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Access to Polyhydroxylated Cycloheptane Derivatives through Stereoselective Nitrile Oxide Intramolecular Cycloaddition. Synthesis of an Analogue of Calystegine B2

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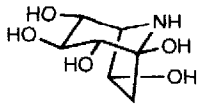
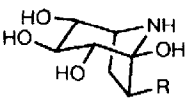
Abstract : A hydroxymethyl substituted calystegine B_2 has been synthesized stereoselectively by intramolecular cycloaddition of an olefinic nitrile oxide derived from D-glucose.

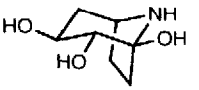
Calystegines B_1, B_2, A_3 are new alkaloids of the tropane family, isolated from the roots of *calystegia sepium* ; they might act as nutritional mediators of specific plant-bacterium relationships[1].



B_1



R=H **B_2**
R=CH_2OH **10**



A_3

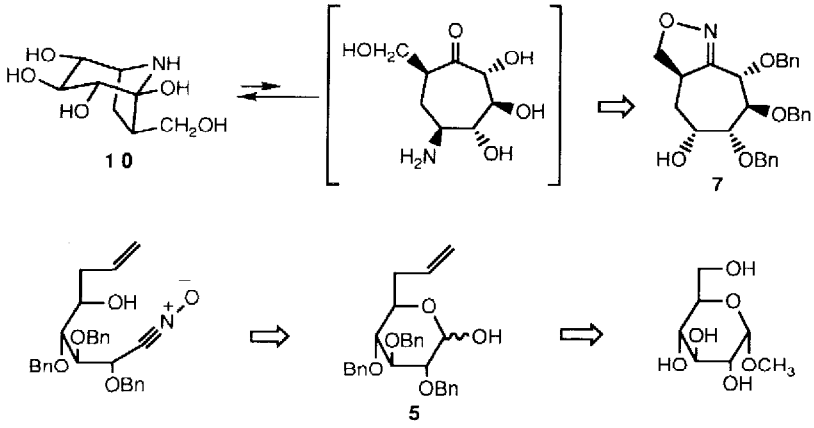
Chemical syntheses of the enantiomerically pure calystegines and of analogues are useful for biological tests[1] and also to confirm the recently spectroscopically established structure of calystegines[2].

Calystegines, polyhydroxylated nortropanes, present an hemiaminoketal function at the bridgehead position. They exist only as bicyclic compounds in the chair conformation but, as previously noticed[3], the formation of the 1-hydroxy nortropane skeleton could result from the intramolecular cyclization of the corresponding 5-aminocycloheptanone.

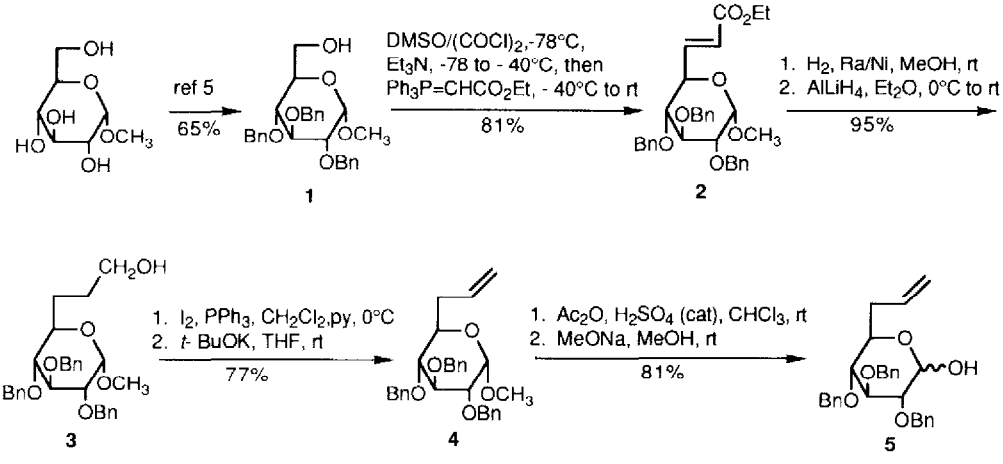
We report here, starting from D-glucose, the stereoselective synthesis of an analogue of calystegine B_2, **10**, which contains as additional asymmetric center the carbon C-7 (of *S* configuration) substituted by an hydroxymethyl group. The key step of the synthesis is the formation of a highly functionalized seven membered carbocycle presenting a masked carbonyl function, by the intramolecular olefinic nitrile oxide cycloaddition.

Recently the intramolecular cycloaddition into isoxazolines of olefinic nitrile oxides derived from sugars has been applied to the synthesis of hydroxylated aminocyclopentane and cyclohexane derivatives[4], but there was till now no example of the synthesis of a highly hydroxylated cycloheptane derivative from an eightcarbon olefinic aldehyde.

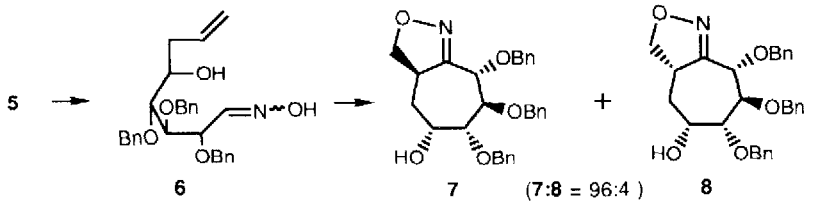
The synthesis of **10** was carried out, starting from α-D-methylglucoside according to the following retrosynthetic scheme



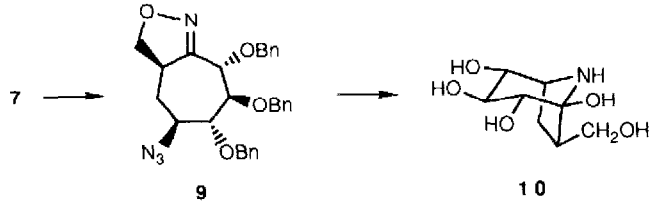
Our synthesis began with the preparation of the olefinic aldehyde **5** starting from alcohol **1**. **1** was readily available from α-D-methylglucoside[5] (yield 65% in our hands). A one pot two-step reaction led to the ethylenic ester **2**[6] in 81% yield, which was completely reduced into the saturated alcohol **3**[6] in 95% yield. The iodination of **3** was followed by an elimination leading to the olefinic pyranoside **4**[6] in 77% yield. **4** was thus prepared in 59% overall yield from **1** (this four-step sequence is easily carried out starting from 10g of **1**). The acetolysis of **4** led to the 6-deoxy-6-vinyl-D-glucopyranose **5**[6] in 81% yield



Pyranose **5** was converted into the oximes **6**[6] in 94% yield by treatment with NH_2OH,HCl and CH_3ONa in refluxing methanol for 3h. Intramolecular cycloaddition was best realized by using 1.75 M aq.NaOCl in CH_2Cl_2 at 20°C for 20h to afford the isoxazoline **7**[6] in 50% yield and 3% of the isoxazoline **8**[6], besides 16% of the recovered oximes. The stereochemistry of 7 was assigned on the basis of ^1H NMR spectral data and of NOE difference experiments[7]. The diastereoselectivity is rationalized by assuming a syn periplanar unfavorable interaction between the forming isoxazoline and the pseudo axial hydroxy group at C-5 in the transition state leading to **8.**



Nitrogen introduction at C-5 with configuration inversion resulted from zinc azide mediated Mitsunobu subtitution[8] by $ZnN_6.2py$ in the presence of the PPh_3-diisopropyl azodicarboxylate couple at 20°C for 1h leading to **9**[6] in 79% yield. Total hydrogenolysis of **9** on Pd black in 80% aqueous acetic acid for three days at 20°C followed by SiO_2 column chromatography led to the enantiomerically pure hydroxymethyl calystegine B_2 **10**[6] in 45% yield, besides some deoxygenated products.



The structure of natural calystegine B_2 has been recently elucidated through ^1H and ^{13}C NMR studies[2]. The structure and the enantiomeric purity of **10** were confirmed by its ^1H and ^{13}C NMR data which showed in particular, a close analogy with the spectroscopic data of calystegine B_2.

Our work is at present focused on the synthesis of the nonsubstituted calystegine B_2 and on the application of this synthetic strategy for the construction of related substances.

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6. All new compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means and elemental analyses. Melting points, optical rotations, significant ^1H and ^{13}C NMR (250 Mz) spectral data [$\delta(CDCl_3)$] are the following; **2** : mp 59°C, $[\alpha]_D$ +74 (*c* 1.05, CH_2Cl_2) ; δ: 3.22 (dd, 1H, $J_{4,3}=J_{4,5}=9.5$ Hz, H-4) ; 3.34 (S, 3H, OCH_3) ; 3.51 (dd, 1H, $J_{2,3}=9.5$ Hz, $J_{2,1}=3.5$ Hz, H-2) ; 4.0 (dd, 1H, H-3) ; 4.25 (ddd, 1H, H-5); 4.59 (d, 1H, H-1) ; 6.1 (dd, 1H, $J_{7,5}=1.5$ Hz, $J_{7,6}=15.5$ Hz, H-7) ; 7.02 (dd, 1H, $J_{6,5}=5$ Hz, H-6). **3** : mp 98°C, $[\alpha]_D$ +54 (*c* 0.94, CH_2Cl_2)]. **4** : $[\alpha]_D$ +41 (*c* 1.25, CH_2Cl_2) ; δ: 2.19 (ddd, 1H, $J_{6,6'}=15$ Hz, $J_{6,5}=J_{6,7}=7.5$ Hz, H-6) ; 2.56 (m, 1H, H-6') ; 3.23 (dd, 1H, $J_{4,3}=J_{4,5}=9.5$ Hz, H-4) ; 3.35 (s, 3H, OCH_3) ; 3.51 (dd, 1H, $J_{2,3}=10$ Hz, $J_{2,1}=3.5$ Hz, H-2) ; 3.67 (ddd, 1H, $J_{5,6'}=3$ Hz, $J_{5,7}=7.5$ Hz, H-5) ; 3.96 (dd, 1H, H-3) ; 4.55 (d, 1H, H-1) ; 5.06 (m, 1H, $J_{8,7}=9$ Hz, H-8) ; 5.08 (m, 1H, $J_{8',7}=17$ Hz ; H-8') ; 5.82 (m, 1H, H-7). **5** : [α/β : 60/40, mp 99°C, $[\alpha]_D$ +18 (*c* 1.01, CH_2Cl_2)]. **6** : (E/Z:60/40) ; δ: 6.95 (d, 0.4H, $J_{1,2}=6.5$ Hz, H-1, Z-isomer) ; 7.46 (d, 0.6H, $J_{1,2}=7.5$ Hz, H-1, E-isomer). **7** : $[\alpha]_D$ -14 (*c*1.02, CH_2Cl_2) ; δ: 1.62 (ddd, 1H, $J_{6,5}=3$ Hz, $J_{6,6'}=14$Hz, $J_{6,7}=2$Hz, H-6) ; 2.14 (ddd, 1H, $J_{6',5}=J_{6',7}=6$ Hz, H-6') ; 3.46 (dd, 1H, $J_{4,3}=7$ Hz, $J_{4,5}=3$ Hz, H-4) ; 3.53 (dddd, 1H, H-7) ; 4.06 (dd, 1H, $J_{8,8'}=9$ Hz, $J_{8,7}=6$ Hz, H-8) ; 4.15-4.22 (m, 2H, H-3, H-5) ; 4.30 (dd, 1H, H-8') ; 4.50, 4.58 (AB, 2H, $J_{AB}=11$ Hz, OCH_2Ph) ; 4.56 (d, 1H, $J_{2,3}=6$ Hz, H-2) ; 4.60 (AB, 2H, OCH_2Ph) ; 4.70 (AB, 2H, OCH_2Ph) ; 7.20-7.42 (m, 15 H_{arom}). **8** : $[\alpha]_D$ +94 (*c*1.03, CH_2Cl_2) ; δ: 1.81 (ddd, 1H, $J_{6,5}=4$Hz, $J_{6,6'}=13$Hz, $J_{6,7}=5$Hz, H-6) ; 2.10 (ddd, 1H, $J_{6',5}=11$Hz, $J_{6',7}=12$Hz, H-6') ; 3.22 (m, 1H, H-7) ; 3.81 (dd, 1H, $J_{4,3}=6$Hz, $J_{4,5}=2$Hz, H-4) ; 4.0-4.1 (m, 3H, H-3, H-5, H-8) ; 4.38 (d, 1H, $J_{2,3}=4$Hz, H-2) ; 4.41 (dd, 1H, $J_{8',7}=8$Hz, $J_{8,8'}=9$Hz, H-8'). **9** : $[\alpha]_D$ -55 (*c* 1.04, CH_2Cl_2) ; δ: 1.82-1.92 (m, 2H, H-6, H-6') ; 3.46 (m, 1H, H-7) ; 3.61 (dd, 1H, $J_{4,3}=1.5$ Hz,$J_{4,5}=9$Hz, H-4) ; 3.86 (dd, 1H, $J_{8,8'}=11.5$Hz, $J_{8,7}=8$Hz, H-8) ; 3.92 (dd, 1H, $J_{3,2}=6.5$Hz, H-3) ; 4.09 (m, 1H, H-5) ; 4.32-4.66 (m, 7H, 3 OCH_2Ph, H-8') ; 4.72 (d, 1H, H-2) ; 7.28-7.46 (m, 15H_{arom}). ^{13}C-NMR, δ : 31.5 (C-6) ; 45.9 (C-7) ; 63.7, 73.1, 76.5 (C-2, C-3, C-4) ; 71.4, 72.0, 72.9, 74.3 ($3OCH_2Ph$, C-8) 86.5 (C-5) ; 127.6, 127.8, 127.9, 128.1, 128.3, 128.4, 137.1 (C_{arom}) ; 158.1(C-1). **10** : $[\alpha]_D$ -18 (*c*1.0, CH_3OH) ; δ (D_2O) : 1.56 (ddd,1H, $J_{6exo,\ 6endo}=14$Hz, $J_{6exo,7}=6$Hz, $J_{6exo,5}=7$Hz, H-6exo); 1.98 (dd, 1H, $J_{6endo,7}=9$Hz, H-6endo) ; 2.20 (m, 1H, H-7) ; 3.26 (ddd, 1H, $J_{5,4}=4$Hz, H-5); 3.33 (d, 1H, $J_{2,3}=9$Hz, H-2) ; 3.35 (dd, 1H, $J_{3,4}=8$Hz, H-3) ; 3.45 (dd, 1H, $J_{8,8'}=11$Hz, $J_{8,7}=7$Hz, H-8) ; 3.55 (dd, 1H, H-4) ; 3.74 (dd,1H, $J_{8',7}=7$Hz, H-8'). ^{13}C NMR(250MHz, D_2O), δ : 29.4(C–6) ; 41.4(C–7) ; 56.9(C–5) ; 65.5(C–8) ; 76.9, 77.2, 80.6(C-2, C-3, C-4) ; 93.8(C-1).

7. We thank Ms. B.Champion of our laboratory for carrying out NOE NMR experiments

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