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Synthetic studies on the 1-hydroxy nortropane system: An approach to *Calystegines*.

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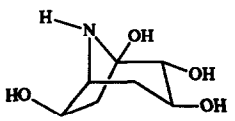
ABSTRACT :*A general synthetic strategy for 1-hydroxy nortropane skeleton, the common feature of* calystegines, *is described.*

Calystegines B_1 **1**, B_2 **2** and A_3 **3**[1], isolated from *Calystegia sepium* roots, are able to provide an exclusive carbon and nitrogen source to some rhizosphere bacteria able to catabolize them[2] and under natural conditions to thus grow faster.



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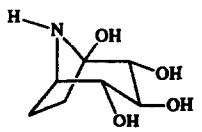

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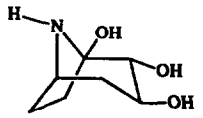

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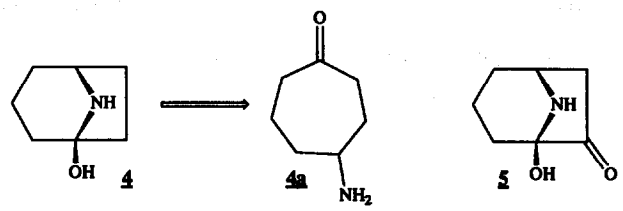
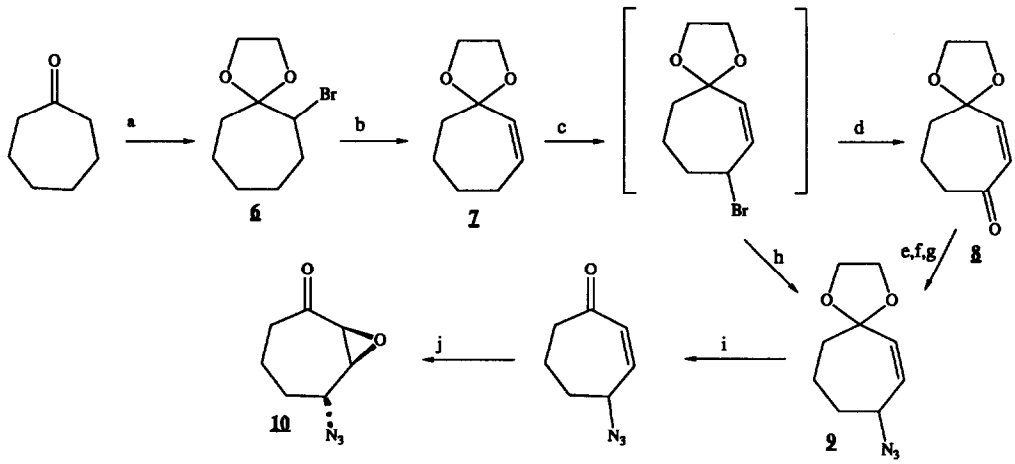
A unique feature of their structure lies in the presence of an aminoketal system at the bridgehead position. Our target was to explore synthetic routes toward models of 1-hydroxy nortropane **4** by intramolecular cyclisation of 4-amino cycloheptanone **4a**. There should be an equilibrium between these two products as described for other related natural products, such as ***physoperuvine***[3], but the presence of substituents on the seven-membered ring could favour the shift toward the cyclised form, since *calystegines* only appear as cyclic compounds.



We present here an efficient synthesis of 5, model compound of *calystegine* B_1 by reduction of 2,3-epoxy 4-azido cycloheptanone 10 as key intermediate which was prepared according to scheme 1.



a:Br_2, $HOCH_2CH_2OH$, 40°C;94%. b:MeONa, MeOH, reflux;84%. c:NBS, CCl_4. d:$((n\text{-}Bu)_4N)_2Cr_2O_7$, $CHCl_3$; 54%. e:DIBAH, $PhCH_3$, 0°C;76%. f:TsCl, pyridine, 0°C;30%. g:NaN_3, DMF, 70°C;50%. h:NaN_3, THF, reflux; 52%. i:H_2SO_4, acetone; 52%. j:H_2O_2, $MeOH/H_2O$; 65%.

Scheme 1

2-Bromo ethylene ketal 6, easily obtained from cycloheptanone [4] using bromine in anhydrous ethylene glycol (94%) affords, while heated with sodium methoxide in methanol, protected cycloheptenone 7 in 84% yield.

Allylic bromination of 7 (N-bromosuccinimide, CCl_4) followed by oxidation with bis(tetra butyl-ammonium)-dichromate[5] furnishes ketone 8[6]. Reduction (DIBAH) followed by tosylation and substitution of the resulting allylic tosylate by sodium azide provides azide 9 (6% overall yield from 7). An alternative and more efficient synthesis of 9 from 7 involves treatment of 7 with N-bromosuccinimide, followed by heating the resulting mixture in anhydrous THF in the presence of one equivalent of sodium azide. Azide 9 is obtained in 52% yield, after purification.

Deprotection of the keto group followed by epoxidation of the double bond of the resulting enone affords compound 10 in 35% yield from azide 9. Epoxidation of the double bond was found to be

necessary to suppress the side chain reactions.

Since several standard methods for reduction of azides, such as catalytic hydrogenation, failed to give the expected product **11**, we turned to the Staudinger reaction[7], which is known to occur under very mild conditions: reduction proceeds smoothly under aqueous conditions (PPh_3, THF, H_2O) at low temperature (-5°C), but affords a compound for which structure **5** was assigned on the basis of ^1H and ^{13}C spectroscopic data:

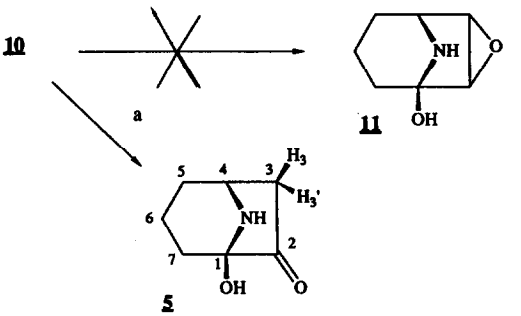
^1H:($CDCl_3$), δ (ppm):H_4 : 3.82(ddd); H_3 : 2.63(dd); $H-3'$: 2.1(d); $H-5, H-6, H-7$: 1.5 – 1.95.

$J_{3,3'} = 16Hz$; $J_{4,3} = 7.5Hz$; $J_{4,5} = J_{4,5'} = 3Hz$.

^{13}C:($CDCl_3$),δ (ppm):C-2:215.06; C-1:86.83; C-4:48.65; C-3:39.42; C-5, C-6, C7:35.11, 29.6, 17.8.

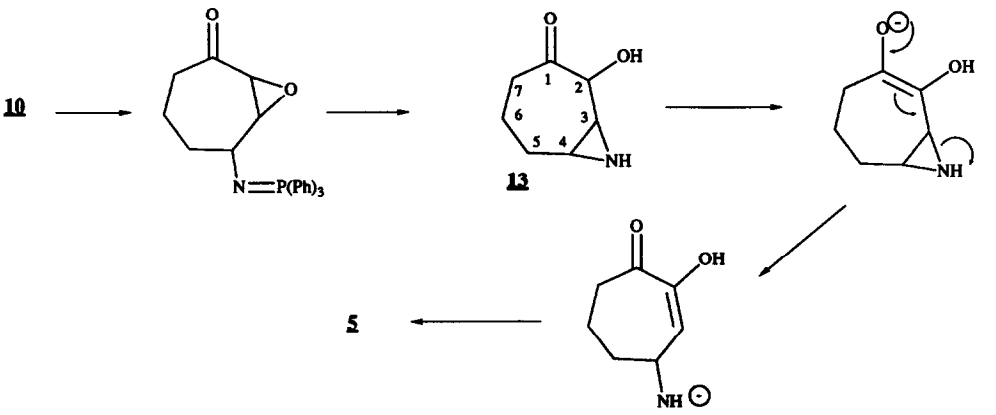
M/z=142 (MH^+)

All measured coupling constants are in good agreement with those measured on *calystegines*.



a: PPh_3, THF/H_2O, -5°C; 30%.

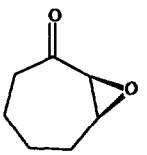
Scheme 2



Scheme 3

The formation of **5** can be explained in the following manner (see *Scheme 3*). Upon enolisation of the imino triphenylphosphorane intermediate, a rearrangement occurs with opening of the epoxide ring to give aziridine **13**.

This mechanism is supported by the isolation in small amount of the aziridine **13**[8], which, by the way, gives an indication on the relative stereochemistry of the azido group and the epoxide in compound **10**: the opening of the epoxide requires an antiparallel geometry for the C-O bond and the C-N bond, for aziridine ring formation. This led us to assign to **10** the following stereochemistry:



10

We did not observe any equilibrium between the open and the closed forms of the aminoketal system. The complete shift toward the cyclised isomer is probably due to the lower stability of the α-diketone system present in the open form, or to a stabilizing hydrogen bond between the hydroxy group and the vicinal carbonyl.

References and notes:

1: See preceding paper

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8: $^1H : (CDCl_3), \delta(ppm) : H-2 : 4.25(d)$; $H-3 : 1.95(t)$; $H-4 : 2.3(td)$; $H-7 : 2.65(ddd)$; $H-7' : 2.43(m)$; $H-5 : 2.23(m)$; $H-5' : 1.6(m)$; $H-6 : 1.85(m)$; $H-6' : 1.68(m)$.
$J_{2,3} = 6.5Hz$; $J_{7,7'} = 17Hz$; $J_{7,6} = 6Hz$; $J_{7,6'} = 4Hz$; $J_{3,4} = 6.5Hz$.
$^{13}C : (CDCl_3), \delta(ppm) : C-1 : 209.89$; $C-2 : 77.34$; $C-3 : 44.21$; $C-4 : 32.6$; $C-5, C-6, C-7 :$ 35.98, 19.29, 20.29.

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