Pergamon

Tetrahedron, Vol. 52, No. 48, pp. 15137-15146, 1996
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0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00948-9

General Access to Polyhydroxylated Nortropane Derivatives through Hetero Diels-Alder Cycloaddition. Part II : Synthesis of (±) Calystegine B2 §.

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Abstract : Calystegine **B2** was prepared by the intramolecular cyclisation of a polyhydroxylated 4-amino-cycloheptanone. This intermediate results from a heterocycloaddition between an acylnitroso compound and a cyclohepta-1,3-diene. The diene is in turn obtained from iron-complexed tropone.
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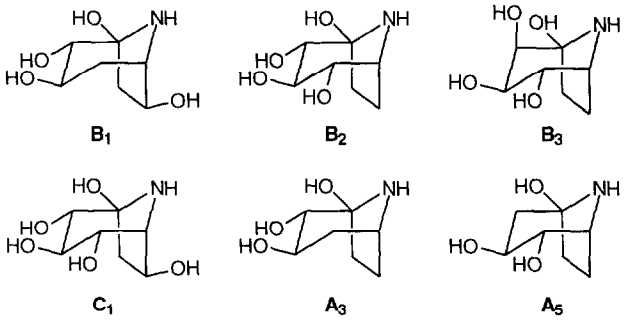
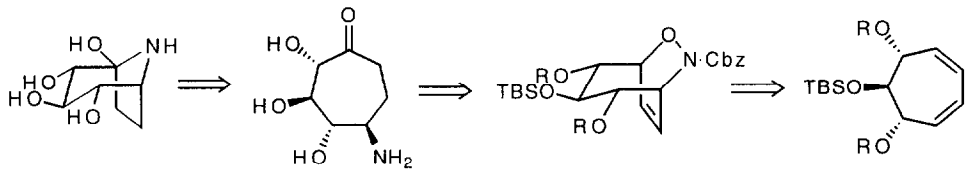
Calystegines are a new class of alkaloids having in common the nortropanic skeleton. To date six compounds have been isolated : calystegines **B1**, **B2** and **A3** from the roots of *Calystegia sepium*[2] and the leaves of *Morus bombycis*;[3a] more recently calystegines **B2** and **A3** from the leaves of *Solarum tuberosum*,[4] and very recently calystegines **C1**, **B3** and **A5** from *Physalis alkebengi*,[3b] and from *Atropa belladonna*.[3c] Calystegines **B2** and **A3** have been shown to exhibit an inhibitory activity of β-glycosidases comparable to that of castanospermine.[3b,3d,5]



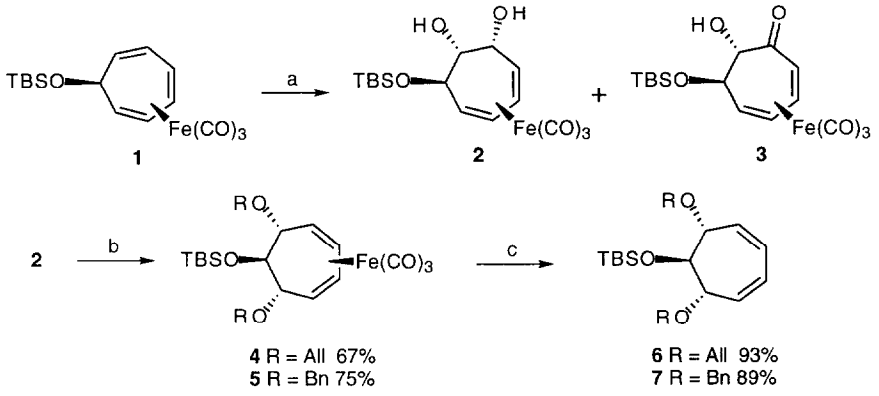
Optically pure calystegine **B2** has been synthesized from glucose.[6,7] However these later methods involve a large number of steps (≥ 17) and the overall yield is low. We describe here a different approach, relying on a hetero Diels-Alder reaction as the key step. This [4+2] cycloaddition involves the reaction of a nitroso group on a cycloheptadiene skeleton and allows the introduction of the amino and alcohol groups

§ Preliminary results concerning this work were presented at 5th B.O.S.S., Namur, 11-15 July 1994.

simultaneously and with the correct stereochemistry. This strategy makes possible the preparation of a variety of calystegines from a common intermediate. We have shown recently[1] the validity of this approach in the preparation of protected calystegine **B2**. This scheme has been re-examined in order to reach calystegine **B2** itself. These nortropane derivatives can be considered as deriving from substituted 4-aminocycloheptanone :



In the case of calystegines (**B2** or **A3** for instance) the cyclisation is instantaneous in basic medium and the polyhydroxylated 4-aminocycloheptanone cannot be isolated. The required cycloheptadiene for the hetero Diels-Alder step can be easily prepared by the method proposed by Pearson[9] with some modifications (scheme 1) :

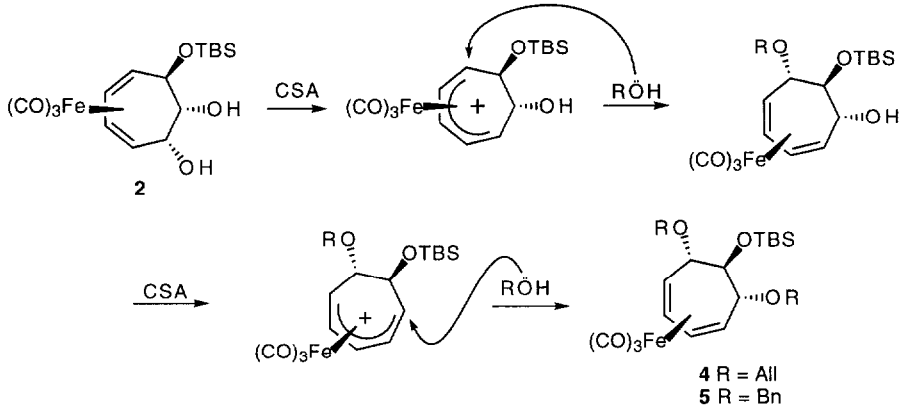


Scheme 1 : a : OsO_4 cat., NMO, acetone-water (9:1) ; b : $(RO)_2C(CH_3)_2$-acetone (1:1), CSA cat. ; c : $(CH_3)_3NO$, acetone.

Compound **1** resulting from reduction and protection of complexed tropone can be converted to the cis-diol by osmium tetraoxide. A catalytic procedure was used to avoid the formation of the higher oxidation product **3**. As in Pearson's method,[9a] the addition of *N*-methylmorpholine-*N*-oxide (NMO) was necessary[10] and the undesired ketol **3** was not detected by NMR. In the previous paper[1] we described the synthesis of the triol **6** from **2** with two oxygen atoms protected as allylethers. However, all methods to remove the allyl groups were unsuccessful.[8] We hoped to cleave them in one or two steps by isomerising the allylether to the corresponding propenyl ether, which is then hydrolysed. We decided to change the 1,3-diol protecting groups. The most appropriate group for this purpose would be the benzyl group which can be removed during the last step by hydrogenolysis.

Preparation of the dibenzylated cycloheptadiene 7

In Pearson's method[9a] the protective group is introduced during isomerization of the iron-complex. The complex **2**, treated by an alcohol in acidic media, under anhydrous conditions, gave exclusively complexes of type of **4** or **5**. The alcohol is produced *in situ* by acidic hydrolysis of 2,2-alkoxypropane in acetone solution. If the mechanism proposed by Pearson is correct, it should not be necessary to use a large excess of acetal as described. The experimental procedure used for methyl and allyl derivatives cannot be



employed in the case of benzyloxy derivatives due to the very high boiling point of the benzylic acetal [b.p.: 83°C (1 mmHg)]. Furthermore the excess of acetal is very difficult to eliminate, as its R_f in chromatography on silica gel is very near to the R_f's compounds **4** or **5**. In order to circumvent these various technical problems we studied the mechanism of this rearrangement varying the quantities of acetal *versus* those of iron-complex. The results of various attempts are reported in Table 1.

eq. of acetal	time	% isolated **5**	% isolated **2**
10	2h 30min	46	0
4	2h 30min	75	0
3	4h	55	10
2	4h	40	25
1	4h	35	25

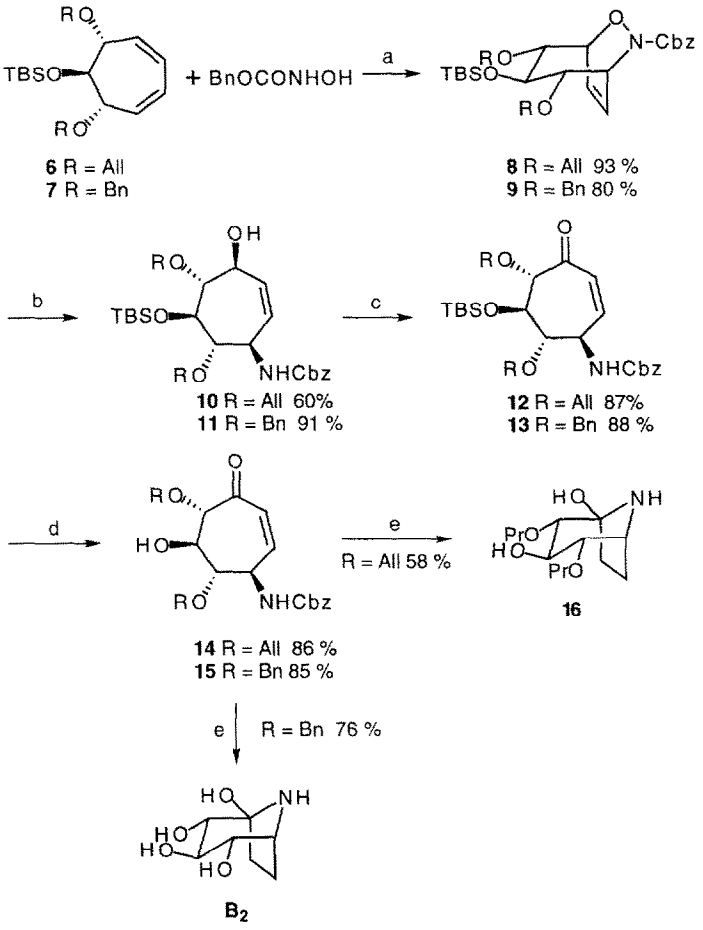
Table 1.

The most interesting observation consists in the fact that the use of 4 eq. of acetal is satifactory for our purpose. After 3h the yield decreased because of polymerisation of compounds **2** and **5**. These results are consistent with Pearson's mechanism.

Preparation of (±)-Calystegine B_2

From the protected compound **7** obtained in 75% yield from **5**, the chemistry used had already been

explored for the O-allyl protected intermediate. Benzyloxynitroso carbamate was prepared *in situ* by oxidation of the corresponding hydroxamic acid[14] with subsequent smooth cycloaddition to the diene. The reductive cleavage of the N-O bond can be achieved in several ways. In our hands the best method



Scheme 2 : a : $(n\text{-}C_4H_9)_4N,IO_4$, 0°C, CH_2Cl_2 ; b : $Mo(CO)_6$, MeCN-H_2O (9:1), reflux ;
c : PCC, CH_2Cl_2 ; d : MeCN-HF (95:5) ; e : H_2 , Pd/C 10%, MeOH.

involved the use of molybdenumhexacarbonyl (scheme 2).[13] The oxidation of compounds **10** and **11** was easily performed with pyridinium chlorochromate to give compounds **12** and **13** respectively. Treatment of compounds **12** and **13** with HF in acetonitrile led to the desilylated intermediates which were then subjected to hydrogenation ; after 4 days compound **15** led to calystegine **(±)-B2** in good yield (76%).

We are currently exploring the application of this promising approach to the enantioselective synthesis of different calystegines.

Experimental Section

NMR spectra were recorded on Bruker WP 200 and AM 400 spectrometers in $CDCl_3$. The chemical shifts of ^1H NMR signals δ are reported in ppm (TMS as internal standard, $\delta = 0$). Coupling constants J are reported in Hertz. The abbreviations s, d, t, q, p, m and br signify : singlet, doublet, triplet, quartet, quintet, multiplet and broad, respectively. The numbering sequence used for reporting NMR parameters is the same as indicated in reference 1.

IR spectra were recorded on a Perkin-Elmer using 1600 FT IR neat films on NaCl plates.

Low resolution mass spectra were recorded on a Ribermag R 10-10 B spectrometer under chemical ionization (NH_3) conditions, high resolution mass spectra were recorded on ZAB.HFQ.VG apparatus.

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. Tetrahydrofuran (THF) was distilled from sodium-benzophenone. Dichloromethane was distilled from P_2O_5. Commercially tropone was distilled prior use.

All reactions were monitored by thin layer chromatrography carried out on Merck silicagel plates (Ref. 5549) using 5 % ethanolic phosphomolybdic acid/heat as developing agent. Merck silicagel (Ref. 9384) was used for flash chromatography.

2,2-Diallyloxypropane was prepared by the method of Howard[11] using cyclohexane as solvent. b.p. : 62°C (18 mmHg); 78 % yield.

^1H NMR (200 MHz) : 1.42 (s); 4.01 (m); 5.15 (dd, J= 5.9, 2.0 Hz); 5.25 (dd, J= 8.5, 2.0 Hz); 5.87 (m). **^{13}C NMR** (50 MHz) : 24.9; 61.9; 100.2; 115.9; 135.2.

2,2-Dibenzyloxypropane was prepared by the method of Borkovec[12] using cyclohexane as solvent. b.p. : 140°C (1.5 mmHg); 77 % yield.

^1H NMR (200 MHz) : 1.58 (s); 4.64 (s); 7.39 (s). **^{13}C NMR** (50 MHz) : 25.2; 63.2; 100.8; 127.3; 127.4; 128.4; 138.9.

Benzyl *N*-hydroxycarbamate was prepared by the method of Streith.[14] The tricarbonyl[(2-5η)cyclohepta-2,4,6-trien-1-one]iron was prepared by the method of Rosenblum[15] using toluene as solvent.

Tricarbonyl[(1-4-η)-7-endo-(*t*-butyldimethyl)silyloxy-5,6-exo-dihydroxycyclohepta-1,3-diene]iron 2

To a stirred solution of 2.5 g (6.9 mmol) of **1** in 50 mL of a mixture acetone-water (4:1) were added, at 0°C, 6 mL of a freshly prepared solution 0.04 M OsO_4 in *t*-butanol stabilized with *t*-butyl hydroperoxide and 1.1 g of NMO (7.9 mmol). The reaction mixture was stirred, at room temperature, for 50 h. Then a saturated sodium bisulfite solution (50 mL) was added, the mixture was stirred for 2 h, diluted with 50 mL of ethyl acetate. After filtration through Celite, extraction with ethyl acetate (2x50 mL), the organic layer was washed with 2x50 mL of brine, dried over magnesium sulfate, filtered, the solvents were removed under reduced pressure, and the crude product was purified by flash chromatography (ethyl acetate-cyclohexane : 30:70) to give 2.3 g of compound **2** ; 84 % yield, mp : 142 °C (litt.[9] : 74%; mp : 140-142°C).

Tricarbonyl[(1-4-η)-6-endo-(*t*-butyldimethyl)silyloxy-5,7-exo-diallyloxycyclohepta-1,3-diene]iron 4

To a stirred solution of 1.35 g (3.4 mmol) of **2** in 140 mL of a mixture acetone-2,2-diallyloxypropane (1:1) was added 0.45 g (1.9 mmol) of camphorsulfonic acid. The reaction mixture was stirred, at room temperature, for 2 h 30 min and diluted with 300 mL of ether. The organic layer was washed with 0.1 N sodium hydroxyde, then with water (2x80 mL), and dried over magnesium sulfate ; the solvents were removed under reduced pressure. The excess of 2,2-diallyloxypropane was distilled under reduced pressure (2.5 mmHg) at 25°C. The residue was purified by flash chromatography (ethyl acetate-cyclohexane : 10:90) to give 1.3 g of compound **3** ; 80 % yield.

^{1}H NMR (200 MHz) : 5.99-5.83 (m, $H_{2'}$, $H_{2''}$); 5.38-5.34 (m, H_2, H_3); 5.24-5.11 (m, $H_{3'}$, $H_{3''}$); 4.07-4.04 (m, H_5, H_6, H_7); 3.99-3.96 (m, $H_{1'}$, $H_{1''}$); 2.63 (m, H_1, H_4); 0.90 (s, $(CH_3)_3CSi$); 0.10 (s, $(CH_3)_2Si$). **^{13}C NMR** (50 MHz) : 210.0 (CO); 135.3 ($C_{2'}$,$C_{2''}$); 117.4 ($C_{3'}$,$C_{3''}$); 86.6 (C_2,C_3); 82.7 (C_5,C_7); 74.4 (C_6); 71.7 (C_1,C_4); 55.5 ($C_{1'}$,$C_{1''}$); 25.9 ($(\underline{C}H_3)_3CSi$); 18.0 ($(CH_3)_3\underline{C}Si$); -4.2 $(CH_3)_2Si$. **IR** ν_{max} : 3081, 1982; 1647; 1255; 1099; 1037; 869.

Tricarbonyl[(1-4-η)-6-endo-(*t*-butyldimethyl)silyloxy-5,7-exo-dibenzyloxycyclohepta-1,3-diene]iron 5

To a stirred solution of 2 g (5.1 mmol) of **2** in 5 mL of acetone was added 5.1 mL of 2,2-dibenzyloxypropane (4 eq.), then 0.62 g (2.9 mmol) of camphorsulfonic acid. The mixture was stirred, at room temperature, for 2 h 30 min and after diluted with 150 mL of ether. The organic layer was washed with 0.1 N sodium hydroxyde, then with water (2x40 mL), dried over magnesium sulfate; the solvents were removed under reduced pressure. The residue was purified by flash chromatography (ethyl acetate-cyclohexane : 5:95) to give 1.7 g of compound **5** ; 75 % yield.

^{1}H NMR (200 MHz) : 7.40-7.34 (m, C_6H_5); 4.35 (dd, *J*= 5.9, 2.6 Hz, H_2, H_3); 4.63 (AB, $CH_2C_6H_5$); 3.65 (dd, *J*= 8.7, 1.5 Hz, H_5, H_7); 3.07 (t, *J*= 8.7 Hz, H_6); 2.76 (ddd, *J*= 5.9, 2.6, 1.5 Hz, H_1, H_4); 1.03 (s, $(CH_3)_3CSi$); 0.19 (s, $(CH_3)_2Si$). **^{13}C NMR** (50 MHz) : 210.3 (CO); 138.9-127.7 (C_6H_5); 88.8 (C_2, C_3); 83.8 (C_5, C_7); 74.8 (C_6); 73.0 ($CH_2C_6H_5$); 56.1 (C_1, C_4); 26.3 ($(\underline{C}H_3)_3CSi$); 18.4 ($(CH_3)_3\underline{C}Si$); -3.9 ($(CH_3)_2Si$). **IR** ν_{max} : 3031, 2050, 1976, 1252, 1054, 858. **MS** m/z : M-84 $(Fe(CO)_3)$: 436.

(5RS,7SR)-5,7-diallyloxy-6-(*t*-butyldimethyl)silyloxycyclohepta-1,3-diene 6

To a stirred solution of 1.3 g (2.7 mmol) of **4** in 30 ml of anhydrous acetone, were added 2.7 g (37 mmol) of anhydrous trimethylamine-N-oxide, at room temperature. The reaction mixture was stirred for 4 h, filtered through Celite, and the Celite pad washed with ether (2x50 mL). The solvents were removed under reduced pressure, the crude product was purified by flash chromatography (ethyl acetate-cyclohexane : 10:90) to give 0.8 g of compound **5** ; 70 % yield.

^{1}H NMR (200 MHz) : 5.92-5.88 (m, H_1, H_2, H_3, H_4, $H_{2'}$, $H_{2''}$); 5.12, 5.30 (dd, *J*= 17.2, 1.7 Hz, $H_{3'}$, $H_{3''}$); 4.04, 4.08 (m, $H_{1'}$, $H_{1''}$); 3.93-3.95 (m, H_5, H_6, H_7); 0.92 (s, $(CH_3)_3CSi$); 0.11 (s, $(CH_3)_2Si$). **^{13}C NMR** (50 MHz) : 135.3 ($C_{2'}$ $C_{2''}$); 132.9, 126.9 (C_1, C_2, C_3, C_4); 116.7 ($C_{3'}$, $C_{3''}$); 80.9 (C_6); 80.6 (C_5, C_7); 71.1 ($C_{1'}$, $C_{1''}$); 26.1 ($(\underline{C}H_3)_3CSi$); 18.4 ($(CH_3)_3\underline{C}Si$); -4.3 ($(CH_3)_2Si$). **IR** ν_{max} : 3080; 3018; 1647; 1252; 1077; 837. **MS** m/z : $M^{+\bullet}$: 336.

(5RS,7SR)-5,7-dibenzyloxy-6-(*t*-butyldimethyl)silyloxycyclohepta-1,3-diene 7

This compound was synthetized according to the same procedure and on the same scale used for compound **6** ; 89 % yield.

^{1}H NMR (200 MHz) : 7.48-7.37 (m, C_6H_5); 6.13-6.05 (m, H_1, H_2, H_3, H_4); 4.70 (AB, $CH_2C_6H_5$); 4.30 (t, *J*= 7.0 Hz, H_6); 4.16 (dd, *J*= 11.9, 3.9 Hz, H_5, H_7); 1.03 (s, $(CH_3)_3CSi$); 0.19 (s, $(CH_3)_2Si$). **^{13}C NMR** (50 MHz) : 138.9-127.7 (C_6H_5); 133.3, 126.7 (C_1, C_2, C_3, C_4); 80.9 (C_6); 80.6 (C_5, C_7); 71.1 ($CH_2C_6H_5$); 26.1 (($\underline{C}H_3)_3CSi$); 18.4 ($(CH_3)_3\underline{C}Si$); -4.4 ($(CH_3)_2Si$). **IR** ν_{max} : 3080, 3019, 1647, 1252, 1077, 837. **HRMS** calculated for $C_{27}H_{36}O_3Si$: 436.2433, found : 436.2432.

(1RS,2SR,3RS,4RS,5SR)-2,4-diallyloxy-7-benzyloxycarbonyl-3-(*t*-butyldimethyl)silyl-oxy-6-oxa-7-azabicyclo[3.2.2]non-8-ene 8

To a stirred solution of 2.7 g (8 mmol) of **6** and 4 g (9.2 mmol) of tetrabutylammonium periodate in 15 mL of anhydrous dichloromethane were added slowly a solution of 1.5 g (9 mmol) of benzyloxyhydroxamic acid in 1 mL of anhydrous dichloromethane at 0°C. After stirring for 1h at 0°C and 2h at room temperature, 200 mL of ether were added. The organic layers were washed with 30 mL of 1N sodium carbonate, then with 30 mL of 0,5N sodium sulfite and dried over magnesium sulfate. The solvents were removed under reduced pressure, the residue was purified by flash chromatography (ethyl acetate-cyclohexane : 20:80) to give 2.1 g of compound **8** ; 93 % yield. For spectroscopic and analytical data, see ref. 1.

(1RS,2SR,3RS,4RS,5SR)-2,4-dibenzyloxy-7-benzyloxycarbonyl-3-(*t*-butyldimethyl)-silyloxy-6-oxa-7-azabicyclo[3.2.2]non-8-ene 9

This compound was synthetized according to the same procedure and on the same scale used for compound **8** ; 80 % yield.

^{1}H NMR (200 MHz) : 7.40-7.27 (m, C_6H_5); 6.44-6.36 (m, H_8, H_9); 5.26 (AB, CH_2 carbamate); 4.95 (br s, H_1); 4.77-4.64 (m, H_5, $CH_2C_6H_5$); 3.63-3.54 (m, H_2, H_3, H_4); 0.90 (s, $(CH_3)_3CSi$); 0.04 (s, $(CH_3)_2Si$). **^{13}C NMR** (50 MHz) : 155.9 (CO); 127.6-128.7 (C_8, C_9, aromatic C); 83.6, 82.4 (C_2, C_4); 76.1 (C_3); 73.1,73.0, 72.5 (C_1',C_1",C_5); 68.1 (CH_2 carbamate); 53.7 (C_1); 26.1 (($\underline{C}H_3)_3CSi$); 18.3 ($(CH_3)_3\underline{C}Si$); -4.1 $(CH_3)_2Si$. **IR** ν_{max} : 1701, 1252, 1080, 836. **Anal. Calc.** for $C_{35}H_{43}NO_6Si$ C : 69.85; H : 7.20; N : 2.33, Found : C : 69.66; H : 7.29; N : 2. 27.

(1SR,4RS,5SR,6RS,7RS)-5,7-diallyloxy-4-(benzyloxycarbonylamino)-6-(*t*-butyl-dimethyl)silyloxycyclohep-2-enol 10

A mixture of 3 g (9.3 mmol) of adduct **8**, 2.45 g (9.3 mmol) of $Mo(CO)_6$, 80 mL of acetonitrile and 6 mL of water was heated under reflux during 9 h, 6 g of silicagel were added to the mixture and the solvent was removed under reduced pressure ; the residue was purified by flash chromatography (ethyl acetate-cyclohexane : 40:60) to give 1.8 g of compound **10** ; 60 % yield.

^{1}H NMR (400 MHz) : 7.37-7.32 (m, C_6H_5); 5.92 (m, H_2',H_2"); 5.86 (d, *J*= 7.0 Hz, H_3); 5.7 (m, NH, H_2); 5.31(m, H_3', H_3", OH); 5.11 (s, $CH_2C_6H_5$); 4.58 (m, H_1); 4.55 (m, H_4); 4.32 (m, H_1', H_1"); 4.08 (m, H_6); 3.60 (dd, *J*= 4.8, 2.9 Hz, H_7); 3.36 (dd, *J*= 9.5, 6.5 Hz, H_5); 0.90 (s, $(CH_3)_3CSi$); 0.18 (s, $(CH_3)_2Si$). **^{13}C NMR** (100 MHz) : 155.8 (CO); 136.7 (C_3); 134.6, 134.4 (C_2', C_2"); 128.6, 128.1

(C_6H_5); 125.5 (C_2); 117.4, 117.1 ($C_{3'}$, $C_{3''}$); 88.2, 79.7, 75.5 (C_5, C_6, C_7); 74.6, 71.2 ($C_{1'}$, $C_{1''}$); 67.9 (C_1); 50.6 (C_4); 26.0 (($\underline{C}H_3)_3C$); 17.9 ($(CH_3)_3\underline{C}$); -4.2 ($(CH_3)_2Si$). **IR** ν_{max} : 3396, 3032, 1720, 1251, 1078, 1044, 837.

(1RS,4SR,5RS,6SR,7SR)-5,7-dibenzyloxy-4-(benzyloxycarbonylamino)-6-(*t*-butyldimethyl)silyloxycyclohept-2-enol 11

This compound was synthetized according to the same procedure and on the same scale used for compound **10** ; 91% yield.

^{1}H NMR (400 MHz) : 7.39-7.27 (m, C_6H_5); 5.87 (d, *J*= 12.0 Hz, H_2); 5.73 (m, H_3, NH); 5.12 (s, CH_2 carbamate); 4.89, 4.70 (d, *J*= 11.0 Hz, $CH_2C_6H_5$); 4.65, 4.53 (d, *J*= 11.5 Hz, $CH_2C_6H_5$); 4.60-4.80 (m, H_1); 4.18-4.21 (ddd, *J*= 6.6, 2.9, 1.0 Hz, H_6); 3.70-3.68 (dd, *J*= 4.3, 3.1 Hz, H_5); 3.57-3.53 (dd, *J*= 9.6, 6.6 Hz, H_7); 3.70-3.68 (m, H_5); 2.57 (d, *J*= 1.7 Hz, OH); 0.88 (s, $(CH_3)_3C$); 0.10 (s, $(CH_3)_2Si$). **^{13}C NMR** (100 MHz) : 155.8 (CO); 134.3 (C_3); 125.4 (C_2); 128.0-127.0 (C_6H_5); 88.9 (C_7); 79.6 (C_5); 78.6 (C_6); 75.6, 72.0 ($CH_2C_6H_5$); 67.9 (C_1); 67.0 ($O\underline{C}H_2C_6H_5$); 50.4 (C_4); 25.9 (($\underline{C}H_3)_3CSi$); 17.9 ($(CH_3)_3\underline{C}Si$); -4.3 ($(CH_3)_2Si$). **IR** ν_{max} : 3787, 3404, 3066, 3032, 1724, 1252, 1081, 1044, 836. **MS** m/z : MH^+ : 604.

(4RS,5SR,6RS,7SR)-5,7-diallyloxy-4-(benzyloxyamino)-6-(*t*-butyldimethyl)silyloxycyclohept-2-enone 12

A solution of 0.9 g (1.85 mmol) of **10**, 2.3 g (10.7 mmol) of pyridinium chlorochromate and 2.2 g of Celite in 30 mL of dichloromethane was stirred at room temperature during 17h. After elimination of solvents under reduced pressure, the crude product was purified by flash chromatography (ethyl acetate-cyclohexane : 20:80) to give 0.8 g of ketone **12** ; 87 % yield.

^{1}H NMR (400 MHz) : 7.35 (m, C_6H_5); 6.52 (dd, *J*= 12.2, 6.0 Hz, H_3); 6.30 (d, *J*= 6.5, NH); 6.06 (d, *J*= 12.0 Hz, H_2); 5.95-5.73 (m, $H_{2'}$, $H_{2''}$); 5.29-5.22 (m, $H_{3'}$, $H_{3''}$); 5.21-5.16 (m, $CH_2C_6H_5$); 4.78 (m, H_4); 4.16 (d, *J*= 6.0 Hz, H_7); 4.13-3.88 (m, $H_{1'}$, $H_{1''}$, H_6); 3.70 (dd, *J*= 5.5, 3.5 Hz, H_5); 0.90 (s, $(CH_3)_3CSi$); 0.16 (s, $(CH_3)_2Si$). **^{13}C NMR** (100 MHz) : 196.2 (CO); 156.0 (NH-CO); 139.5 (C_3); 130.2 (C_2); 134.2, 133.9 ($C_{2'}$, $C_{2''}$); 117.9, 117.8 ($C_{3'}$, $C_{3''}$); 89.3, 78.9, 77.7 (C_7, C_6, C_5); 71.9, 71.3 ($C_{1'}$, $C_{1''}$); 67.2 ($COO\underline{C}H_2$); 52.2 (C_4); 25.8 (($\underline{C}H_3)_3CSi$); 18.0 ($(CH_3)_3\underline{C}Si$); -4.5 ($(CH_3)_2Si$). **IR** ν_{max} : 3371, 3066, 3032, 1725, 1703, 1252, 1096, 837. **Anal. Calc.** for $C_{27}H_{39}O_6NSi$ C : 64.64; H : 7.84; N : 2.89. Found C : 64.44; H : 7.83; N : 2.82.

(4RS,5SR,6RS,7SR)-5,7-dibenzyloxy-4-(benzyloxycarbonylamino)-6-(*t*-butyldimethyl)-silyloxycyclohept-2-enone 13

This compound was synthetized according to the same procedure and on the same scale used for compound **12** ; 88% yield.

^{1}H NMR (400 MHz) : 7.20-7.40 (m, C_6H_5); 6.50 (dd, *J*= 12.1, 5.7 Hz, H_3); 6.10 (d, *J*= 12.1, H_2); 6.20 (d, *J*= 6.7 Hz, NH); 5.12 (s, CH_2carbamate); 4.54, 4.51 (d, *J*= 12.0 Hz, $CH_2C_6H_5$); 4.83 (m, H_4); 4.66, 4.35 (d, *J*= 11.0 Hz, $CH_2C_6H_5$); 4.21 (d, *J*= 5.8 Hz, H_7); 4.17 (dd, *J*= 4.0, 3.5 Hz, H_5); 3.75 (dd, *J*= 5.8, 3.5 Hz, H_6); 0.90 (s, $(CH_3)_3CSi$); 0.05 (s, $(CH_3)_2Si$). **^{13}C NMR** (100 MHz) : 195.5 (CO); 156.0 (NH-CO); 137.0-127.0 (C_6H_5); 139.9 (C_3); 128.5 (C_2); 89.1 (C_7);79.0, 76.5 (C_5,C_6);

72.7, 72.2 ($CH_2C_6H_5$); 67.1 (CH_2carbamate); 51.9 (C_4); 25.7 (($\underline{C}H_3)_3CSi$); 17.8 (($CH_3)_3\underline{C}Si$); -4.7 (($CH_3)_2Si$). **IR** ν_{max} : 3389, 3090, 3066, 3033, 1727, 1707, 1258, 1095, 838.

(4RS,5SR,6RS,7SR)-5,7-diallyloxy-4-(benzylcarbonylamino)-6-hydroxycyclohept-2-enone 14

0.03 g (0.06 mmol) of **12** were stirred, at room temperature, during 7 h in 1 mL of CH_3CN-HF mixture (95:5). After concentration the crude product was purified by flash chromatography (ethyl acetate-cyclohexane : 50:50) to give 0.2 g of compound **14** ; 86 % yield.

^{1}H NMR (400 MHz) : 7.40-7.35 (m, C_6H_5); 6.60 (dd, *J*= 12.0, 4.5 Hz, H_3); 6.08 (d, *J*= 12.0 Hz, NH); 5.96-5.75 (m, H_2', H_2"); 5.31-5.14 (m, H_3',H_3", $CH_2C_6H_5$); 4.77 (dd, *J*= 12.0, 5.5 Hz, H_4); 4.20-3.90 (m, OCH_2, H_7, H_6); 3.79 (dd, *J*= 10, 5.5 Hz, H_5); 2.87 (br s, OH). **^{13}C NMR** (100 MHz) : 198.0 (CO); 157.0 (CO carbamate); 141.9 (C_3); 133.8 (C_2'); 128.6 (C_2); 118.4, 117.9 (C_3'); 138.0-128.0 (C_6H_5); 87.8 (C_7); 79.3 (C_5); 75.4, 75.7 (OCH_2); 67.2 ($CH_2C_6H_5$). **IR** ν_{max} : 3575, 3386, 3085, 3060, 3030, 1724, 1705, 1093.

(4RS,5SR,6RS,7SR)-5,7-dibenzyloxy-4-(benzyloxycarbonylamino)-6-hydroxycyclohept-2-enone 15

This compound was synthetized according to the same procedure and on the same scale used for compound **14** ; 85 % yield.

^{1}H NMR (400 MHz) : 7.40-7.20 (m, C_6H_5); 6.64 (dd, *J*= 12.3, 4.5 Hz, H_3); 6.10 (d, *J*= 12.3 Hz, H_2); 5.73(d, *J*= 5.7 Hz, NH); 5.12 (s, CH_2 carbamate); 4.80 (m, H_4); 4.73, 4.35 (d, *J*= 11.2 Hz, $CH_2C_6H_5$); 4.62-4.54 (d, *J*= 11.7 Hz, $CH_2C_6H_5$); 4.27 (d, *J*= 5.9 Hz, H_7); 4.16 (m, H_6); 3.80 (m, H_5); 2.60 (d, *J*= 3.2 Hz, OH). **^{13}C NMR** (100 MHz) : 197.0 (CO); 156.2 (CO carbamate); 142.9 (C_3); 129.5 (C_2); 137.0-127.0 (C_6H_5); 87.9 (C_7); 80.4 (C_6); 75.4 (C_5); 73.0 (OCH_2); 67.3 (OCH_2 carbamate); 52.4 (C_4). **IR** ν_{max} : 3587, 3400, 3090, 3066, 3033, 1724, 1704, 1094.

(1RS,2SR,3RS,4SR,5RS)-2,4-dipropylyloxy-8-azabicyclo[3.2.1]octan-1,3-diol 16

A solution of 0.06 g of **12** (0.12 mmol) in methanol (20 mL) with 10% palladium on charcoal was stirred, at room temperature, under a hydrogen atmosphere for 12 hours. After filtration of the catalyst and concentration, the crude product **16** was purified by flash chromatography (ethyl acetate-cyclohexane : 40:60) to give 0.22 g of compound **16** ; 58% yield. For spectroscopic and analytical data, see ref.1.

(±)-Calystegine B_2 (1RS,2SR,3RS,4SR,5RS)-8-azabicyclo[3.2.1]octane-1,2,3,4-tetrol

A solution of 0.128 g of **14** (0.123 mmol) in a mixture of acetic acid (3 mL) and water (3 mL) with 10% palladium on charcoal was stirred, at room temperature, under a hydrogen atmosphere for 4 days. The suspension was filtered through Celite and the resulting solution was neutralised with concentrated ammonium hydroxyde at -15°C, then diluted by water and concentrated under reduced pressure. The residue was purified on Dowex 50 (H^+) and eluted with 1N ammonium hydroxyde to give finally 0,035 g of Calystegine **B_2** ; 76% yield. Spectroscopic and analytical data were in good agreement with those reported in references 2, 6 and 3.

Acknowledgement: We wish to thank Dr A. Goldmann (I.N.R.A. Versailles) for her advice and help concerning purification of Calystegine $\mathbf{B_2}$.

References

1 Part I : Soulié, J.; Betzer, J.-F.; Muller, B. and Lallemand, J.-Y. *Tetrahedron Lett.* **1995**, *52*, 9485-9488.

2 Goldmann, A.; Milat, M.L.; Ducrot, P.H.; Lallemand, J.-Y.; Maille, M.; Lepingle, A.; Charpin, I. and Tepfer, D. *Phytochemistry* **1990**, *29*, 2125-2127. Ducrot, P.H. and Lallemand, J.-Y. *Tetrahedron Lett.* **1990**, *31*, 3879-3882.

3 a: Asano, N.; Oseki, K.; Tomioka, E.; Kizu, H. and Matsui, K. *Carbohydrate Res.* **1994,** *259*, 243-255. b: Asano, N.; Kato, A.; Oseki, K.; Kizu, H. and Matsui, K. *Eur. J. Biochem.* **1995**, *229*, 369-376. c: Dräger, B. *Phytochem. Anal.* **1995**, *6*, 31-37. d: Asano, N.; Tomioka, E.; Kizu, H. and Matsui, K. *Carbohydrate Res.* **1994**, *253*, 235-245.

4 Nash, R.J.; Rothschild, M.; Porter, E.A.; Watson, A.A.; Waigh, R.D. and Waterman, P.G. *Phytochemistry* **1993**, *34*, 1281-1283.

5 Molyneux, R.J.; Pan, Y.T.; Goldmann, A.; Tepfer, D. and Elbein, A.D. *Arch. Biochem. Biophys.* **1993**, *304*, 81-88. Molyneux, R.J.; McKenzie, R.A.; O'Sullivan, B.M. and Elbein, A.D. *J. Nat. Prod.* **1995**, *58*, 878-886.

6 Duclos, O.; Mondange, M.; Duréault, A. and Depezay, J.-C. *Tetrahedron Lett.* **1992**, *33*, 8061-8064.

7 Boyer, F.D. and Lallemand, J.-Y. *Synlett* **1992**, 969-972. Boyer, F.D. and Lallemand, J.-Y. *Tetrahedron* **1994**, *50*, 10443-10458.

8 Boss, R. and Scheffold, R. *Angew. Chem. Int. Engl.* **1976**, *15*, 558-559. Gigg, J.; Gigg, R. *J. Chem. Soc. C* **1966** , 82-86. Corey, E.J. and Suggs, J.W. *J. Org. Chem.* **1973**, *38*, 3224. Mereyala, H.B. and Guntha, S. *Tetrahedron Lett.*, **1970**, *33* , 2885-2888. Gigg, R. and Warren,C. *J. Chem. Soc. C* **1968**, 1903-1911.

9 a: Pearson, A.J. and Srinivasan, K. *J. Org. Chem.* **1992**, *57*, 3965-3973; b: Pearson, A.J. and Srinivasan, K. *J. Chem. Soc., Chem. Commun.*, **1991**, 392-394.

10 VanRheenen, V.; Kelly, R.C. and Cha, D.Y. *Tetrahedron Lett.* **1976**, *23*, 1973-1976.

11 Lorette, N.B. and Howard, W.L. *J. Org. Chem.* **1960**, *25*, 521-525.

12 Borkovec, A.B. *J. Org. Chem.* **1961**, *26*, 4866-4868.

13 Cicchi, S.; Goti, A.; Guarna, A. and De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351-3354.

14 Defoin, A.; Pires, J. and Streith, J. *Helv. Chim. Acta* **1991**, *74*, 1653-1670.

15 Rosenblum, M. and Watkins, J.C. *J. Am. Chem. Soc.* **1990**, *112*, 6316-6322.

(*Received in Belgium* 29 *July* 1996; *accepted* 15 *October* 1996)