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Synthesis of Calystegine A_3 from Glucose by the Use of Ring-Closing Metathesis

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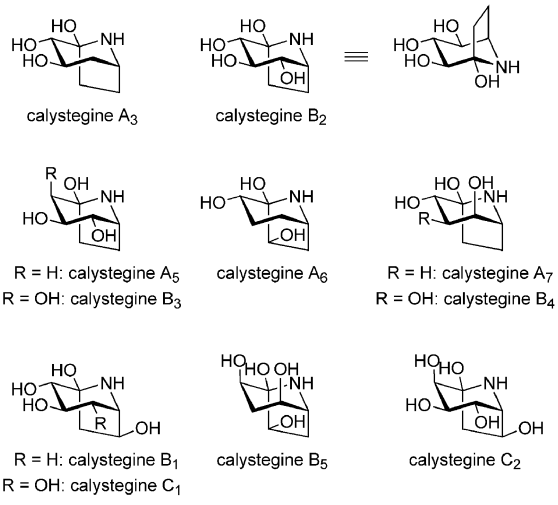
A synthesis of the nortropane alkaloid calystegine A_3 is described from D-glucose. The key step employs a zinc-mediated tandem reaction where a benzyl-protected methyl 6-iodo glucoside is fragmented to give an unsaturated aldehyde, which is then transformed into the corresponding benzylimine and allylated in the same pot. The functionalized nona-1,8-diene, thus obtained, is converted into the seven-membered carbon skeleton in calystegine A_3 by ring-closing olefin metathesis. Subsequent deoxygenation by the Barton–McCombie protocol, hydroboration and oxidative workup followed by hydrogenolysis affords calystegine A_3. The synthesis uses a total of 13 steps from glucose and confirms the absolute configuration of the natural product.

Introduction

The calystegines are a class of naturally occurring imino sugar mimetics containing a nortropane ring system.[1] More than 10 different calystegines have been identified in a number of edible vegetables such as tomatoes, potatoes and cabbage (Scheme 1). They are divided into three categories depending on the number of hydroxy groups: calystegine A (three hydroxy groups), calystegine B (four hydroxy groups) and calystegine C (five hydroxy groups). As a common feature, they all contain a tertiary hydroxy group as part of a hemiaminal functionality. In addition, derivatives of the calystegines containing a glycosidic linkage, an *N*-methyl group, or an amino group, where the latter has replaced the tertiary hydroxy group, have also been isolated.[1] Several calystegines show significant inhibition of glycosidases in particular calystegine A_3, B_1, B_2, B_4, and C_1, which are all inhibitors of β-glucosidase.[2] Recently, the binding of calystegine B_2 to β-glucosidase from *Thermotoga maritima* was investigated by X-ray crystallography.[3] Because all the hydroxy groups are equatorial, the natural product could either bind with the ethylene bridge below or above the plane of the ring as compared to the natural substrate glucose (Scheme 1). The studies showed that calystegine B_2 binds with the ethylene bridge above the plane, i.e. with the amino group at the position of the anomeric carbon in the corresponding glucose structure.[3]



Scheme 1. The calystegines.

The most abundant calystegines in plants are A_3, B_1, and B_2.[1] Calystegine A_3 was first isolated from *Calystegia sepium* in 1988[4] and the relative configuration established in 1990.[5] There have only been two syntheses of calystegine A_3: a racemic synthesis in 8 steps from 4-aminocyclohexanol[6] and an asymmetric synthesis in 18 steps from cycloheptatriene.[7] Unfortunately, the optical rotation of the final product in the latter synthesis could not be measured and as a result the absolute configuration of calystegine A_3 has not yet been unambiguously established. Naturally occurring calystegine A_7, B_2, B_3 and B_4 have all been prepared by synthesis starting from either a hexose[8] or from a cycloheptadiene derivative.[9] The most efficient route to the calystegine alkaloids employs a zinc-mediated tandem reaction for converting hexoses into acyclic dienes which are then

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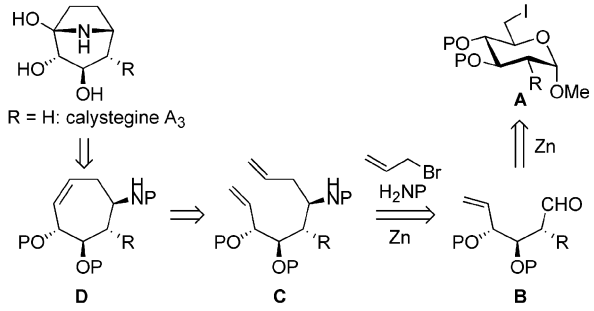
cyclized by ring-closing olefin metathesis to furnish the seven-membered carbocycle.[8a–8d] In this transformation, methyl 6-iodohexopyranosides are treated with zinc metal, benzylamine and allyl bromide (Scheme 2).[10,11] First, a reductive fragmentation of the iodopyranoside takes place to produce an unsaturated aldehyde **B** which is then converted into the corresponding imine and allylated. Zinc serves a dual role in this tandem reaction by promoting both the reductive fragmentation and the allylation reaction. The resulting diene **C** is subsequently cyclized by olefin metathesis to generate the seven-membered carbon skeleton in the calystegines. Recently, we have also used this sequence for preparation of other carbocyclic natural products from carbohydrates including cyclophellitol,[12] 7-deoxypancratistatin[13] and gabosine A and N.[14]



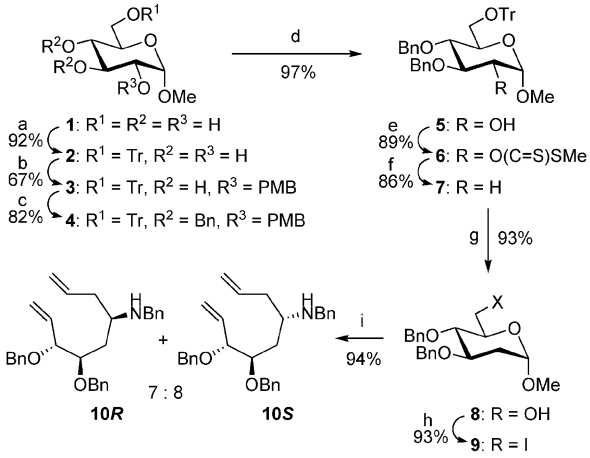
Scheme 2. Calystegine retrosynthesis.

Herein, we describe a concise synthesis of calystegine A_3 from D-glucose by the use of ring-closing metathesis and confirm the absolute configuration of the natural product.

Results and Discussion

Calystegine A_3 contains two secondary hydroxy groups with the same stereochemical relationship as the hydroxy groups at C-3 and C-4 in D-glucose. On the other hand, the hydroxy group at C-2 in the starting material must be removed at some point during the synthesis. The strategy employs the zinc-mediated tandem reaction with iodoglycoside **A** followed by ring-closing metathesis into cycloheptene **D** (Scheme 2). The deoxygenation can either be carried out before the tandem reaction or after the metathesis reaction. The most straightforward approach is to remove the C-2 hydroxy group early in the synthesis. As a result, it was decided to prepare a 2-deoxy-6-iodo glycoside from glucose and investigate the tandem reaction with this substrate (Scheme 3).

The synthesis began with the introduction of temporary protecting groups in the 6- and the 2-position in methyl α-D-glucopyranoside (**1**). A trityl ether was chosen for regioselective protection of the 6-position because it can be introduced in high yield and the product isolated by crystallization from toluene. A *p*-methoxybenzyl ether was selected for protection of the 2-position and installed by a tin-mediated alkylation.[15] The best result was obtained by generating the tin acetal in situ in the presence of the alkylating agent,[16] which afforded the desired 2-*p*-methoxybenzyl



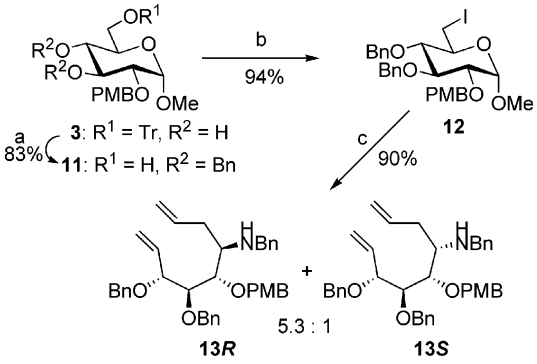
Scheme 3. Reagents and conditions: (a) TrCl, pyridine, 90 °C. (b) PMBCl, Bu_2SnO, Bu_4NI, MeCN, 4-Å MS, 82 °C. (c) BnBr, NaH, Bu_4NI, DMF, room temp. (d) DDQ, H_2O, CH_2Cl_2, room temp. (e) CS_2, imidazole, NaH, THF, room temp., then MeI, room temp. (f) Bu_3SnH, AIBN, toluene, 110 °C. (g) H_2SO_4, MeOH, room temp. (h) I_2, PPh_3, imidazole, THF, 67 °C. (i) Zn, TMSCl, THF, 40 °C, sonication, then $BnNH_2$, then $CH_2=CHCH_2Br$, 40 °C, sonication.

ether **3** in 67% yield. Attempts to form the tin acetal in refluxing toluene in a separate step followed by alkylation with *p*-methoxybenzyl chloride only gave **3** in low yield due to poor conversion and decomposition. Diol **3** was then protected with benzyl groups followed by cleavage of the *p*-methoxybenzyl ether to furnish 2-hydroxy glycoside **5**. The hydroxy group at C-2 was removed by a Barton–McCombie radical deoxygenation[17] to afford 2-deoxy glycoside **7** in good yield. Deprotection of the trityl ether and treatment of the resulting alcohol **8** with iodine, triphenylphosphane and imidazole[18] then gave iodo glycoside **9**.

With this substrate in hand the zinc-mediated tandem reaction was then investigated under various conditions. In all previous applications of this reaction the imines have contained an ether protecting group at C-2 to secure a good 1,2-stereochemical induction in the allylation.[8a–8d,10,19] Although good 1,3-induction can be achieved for certain addition reactions to β-alkoxy aldehydes[20] there was no precedence for the addition to imines derived from **9**. Thus, 2-deoxy glycoside **9** was fragmented with zinc in THF and the intermediate aldehyde converted into the imine and allylated with allyl bromide (Scheme 3). This gave a good yield of the desired aminodiene **10**, but unfortunately the ratio between the desired diastereomer **10*R*** and the undesired isomer **10*S*** was only 7:8. The stereochemistry at the new stereocenter in **10*R*** and **10*S*** was established after the ring-closing metathesis reaction (see Supporting Information for details). We have previously observed that sugar-derived imines could be allylated in excellent selectivity with magnesium and indium metal.[8b] However, when the 2-deoxy imine derived from **9** was subjected to allyl bromide in the presence of magnesium or indium, the result was a 3:4 ratio between **10*R*** and **10*S*** in both cases. Changing the solvent to the more apolar toluene/dichloromethane (4:1) mixture had no influence on the diastereoselectivity. As a re-

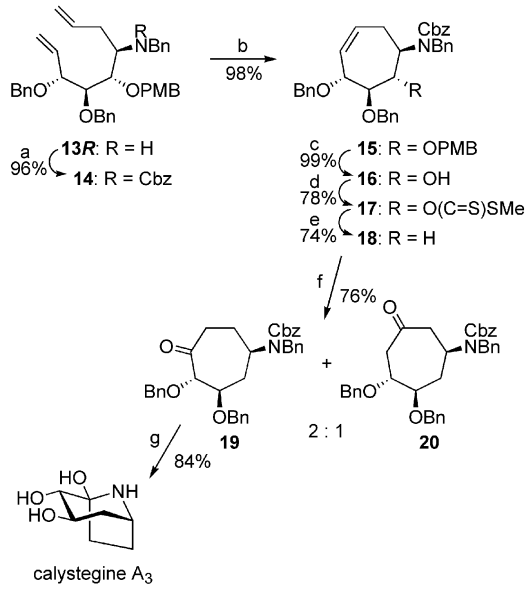
sult, it was clear that 2-deoxy glycosides cannot be used for synthesis of the calystegines by this route and that the ether group in the 2-position is necessary as a stereochemical control element in the allylation. A revised strategy was therefore devised where the deoxygenation was postponed until after the metathesis reaction.

For this purpose diol **3** was benzyl-protected and the trityl ether removed in the workup to afford alcohol **11** (Scheme 4). The hydroxy group was replaced with iodine to give **12** which was then submitted to the tandem reaction with zinc, benzylamine and allyl bromide. Again, the aminodienes were obtained in good yield, but the ratio had now changed to 5.3:1 in favor of the desired diastereomer **13*R*** in line with our earlier observations.[8b]



Scheme 4. Reagents and conditions: (a) BnBr, NaH, Bu_4NI, DMF, room temp., then H_2SO_4, MeOH, room temp. (b) I_2, PPh_3, imidazole, THF, 67 °C. (c) Zn, TMSCl, THF, 40 °C, sonication, then $BnNH_2$, then $CH_2=CHCH_2Br$, 40 °C, sonication.

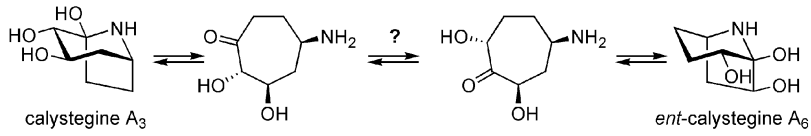
Amino dienes **13*R*** and **13*S*** were separated by silica gel chromatography and the amino group in **13*R*** was protected with a Cbz group (Scheme 5). The fully protected diene **14** was cyclized by olefin metathesis to afford the seven-membered carbocycle **15** in high yield. Subsequent cleavage of the *p*-methoxybenzyl ether with DDQ gave alcohol **16** in near quantitative yield while the same reaction with ceric ammonium nitrate afforded 68% yield. Alcohol **16** was then ready for the ensuing deoxygenation reaction which proved to be more troublesome than with monosaccharide **5**. Again, the Barton-McCombie protocol was selected and it was attempted to form xanthate **17** by the same procedure as used above for compound **6**. However, the basic conditions resulted in cleavage of the neighboring Cbz group and the formation of a cyclic carbamate as the major product. Eventually, by using carbon disulfide as a co-solvent it was possible to diminish this side reaction and obtain xanthate **17** in a satisfying 78% yield. The following reaction with tributyltin hydride also required significant optimization. The first experiment was performed by mixing **17**, AIBN and tributyltin hydride in toluene and heating the solution to reflux. This afforded deoxy compound **18** in 29% yield together with several byproducts which were not further identified. A better result was obtained by adding **17** slowly to a refluxing toluene solution of tributyltin hydride and AIBN, which ensures a high concentration of tributyltin hydride compared to the thiocarbonyl derivative and in this way a rapid capture of the generated alkyl radical. The best result, however, was obtained by slow addition of **17** and AIBN to a toluene solution of tributyltin hydride which furnished **18** in 74% yield.



Scheme 5. Reagents and conditions: (a) CbzCl, $KHCO_3$, H_2O, CH_2Cl_2, 0 °C → room temp. (b) 5% $(PCy_3)(C_3H_4N_2Mes_2)Cl_2Ru$=CHPh, CH_2Cl_2, room temp. (c) DDQ, H_2O, CH_2Cl_2, room temp. (d) imidazole, NaH, CS_2, THF, room temp., then MeI, room temp. (e) Bu_3SnH, AIBN, toluene, 110 °C. (f) BH_3·THF, THF –40 °C, then H_2O_2, NaOH, H_2O, room temp., then Dess–Martin periodinane, CH_2Cl_2, room temp. (g) $Pd(OH)_2/C$, H_2, H_2O, dioxane, room temp.

To complete the synthesis of calystegine A_3 olefin **18** was subjected to hydroboration followed by oxidative workup to give a mixture of four isomeric alcohols. These were not purified, but submitted directly to oxidation with the Dess–Martin periodinane[21] to furnish a 2:1 mixture of the two regioisomeric ketones **19** and **20**. The major isomer **19** was deprotected by hydrogenolysis with Pearlman's catalyst to furnish calystegine A_3. In the earlier synthesis isolation of the target molecule failed due to decomposition under basic conditions.[7] Therefore, hydrochloric acid was added during the deprotection to secure ring-closure into the nortropane ring system. Workup with basic ion-exchange resin and purification on a Sephadex column afforded the natural product with optical rotation and spectroscopic data in agreement with literature data[2b,5] which confirms the absolute configuration of the target molecule.

Previously, there have been speculations whether calystegine A_6 is derived from calystegine A_3 by an isomerization reaction (Scheme 6).[1] Calystegine A_6 has only been found in a few cases and always together with calystegine A_3.[1] If this isomerization is in fact occurring, the correct structure of calystegine A_6 would be the enantiomer of the originally proposed structure. To investigate this possibility we treated



Scheme 6.

synthetic calystegine A_3 with base under different conditions. In pyridine at 100 °C no reaction was observed after 1 d. In 1 M aqueous calcium hydroxide at room temperature the natural product underwent slow degradation into a complex mixture during two weeks. At 100 °C the degradation was almost complete within 4 h and at no time did we observe any formation of calystegine A_6. Hence, it appears that calystegine A_3 is moderately stable to base and that calystegine A_6 is not derived from calystegine A_3 by a simple base-mediated isomerization.

Conclusions

In summary, we have developed a 13-step synthesis of calystegine A_3 from D-glucose in an overall yield of 5.5%. The cycloheptane skeleton of the natural product is created by a zinc-mediated tandem reaction followed by ring-closing olefin metathesis. In the zinc reaction an ether substituent was necessary in the 2-position of the carbohydrate in order to secure a good diastereoselectivity. The results confirm the absolute configuration of calystegine A_3 and emphasize the utility of the two organometallic reactions for developing short syntheses of carbocyclic natural products from carbohydrates.

Experimental Section

General: CH_2Cl_2 was dried by distillation from CaH_2 while MeOH and DMF were dried with 4-Å molecular sieves. THF and toluene were dried by distillation from sodium while pyridine was dried with KOH and distilled prior to use. Zinc dust (< 10 micron) was activated immediately before use: zinc (5 g) in 1 M HCl (50 mL) was stirred at room temperature for 20 min and then filtered, rinsed with water and Et_2O and finally dried at high vacuum with a heat gun. Sonications were performed in a Branson 1210 sonic bath. PMBCl was prepared by vigorous stirring of PMBOH with 6 M aqueous HCl followed by phase separation and drying over K_2CO_3. All other reagents were obtained from commercial sources and used without further purification. Reactions were monitored by TLC using aluminium plates precoated with silica gel 60. Compounds were visualized by dipping in a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $Ce(SO_4)_2$ (10 g/L) in 10% aqueous H_2SO_4 followed by heating. Flash column chromatography was performed with E. Merck silica gel 60 (particle size 0.040–0.063 mm). Optical rotations were measured with a Perkin–Elmer 241 polarimeter while IR spectra were recorded with a Bruker Alpha FT-IR spectrometer. NMR spectra were recorded with a Varian Mercury 300 instrument. Residual solvent peaks were used as internal reference in ^1H NMR [$\delta(CHCl_3)$ = 7.26 ppm, $\delta(CD_2HCOCD_3)$ = 2.05 ppm, $\delta(CD_2HSOCD_3)$ = 2.50 ppm, δ(HDO) = 4.79 ppm] while $CDCl_3$ (δ = 77.16 ppm), $(CD_3)_2CO$ (δ = 29.84 ppm), $(CD_3)_2SO$ (δ = 39.52 ppm) and dioxane in D_2O (δ = 67.19 ppm) served as the internal standards in ^{13}C NMR spectroscopy. Only the major rotamer is reported in the ^{13}C NMR of Cbz-protected amines. High resolution mass spectra were recorded at the Department of Physics and Chemistry, University of Southern Denmark.

Methyl 6-*O*-Trityl-α-D-glucopyranoside (2): A solution of methyl α-D-glucopyranoside (23.2 g, 120 mmol) and TrCl (36.6 g, 131 mmol) in pyridine (350 mL) was stirred at 90 °C for 3 h. The mixture was concentrated in vacuo and co-concentrated with toluene (2 × 100 mL). The residue was dissolved in CH_2Cl_2 (600 mL) and washed with H_2O (600 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. The crude product was crystallized from toluene to afford **2** (47.9 g, 92%) as white crystals. R_f = 0.21 (EtOAc). $[\alpha]_D^{25}$ = +62.0 (c = 2.0, $CHCl_3$) [lit.[22] $[\alpha]_D$ = +59.4 (c = 0.7, $CHCl_3$)]. M.p. 143–145 °C (toluene) [lit.[23] 151–152 °C (EtOH)]. IR (KBr): $\tilde{\nu}$ = 3424, 3058, 2930, 1490, 1449, 1147, 1049, 901, 760, 740, 703, 630 cm^{-1}. ^1H NMR [300 MHz, $(CD_3)_2CO$]: δ = 7.57–7.48 (m, 6 H), 7.36–7.20 (m, 9 H), 4.73 (d, J = 3.7 Hz, 1 H), 4.21 (d, J = 3.8 Hz, OH), 4.06 (d, J = 4.6 Hz, OH), 3.78 (ddd, J = 1.7, 6.8, 9.7 Hz, 1 H), 3.71 (d, J = 7.9 Hz, 1 H), 3.62 (td, J = 3.9, 9.2 Hz, 1 H), 3.48 (s, 3 H), 3.45–3.37 (m, 2 H), 3.30 (ddd, J = 4.2, 8.2, 9.5 Hz, 1 H), 3.24 (dd, J = 6.7, 9.6 Hz, 1 H) ppm. ^{13}C NMR [75 MHz, $(CD_3)_2CO$]: δ = 145.3, 129.5, 128.5, 127.7, 100.8, 87.0, 75.5, 73.4, 72.1, 71.9, 64.7, 55.1 ppm. HRMS: calcd. for $C_{26}H_{28}NaO_6$ $[M + Na]^+$ m/z 459.1778; found m/z 459.1805.

Methyl 2-*O*-(*p*-Methoxybenzyl)-6-*O*-trityl-α-D-glucopyranoside (3): A suspension of triol **2** (2.0 g, 4.6 mmol), Bu_2SnO (1.31 g, 5.3 mmol), Bu_4NI (1.7 g, 4.6 mmol) and freshly made PMBCl (0.68 mL, 5.0 mmol) in anhydrous MeCN (120 mL) was heated to reflux for 16 h via a soxhlet containing 4 Å molecular sieves. The reaction mixture was allowed to reach room temperature and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (100 mL) and stirred with saturated aqueous $NaHCO_3$ (40 mL) for 1 h. The mixture was filtered through a plug of Celite and the phases were separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane/Et_3N, 1:3:0.01 → EtOAc) to give **3** (1.71 g, 67%) as a white foam. R_f = 0.53 (EtOAc). $[\alpha]_D^{25}$ = +31.4 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3443, 3057, 2930, 2834, 1612, 1513, 1490, 1449, 1250, 1151, 1053, 903, 765, 747, 707, 632 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.42 (m, 6 H), 7.33–7.19 (m, 11 H), 6.91–6.85 (m, 2 H), 4.64 (d, J = 11.9 Hz, 1 H), 4.60 (d, J = 3.4 Hz, 1 H), 4.59 (d, J = 11.9 Hz, 1 H), 3.86 (td, J = 2.0, 9.2 Hz, 1 H), 3.79 (s, 3 H), 3.71–3.63 (m, 1 H), 3.49 (td, J = 2.6, 9.2 Hz, 1 H), 3.40–3.29 (m, 3 H), 3.36 (s, 3 H), 2.68 (d, J = 2.1 Hz, OH), 2.62 (d, J = 2.7 Hz, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 143.6, 130.0, 129.7, 128.6, 127.8, 127.1, 113.9, 97.5, 86.9, 78.8, 72.9, 72.6, 71.7, 69.4, 66.9, 55.2, 55.1 ppm. HRMS: calcd. for $C_{34}H_{36}NaO_7$ $[M + Na]^+$ m/z 579.2353; found m/z 579.2386.

Methyl 3,4-Di-*O*-benzyl-2-*O*-(*p*-methoxybenzyl)-6-*O*-trityl-α-D-glucopyranoside (4): Bu_4NI (2.1 g, 5.7 mmol) was added to a suspension of diol **3** (31.5 g, 56.6 mmol) and NaH (8.25 g, 50%, 171.9 mmol, washed with heptane) in anhydrous DMF (600 mL) at 0 °C followed by dropwise addition of BnBr (21.7 mL,

183 mmol). The mixture was left at ambient temperature overnight while it warmed to room temperature. The reaction mixture was quenched with MeOH (60 mL), diluted with Et_2O (600 mL) and washed with H_2O (700 mL). The aqueous phase was extracted with Et_2O (2 × 500 mL), and the combined organic phases were dried ($MgSO_4$), filtered and concentrated on Celite. Dry column vacuum chromatography[24] (EtOAc/heptane, 1:5) afforded **4** (34.4 g, 82%) as a white foam. R_f = 0.47 (EtOAc/heptane, 1:2). $[\alpha]_D^{25}$ = +10.9 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3061, 3030, 2926, 1612, 1513, 1449, 1249, 1159, 1072, 1036, 1028, 755, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 6 H), 7.30–7.06 (m, 19 H), 6.83–6.74 (m, 4 H), 4.86 (d, J = 10.7 Hz, 1 H), 4.71 (d, J = 10.7 Hz, 1 H), 4.69 (d, J = 11.8 Hz, 1 H), 4.62 (d, J = 3.7 Hz, 1 H), 4.57 (d, J = 11.1 Hz, 1 H), 4.61 (d, J = 9.0 Hz, 1 H), 4.20 (d, J = 10.4 Hz, 1 H), 3.86 (t, J = 8.8 Hz, 1 H), 3.76–3.68 (m, 1 H), 3.73 (s, 3 H), 3.57–3.49 (m, 2 H), 3.41 (d, J = 10.0 Hz, 1 H), 3.36 (s, 3 H), 3.10 (dd, J = 4.7, 9.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 144.1, 138.8, 138.0, 130.5, 129.8, 128.9, 128.6, 128.3, 128.3, 128.2, 127.9, 127.8, 127.7, 127.0, 114.0, 98.1, 86.4, 82.4, 79.9, 78.2, 76.1, 75.1, 73.1, 70.3, 62.7, 55.4, 55.1 ppm. HRMS: calcd. for $C_{48}H_{48}NaO_7$ [M + Na]$^+$ m/z 759.3292; found m/z 759.3257.

Methyl 3,4-Di-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside (5): DDQ (6.84 g, 30.1 mmol) was added to a solution of fully protected **4** (14.8 g, 20.1 mmol) in CH_2Cl_2/H_2O (19:1, 350 mL). The atmosphere was exchanged with argon and the mixture was stirred at room temperature for 2.5 h. The solution was diluted with CH_2Cl_2 (700 mL) and quenched by stirring with saturated aqueous $NaHCO_3$ (500 mL) for 1.5 h. The aqueous phase was extracted with CH_2Cl_2 (2 × 500 mL) and the combined organic phases were washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated on Celite. Purification by dry column vacuum chromatography[24] (EtOAc/heptane, 2:1) gave **5** (12.0 g, 97%) as a colorless oil. R_f = 0.49 (EtOAc/heptane, 1:1). $[\alpha]_D^{25}$ = +71.5 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3448, 3060, 3029, 2929, 1490, 1449, 1156, 1125, 1047, 745, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.45 (m, 6 H), 7.41–7.15 (m, 17 H), 6.87 (dd, J = 1.8, 7.7 Hz, 2 H), 4.91–4.81 (m, 3 H), 4.67 (d, J = 10.4 Hz, 1 H), 4.29 (d, J = 10.4 Hz, 1 H), 3.84–3.62 (m, 4 H), 3.53 (dd, J = 1.8, 10.1 Hz, 1 H), 3.47 (s, 3 H), 3.22 (dd, J = 4.6, 10.0 Hz, 1 H), 2.17 (d, J = 7.4 Hz, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.1, 138.7, 137.9, 128.9, 128.6, 128.3, 128.2, 128.1, 127.9, 127.7, 127.1, 99.3, 86.5, 83.6, 78.0, 75.7, 75.0, 73.2, 70.7, 62.6, 55.1 ppm. HRMS: calcd. for $C_{40}H_{40}NaO_6$ [M + Na]$^+$ m/z 639.2717; found m/z 639.2734.

Methyl 3,4-Di-*O*-benzyl-2-*O*-(methylsulfanylthiocarbonyl)-6-*O*-trityl-α-D-glucopyranoside (6): A solution of alcohol **5** (7.06 g, 11.4 mmol) in CS_2 (13.8 mL, 22.8 mmol) and THF (140 mL) were added to NaH (1.65 g, 50%, 34.4 mmol, washed with heptane) and imidazole (374 mg, 5.5 mmol) under nitrogen. The reaction was stirred at room temperature for 3.5 h after which time MeI (3.6 mL, 57.8 mmol) was added. After an additional 1.5 h at room temperature, the mixture was concentrated. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with H_2O (2 × 100 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL) and the combined organic phases were dried (Na_2SO_4), filtered, concentrated on Celite followed by dry column vacuum chromatography[24] (heptane → EtOAc/heptane, 1:19) to afford **6** (7.2 g, 89%) as a yellow solid. R_f = 0.71 (EtOAc/heptane, 1:1). $[\alpha]_D^{25}$ = +52.9 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3058, 3030, 2926, 1491, 1449, 1359, 1207, 1171, 1046, 740, 688, 630 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.46 (m, 6 H), 7.32–7.16 (m, 17 H), 6.87 (dd, J = 1.7, 7.7 Hz, 2 H), 5.80 (dd, J = 3.7, 9.9 Hz, 1 H), 5.17 (d, J = 3.7 Hz, 1 H), 4.78 (d, J = 10.7 Hz, 1 H), 4.72 (d, J = 10.7 Hz, 1 H), 4.68 (d, J = 10.4 Hz, 1 H), 4.30 (d, J = 10.4 Hz, 1 H), 4.16 (dd, J = 8.7, 9.9 Hz, 1 H), 3.90–3.83 (m, 1 H), 3.76 (dd, J = 8.7, 10.1 Hz, 1 H), 3.53 (dd, J = 1.5, 9.9 Hz, 1 H), 3.43 (s, 3 H), 3.24 (dd, J = 4.5, 10.1 Hz, 1 H), 2.60 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.1, 144.0, 138.2, 137.8, 128.9, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.1, 96.2, 86.5, 81.6, 80.4, 78.2, 75.8, 75.2, 70.4, 62.5, 55.1, 19.6 ppm. HRMS: calcd. for $C_{42}H_{42}NaO_6S_2$ [M + Na]$^+$ m/z 729.2315; found m/z 729.2330.

Methyl 3,4-Di-*O*-benzyl-2-deoxy-6-*O*-trityl-α-D-glucopyranoside (7): The methyl xanthate **6** (10.3 g, 14.6 mmol) was dissolved in anhydrous toluene (190 mL) under nitrogen and heated to reflux. A solution of AIBN (239 mg, 1.46 mmol) and Bu_3SnH (8.9 mL, 33.6 mmol) in anhydrous toluene (60 mL) was added dropwise to the reaction mixture over a period of 1 h. The solution was stirred at reflux for 6 h, cooled to room temperature and concentrated on Celite. The product was purified by dry column vacuum chromatography[24] (heptane → EtOAc/heptane, 1:19) to afford **7** (7.53 g, 86%) as a white solid. R_f = 0.55 (EtOAc/heptane, 1:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.37 (m, 6 H), 7.39–7.07 (m, 17 H), 6.83 (dd, J = 2.0, 7.2 Hz, 2 H), 4.84 (d, J = 2.5 Hz, 1 H), 4.67 (d, J = 10.5 Hz, 1 H), 4.59–4.56 (m, 2 H), 4.26 (d, J = 10.5 Hz, 1 H), 3.92–3.81 (m, 1 H), 3.71 (dd, J = 3.3, 9.8 Hz, 1 H), 3.57–3.48 (m, 1 H), 3.47–3.41 (m, 1 H), 3.30 (s, 3 H), 3.17 (dd, J = 4.8, 9.9 Hz, 1 H), 2.25 (dd, J = 5.0, 12.9 Hz, 1 H), 1.70 (ddd, J = 3.6, 11.7, 13.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2, 138.8, 138.3, 129.0, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.0, 98.4, 86.4, 78.8, 77.9, 75.0, 72.2, 70.9, 63.1, 54.5, 35.8 ppm. HRMS: calcd. for $C_{40}H_{40}NaO_5$ [M + Na]$^+$ m/z 623.2768; found m/z 623.2764.

Methyl 3,4-Di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (8): A suspension of trityl ether **7** (7.5 g, 12.5 mmol) in 1% H_2SO_4 in MeOH (550 mL) was stirred at room temperature under argon for 2.5 h. The mixture was neutralized by stirring with Na_2CO_3 (10 g), filtered and concentrated on Celite. Purification by dry column vacuum chromatography[24] (EtOAc/heptane, 1:9 → 1:4) gave **8** (4.15 g, 93%) as a colorless oil. R_f = 0.38 (EtOAc/heptane, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 10 H), 4.95 (d, J = 11.1 Hz, 1 H), 4.80 (d, J = 3.2 Hz, 1 H), 4.72–4.60 (m, 3 H), 4.05–3.94 (m, 1 H), 3.85–3.72 (m, 2 H), 3.68–3.60 (m, 1 H), 3.55–3.47 (m, 1 H), 3.30 (s, 3 H), 2.29 (dd, J = 5.0, 13.1 Hz, 1 H), 1.95 (s, OH), 1.66 (ddd, J = 3.6, 11.5, 13.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 138.5, 128.5, 128.5, 128.1, 127.9, 127.7, 127.7, 98.6, 78.2, 77.6, 75.0, 71.9, 71.2, 62.3, 54.7, 35.6 ppm. ^1H NMR spectroscopic data are in accordance with literature values.[25] HRMS: calcd. for $C_{21}H_{26}NaO_5$ [M + Na]$^+$ m/z 381.1672; found m/z 381.1693.

Methyl 3,4-Di-*O*-benzyl-2,6-dideoxy-6-iodo-α-D-glucopyranoside (9): Alcohol **8** (4.4 g, 12.2 mmol), PPh_3 (5.1 g, 19.4 mmol) and imidazole (2.0 g, 29.4 mmol) were co-concentrated with toluene (2 × 125 mL) and then dissolved in THF (250 mL) under argon. The solution was heated to reflux and a solution of I_2 in THF (0.17 mmol/mL) was added dropwise to the reaction mixture until a permanent color change was achieved (79.4 mL, 13.3 mmol). Full conversion was confirmed by TLC analysis, and the mixture was cooled to room temperature, filtered, and concentrated on Celite. The product was purified by dry column vacuum chromatography[24] (EtOAc/heptane, 1:49 → 1:9) to afford **9** (5.33 g, 93%) as a colorless oil. R_f = 0.53 (EtOAc/heptane, 1:2). IR (film): $\tilde{\nu}$ = 3030, 2933, 2901, 1496, 1453, 1366, 1213, 1130, 1100, 1047, 955, 741, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.15 (m, 10 H), 4.93 (d, J = 11.0 Hz, 1 H), 4.75 (d, J = 3.0 Hz, 1 H), 4.64 (d, J = 11.0 Hz, 1 H), 4.58 (d, J = 11.5 Hz, 1 H), 4.51 (d, J = 11.5 Hz, 1 H), 3.93 (ddd, J = 5.1, 8.3, 11.5 Hz, 1 H), 3.52–3.20 (m, 4 H), 3.28

(s, 3 H), 2.23 (dd, J = 5.1, 13.1 Hz, 1 H), 1.62 (ddd, J = 3.6, 11.6, 13.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 138.4, 128.6, 128.5, 128.1, 127.9, 127.8, 98.6, 82.2, 77.3, 75.4, 71.8, 69.9, 55.1, 35.5, 8.7 ppm. ^{1}H NMR spectroscopic data are in accordance with literature values.[25] HRMS: calcd. for $C_{21}H_{25}INaO_4$ [M + Na]$^+$ m/z 491.0690; found m/z 491.0698.

(3*R*,4*R*,6*R*)- and (3*R*,4*R*,6*S*)-6-(Benzylamino)-3,4-bis(benzyloxy)-nona-1,8-diene (10*R* and 10*S*): A suspension of activated Zn (140 mg, 2.14 mmol) and iodide **9** (100 mg, 0.214 mmol) in THF (4 mL) was sonicated at 40 °C under argon in a conical flask. TMSCl (13.5 μL, 0.107 mmol) was added in two portions, after 15 and 25 min of sonication. When NMR revealed full conversion to the aldehyde (1 h and 15 min), $BnNH_2$ (117 μL, 1.07 mmol) was added dropwise to the solution. When NMR revealed full conversion of the aldehyde to the imine (45 min), allyl bromide (55.4 μL, 0.64 mmol) was added dropwise to the solution. After an additional 2 h of sonication, the solution was cooled to room temperature, diluted with Et_2O (60 mL) and H_2O (20 mL) and filtered through a plug of Celite. The layers were separated and the organic phase was washed with H_2O (3 × 20 mL) and brine (20 mL), dried (K_2CO_3), filtered, and concentrated in vacuo to give a colorless oil, which was purified by flash column chromatography (EtOAc/heptane, 1:4) to afford a separable 7:8 diastereomeric mixture of **10*R*** and **10*S*** (89 mg, 94%) as colorless oils.

10*R*: R_f = 0.20 (EtOAc/heptane, 1:2). $[\alpha]_D^{23}$ = +10.9 (c = 1.6, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3064, 3029, 2925, 2861, 1496, 1454, 1353, 1206, 1092, 1069, 1027, 995, 918, 735, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.09 (m, 15 H), 5.74 (ddd, J = 7.5, 10.6, 17.1 Hz, 1 H), 5.68–5.53 (m, 1 H), 5.27–5.17 (m, 2 H), 5.01–4.92 (m, 2 H), 4.66 (d, J = 11.5 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.41 (d, J = 11.5 Hz, 1 H), 4.29 (d, J = 12.0 Hz, 1 H), 3.83 (dd, J = 5.6, 7.4 Hz, 1 H), 3.61 (s, 2 H), 3.58–3.50 (m, 1 H), 2.62 (p, J = 6.3 Hz, 1 H), 2.18–2.06 (m, 1 H), 2.04–1.93 (m, 1 H), 1.62–1.54 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8, 138.7, 138.6, 135.5, 135.3, 128.4, 128.3, 128.1, 127.9, 127.6, 127.6, 126.8, 119.0, 117.5, 82.2, 79.0, 72.9, 70.6, 53.8, 51.1, 38.3, 35.3 ppm. HRMS: calcd. for $C_{30}H_{36}NO_2$ [M + H]$^+$ m/z 442.2741; found m/z 442.2733.

10*S*: R_f = 0.27 (EtOAc/heptane, 1:2). $[\alpha]_D^{23}$ = +32.5 (c = 1.0, $CDCl_3$). IR (film): $\tilde{\nu}$ = 3064, 3028, 2918, 2859, 1495, 1453, 1355, 1261, 1207, 1089, 1065, 1027, 993, 913, 733, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.27 (m, 15 H), 5.94–5.75 (m, 2 H), 5.41–5.31 (m, 2 H), 5.19–5.10 (m, 2 H), 4.82–4.64 (m, 2 H), 4.49 (d, J = 11.4 Hz, 1 H), 4.46 (d, J = 12.0 Hz, 1 H), 3.96 (t, J = 6.6 Hz, 1 H), 3.90–3.80 (m, 2 H), 3.65 (d, J = 12.9 Hz, 1 H), 2.96–2.86 (m, 1 H), 2.32 (dd, J = 6.9, 14.5 Hz, 2 H), 2.04 (br. s, NH), 1.70–1.62 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8, 138.8, 138.6, 135.4, 135.3, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.5, 127.4, 126.9, 118.9, 117.4, 82.6, 78.6, 73.4, 70.6, 52.9, 50.5, 38.7, 35.6 ppm. HRMS: calcd. for $C_{30}H_{36}NO_2$ [M + H]$^+$ m/z 442.2741; found m/z 442.2728.

Methyl 3,4-Di-*O*-benzyl-2-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (11): NaH (3.70 g, 50%, 77.1 mmol, washed with heptane) was added to a solution of diol **3** (14.2 g, 25.5 mmol) in anhydrous DMF (350 mL) and the mixture was stirred at room temperature for 25 min. The reaction was cooled to 0 °C followed by addition of Bu_4NI (660 mg, 1.80 mmol) and dropwise addition of BnBr (9.10 mL, 76.6 mmol). After stirring at ambient temperature overnight, the mixture was quenched with MeOH (20 mL), diluted with Et_2O (600 mL) and washed with H_2O (600 mL). The aqueous phase was extracted with Et_2O (2 × 600 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was stirred in 1% H_2SO_4 in MeOH (800 mL) and when TLC revealed no further conversion (3 h and 15 min), Na_2CO_3 (30 g) was added followed by stirring at room temperature until pH > 7. The mixture was filtered and concentrated under reduced pressure to give a residue which was dissolved in CH_2Cl_2 (500 mL) and washed with H_2O (500 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 500 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/heptane, 3:2) to afford **11** (10.5 g, 83%) as a sticky white solid. R_f = 0.30 (EtOAc/heptane, 1:1). $[\alpha]_D^{25}$ = +20.3 (c = 2.2, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3475, 3063, 3030, 2925, 1700, 1612, 1586, 1512, 1496, 1456, 1359, 1303, 1251, 1093, 913, 822, 735, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.25 (m, 12 H), 6.87 (d, J = 8.3 Hz, 2 H), 4.99 (d, J = 10.8 Hz, 1 H), 4.89 (d, J = 10.9 Hz, 1 H), 4.83 (d, J = 10.9 Hz, 1 H), 4.75 (d, J = 11.8 Hz, 1 H), 4.64 (d, J = 11.8 Hz, 1 H), 4.60 (d, J = 11.7 Hz, 1 H), 4.52 (d, J = 3.5 Hz, 1 H), 4.00 (t, J = 9.2 Hz, 1 H), 3.81 (s, 3 H), 3.79–3.62 (m, 3 H), 3.57–3.46 (m, 2 H), 3.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 138.9, 138.2, 130.3, 129.9, 128.6, 128.5, 128.2, 128.1, 128.0, 127.7, 114.0, 98.4, 82.1, 79.7, 77.5, 75.9, 75.2, 73.2, 70.7, 62.0, 55.4, 55.3 ppm. HRMS: calcd. for $C_{29}H_{34}NaO_7$ [M + Na]$^+$ m/z 517.2197; found m/z 517.2198.

Methyl 3,4-Di-*O*-benzyl-6-deoxy-6-iodo-2-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (12): A mixture of alcohol **11** (9.62 g, 19.5 mmol), PPh_3 (7.67 g, 29.2 mmol) and imidazole (2.67 g, 39.2 mmol) was co-concentrated with toluene (2 × 500 mL) and then dissolved in THF (350 mL) and heated to reflux. A solution of I_2 in THF (0.49 mmol/mL) was added dropwise until the reaction permanently retained an iodine color (53.0 mL, 26.0 mmol). The completion of the reaction was verified by TLC analysis. The mixture was cooled to room temperature, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/heptane, 1:2) to afford **12** (11.1 g, 94%) as a white glass, which slowly crystallized upon standing. R_f = 0.68 (EtOAc/heptane, 1:1). $[\alpha]_D^{25}$ = +27.2 (c = 2.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3030, 2916, 2906, 2838, 1613, 1514, 1453, 1358, 1300, 1245, 1171, 1112, 1088, 1073, 1047, 1030, 1012, 735, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 12 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.99 (d, J = 10.8 Hz, 1 H), 4.94 (d, J = 11.0 Hz, 1 H), 4.79 (d, J = 10.8 Hz, 1 H), 4.74 (d, J = 11.8 Hz, 1 H), 4.68 (d, J = 10.9 Hz, 1 H), 4.59 (d, J = 11.8 Hz, 1 H), 4.55 (d, J = 3.6 Hz, 1 H), 4.00 (dd, J = 8.8, 9.5 Hz, 1 H), 3.81 (s, 3 H), 3.54–3.42 (m, 3 H), 3.41 (s, 3 H), 3.37–3.25 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 138.5, 137.9, 130.0, 129.7, 128.5, 128.4, 127.9, 127.8, 127.6, 113.8, 98.1, 81.5, 81.4, 79.6, 75.7, 75.3, 73.0, 69.2, 55.5, 55.2, 7.7 ppm. HRMS: calcd. for $C_{29}H_{33}INaO_6$ [M + Na]$^+$ m/z 627.1214; found m/z 627.1191.

(3*R*,4*S*,5*S*,6*R*)-6-(Benzylamino)-3,4-bis(benzyloxy)-5-(*p*-methoxybenzyloxy)nona-1,8-diene (13*R*): Activated Zn (639 mg, 9.77 mmol) was added to a solution of iodide **12** (567 mg, 0.94 mmol) in THF (15 mL). The solution was degassed for 20 min and then placed in a sonic bath at 40 °C. After 10 min and after 20 min of sonication two portions of TMSCl (0.06 mL, 0.47 mmol) were added to the mixture. When NMR revealed full conversion of the starting material (2 h), $BnNH_2$ (0.31 mL, 2.82 mmol) was added dropwise. When NMR revealed full conversion of the aldehyde to the imine (1 h), allyl bromide (0.24 mL, 2.82 mmol) was added dropwise and after sonicating for an additional 1 h and 25 min, the mixture was allowed to reach room temperature. H_2O (10 mL) and Et_2O (40 mL) were added and the suspension was filtered through a plug of Celite. The organic phase was washed with H_2O (2 × 15 mL) and brine (15 mL), dried (K_2CO_3), filtered, and concentrated in vacuo. The

residue was purified by flash column chromatography (EtOAc/heptane/Et_3N, 1:2:0.01) to afford a 5.3:1 diastereomeric mixture of **13*R*** and **13*S*** (487 mg, 90%) as a colorless oil. Additional purification by chromatography gave the major diastereomer **13*R*** as a colorless oil.

13*R*: R_f = 0.42 (EtOAc/heptane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 17 H), 6.85–6.79 (m, 2 H), 5.92 (ddd, J = 7.6, 10.5, 17.4 Hz, 1 H), 5.68–5.54 (m, 1 H), 5.25 (dd, J = 1.8, 10.5 Hz, 1 H), 5.20 (dd, J = 1.8, 17.4 Hz, 1 H), 5.05–4.96 (m, 2 H), 4.78 (d, J = 10.9 Hz, 1 H), 4.76 (d, J = 11.2 Hz, 1 H), 4.65 (d, J = 11.2 Hz, 1 H), 4.51 (d, J = 11.9 Hz, 1 H), 4.50 (d, J = 10.8 Hz, 1 H), 4.08 (d, J = 11.9 Hz, 1 H), 3.93 (dd, J = 3.2, 7.6 Hz, 1 H), 3.82 (d, J = 13.0 Hz, 1 H), 3.79–3.75 (m, 2 H), 3.78 (s, 3 H), 3.69 (dd, J = 3.0, 7.7 Hz, 1 H), 3.43 (d, J = 13.1 Hz, 1 H), 2.45–2.35 (m, 2 H), 2.30–2.15 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 141.0, 138.8, 138.1, 136.3, 136.3, 131.5, 129.2, 128.7, 128.6, 128.4, 128.3, 128.2, 127.6, 127.4, 126.8, 118.3, 116.8, 113.6, 83.4, 80.5, 79.6, 75.3, 74.4, 70.1, 56.5, 55.3, 50.8, 35.1 ppm. HRMS: calcd. for $C_{38}H_{43}NNaO_4$ [M + Na]$^+$ *m*/*z* 600.3084; found *m*/*z* 600.3112.

13*S*: R_f = 0.36 (EtOAc/heptane, 1:2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 141.4, 138.7, 138.2, 136.5, 135.6, 131.2, 129.5, 128.7, 128.6, 128.4, 128.3, 128.2, 127.5, 127.5, 126.7, 118.7, 116.7, 113.8, 82.5, 81.0, 78.8, 74.9, 73.4, 70.6, 57.8, 54.4, 51.5, 35.0 ppm.

(3*R*,4*S*,5*S*,6*R*)-6-[(Benzyl)(benzyloxycarbonyl)amino]-3,4-bis(benzyloxy)-5-(*p*-methoxybenzyloxy)nona-1,8-diene (14): $KHCO_3$ (2.98 g, 29.7 mmol) was added to a solution of amine **13*R*** (2.86 g, 4.96 mmol) in CH_2Cl_2/H_2O (1:1, 140 mL) at 0 °C followed by dropwise addition of CbzCl (0.77 mL, 5.45 mmol) under vigorous stirring. The mixture was slowly allowed to reach room temperature and when TLC revealed full conversion of the starting material (2 h), the phases were separated, and the organic phase was washed with H_2O (30 mL), dried (K_2CO_3), filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/heptane, 1:3) to afford **14** (3.40 g, 96%) as a colorless oil. R_f = 0.49 (EtOAc/heptane, 1:2). $[\alpha]_D^{25}$ = –4.9 (c = 2.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3062, 3031, 2923, 1696, 1641, 1612, 1585, 1514, 1497, 1453, 1407, 1321, 1300, 1248, 1173, 1078, 924, 915, 823, 735, 700 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 60 °C): δ = 7.36–7.16 (m, 20 H), 7.12 (d, J = 8.5 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 5.85 (ddd, J = 7.6, 10.3, 17.5 Hz, 1 H), 5.35–5.03 (m, 5 H), 4.88–4.75 (m, 2 H), 4.70–4.60 (m, 1 H), 4.58–4.02 (m, 9 H), 3.93–3.83 (m, 1 H), 3.75 (s, 2.7 H), 3.73 (s, 0.3 H), 3.52–3.43 (m, 1 H), 2.44–2.29 (m, 1 H), 2.27–2.13 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 157.4, 138.6, 136.5, 135.9, 135.1, 134.8, 131.0, 129.7, 129.4, 129.2, 128.5, 128.4, 128.3, 128.1, 127.9, 127.6, 127.5, 126.7, 118.5, 117.5, 113.7, 83.1, 80.8, 79.9, 75.4, 75.2, 70.8, 67.2, 56.5, 55.4, 53.6, 35.2 ppm. HRMS: calcd. for $C_{46}H_{50}NO_6$ [M + H]$^+$ *m*/*z* 712.3633; found *m*/*z* 712.3614. $C_{46}H_{49}NO_6$ (711.9): calcd. C 77.61, H 6.94; found C 77.56, H 7.18.

(3*R*,4*S*,5*S*,6*R*)-6-[(Benzyl)(benzyloxycarbonyl)amino]-3,4-bis(benzyloxy)-5-(*p*-methoxybenzyloxy)cycloheptene (15): A solution of diene **14** (21.77 g, 30.6 mmol) in CH_2Cl_2 (1.2 L) was degassed by bubbling nitrogen through the mixture for 15 min. Grubbs' 2nd generation catalyst (1.3 g, 1.5 mmol) was added to the solution under nitrogen, and the reaction was protected from sunlight and left stirring at room temperature for 48 h. The reaction mixture was concentrated on Celite and purified by dry column vacuum chromatography[24] (heptane → EtOAc/heptane, 1:3) to give **15** (20.4 g, 98%) as a colorless syrup. R_f = 0.45 (EtOAc/heptane, 1:2). $[\alpha]_D^{25}$ = –19.1 (c = 2.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3064, 3031, 2921, 1700, 1612, 1586, 1514, 1496, 1456, 1355, 1246, 1174, 1073, 824, 734, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.03 (m, 22 H), 6.86–6.74 (m, 2 H), 5.73–5.54 (m, 2 H), 5.25–5.06 (m, 2 H), 4.98–4.56 (m, 6 H), 4.42–4.00 (m, 5 H), 3.76 (s, 1 H), 3.73 (s, 2 H), 3.62–3.52 (m, 1 H), 3.31 (t, J = 10.1 Hz, 0.3 H), 2.94–2.78 (m, 0.7 H), 2.58 (t, J = 12.9 Hz, 0.3 H), 2.02–1.82 (m, 0.7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 156.8, 139.0, 138.5, 138.2, 136.7, 132.8, 130.9, 129.7, 129.1, 128.5, 128.3, 128.1, 127.7, 127.7, 127.5, 127.3, 113.7, 84.7, 83.3, 77.9, 75.3, 75.0, 72.7, 66.9, 61.9, 55.3, 53.8, 30.0 ppm. HRMS: calcd. for $C_{44}H_{46}NO_6$ [M + H]$^+$ *m*/*z* 684.3320; found *m*/*z* 684.3325.

(3*R*,4*R*,5*S*,6*R*)-6-[(Benzyl)(benzyloxycarbonyl)amino]-3,4-bis(benzyloxy)-5-hydroxycycloheptene (16): DDQ (265 mg, 1.17 mmol) was added to a solution of PMB ether **15** (526 mg, 0.77 mmol) in CH_2Cl_2/H_2O (19:1, 15 mL) and the reaction was stirred at room temperature for 2.5 h. The mixture was diluted with CH_2Cl_2 (40 mL) and washed with saturated aqueous $NaHCO_3$ (40 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (EtOAc/heptane, 1:4) afforded **16** (431 mg, 99%) as a colorless oil. R_f = 0.39 (EtOAc/heptane, 1:2). $[\alpha]_D^{25}$ = –13.1 (c = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3545, 3483, 3063, 3031, 2889, 1695, 1496, 1453, 1416, 1248, 1031, 734, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.06 (m, 20 H), 5.76–5.51 (m, 2 H), 5.16–4.99 (m, 2 H), 4.97–4.22 (m, 5 H), 4.14–3.67 (m, 4 H), 3.42 (t, J = 7.7 Hz, 1 H), 2.52–2.18 (m, 1 H), 2.01–1.80 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4 138.9, 138.2, 136.7, 132.6, 130.6, 129.5, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.4, 127.2, 84.0, 78.3, 75.3, 75.0, 72.3, 67.3, 60.0, 50.1, 30.2 ppm. HRMS: calcd. for $C_{36}H_{38}NO_5$ [M + H]$^+$ *m*/*z* 564.2744; found *m*/*z* 564.2773.

(3*R*,4*S*,5*S*,6*R*)-6-[(Benzyl)(benzyloxycarbonyl)amino]-3,4-bis(benzyloxy)-5-[(methylsulfanyl)thiocarbonyloxy]cycloheptene (17): A solution of imidazole (47 mg, 0.69 mmol) in CS_2 (42 mL, 0.69 mol) was added to NaH (267 mg, 50%, 5.56 mmol, washed with heptane) under nitrogen. A solution of alcohol **16** (773 mg, 1.37 mmol) in CS_2 (42 mL, 0.69 mol) and THF (35 mL) was added dropwise to the reaction mixture under vigorous stirring over a period of 1 h and 15 min. After 3 h, MeI (432 μL, 3.82 mmol) was added dropwise and the solution was stirred at room temperature overnight. The mixture was concentrated on Celite and purified by flash column chromatography (EtOAc/heptane, 1:6) to afford **17** (700 mg, 78%) as a yellow oil. R_f = 0.50 (EtOAc/heptane, 1:2). $[\alpha]_D^{23}$ = –29.0 (c = 2.4, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3087, 3063, 3029, 2923, 2865, 1697, 1496, 1453, 1229, 1202, 1118, 1055, 734, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.01 (m, 20 H), 5.79–5.48 (m, 2 H), 5.16–4.98 (m, 2 H), 4.70 (q, J = 11.3 Hz, 1 H), 4.57–3.91 (m, 8 H), 3.82–3.65 (m, 1 H), 2.83–2.52 (m, 1 H), 2.38 (s, 1.5 H), 2.32 (s, 1.5 H), 2.09–1.84 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.0, 156.5, 138.5, 138.4, 138.2, 138.1, 130.7, 130.2, 128.8, 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 84.6, 79.9, 76.2, 74.2, 72.4, 67.3, 58.9, 54.5, 30.0, 19.2 ppm. HRMS: calcd. for $C_{38}H_{39}NNaO_5S_2$ [M + Na]$^+$ *m*/*z* 676.2162; found *m*/*z* 676.2182.

(3*R*,4*R*,6*R*)-6-[(Benzyl)(benzyloxycarbonyl)amino]-3,4-bis(benzyloxy)cycloheptene (18): A solution of freshly distilled Bu_3SnH (243 μL, 0.92 mmol) in toluene (6 mL) was evacuated for 15 min, purged with nitrogen and heated to reflux. To this solution were added methyl xanthate **17** (200 mg, 0.31 mmol) and AIBN (10 mg, 0.061 mmol) in toluene (4 mL) dropwise under nitrogen over a period of 20 min. Additional toluene (1.5 mL) was used to transfer the material. Full conversion was achieved after 50 min and the mixture was cooled to room temperature and concentrated in

vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/heptane, 4:1) to give **18** (124 mg, 74%) as a colorless oil. R_f = 0.45 (EtOAc/heptane, 1:2). $[\alpha]_D^{25}$ = –10.6 (*c* = 2.0, $CDCl_3$). IR (film): $\tilde{\nu}$ = 3087, 3063, 3029, 2961, 2927, 2857, 1693, 1496, 1453, 1413, 1357, 1305, 1259, 1233, 1090, 1070, 1027, 801, 733, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.00 (m, 20 H), 5.64–5.51 (m, 2 H), 5.18–4.97 (m, 2 H), 4.66–4.19 (m, 6 H), 4.00–3.80 (m, 2 H), 3.43–3.18 (m, 1 H), 2.35–1.83 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7, 138.9, 138.7, 136.6, 133.0, 128.5, 128.3, 127.9, 127.8, 127.6, 127.5, 127.4, 127.1, 81.9, 79.2, 73.0, 72.6, 67.2, 53.9, 47.9, 39.6, 33.0 ppm. HRMS: calcd. for $C_{36}H_{37}NNaO_4$ $[M + Na]^+$ *m*/*z* 570.2615; found *m*/*z* 570.2633.

(2*S*,3*R*,5*R*)-5-[(Benzyl)(benzyloxycarbonyl)amino]-2,3-bis(benzyloxy)cycloheptanone (19) and (3*R*,4*R*,6*S*)-6-[(benzyl)(benzyloxycarbonyl)amino]-3,4-bis(benzyloxy)cycloheptanone (20): Cycloheptene **18** (600 mg, 1.1 mmol) was dissolved in THF (30 mL) under argon and cooled to –40 °C. BH_3·THF (1 M in THF, 2.30 mL, 2.3 mmol) was added dropwise to the solution over a period of 20 min. After 3 h at –40 °C, the mixture was allowed to reach room temperature, and after 4 h 2 M aqueous NaOH (2 mL) and 35% aqueous H_2O_2 (4 mL) were added to the reaction. The solution was stirred at ambient temperature for 1 h, diluted with Et_2O (70 mL) and washed with H_2O (3 × 10 mL) and brine (10 mL). The organic phase was dried (K_2CO_3), filtered, and concentrated in vacuo to give a mixture of alcohols, which was used directly in the next step. The crude alcohols were dissolved in CH_2Cl_2 (19 mL) and added to a solution of the Dess–Martin periodinane[21] (929 mg, 2.2 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 1 h, after which time Et_2O (100 mL) was added. The resulting white suspension was stirred for 30 min and then filtered. The filtrate was washed with saturated aqueous $Na_2S_2O_3$ (2 × 20 mL) and brine (30 mL), and the organic phase was dried (K_2CO_3), filtered and concentrated. Flash column chromatography (EtOAc/heptane, 1:9) of the residue gave a separable 2:1 mixture of the isomeric cycloheptanones (468 mg, 76% combined yield) as colorless oils; **19** (308 mg, 50%) and **20** (160 mg, 26%).

19: R_f = 0.38 (EtOAc/heptane, 1:2). $[\alpha]_D^{25}$ = –4.5 (*c* = 1.0, $CDCl_3$). IR (film): $\tilde{\nu}$ = 3088, 3063, 3031, 2930, 2869, 1696, 1496, 1454, 1415, 1357, 1238, 1096, 1072, 1028, 736, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.00 (m, 20 H), 5.21–5.02 (m, 2 H), 4.59–4.15 (m, 6 H), 4.07–3.38 (m, 3 H), 2.69–2.41 (m, 1 H), 2.26–2.12 (m, 1 H), 2.01–1.75 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.2, 155.7, 138.6, 138.0, 137.2, 136.4, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.3, 126.9, 88.7, 79.4, 72.5, 72.2, 67.3, 55.4, 48.3, 37.3, 36.6, 30.5 ppm. HRMS: calcd. for $C_{36}H_{37}NNaO_5$ $[M + Na]^+$ *m*/*z* 586.2564; found *m*/*z* 586.2549.

20: R_f = 0.31 (EtOAc/heptane, 1:2). $[\alpha]_D^{23}$ = –8.7 (*c* = 3.8, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3087, 3063, 3030, 2930, 2871, 1695, 1496, 1454, 1415, 1352, 1246, 1095, 1071, 1028, 736, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.04 (m, 20 H), 5.18–5.00 (m, 2 H), 4.62–3.95 (m, 7 H), 3.57–3.28 (m, 2 H), 2.86–2.31 (m, 4 H), 2.14–1.74 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.2, 155.8, 138.4, 138.2, 138.0, 136.5, 128.9, 128.8, 128.7, 128.62, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.3, 81.2, 79.3, 72.3, 72.3, 67.6, 50.6, 48.3, 44.9, 36.9, 29.9 ppm. HRMS: calcd. for $C_{36}H_{37}NNaO_5$ $[M + Na]^+$ *m*/*z* 586.2564; found *m*/*z* 586.2582.

Calystegine A_3: A solution of cycloheptanone **19** (39 mg, 0.069 mmol) in dioxane/H_2O (9:1, 3.3 mL) was degassed by bubbling nitrogen through the mixture for 10 min. Pearlman's catalyst (8 mg, 7.5 μmol) was added to the solution and H_2 was bubbled through the solution for 10 min after which time the reaction was stirred at room temperature under 1 atmosphere of H_2 for 15 h. TLC analysis revealed disappearance of the protected cycloheptanone, and 1 M aqueous HCl (0.7 mL) was added to the solution, which was stirred at room temperature under 1 atmosphere of H_2 for an additional 32 h. The mixture was neutralized by addition of Amberlite IRA-400 OH^-, filtered through a plug of Celite and thoroughly washed with H_2O (15 × 10 mL). The filtrate was concentrated, co-concentrated with EtOH and purified by Sephadex LH-20 column chromatography (EtOAc/EtOH, 4:1) to give calystegine A_3 (9.2 mg, 84%). R_f = 0.42 (1-propanol/AcOH/H_2O, 4:1:1). $[\alpha]_D^{23}$ = –14.0 (*c* = 0.1, H_2O) [lit.[2b] $[\alpha]_D$ = –17.3 (*c* = 0.47, H_2O)]. IR (film): $\tilde{\nu}$ = 3382, 2954, 2929, 2857, 1635, 1399, 1387, 1259, 1088, 1056, 1026, 934 cm^{-1}. ^1H NMR (800 MHz, D_2O): δ = 3.62 (ddd, *J* = 6.9, 8.4, 10.5 Hz, 1 H), 3.46–3.42 (m, 1 H), 3.35 (d, *J* = 8.5 Hz, 1 H), 2.04–1.93 (m, 2 H), 1.92 (ddd, *J* = 2.1, 6.5, 13.2 Hz, 1 H), 1.51–1.43 (m, 3 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 93.4, 82.5, 72.7, 54.2, 42.6, 31.8, 29.3 ppm. C-1 at δ = 93.4 ppm was assigned by HSQC. NMR spectroscopic data are in accordance with literature values.[2b,5] HRMS: calcd. for $C_7H_{13}NNaO_3$ $[M + Na]^+$ *m*/*z* 182.0788; found *m*/*z* 182.0793.

Supporting Information (see also the footnote on the first page of this article): Structural proof for **10*R*** and **10*S***, ^1H and ^{13}C NMR spectra for compounds **3**–**20** and calystegine A_3.

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