24**.

to afford an easy separable mixture of azides **27** in an 80% yield (Scheme 4). The desired *R*-configured azide **27*R*** was then treated with TBAF in THF to give secondary alcohol **28** in good yield. Subsequent oxidation of alcohol **28** by Dess–Martin periodinane[39] (DMP) afforded azido ketone **29** in a 95% yield (Scheme 4). Based on our previous experience from the synthesis of the calystegine B_2 analogue, noeurostegine (**5**),[20] we chose to conduct the cyclisation and deprotection in two separate steps. Accordingly, azido ketone **29** was treated with triphenyl phosphine under Staudinger conditions[40] to afford the spontaneously cyclized product **30** in an 83% yield. A hemiaminal ^{13}C chemical shift of 93.4 ppm instead of a ketone resonance at around 209 ppm indicated the presence of the bicyclic compound. Catalytic hydrogenation over either Pearlman's catalyst or palladium on charcoal was not successful, even under acidic conditions (TFA or hydrochloride acid). Deprotection of the two ether protection groups was instead achieved via Birch reduction which yielded the natural product **1** in moderate yield (Scheme 4).[41–47] Calystegine A_3 was separated from ammonium chloride by an acidic ion-exchange column and the optical rotation and spectroscopic data were in agreement with the literature data.[2,15,16]

3. Conclusion

The naturally occurring compound calystegine A_3 has been successfully synthesised in 17 steps from 2-deoxy-D-glucose with nitrogen introduced as an azide allowing for well resolved NMR spectra and thereby easy structural determination. Brown allylation of an intermediate α-unsubstituted aldehyde proceeded with in good diastereoisomeric control (11:1) and formation of a significant amount of the unusable diastereoisomer was thereby avoided.

4. Experimental section

4.1. General methods

All reagents except otherwise stated were used as purchased without further purification. Zinc was activated as previously described.[20] Oven dried glassware (ca. 120 °C) was used for reactions carried out under nitrogen or argon atmosphere. Solvents were dried using MB-SPS Solvent Purification System. Flash chromatography was performed with Merck Silica 60 (230–400 mesh) as the stationary phase and TLC was performed on silica-coated aluminium plates (Merck 60 F_{254}). TLC plates were first observed in UV-light and then visualised with ceric sulphate/ammonium molybdate in 10% H_2SO_4 stain or $KMnO_4$-stain. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded at a Varian Mercury 400 spectrometer. $CDCl_3$ (δ 7.26 ppm ($CHCl_3$) for proton and δ 77.16 ppm for carbon resonances) and D_2O (δ 4.79 ppm for proton) were used as internal references. Spectra were assigned based on *g*COSY, *g*HMQC, and DEPT-135 experiments. MS spectra were recorded at a Micromass LC-TOF instrument by using electrospray ionization (ESI). High resolution spectra were recorded with either of the following compounds as internal standard: (Boc-L-alanine: $C_8H_{15}NO_4Na$: 212.0899; BzGlyPheOMe: $C_{19}H_{20}N_2O_4Na$: 363.1321; BocSer(OBn)SerLeuOMe: $C_{25}H_{39}N_3O_8Na$: 532.2635; erythromycin: $C_{37}H_{67}NO_{13}Na$: 756.4510) Masses of standards and analytes are calculated and reported in Daltons for un-charged species. Optical rotation was measured on a PE-241 polarimeter and reported in units of deg·cm^2/g. Concentrations are reported in g/100 mL. Sonication was conducted by the use of a Branson 1510 sonic bath. Microwave experiments were carried out on a Biotage Initiator (Biotage, Sweden). Reaction times listed refer to 'hold time' at the specified temperature.

4.2. Methyl 3-*O*-benzyl-2-deoxy-4,6-*O*-(*p*-methoxybenzylidene)-α/β-D-glucopyranoside (16)

2-Deoxy-D-glucose (**6**) (4.77 g, 0.05 mol) was dissolved in dry MeOH (75 mL) under an atmosphere of nitrogen. Amberlite IR-120 (H^+) ion exchange resin (10 mL) was added and the reaction mixture was stirred at 30 °C for 3 days. The reaction mixture was filtered and the ion exchange resin was washed with MeOH (3 × 50 mL) and concentrated. The resulting product **11** (5.58 g) was concentrated twice from toluene prior to dissolution in dry DMF (80 mL). Anisaldehyde dimethyl acetal (7.5 mL, 0.04 mol, 1.4 equiv) and enough of a catalytic amount of *p*-TsOH to make an acidic solution (pH-paper) were added and the reaction mixture was stirred under reduced pressure (200 mbar) at 40 °C for 1 h. The reaction mixture was cooled to 0 °C and sodium hydride (60%, 6.27 g, 0.16 mol, 5 equiv) was added in small portions. After stirring for 10 min at 0 °C benzyl bromide (7.5 mL, 0.06 mol, 2 equiv) was added. The reaction mixture was warmed to rt and stirred for 17 h. To obtain reaction completion, the reaction mixture again was cooled to 0 °C and further portions of sodium hydride (2.5 g, 0.06 mol, 2 equiv) and benzyl bromide (8.0 mL, 0.07 mol, 2.2 equiv) were added. The reaction mixture was then warmed to rt and stirred for three another hours after which TLC analysis indicated full conversion of starting material. The reaction was quenched by dropwise addition of MeOH (60 mL) and then diluted with EtOAc (250 mL). The organic phase was washed with H_2O (3 × 250 mL) and brine (3 × 250 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (pentane/EtOAc 20:1→10:1→5:1) to give the desired product **16** (9.32 g, 83% (three steps) colourless oil) as a 7:1 (determined by ^{13}C NMR) mixture of α/β anomers. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) α-anomer: 7.44–7.27 (m, 7H, Ar*H*), 6.90 (m, 2H, *Ph*OCH$_3$), 5.58 (s, 1H, C*H*PhOCH$_3$), 4.82 (d, 1H, *J* 12.0 Hz, CH_2Ph), 4.80 (br s, 1H, H1), 4.67 (d, 1H, *J* 12.0 Hz, CH_2Ph), 4.24 (m, 1H, H6a), 4.00 (m, 1H, H3), 3.82 (s, 3H, CH_3OPh), 3.79–3.73 (m, 2H, H6b,H5), 3.67 (m, 1H, H4), 3.33 (s, 3H, OCH_3), 2.26 (m, 1H, H2ax), 1.79 (ddd, 1H, *J* 4.0 Hz, *J* 11.2 Hz, *J* 13.2 Hz, H2eq). NMR was in accordance with previous reported data.[48]

4.3. Methyl 3-*O*-benzyl-2,6-dideoxy-6-iodo-4-*O*-*p*-methoxybenzyl-α/β-D-glucopyranoside (18)

DIBAL-H (1 M in toluene, 40 mL, 40.0 mmol, 3 equiv) was added over 30 min to a solution of **16** (5.18 g, 13.4 mmol) in dry CH_2Cl_2 (170 mL) at 0 °C. The reaction was quenched, after stirring for 45 min, by dropwise addition of aq HCl (1 M, 100 mL). The organic phase was washed with a satd aq solution of $NaHCO_3$ (100 mL), brine (3 × 200 mL), dried over $MgSO_4$, filtered and concentrated. The resulting alcohol product **17** (5.20 g) (the 4-OH isomer could not be detected by crude ^{13}C NMR) was dissolved in dry toluene (100 mL) and PPh_3 (8.32 g, 31.7 mmol, 2.5 equiv), I_2 (3.55 g, 14.0 mmol, 1.1 equiv) and imidazole (1.74 g, 25.6 mmol, 2.0 equiv) were added. The reaction mixture was heated at reflux for 1.5 h then cooled to rt and added a sated aq solution of $Na_2S_2O_3$ (140 mL). The organic phase was washed with brine (3 × 200 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (pentane/EtOAc 20:1→15:1) to give the desired product **18** (5.33 g, 80% (two steps)) as a 7:1 mixture of α/β anomers. α anomer: R_f (pentane/EtOAc 10:1) 0.48. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.37–7.23 (m, 7H, Ar*H*), 6.87 (m, 2H, *Ph*OCH$_3$), 4.92 (d, 1H, *J* 10.4 Hz, CH_2Ph), 4.82 (d, 1H, *J* 3.6 Hz, H1), 4.67 (d, 1H, *J* 11.6 Hz, CH_2Ph), 4.65 (d, 1H, *J* 10.4 Hz, CH_2Ph), 4.61 (d, 1H, *J* 11.6 Hz, CH_2Ph), 3.98 (m, 1H, H3), 3.81 (s, 3H, CH_3OPh), 3.52 (m, 1H, H6a), 3.43–3.29 (m, 6H, H4, H5, H6b, OCH_3), 2.29 (m, 1H, H2ax), 1.69 (dt, 1H, *J* 3.6 Hz, *J* 11.6 Hz, H2 eq). ^{13}C NMR (100 MHz, $CDCl_3$):

δ_C (ppm) 159.3, 138.5, 130.4, 129.6, 128.4, 127.6, 113.8 (ArC), 98.4 (C1), 81.8, 77.1, 74.9, 71.6, 69.9, 55.2, 54.9, 35.4, 8.6 (C6). HRMS(ES+): calcd for $C_{22}H_{27}I\ NaO_5$: 521.0801, found 521.0804.

4.4. (*3R,4R*)-3-*O*-Benzyloxy-4-*O*-*p*-methoxybenzyloxy-hex-5-enal (19)

To a solution of iodide **18** (1.80 g, 3.62 mmol) in THF (70 mL) was added pre-activated Zn dust[20] (2.60 g, 39.8 mmol, 11 equiv) and H_2O (10 mL). The resulting suspension was sonicated at 40 °C until TLC-analysis showed full conversion (2.5 h). The reaction mixture was then diluted with Et_2O (150 mL) and H_2O (60 mL) and the resulting mixture filtered through a pad of Celite and the organic phase washed with H_2O (100 mL) and brine (100 mL), and dried over Na_2SO_4 and concentrated. The isolated aldehyde **19** (1.26 g) was used directly in the next reaction without further purification. R_f (pentane/EtOAc 10:1) 0.31. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 9.70 (s, 1H, C*H*O), 7.35–7.21 (m, 7H, Ar*H*), 6.87 (m, 2H, *Ph*OCH$_3$), 5.83 (ddd, 1H, $J_{4,5}$ 6.8 Hz, J_{cis} 10.4 Hz, J_{trans} 17.2 Hz, H5), 5.36 (m, 2H, H6a, H6b), 4.69 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.62 (d, 1H, *J* 11.6 Hz, C*H*$_2$Ph), 4.57 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.32 (d, 1H, *J* 11.6 Hz, C*H*$_2$Ph), 4.08 (m, 1H, H3), 3.97 (t, 1H, *J* 6.8 Hz, H4), 3.81 (s, 3H, C*H*$_3$OPh), 2.66 (ddd, 1H, $J_{1,2a}$ 1.6 Hz, $J_{2a,3}$ 4.4 Hz, J_{gem} 16.8 Hz, H2a), 2.58 (ddd, 1H, $J_{1,2b}$ 2.4 Hz, $J_{2b,3}$ 8.4 Hz, J_{gem} 16.8 Hz, H2b).

4.5. (*3R,4R,6R/S*)-4-*O*-Benzyloxy-6-hydroxy-3-*O*-*p*-methoxybenzyloxy-nona-1,8-diene (20*R*/*S*)

To a stirred solution of the intermediate aldehyde **19** (1.26 g, 3.70 mmol) in dry Et_2O (50 mL) at −100 °C a solution of (−)-Ipc-allylborane in pentane (1 M, 10 mL, 10.0 mmol, 2.7 equiv) slowly cannulated at −78 °C into the cooled Et_2O solution. The reaction mixture was stirred at −100 °C for 2 h and then quenched by dropwise addition of MeOH (6 mL). The mixture was warmed to rt and then concentrated. The resulting residue was dissolved in THF/H_2O (1:1, 40 mL) and $NaBO_3{\cdot}H_2O$ (1.43 g, 9.26 mmol, 2.5 equiv) was added and the reaction mixture was stirred at rt for 17 h. The mixture was diluted with brine (100 mL) and the aqueous phase extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated before the crude product was purified by column chromatography (pentane/EtOAc 25:1→20:1→10:1) to give the desired product **20** (1.09 g, 79% (two steps)) as a 1:11 non-separable mixture of *R*- and *S*-diastereoisomers. R_f (pentane/EtOAc 7:1) 0.27. *S*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.33–7.24 (m, 7H, Ar*H*), 6.86 (m, 2H, *Ph*OCH$_3$), 5.70 (m, 2H, H2, H8), 5.32 (m, 2H, H1/H9), 5.08 (m, 2H, H9/H1), 4.77 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.59 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.58 (d, 1H, *J* 11.6 Hz, C*H*$_2$Ph), 4.35 (d, 1H, *J* 11.6 Hz, C*H*$_2$Ph), 3.96 (m, 1H, H3) 3.84–3.77 (m, 5H, H4, H6, C*H*$_3$OPh) 2.18 (m, 2H, H7) 1.62 (dd, 2 H, *J* 5.6 Hz, *J* 6.4 Hz, H5). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 159.2, 138.6 (ArC), 135.1, 135.0 (C2,C8) 130.4, 129.4, 128.5, 128.4, 128.1, 127.7 (ArC) 119.0, 117.6 (C1,C9) 113.8 (ArC), 82.1 (C3) 78.4 (C4/C6) 73.5 (*C*H$_2$Ph) 70.3 (*C*H$_2$Ph) 67.7 (C6/C4) 55.2 (*C*H$_3$OPh) 42.4 (C7) 37.5(C5). HRMS(ES+): calcd for $C_{24}H_{30}NaO_4$: 405.2042, found 405.2039.

4.6. (*3R,4R,6R/S*)-6-*O*-benzoyloxy-4-*O*-benzyloxy-3-*O*-*p*-methoxybenzyloxycycloheptene (22)

To a stirred solution of hydroxydiene **20** (1.10 g, 2.87 mmol) in dry pyridine (40 mL) were added BzCl (0.7 mL, 6.04 mmol, 2 equiv) and a catalytic amount of DMAP (35 mg, 0.29 mmol, 0.1 equiv). The reaction mixture was stirred at rt for 16 h and then quenched by dropwise addition of H_2O (50 mL) and continuous stirring for 10 min. The mixture was diluted with EtOAc (120 mL) and the organic phase washed with 1 M HCl (3 × 100 mL), a satd aq solution of $NaHCO_3$ (3 × 100 mL), brine (2 × 100 mL), dried over $MgSO_4$ and concentrated. The resulting product **21** (1.38 g) and Hoveyda–Grubbs 2nd generation catalyst (35 mg, 0.056 mmol, 0.02 equiv) were dissolved in dry CH_2Cl_2 (15 mL) in a sealed microwave vial. The reaction mixture was heated by microwave irradiation for 3 min (80 °C) after which the formed ethylene gas was released; the microwave irradiation was then continued for 10 min. Then more Hoveyda–Grubbs 2nd generation catalyst (10 mg, 0.016 mmol, 0.006 equiv) was added and microwave irradiation was resumed for another 10 min. The solvent was removed under reduced pressure and the remaining residue was purified by column chromatography (pentane/EtOAc 20:1) to give the desired cycloheptene **24** as a 1:11 diastereoisomeric mixture (1.10 g, 84 % (two steps)). R_f (pentane/EtOAc 10:1) 0.47. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 8.00 (m, 2H, Ar*H*), 7.55 (m, 1H, Ar*H*), 7.43 (m, 2H, ArH), 7.34–7.25 (m, 7H, Ar*H*), 6.87 (m, 2H, *Ph*OCH$_3$), 5.86 (m, 2H, H1, H2), 5.35 (m, 1H, H6), 4.72 (d, 1H, *J* 11.6 Hz, C*H*$_2$Ph), 4.65 (d, 1 H, *J* 11.6 Hz, C*H*$_2$Ph), 4.62 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.52 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.17 (dd, 1H, *J* 3.6 Hz, *J* 7.2 Hz, H3), 3.88 (dt, 1H, *J* 7.2 Hz, *J* 2.8 Hz, H4), 3.81 (s, 3H, C*H*$_3$OPh), 2.66 (m, 1H, H7), 2.52 (m, 1H, H7′), 2.40 (ddd, 1H, *J* 2.8 Hz, *J* 8.8 Hz, *J* 14.4 Hz, H5), 2.26 (ddd, 1H, *J* 3.2 Hz, *J* 7.2 Hz, *J* 14.4 Hz, H5′). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 165.8 (*C*O), 159.3, 138.7 (ArC), 133.0 (C1/C2), 132.3, 130.8–127.6 (ArC, C2/C1), 113.9 (ArC), 78.7 (C3), 75.9 (C4), 71.8 (*C*H$_2$Ph), 71.4 (*C*H$_2$Ph), 69.2 (C6), 55.4 (*C*H$_3$OPh), 36.2 (C7), 33.1 (C5). HRMS(ES+): calcd for $C_{29}H_{30}NaO_5$: 481.1991, found 481.1995.

4.7. (*1R/S,3R,4R,6R/S*)-1-*O*-Benzoyloxy-3-*O*-benzyloxy-4-*O*-*p*-methoxybenzyloxy-cycloheptane 6-ol (23) and (*1R/S,3R,4R,5R*)-1-*O*-benzoyloxy-3-*O*-benzyloxy-4-*O*-*p*-methoxybenzyloxy-cycloheptane-5-ol (24)

$BH_3{\cdot}$THF complex (1 M solution in THF, 4.8 mL, 4.80 mmol, 2 equiv) was added in a dropwise fashion to a stirred solution of **22** (1.10 g, 2.40 mmol) in dry THF (25 mL) at 0 °C. After stirring for 2 h at 0 °C, NaOH (2 M, 5 mL) and aq H_2O_2 (35%, 10 mL) was added. The reaction mixture was allowed to reach rt and stirred for additional 2 h before diluted with Et_2O (100 mL). The organic phase was washed with H_2O (2 × 100 mL), brine (3 × 100 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (pentane/EtOAc 4:1) to give regioisomers **24** and **25** (0.96 g, 84% (overall yield)) as a 2:1 mixture which were easily separated.

4.8. (*1R/S,3R,4R,6R/S*)-1-*O*-Benzoyloxy-3-*O*-benzyloxy-4-*O*-*p*-methoxybenzyloxy-cycloheptane-6-ol (23)

Colourless oil (0.33 g, 29%). R_f (pentane/EtOAc 2:1) 0.29. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 8.03 (m, 2H, Ar*H*), 7.55 (m, 1H, Ar*H*), 7.42 (m, 2H, Ar*H*), 7.34–7.22 (m, 7H, Ar*H*), 6.86 (m, 2H, *Ph*OCH$_3$), 5.50 (m, 1H, H1), 4.68 (d, 1H, *J* 11.6 Hz, C*H*$_2$Ph), 4.57 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.47 (m, 2H, C*H*$_2$Ph), 4.24 (m, 1H, H6), 3.85 (m, 2H, H3, H4), 3.80 (s, 3H, C*H*$_3$OPh), 2.22 (m, 3H, H2, H5, H7), 2.14 (m, 3H, H2′, H5′, H7′). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 165.8 (*C*O), 159.3, 138.2, 133.0 (ArC), 130.7–127.7 (ArC) 113.9 (ArC), 77.6, 77.0, 71.5, 71.3, 68.5, 64.3, 55.4 (*C*H$_3$OPh), 43.9, 38.7, 33.3. HRMS(ES+): calcd for $C_{29}H_{32}NaO_6$: 499.2097, found 499.2101.

4.9. (*1R/S,3R,4R,5R*)-1-*O*-Benzoyloxy-3-*O*-benzyloxy-4-*O*-*p*-methoxybenzyloxy-cycloheptane-5-ol (24)

Colourless oil (0.63 g, 55%). R_f (pentane/EtOAc 4:1) 0.17. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 8.03 (m, 2H, Ar*H*), 7.57 (m, 1H,

Ar*H*), 7.47–7.21 (m, 9H, Ar*H*), 6.88 (m, 2H, *Ph*OCH$_3$), 5.36 (m, 1H, H1), 4.78 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.71 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.55 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 4.50 (d, 1H, *J* 11.2 Hz, C*H*$_2$Ph), 3.87 (m, 1H, H3), 3.81 (s, 3H, C*H*$_3$OPh), 3.72 (m, 1H, H5), 3.48 (dd, 1H, *J* 7.6 Hz, *J* 4.8 Hz, H4), 2.65 (br s, 1H, O*H*), 2.34 (ddd, 1H, *J* 2.4 Hz, *J* 7.2 Hz, *J* 14.8 Hz, H2), 2.24 (m, 1H, H7), 2.10–1.97 (m, 2H, H2′, H6), 1.70 (m, 2H, H6′, H7′). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 165.9 (*C*O), 159.5, 138.1, 133.0 (Ar*C*), 130.7–127.9 (Ar*C*), 114.1 (Ar*C*), 87.5 (C4), 77.1 (C3), 73.3 (*C*H$_2$Ph), 73.0 (C5), 71.2 (*C*H$_2$Ph), 70.9 (C1), 55.4 (*C*H$_3$OPh), 33.3 (C2), 30.1, 28.0 (C6,C7). HRMS(ES+): calcd for $C_{29}H_{32}NaO_6$: 499.2097, found 499.2094.

4.10. (3*R*,4*S*,5*R*)-3-*O*-Benzyloxy-4-*O*-*p*-methoxybenzyloxy-5-*O*-triisopropylsilyl-cycloheptan-1-ol (26)

TIPS-OTf (0.60 mL, 2.22 mmol, 1.7 equiv) and 2,4,6-collidine (0.38 mL, 2.88 mmol, 2.2 equiv) were added to a solution of **24** (0.63 g, 1.31 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 90 min and then quenched by addition of satd aq solution of $NaHCO_3$ (80 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic phases were washed with aq HCl (1 M, 50 mL), satd aq $NaHCO_3$ (2 × 50 mL), brine (2 × 50 mL), dried over $MgSO_4$ and concentrated. The resulting product **25** (0.98 g, 1.55 mmol) was used directly in the next reaction without further purification. Sodium (105 mg, 4.57 mmol, 2.9 equiv) was dissolved in dry MeOH (12 mL) and the resulting solution added to the crude product **25** (0.98 g, 1.55 mmol) under an atmosphere of nitrogen. The reaction mixture was stirred overnight before being diluted with EtOAc (80 mL) and the organic phase washed with water (3 × 80 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (pentane/EtOAc 7:1→5:1) to give the desired product **26** (0.64 g, 92%) as a colourless oil. R_f (pentane/EtOAc 5:1) 0.33. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.36–7.23 (m, 7H, Ar*H*), 6.85 (m, 2H, *Ph*OCH$_3$), 4.58 (m, 4H, C*H*$_2$Ph), 4.10 (m, 2H, H1, H5), 3.93 (m, 1H, H3), 3.80 (s, 3H, C*H*$_3$OPh), 3.63 (m, 1H, H4), 2.17 (m, 2H, H2, H6/H7), 1.93 (m, 2H, H2, H7/H6), 1.77 (m, 1H, H6/H7) 1.60 (br s, 1H, O*H*), 1.51 (m, 1H, H2/H6/H7), 1.08 (s, 21 H, C*H*CH$_3$, CHC*H*$_3$. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 159.2, 139.0, 131.0, 129.4, 128.4, 127.8, 127.5, 113.8 (Ar*C*), 87.1 (C4), 77.6 (C3), 73.5 (C1/C5), 72.6 (*C*H$_2$Ph), 71.3 (C*H*$_2$Ph) 67.2 (C5/C1) 55.4 (C*H*$_3$OPh) 36.3 (C2), 31.7, 26.0 (C6,C7), 18.3 (CH*C*H$_3$), 12.5 (*C*HCH$_3$). HRMS(ES+): calcd for $C_{31}H_{48}NaO_5Si$: 551.3169, found 551.3170.

4.11. (1*R*,2*S*,3*R*,5*R*/*S*)-5-Azido-3-*O*-benzyloxy-2-*O*-*p*-methoxybenzyloxy-1-*O*-triisopropylsilyl-cycloheptane (27)

To a cooled (0 °C) and stirred solution of alcohol **26** (0.64 g, 1.21 mmol) in dry THF (20 mL) were consecutively added PPh_3 (0.95 g, 3.61 mmol, 3 equiv), DPPA (0.69 mL, 3.20 mmol, 2.6 equiv) and DIAD (0.66 mL, 3.18 mol, 2.6 equiv) in a dropwise fashion. The reaction mixture was allowed to reach rt and then stirred for 2 h. The reaction mixture was concentrated and the resulting residue was purified by flash column chromatography (pentane/EtOAc 80:1) to give the product **27** (0.54 g, 80%) as a 1:8 separable mixture of *S*- and *R*-diastereoisomers.

4.12. (1*R*, 2*S*, 3*R*, 5*R*)-5-azido-3-*O*-benzyloxy-2-*O*-*p*-methoxybenzyloxy-1-*O*-triisopropylsilyl-cycloheptane (27*R*)

Colourless oil (0.47 g, 71%). 0.23. $[\alpha]_D^{20}$ −32 (*c* 1.0, $CHCl_3$). R_f (pentane/EtOAc 80:1) ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.35–7.22 (m, 7H, Ar*H*), 6.86 (m, 2H, *Ph*OCH$_3$), 4.65 (d, 1H, *J* 11.6 Hz, C*H*$_2$Ph), 4.63 (d, 1H, *J* 10.8 Hz, C*H*$_2$Ph), 4.58 (d, 1H, *J* 10.8 Hz, C*H*$_2$Ph), 4.55 (d, 1H, *J* 10.8 Hz, C*H*$_2$Ph), 4.17 (dd, 1H, *J* 7.2 Hz, *J* 2.4 Hz, H1), 3.80 (s, 3H, C*H*$_3$OPh), 3.64 (dd, 1H, *J* 2.0 Hz, *J* 6.0 Hz, H2), 3.52 (ddd, 1H, *J* 1.6 Hz, *J* 6.4 Hz, *J* 10.8 Hz, H3), 3.27 (ddt, 1H, *J* 2.4 Hz, *J* 4.4 Hz, *J* 11.2 Hz, H5), 2.35 (m, 1H, H4), 2.05 (m, 2H, H4′,H6), 1.87 (m, 1H, H7), 1.77 (m, 1H, H6′), 1.68 (m, 1H, H7′), 1.09 (s, 21H, C*H*CH$_3$, CHC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 159.3, 150.0, 149.9, 138.5, 130.8, 130.2, 129.6, 128.5, 127.9, 127.7, 126.2, 120.4, 113.8 (Ar*C*), 87.0 (C2) 82.0 (C3), 72.7 (*C*H$_2$Ph), 71.6 (*C*H$_2$Ph), 70.5 (C1) 60.3 (C5) 55.4 (*C*H$_3$OPh), 34.6 (C4), 26.7, 25.9 (C6,C7), 18.2, 12.4 (*C*HCH$_3$, CHCH$_3$). HRMS(ES+): calcd for $C_{31}H_{47}N_3NaO_4Si$: 576.3234, found 576.3234.

4.13. (1*R*,2*S*,3*R*,5*S*)-5-Azido-3-*O*-benzyloxy-2-*O*-*p*-methoxybenzyloxy-1-*O*-triisopropylsilyl-cycloheptane (27*S*)

Colourless oil (66 mg, 10%). R_f (pentane/EtOAc 80:1) 0.43.

4.14. (1*R*,2*R*,3*R*,5*R*)-5-Azido-3-*O*-benzyloxy-2-*O*-*p*-methoxybenzyloxy-cycloheptan-1-ol (28)

TBAF (1 M in THF, 2.0 mL, 2.0 mmol, 5 equiv) was added to a stirred solution of **27*R*** (0.22 g, 0.40 mmol) in dry THF (6 mL). The reaction mixture was stirred for 2 h before being quenched by addition of satd aq NH_4Cl (40 mL). The aqueous phase was extracted with EtOAc (3 × 40 mL) and the combined organic phases were washed with brine (3 × 60 mL), dried over $MgSO_4$ and concentrated. The resulting product was purified by flash column chromatography (pentane/EtOAc 4:1) to give the desired product **28** (0.14 g, 89%) as a colourless oil. $[\alpha]_D^{20}$ −22 (*c* 1.0, $CHCl_3$). R_f (pentane/EtOAc 5:1) 0.15. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.37–7.21 (m, 7H, Ar*H*), 6.88 (m, 2H, *Ph*OCH$_3$), 4.83 (d, 1H, *J* 12.0 Hz, C*H*$_2$Ph), 4.73 (d, 1H, *J* 12.0 Hz, C*H*$_2$Ph), 4.60 (d, 1H, *J* 12.0 Hz, C*H*$_2$Ph), 4.57 (d, 1H, *J* 12.0 Hz, C*H*$_2$Ph), 3.81 (s, 3H, C*H*$_3$OPh), 3.60 (m, 3H, H1, H3, H5), 3.47 (m, 1H, H2), 2.73 (br s, 1H, O*H*), 2.19 (ddd, 1H, *J* 4.0 Hz, *J* 4.0 Hz, *J* 16.0 Hz, H4), 1.97 (m, 1H, H4′), 1.85 (m, 4H, H6, H6′, H7, H7′). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 159.5, 138.0, 130.5, 129.6, 128.5, 127.9, 114.1 (Ar*C*), 86.8 (C2) 79.6 (C3), 74.3 (*C*H$_2$Ph), 72.3 (*C*H$_2$Ph), 71.3 (C1/C5), 58.0 (C5/C1), 55.3 (*C*H$_3$OPh), 34.0 (C4), 27.6, 26.9 (C6,C7). HRMS(ES+): calcd for $C_{22}H_{27}N_3NaO_4$: 420.1899, found 420.1914.

4.15. (2*S*,3*R*,5*R*)-5-Azido-3-*O*-benzyloxy-2-*O*-*p*-methoxybenzyloxy-cycloheptanone (29)

Dess–Martin periodinane (0.24 g, 0.56 mmol, 1.6 equiv) was added to a stirred solution of **28** (0.14 g, 0.36 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 1 h and then diluted with Et_2O (20 mL) after which stirring was continued for 30 min. The resulting mixture was washed with a satd aq solution of $Na_2S_2O_3$ (3 × 25 mL), brine (2 × 25 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (pentane/EtOAc 10:1) to give product **29** (0.13 g, 95%) as a colourless oil. $[\alpha]_D^{20}$ −11 (*c* 1.0, $CHCl_3$). R_f (pentane/EtOAc 7:1) 0.39. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.34–7.21 (m, 7H, Ar*H*), 6.85 (m, 2H, *Ph*OCH$_3$), 4.59 (s, 2H, C*H*$_2$Ph), 4.50 (d, 1H, *J* 11.6 Hz, C*H*$_2$Ph), 4.37 (d, 1H, *J* 11.6 Hz, C*H*$_2$Ph), 4.07 (d, 1H, *J* 6.0 Hz, H2), 3.79 (s, 3H, C*H*$_3$OPh), 3.74 (m, 2H, H3, H5), 2.58 (ddd, 1H, *J* 4.0 Hz, *J* 10.8 Hz, *J* 14.8 Hz, H7), 2.47 (ddd, 1H, *J* 4.0 Hz, *J* 7.6 Hz, *J* 14.8 Hz, H7′), 2.18 (m, 2H, H4, H6), 1.95 (m, 1H, H4′), 1.85 (m, 1H, H6′). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 208.8 (*C*O), 159.6, 137.9, 129.9, 128.4, 127.8, 127.7, 113.9 (Ar*C*), 87.4 (C2), 77.0 (C3/C5), 72.3 (*C*H$_2$Ph), 72.1 (*C*H$_2$Ph), 58.5 (C5/C3), 55.3 (*C*H$_3$OPh), 36.4 (C7), 35.2 (C4), 29.3 (C6). HRMS(ES+): calcd for $C_{22}H_{25}N_3NaO_4$: 418.1743, found 418.1748.

4.16. (1*R*,2*S*,3*R*,5*R*)-3-*O*-Benzyloxy-2-*O*-*p*-methoxybenzyloxy-8-azabicyclo[3.2.1]octane-1-ol (30)

PPh_3 (0.39 g, 1.49 mmol, 2 equiv) was added to a stirred solution of ketone **29** (0.29 g, 0.74 mmol) in THF (10 mL) and H_2O (1 mL). The reaction mixture was stirred at 40 °C for 2 h during which N_2 evolution was observed. The reaction mixture was concentrated and the crude product purified by flash column chromatography (EtOAc/MeOH 20:1) to give the desired product **30** (0.22 g, 83%) as a colourless oil. $[\alpha]_D^{20}$ −4 (*c* 1.0, $CHCl_3$). R_f (H_2O/isopropanol/EtOAc 1:2:3) 0.59. ^1H NMR (400 MHz, CD_3OD): δ_H (ppm) 7.30–7.24 (m, 7H, Ar*H*), 6.82 (m, 2H, *Ph*OCH_3), 4.89 (br s, 2H, N*H*, O*H*), 4.87 (d, 1H, *J* 10.8 Hz, CH_2Ph), 4.69 (d, 1H, *J* 10.8 Hz, CH_2Ph), 4.59 (d, 1H, *J* 11.6 Hz, CH_2Ph), 4.54 (d, 1H, *J* 11.6 Hz, CH_2Ph), 3.74 (s, 3H, CH_3OPh), 3.58 (m, 1H, H3), 3.39 (m, 2H, H2, H5), 2.13–1.99 (m, 3H, H4, H6, H7), 1.53–1.40 (m, 3H, H4′, H6′, H7′). ^{13}C NMR (100 MHz, CD_3OD): δ_C (ppm) 160.6, 140.2, 132.7, 130.7, 129.2, 128.8, 128.5, 114.5 (ArC), 93.4 (C1), 88.5 (C2) 79.6 (C3), 75.9 (*C*H_2Ph), 73.1 (*C*H_2Ph), 55.7 (*C*H_3OPh), 53.0 (C5), 39.6, 31.4, 28.4 (C4,C6,C7). HRMS(ES+): calcd for $C_{22}H_{28}NO_4$: 370.2018, found 370.2017.

4.17. (1*R*,2*S*,3*R*,5*R*)-8-Azabicyclo[3.2.1]octane-1,2,3-triol (1)

To a stirred solution of liquid NH_3 at −78 °C was consecutively added a solution of **30** (0.22 g, 0.61 mmol) in THF (5 mL) and sodium (111 mg, 4.83 mmol, 8 equiv) in small portions which produced a blue solution. The reaction mixture was stirred at −78 °C for overall 1 h, and then NH_4Cl (solid) was added until the blue colour disappeared. The solution was allowed to warm to rt, filtered and concentrated. The crude product was partly purified by flash column chromatography (water/isopropanol/EtOAc 1:2:3) to yield the desired product **1** along with NH_4Cl. The resulting residue was purified by ion exchange chromatography (Amberlite IR 120, H^+) and released with 2.5% ammonium hydroxide to give **1** (46 mg, 47%) as a clear oil. $[\alpha]_D^{20}$ −13 (*c* 1.0, H_2O). R_f (H_2O/isopropanol/EtOAc 1:1:1) 0.21. ^1H NMR (400 MHz, D_2O): δ_H (ppm) 3.71 (ddd, 1H, *J* 6.4 Hz, *J* 8.4 Hz, *J* 15.2 Hz, H3), 3.50 (m, 1H, H5), 3.42 (d, 1H, *J* 8.8 Hz, H2), 2.02 (m, 3H, H4, H6, H7), 1.53 (m, 3H, H4′, H6′, H7′). ^{13}C NMR (100 MHz, D_2O): δ_C (ppm) 90.8 (C1), 79.4 (C2/C3), 69.8 (C3/C2), 51.4 (C5), 39.5, 28.8, 26.4 (C4,C6,C7). HRMS(ES+): calcd for $C_7H_{13}NO_3$: 160,0974, found 160.0974. The optical rotation and spectroscopic data were in agreement with literature data.[2,15,16]

Acknowledgements

We are grateful for support from The Faculty of Science and OChem Graduate School, Aarhus University and the Carlsberg Foundation.

Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra for compounds **14**, **20**–**31** and for Calystegine A_3 (**1**)) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.10.025.

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