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Total Synthesis of Calystegine B_4

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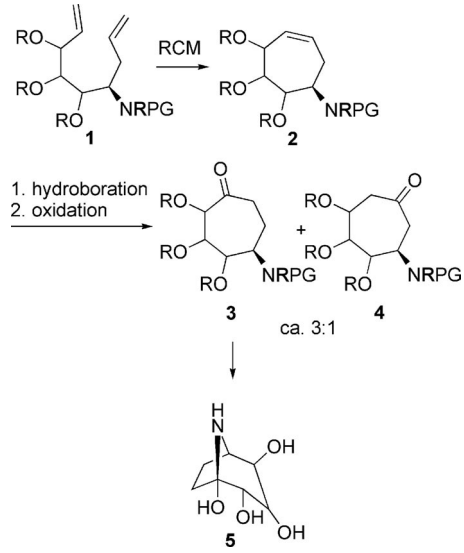
The total synthesis of calystegine B_4 was achieved in 10 steps from (–)-D-lyxose by using a new synthetic strategy to obtain the requisite protected hydroxylated 4-aminocyclohept-2-en-1-one without the problem of regioisomer formation that was a problem in the earlier synthesis of this natural product. The key steps included a Petasis–borono-Mannich reaction and a ring-closing metathesis reaction.

Introduction

The calystegine alkaloids comprise 13 different polyhydroxylated, 1-hydroxynortropane molecules and one trihydroxylated 1-aminonortropane (calystegine N_1).[1,2] In addition, the *N*-methyl derivatives of calystegine B_2 and C_1 are also natural products along with the glycoside derivatives.[1,2] This group, along with the polyhydroxylated pyrrolidine, piperidine, indolizidine and pyrrolizidine alkaloids, have glycosidase inhibitory activities and thus have potential utility as antiviral, anticancer, antidiabetic and anti-obesity drugs.[3] These potentially useful biological activities along with the novel hemiaminal structure of the calystegine alkaloids have made these compounds and their analogues attractive and important synthetic targets.[4–10] A significant number of these syntheses have employed a ring-closing metathesis (RCM) reaction of a protected di- or trihydroxylated 4-amino-1,8-octadiene **1** to provide a protected di- or tri-hydroxylated 4-aminocycloheptene **2**.[5a,6,7,8a,8b] Hydroboration of the alkene functionality of **2**, followed by oxidation of the resulting secondary alcohol then provided a protected hydroxylated 4-aminocycloheptanone **3**, which upon deprotection underwent hemiaminal formation to provide the 1-hydroxynorptropane structure **4** of the target natural product or analogue. One major problem with this synthetic strategy is that the hydroboration reaction occurs with moderate regioselectivity (typically 3:1), in favour of the desired secondary alcohol, giving ultimately mixtures of the ketones **3** and **4** (Scheme 1). Separation of these ketones and then global deprotection of the major regioisomer **3** then gives the target nortropane **5** (Scheme 1).



Scheme 1. Previous RCM/hydroboration/oxidation strategy for calystegine synthesis.

One way of avoiding this regioselectivity problem is to employ the RCM reaction on a protected polyhydroxylated 3-oxo- or 3-hydroxy-7-amino-1,8-octadiene **6a** or **6b**. Starting from **6a** for example, the requisite protected hydroxylated 4-aminocycloheptenone **7a** would be obtained directly without the possibility of regioisomeric ketones (Scheme 2). Alternatively, ketone **7a** could be accessed by oxidation of the ring-closed product **7b**. In this paper we report the synthesis of calystegine B_4 (**20**) using this new synthetic strategy.

Calystegine B_4 (**20**) was first isolated in 1996 from the root extracts of *Scopolia japonica*.[1c] Of the glycosidases screened against this molecule, the strongest inhibitory activity found was against pig kidney trehalase, with an IC_{50} of 4.8 μM.[1c] To date the only total synthesis of

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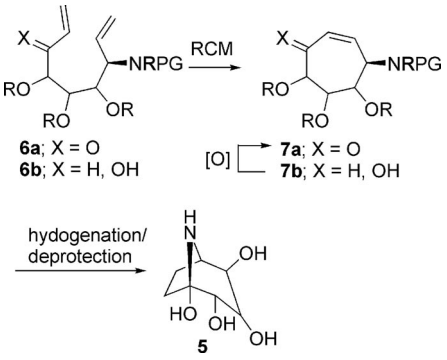


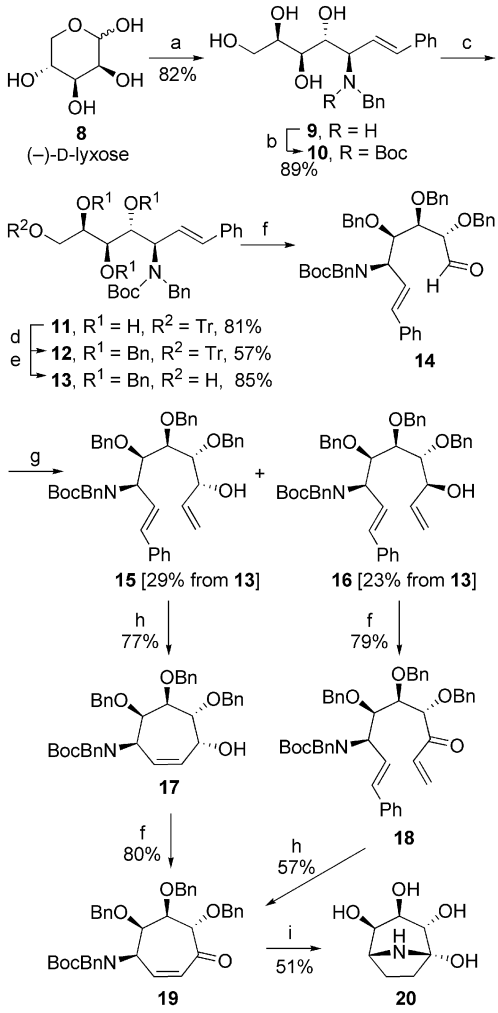
Scheme 2. New strategy for calystegine synthesis.

calystegine B_4 (**20**) is that of Madsen,[7] who used the RCM/hydroboration/oxidation strategy shown in Scheme 1 to prepare not only **20** but also calystegines B_2 and B_3.

Results and Discussion

The synthesis of calystegine B_4 (**20**) is outlined in Scheme 3. The Petasis–borono-Mannich reaction of (–)-D-lyxose (**8**) with benzylamine and [(*E*)-2-phenylvinyl]boronic acid gave the aminotetrol **9** in 82% yield (Scheme 3).[11] This compound was treated with $(Boc)_2O$ under basic conditions (Et_3N, MeOH) to efficiently provide the *N*-Boc-protected product **10** in 89% yield. The primary alcohol of **10** underwent regioselective *O*-tritylation to give **11** before the remaining alcohol groups were protected as *O*-benzyl ethers to give **12**. The *O*-trityl group of **12** was selectively removed to give **13**, which was easily oxidised to the aldehyde **14**. Treatment of this aldehyde with vinylmagnesium bromide gave a 1:1 mixture of the alcohols **15/16** from ^{1}H NMR analysis of the crude reaction mixture. This poor diastereoselectivity, however, was not of a major concern since this carbinol centre was to be oxidized to the corresponding ketone in future steps. However, we decided to separate these diastereomers by column chromatography to examine their independent chemistry. In this way the carbinols **15** and **16** were obtained diastereomerically pure in 29% and 23% overall yields from **13**, respectively.

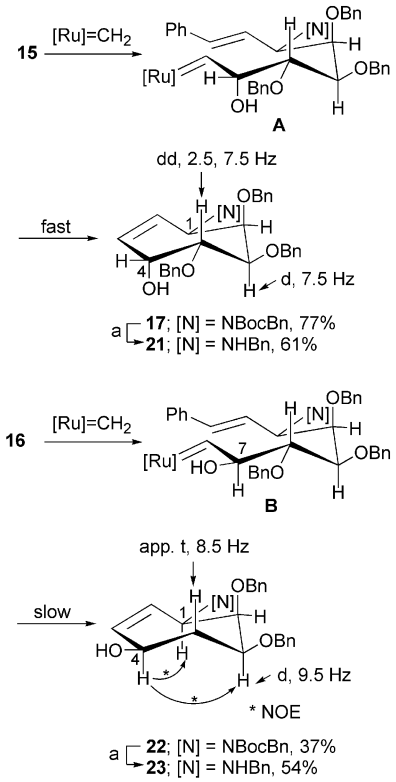
The RCM reaction of **15** by using Grubbs' 2nd generation ruthenium catalyst with microwave heating at 90 °C for 90 min gave the desired cycloheptenol **17** in 77% yield after purification. The RCM reaction of the diastereomer **16**, however, was much slower under similar conditions. After three successive treatments of **16** with Grubbs' 2nd generation catalyst with microwave heating at 90 °C for 2 h, the yield of the cycloheptene **22** was in contrast only 37% (Scheme 4). To assist in the identification of the stereochemistry of **17** and **22** these individual products were treated with acid to remove their *N*-Boc groups, which provided compounds **21** and **23**, respectively, which showed sharp NMR signals (Scheme 4). The ^{1}H NMR spectrum of **22** showed that 5-H had two 1,2-diaxial vicinal couplings and resonated as an apparent triplet of ca. 9 Hz, whereas



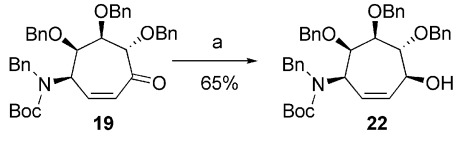
Scheme 3. Reagents and conditions: (a) (*E*)-PhCH=CHB(OH)$_2$, $BnNH_2$, EtOH, room temp., 3 d; (b) $(Boc)_2O$, Et_3N, MeOH, room temp., 3 d; (c) TrCl, pyridine, room temp., 1 d; (d) BnBr, Ag_2O, Bu_4NI, room temp., 16 h; (e) *p*TsOH, $CHCl_3$, MeOH, room temp., 16 h; (f) Dess–Martin periodinane, CH_2Cl_2, room temp. (for **14**, 1.5 h; for **18**, 30 min; for **19**, 30 min); (g) CH_2=CHMgBr, THF, 0 °C to room temp., 3 h; (h) Grubbs' 2nd generation catalyst, CH_2Cl_2, microwave irradiation at 90 °C (for **17**, 1.5 h; for **19**, 2 h); (i) 20% Pd(OH)$_2$/C, H_2, THF/H_2O (1:1), room temp., 4.5 h; then $PdCl_2$, H_2, THF/H_2O (1:1), room temp., 4 h; then $PdCl_2$, H_2, MeOH, room temp., 1.5 h; and then Amberlyst® A-26(OH) as resin.

the 6-H signal was a doublet (9.5 Hz). This information and the observed NOESY correlations between 1-H and 4-H and 4-H and 6-H (Scheme 4) confirmed the equatorial configuration of the hydroxy group of **22**. Consistent with this assignment were the vicinal couplings observed in the ^{1}H NMR spectrum of **15** for 5-H and 6-H. The former proton resonated as a doublet of doublets with one 1,2-diaxial-like coupling ($J_{4,5}$ = 7.5 Hz) and one 1,2-axial-equatorial-like coupling ($J_{5,6}$ = 2.5 Hz), whereas the 6-H signal was a doublet ($J_{4,5}$ = 7.5 Hz) (Scheme 4). This is in agreement with an axial-like configuration of the 4-OH group in **21**. Further supporting evidence for these stereochemical assignments came from the reduction of **19** with $NaBH_4$/

$CeCl_3 \cdot 7H_2O$, which gave exclusively the equatorial alcohol **22** (Scheme 5); this reducing reagent is known to favour the formation of the equatorial alcohol product in the reductions of cyclic ketones and enones.[12]



Scheme 4. Reagents and conditions: (a) MeOH, HCl, room temp., 18 h.



Scheme 5. Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, room temp., 20 min.

We speculate that the difference in rates in the RCM reactions of **15** and **16** is due to coordination of the secondary hydroxy group to the Ru centre in intermediates **A** and **B** (Scheme 4). In intermediate **B** such coordination would make it energetically more difficult for the ruthenium–carbene double bond to be parallel to the styrene double bond that is required for the RCM process resulting in a much reduced rate of reaction.

Oxidation of **17** by using the Dess–Martin periodinane then gave the enone **19** (Scheme 3). Whereas the same ketone could be obtained from the oxidation of **22**, the most efficient way to prepare enone **19** from **16** involved its oxidation to the enone **18** first, and then an RCM reaction of **18** gave **19** in 57% yield (Scheme 3). This RCM reaction was much faster and more efficient than that of its alcohol congener **16**.

After many unsuccessful attempts to convert enone **19** to calystegine B_4 (**20**), we found the best method to achieve this was by first treatment of **19** with $Pd(OH)_2/H_2$ in THF/H_2O to reduce the double bond and remove one or two benzyl groups (as evident from ESIMS analysis). The crude reaction mixture was then treated with $PdCl_2/H_2$ in THF/H_2O to removed more benzyl groups, and finally treatment with $PdCl_2/H_2$ in MeOH removed the remaining benzyl groups and the Boc group due to in situ formation of HCl.[11d] The hydrochloride salt of **20** was deprotonated and purified by ion exchange chromatography using Amberlyst® A-26(OH) resin to give **20** in 51% overall yield and in 92–95% purity according to ^1H NMR analysis. Attempts to purify this material further were not successful. It is worth noting that **20** gives a much clearer and more resolved ^1H NMR spectrum when run in [D_5]pyridine/D_2O (4:1) than just D_2O. The ^1H NMR spectrum of **20** in [D_5]-pyridine/D_2O (4:1) was essentially identical to that of the natural product run in the same solvent.[1c] The ^{13}C NMR chemical shifts in D_2O, however, were all 2.2 ppm upfield from those reported for the natural product. These types of consistent differences in the ^{13}C NMR spectroscopic data have been noted before for azasugars.[11d,11f] The signal of the quaternary carbon atom C-1 of **20** was not observed but was able to be confirmed by gHMBC correlations. The optical rotation of the synthetic product $[\alpha]_D^{19} = -29.5$ (c = 0.185, H_2O) was of the same sign but different in magnitude to that of the natural product $[\alpha]_D = -63.0$ (c = 0.65, H_2O) or to that prepared earlier by synthesis {$[\alpha]_D = -46.4$ (c = 0.18, H_2O)}.[7] In our case the lower optical rotation may be a reflection of the 92–95% purity of our compound.

Conclusions

We have developed a 10-step synthesis of calystegine B_4 (**20**) using the Petasis–borono-Mannich reaction to introduce the amino group with the correct configuration. This synthesis produced two diene carbinol diastereomers (**15** and **16**) that underwent the RCM reaction at different rates and efficiencies. One diene carbinol diastereomer (**15**) efficiently gave the key fully functionalized 4-aminocyclohept-2-en-1-one **19** after an RCM reaction and then oxidation. Deprotection then gave the natural product target. The other diene carbinol diastereomer (**16**) efficiently gave the same key cyclohept-2-en-1-one **19** after first oxidation and then an RCM reaction. In this way both diastereomeric diene carbinols could be efficiently processed through to the natural product target **20**. The overall yield of **20** via the diene carbinol **15** was 4.7%, whereas that from diene carbinol **16** was 3.4%. This synthetic method should be useful for the preparation of other calystegines and their epimers and analogues by using different sugar starting materials.

Experimental Section

General: General methods were as described previously.[11d]

(2*R*,3*R*,4*R*,5*R*,*E*)-5-(Benzylamino)-7-phenylhept-6-ene-1,2,3,4-tetraol (9): To a solution of (–)-D-lyxose (200 mg, 1.332 mmol) in ethanol (2 mL) was added benzylamine (0.146 mL, 142.7 mg, 1.332 mmol) and [(*E*)-2-phenylvinyl]boronic acid (197.1 mg, 1.332 mmol), and the mixture was stirred at room temp. for 3 d. The reaction was monitored by ESIMS. The solvent was removed in vacuo and the crude product purified by column chromatography (EtOAc to 20% MeOH/EtOAc) to give **9** as a brown foamy solid in 82% yield (375.7 mg, 1.095 mmol). A small amount was repurified for analysis to give a white solid. R_f = 0.22 [EtOAc/MeOH/NH_3 (8:1:1)]; m.p. 114–116 °C. LRMS (ESI): *m*/*z* (%) = 343.8 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* = 344.1867 $[M + H]^+$, calcd. for $C_{20}H_{26}NO_4$ 344.1862. IR: $\tilde{\nu}_{max}$ = 3355, 3283, 2909, 2848, 2356, 1491, 1347, 1019 cm^{-1}. $[\alpha]_D^{24}$ = –45.8 (*c* = 0.95, CH_3OH). ^1H NMR (500 MHz, CD_3OD): δ = 7.45 (d, *J* = 8 Hz, 2 H, 2× ArCH), 7.32 (m, 6 H, 6× ArCH), 7.23 (m, 2 H, 2× ArCH), 6.58 (d, *J* = 16.0 Hz, 1 H, 7-H), 6.22 (dd, *J* = 16.0, 9.0 Hz, 1 H, 6-H), 3.88 (d, *J* = 13.0 Hz, 1 H, 1× NCH_2), 3.87 (d, *J* = 7.0 Hz, 1 H, 2-H), 3.80 (ddd, *J* = 9.0, 5.0, 2 Hz, 1 H, 3-H or 4-H), 3.69 (d, *J* = 13.0 Hz, 1 H, 1× NCH_2), 3.60 (d, *J* = 6.5 Hz, 2 H, 2× 1-H), 3.53 (apparent br. d, *J* = 9.0 Hz, 2 H, 3-H or 4-H and 5-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 140.6 (ArC), 138.4 (ArC), 135.6 (C-7), 129.7 (ArCH), 129.6 (ArCH), 129.5 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 128.2 (C-6), 127.5 (ArCH), 74.1 (C-3 or C-4), 72.8 (C-3 or C-4), 71.8 (C-2), 64.8 (C-1), 64.3 (C-5), 51.6 (N*C*H_2) ppm.

***tert*-Butyl (1*E*,3*R*,4*R*,5*R*,6*R*)-*N*-Benzyl-4,5,6,7-tetrahydroxy-1-phenylhept-1-en-3-ylcarbamate (10):** To a solution of **9** (373.5 mg, 1.089 mmol) in methanol (3.3 mL) was added triethylamine (0.3 mL, 220.4 mg, 2.178 mmol), then di-*tert*-butyl dicarbonate (594.1 mg, 2.722 mmol). The reaction mixture was stirred at room temp. for 1 d. The volatiles were removed in vacuo, and the residue was purified by column chromatography [EtOAc/petroleum ether (80:20) to EtOAc to MeOH/EtOAc (15:85)] to give **10** as a white solid in 89% yield (431.3 mg, 0.974 mmol) (73% over 2 steps). (–)-D-Lyxose can be taken through to **10** in one pot, but gives a lower yield (62% over 2 steps). R_f = 0.26 [EtOAc/petroleum ether (20:80)]; m.p. 144–146 °C. LRMS (ESI) = *m*/*z* (%) = 443.8 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* = 444.2379 $[M + H]^+$, calcd. for $C_{25}H_{34}NO_6$ 444.2386. IR: $\tilde{\nu}_{max}$ = 3442, 3314, 2976, 1614, 1416, 1158, 1078, 1040 cm^{-1}. $[\alpha]_D^{24}$ = –80.5 (*c* = 1.12, CH_3OH). ^1H NMR (500 MHz, CD_3OD): δ = 7.21 (m, 8 H, 8× ArCH), 7.13 (d, *J* = 4.0 Hz, 2 H, 2× ArCH), 6.43 (br. s, 2 H, 2-H and 1-H), 4.80 (s, 1 H, 3-H), 4.63 (br. s, 2 H, 2× NCH_2), 4.00 (d, *J* = 9.0 Hz, 1 H, 4-H), 3.87 (t, *J* = 6.5 Hz, 1 H, 6-H), 3.59 (d, *J* = 6.5 Hz, 2 H, 7-H), 3.34 (d, *J* = 9.0 Hz, 1 H, 5-H), 1.35 (br. s, 9 H, 9× CH_3) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 158.1 (C=O), 141.0 (ArC), 138.3 (ArC), 136.0 (C-1), 129.5 (ArCH), 129.4 (ArCH), 129.2 (ArCH), 129.16 (ArCH), 128.7 (ArCH), 128.2 (ArCH), 128.06 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 124.3 (C-2), 81.8 [*C*-$(CH_3)_3$], 75.6 (C-4), 71.9 (C-5), 71.3 (C-6), 64.8 (C-7), 62.7 (C-3), 52.0 (N*C*H_2), 28.6 (CH_3) ppm.

***tert*-Butyl (1*E*,3*R*,4*R*,5*R*,6*R*)-*N*-Benzyl-4,5,6-trihydroxy-1-phenyl-7-(trityloxy)hept-1-en-3-ylcarbamate (11):** To a solution of **10** (6.862 g, 15.49 mmol) in dry pyridine (47.0 mL) was added trityl chloride (6.477 g, 23.23 mmol), and the mixture was stirred under N_2 at room temp. for 1 d. The reaction was quenched with H_2O and the mixture extracted with CH_2Cl_2 (3 × 70 mL). The combined organic extracts were washed with saturated $CuSO_4$ solution (2 × 70 mL), then brine (2 × 70 mL) and dried ($MgSO_4$). The crude product was purified by column chromatography [EtOAc/petroleum ether (20:80 to 30:70)] to give **11** as a white solid in 81% yield (8.596 g, 12.55 mmol). R_f = 0.19 [EtOAc/petroleum ether (20:80)]; m.p. 62–68 °C (clear), 120–125 °C (melted). LRMS (ESI): *m*/*z* (%) = 683.7 (68) $[M - H]^+$. HRMS (ESI): *m*/*z* = 708.3315 $[M + Na]^+$, calcd. for $C_{44}H_{47}NO_6Na$ 708.3301. IR: $\tilde{\nu}_{max}$ = 3396, 3063, 2976, 1660, 1450, 1368, 1161, 1076 cm^{-1}. $[\alpha]_D^{23}$ = +9.40 (*c* = 1.18, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.5 Hz, 6 H, 6× ArCH), 7.32–7.19 (m, 19 H, 19× ArCH), 6.54 (dd, *J* = 15.5, 8.5 Hz, 1 H, 2-H), 6.29 (d, *J* = 16.0 Hz, 1 H, 1-H), 5.87 (br. s, 1 H, OH), 4.55 (d, *J* = 15.5 Hz, 1 H, 1× NCH_2), 4.33 (d, *J* = 14.0 Hz, 1 H, 1× NCH_2), 4.18 (br. s, 2 H, 1× C*H*OH and 3-H), 3.85 (d, *J* = 9.0 Hz, 1 H, 1× C*H*OH), 3.29 (m, 3 H, 2× 7-H and 1× C*H*OH), 2.86 (d, *J* = 6.0 Hz, 1 H, OH), 2.57 (d, *J* = 8.5 Hz, 1 H, OH), 1.47 (s, 9 H, 9× CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.3 (C=O), 143.5 (ArC), 138.0 (ArC), 136.7 (ArC), 133.9 (C-1), 128.5 (ArCH), 128.4 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 127.1 (ArCH), 126.6 (ArCH), 122.6 (C-2), 87.2 (*C*-Ph_3), 81.3 [*C*-$(CH_3)_3$], 75.8 (*C*HOH), 71.6 (*C*HOH), 68.6 (*C*HOH), 66.1 (C-7), 64.5 (C-3), 53.6 (N*C*H_2), 28.4 (CH_3) ppm.

***tert*-Butyl (1*E*,3*R*,4*R*,5*R*,6*R*)-*N*-Benzyl-4,5,6-tris(benzyloxy)-1-phenyl-7-(trityloxy)hept-1-en-3-ylcarbamate (12):** To a solution of **11** (979.2 mg, 1.429 mmol) in benzyl bromide (3.6 mL) was added tetrabutylammonium iodide (57.0 mg, 0.154 mmol), and the mixture was stirred at room temp. for 25 min before adding silver oxide (3.216 g, 13.88 mmol). The reaction mixture was stirred at room temp. overnight and was then filtered through Celite and the solvent removed in vacuo. Triethylamine was added to the residue and the mixture stirred for 45 min, then diluted with H_2O. The product was extracted with diethyl ether (3 × 20 mL) and dried ($MgSO_4$). The crude product was purified by column chromatography [EtOAc/petroleum ether (0:100 to 5:95)] to give **12** as an off-white semicrystalline solid in 57% yield (771.8 mg, 0.808 mmol). R_f = 0.44 [EtOAc/petroleum ether (20:80)]. LRMS (ESI): *m*/*z* (%) = 955.3 (6) $[M + H]^+$. HRMS (ESI): *m*/*z* = 973.4932 $[M + H]^+$, calcd. for $C_{65}H_{67}NO_7$ 973.4918. IR: $\tilde{\nu}_{max}$ = 3048, 2899, 2346, 1690, 1450, 1158, 1067 cm^{-1}. $[\alpha]_D^{25}$ = –21.9 (*c* = 1.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45 (m, 6 H, 6× ArCH), 7.37 (d, *J* = 7.5 Hz, 3 H, 3× ArCH), 7.30–7.28 (m, 8 H, 8× ArCH), 7.24–7.16 (m, 14 H, 14× ArCH), 7.14–7.12 (m, 3 H, 3× ArCH), 7.09 (br. s, 3 H, 3× ArCH), 7.00 (br. s, 3 H, 3× ArCH), 6.42 (br. m, 1 H, 1-H), 6.32 (br. m, 1 H, 2-H), 4.74 (d, *J* = 11.5 Hz, 1 H, 1× OCH_2Ph-5 or -6), 4.73 (s, 2 H, OCH_2Ph-5 or -6), 4.66 (d, *J* = 12.0 Hz, 1 H, 1× OCH_2Ph-5 or -6), 4.58 (d, *J* = 11.5 Hz, 1 H, 1× OCH_2Ph-4), 4.47 (m, 1 H, 3-H), 1.37 (d, *J* = 11.5 Hz, 1 H, 1× OCH_2Ph-4), 4.20 (br. s, 1 H, 5-H), 4.11 (m, 1 H, 4-H), 3.57 (br. s, 1 H, 6-H), 3.53 (dd, *J* = 10.0, 3.0 Hz, 1 H, 1× 7-H), 3.28 (br. s, 1 H, 1× 7-H), 1.25 (s, 9 H, 9× CH_3) ppm; NCH_2 signal not observed due to peak broadening. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.5 (C=O), 144.0 (ArC), 139.3 (ArC), 138.8 (ArC), 138.6 (ArC), 137.3 (ArC), 133.5 (C-1), 128.7 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 127.1 (ArCH), 127.0 (ArCH), 126.6 (ArCH), 126.3 (C-2), 86.7 (*C*-Ph_3), 80.6 (C-4), 79.9 (C-5), 79.1 (C-6), 74.5 (O*C*H_2Ph-5 or -6), 73.1 (O*C*H_2Ph-4), 73.0 (O*C*H_2Ph-5 or -6), 63.6 (C-7), 60.6 (C-3), 59.7 (rotamer C-3), 50.9 (N*C*H_2), 28.4 (CH_3) ppm.

***tert*-Butyl (1*E*,3*R*,4*R*,5*R*,6*R*)-*N*-Benzyl-4,5,6-tris(benzyloxy)-7-hydroxy-1-phenylhept-1-en-3-ylcarbamate (13):** To a solution of **12** (599.2 mg, 0.627 mmol) in chloroform (1.6 mL) and methanol (16 mL) was added *p*-toluenesulfonic acid (11.9 mg, 0.063 mmol) in methanol (8 mL), and the reaction mixture was stirred at room temp. overnight. The reaction was quenched with saturated

$NaHCO_3$ (2 mL) and mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). The crude product was purified by column chromatography [EtOAc/petroleum ether (10:90 to 20:80)] to give **13** as a colourless oil in 85% yield (379.3 mg, 0.532 mmol). R_f = 0.33 [EtOAc/petroleum ether (30:70)]. LRMS (ESI): *m*/*z* (%) = 713.4 (35) $[M + H]^+$, 730.6 (35) $[M + NH_3]^+$. HRMS (ESI): *m*/*z* = 714.3810 $[M + H]^+$, calcd. for $C_{46}H_{52}NO_6$ 714.3795. IR: $\tilde{\nu}_{max}$ = 3442, 3027, 2935, 1687, 1450, 1163, 1058 cm^{-1}. $[\alpha]_D^{20}$ = –22.9 (*c* = 1.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 10 H, 10× ArCH), 7.24–7.21 (m, 6 H, 6× ArCH), 7.17 (m, 5 H, 5× ArCH), 7.07 (m, 4 H, 4× ArCH), 6.47 (br. m, 1 H, 1-H or 2-H), 6.08 (br. m, 1 H, 1-H or 2-H), 4.77 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.76 (s, 2 H, 2× OC*H*$_2$Ph), 4.70 (d, *J* = 5.0 Hz, 1 H, 1× OC*H*$_2$Ph), 4.67 (d, *J* = 4.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.51 (d, *J* = 12.0 Hz, 1 H, 1× OC*H*$_2$Ph), 4.37 (br. s, 1 H, 3-H), 4.20 (d, *J* = 15.5 Hz, 2 H, NC*H*$_2$), 3.99 (d, *J* = 7.0 Hz, 1 H, C*H*OBn), 3.84–3.82 (m, 1 H, 1× 7-H), 3.75 (br. s, 1 H, 1× 7-H), 3.67 (quint, *J* = 3.5 Hz, 1 H, C*H*OBn), 1.36 (s, 9 H, 9× CH_3) ppm; signal of 1× C*H*OBn not seen due to peak broadening. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.4 (C=O), 143.5 (ArC), 138.9 (ArC), 138.7 (ArC), 138.4 (ArC), 137.2 (ArC), 133.5 (poss. C-1), 128.7 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.30 (ArCH), 128.26 (ArCH), 128.13 (ArCH), 128.08 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.83 (ArCH), 127.75 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.2 (poss. C-2), 126.9 (ArCH), 126.4 (ArCH), 80.3 (*C*HOBn), 79.9 (*C*HOBn), 79.3 (*C*HOBn), 74.6 (OCH_2Ph), 73.0 (OCH_2Ph), 72.8 (OCH_2Ph), 61.5 (C-7), 61.2 (C-3), 51.4 (NCH_2), 28.4 (CH_3) ppm.

***tert*-Butyl (1*E*,3*R*,4*R*,5*R*,6*S*)-*N*-Benzyl-4,5,6-tris(benzyloxy)-7-oxo-1-phenylhept-1-en-3-ylcarbamate (14), *tert*-Butyl (1*E*,3*R*,4*R*,5*R*,6*R*,7*R*)-*N*-Benzyl-4,5,6-tris(benzyloxy)-7-hydroxy-1-phenylnona-1,8-dien-3-ylcarbamate (15) and *tert*-Butyl *N*-Benzyl-(1*E*,3*R*,4*R*,5*R*,6*R*,7*S*)-4,5,6-tris(benzyloxy)-7-hydroxy-1-phenylnona-1,8-dien-3-ylcarbamate (16):** To a solution of **13** (1.005 g, 1.410 mmol) in dry CH_2Cl_2 (47.2 mL) was added Dess–Martin periodinane (897.1 mg, 2.115 mmol), and the mixture was stirred at room temp. under N_2 for 1.5 h. The mixture was then diluted with diethyl ether (18 mL) and the reaction quenched with saturated $NaHCO_3$ solution (18 mL) and sodium thiosulfate (5.5 g). The product was extracted with diethyl ether (3 × 60 mL), and the combined organic extracts were washed with saturated $NaHCO_3$ solution (100 mL), then H_2O (100 mL) and dried ($MgSO_4$). The solvent was removed to give the crude aldehyde **14** as a yellow oil in 91% yield (916.5 mg, 1.289 mmol). Then, to a solution of crude **14** (916.5 mg, 1.289 mmol) in dry THF (18.1 mL) was added vinylmagnesium bromide (1.0 M THF, 1.93 mL, 1.934 mmol) at 0 °C under N_2. The mixture was then warmed to room temp. and stirred for 2 h before quenching the reaction with saturated ammonium chloride solution (12 mL); CH_2Cl_2 (12 mL) was added, and the product was extracted with CH_2Cl_2 (3 × 50 mL) and dried ($MgSO_4$). The crude products were purified and separated by column chromatography [EtOAc/petroleum ether (5:95 to 10:90)] to give **15** as a colourless oil in 29.4% yield (306.0 mg, 0.414 mmol) and **16** as a colourless oil in 23.4% (243.8 mg, 0.330 mmol).

15: R_f = 0.29 [EtOAc/petroleum ether (20:80)]. LRMS (ESI): *m*/*z* (%) = 740.7 (41) $[M + H]^+$. HRMS (ESI): *m*/*z* = 740.3972 $[M + H]^+$, calcd. for $C_{48}H_{54}NO_6$ 740.3951. IR: $\tilde{\nu}_{max}$ = 3032, 2920, 1690, 1450, 1368, 1162, 1067 cm^{-1}. $[\alpha]_D^{24}$ = –7.13 (*c* = 0.44, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 11 H, 11× ArCH), 7.24–7.17 (m, 11 H, 11× ArCH), 7.11 (m, 3 H, 3× ArCH), 6.45 (br. s, 1 H, 2-H), 6.18 (br. s, 1 H, 1-H), 6.02 (ddd, *J* = 6.5 Hz, 1 H, 8-H), 5.37 (d, *J* = 17.5 Hz, 1 H, 1× 9-H), 5.25 (d, *J* = 10.0 Hz, 1 H, 1× 9-H), 4.83 (d, *J* = 11.0 Hz, 1 H, 1× OC*H*$_2$Ph), 4.72–4.63 (m, 5 H, 4× OC*H*$_2$Ph and 3-H), 4.46 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.35 (d, *J* = 5.5 Hz, 1 H, 7-H), 4.25 (br. s, 3 H, NC*H*$_2$ and C*H*OBn), 3.91 (br. s, 1 H, C*H*OBn), 3.71 (t, *J* = 5.5 Hz, 1 H, C*H*OBn), 2.68 (br. s, 1 H, OH), 1.42 (s, 9 H, 9× CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6 (C=O), 139.1 (ArC), 138.5 (ArC), 138.3 (ArC), 137.3 (C-8), 137.1 (ArC), 133.9 (C-1), 128.35 (ArCH), 128.29 (ArCH), 128.26 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.60 (ArCH), 127.55 (ArCH), 127.3 (ArCH), 126.8 (C-2), 126.4 (ArCH), 117.0 (C-9), 81.6 (*C*HOBn), 80.6 (*C*HOBn), 80.4 (*C*HOBn), 74.4 (OCH_2Ph), 74.3 (OCH_2Ph), 73.1 (OCH_2Ph), 72.9 (C-7), 60.3 (C-3), 50.6 (NCH_2), 28.4 (CH_3) ppm.

16: R_f = 0.36 [EtOAc/petroleum ether (20:80)]. LRMS (ESI): *m*/*z* (%) = 740.7 (43) $[M + H]^+$. HRMS (ESI): *m*/*z* = 740.3967 $[M + H]^+$, calcd. for $C_{48}H_{54}NO_6$ 740.3951. IR: $\tilde{\nu}_{max}$ = 3476, 3032, 2919, 1685, 1450, 1162, 1063 cm^{-1}. $[\alpha]_D^{24}$ = –34.3 (*c* = 0.53, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.02 (m, 25 H, 25× ArCH), 6.52 (br. s, 1 H, 1-H or 2-H), 6.16 (br. s, 1 H, 1-H or 2-H), 5.97 (t, *J* = 11.5 Hz, 1 H, 8-H), 5.40 (d, *J* = 17.0 Hz, 1 H, 1× 9-H), 5.21 (d, *J* = 8.5 Hz, 1 H, 1× 9-H), 4.86 (d, *J* = 9.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.78 (m, 2 H, 2× OC*H*$_2$Ph), 4.71 (d, *J* = 11.0 Hz, 1 H, 1× OC*H*$_2$Ph), 4.62 (dd, *J* = 11.0, 2.0 Hz, 1 H, 1× OC*H*$_2$Ph), 4.57 (m, 1 H, 3-H), 4.49 (m, 1 H, 1× OC*H*$_2$Ph), 4.40 (m, 1 H, 7-H), 4.27 (d, *J* = 13.0 Hz, 2 H, 2× NC*H*$_2$), 4.06 (s, 1 H, C*H*OBn), 3.68 (br. s, 1 H, C*H*OBn), 2.84 (br. s, 1 H, OH), 1.36 (s, 9 H, 9× CH_3) ppm; signal of 1× C*H*OBn not seen due to peak broadening. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7 (C=O), 138.8 (C-8), 137.2 (ArC), 134.9 (ArC), 133.6 (poss. C-1), 128.3 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 127.1 (ArCH), 126.4 (ArCH), 115.3 (C-9), 82.0 (*C*HOBn), 81.0 (*C*HOBn), 75.2 (OCH_2Ph), 74.6 (OCH_2Ph), 73.0 (OCH_2Ph), 71.8 (C-7), 60.7 (C-3), 51.1 (NCH_2), 28.4 (CH_3) ppm; several signals were not seen due to extensive peak broadening.

***tert*-Butyl (1*R*,2*Z*,4*R*,5*R*,6*R*,7*R*)-*N*-Benzyl-5,6,7-tris(benzyloxy)-4-hydroxycyclohept-2-enylcarbamate (17):** To a solution of **15** (22.2 mg, 0.030 mmol) in anhydrous CH_2Cl_2 (1.47 mL) was added 10 mol-% Grubbs' 2nd generation catalyst (2.55 mg, 0.003 mmol). The mixture was subjected to microwave irradiation in a sealed tube in a CEM Discover microwave reactor at 90 °C, 100 W and 100 psi for 2 h. The solvent was then removed and the product purified by column chromatography [EtOAc/petroleum ether (5:95 to 15:85)] to give **11** as a colourless oil in 77% yield (14.7 mg, 0.023 mmol). R_f = 0.20 [EtOAc/petroleum ether (20:80)]. LRMS (ESI): *m*/*z* (%) = 636 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* = 636.3339 $[M + H]^+$, calcd. for $C_{40}H_{46}NO_6$ 636.3325. IR: $\tilde{\nu}_{max}$ = 3432, 2960, 2919, 1685, 1455, 1261, 1062 cm^{-1}. $[\alpha]_D^{23}$ = –55.2 (*c* = 1.47, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 16 H, 16× ArCH), 7.17 (t, *J* = 7.0 Hz, 2 H, 2× ArCH), 7.12 (m, 2 H, 2× ArCH), 5.70 (d, *J* = 12.0 Hz, 1 H, 2-H or 3-H), 5.33 (d, *J* = 11.0 Hz, 1 H, 2-H or 3-H), 5.03 (br. s, 2 H, 1-H and 4_β-H), 4.93 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.84 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.74 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph-6), 4.63 (m, 1 H, 1× OC*H*$_2$Ph), 4.61 (t, *J* = 4.0 Hz, 1 H, 1× OC*H*$_2$Ph), 4.57 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph-6), 4.50 (br. s, 1 H, 5-H or 7-H), 4.49 (d, *J* = 13.0 Hz, 1 H, 1× NC*H*$_2$), 4.25 (br. s, 1 H, 1× NC*H*$_2$), 4.06 (t, *J* = 4.5 Hz, 1 H, 5-H or 7-H), 3.74 (d, *J* = 6.0 Hz, 1 H, 6-H), 2.78 (d, *J* = 9.5 Hz, 1 H, OH), 1.31 (s, 9 H, 9× CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7 (C=O), 140.7 (ArC), 138.2 (ArC), 136.1 (C-2 or C-3), 128.5 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.75 (ArCH), 127.67 (ArCH), 126.6 (ArCH), 126.2 (ArCH), 126.1 (ArCH), 125.4 (C-2 or C-3), 84.7 (C-5 or C-7), 84.3 (C-6), 80.1 [*C*$(CH_3)_3$], 78.9 (C-5 or C-7),

74.8 (O*C*H$_2$Ph), 74.7 (O*C*H$_2$Ph), 72.2 (O*C*H$_2$Ph-6), 67.2 (C-4), 57.4 (C-1), 49.4 (N*C*H$_2$), 28.2 (CH$_3$), 28.5 (rotamer CH$_3$) ppm.

***tert*-Butyl (1*E*,3*R*,4*R*,5*R*,6*S*)-*N*-Benzyl-4,5,6-tris(benzyloxy)-7-oxo-1-phenylnona-1,8-dien-3-ylcarbamate (18):** To a solution of **16** (161.2 mg, 0.218 mmol) in dry CH_2Cl_2 (5.4 mL) was added Dess–Martin periodinane (120.3 mg, 0.284 mmol), and the mixture was stirred at room temp. under N_2 for 2 h. The mixture was then diluted with diethyl ether (5 mL) and the reaction quenched with saturated $NaHCO_3$ solution (5 mL) and $Na_2S_2O_3$ (1 g). The product was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with saturated $NaHCO_3$ solution (40 mL), then H_2O (40 mL) and dried ($MgSO_4$). The crude product was purified by column chromatography [EtOAc/petroleum ether (0:100 to 10:90)] to give **18** as a clear oil in 79% yield (126.9 mg, 0.172 mmol). R_f = 0.41 [EtOAc/petroleum ether (20:80)]. LRMS (ESI): *m*/*z* (%) = 737.5 (28) [M + H]$^+$, 754.5 (100) [M + NH$_3$]. HRMS (ESI): *m*/*z* = 738.3784 [M + H]$^+$, calcd. for $C_{48}H_{52}NO_6$ 738.3795. IR: $\tilde{\nu}_{max}$ = 3385, 3027, 2976, 1689, 1455, 1162, 1072 cm^{-1}. $[\alpha]_D^{22}$ = –52.2 (*c* = 1.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 20 H, 20× ArCH), 7.16–7.09 (m, 4 H, 4× ArCH), 7.06 (m, 1 H, 1× ArCH), 6.84 (dd, *J* = 17.0, 11.0 Hz, 1 H, 8-H), 6.33 (d, *J* = 17.0 Hz, 2 H, 2-H and 1× 9-H), 6.15 (br. s, 1 H, 1-H), 5.64 (d, *J* = 10.0 Hz, 1 H, 1× 9-H), 4.76 (m, 1 H, 3-H), 4.64 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.58–4.52 (m, 5 H, 4× OC*H*$_2$Ph and 1× NC*H*$_2$), 4.48 (m, 1 H, 1× NC*H*$_2$), 4.43 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.31 (t, *J* = 5.5 Hz, 1 H, 4-H), 4.28 (d, *J* = 4.0 Hz, 1 H, 6-H), 3.98 (br. s, 1 H, 5-H), 4.05 (rot., 5-H), 1.40 (s, 9 H, 9× CH$_3$), 1.42 (rot. CH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.5 (C-7), 155.4 (ArC), 139.4 (ArC), 138.3 (ArC), 138.1 (ArC), 137.4 (ArC), 136.8 (ArC), 135.2 (ArC), 132.5 (C-8), 128.9 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.25 (ArCH), 128.20 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.93 (ArCH), 127.86 (ArCH), 127.55 (ArCH), 127.48 (ArCH), 127.3 (ArCH), 126.9 (ArCH), 126.6 (ArCH), 126.4 (ArCH), 125.1 (C-2), 115.3 (C-9), 83.7 (C-6), 81.1 (C-5), 80.5 (C-4), 80.2 [*C*(CH$_3$)$_3$], 73.9 (O*C*H$_2$Ph), 73.5 (O*C*H$_2$Ph), 72.9 (O*C*H$_2$Ph), 59.8 (C-3), 49.7 (N*C*H$_2$), 28.4 (CH$_3$) ppm.

Benzyl[(1*R*,2*Z*,4*R*,5*R*,6*R*,7*R*)-5,6,7-tris(benzyloxy)-4-hydroxycyclohept-2-enyl]amine (21): To a solution of **17** (58.7 mg, 0.092 mmol) in MeOH (2.45 mL) was added concentrated HCl (0.54 mL) dropwise, and the mixture was stirred at room temp. for 18 h. The reaction mixture was basified with NH_3 (1.5 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried (Na_2CO_3), and the solvent was removed in vacuo. Purification by column chromatography [EtOAc/petroleum ether (0:100 to 60:40)] gave **21** as a colourless oil in 61% yield (30.4 mg, 0.057 mmol). R_f = 0.41 (EtOAc). LRMS (ESI): *m*/*z* (%) = 535.7 (13) [M + H]$^+$. HRMS (ESI): *m*/*z* = 536.2774 [M + H]$^+$, calcd. for $C_{35}H_{38}NO_4$ 536.2801. IR: $\tilde{\nu}_{max}$ = 3050, 2914, 2843, 1650, 1496, 1450, 1068, 1028 cm^{-1}. $[\alpha]_D^{25}$ = –47.8 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = (m, 20 H, 20× ArCH), 5.74 (dd, *J* = 12.0, 5.5 Hz, 1 H, 3-H), 5.69 (dd, *J* = 12.0, 3.5 Hz, 1 H, 2-H), 4.90 (d, *J* = 12.0 Hz, 1 H, 1× OC*H*$_2$Ph-7), 4.77 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph-5), 4.72 (m, 4 H, 2× OC*H*$_2$Ph-6, 1× OC*H*$_2$Ph-7 and 4-H), 4.63 (d, *J* = 12.0 Hz, 1 H, 1× OC*H*$_2$Ph-5), 4.10 (br. s, 1 H, 7-H), 3.94 (dd, *J* = 7.5, 2.5 Hz, 1 H, 5-H), 3.89 (d, *J* = 7.5 Hz, 1 H, 6-H), 3.66 (d, *J* = 13.5 Hz, 1 H, 1× NC*H*$_2$), 3.62 (d, *J* = 13.5 Hz, 1 H, 1× NC*H*$_2$), 3.46 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.2 (ArC), 138.9 (ArC), 138.5 (ArC), 138.3 (ArC), 134.1 (C-2), 129.4 (C-3), 128.43 (ArCH), 128.41 (ArCH), 128.35 (ArCH), 128.29 (ArCH), 128.0 (ArCH), 127.95 (ArCH), 127.94 (ArCH), 127.86 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 126.8 (ArCH), 82.8 (C-6), 81.9 (C-5), 79.1 (C-7), 74.0 (O*C*H$_2$Ph), 73.7 (2× O*C*H$_2$Ph), 68.1 (C-4), 57.5 (C-1), 51.2 (N*C*H$_2$) ppm.

***tert*-Butyl (1*R*,2*Z*,4*S*,5*R*,6*R*,7*R*)-*N*-Benzyl-5,6,7-tris(benzyloxy)-4-hydroxycyclohept-2-enylcarbamate (22):** To a solution of **16** (23.8 mg, 0.032 mmol) in anhydrous CH_2Cl_2 (1.58 mL) was added 10 mol-% Grubbs' 2nd generation catalyst (2.73 mg, 0.003 mmol). The mixture was subjected to microwave irradiation in a sealed tube in a CEM Discover microwave reactor at 90 °C, 100 W and 100 psi for 2 × 2 h. Another 10 mol-% Grubbs' 2nd generation catalyst (2.73 mg, 0.003 mmol) was added, and the mixture subjected to microwave irradiation for another 2 h. The product was purified by column chromatography [EtOAc/petroleum ether (5:95 to 15:85)] to give **22** as a colourless oil in 37% yield (7.6 mg, 0.012 mmol). Decomposition occurred to a large extent. R_f = 0.30 [EtOAc/petroleum ether (20:80)]. LRMS (ESI): *m*/*z* (%) = 635.6 (39) [M + H]$^+$. HRMS (ESI): *m*/*z* = 636.3325 [M + H]$^+$, calcd. for $C_{40}H_{46}NO_6$ 636.3325. IR: $\tilde{\nu}_{max}$ = 3339, 2981, 1080, 1050, 884 cm^{-1}. $[\alpha]_D^{22}$ = +40.8 (*c* = 0.41, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.2 (m, 16 H, 16× ArCH), 7.19 (t, *J* = 7.0 Hz, 2 H, 2× ArCH), 7.12 (d, *J* = 7.0 Hz, 2 H, 2× ArCH), 5.69 (br. d, 1 H, 2-H), 5.48 (d, *J* = 11.5 Hz, 1 H, 3-H), 5.07 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.97 (apparent d, *J* = 10.5 Hz, 2 H, 1-H and 1× OC*H*$_2$Ph), 4.81 (m, 2 H, 2× OC*H*$_2$Ph), 4.59 (d, *J* = 10.5 Hz, 1 H, 1× OC*H*$_2$Ph), 4.50–4.47 (br. m, 3 H, 1× OC*H*$_2$Ph and 2× NC*H*$_2$), 4.18 (m, 2 H, 4$_\alpha$-H and C*H*OBn), 3.74 (s, 2 H, 2× C*H*OBn), 3.19 (s, 1 H, OH), 1.27 (s, 9 H, 9× CH$_3$), 1.44 (rot. CH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.6 (C=O), 140.2 (ArC), 138.6 (ArC), 138.0 (ArC), 131.3 (C-2 or C-3), 128.6 (ArCH), 128.5 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 126.3 (ArCH), 125.9 (C-2 or C-3), 125.6 (ArCH), 86.8 (*C*HOBn), 82.5 (*C*HOBn), 80.6 (*C*HOBn), 76.0 (O*C*H$_2$Ph), 74.2 (O*C*H$_2$Ph), 74.1 (O*C*H$_2$Ph), 70.5 (C-4), 55.7 (C-1), 48.2 (N*C*H$_2$), 28.2 (CH$_3$) ppm. Compound **22** was also prepared from a solution of **19** (6.5 mg, 0.010 mmol) in anhydrous methanol (0.78 mL), to which was added $CeCl_3 \cdot 7H_2O$ (3.8 mg, 0.010 mmol), then $NaBH_4$ (0.39 mg, 0.010 mmol); the mixture was then stirred at room temp. under N_2 for 20 min. The reaction was quenched with H_2O, the mixture extracted with CH_2Cl_2 (3 × 5 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give **22** as a colourless oil in 65% yield (4.2 mg, 0.007 mmol).

Benzyl[(1*R*,2*Z*,4*S*,5*R*,6*R*,7*R*)-5,6,7-tris(benzyloxy)-4-hydroxycyclohept-2-enyl]amine (23): The title compound was prepared according to the method described for the synthesis of **21** by using **22** (3.1 mg, 0.0049 mmol) as starting material to give **23** as a colourless oil in 54% yield (1.4 mg, 0.003 mmol). R_f = 0.67 (EtOAc). LRMS (ESI): *m*/*z* (%) = 535.9 (100) [M + H]$^+$. HRMS (ESI): *m*/*z* = 536.2780 [M + H]$^+$, calcd. for $C_{35}H_{38}NO_4$ 536.2801. $[\alpha]_D^{25}$ = +56.7 (*c* = 0.07, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = (m, 20 H, 20× ArCH), 5.80 (ddd, *J* = 11.0, 3.5, 2 Hz, 1 H, 3-H), 5.57 (br. d, *J* = 11.5 Hz, 1 H, 2-H), 4.98 (d, *J* = 10.5 Hz, 1 H, 1× COC*H*$_2$-5), 4.96 (d, *J* = 10.5 Hz, 1 H, 1× OC*H*$_2$Ph-7), 4.77 (d, *J* = 12.0 Hz, 1 H, 1× OC*H*$_2$Ph-6), 4.75 (d, *J* = 11.5 Hz, 1 H, 1× OC*H*$_2$Ph-7), 4.71 (d, *J* = 12.0 Hz, 1 H, 1× OC*H*$_2$Ph-6), 4.61 (d, *J* = 11.0 Hz, 1 H, 1× OC*H*$_2$Ph-5), 4.09 (d, *J* = 8.5 Hz, 1 H, 4-H), 4.01 (s, 1 H, 7-H), 3.73 (apparent t, *J* = 8.5 Hz, 1 H, 5-H), 3.65 (d, *J* = 13.0 Hz, 1 H, 1× NC*H*$_2$), 3.54 (d, *J* = 13.0 Hz, 1 H, 1× NC*H*$_2$), 3.54 (d, *J* = 9.5 Hz, 1 H, 6-H), 3.16 (s, 1 H, 1-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2 (ArC), 131.5 (C-2), 131.4 (C-3), 128.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.04 (ArCH), 128.02 (ArCH), 127.95 (ArCH), 127.85 (ArCH), 127.81 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.0 (ArCH), 86.2 (C-6), 80.6 (C-5), 79.1 (C-7), 75.9 (O*C*H$_2$Ph-5), 73.8 (O*C*H$_2$Ph-7), 73.7 (O*C*H$_2$Ph-6), 70.3 (C-4), 57.5 (C-1), 51.2 (N*C*H$_2$) ppm.

***tert*-Butyl (1*R*,2*Z*,5*S*,6*R*,7*R*)-*N*-Benzyl-5,6,7-tris(benzyloxy)-4-oxocyclohept-2-enylcarbamate (19):** To a solution of **17** (28.2 mg, 0.044 mmol) in dry CH_2Cl_2 (1.1 mL) was added Dess–Martin periodinane (24.5 mg, 0.058 mmol), and the mixture was stirred at room temp. under N_2 for 30 min. The mixture was then diluted with diethyl ether (1 mL) and the reaction quenched with saturated $NaHCO_3$ solution (1 mL) and $Na_2S_2O_3$ (200 mg). The product was extracted with diethyl ether (3 × 15 mL) and the combined organic extracts were washed with saturated $NaHCO_3$ solution (40 mL), then H_2O (40 mL) and dried ($MgSO_4$). The crude product was purified by column chromatography [EtOAc/petroleum ether (10:90)] to give **19** as a colourless oil in 80% yield (22.4 mg, 0.035 mmol). R_f = 0.40 [EtOAc/petroleum ether (20:80)]. LRMS (ESI): *m*/*z* (%) = 633.7 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* = 634.3137 $[M + H]^+$, calcd. for $C_{40}H_{44}NO_6$ 634.3169. IR: $\tilde{\nu}_{max}$ = 2917, 2848, 1686, 1454, 1058, 733 cm^{-1}. $[\alpha]_D^{22}$ = –119.2 (*c* = 0.85, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 15 H, 15 × ArCH), 7.19–7.15 (m, 3 H, 3 × ArCH), 7.08 (d, *J* = 7.0 Hz, 2 H, 2 × ArCH), 5.98 (d, *J* = 13.0 Hz, 1 H, 3-H), 5.88 (d, *J* = 13.5 Hz, 1 H, 2-H), 5.12 (s, 1 H, 1-H), 4.87 (d, *J* = 11.5 Hz, 1 H, 1 × OC*H*$_2$Ph-7), 4.71 (d, *J* = 9.0 Hz, 1 H, 1 × OC*H*$_2$Ph-5), 4.70 (m, 2 H, 2 × OC*H*$_2$Ph-6), 4.53 (d, *J* = 11.5 Hz, 1 H, 1 × OC*H*$_2$Ph-5), 4.49 (d, *J* = 11.5 Hz, 1 H, OC*H*$_2$Ph-7), 4.44 (d, *J* = 17.0 Hz, 1 H, 1 × NC*H*$_2$), 4.36 (s, 1 H, 7-H), 4.28 (d, *J* = 17.0 Hz, 1 H, 1 × NC*H*$_2$), 4.17 (s, 1 H, 5-H or 6-H), 3.96 (d, *J* = 6.5 Hz, 1 H, 5-H or 6-H), 3.86 (rot. 5-H or 6-H), 1.28 (s, 9 H, 9 × CH_3), 1.40 (rot. CH_3), 4.78 (rot. m, 1 H), 4.64 (rot. m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.8 (C-4), 155.6 (C=O), 140.3 (ArC), 138.1 (ArC), 137.3 (ArC), 136.3 (C-2), 130.5 (C-3), 128.4 (ArCH), 128.2 (ArCH), 128.14 (ArCH), 128.06 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 126.3 (ArCH), 125.9 (ArCH), 86.4 (C-5 or C-6), 82.8 (C-5 or C-6), 80.7 (C-7), 80.5 [*C*$(CH_3)_3$], 73.6 (O*C*H$_2$Ph-7), 73.0 (O*C*H$_2$Ph-5 or -6), 72.7 (O*C*H$_2$Ph-5 or -6), 58.5 (C-1), 49.4 (N*C*H$_2$), 28.1 (CH_3), 28.4 (rot. CH_3) ppm. Compound **19** was also prepared in 57% yield (5.3 mg, 0.0084 mmol) according to the method described for **17** by using **18** (10.9 mg, 0.015 mmol) and ca. 20 mol-% Grubbs' 2nd generation catalyst (2.52 mg, 0.003 mmol).

Calystegine B_4 (20): To a solution of **19** (28.2 mg, 0.045 mmol) in THF/H_2O (1:1) (0.87 mL) was added 20% palladium hydroxide on carbon (5.64 mg). The reaction flask was flushed with N_2 and then H_2 and the mixture stirred at room temp. under H_2 atmosphere for 4.5 h. The mixture was filtered, then concentrated, and MS and NMR data showed the reduction of the double bond and a mixture of products having various benzyl groups removed. The crude product was then taken up again in THF/H_2O (1:1) (0.87 mL), and palladium chloride (11.9 mg, 0.067 mmol) was added. The reaction flask was flushed with N_2 and then H_2 and the mixture stirred at room temp. under H_2 for 4 h. MS analysis indicated incomplete reaction, so more palladium chloride (2 mg, 0.01128 mmol) was added, and the mixture was stirred for a further 1.5 h. The reaction was still incomplete, but the mixture was filtered then and the filtrate concentrated. The crude product was then taken up in methanol (0.87 mL), and palladium chloride (7.9 mg, 0.045 mmol) was added. The reaction flask was flushed with N_2 and then H_2 and the mixture stirred at room temp. under H_2 for 1.5 h, after which time MS analysis indicated a complete reaction. The mixture was filtered and the filtrate then concentrated to give the hydrochloride salt of **20** in 57% yield (5.4 mg, 0.026 mmol). The crude product was purified by ion exchange chromatography using Amberlyst® A-26(OH) as resin. The resin was first washed with H_2O, basified with NH_3 and then neutralised with H_2O. The product was eluted with H_2O to give **20** as a white solid in 51% yield (4.0 mg, 0.023 mmol) in 92–95% purity as judged by ^1H NMR analysis. R_f = 0.17 [MeOH/EtOAc/NH_3 (8.5:1:0.5)]. LRMS (ESI): *m*/*z* (%) = 175.9 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* = 176.0918 $[M + H]^+$, calcd. for $C_7H_{14}NO_4$ 176.0923. IR: $\tilde{\nu}_{max}$ = 3283, 2899, 1668, 1585 cm^{-1}. $[\alpha]_D^{19}$ = –29.5 (*c* = 0.185, H_2O); ref.[1c] $[\alpha]_D$ = –63.0 (*c* = 0.65, H_2O). ^1H NMR {500 MHz, [D_4]pyridine/D_2O (4:1)}: δ = 4.35 (d, *J* = 9.0 Hz, 1 H, 2-H), 4.06 (dd, *J* = 9.0, 4.5 Hz, 1 H, 3-H), 4.03 (d, *J* = 3.0 Hz, 1 H, 4-H), 3.72 (dd, *J* = 8.0, 2.5 Hz, 1 H, 5-H), 2.42 (ddd, *J* = 12.8, 10.0, 4.5 Hz, 1 H, 7_α-H), 2.21 (tdd, *J* = 12.8, 4.5, 3.0 Hz, 1 H, 6_β-H), 1.97 (tdd, *J* = 12.5, 4.5, 1.5 Hz, 1 H, 7_β-H), 1.36 (ddd, *J* = 13.3, 10.0, 5.0 Hz, 1 H, 6_α-H) ppm; the ^1H NMR spectroscopic data agree with that in the literature except for the multiplicity of the signal for 4-H, which was published as a dd signal.[1c] ^{13}C NMR (125 MHz, D_2O): δ = 90.3 (C-1), 77.3 (C-2), 72.6 (C-4), 71.6 (C-3), 56.9 (C-5), 27.6 (C-7), 22.9 (C-6) ppm; all peaks are 2.2 ppm upfield, except that for C-2 (δ =2.3 ppm), from literature values for the natural product;[1c] the signal for C-1 was not observed in the ^{13}C NMR spectrum but was able to be determined from the gHMBC spectrum.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra of compounds, **1**, **3**–**7** and **9**–**16**.

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