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General access to polyhydroxylated nortropane derivatives through hetero Diels–Alder cycloadditions. Part 3: Synthesis of natural (+)-calystegine B_2

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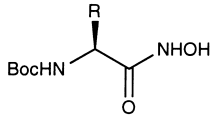
Abstract

Cycloaddition of chiral nitroso derivatives with cyclohepta-1,3-diene gave one single stereoisomer with an excellent selectivity. The structures including absolute configurations have been assigned by spectroscopy and X-ray crystallography. These studies have been applied to the total synthesis of the naturally occurring calystegine B_2.

1. Introduction

Nitroso compounds are known to behave as good dienophiles in hetero Diels–Alder cycloadditions to furnish bicyclo-dihydroxazines.[1] We have shown in a previous communication that the resulting adducts are effective precursors of calystegines in their racemic form (Scheme 1).[2] Calystegines are chiral polyhydroxylated nortropanic compounds, and the absolute configuration of natural calystegine B_2 has been established as (1*R*,2*S*,3*R*,4*S*,5*R*).[3] Following our preliminary approach the chirality could be introduced in several ways; one possibility is to introduce it during the Diels–Alder cycloaddition involving a chiral nitroso compound. Among the numerous chiral precursors of nitroso compounds that are most often used, we chose to test compounds **1**, **2** and **3**.



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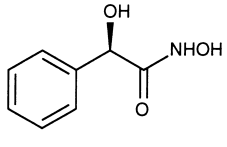

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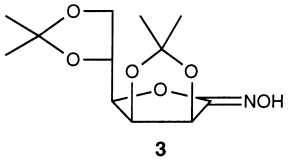

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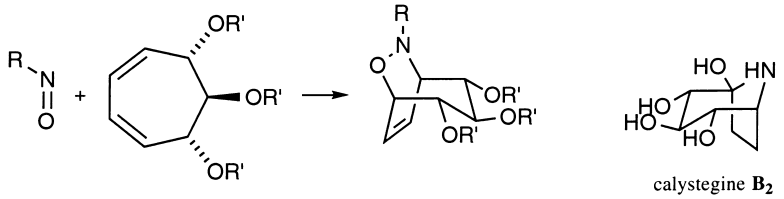
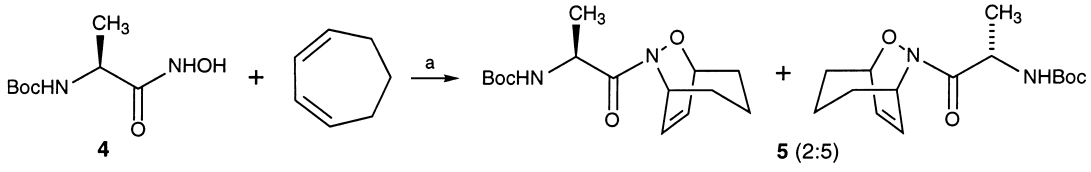


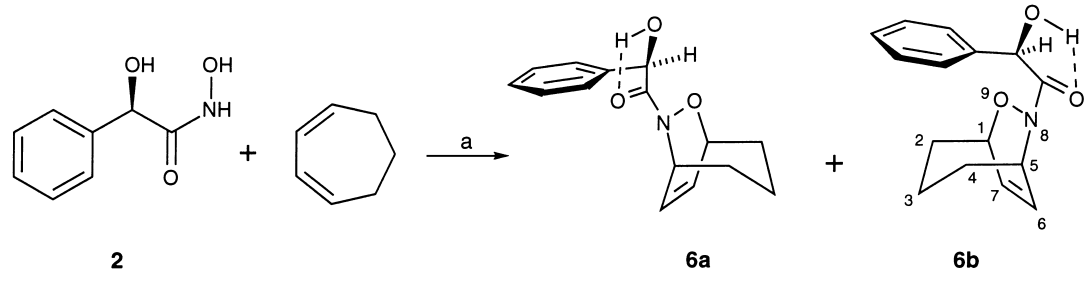
Scheme 1. Key step of calystegines synthesis

2. Results and discussion

Amino acid-derived hydroxamic acids **1** were easily obtained through the transformation of the corresponding commercially available *N*-protected amino acid methyl esters. We studied the cycloaddition of a nitroso compound derived from L-alanine[4] on cyclohepta-1,3-diene chosen as the model (Scheme 2). NMR studies (COSY and HETCOR) showed that the products obtained are a mixture of two diastereoisomers **5** (2:5) which could not be separated by chromatography. These results led us to examine other nitroso compounds such as mandelic derivatives **2**. The two enantiomeric methyl esters are cheap and commercially available. The corresponding hydroxamic acids are easy to prepare. Several authors[5] have studied this cycloaddition on cyclopentadiene and (or) cyclohexa-1,3-diene, and have obtained interesting selectivity at low temperature with cyclohexadiene. These results have prompted us to attempt the cycloaddition on our cyclohepta-1,3-diene model, under similar temperature conditions (Scheme 3).



Scheme 2. a: $(n\text{-}C_4H_9)_4NIO_4$, CH_3OH, 0°C



Scheme 3. a: $(n\text{-}C_4H_9)_4NIO_4$, CH_2Cl_2:CH_3OH (3:1)

As exemplified in Table 1, the results obtained with cyclohepta-1,3-diene at −90°C, are very good (entry 3, Table 1): the structure of compounds **6a** and **6b** was determined by infra-red spectroscopy and extensive NMR studies including COSY and HETCOR experiments. The infra-red spectra of compounds **6a** and **6b** indicate the presence of a hydrogen bond between the hydroxyl and carbonyl functions of the mandelic moiety. Concerning the minor isomer, the ^1H NMR spectrum shows that the axial H-2 hydrogen (H-2a) is strongly shielded (δ=0.5 ppm) by the phenyl ring. These infra-red and NMR results allow us to assign an unambiguous structure **6b** for the minor isomer and accordingly **6a** for the main product.

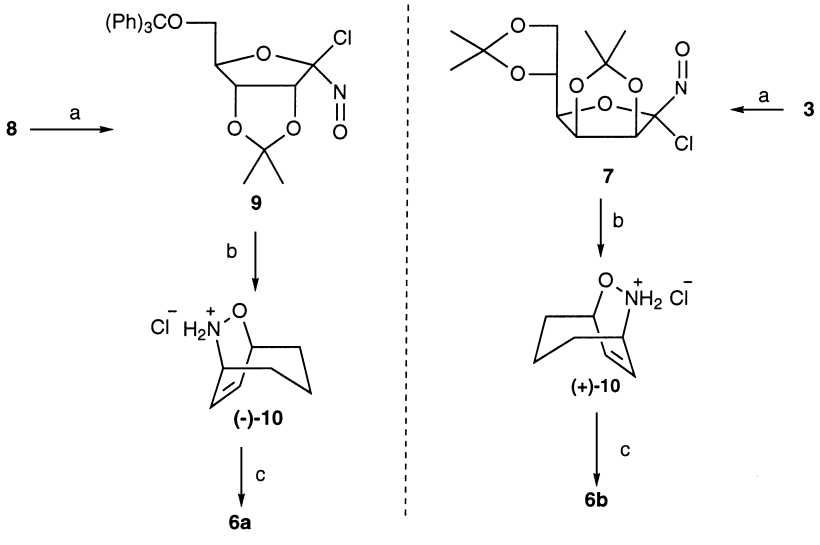
The cycloadducts **6a** and **6b** can be synthesised individually by an alternative route. A few years ago Kresze[6] described chiral nitroso Diels–Alder cycloadditions with chiral 1-chloro-1-nitroso substrates.

Table 1
Variation of diastereoisomeric excess versus temperature

entry	T °C	d.e. %[a]	yield %[c]	time h
1	20	45	80	2
2	-50	62	40	2
3	-90	≥ 95[b]	64	6

a : d. e. estimated by 400 MHz ^{1}H NMR on the crude product ; b : compound **6b** was not detected by NMR ; c : pure product after column chromatography.

The mannose derivative **7** proved to be one of the most effective auxiliaries. This dienophile is equally reactive with cyclic and acyclic dienes, affording adducts with very high enantiomeric excesses. Interestingly, the ribose derivative **9** permits the other enantiomer to be obtained under the same conditions with the same enantiomeric excess. These chloronitroso compounds react smoothly with the cyclohepta-1,3-diene (Scheme 4). The enantiomeric oxazines (−)-**10** and (+)-**10** have been coupled with (*R*)-mandelic acid, in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC), according to the method used by Defoin et al.[5a] in the case of cyclohexadiene. The yields are good and the compounds are identical to those obtained by cycloaddition with nitrosomandelic derivatives. X-Ray diffraction analysis of the two compounds **6a** and **6b** is in good agreement with the above described results (Fig. 1).



Scheme 4. a: *t*-C_4H_9OCl; b: cyclohepta-1,3-diene, ethanol; c: (*R*)-mandelic acid, DCC

These good selectivities observed with cyclohepta-1,3-diene have encouraged us to carry out the same reactions on the trisubstituted cycloheptadiene **11**, precursor of calystegine $\mathbf{B}_2$.[2b] With the mandelic derivative we obtained a single cycloadduct, but the yield, as yet unoptimised, remains very poor (15%). On the other hand, with sugar derivative **3** the reaction works better and the dihydrooxazine **12** is obtained readily (67%). To confirm the enantioselectivity of the reaction, the compound **12** was derivatised with (*S*)-mandelic acid, to give only one diastereoisomer **13** in good yield. This compound has the opposite specific rotation to the compound (−)-**13** (Scheme 5). The crystal structure of (+)-**12** has allowed us to attribute the absolute configuration given in Fig. 2. To complete the synthesis of natural calystegine $\mathbf{B}_2$ the free dihydroxazine **12** was protected as its benzylcarbamate derivative and the subsequent steps are identical to those previously described for the racemic compound (Scheme 6).[2b,3]

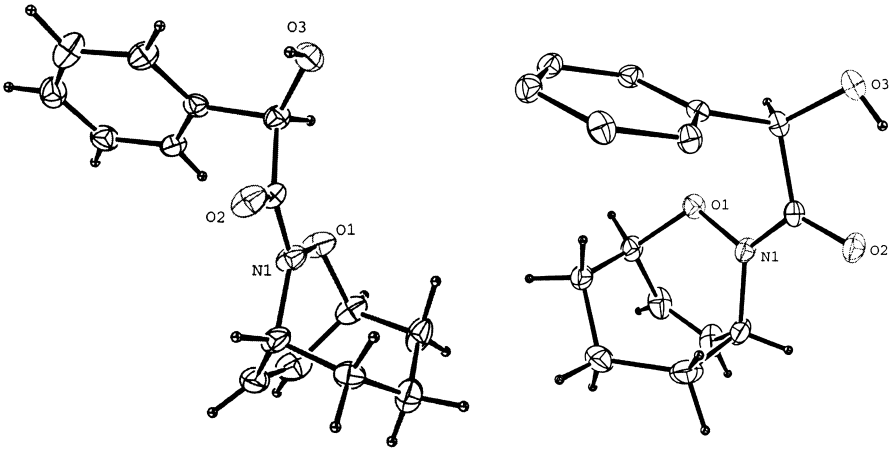
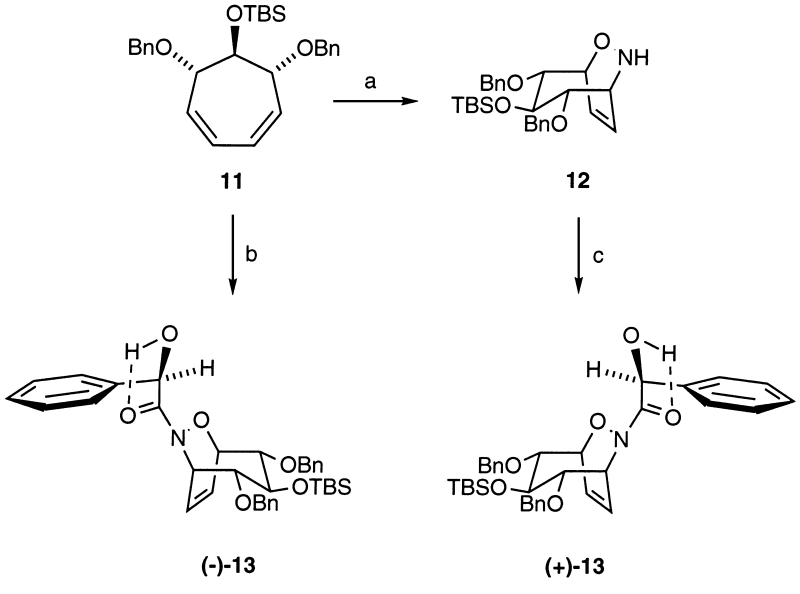


Figure 1. Crystal structure analyses of **6a** and **6b**



Scheme 5. a: **3**, *t*-C_4H_9OCl; b: **2**, $(n\text{-}C_4H_9)_4NIO_4$, CH_2Cl_2:CH_3OH (3:1); c: (*S*)-mandelic acid, DCC

This synthesis of natural calystegine $\mathbf{B}_2$ shows a significant improvement: 12 steps (instead of 17[3b] and 21[3a]) and a satisfactory 13% overall yield. Furthermore, this scheme has the potential to be easily generalised to several other calystegines such as $\mathbf{C}_1$.

3. Experimental

NMR spectra were recorded in $CDCl_3$ on Bruker WP 200 and AM 400 spectrometers. The chemical shifts of ^1H NMR signals δ are reported in ppm (TMS as internal standard, δ=0). Coupling constants *J* are reported in hertz. The abbreviations s, d, t, m and br signify: singlet, doublet, triplet, multiplet and broad, respectively. ^{13}C NMR spectra were recorded on the same instruments. ^{13}C NMR chemical shifts are expressed in ppm, reported from the central peak of deuterochloroform (77.1 ppm). The numbering sequence used for reporting NMR parameters is the same as that used for calystegines as indicated in

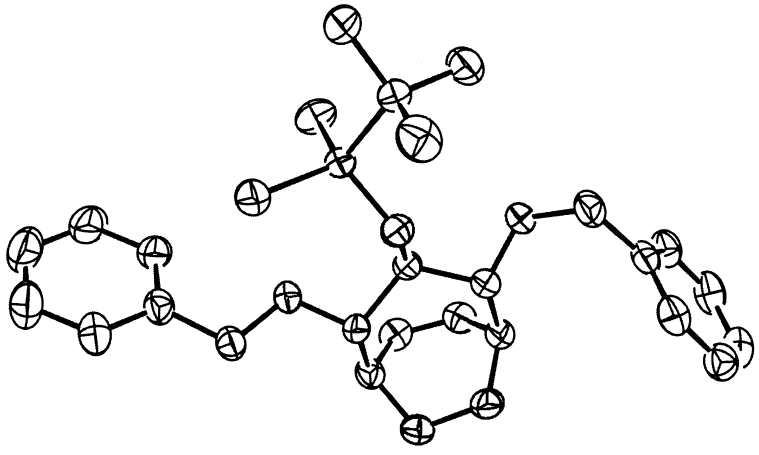
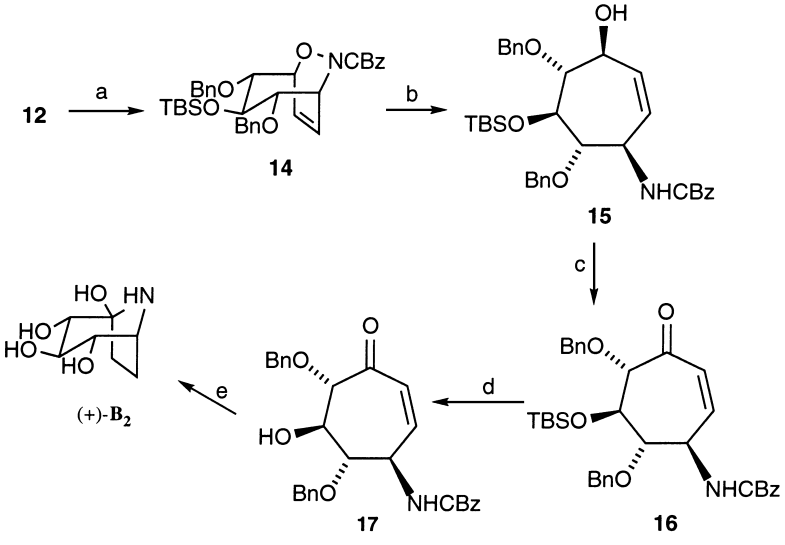


Figure 2. Crystal structure analysis of (+)-**12**



Scheme 6. a: $C_6H_5CH_2OCOCl$, CH_2Cl_2, aq. Na_2CO_3; b: $Mo(CO)_6$, CH_3CN:H_2O (9:1); c: PCC, CH_2Cl_2; d: HF, H_2O:CH_3CN (9:1); e: H_2, Pd/C 10%, CH_3OH, 4 days

Scheme 3 for the compound **6b**. IR spectra were recorded on a Perkin–Elmer FT 1600 instrument and are reported in terms of frequency of absorption (ν, cm^{-1}). Low resolution mass spectra (MS) were recorded on a Hewlett–Packard HP 5989B spectrometer under chemical ionisation (NH_3) conditions. High resolution mass spectra (HRMS) were recorded on a ZAB HFQ VG apparatus. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in a 1 dm cell. Melting points were determined on a Büchi 510 apparatus and are uncorrected.

All reactions were carried out under an inert atmosphere. Dry solvents were freshly distilled before use. Methanol was distilled from magnesium methoxide. Dichloromethane was distilled from P_2O_5.

All reactions were monitored by thin layer chromatrography carried out on Merck silica gel plates (Ref. 5549) using 5% ethanolic phosphomolybdic acid/heat as developing agent. Merck silica gel (Ref. 9385) was used for flash chromatography.

D-(+)-Mannose and D-(−)-ribose were purchased from Lancaster, (*R*)- and (*S*)-mandelic acid from Acros, cyclohepta-1,3-diene from Fluka and *N*-(*t*-butoxycarbonyl)-L-alanine methyl ester from Al-

drich. *N*-(*t*-Butoxycarbonyl)-L-alanine-*N*-hydroxyamide **4** was prepared according to the literature.[4] Colourless crystals. Mp 97°C; $[\alpha]_D$=+23 (*c*=1.0, methanol). (2*R*)-2-Hydroxy-2-phenylacetohydroxamic acid **2** was prepared according to the literature.[5a] Mp 136°C (mp 155°C,[5a] 137–139°C[5c]); $[\alpha]_D$=−44 (*c*=0.5, methanol) ($[\alpha]_D$=−48 (*c*=0.6, methanol),[5a] $[\alpha]_D$=−63 (*c*=1.6, water)[5c]). *N*-Hydroxy-2,3:5,6-di-*O*-isopropylidene-D-mannonimido-1,4-lactone **3** was prepared according to the literature.[8–10] *N*-Hydroxy-2,3-*O*-isopropylidene-5-*O*-trityl-D-ribonimido-1,4-lactone **8** was prepared according to the literature.[7–9] (5*R*,6*S*,7*S*)-5,7-Dibenzyloxy-6-[(*t*-butyldimethylsilyl)oxy]cyclohepta-1,3-diene **12** was prepared according to the literature.[2b]

*3.1. Mixture of (1*R,*5*S*)- and (1*S,*5*R*)-3-[*N-(t-*butoxycarbonyl)-L-*alanyl]-9-oxa-8-azabicyclo[3.2.2]-non-6-ene* **5**

A solution of **4** (2.5 mmol, 0.5 g) in methanol (25 mL) was added to a mixture of tetrabutylammonium periodate (2.5 mmol, 1.1 g), cyclohepta-1,3-diene (12.4 mmol, 1.33 mL) and methanol (25 mL), cooled to 0°C in an ice-water bath. A yellow colour began to appear quickly. Then sodium metabisulfite (0.5 M, 15 mL) was added. After the colour had disappeared, sodium carbonate (0.5 M, 50 mL) was added. The mixture was extracted with dichloromethane, dried ($MgSO_4$) and concentrated to give a brown solid. This was then purified by flash chromatography (ethyl acetate:cyclohexane, 30:70) to give **5**. Yield: 0.62 g (85%). ^{1}H NMR (400 MHz): major isomer: 6.35 (dd, ^3J(H-7, H-6)=6.1 Hz, ^3J(H-7, H-1)=8.9 Hz, 1H: H-7), 6.20 (dd, ^3J(H-6, H-7)=6.2 Hz, ^3J(H-6, H-5)=9.25 Hz, 1H: H-6), 5.43 (s, 1H: NH), 5.16 (m, 1H: H-5), 4.74 (m, 1H: H-1), 4.68 (m, 1H: H-2′), 1.9–1.4 (m, 6H: H-2, H-3, H-4), 1.24 (d, ^3J=6.8 Hz, 3H: H-3′), 1.43 (s, 9H: C(CH_3)$_3$); minor isomer: 6.28 (m, 1H: H-7), 6.25 (m, 1H: H-6), 5.43 (s, 1H: NH), 5.24 (m, 1H: H-5), 4.74 (m, 1H: H-1), 4.68 (m, 1H: H-2′), 1.9–1.4 (m, 6H: H-2, H-3, H-4), 1.33 (d, ^3J=6.8 Hz, 3H: H-3′), 1.43 (s, 9H: C(CH_3)$_3$); ^{13}C NMR (100 MHz): major isomer: 168.6 (C-1′), 156.0 (C=O carbamate), 130.2, 126.7 (C-6, C-7), 79.3 (*C*(CH$_3$)$_3$), 77.0 (C-1), 51.1 (C-5), 47.3 (C-2′), 30.0–28.5 (C-2, C-3, C-4), 29.1 (C(*C*H$_3$)$_3$), 18.6 (C-3′); minor isomer: 168.6 (C-1′), 156.0 (C=O carbamate), 129.3, 127.5 (C-6, C-7), 79.3 (*C*(CH$_3$)$_3$), 77.0 (C-1), 50.4 (C-5), 47.2 (C-2′), 30.0–28.5 (C-2, C-3, C-4), 29.1 (C(*C*H$_3$)$_3$), 18.6 (C-3′).

3.2. General procedure for the Diels–Alder cycloaddition with cyclohepta-1,3-dienes

To a stirred solution of tetrabutylammonium periodate (1 mmol) and cyclohepta-1,3-diene (1.5 mmol) in dichloromethane (25 mL), hydroxamic acid (1 mmol) in a mixture of methanol (12.5 mL) and dichloromethane (12.5 mL) was added dropwise. After several hours, sodium sulfite (0.5 M, 10 mL) was added, until the solution turned colourless. Finally, the mixture was treated with sodium carbonate (1 M, 25 mL). The aqueous phase was extracted several times with dichloromethane, and the combined organic layers were dried ($MgSO_4$) and evaporated.

*3.3. (1*S,*5*R*)-8-[(2*R*)-2-Hydroxy-2-phenylacetyl]-9-oxa-8-azabicyclo[3.2.2]non-6-ene* **6a**

The title compound was prepared at −90°C from cyclohepta-1,3-diene (1.5 mmol, 0.163 mL), tetrabutylammonium periodate (1 mmol, 0.43 g) in dichloromethane (25 mL), and a solution of hydroxamic acid **2** (1 mmol, 0.17 g) in a mixture of methanol (12.5 mL) and dichloromethane (12.5 mL). The crude product was purified by flash chromatography (ethyl acetate:cyclohexane, 40:60) to give **6a** as colourless crystals. Yield: 0.21 g (64%). Mp 151°C (sublimation); $[\alpha]_D$=−43 (*c*=0.65, methanol); ^{1}H NMR (400 MHz): 7.32–7.24 (m, 5H: Ph), 6.14 (ddd, ^3J(H-6, H-5)=8.0 Hz, ^3J(H-6, H-7)=7.1 Hz, ^4J(H-6, H-1)=1.0

Hz, 1H: H-6), 5.94 (ddd, ^3J(H-7, H-6)=7.1 Hz, ^3J(H-7, H-1)=6.1 Hz, ^4J(H-7, H-5)=1.1 Hz, 1H: H-7), 5.37 (d, ^3J=6.9 Hz, 1H: H-2′), 5.17 (m, 1H: H-4), 4.47 (m, 1H: H-1), 4.35 (d, ^3J=6.9 Hz, 1H: OH), 1.85–1.72 (m, 4H: H-2, H-4), 1.56, 1.38 (m, 2H: H-3a, H-3e); ^{13}C NMR (100 MHz): 169.0 (C=O), 139.2, 128.2, 127.8, 127.5 (Ph), 128.9 (C-7), 127.2 (C-6), 76.6 (C-1), 71.3 (C-2′), 52.0 (C-5), 29.9, 27.9 (C-2, C-4), 18.4 (C-3); IR ν-max: 3425 (OH), 3058 (HC=), 1641 (C=O), 1621 (C=C), 736 (HC=), 710 (C_6H_5); HRMS: calcd for $C_{15}H_{17}NO_3$: 259.1208; found: 259.1207.

*3.4. (1S,5R)-9-Oxa-8-azabicyclo[3.2.2]non-6-ene, hydrochloride (−)-**10***

A solution of *t*-C_4H_9OCl (1 mmol, 0.108 g) in dichloromethane (2.5 mL) was added dropwise at −10°C in the dark to a stirred solution of *N*-hydroxy-2,3-*O*-isopropylidene-5-*O*-trityl-D-ribonimido-1,4-lactone **8** (1 mmol) in dichloromethane (5 mL). The mixture was stirred for an additional hour at −10°C to obtain crude **7** in solution. Then cyclohepta-1,3-diene (4 mmol, 0.43 mL) in ethanol (4 mL) was directly added. When the blue colour had disappeared, extraction with water (3 mL), then with hydrochloric acid (0.05 M, 1 mL), gave crude (−)-**9** after evaporation of the combined aqueous layers. A sample was purified according to the literature.[10] Mp 149°C; $[\alpha]_D$=−24 (*c*=1.1, water); ^{1}H NMR (400 MHz): 6.42 (ddd, ^3J(H-7, H-6)=7.7 Hz, ^3J(H-7, H-1)=6.4 Hz, ^4J(H-7, H-5)=1.1 Hz, 1H: H-7), 6.29 (ddd, ^3J(H-6, H-7)=7.7 Hz, ^3J(H-6, H-5)=6.9 Hz, ^4J(H-6, H-1)=0.7 Hz, 1H: H-6), 4.81 (m, 1H: H-1), 4.44 (m, 1H: H-5), 2.09, 2.00 (m, 2H: H-4a, H-4e), 1.88 (m, 2H: H-2), 1.54 (m, 1H: H-3e), 1.30 (m, 1H: H-3a); ^{13}C NMR (100 MHz): 130.8 (C-7), 125.1 (C-6), 77.5 (C-1), 54.0 (C-5), 30.6 (C-2), 26.1 (C-4), 17.8 (C-3); IR ν-max: 3010–2400 (NH_2^+), 1050 (C–O), 714 (HC=); MS: *m/z* (%): 126 (100) [MH^+], 143 (90) [$M+NH_4^+$]. Anal. calcd for $C_7H_{12}NOCl$: C, 52.02; H, 7.48; N, 8.67; found: C, 52.14; H, 7.27; N, 8.4

*3.5. (1R,5S)-9-Oxa-3-azabicyclo[3.2.2]non-6-ene, hydrochloride (+)-**10***

This compound was synthesised according to the procedure, and on the same scale used for the compound (−)-**10**, with *N*-hydroxy-2,3:5,6-di-*O*-isopropylidene-D-mannonimido-1,4-lactone **3** and was purified as above. Yield: 81%. Mp 149°C; $[\alpha]_D$=+24 (*c*=1.0, water).

*3.6. (1R,5S)-8-[(2R)-2-Hydroxy-2-phenylacetyl]-9-oxa-8-azabicyclo[3.2.2]non-6-ene **6b***

To a stirred solution of (+)-**10** (1 mmol, 0.16 g) in dry ethanol (3.5 mL) were added sequentially (*R*)-mandelic acid (1 mmol, 0.15 g), triethylamine (1 mmol, 0.14 mL) and a solution of DCC (1 mmol, 0.21 g) in anhydrous chloroform (3.5 mL). After 24 h, at room temperature, the solid was filtered and washed with chloroform. The filtrate was diluted with tetrahydrofuran, DCU was filtered again, the residue was evaporated and the crude compound **6b** purified by recrystallisation (ether:dichloromethane, 1:4) to give **6b** as colourless crystals. Yield: 0.21 g (81%). Mp 71–72°C; $[\alpha]_D$=−114 (*c*=0.5, methanol); ^{1}H NMR (400 MHz): 7.40–7.27 (m, 5H: Ph), 6.34 (ddd, ^3J(H-7, H-1)=9.1 Hz, ^3J(H-7, H-6)=6.1 Hz, ^4J(H-7, H-5)=1.1 Hz, 1H: H-7), 6.16 (ddd, ^3J(H-6, H-5)=7.1 Hz, ^3J(H-6, H-7)=6.1 Hz, ^4J(H-6, H-1)=1.2 Hz, 1H: H-5), 5.29 (d, ^3J=6.5 Hz, 1H: H-2′), 5.20 (m, 1H: H-5), 4.50 (m, 1H: H-1), 4.46 (d, ^3J=6.5 Hz, 1H: OH), 1.68, 1.59 (m, 2×1H: H-4a, H-4e), 1.48 (m, 1H: H-2e), 1.24 (m, 2H: H-3), 0.56 (m, 1H: H-2a); ^{13}C NMR (100 MHz): 167.3 (C=O), 129.8, 128.3, 128.0, 127.7 (Ph), 130.4 (C-7), 125.5 (C-6), 76.7 (C-1), 71.3 (C-1′), 51.2 (C-5), 28.6 (C-4), 27.4 (C-2), 18.0 (C-3); IR ν-max: 3351 (OH), 3065 (HC=), 1643 (C=O), 1626 (C=C), 704 (C_6H_5); MS: *m/z* (%): 260 (100) [MH^+], 277 (50) [$M+NH_4^+$]. Anal. calcd for $C_{15}H_{17}NO_3$: C, 69.47; H, 6.61; N, 5.40; found: C, 69.26; H, 7.03; N, 5.67.

3.7. (1S,2R,3R,4S,5R)-2,4-Dibenzyloxy-3-[(t-butyldimethylsilyl)oxy]-9-oxa-8-azabicyclo-[3.2.2]-non-6-ene ***12***

This compound was synthesised according to the same procedure and on the same scale used for the compound (+)-**10**. Yield: 67%; mp 96°C; $[\alpha]_D$=+9.6 (*c*=1, $CHCl_3$); ^{1}H NMR (400 MHz): 7.40–7.28 (10H: Ph), 6.58 (dd, ^3J(H-7, H-6)=8.7 Hz, ^3J(H-7, H-1)=7.2 Hz, 1H: H-7), 6.24 (ddd, ^3J(H-6, H-7)=8.7 Hz, ^3J(H-6, H-5)=6.6 Hz, ^4J(H-6, H-1)=1.4 Hz, 1H: H-6), 4.74–4.61 (m, 4H: H-1′, H-1′′), 4.46 (dd, ^3J(H-1, H-7)=7.2 Hz, ^3J(H-1, H-6)=1.4 Hz, 1H: H-1), 3.67 (m, 2H: H-5, H-3), 3.44 (m, 2H: H-2, H-3), 0.89 (s, 9H: (CH_3)$_3$CSi), 0.02, 0.01 (s, 2×3H: (CH_3)$_2$Si); ^{13}C NMR (100 MHz):135.5 (C quat. Ph), 132.0 (C-7), 128.3, 127.5, 126.9 (Ph), 126.4 (C-6), 84.7 (C-2), 82.8 (C-4), 75.9 (C-3), 72.9, 70.3 (C-1′, C-1′′), 72.3 (C-1), 55.6 (C-5), 26.0 ((*C*H$_3$)$_3$CSi), 18.1 ((CH$_3$)$_3$*C*Si), −4.1, −4.2 ((CH$_3$)$_2$Si); IR ν-max: 3211 (NH), 1244 (C–Si), 1105, 1071 (C–O), 870 (C–Si); MS: *m/z* (%): 468 [MH$^+$], 454.

3.8. (1S,2R,3R,4S,5R)-2,4-Dibenzyloxy-8-benzyloxycarbonyl-3-[(t-butyldimethylsilyl)oxy]-9-oxa-8-azabicyclo[3.2.2]non-6-ene (+)- ***13***

This compound was synthesised according to the same procedure and on the same scale used for the compound (+)-**10**. Yield: 85%; $[\alpha]_D$=+62.3 (*c*=0.22, $CHCl_3$).

3.9. (1R,2S,3S,4R,5S)-2,4-Dibenzyloxy-8-benzyloxycarbonyl-3-[(t-butyldimethylsilyl)oxy]-9-oxa-8-azabicyclo[3.2.2]non-6-ene (−)- ***14***

This compound was synthesised according to the same procedure and on the same scale used for the compound **6a**. Yield: 15%; $[\alpha]_D$=−62 (*c*=0.65, $CHCl_3$); ^{1}H NMR (400 MHz): 7.35–7.27 (m, 15H: Ph), 6.23 (t, ^3J(H-6, H-7)=^3J(H-6, H-5)=7.8 Hz, 1H: H-6), 6.36 (dd, ^3J(H-7, H-6)=7.8 Hz, ^3J(H-7, H-1)=6.0 Hz, 1H: H-7), 5.31 (d, ^3J(H-2′′′, OH)=7.4 Hz, 1H: H-2′′′), 5.24 (d, ^3J(H-5, H-6)=7.8 Hz, 1H: H-5), 4.79, 4.72 (d, ^2J=11.9 Hz, 2×1H: H1′ or H-1′′), 4.76, 4.57 (d, ^2J=11.7 Hz, 2×1H: H1′ or H-1′′), 4.34–4.30 (m, 2H: H-2, H-4), 4.20 (d, ^3J(H-1, H-7)=6.0 Hz, 1H: H-1), 4.18 (d, ^3J(OH, H-2′′′)=7.4 Hz, 1H: OH), 3.50 (m, 1H: H-3), 0.88 (s, 9H: (CH_3)$_3$CSi), 0.08, 0.00 (s, 2×1H: (CH_3)$_2$Si); ^{13}C NMR (100 MHz): 165.9 (C=O), 138, 136 (C quat. Ph), 130.9 (C-6), 128.8–127.5 (Ph), 127.3 (C-7), 82.4 (C-2), 81.4 (C-4), 75.8 (C-3), 75.4 (C-1), 73.3, 71.3 (C-1′, C-1′′), 72.3 (C-2′′′), 52.4 (C-5), 25.3 ((*C*H$_3$)$_3$CSi), 16.7 ((CH$_3$)$_3$*C*Si), −5.8 ((CH$_3$)$_2$Si); MS: *m/z* (%): 603 (M$^{+\cdot}$), 585, 494, 403.

3.10. (1S,2R,3R,4S,5R)-2,4-Dibenzyloxy-5-benzyloxycarbonylamino-3[(t-butyldimethylsilyl)oxy]-cyclohept-6-en-1-ol ***15***

This compound was synthesised according to the same procedure and on the same scale used for the racemic compound.[1b] Yield: 91%; $[\alpha]_D$=−23.7 (*c*=0.53, $CHCl_3$).

3.11. (2S,3R,4S,5R)-2,4-Dibenzyloxy-5-benzyloxycarbonylamino-3-[(t-butyldimethylsilyl)oxy]-cyclohept-6-en-1-one ***16***

This compound was synthesised according to the same procedure and on the same scale used for the racemic compound.[2b] Yield: 76%; $[\alpha]_D$=−98.5 (*c*=0.25, $CHCl_3$).

Table 2
Crystallographic data for **6a**, **6b** and (+)-**12**

Compound	**6a**	**6b**	**(+)12**
formula	$C_{15}H_{17}NO_3$	$C_{15}H_{17}NO_3$	$C_{27}H_{37}SiNO_4$
M_r	259.31	259.31	467.69
dimensions(mm)	0.34x0.34x0.34	0.22x0.30x0.30	0.30x0.30x0.34
crystal system	orthorhombic	monoclinic	quadratic
space group	$P2_12_12_1$	$P2_1$	$P4_1$
a(Å)	8.454(1)	8.967(2)	14.692(2)
b(Å)	10.930(1)	13.031(2)	
c(Å)	27.891(4)	11.485(2)	12.413(1)
β(°)		102.60(1)	
V(Å^3)	2577.22(91)	1309.70(79)	2679.20(76)
Z	4	4	4
ρ(g cm^{-3})	1.337	1.315	1.159
μ(mm^{-1})	0.9	0.9	10.0
F(000)	1104	552	1008
radiation	Mo Kα	Mo Kα	Cu Kα
λ(Å)	0.71073	0.71073	1.54184
$2\theta_{max}$(°)	60.0	60.0	120.0
h	-11 to 0	-12 to 0	0 to 15
k	-15 to 0	-18 to 0	0 to 16
l	-39 to 0	-15 to 16	0 to 13
data measured	4239	4200	2054
data observed for($F^2>3\sigma F^2$)	2237	3078	2047
refinement on	F	F	F
no. of parameters	479	479	446
R	0.041	0.032	0.032
R_ω	0.054	0.043	0.050
Flack parameter			0.03
S	1.04	1.03	1.27
max/min peaks (e/Å^3)	0.24(4) / -0.11(4)	0.19(3) / -0.11(3)	0.12(3) / 0.20(3)

*3.12. (2S,3R,4S,5R)-2,4-Dibenzyloxy-5-benzyloxycarbonylamino-3-hydroxycyclohept-6-en-1-one **17***

This compound was synthesised according to the same procedure and on the same scale used for the racemic compound.[2b] Yield: 85%; $[\alpha]_D=-104.4$ (c=0.51, $CHCl_3$).

3.13. (+)-Calystegine B_2

This compound was synthesised according to the same procedure as in the literature.[3b]

*3.14. X-Ray structure determination for **6a**, **6b** and (+)-**12***

Crystals suitable for X-ray diffraction were obtained from methanolic solutions of the compounds. Data were collected at 123±0.5 K on an Enraf Nonius CAD4 diffractometer. The crystal structures were solved and refined using the Enraf Nonius MOLEN package. Positional and isotropic temperature factors were refined for all hydrogen atoms in the final stages of least-squares analysis. Crystal data are assembled in Table 2.

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