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Synthesis of nortropane alkaloid calystegine B_2 from methyl α-D-xylopyranoside

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ABSTRACT

A new synthetic route for formation of a central cycloheptanone intermediate leading to the nortropane alkaloid calystegine B_2 is described. The approach installs the desired ketone functionality directly in a ring-closing metathesis step. The target compound was prepared over 10 steps from commercially available methyl α-D-xylopyranoside.

1. Introduction

The calystegines with their hydroxylated nortropane skeletons of which calystegine B_2 is a prime example represent a well-studied subgroup of iminosugars (Fig. 1). The first calystegine was isolated from *Calystegia sepium* in 1988 [1], since then more than 10 calystegines have been found in various plants [2–4] and have been classified into three types: A (with three hydroxyl groups), B (with four hydroxyl groups), and C (with five hydroxyl groups) [3]. Despite the presence of a hemiaminal functionality the bicyclic calystegines are generally very stable compounds, prevented from breakdown via dehydration and Amadori rearrangement due to the presence of a bridgehead according to Bredt's rule [5–7]. Additionally, it has been found, that calystegines exhibit potent and selective glycosidase inhibition and been shown to have potential in the treatment of cancer [8,9], diabetes [10], viral infections [11], and lysosomal storage diseases [12]. Due to difficulty of purification from natural sources and important biological properties, synthesis of these compounds have attracted attention.

Several different approaches to the synthesis of calystegines have previously been published including ring-closing metathesis (RCM) [13–19], ring expansion [20–22], cycloaddition [23–25], intramolecular Nozaki–Hiyama–Kishi reaction [26], radical cyclization [27], and polar cyclisation [28,29]. For many of the syntheses of calystegines the key step is the RCM reaction, where the popularity arise due to the efficiency and generality of the construction of a cycloheptanone ring. Previous uses of RCM has produced a cycloheptene intermediate, which needed further modification to the cycloheptanone by installation of the hydroxyl group through a hydroboration-oxidation sequence. This, however lead to mixtures of regioisomeric cycloheptanols/cycloheptanones [13,15–19], giving this approach some drawbacks (Scheme 1). We have previously also used this approach with its inherent disadvantages for the synthesis of noeurostegines [30–32] being hybrid molecules of calystegine B_2 (**1**) and noeuromycin (Fig. 1) [33]. Consequently, we became interested in assembling the amino cycloheptanone frame of calystegine B_2 (**1**) using an RCM reaction but in a fashion that installed the oxygen atom of the target ketone directly thereby avoiding the regioselectivity issues previously encountered in the hydroboration step, in the hope to develop a general and efficient access to calystegines and noeurostegines.

Accordingly, we here present our results with regards to the synthesis of calystegine B_2 (**1**) via an RCM reaction directly installing the needed ketone functionality, hence eliminating the need of a subsequent hydroboration reaction involving regioselectivity issues.

2. Results and discussion

Methyl α-D-xylopyranoside (**2**) was chosen as the starting material as it is readily available and contains three hydroxyl groups with the required absolute stereochemistry for the synthesis of calystegine B_2 (Scheme 2). 2,3,4-Tri-*O*-benzyl-D-xylopyranose (**3**) was prepared utilizing standard *O*-benzyl protection procedures and glycoside hydrolysis [34,35]. Next, the *N*-benzyl glycosyl amine was prepared and treated with vinyl magnesium bromide to provide the allylic amine **4** as a single stereoisomer in 75% over 2 steps [36,37]. The high diastereoselectivity of the reaction can be explained by the Cram-chelation model and is in accordance with previous reports [37,38]. The secondary amine of **4** was Cbz protected to give the carbamate **5**. Introduction of the carbamate gave rise to rotamers making NMR characterization challenging even when data was obtained at 60 °C. The primary alcohol of **5** was next oxidized to the aldehyde using Dess-

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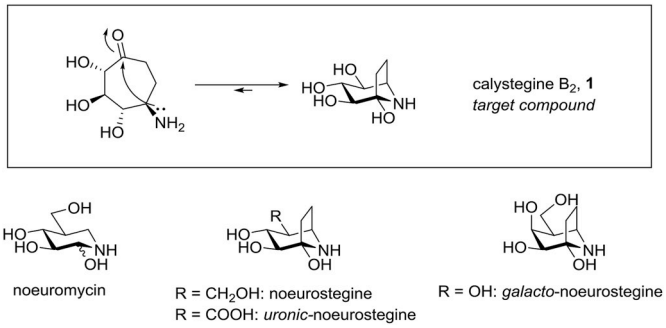
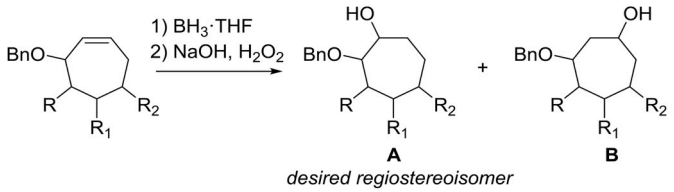


Fig. 1. Calystegine B_2 and synthetic analogues.



Scheme 1. Schematic overview of regioselectivity (**A**:**B**) of hydroboration. Different examples of regioselectivity: R: OBn, R_1: H, R_2: NBnCbz, ratio **A**/**B** 2:1 [15]. or R: H, R_1: OBn, R_2: NBnCbz, ratio **A**/**B** 1.7:1[16] or R: OBn, R_1: OBn, R_2: NBnCbz, ratio **A**/**B** 3:1[17,18] or 2.6:1[19] or R: OBn, R_1: CH_2OBn, R_2: OPMB, ratio **A**/**B** 3:1[30] or R: OBn, R_1: CH_2OBn, R_2: OH, ratio **A**/**B**; 3:1[32].

Martin periodinane (DMP), which subsequently was reacted with vinyl magnedium bromide to provide the diene **6**. Again, oxidation was performed with the DMP reagent and provided ketone **7**, which next underwent RCM using Grubbs 2nd generation catalyst to produce cycloheptenone **8** in 42% yield (63% corrected yield after isolation of unreacted starting material). The RCM reaction was also attempted on the stage of the secondary alcohol (**6**) as well as its *O*-acetylated derivative, but inferior yields were obtained. The final step involving alkene reduction and global deprotection was accomplished using Pearlman's catalyst (Degussa type), which gave rise to spontaneous cyclization to calystegine B_2 (**1**). Other Pd-sources were also tried (non-Degussa type), but these did not provide the target compound. Calystegine B_2 (**1**) was fully characterized by NMR showing consistency with the previously reported data of the natural compound [17,39]. Furthermore, the specific optical rotation of the synthesized compound ($[\alpha]_D$ +29.3 (*c* 0.5, H_2O)) was in accordance with that of the natural compound ($[\alpha]$ +28.1 (*c* 0.27, H_2O)) [17].

2.1. Conclusion

Calystegine B_2 (**1**) was synthesized over 10 steps in an overall yield of 19% from the readily available methyl α-D-xylopyranoside (**2**). In comparison, Wang et al. prepared calystegine B_2 over 12 steps (overall yield 27%) from tri-*O*-benzyl-D-xylopyranose (**3**) [26]. Our method features a stereoselective nucleophilic addition of vinyl magnesium bromide, two DMP oxidations, and an intra-molecular ring-closing metathesis to form the central cycloheptenone. To the best of our knowledge this is the first example of synthesis of calystegine B_2 featuring ring-closing metathesis avoiding a hydroboration step for installation of the impending ketone oxygen atom. The strategy can provide a general approach to this class of compounds by selection of other common sugar-derived starting materials.

3. Experimental

3.1. General methods

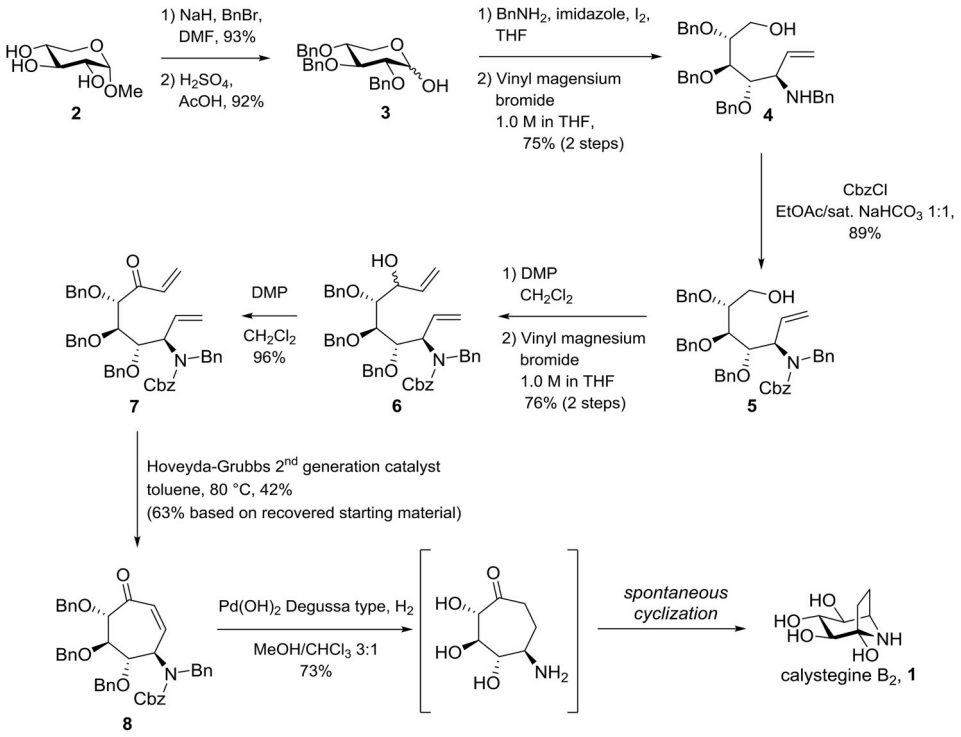
All reagents were used as received from commercial sources. Analytical TLC analysis was performed with silica-coated aluminium plates (Merck Kieselgel 60 F_{254}) and visualized by treatment of $KMnO_4$ (1.5 g $KMnO_4$ in 1.25 g 10% NaOH and 200 mL H_2O) or C-mol (0.2% Cerium(IV) sulfate and 5% ammoniummolydate in 10% sulfuric acid). Flash column chromatography purification of products were done using Merck silica gel 60 (230–400 mesh).

3.2. Instrumentation

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Due to the poor data caused by rotamers the NMR spectra of Cbz-protected compounds were observed at 60 °C for slight improvement. Spectral assignments were made according to 2D-COSY, HMQC and DEPT-135. Numbering of counds can be found in the supporting information document. Melting points were measured on a Büchi B-540 instrument and are uncorrected. Optical rotation was measured on an ADP440 + polarimeter and reported in units of deg $cm^2\ g^{-1}$, and concentrations are given in g/100 mL. Mass spectra were recorded on a Micromass LC-TOF spectrometer with positive electrospray ionization.

3.3. 2,3,4-Tri-O-benzyl-α/β-D-xylopyranose (3)

Methyl α-D-xylopyranoside (**2**) (5.018 g, 30.6 mmol, 1.0 equiv.) was dissolved in dry DMF (75 mL). NaH as a 60% suspension in mineral oil (5.505 g, 138 mmol, 4.5 equiv.) was added and the solution was left to stir for 15 min in a cool water bath before BnBr (16.5 mL, 139 mmol, 4.5 equiv.) was added. The mixture stirred at rt. for 18 h at which point TLC analysis (EtOAc/MeOH 4:1) showed full consumption of starting material and TLC (pentane/EtOAc 10:1) indicated the formation of only one product. The reaction was stopped upon addition of aq. sat. NH_4Cl at 0 °C. Water and EtOAc was added and the phases separated. Extraction of the aqueous phase with EtOAc was completed before the combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (pentane/EtOAc 12:1) resulting in the product methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranoside as a colorless solid (12.279 g, 93%). M_p(uncorr.) 61.9–63.5 °C ($CHCl_3$), lit. 68–69 °C [40]; $[\alpha]_D^{295}$ +19.6 (*c* 1, $CHCl_3$), lit. $[\alpha]_D^{295}$ +16 (*c* 0.7, $CHCl_3$) [40]; R_f(pentane/EtOAc 7:1): 0.57; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.41–7.32 (m, 14H, Ar*H*), 4.96 (d, J_{gem} 10.9 Hz, 1H, OCH_2Ph), 4.90 (d, J_{gem} 10.9 Hz, 1H, OCH_2Ph), 4.84–4.76 (m, 2H, OCH_2Ph), 4.70–4.63 (m, 2H, OCH_2Ph), 4.56–4.55 (m, *J* 2.9 Hz, 1H, H-1), 3.93 (t, *J* 8.4 Hz, 1H, H-3), 3.63–3.53 (m, 3H, H-4, H-5, H-5′), 3.51–3.44 (m, 1H, H-2), 3.40 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 139.0, 138.4, 138.3 (Ar*C*), 128.5, 128.5, 128.2, 127.9, 127.9, 127.7 (Ar*C*H), 98.4 (C-1), 81.6 (C-3), 79.7 (C-2), 78.2 (C-4), 75.9 (OCH_2Ph), 73.6 (OCH_2Ph, double intensity), 59.9 (C-5), 55.3 (OCH_3). HRMS (ESI): calculated (calcd.) for $C_{26}H_{28}O_5NH_4^+$ 452.2431; found 452.2436. NMR data are in accordance with previous reported values [35]. Methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranoside (1.617 g, 3.7 mmol, 1.0 equiv.) was dissolved in 1 M H_2SO_4 (2.0 mL) and AcOH (16.0 mL) and heated to 80 °C. After 8 h TLC analysis (pentane/EtOAc 3:1) indicated full consumption of starting material. The reaction mixture was poured into ice water before EtOAc was added and the aqueous phase extracted with additional EtOAc. The combined organic phases were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product **3** was isolated as a colorless powder (1.432 g, 92%) with an α/β ratio of 3:2 as measured by NMR M_p (uncorr.) 128.0–131.1 °C ($CHCl_3$), lit. 129–130 °C [41]; R_f^{α}(pentane/EtOAc 2:1): 0.54; R_f^{β}(pentane/EtOAc 2:1): 0.62; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.4–7.2 (m, 26H, Ar*H*), 5.12 (s, 1H, H-1α), 4.93–4.89 (m, 4H, OCH_2Ph), 4.80–4.70 (m, 4H, OCH_2Ph), 4.67–4.63 (m, 3H, OCH_2Ph, H-1β), 3.98–3.88 (m, 2H, H-5β, H-3α), 3.82 (t, $J_{5,5'}$ 10.7 Hz, 1H, H-5α), 3.70–3.54 (m, 4H, H-5′α, H-4α, H-3β, H-4β, OHβ), 3.51 (d, $J_{2,3}$ 8.9 Hz, 1H, H-2α), 3.36–3.25 (m, 1H, H-2β, H-5′β), 3.21 (bs, 1H, OHα). ^{13}C



Scheme 2. Synthesis of calystegine B_2.

NMR (101 MHz, $CDCl_3$): δ_C 138.7 (Ar*C*α), 138.6 (Ar*C*β), 138.4 (Ar*C*β), 138.3 (Ar*C*α), 138.2 (Ar*C*β), 137.9 (Ar*C*α)128.6–127.8 (Ar*C*H), 97.9 (C-1β), 91.5 (C-1α), 83.3 (C-3β), 82.5 (C-2β), 80.6 (C-3α), 79.5 (C-2α), 77.7 (C-4β), 77.6 (C-4α), 75.6 (O*C*H$_2$Phα), 75.6 (O*C*H$_2$Phβ), 74.9 (O*C*H$_2$Phβ), 73.5 (O*C*H$_2$Phα), 73.4 (O*C*H$_2$Phβ), 73.3 (O*C*H$_2$Phα), 63.8 (C-5β), 60.4 (C-5α). HRMS (ESI): calcd. for $C_{26}H_{28}O_5NH_4^+$ 438.2275; found 438.2284. NMR data are in accordance with previously reported data [42].

3.4. (2R,3R,4S,5R)-5-(N-Benzyl-amino)-2,3,4-tris-(benzyloxy)-hept-6-en-1-ol (4)

$BnNH_2$ (2.6 mL, 23.8 mmol, 2.05 equiv.) and imidazole (1.580 g, 23.2 mmol, 2.0 equiv.) was added to a solution of lactol **3** (4.880 g, 11.6 mmol, 1.0 equiv.) in dry THF (116.0 mL) and added. The solution was left to stir at rt. for 5 min before I_2 (5.891 g, 23.2 mmol, 2.0 equiv.) was added and the mixture was stirred further at rt. After 22 h TLC analysis (pentane/EtOAc 3:1) indicated full consumption of starting material. A saturated solution of aq. Na_2SO_3 was added to the reaction mixture until the dark brown color disappeared. The aqueous layer was extracted with EtOAc and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was used directly in the next step where it was reacted with vinyl magnesium bromide (111 mL, 111 mmol, 9.6 equiv. 1 M solution in THF) at 0 °C and then rt. for a further 18 h at which point TLC analysis (pentane/EtOAc 2:1) indicated full consumption of starting material. The reaction was quenched by addition of saturated aq. NH_4Cl at 0 °C and diluted and further extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*.Purification of the residue by flash column chromatography (pentane/EtOAc 3:1) gave the product (**4**) as a yellow oil (4.663 g, 75% over 2 steps). $[\alpha]_D^{295}$ -17.5 (*c* 1, $CHCl_3$), lit. $[\alpha]_D^{295}$ 9.7 (*c* 0.8, CH_2Cl_2) [37]; R_f(pentane/EtOAc 2:1): 0.25; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33–7.24 (m, 21H, Ar*H*), 5.80–5.71 (m, 1H, H6), 5.22 (dd, $J_{7,6}$ 10.2 Hz, $J_{7,7'}$ 1.7 Hz, 1H, H-7(cis)), 5.03 (dd, $J_{7',6}$ 17.3 Hz, $J_{7',7}$ 1.5 Hz, 1H, H-7′(trans)), 4.79 (d, J_{gem} 11.2 Hz, 2H, OCH*H*Ph), 4.72 (d, J_{gem} 11.4 Hz, 1H, OC*H*$_2$Ph), 4.61 (d, J_{gem} 9.3 Hz, 1H, OC*H*$_2$Ph), 4.58 (d, J_{gem} 9.7 Hz, 1H, OC*H*$_2$Ph), 4.36 (d, J_{gem} 11.7 Hz, 1H, OC*H*$_2$Ph), 4.06 (dd, $J_{2,3}$ 6.5 Hz, $J_{2,1}$ 4.4 Hz, 1H, H-2), 3.84–3.75 (m, 3H, H-4, NHC*H*$_2$Ph), 3.67 (dd, $J_{1,1'}$ 11.8 Hz, $J_{1,2}$ 4.1 Hz, 1H, H-1), 3.49–3.44 (m, 2H, H-3, H-1'), 3.09 (dd, $J_{5,4}$ 8.2 Hz, $J_{5,6}$ 3.8 Hz, 1H, H-5), 2.07 (bs, 2H, NH, OH). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 140.6, 138.6, 138.4, 138.2 (Ar*C*), 138.2 (C-6), 128.7, 128.5, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.0 (Ar*C*H), 117.4 (C-7), 82.7 (C-4), 80.2 (C-2), 78.3 (C3), 74.9 (O*C*H$_2$Ph), 74.6 (O*C*H$_2$Ph), 72.1 (O*C*H$_2$Ph), 61.8 (N*C*H$_2$Ph), 60.6 (C-5), 50.6 (C-1). HRMS (ESI): calcd. for $C_{35}H_{39}NO_4H^+$ 538.2952; found 538.2964. NMR data are in accordance with lit [37].

3.5. (2R,3S,4R,5R)-5-[(N-benzyl-N-(benzyloxycarbonyl))amino]-2,3,4-tris(benzyloxy)-hept-6-en-1-ol (5)

Secondary amine **4** (1.042 g, 1.94 mmol, 1.0 equiv.) was dissolved in EtOAc (7 mL) and sat. aq. $NaHCO_3$ (7 mL) before a 50% solution of benzyl chloroformate in toluene (1.66 mL, 5.81 mmol, 3.0 equiv.) was added and the mixture let to stir at rt. After 4.5 h TLC analysis (pentane/EtOAc 1:1) indicated reaction completion. The phases were separated, the aqueous phase was extracted with EtOAc and the combined organic phases washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue was performed by flash column chromatography (pentane/EtOAc 3:1) resulting in **5** as a yellow oil (1.163 g, 90%). $[\alpha]_D^{295}$ +3.6 (*c* 1.0, $CHCl_3$); R_f(pentane/EtOAc 2:1): 0.46; ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ_H 7.39–7.21 (m, 25H, Ar*H*), 6.08–5.99 (m, 1H, H-6), 5.23–5.16 (m, 2H), 5.04 (d, $J_{7,6}$ 10.4 Hz, 1H, H-7$_{cis}$), 4.90 (d, *J* 15.6, 1H, OC*H*$_2$Ph), 4.82 (d, 1H, H-7$_{trans}$), 4.69–4.41 (m, 9H, H-5), 4.28 (bs, 1H), 3.81–3.60 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, 60 °C): δ_C 156.7–156.4 (m, *C*O, Cbz), 139.1, 138.8, 138.7, 138.7, 138.6, 136.8, 135.1–134.8 (m), 128.9–127.0 (m), (Ar*C*, Ar*C*H) 119.3–118.8 (m, C-7), 79.8–79.3 (m), 74.7–74.2 (m), 73.3–73.0 (m), 67.7–67.3 (m), 62.4–61.8 (m), 52.3–51.8 (m). HRMS (ESI): calcd. for $C_{35}H_{39}NO_4H^+$ 672.3320; found 672.3328.

3.6. (4R,5R,6S,7R)-7-[N-benzyl-N-(benzyloxycarbonyl)-amine]-4,5,6-tris (benzyloxy)-3-hydroxy-nona-1,8-diene (6)

Carbamate **5** (3.357 g, 5.00 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (40 mL) before Dess Martin periodinane (3.173 g, 7.48 mmol, 1.5 equiv.) was added. The reaction was left to stir for 1 h at rt. before TLC analysis (pentane/EtOAc 3:1) indicated full consumption of starting material. The reaction mixture was diluted with Et_2O (60 mL), sat. aq. $Na_2S_2O_3$ (15 mL) and sat. aq. $NaHCO_3$ (30 mL) and stirred vigorously for 1.5 h at rt. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The aldehyde product, a yellow oil, was sufficiently clean and used directly in the next step. $[\alpha]_D^{295}$ -4.4 (*c* 1.0, $CHCl_3$); R_f(pentane/EtOAc 6:1): 0.21; ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ_H 9.72 (s, 1H, H-1), 7.36–7.20 (m, 30H, Ar*H*), 6.04 (bs, 1H, H-6), 5.20 (s, 2H, OCH_2Ph), 5.00 (d, $J_{7,6}$ 10.1 Hz, 1H, H-7$_{cis}$), 4.94–4.82 (m, 3H, OCH_2Ph), 4.73 (d, $J_{7,6}$ 17.2 Hz, 1H, H-7$_{trans}$), 4.61–4.30 (m, 8H, H-4, H-5, OCH_2Ph), 4.28 (d, *J* 15.7 Hz, 1H, OCH_2Ph), 4.02 (bs, 1H, H-2), 3.84 (bs, 1H, H-3). ^{13}C NMR (101 MHz, $CDCl_3$, 60 °C): δ_C 200.3–200.1 (m, *C*HO, C-1), 156.3–156.1 (m, *C*O, Cbz), 138.4, 138.1, 137.7, 137.5, 136.5 (Ar*C*), 134.7–134.5 (m, C-6), 128.9–127.0 (m, Ar*C*H), 119.3–118.9 (m, C-7), 81.3–81.1 (m), 80.4–80.2 (m), 78.4, 74.3–74.2 (m), 73.9–73.8 (m), 73.5–73.3 (m), 67.5–67.1 (m), 62.4–62.2 (m), 52.8–52.5 (m). HRMS (ESI): calcd. for $C_{43}H_{43}NO_6NH_4^+$ + MeOH 719.3691; found 719.3699 (found as the hemiacetal upon reaction with methanol in which the sample was dissolved). Vinylmagnesium bromide (1.0 M in THF, 50 mL, 50 mmol, 10 equiv.) was added to the crude aldehyde (5.0 mmol, 1.0 equiv) at 0 °C. After 40 min TLC analysis (pentane/EtOAc 5:1) indicated full consumption of starting material. The reaction was quenched by addition of sat. aq. NH_4Cl, and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (pentane/EtOAc 5:1) to give allylic alcohol **6** as a clear oil (2.640 g, 76% over 2 steps). R_f(pentane/EtOAc 4:1): 0.34 and 0.39.; ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ_H 7.32–7.26 (m, 25H, Ar*H*), 6.03–5.77 (m, 2H, H-2, H-8), 5.38–4.19 (m, 17H, H-1, H-1′, H-3, H-7, H-9, H-9', OCH_2Ph), 3.74–3.67 (m, 2H, H-4), 2.86 (bs, 1H, OH), 2.50 (bs, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$, 60 °C): δ_C 156.8–156.4 (m, *C*O, Cbz), 139.0, 138.8–138.7 (m), 138.6–138.5 (m), 138.0–137.9 (m) (Ar*C*), 136.8–136.7 (m, C-2/C-8), 135.0–134.8 (m, C-2/C-8), 128.9–127.1 (m, Ar*C*H), 119.4–118.9 (m, C-1/C-9), 115.8–115.5 (m, C-1/C-9), 82.2–81.9 (m), 80.6–80.1 (m), 79.9–79.5 (m), 75.3–74.8 (m), 74.5–74.2 (m), 73.6–73.4 (m), 72.7–72.5 (m), 67.7–67.3 (m), 62.5–62.2 (m), 52.5–52.1 (m). HRMS (ESI): calcd. for $C_{45}H_{47}NO_6H^+$ 698.3476; found 698.3485. ^{1}H NMR has been normalized based on the number of Ar*H* corresponding to one of the diastereoisomers. The ratio of R/S cannot be decided based on NMR due to the presence of rotamers.

3.7. (4R,5R,6S,7R)-7-[N-benzyl-N-(benzyloxycarbonyl)-amine]-4,5,6-tris (benzyloxy)-3-oxo-nona-1,8-diene (7)

DMP (2.246 g, 5.29 mmol, 1.5 equiv was added to a solution of alcohol **6** (2.465 g, 3.53 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL). The reaction mixture was to stir for 80 min at rt. before TLC analysis (pentane/EtOAc 5:1) indicated full consumption of the starting material and formation of a product. The reaction mixture was added Et_2O (40 mL), sat. aq. $Na_2S_2O_3$ (20 mL) and sat. aq. $NaHCO_3$ (10 mL) and stirred vigorously for 2 h at rt. The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was obtained as a clear oil (2.367 g, 96%), which was sufficiently pure for further reaction. $[\alpha]_D^{295}$ -1.3 (*c* 1.0, $CHCl_3$); R_f(pentane/EtOAc 10:1): 0.26; ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ_H 7.29–7.05 (m, 30H, Ar*H*), 6.74–6.67 (m, 1H, H2), 6.25 (d, $J_{1,2}$ 17.5 Hz, 1H, H-1$_{trans}$), 5.97–5.89 (m, 1H, H-8), 5.57 (d, $J_{1,2}$ 10.6 Hz, 1H, H-1$_{cis}$), 5.15–5.08 (m, 2H, OCH_2Ph), 5.01 (d, $J_{9,8}$ 10.2 Hz, 1H, H-9$_{cis}$), 4.84 (m, 2H, H-9', OCH_2Ph), 4.65–4.58 (m, 4H, H-7, OCH_2Ph), 4.45–4.32 (m, 7H, H-4, OCH_2Ph), 4.14 (s, 1H, H-6), 3.85 (s, 1H, H-5). ^{13}C NMR (101 MHz, $CDCl_3$, 60 °C): δ_C 199.4 (*C*O, C3), 157.0 (*C*O, Cbz), 139.2, 138.8, 138.4, 137.7, 136.8, 136.8 (Ar*C*), 135.0–134.8 (m, C-2/C-8), 133.0–132.8 (m, C-2/C-8), 129.0–127.1 (m, Ar*C*H), 84.4, 81.0–80.6 (m), 75.5–75.3 (m), 75.0, 73.7–73.3 (m), 67.9–67.4 (m), 61.7–61.1 (m), 51.5–51.0 (m). HRMS (ESI): calcd. for $C_{45}H_{45}NO_6NH_4^+$ 713.3585; found 713.3592. Some signals in the ^{13}C NMR are missing, especially obvious are C1 and C9 this can be explained by the presence of rotamers.

3.8. (2R,3R,4S,5R)-5-[N-benzyl-N-(benzyloxycarbonyl)-amine]-2,3,4-tris (benzyloxy)-cyclo-hept-6-en-1-one (8)

Diene **7** (2.367 g, 3.40 mmol, 1.0 equiv.) was dissolved in dry toluene (17 mL, c = 0.2 M) and heated to 80 °C at which point Hoveyda-Grubbs 2nd generation catalyst (0.106 g, 0.17 mmol, 0.05 equiv.) was added. The reaction was stopped after 16.5 h, TLC analysis (pentane/EtOAc 8:1) did not show complete consumption of starting materials but showed formation of several products. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (pentane/EtOAc 12:1). The product was a yellow oil (0.824 g, 36%), additionally was the remaining starting material collected (0.983 g, 42%), giving a corrected yield of 63%. $[\alpha]_D^{295}$ -78.6 (*c* 1.0, $CHCl_3$); R_f(pentane/EtOAc 7:1): 0.46; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.30–7.13 (m, 44H, Ar*H*), 6.70 (d, $J_{7,6}$ 12.3 Hz, 1H, H-7), 6.51 (d, $J_{7,6}$ 12.2 Hz, 1H, H-7*), 5.89 (d, $J_{6,7}$ 12.3 Hz, 1H, H-6), 5.77 (d, $J_{6,7}$ 12.7 Hz, 1H, H-6*), 5.23–5.11 (m, 4H, OCH_2Ph), 4.91 (bs, 2H, OCH_2Ph), 4.71–4.66 (m, 2H, OCH_2Ph), 4.59–4.29 (m, 10H, H-2, H-3, OCH_2Ph), 4.16–4.01 (m, 7H, H-4, H-5, OCH_2Ph). ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 199.4 (*C*O), 199.3 (C*O), 156.5 (*C*O, Cbz), 156.0 (*C*O, Cbz), 150.1–149.8 (m, C6), 138.5, 138.0, 137.7, 137.5, 137.3, 136.9, 136.8, 136.4, 136.1, 128.7–127.5 (m) (Ar*C*, Ar*C*H), 126.2–126.0 (m, C-7), 83.8, 83.3, 82.5, 81.6, 74.7, 74.2, 72.8, 72.7, 72.5, 72.4, 67.6, 67.4, 59.8, 59.1, 54.1–53.6 (m). HRMS (ESI): calcd. for $C_{43}H_{41}NO_6NH_4^+$ 685.3272; found 685.3279. "*" refer to signals, which are clearly for the other rotamer. Ratio rotomers approx. 1:0.6.

3.9. (+)-Calystegine B_2 (1)

Pd/C Degussa type (Pd 20%) (0.024 g, 0.035 mmol, 0.22 equiv.), then H_2 (balloon, 1 atmosphere) was added to a solution of cycloheptenone **8** (0.106 g, 0.16 mmol, 1.0 equiv.) dissolved in MeOH (3.0 mL) and $CHCl_3$ (1.0 mL).and H_2. The reaction mixture was stirred overnight at rt. before it was filtered and concentrated *in vacuo*. Disappearance of the starting material could be monitored by TLC analysis in pentane/EtOAc 6:1, while TLC analysis in EtOAc/25% ammonium hydroxide 4:1 was suitable for monitoring the on-going reaction. The reaction mixture was resubmitted by dissolving in MeOH (3.0 mL) and $CHCl_3$ (1.0 mL) in the presence of fresh Pd/C Degussa type (Pd 20%) (0.033 g, 0.31 mmol, 0.19 equiv.) and H_2 (balloon, 1 atmosphere) The reaction mixture was additionally stirred overnight at rt. before it was filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2/EtOH/MeOH/ammonia water 5:2:2:1) to give a colorless glass (0.020 g, 73%). $[\alpha]_D^{295}$ +29.3 (*c* 0.5, H_2O), lit. $[\alpha]_D^{295}$ +28.1 (*c* 0.27, H_2O) [17]; R_f(CH_2Cl_2/EtOH/MeOH/ammonium hydroxider 5:2:2:1) 0.31; ^{1}H NMR (400 MHz, D_2O): δ_H 3.55 (dd, $J_{4,3}$ 8.3 Hz, $J_{4,5}$ 3.7 Hz, 1H, H-4), 3.39 (dd, $J_{2,3}$ 8.6 Hz, $J_{2,4}$ 1.7 Hz, 1H, H-2), 3.35–3.27 (m, 2H, H-3, H-5), 2.02–1.87 (m, 2H, H-6, H-7), 1.78–1.68 (m, 1H, H-6′), 1.57–1.47 (m, 1H, H-7'). ^{13}C NMR (101 MHz, D_2O): δ_C 93.3 (C-1), 80.4 (C-2), 77.7 (C-3), 77.6 (C-4), 58.7 (C-5), 31.5 (C-7), 24.5 (C-6). HRMS (ESI): calcd. for $C_7H_{13}NO_4H^+$

176.0917; found 176.0918. The ^{13}C NMR have been referenced by using the C2 chemical shift, δ 80.4 ppm, reported in the literature [17,39]. The data are in accordance with literature values [17,39].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2018.12.002.

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