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A Short Synthetic Route to the Calystegine Alkaloids

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An efficient strategy is described for the synthesis of enantiopure calystegine alkaloids. The key step employs a zinc-mediated fragmentation of benzyl-protected methyl 6-iodo-glycosides followed by in situ formation of the benzyl imine and Barbier-type allylation with zinc, magnesium, or indium metal. Stereochemistry in the pivotal allylation is controlled by the choice of the metal. The functionalized 1,8-nonadienes, thus formed, are converted into cycloheptenes by ring-closing olefin metathesis. Regioselective hydroboration and oxidation give the corresponding cycloheptanones, which are deprotected to afford the desired calystegines. Hereby, calystegine B_2, B_3, and B_4 are prepared from D-glucose, D-galactose, and D-mannose, respectively. This route constitutes the shortest synthesis of calystegine B_2 and gives rise to the first total syntheses of calystegine B_3 and B_4.

Introduction

The calystegines are a family of polyhydroxylated nortropane alkaloids, which were first isolated in 1988 from *Calystegia sepium*.[1] More than 10 different calystegines have since then been found in a variety of fruits and vegetables.[2,3] They are subdivided into three groups on the basis of the number of hydroxy groups present: calystegine A (with three hydroxy groups), calystegine B (with four hydroxy groups), and calystegine C (with five hydroxy groups). In all cases, a tertiary hydroxy group is part of an aminoketal functionality at the bicyclic ring bridgehead. Several derivatives of the calystegines have also been isolated containing a glycoside, an *N*-methyl group, or an amino group, the latter instead of the tertiary hydroxy group.[2] Due to their structural resemblance to monosaccharides, many calystegines show potent glycosidase inhibitory activity particularly of glucosidases and galactosidases and are interesting lead compounds for pharmaceutical research.[2,3] However, the calystegines have been significantly less explored than the other classes of sugar mimics with nitrogen in the ring, e.g. polyhydroxylated pyrrolidines, piperidines, pyrrolizidines, and indolizidines.[3]

Some of the most abundant calystegines in plants are calystegine A_3, A_5, B_2, B_3, B_4, and C_1 (Figure 1).[2,4] Calystegine A_3, B_2, B_3, and B_4 are all inhibitors of trehalases from various origins.[5] Calystegine B_2 and C_1

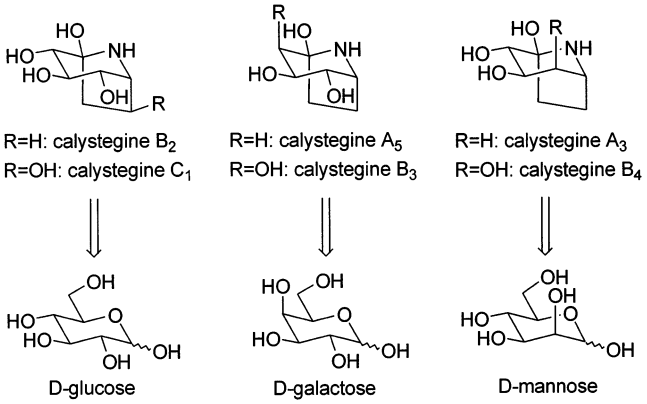

FIGURE 1. Structures of common calystegines and hexoses.

are both potent inhibitors of almond β-glucosidase with K_i values of 1.2 and 0.45 μM, respectively.[6] In addition, calystegine B_2 is also a strong inhibitor of green coffee bean α-galactosidase ($K_i = 0.86$ μM).[6] For all compounds, the structural similarity to D-glucose, D-galactose, and D-mannose is noteworthy, although the absolute configuration has only been established for calystegine B_2. The configuration of the remaining calystegines has been determined by NMR spectroscopy studies and based on biosynthetic arguments they are also believed to be derived from D-sugars. Indeed, these cheap monosaccharides are obvious starting materials for chemical synthesis of the calystegines. However, creating the seven-membered carbocycle with the nitrogen bridge from these

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(3) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. Stütz, A. E., Ed. *Iminosugars as Glycosidase Inhibitors—Nojirimycin and Beyond*; Wiley-VCH: Weinheim, Germany, 1999.

(4) Rothe, G.; Garske, U.; Dräger, B. *Plant Sci.* **2001**, *160*, 1043. Bekkouche, K.; Daali, Y.; Cherkaoui, S.; Veuthey, J.-L.; Christen, P. *Phytochemistry* **2001**, *58*, 455. Keiner, R.; Dräger, B. *Plant Sci.* **2000**, *150*, 171.

(5) Asano, N.; Kato, A.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *Carbohydr. Res.* **1996**, *293*, 195.

(6) Asano, N.; Kato, A.; Oseki, K.; Kizu, H.; Matsui, K. *Eur. J. Biochem.* **1995**, *229*, 369.

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sugars is not an easy task. Previously, several syntheses of enantiopure calystegine B_2 have been achieved from D-glucose.[7,8] A number of calystegine analogues have also been prepared from D-glucose and tested for glycosidase inhibition.[9]

In recent years ring-closing olefin metathesis has been introduced for converting sugars into carbocycles.[10] In this context, we have developed a zinc-mediated tandem reaction for preparation of the diene precursors, which employs a reductive ring-opening of methyl ω-iodoglycosides followed by an alkylation (e.g. allylation) in the same pot.[11] The obtained α,ω-dienes are subjected to metathesis to form the carbocyclic ring and all ring-sizes from five- to eight-membered rings have been prepared by the combination of these two reactions.[11,12]

Herein, we report a full account on a concise synthetic strategy to the calystegine alkaloids starting from hexoses using a zinc-mediated tandem reaction, ring-closing metathesis, and a regioselective olefin oxidation as the crucial transformations.[13] This strategy has led to the preparation of calystegine B_2, B_3, and B_4.

Results and Discussion

Retrosynthesis. Assembling the bicyclic skeleton of the calystegines in a few steps from sugars represents a very interesting challenge. A key feature in the synthetic planning will be to introduce and manipulate carbon−carbon double bonds to create the seven-membered carbocycle by olefin metathesis. Neither the product calystegines nor the starting monosaccharides contain any double bonds that can take part in a metathesis reaction. As in the previous syntheses of calystigine B_2[7] we envisioned preparing the nortropane ring structure by deprotection of aminoketone **A** (Figure 2). The ketone could emerge from a regioselective oxidation of cycloheptene **B**, which on the other hand can be prepared by ring-closing metathesis from diene **C**. This diene can be disconnected into an allyl group, an amino group, and an enal **D**, where the latter would derive from fragmentation of a methyl 6-iodo-glycoside. Hereby, diene **C** would be assembled by a zinc-mediated tandem reaction where zinc serves a dual purpose by mediating both the fragmentation of the iodoglycoside and the allylation of the intermediate imine.[11,14] Controlling stereochemistry in this allylation reaction is crucial because the (*R*)-amine is the required isomer for further synthesis regardless of the sugar starting material.

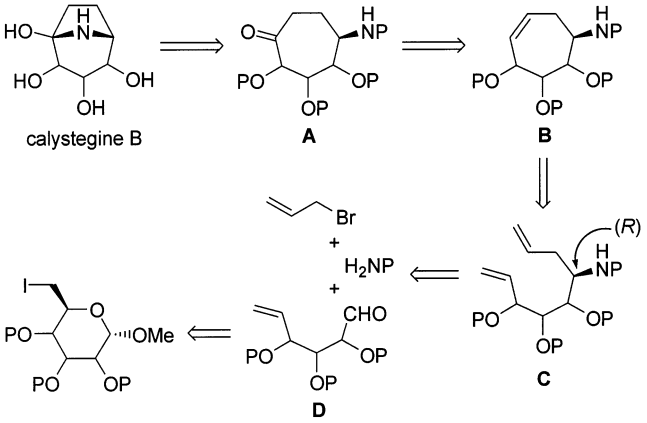

FIGURE 2. Retrosynthesis for the calystegines.

Calystegine B_2. We decided to probe the synthetic strategy starting from D-glucose, which would lead to calystegine B_2. For the first experiments, triethylsilylated glucopyranoside **2** was chosen as the iodoglycoside because this compound has previously been used in a tandem reaction for synthesis of conduritols.[11,15] In fact, treating **2** with zinc and benzylamine under sonication while slowly adding allyl bromide gave rise to aminodiene **3** in very good yield (Scheme 1). The two diastereomers were obtained in a 5:1 ratio and could be separated by flash chromatography. At this point, the absolute stereochemistry of these two diastereomers was not known. Nevertheless, the synthesis continued with the major diastereomer, which was shown to be the desired diastereomer **3R** after completing the synthesis (vide infra). The next step involved ring-closing metathesis to form the seven-membered carbocycle. However, in our previous metathesis reactions with sugar substrates and catalyst **1** we have been unable to achieve good conversion with dienes containing a free amino group.[11,14] A solution to this problem has been to convert the amino group into an amide or a carbamate. Hence, **3R** was protected with a Cbz group to afford **4R**. Unfortunately, this compound turned out to be a very poor substrate for olefin metathesis with catalyst **1**. Presumably, the triethylsilyl groups are too sterically demanding for the ring-closure to take place. Accordingly, **4R** was deprotected with TBAF in acetic acid to give trihydroxy diene **5R**. This could be metathesized with **1** to afford cycloheptene **6**, although in a moderate yield. At this point, the metathesis reaction was not further optimized. In the next step, the double bond has to be regioselectively oxidized and the Wacker oxidation[16] was chosen for this purpose. Although the Wacker oxidation is very selective for monosubstituted double bonds, internal olefins may also be oxidized by this procedure.[16,17] In some cases, this oxidation of internal olefins appears to be aided by an additional

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(8) Calystegine B_2 and A_3 have also been prepared by asymmetric reactions from cycloheptadiene derivatives: Faitg, T.; Soulié, J.; Lallemand, J.-Y.; Ricard, L. *Tetrahedron: Asymmetry* **1999**, *10*, 2165. Johnson, C. R.; Bis, S. J. *J. Org. Chem.* **1995**, *60*, 615.

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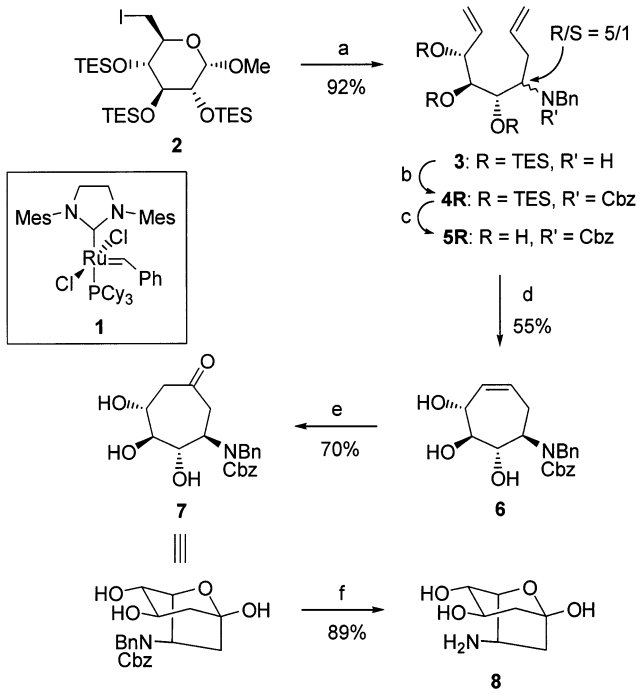
(13) Preliminary communication: Skaanderup, P. R.; Madsen, R. *Chem. Commun.* **2001**, 1106.

(14) Poulsen, C. S.; Madsen, R. *J. Org. Chem.* **2002**, *67*, 4441.

(15) Skaanderup, P. R.; Poulsen, C. S.; Hyldtoft, L.; Jørgensen, M. R.; Madsen, R. *Synthesis* **2002**, 1721.

(16) Tsuji, J. *Synthesis* **1984**, 369.

SCHEME 1[a]

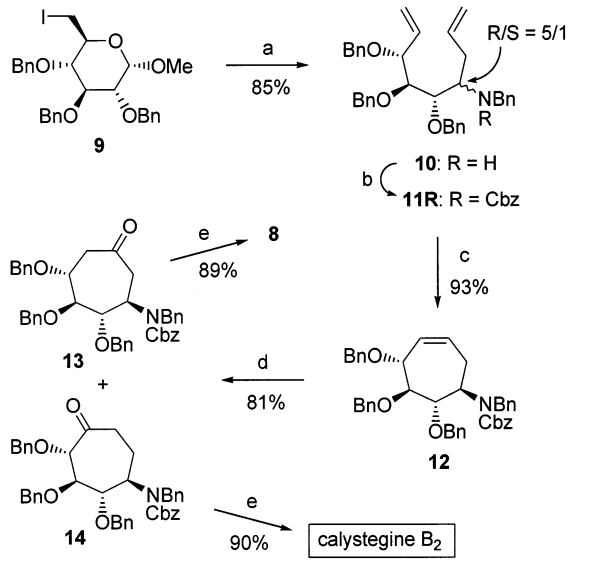


[a] Reagents and conditions: (a) Zn, $BnNH_2$, $CH_2{=}CHCH_2Br$, THF, ultrasound, 40 °C. (b) CbzCl, $KHCO_3$, EtOAc, H_2O. (c) TBAF, THF. (d) 10% **1**, CH_2Cl_2, rt. (e) 10% $PdCl_2$, CuCl, O_2, H_2O, DMF, 50 °C. (f) H_2, $Pd(OH)_2/C$, THF, H_2O.

coordination between palladium and a heteroatom in the substrate. Interestingly, when cycloheptene **6** was subjected to the standard Wacker conditions at elevated temperature only one ketone regioisomer was obtained. Unfortunately, it was the unwanted regioisomer **7**, which on deprotection furnished aminotriol **8**. NMR analysis revealed that these compounds close into an 8-oxabicyclo-[3.2.1]octane ring system that still resembles the calystegine structure. Compound **8** was tested as an inhibitor of yeast α-glucosidase, almond *β*-glucosidase, green coffee bean α-galactosidase, *E. coli β*-galactosidase, and Jack bean α-mannosidase.[18] However, it showed no inhibition of these enzymes. At this point, no further oxidation experiments were carried out with cycloheptene **6**. Due to the difficulties with the metathesis reaction another starting material was tried and it was decided to change the triethylsilyl groups in **2** to benzyl groups.

Benzyl-protected iodoglycoside **9** is available in 2 steps from methyl α-D-glucopyranoside.[15] Treating **9** under the same conditions as employed for **2** gave aminodiene **10** in 85% yield (Scheme 2). Again, a 5:1 mixture of two diastereomers was formed and the major diastereomer was shown to be **10R** after completion of the synthesis. After separating **10R** and **10S** by chromatography, aminodiene **10R** was Cbz-protected and transformed into cycloheptene **12** by ring-closing metathesis. In this case, a very good yield was obtained with relatively low catalyst loading, which illustrates the importance of the

SCHEME 2[a]



[a] Reagents and conditions: (a) Zn, $BnNH_2$, $CH_2{=}CHCH_2Br$, THF, ultrasound, 40 °C. (b) CbzCl, $KHCO_3$, EtOAc, H_2O. (c) 2% **1**, CH_2Cl_2, rt. (d) $BH_3{\cdot}$THF, THF, −40 → 0 °C, then H_2O_2, NaOH, H_2O, 0 °C, then Dess−Martin periodinane, CH_2Cl_2, rt. (e) H_2, $Pd(OH)_2/C$, THF, H_2O.

benzyl ethers compared to the triethylsilyl groups and the free hydroxy groups in previous dienes **4R** and **5R**. The benzyl ether protecting groups in cycloheptene **12** also give new opportunities for the next oxidation to ketone. Initially, the Wacker oxidation was also attempted, but conversion was low and only gave the unwanted regioisomer **13**. Therefore, another method was investigated and particular attention was given to hydroboration−oxidation, which has shown promising selectivity in a similar system.[19] Treatment of **12** with borane followed by alkaline hydrogen peroxide solution gave a mixture of all four possible alcohols that was not further characterized. Without purification this mixture was oxidized to the corresponding ketones with the Dess−Martin periodinane.[20] Hereby, ketones **13** and **14** were obtained in an overall yield of 81% as a 1:3 mixture, which could be separated by chromatography. Interestingly, the hydroboration favors the opposite ketone regioisomer as compared to the Wacker oxidation. Hydrogenolysis of **13** gave the same aminotriol **8** as prepared in Scheme 1. Hydrogenolysis of **14** afforded calystegine B_2 with spectral data and optical rotation in accordance with those reported for the natural product.[6] The deprotection was carried out in THF:H_2O mixture followed by purification on a Sephadex LH-20 column eluting with ethanol.[21] If the hydrogenolysis was performed in ethanol the *N*-methylated derivative of calystegine B_2 was obtained as the main product.[22] *N*-Methyl calystegine B_2 has been isolated from the same

(17) For recent examples, see: Kishi, A.; Higashino, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2000**, *41*, 99. Kang, S.-K.; Jung, K.-Y.; Chung, J.-U.; Namkoong, E.-Y.; Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678.

(18) For details of the enzymatic assays, see: Andersen, S. M.; Ekhart, C.; Lundt, I.; Stütz, A. E. *Carbohydr. Res.* **2000**, *326*, 22.

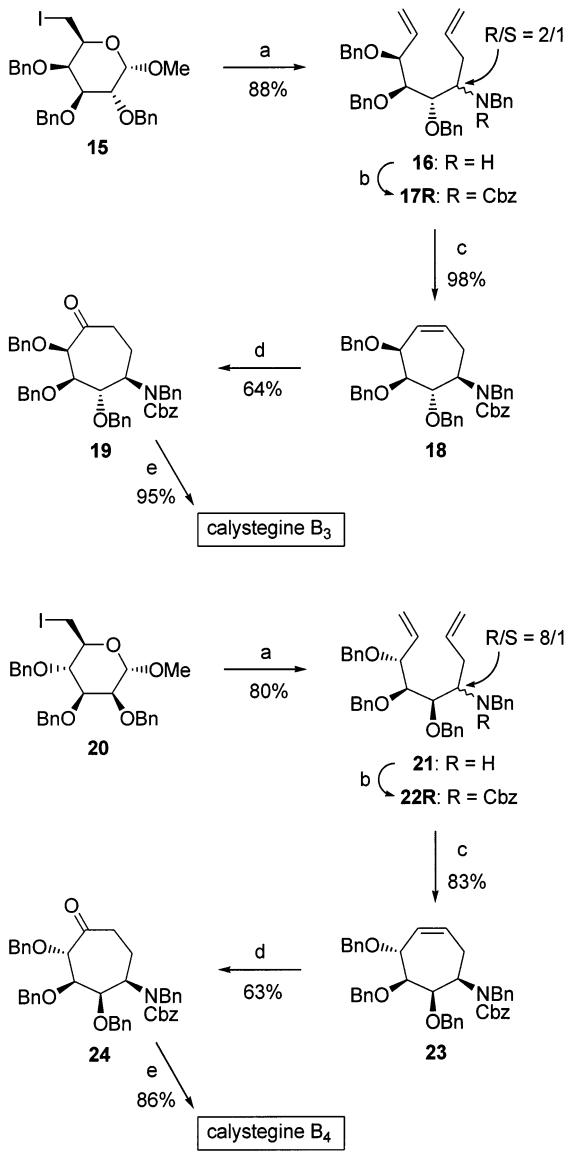
(19) Wang, W.; Zhang, Y.; Zhou, H.; Blériot, Y.; Sinaÿ, P. *Eur. J. Org. Chem.* **2001**, 1053.

(20) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(21) Henke, H. *Preparative Gel Chromatography on Sephadex LH-20*; Hüthig Verlag: Heidelberg, Germany, 1995.

(22) Partial *N*-methylation of amino groups in amino acids has previously been observed during hydrogenations in methanol: Mazaleyrat, J.-P.; Xie, J.; Wakselman, M. *Tetrahedron Lett.* **1992**, *33*, 4301.

SCHEME 3[a]



[a] Reagents and conditions: (a) Zn, $BnNH_2$, $CH_2{=}CHCH_2Br$, THF, ultrasound, 40°C. (b) CbzCl, $KHCO_3$, EtOAc, H_2O. (c) 2% **1**, CH_2Cl_2, rt. (d) $BH_3{\cdot}$THF, THF, −40 → 0 °C, then H_2O_2, NaOH, H_2O, 0 °C, then Dess−Martin periodinane, CH_2Cl_2, rt. (e) H_2, $Pd(OH)_2/C$, THF, H_2O.

sources as the parent compound and is a very selective inhibitor of green coffee bean α-galactosidase.[23]

Calystegine B_3 and B_4. Having successfully completed the synthesis of calystegine B_2, attention was then shifted toward calystegine B_3 and B_4 to investigate the general applicability of the synthetic strategy. Due to the configuration of the secondary hydroxy groups these two alkaloids will require D-galactose and D-mannose as starting materials. For the synthesis of calystegine B_3 benzyl-protected methyl 6-iodo-galactopyranoside **15**[15] was treated with zinc, benzylamine, and allyl bromide (Scheme 3). Thereby, aminodiene **16** was obtained in a satisfying 88% yield. To our disappointment, the diastereoselectivity was only 2:1. The two diastereomers could be separated and the major diastereomer was shown to be **16R** after finishing the synthesis of calystegine B_3. Cbz-protection and ring-closing metathesis proceeded very well to afford cycloheptene **18**. Applying the same hydroboration−oxidation procedure as described above gave a 3:1 mixture of the two ketones with the desired regioisomer **19** as the main component. Deprotection of the benzyl groups then furnished calystegine B_3 with spectral and physical data in accordance with those reported for the natural substance.[6]

Following the same strategy benzyl-protected methyl 6-iodo-mannopyranoside **20**[15] was also subjected to the tandem reaction (Scheme 3). Aminodiene **21** was isolated in 80% yield as an 8:1 mixture of diastereomers. Gratifyingly, the major diastereomer was again the desired (*R*)-isomer, which was verified after completing the synthesis of calystegine B_4. Cbz-protection and metathesis occurred in good yield although the ring-closing metathesis reaction of **22R** was slower than with the previous dienes **11R** and **17R**. Hydroboration and oxidation of cycloheptene **23** gave a 3:1 mixture of the two ketone regioisomers, which could be separated. The major isomer **24** was subjected to hydrogenolysis to afford calystegine B_4 with analytical data in accordance with literature values.[5] These syntheses confirm the absolute configuration of calystegine B_3 and B_4.

Imine Allylations. The stereochemical outcome of the three tandem reactions is noteworthy. In all three cases the (*R*)-isomer is formed as the major product regardless of the sugar stereochemistry although the diastereoselectivity varies from 2:1 to 8:1. In our previous zinc-mediated alkylations of protected sugar aldehydes we have observed that sugars with 2,3-*erythro* configuration give very good selectivity for the 1,2,3-*ribo* product while the outcome with 2,3-*threo* sugar aldehydes is less certain and in some cases the 1,2,3-*xylo* product dominates.[11,14] These observations are in accordance with the imine allylations in Schemes 1−3, but a systematic model explaining these additions to 2,3-alkoxy aldehydes and imines has not yet been developed.[24,25]

The poor diastereoselectivity with galacto substrate **15** prompted us to analyze the allylation with other metals. We have recently investigated the fragmentation of benzyl-protected methyl 6-iodo-glycopyranosides with a variety of metals and found that only zinc would fragment these pyranosides efficiently.[26] This afforded enals **25**−**27** in high yields from glycosides **9**, **15**, and **20**.[26] Therefore, we decided to treat these enals with benzylamine, allyl bromide, and different metals under sonication conditions (Table 1). Notably, when glucose-derived enal **25** was reacted under these Barbier conditions with magnesium metal, an improved 16:1 ratio was obtained between **10R** and **10S** as compared to the 5:1 ratio with zinc metal in Scheme 2. This ratio could be even further improved with indium metal (entry 2),[27] where the (*S*)-isomer could not be detected at all. A number of other metals did not give any imine allylation

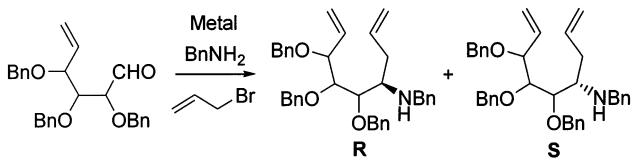
(23) Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Tomimori, T.; Matsui, K.; Nash, R. J.; Molyneux, R. J. *Eur. J. Biochem.* **1997**, *248*, 296.

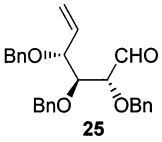
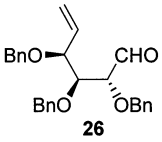
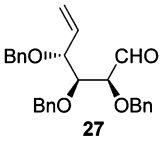
(24) For a review on 1,2- and 1,3-induction in carbonyl addition reactions, see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(25) For a review on addition of organometallic reagents to imines, see: Bolch, R. *Chem. Rev.* **1998**, *98*, 1407.

(26) Skaanderup, P. R.; Hyldtoft, L.; Madsen, R. *Monatsh. Chem.* **2002**, *133*, 467.

TABLE 1. Allylation of Imines Derived from Aldehydes 25−27[a]



Entry	Unsaturated Sugar	Metal	Product	R/S	Yield
1	 **25**	Mg	**10**	16/1	86%
2		In	**10**	1/0	92%
3	 **26**	Mg	**16**	8/1	88%
4		In	**16**	1/0	62%
5	 **27**	Mg	**21**	1/8	90%
6		In	**21**	0/1	89%

[a] All reactions were carried out in THF by sonication at 40 °C.

under these conditions, including iron, tin, antimony, bismuth, copper, and aluminum. When the imine of galactose-derived enal **26** was allylated with magnesium a 8:1 ratio was obtained between **16R** and **16S** (entry 3), which is a significant improvement over the 2:1 ratio produced with zinc in Scheme 3. With indium the (*R*)-isomer was again formed exclusively (entry 4). This reaction was slower than that with glucose-derived substrate **25** and was accompanied by some decomposition. On the other hand, allylating the imine from mannose-derived enal **27** gave the (*S*)-isomer of **21** (entries 5 and 6). In this case, magnesium and indium completely reversed the facial selectivity as compared to zinc in Scheme 3. These results strongly implicate that the magnesium- and indium-mediated allylations occur with chelation to the α-benzyloxy group.

By varying the metal in the allylation reaction the necessary (*R*)-amines for the calystegine syntheses can all be prepared in high yields. The corresponding (*S*)-amines can also be isolated from these reactions. Amines **10S** and **16S** are best isolated as the minor diastereomers from the zinc-mediated allylations in Schemes 2 and 3, while **21S** is obtained as the major product with magnesium and indium in Table 1. We decided to subject these (*S*)-amines to the same synthetic sequence as employed for the (*R*)-amines. The reactions were carried out under the same conditions as in Schemes 2 and 3 and gave rise to similar results and selectivities. Hereby,

(27) For recent examples on indium-mediated allylations of imines, see: Hilt, G.; Smolko, K. I.; Waloch, C. *Tetrahedron Lett.* **2002**, *43*, 1437. Vilaivan, T.; Winotapan, C.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2001**, *42*, 9073. Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589. Choucair, B.; Léon, H.; Miré, M.-A.; Lebreton, C.; Mosset, P. *Org. Lett.* **2000**, *2*, 1851. Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376.

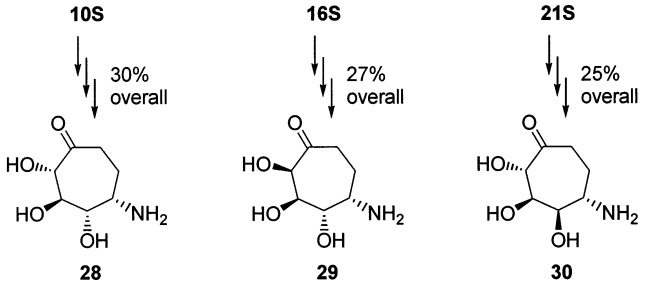


FIGURE 3. Epimeric compounds **28**−**30** derived from (*S*)-amines.

cycloheptanones **28**, **29**, and **30** were prepared (Figure 3), which can be considered as epimers of calystegine B_2, B_3, and B_4, respectively. Unfortunately, the structures of these epimers were not well defined. Compounds **28**−**30** were isolated by Sephadex LH-20 gel chromatography. They had similar retention times as the parent calystegines and showed only one spot by TLC. The ^{1}H NMR spectra of **28**−**30** were complex and only showed broad signals in the 3.9−3.3 and 2.0−1.4 ppm range. The protons in the parent calystegines are observed in the same areas. It was impossible to obtain useful ^{13}C NMR spectra of **28**−**30**. Apparently, compounds **28**−**30** are not able to form stable bicyclic ring systems, but exist as mixtures of monomers and oligomers. The same has been observed with other calystegine analogues.[7c,28] Additional work will be necessary to characterize these three epimers.

Conclusion. We have described here an effective synthetic route to calystegine B_2, B_3, and B_4 starting from D-glucose, D-galactose, and D-mannose, respectively. The strategy highlights the utility of our previously developed zinc-mediated tandem reaction, which combined with ring-closing metathesis converts iodo-sugars into carbocycles in just two steps. Other calystegines containing a different number of hydroxy groups can potentially be prepared by the same route. With this strategy in hand, analogue preparation and screening have also been greatly accelerated.

Experimental Section

General Procedures. Thin-layer chromatography was performed on aluminum plates precoated with silica gel 60. Compounds were visualized by heating after dipping in a solution of $Ce(SO_4)_2$ (2.5 g) and $(NH_4)_6Mo_7O_{24}$ (6.25 g) in 10% aqueous H_2SO_4 (250 mL) or in a solution of 0.3% ninhydrin and 3% AcOH in *n*-BuOH. Flash chromatography was performed with silica gel 60. Lipophilic Sephadex LH-20 (bead size 25−100 μm) was used for gel chromatography. Microanalyses were conducted by the Department of Chemistry at the University of Copenhagen.

General Procedure for the Zinc-Mediated Tandem Reaction. To a solution of the benzyl-protected methyl 6-iodoglycoside (3.0 g, 5.2 mmol) in THF (40 mL) was added preactivated zinc dust[11,14] (3.4 g, 52 mmol). The mixture was sonicated at 40 °C with use of a Branson 1210 sonic bath. TMSCl (0.33 mL, 2.6 mmol) was added in two portions after 10 and 20 min. When TLC or NMR revealed full consumption of the iodo-sugar (8−10 h) benzylamine (2.8 mL, 26 mmol) was added and the sonication was continued for an additional hour

(28) Boyer, F.-D.; Ducrot, P.-H.; Henryon, V.; Soulié, J.; Lallemand, J.-Y. *Synlett* **1992**, 357.

at 40 °C. Allyl bromide (1.3 mL, 16 mmol) was then added carefully in small portions over a period of 20 min during which time the sonication was maintained at 40 °C. The reaction was worked up by cooling to room temperature followed by addition of Et_2O (100 mL) and water (20 mL). Filtration of the resulting suspension through a pad of Celite removed all precipitated zinc salts. The layers were separated and the organic phase was washed with water (3 × 20 mL) and brine (10 mL) and dried (K_2CO_3), followed by removal of the solvent in vacuo. Purification by silica gel flash chromatography (hexane:Et_2O = 3:1 → 1:1) yielded the desired diastereomeric aminodienes.

General Procedure for Cbz-Protection. To an ice-cooled suspension of the aminodiene (347 mg, 0.60 mmol) and $KHCO_3$ (362 mg, 3.6 mmol) in CH_2Cl_2 (20 mL) and water (20 mL) was added benzyl chloro formate (94 μL, 0.66 mmol) dropwise over 2 min with vigorous stirring. The reaction mixture was stirred for 1 h, during which time the mixture warmed to room temperature. The layers were separated and the organic phase was washed with water (10 mL) and dried (K_2CO_3), and the solvent was removed in vacuo to give a colorless syrup, which was purified by silica gel flash chromatography (hexane:Et_2O = 4:1).

General Procedure for Ring-Closing Olefin Metathesis. The protected aminodiene (408 mg, 0.60 mmol) was dissolved in CH_2Cl_2 (30 mL). The solution was degassed under reduced pressure for 5 min followed by addition of **1** (10 mg, 0.012 mmol, 2 mol %). The reaction mixture was stirred at room temperature until TLC showed complete consumption of the starting diene (10−20 h). The solvent was removed in vacuo and the residue purified by silica gel flash chromatography (hexane:Et_2O = 4:1).

General Procedure for Hydroboration−Oxidation. To a stirred solution of the cycloheptene (368 mg, 0.56 mmol) in THF (15 mL) at −40 °C under nitrogen was added BH_3·THF complex (1.1 mL of a 1 M solution in THF, 1.1 mmol) dropwise. The mixture was stirred for 4 h, during which time it warmed to 0 °C. Then 2 M aqueous NaOH (1 mL) and 35% aqueous H_2O_2 (2 mL) were added. The reaction turned cloudy instantly and the slurry was stirred for an additional hour at ambient temperature. The mixture was then diluted with Et_2O (30 mL) and the organic layer was washed with water (3 × 5 mL) and brine (5 mL). Removal of the solvent in vacuo gave the crude alcohols, which were used immediately in the next step. To a stirred solution of Dess−Martin periodinane (382 mg, 0.90 mmol) in CH_2Cl_2 (20 mL) at room temperature was added the crude alcohols in CH_2Cl_2 (1 mL). The resultant milky white suspension was stirred at room temperature for 30 min. The mixture was then diluted with Et_2O (50 mL) and stirred for an additional 30 min. The solution was filtered and washed with saturated aqueous $Na_2S_2O_3$ (2 × 10 mL) and brine (10 mL). The organic phase was then dried (K_2CO_3) and concentrated to give a pale white residue that was purified by flash chromatography (hexane:Et_2O = 3:1).

General Procedure for Catalytic Hydrogenolysis. The cycloheptanone (141 mg, 0.21 mmol) was dissolved in THF (4.5 mL) and water (0.5 mL) and H_2 was bobbled through the solution for 10 min. Pearlman's catalyst (22 mg, 0.021 mmol) was added and the reaction mixture was stirred at room temperature under 1 atm of H_2 for 12 h. TLC indicated complete disappearance of the fully protected cycloheptanone and the mixture was acidified by addition of 1 M aqueous HCl (1 mL). The reaction was stirred for an additional 36 h at room temperature and 1 atm of H_2. The mixture was then neutralized by addition of Amberlite IRA-400 OH^- and the resulting suspension was filtered through a glass frit. The resin was washed thoroughly with water (15 × 10 mL). The filtrate was concentrated in vacuo to give a colorless residue that was purified on Sephadex LH-20 eluting with EtOH.

(3*R*,4*S*,5*S*,6*R*)-6-Amino-3,4,5-trihydroxycycloheptanone (8). Clear glass, R_f 0.49 (*n*-PrOH:AcOH:H_2O = 4:1:1). $[\alpha]_D$ −28.3 (*c* 2.0, H_2O). ^{1}H NMR (500 MHz, D_2O:CD_3COOD = 99:1): δ 4.75 (ddd, J = 11.1, 6.8, 3.8 Hz, 1H), 4.26 (dd, J = 6.8, 4.3 Hz, 1H), 3.86−3.81 (m, 1H), 3.76 (dd, J = 9.8, 4.3 Hz, 1H), 2.34 (dd, J = 12.8, 6.0 Hz, 1H), 2.24 (dd, J = 14.1, 11.1 Hz, 1H), 1.92 (dd, J = 14.1, 3.8 Hz, 1H), 1.86 (br d, J = 12.8 Hz, 1H). ^{13}C NMR (125 MHz, D_2O:CD_3COOD = 99:1): δ 103.9, 75.8, 71.9, 70.9, 50.5, 43.2, 39.7. ESI HRMS calcd for $C_7H_{14}NO_4$ $[M + H]^+$ *m*/*z* 176.0923, found *m*/*z* 176.0918.

(3*R*,4*S*,5*S*,6*R*)-6-[(*N*-Benzyl)amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (10R). Colorless syrup, R_f 0.51 (hexane:EtOAc = 3:1). $[\alpha]_D$ −20.0 (*c* 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.28 (m, 20H), 5.98 (ddd, J = 17.5, 10.2, 7.7 Hz, 1H), 5.67 (dddd, J = 17.1, 10.2, 7.7, 6.4 Hz, 1H), 5.30 (dd, J = 10.2, 1.7 Hz, 1H), 5.26 (dd, J = 17.5, 1.7 Hz, 1H), 5.04 (dd, J = 17.1, 1.8 Hz, 1H), 5.03 (dd, J = 10.2, 1.8 Hz, 1H), 4.90 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 11.1 Hz, 1H), 4.70 (d, J = 11.1 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.15 (d, J = 11.9 Hz, 1H), 4.00 (dd, J = 7.3, 3.4 Hz, 1H), 3.88 (d, J = 13.2 Hz, 1H), 3.83 (dd, J = 7.3, 2.6 Hz, 1H), 3.78 (dd, J = 7.7, 3.4 Hz, 1H), 3.52 (d, J = 13.2 Hz, 1H), 2.51 (ddd, J = 8.1, 5.1, 2.6 Hz, 1H), 2.46 (m, 1H), 2.28 (ddd, J = 13.7, 8.1, 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 139.2, 138.7, 138.0, 136.2, 136.1, 128.8, 128.4, 128.1, 127.4, 127.2, 127.1, 126.7, 118.1, 116.6, 83.3, 80.7, 79.6, 75.2, 74.5, 70.0, 56.4, 50.8, 35.1. Anal. Calcd for $C_{37}H_{41}NO_3$: C, 81.13; H, 7.54; N, 2.56. Found: C, 81.10; H, 7.53; N, 2.50.

(3*R*,4*S*,5*S*,6*S*)-6-[(*N*-Benzyl)amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (10S). Colorless syrup, R_f 0.40 (hexane:EtOAc = 3:1). $[\alpha]_D$ −31.5 (*c* 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.20 (m, 20H), 5.88 (ddd, J = 17.1, 10.7, 7.5 Hz, 1H), 5.79 (dddd, J = 17.1, 10.1, 7.3, 6.8 Hz, 1H), 5.28 (br dd, J = 10.7, 0.9 Hz, 1H), 5.25 (br dd, J = 17.1, 0.9 Hz, 1H), 5.06 (br dd, J = 10.7, 1.3 Hz, 1H), 5.05 (br dd, J = 17.1, 1.3 Hz, 1H), 4.76 (d, J = 11.1 Hz, 1H), 4.74 (d, J = 11.1 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.35 (d, J = 11.7 Hz, 1H), 4.02 (dd, J = 7.5, 5.1 Hz, 1H), 3.81 (dd, J = 5.5, 4.3 Hz, 1H), 3.75 (dd, J = 5.5, 5.1 Hz, 1H), 3.55 (d, J = 13.7 Hz, 1H), 3.35 (d, J = 13.7 Hz, 1H), 2.86 (dt, J = 7.7, 4.3 Hz, 1H), 2.36 (m, 1H), 2.29 (br dd, J = 14.5, 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 139.0, 138.6, 138.1, 136.3, 135.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 127.4, 127.3 (2C), 126.6, 118.5, 116.6, 82.3, 81.0, 79.3, 74.8, 73.7, 70.5, 57.6, 51.4, 34.8. Anal. Calcd for $C_{37}H_{41}NO_3$: C, 81.13; H, 7.54; N, 2.56. Found: C, 81.25; H, 7.51; N, 2.53.

(3*R*,4*S*,5*S*,6*R*)-6-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (11R). Colorless syrup, R_f 0.64 (hexane:EtOAc = 3:1). $[\alpha]_D$ −8.2 (*c* 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44−7.21 (m, 25H), 5.85 (m, 1H), 5.46 (m, 1H), 5.23−5.19 (m, 3H), 5.11 (d, J = 11.9 Hz, 1H), 4.90−4.75 (m, 5H), 4.64 (m, 1H), 4.51−4.44 (m, 3H), 4.40 (m, 1H), 4.22 (m, 1H), 4.02 (m, 1H), 3.91 (m, 1H), 3.37 (m, 1H), 2.42 (m, 1H), 2.19 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2, 139.0, 138.7 (2C), 136.7, 136.1, 135.2 (2C), 128.6, 128.4 (2C), 128.3, 128.1, 127.8, 127.7, 127.6, 126.8, 118.5, 117.3, 83.2, 81.0 (2C), 75.4 (2C), 70.9, 67.4, 56.8, 47.7, 35.0. Anal. Calcd for $C_{45}H_{47}NO_5$: C, 79.27; H, 6.95; N, 2.05. Found: C, 79.10; H, 6.89; N, 2.01.

(3*R*,4*S*,5*S*,6*R*)-6-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-3,4,5-tris(benzyloxy)cycloheptene (12). Colorless syrup, R_f 0.54 (hexane:EtOAc = 3:1). $[\alpha]_D$ −23.4 (*c* 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.18 (m, 25H), 5.72−5.58 (m, 2H), 5.22−5.16 (m, 3H), 5.09 (d, J = 12.2 Hz, 1H), 4.89 (d, J = 11.1 Hz, 1H), 4.85 (d, J = 10.7 Hz, 1H), 4.74 (d, J = 11.1 Hz, 1H), 4.67 (d, J = 11.9 Hz, 1H), 4.64 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 10.7 Hz, 1H), 4.36 (m, 1H), 4.21 (m, 1H), 4.16−4.04 (m, 1H), 3.64−3.56 (m, 1H), 2.86 (m, 1H), 1.98−1.88 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 139.0, 138.9, 138.7, 138.3, 136.8, 132.6, 129.3, 128.6, 128.4, 128.2, 128.1, 128.0 (2C), 127.9, 127.8, 127.6, 127.5 (3C), 127.3, 84.7, 83.6, 78.0, 75.6, 75.1, 72.7, 67.0, 62.0, 53.8, 30.2. Anal. Calcd for $C_{43}H_{43}NO_5$: C, 78.99; H, 6.63; N, 2.14. Found: C, 78.84; H, 6.57; N, 2.14.

(3*S*,4*R*,5*S*,6*R*)-6-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-3,4,5-tris(benzyloxy)cycloheptanone (13). Color-

less syrup, R_f 0.36 (hexane:EtOAc = 3:1). $[\alpha]_D$ −41.7 (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.35−7.12 (m, 25H), 5.21−4.96 (m, 3H), 4.85−4.66 (m, 2H), 4.56−4.32 (m, 5H), 4.14−4.09 (m, 2H), 3.94−3.90 (m, 2H), 3.34−3.05 (m, 1H), 2.97−2.79 (m, 1H), 2.73−2.59 (m, 1H), 2.47−2.32 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 138.6, 138.1, 137.8, 137.7, 136.7, 128.7, 128.6, 128.5, 128.1, 128.0, 127.8 (2C), 127.6, 82.7, 81.0, 75.5, 74.3, 73.1, 71.6, 67.1, 57.4, 46.7, 44.2. ESI HRMS calcd for $C_{43}H_{44}NO_6$ $[M + H]^+$ *m*/*z* 670.3168, found *m*/*z* 670.3143.

(2*S*,3*R*,4*S*,5*R*)-5-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-2,3,4-tris(benzyloxy)cycloheptanone (14). Colorless syrup, R_f 0.47 (hexane:EtOAc = 3:1). $[\alpha]_D$ −8.1 (*c* 1.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.32−7.07 (m, 25H), 5.15 (s, 2H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.67 (d, *J* = 11.1 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.32−4.27 (m, 1H), 4.22−4.18 (m, 1H), 4.01−3.86 (m, 1H), 3.82 (t, *J* = 5.8 Hz, 1H), 2.42−2.14 (m, 2H), 1.68−1.51 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 156.3, 146.3, 145.1, 141.4, 139.2, 139.0, 129.8, 129.2, 129.0, 128.7, 128.6, 128.2, 127.9, 85.8, 82.3, 82.0, 74.3, 74.2, 73.2 (3C), 67.7, 40.0, 26.3. Anal. Calcd for $C_{43}H_{43}NO_6$: C, 77.11; H, 6.47; N, 2.09. Found: C, 76.93; H, 6.26; N, 2.02.

(3*S*,4*S*,5*S*,6*R*)-6-[(*N*-Benzyl)amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (16R). Colorless syrup, R_f 0.35 (hexane:EtOAc = 5:1). $[\alpha]_D$ +1.2 (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.36−7.23 (m, 20H), 5.99 (ddd, *J* = 17.5, 10.2, 8.1 Hz, 1H), 5.66 (dddd, *J* = 17.1, 10.2, 7.7, 6.4 Hz, 1H), 5.32 (dd, *J* = 10.2, 2.1 Hz, 1H), 5.16 (dd, *J* = 17.5, 2.1 Hz, 1H), 5.01 (br dd, *J* = 10.2, 1.7 Hz, 1H), 5.00 (br dd, *J* = 17.1, 1.7 Hz, 1H), 4.93 (d, *J* = 11.1 Hz, 1H), 4.86 (d, *J* = 11.3 Hz, 1H), 4.73 (d, *J* = 11.1 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.30 (d, *J* = 12.2 Hz, 1H), 4.20 (dd, *J* = 7.3, 3.6 Hz, 1H), 3.90 (d, *J* = 13.2 Hz, 1H), 3.84 (dd, *J* = 8.1, 3.6 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 3.54 (dd, *J* = 7.3, 3.0 Hz, 1H), 2.67 (ddd, *J* = 8.1, 4.7, 3.0 Hz, 1H), 2.45 (m, 1H), 2.29 (ddd, *J* = 14.1, 8.1, 7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.7, 139.2 (2C), 138.8, 135.9, 135.2, 128.4, 128.1 (3C), 128.0, 127.9, 127.6, 127.2, 127.1, 126.7, 119.1, 116.8, 82.6, 81.7, 80.3, 74.8, 74.6, 69.9, 56.9, 50.9, 34.7. Anal. Calcd for $C_{37}H_{41}NO_3$: C, 81.13; H, 7.54; N, 2.56. Found: C, 81.15; H, 7.52; N, 2.49.

(3*S*,4*S*,5*S*,6*S*)-6-[(*N*-Benzyl)amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (16S). Colorless syrup, R_f 0.29 (hexane:EtOAc = 5:1). $[\alpha]_D$ −5.2 (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.32−7.18 (m, 20H), 5.96 (ddd, *J* = 17.5, 10.2, 8.1 Hz, 1H), 5.80 (dddd, *J* = 17.9, 11.1, 7.3, 5.1 Hz, 1H), 5.34 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.25 (dd, *J* = 17.5, 1.7 Hz, 1H), 5.03 (dd, *J* = 17.9, 1.7 Hz, 1H), 5.02 (dd, *J* = 11.1, 1.7 Hz, 1H), 4.77 (d, *J* = 10.9 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 10.9 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.22 (d, *J* = 11.7 Hz, 1H), 3.91 (dd, *J* = 8.1, 5.1 Hz, 1H), 3.86 (t, *J* = 5.1 Hz, 1H), 3.73 (dd, *J* = 5.1, 4.7 Hz, 1H), 3.65 (d, *J* = 13.2 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 2.80 (dt, *J* = 7.3, 4.7 Hz, 1H), 2.33−2.28 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.0, 139.3, 139.0, 138.7, 136.5, 135.7, 128.4 (3C), 128.3 (2C), 128.2, 127.9, 127.8, 127.6, 127.5 (2C), 126.9, 119.6, 116.9, 82.5, 81.2, 79.5, 74.6, 74.4, 70.1, 57.7, 51.4, 34.8. Anal. Calcd for $C_{37}H_{41}NO_3$: C, 81.13; H, 7.54; N, 2.56. Found: C, 81.05; H, 7.50; N, 2.51.

(3*S*,4*S*,5*S*,6*R*)-6-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (17R). Colorless syrup, R_f 0.62 (hexane:EtOAc = 5:1). $[\alpha]_D$ +2.1 (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.34−6.97 (m, 25H), 6.15 (m, 1H), 5.97 (m, 1H), 5.50−5.35 (m, 2H), 5.18−5.02 (m, 2H), 4.92−4.66 (m, 4H), 4.58 (br d, *J* = 12.0 Hz, 1H), 4.50−4.26 (m, 3H), 4.15 (br s, 2H), 4.02−3.60 (m, 3H), 2.55−2.32 (m, 2H), 2.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 138.8 (2C), 138.5, 136.3, 135.2, 134.8 (2C), 128.2, 128.0, 127.8, 127.2, 126.7, 119.7, 117.1, 82.4, 81.3, 80.6, 75.3, 74.5, 69.8, 67.1, 57.3, 48.7, 34.6. Anal. Calcd for $C_{45}H_{47}NO_5$: C, 79.27; H, 6.95; N, 2.05. Found: C, 79.31; H, 6.96; N, 2.01.

(3*S*,4*S*,5*S*,6*R*)-6-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-3,4,5-tris(benzyloxy)cycloheptene (18). Colorless syrup, R_f 0.43 (hexane:EtOAc = 5:1). $[\alpha]_D$ +27.2 (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.34−7.14 (m, 25H), 5.77−5.50 (m, 2H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.60−3.88 (m, 11H), 3.07 (m, 1H), 1.96 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 138.8, 138.5, 138.3, 138.1, 136.7, 133.4, 129.8, 129.0, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 80.8, 79.2, 79.1, 76.2, 72.2, 71.2, 67.4, 65.2, 52.6, 31.1. Anal. Calcd for $C_{43}H_{43}NO_5$: C, 78.99; H, 6.63; N, 2.14. Found: C, 78.92; H, 6.61; N, 2.12.

(2*R*,3*R*,4*S*,5*R*)-5-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-2,3,4-tris(benzyloxy)cycloheptanone (19). Colorless syrup, R_f 0.36 (hexane:EtOAc = 3:1). $[\alpha]_D$ −3.3 (*c* 0.46, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.33−7.14 (m, 25H), 5.19−5.11 (m, 2H), 4.77−3.88 (m, 11H), 2.53 (br d, *J* = 14.5 Hz, 1H), 2.44 (m, 1H), 2.21 (m, 1H), 1.55 (br d, *J* = 12.8 Hz, 1H), 1.41 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 156.6, 138.4, 137.6 (3C), 136.3, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 127.0, 84.1, 80.5, 78.9, 72.8, 72.5, 72.3 (2C), 67.2, 62.2, 42.0, 25.8. Anal. Calcd for $C_{43}H_{43}NO_6$: C, 77.11; H, 6.47; N, 2.09. Found: C, 76.76; H, 6.44; N, 2.08.

(3*R*,4*S*,5*R*,6*R*)-6-[(*N*-Benzyl)amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (21R). Colorless syrup, R_f 0.61 (hexane:EtOAc = 3:1). $[\alpha]_D$ +4.9 (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.46−7.23 (m, 20H), 6.00 (ddd, *J* = 17.5, 10.2, 6.8 Hz, 1H), 5.79 (dddd, *J* = 17.9, 9.8, 7.3, 2.6 Hz, 1H), 5.39 (br d, *J* = 17.5 Hz, 1H), 5.33 (dd, *J* = 10.2, 0.9 Hz, 1H), 5.10 (d, *J* = 9.8 Hz, 1H), 5.09 (d, *J* = 17.9 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.29 (dd, *J* = 6.8, 5.3 Hz, 1H), 3.88 (dd, *J* = 4.7, 4.0 Hz, 1H), 3.83 (d, *J* = 12.6 Hz, 1H), 3.82 (dd, *J* = 5.3, 4.7 Hz, 1H), 3.77 (d, *J* = 12.6 Hz, 1H), 3.08 (dt, *J* = 8.1, 4.0 Hz, 1H), 2.51 (br d, *J* = 14.1 Hz, 1H), 2.36 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6, 138.8, 138.6, 138.5, 136.4, 136.3, 128.8, 128.7, 128.1, 127.8 (2C), 127.5, 127.3, 126.6, 126.2, 125.9, 118.1, 117.0, 82.3, 81.1, 79.4, 74.4, 73.1, 70.5, 57.1, 51.7, 34.6. Anal. Calcd for $C_{37}H_{41}NO_3$: C, 81.13; H, 7.54; N, 2.56. Found: C, 81.08; H, 7.54; N, 2.61.

(3*R*,4*S*,5*R*,6*S*)-6-[(*N*-Benzyl)amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (21S). Colorless syrup, R_f 0.42 (hexane:EtOAc = 1:1). $[\alpha]_D$ −12.6 (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.24−7.09 (m, 20H), 5.76 (ddd, *J* = 17.7, 10.2, 7.7 Hz, 1H), 5.64 (dddd, *J* = 17.1, 10.2, 8.1, 6.0 Hz, 1H), 5.16 (dd, *J* = 17.7, 2.1 Hz, 1H), 5.14 (dd, *J* = 10.2, 2.1 Hz, 1H), 4.92 (br d, *J* = 10.2 Hz, 1H), 4.89 (br d, *J* = 17.1 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.37 (s, 2H), 4.20 (d, *J* = 11.7 Hz, 1H), 3.85 (dd, *J* = 7.7, 4.3 Hz, 1H), 3.82 (d, *J* = 13.0 Hz, 1H), 3.79 (dd, *J* = 6.6, 4.3 Hz, 1H), 3.63 (dd, *J* = 6.6, 2.1 Hz, 1H), 3.53 (d, *J* = 13.0 Hz, 1H), 2.83 (m, 1H), 2.41 (m, 1H), 2.17 (ddd, *J* = 15.4, 8.1, 7.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 138.6, 138.5, 138.4, 136.2, 136.1, 128.3, 128.0, 127.7, 127.4, 127.2, 126.5, 118.4, 116.6, 81.9, 81.0, 78.6, 74.8, 73.1, 70.0, 56.6, 51.0, 35.5. Anal. Calcd for $C_{37}H_{41}NO_3$: C, 81.13; H, 7.54; N, 2.56. Found: C, 81.02; H, 7.60; N, 2.56.

(3*R*,4*S*,5*R*,6*R*)-6-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-3,4,5-tris(benzyloxy)-1,8-nonadiene (22R). Colorless syrup, R_f 0.56 (hexane:EtOAc = 4:1). $[\alpha]_D$ +3.6 (*c* 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.41−7.02 (m, 25H), 5.81 (m, 1H), 5.66 (m, 1H), 5.37 (br d, *J* = 17.1 Hz, 1H), 5.31 (br d, *J* = 9.8 Hz, 1H), 5.30−5.09 (m, 4H), 4.84−4.20 (m, 8H), 4.05 (m, 1H), 3.93 (m, 1H), 3.77−3.70 (m, 1H), 2.69 (m, 1H), 2.59 (m, 1H), 2.40 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 139.1, 139.0, 138.8, 138.5, 136.9, 136.4, 135.5, 129.0, 128.7, 128.5, 128.4 (2C), 128.1, 128.0, 127.9, 127.5, 127.0, 119.4, 116.3, 82.1, 81.8, 81.5, 75.0, 70.9, 67.7, 67.1, 58.0, 49.3, 33.6. Anal. Calcd for $C_{45}H_{47}NO_5$: C, 79.27; H, 6.95; N, 2.05. Found: C, 79.04; H, 7.14; N, 2.02.

(3*R*,4*S*,5*R*,6*R*)-6-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-3,4,5-tris(benzyloxy)cycloheptene (23). Colorless syrup, R_f 0.41 (hexane:EtOAc = 4:1). $[\alpha]_D$ +59.5 (*c* 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.03 (m, 25H), 5.71 (m, 1H), 5.60 (m, 1H), 5.25−5.13 (m, 1H), 5.09 (d, *J* = 11.1 Hz, 1H), 4.93 (d, *J* = 11.1 Hz, 1H), 4.80−4.76 (m, 1H), 4.73 (d, *J* = 11.9 Hz, 1H), 4.68 (d, *J* = 11.9 Hz, 1H), 4.65−3.96 (m, 7H), 3.67−3.47 (m, 1H), 2.69 (br t, *J* = 13.2 Hz, 1H), 1.84 (br dd, *J* = 13.2, 9.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 140.0 (2C), 139.1, 138.8 (2C), 136.6, 134.0, 129.0 (2C), 128.4 (2C), 128.1, 127.9, 127.8, 127.6, 127.5, 126.6, 126.1, 85.0, 82.9, 77.0, 74.6, 74.2, 73.2, 67.4, 56.7, 47.5, 25.8. Anal. Calcd for $C_{43}H_{43}NO_5$: C, 78.99; H, 6.63; N, 2.14. Found: C, 78.72; H, 6.67; N, 2.14.

(2*S*,3*R*,4*R*,5*R*)-5-[(*N*-Benzyl-*N*-(benzyloxycarbonyl))-amino]-2,3,4-tris(benzyloxy)cycloheptanone (24). Colorless syrup, R_f 0.50 (hexane:EtOAc = 3:1). $[\alpha]_D$ +21.9 (*c* 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−6.98 (m, 25H), 5.14 (d, *J* = 11.5 Hz, 1H), 5.08 (d, *J* = 11.9 Hz, 1H), 4.91 (d, *J* = 11.5 Hz, 1H), 4.76 (s, 2H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.44−4.15 (m, 3H), 4.03−3.97 (m, 1H), 3.94 (dd, *J* = 7.3, 0.9 Hz, 1H), 3.91−3.81 (m, 1H), 2.71 (br t, *J* = 11.9 Hz, 1H), 2.29 (ddd, *J* = 11.9, 5.6, 1.7 Hz, 1H), 2.19−2.09 (m, 1H), 1.69 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.2, 157.5, 139.7, 138.3, 137.9, 137.6, 136.5, 129.1, 128.9, 128.5, 128.4, 128.2, 128.0, 127.8, 126.7, 126.1, 86.0, 85.4, 83.0, 73.6 (2C), 72.6, 67.5, 58.5, 47.1 37.0, 26.0. Anal. Calcd for $C_{43}H_{43}NO_6$: C, 77.11; H, 6.47; N, 2.09. Found: C, 76.91; H, 6.77; N, 2.02.

(+)-Calystegine B_2. Colorless glass. $[\alpha]_D$ +28.1 (*c* 0.27, H_2O) (lit.[6] $[\alpha]_D$ +27.2 (*c* 0.5, H_2O)). ^{1}H NMR (500 MHz, D_2O): δ 3.64 (dd, *J* = 8.5, 3.8 Hz, 1H), 3.48 (dd, *J* = 8.5, 2.1 Hz, 1H), 3.41 (t, *J* = 8.5 Hz, 1H), 3.38 (dd, *J* = 6.8, 3.8 Hz, 1H), 2.09−1.98 (m, 2H), 1.86−1.80 (m, 1H), 1.63−1.57 (m, 1H). ^{13}C NMR (125 MHz, D_2O): δ 93.3, 80.4, 77.7, 77.6, 58.6, 31.5, 24.5. NMR data are in accordance with literature values.[6]

(+)-Calystegine B_3. White powder. $[\alpha]_D$ +76.8 (*c* 0.88, H_2O) (lit.[6] $[\alpha]_D$ +82.8 (*c* 0.50, H_2O)). ^{1}H NMR (500 MHz, D_2O): δ 3.89 (d, *J* = 3.8 Hz, 1H), 3.70 (dd, *J* = 9.4, 3.8 Hz, 1H), 3.67 (dd, *J* = 9.4, 3.8 Hz, 1H), 3.33 (dd, *J* = 6.8, 3.8 Hz, 1H), 2.02−1.96 (m, 1H), 1.88−1.78 (m, 3H). ^{13}C NMR (125 MHz, D_2O): δ 93.0, 77.3, 75.3, 73.1, 58.3, 34.1, 23.0. NMR data are in accordance with literature data.[6]

(−)-Calystegine B_4. Colorless glass. $[\alpha]_D$ −46.4 (*c* 0.18, H_2O) (lit.[5] $[\alpha]_D$ −63.0 (*c* 0.65, H_2O)). ^{1}H NMR (500 MHz, D_2O): δ 3.70 (dt, *J* = 3.0, 1.2 Hz, 1H), 3.54−3.49 (m, 2H), 3.32 (dd, *J* = 7.7, 3.0 Hz, 1H), 2.04−1.89 (m, 2H), 1.46−1.36 (m, 2H). ^{13}C NMR (125 MHz, D_2O): δ 92.5, 79.6, 74.9, 73.8, 59.2, 29.8, 25.1. NMR data are in accordance with literature data.[5]

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