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The first syntheses of 6,7-dihydroxylated calystegines and homocalystegines

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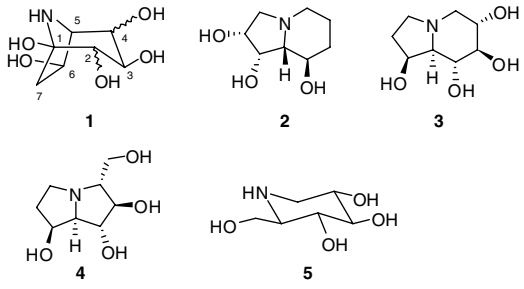
Abstract—The synthesis of novel calystegine analogues containing hydroxyl substituents on both C6 and C7 positions has been achieved. The synthetic strategy employed is based on stereoselective dihydroxylation reactions and has also been utilised for the preparation of homocalystegines.

Calystegines **1** are polyhydroxylated nortropane alkaloids that were first isolated by Tepfer et al. from the roots and root extrudates of *Calystegia sepium*.[1] They are rigid azasugar derivatives and have bicyclic structures that are similar to swainsonine **2**, castanospermine **3** and australine **4**. Azasugars are often strong inhibitors of glycosidase enzymes and have consequently been investigated as potential therapies in the treatment of diabetes, HIV and cancer.[2] In common with these biological properties, calystegines have also been shown to be selective glycosidase inhibitors. For example, calystegine B_2, which has a hydroxylation pattern resembling that of D-glucose, shows 100-fold higher inhibition of β-glycosidases from almonds and *Caldocellum saccharolyticum* than deoxynojirimycin **5**.[3]

A number of naturally occurring calystegines have been isolated (and synthesised) to date.[4] These compounds have been found to possess between three to five hydroxyl groups around the bicyclic core. However, in spite of this variable hydroxylation pattern, none of them contain hydroxyl groups on both C6 and C7. In addition, only a small number of non-natural calystegines have been synthesised and few have been tested with respect to their biological activity.[5] This prompted us to explore an easily adaptable synthetic route to non-natural calystegines in order to further elucidate the structure–activity profile of this class of compounds as glycosidase inhibitors. This letter presents our initial results concerning the synthesis of novel 6,7-dihydroxylated calystegines and the corresponding homocalystegine analogues.



1 **2** **3**

4 **5**

Our synthetic strategy towards non-natural calystegines and homocalystegines is outlined in Scheme 1. The known bicyclic starting materials **6a**[6] and **6b**[7] can be readily accessed via cycloaddition of a nitroso-compound (generated in situ from the reaction of benzyl *N*-hydroxycarbamate with tetra-*n*-butyl-ammonium periodate)[8] with cycloheptadiene or cyclooctadiene, respectively. We envisaged that the known conversion[6,7] of **6a**–**b** to the corresponding alcohols **7a**–**b** and ketones **8a**–**b** would allow us to investigate the stereoselective dihydroxylation of each of these three species with a view to access both possible *syn*-diols at C6 and C7. Although the syntheses described below are racemic, it should be noted that an enantioselective version of the cycloaddition reaction to produce **6a**–**b** is possible thus allowing the methods reported here to be used for the production of homochiral material.[9]

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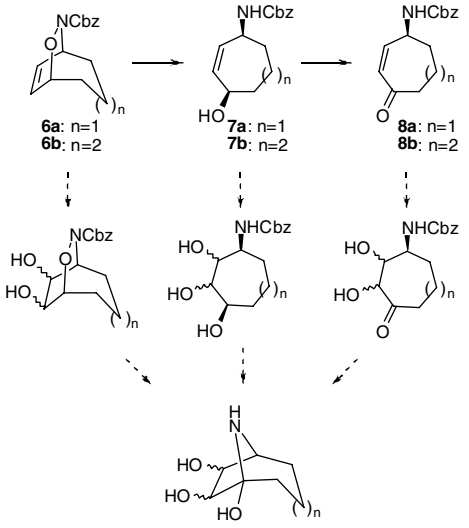
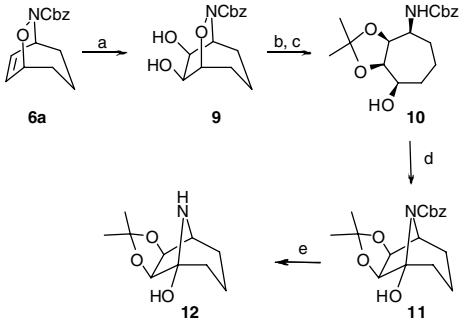


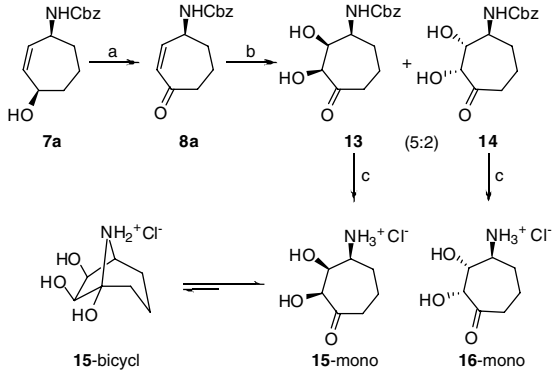
Scheme 1.

We started our investigations with the seven-membered calystegine series. Dihydroxylation of **6a** under Upjohn conditions gave the β-diol **9** exclusively in good yield and with no evidence of attack from the α-face (Scheme 2).[10] The stereostructure of **9** was determined by NOESY spectroscopy which indicated strong cross peaks between the C6 and C7 hydrogen atoms and the C3 α-hydrogen.[11,12] Whilst the stereoselectivity for the dihydroxylation of **6a** is in agreement with the *exo*-attack observed for bicyclo[2.2.1]heptenes,[13] it should be noted that an analogous bicyclo[2.2.2]oxazine substrate reportedly undergoes *endo*-selective dihydroxylation.[14] Protection of the diol **9** followed by N–O bond cleavage using samarium diiode[15] gave the alcohol **10**. Dess–Martin oxidation of **10** then generated the corresponding ketone which existed predominantly as the hemiaminal **11** (>90% by NMR). Removal of the Cbz group to give **12** proved straightforward, but unfortunately all efforts to remove the isopropylidene protecting group from **12** using acidic catalysis met with failure due to significant decomposition of the starting material and/or product under the reaction conditions.

In view of the failure to effect the deprotection of **12** we turned our attention to the dihydroxylation reactions of



Scheme 2. Reagents and conditions: (a) OsO_4, NMO, acetone/H_2O, rt, 48 h, (76%); (b) dimethoxypropane, *p*-TSA, acetone, rt, 72 h, (67%); (c) SmI_2, THF, rt, 1 h, (88%); (d) Dess–Martin periodinane, CH_2Cl_2, rt, 18 h, (48%) and (e) $Pd(OH)_2$, H_2, EtOAc, 18 h, (99%).

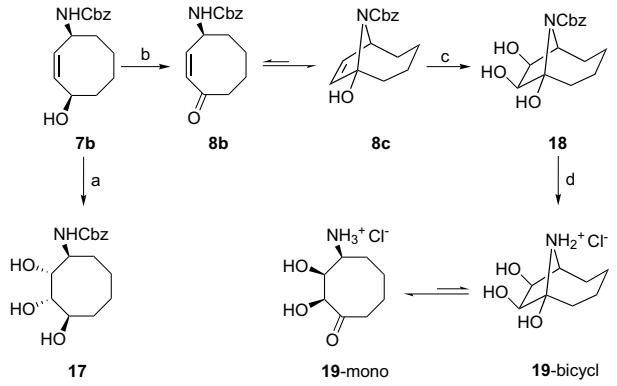


Scheme 3. Reagents and conditions: (a) Jones reagent, acetone, 0 °C, 5 min (62%); (b) OsO_4, NMO, acetone/H_2O, rt, 24 h (**13**–51%; **14**–20%) and (c) $Pd(OAc)_2$, H_2, EtOH:HOAc 18:1, rt; then H_2O/HCl (**15**-100%; **16**–68%).

7a and **8a** (Scheme 3). The alcohol **7a** was readily accessed from **6a** by N–O bond cleavage using $Mo(CO)_6$.[16] However, *syn*-dihydroxylation of **7a** under Upjohn conditions was non-selective and gave an inseparable (1:1) mixture of diastereoisomeric triols. A similar lack of facial selectivity has previously been observed in the epoxidation of **7a**.[17]

Jones oxidation of **7a** produced the ketone **8a**[18] in good yield. Pleasingly, dihydroxylation of **8a** proved to be more facially selective than the reaction of **7a** and afforded a mixture of **13** and **14** (ratio ca. 5:2) which could be separated by careful column chromatography and recrystallisation.[19] Subsequent deprotection of **13** cleanly generated the novel calystegine analogue **15**. Interestingly, NMR analysis indicated that **15** exists predominantly in its monocyclic form rather than as the hemiaminal (**15**-mono:**15**-bicycl = 10:1).[20] This is in contrast to the majority of naturally occurring calystegines that have been isolated.[4] In an analogous manner, deprotection of **14** gave the novel calystegine analogue **16** which again exists mainly as the monocyclic isomer (**16**-mono:**16**-bicycl = 2:1).[21]

Having successfully accessed the novel calystegine analogues **15** and **16** we next examined the dihydroxylation reactions of **6b**–**8b** with a view to produce the corresponding homocalystegines. However, in contrast to the reaction of **6a**, the dihydroxylation of the bicyclic oxazine **6b** led only to a mixture of unidentifiable products. The reaction of alcohol **7b** (produced from **6b**)[7] was more successful, affording **17** as a single stereoisomer (Scheme 4).[22] The increased facial selectivity in the dihydroxylation reaction of **7b** compared to **6b** has been noted before in the corresponding epoxidation of these substrates.[17,23] Disappointingly, all attempts to protect the *syn*-diol in **17** led only to selective protection of the *anti*-1,2-diol functionality,[24] thus limiting the effectiveness of this route. Oxidation of the alcohol **7b** gave the corresponding ketone as a separable mixture of keto-**8b** and hemiaminal-**8c** tautomers (**8b**:**8c** = 1:2).[7,25] Gratifyingly, dihydroxylation of the bicyclic tautomer **8c** proceeded in a stereoselective manner to afford the triol **18** in good yield.[26] Subsequent deprotec-



Scheme 4. Reagents and conditions: (a) OsO_4, NMO, acetone/H_2O, rt, 72 h (72%); (b) Jones reagent, acetone, 0 °C, 5 min (77%–**8b**:**8c**; 1:2); (c) OsO_4, NMO, acetone/H_2O, rt, 72 h (68%); (d) $Pd(OAc)_2$, H_2, EtOH:HOAc 18:1, rt; then H_2O/HCl (68%).

tion gave the novel homocalystegine **19** which again exists mainly as the monocyclic isomer (**19**-mono:**19**-bicycl = 10:3).[27]

In summary, we have reported the first synthesis of non-natural calystegines **15** and **16** and the first homocalystegine **19** in racemic form. Surprisingly, we have found that these natural product analogues exist mainly as the monocyclic keto-tautomer which is in contrast to the bicyclic hemiaminal-form reported for the majority of the calystegines isolated to date. Biological testing of **15**, **16** and **19** produced in the course of this work is currently underway and these results together with the synthesis of further calystegine analogues will be reported in due course.

Acknowledgement

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References and notes

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8. For safety reasons we replaced the Me_4NIO_4 used in the original preparations of **6a** and **6b** with *n*-Bu_4NIO_4—see Malpass, J. R.; Hemmings, D. A.; Wallis, A. L.; Fletcher, S. R.; Patel, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1044–1050.
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10. The α- and β-faces are defined as used in tropane systems.
11. All new compounds gave satisfactory spectroscopic and microanalytical and/or HRMS analysis.
12. For **9**, δ_H (300 MHz, $CDCl_3$): 1.30–1.47 (1H, m, α-H3), 1.67–1.74 (1H, m, β-H3), 1.85–1.97 (3H, m, 2 × H4 & 1 × H2), 2.01–2.10 (1H, m, 1 × H2), 3.91 (1H, d, $J = 8.3$ Hz, H7), 4.03 (1H, dd, $J = 8.3$, 1.8 Hz, H6), 4.48 (1H, dd, $J = 3.8$, 1.8 Hz, H1), 4.58 (1H, br s, H5), 5.21 (2H, s, CH_2–Ph), 7.29–7.40 (5H, m, Ph). δ_C (75 MHz, $CDCl_3$) 19.1 (CH_2), 28.9 (CH_2), 29.8 (CH_2), 57.5 (CH), 65.1 (CH), 65.8 (CH), 67.7 (CH_2), 82.0 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 136.1 (C), 155.5 (C). Accurate mass (FAB): found: 294.1342 ($M+H^+$); calcd. for $C_{15}H_{20}NO_5$: 294.1342.
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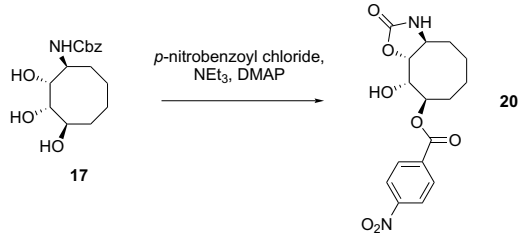
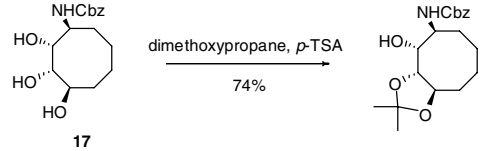
17. Justice, D. E.; Malpass, J. R. *Tetrahedron* **1996**, *52*, 11963–11976.
18. Ketone **8a** exists solely as the monocyclic tautomer shown—see Ref. 6.
19. Compound **13** exists solely as the monocyclic keto-tautomer shown. The stereostructure of **13** was confirmed by protection of the diol as the isopropylidene acetal to give **11** and comparison to the material synthesised by the route shown in Scheme 2.
20. For **15**-mono (assignments based on calystegine numbering); δ_H (300 MHz, D_2O): 1.52–1.75 (2H, m, 1 × H3 & 1 × H4), 1.80–1.95 (2H, m, 1 × H3 & 1 × H4), 2.30 (1H, dddd, $J = 2.1$, 6.6, 10.0, 12.8 Hz, 1 × H2), 2.57 (1H, dt, $J = 12.8$, 3.5 Hz, 1 × H2), 3.50–3.59 (1H, m, H5), 4.04 (br s, 1H, H6), 4.70 (1H, H7 overlap with D_2O); δ_C (75 MHz, D_2O) 17.7 (CH_2), 26.4 (CH_2), 40.2 (CH_2), 53.9 (CH), 72.8 (CH), 77.1 (CH), 212.5 (C); accurate mass (FAB): found: 160.0973 ($M-Cl^-$); calcd. for $C_7H_{14}NO_3$: l60.0974. Selected signals for **15**-bicycl; δ_H (300 MHz, D_2O): 3.99 (1H, d, $J = 6.9$ Hz, H6 or H7), 4.19 (1H, d, $J = 6.9$ Hz, H6 or H7), all other ^1H signals overlap with **15**-mono; δ_C (75 MHz, D_2O) 16.2 (CH_2), 24.1 (CH_2), 32.4 (CH_2), 61.9 (C), 69.8 (CH), 70.9 (CH), 92.8 (C).
21. For **16**-mono (assignments based on calystegine numbering); δ_H (300 MHz, D_2O): 1.50–2.06 (4H, m, 2 × H3 & 2 × H4), 2.46 (1H, dddd, $J = 16.5$, 15.2, 8.1, 7.2 Hz, 1 × H2), 2.65 (1H, dt, $J = 16.5$, 5.6 Hz, 1 × H2), 3.45 (1H, dt, $J = 3.2$, 8.7 Hz, H5), 3.88 (1H, dd, $J = 8.7$, 2.4 Hz, H6), 4.47 (1H, d, $J = 2.4$ Hz, H7); δ_C (75 MHz, D_2O) 18.0 (CH_2), 27.6 (CH_2), 39.3 (CH_2), 54.7 (CH), 71.9 (CH), 78.5 (CH), 214.9 (C); accurate mass (FAB): found: 160.0975 ($M-Cl^-$); calcd. for $C_7H_{14}NO_3$: 160.0974.
22. The stereostructure of **17** was confirmed by X-ray crystallographic analysis of the derivative **20**.



Crystal data for compound **20**: $C_{16}H_{18}N_2O_7$, $M = 350.32$, triclinic, space group P-1, $a = 7.082(2)$, $b = 7.129(2)$, $c = 17.347(5)$ Å, $V = 781.4(4)$ Å^3, $T = 150(2)$ K, $Z = 2$, $Dc = 1.489$ g cm^{-3}, μ (Mo-Kα) $= 0.118$ mm^{-1}. Final, $R_1 = 0.0518$ (for 5693 reflections with $I > 2\sigma(I)$) and $wR2 = 0.0642$ for all data. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 617411. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

23. Justice, D. E.; Malpass, J. R. *Tetrahedron* **1996**, *52*, 11947–11962.
24. For example:



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25. Once separated **8c** appears to be stable and does not re-equilibrate with **8b** to any appreciable extent after standing for 24 h at room temperature in $CDCl_3$. Storage of ketone **8b** under these conditions, however, re-establishes the 1:2 ratio of **8b**:**8c**.
26. Triol **18** exists mainly as the hemiaminal tautomer shown.
27. For **19**-mono (assignments based on calystegine numbering); δ_H (300 MHz, D_2O): 1.31–2.04 (6H, m, 2 × H3, 2 × H4 and 2 × H5), 2.26–2.34 (1H, m, 1 × H2), 2.73 (1H, dt, $J = 3.5$, 12.8 Hz, 1 × H2), 3.44–3.51 (1H, m, H6), 4.55 (1H, d, $J = 2.5$ Hz, H8), 4.69 (1H, H7, overlap with D_2O); δ_C (75 MHz, D_2O) 22.6 (CH_2), 26.6 (CH_2), 35.8 (CH_2), 38.2 (CH_2), 54.9 (CH), 72.5 (CH), 78.7 (CH), 215.7 (C); accurate mass (FAB): found: 174.1130 ($M-Cl^-$); calcd. for $C_8H_{16}H_{16}NO_3$: 174.1130. Selected signals for **19**-bicycl; δ_H (300 MHz, D_2O): 3.65–3.67 (1H, m, H6), 4.12 (1H, d, $J = 5.3$ Hz, H8), 4.24 (1H, dd, $J = 2.5$, 5.3 Hz, H7), all other ^1H signals overlap with **19**-mono; δ_C (75 MHz, D_2O) 20.4 (CH_2), 21.7 (CH_2), 26.8 (CH_2), 27.5 (CH_2), 60.4 (C), 66.6 (CH), 73.9 (CH), 95.5 (C).