Tetrahedron Letters, Vol. 34, No. 51, pp. 8221-8224, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis of Novel Polyhydroxylated Quinolizidines: Ring Expanded Analogs of Glycosidase Inhibitory Indolizidines

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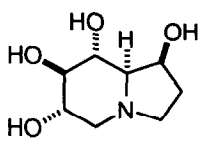
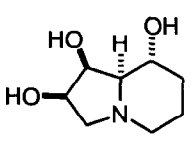
Abstract: Two polyhydroxylated quinolizidines, (1*R*,2*R*,3*R*,9*S*,9a*R*)-1,2,3,9-tetrahydroxyquinolizidine **9** and (1*R*,2*R*,3*R*,9*R*,9a*S*)-1,2,3,9-tetrahydroxyquinolizidine **10**, have been synthesized by the reductive double cyclization of **15**α and **15**β. Quinolizidine **9** can be viewed either as a ring expanded analog of 6-epicastanospermine or of 8-episwainsonine, while **10** is a ring expanded analog of 1,6,8a-triepicastanospermine or of 8a-episwainsonine.

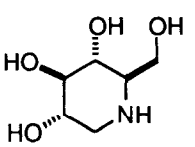
Polyhydroxylated alkaloids such as castanospermine **1**, swainsonine **2**, deoxynojirimycin **3**, deoxymannojirimycin **4**, alexine **5**, and their derivatives have attracted considerable interest in recent years due to their potent activity as glycosidase inhibitors.[1] Further interest in this class of compounds has been generated by their wide range of pharmacological activity, including anti-viral, anti-HIV, anti-cancer, anti-feedant, and immunoregulatory activity.[1,2,3]



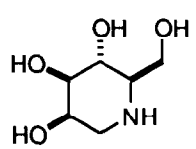
Castanospermine
1



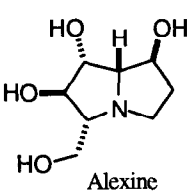
Swainsonine
2



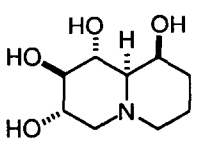
Deoxynojirimycin
3



Deoxymannonojirimycin
4



Alexine
5



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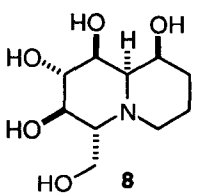

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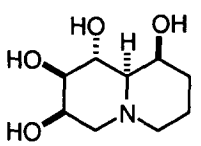
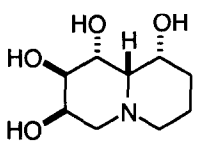


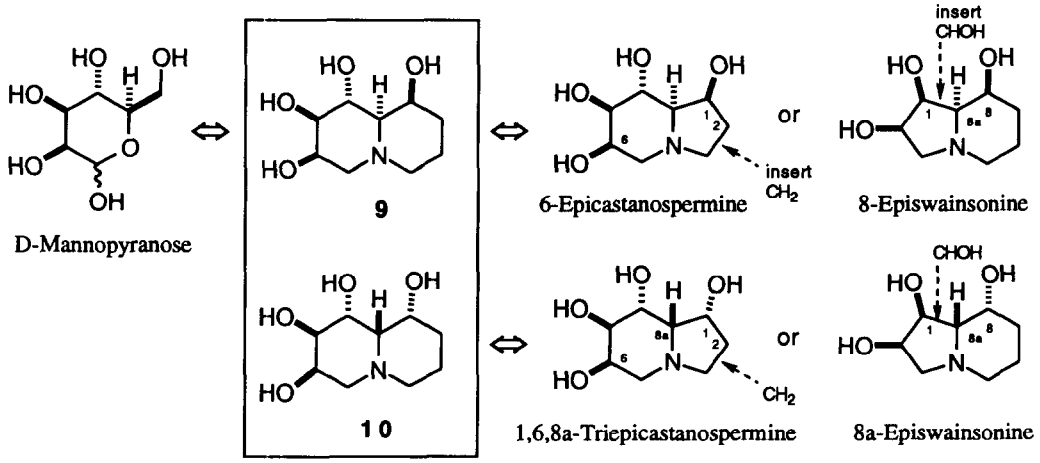
9



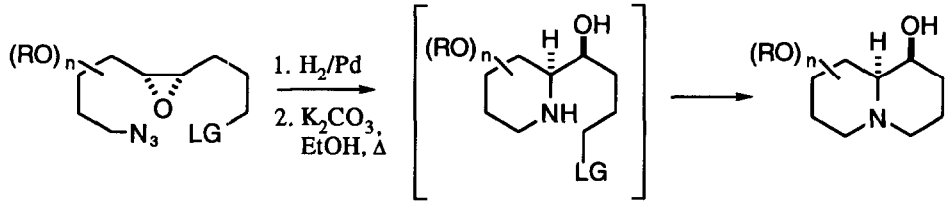
10

Considerable effort has been put forth by a number of researchers to investigate the structure-activity relationships of the polyhydroxylated indolizidines, resulting in the synthesis of many of the stereoisomers of castanospermine **1** and swainsonine **2** for biological evaluation.[2,3] Stereoisomers of polyhydroxylated pyrrolizidines (e.g. alexine **5** and australine) as well as ring contracted versions of polyhydroxylated indolizidine alkaloids have also been prepared and in some cases evaluated for inhibitory activity.[4] Few

reports of *ring expanded* analogs of polyhydroxylated indolizidines have appeared. Grandig and Stütz *et al* prepared the castanospermine homologue (1*R*,2*R*,3*S*,9*S*,9a*R*)-1,2,3,9-tetrahydroxyquinolizidine **7**, which has shown β-glucosidase inhibitory activity.[5] Liu *et al* prepared the hydroxymethyl substituted quinolizidine **8**, which strongly inhibits α-glucosidase I from pig kidney.[6] To further explore the chemistry of this family of compounds we have undertaken the synthesis the polyhydroxylated quinolizidines **9** and **10**. Compound **9** closely resembles D-mannopyranose. It can be viewed as a ring expanded analog of the naturally occuring amyloglucosidase inhibitor 6-epi-castanopermine **8**,[3] or as a hydroxymethine ring expanded version of 8-epi-swainsonine.[2] Similarily, **10** can be viewed as a ring expanded analog of 1,6,8a-triepicastanospermine, or of 8a-epi-swainsonine.[2]



The key step in the synthesis of **9** and **10** is the efficient formation of the quinolizidine ring system via a reductive double alkylation of an azido-epoxide that possesses an ω-leaving group (Scheme 1). We[4c,7] and others[4a,d,8] have previously employed a similar strategy to assemble pyrrolizidine and indolizidine ring systems.

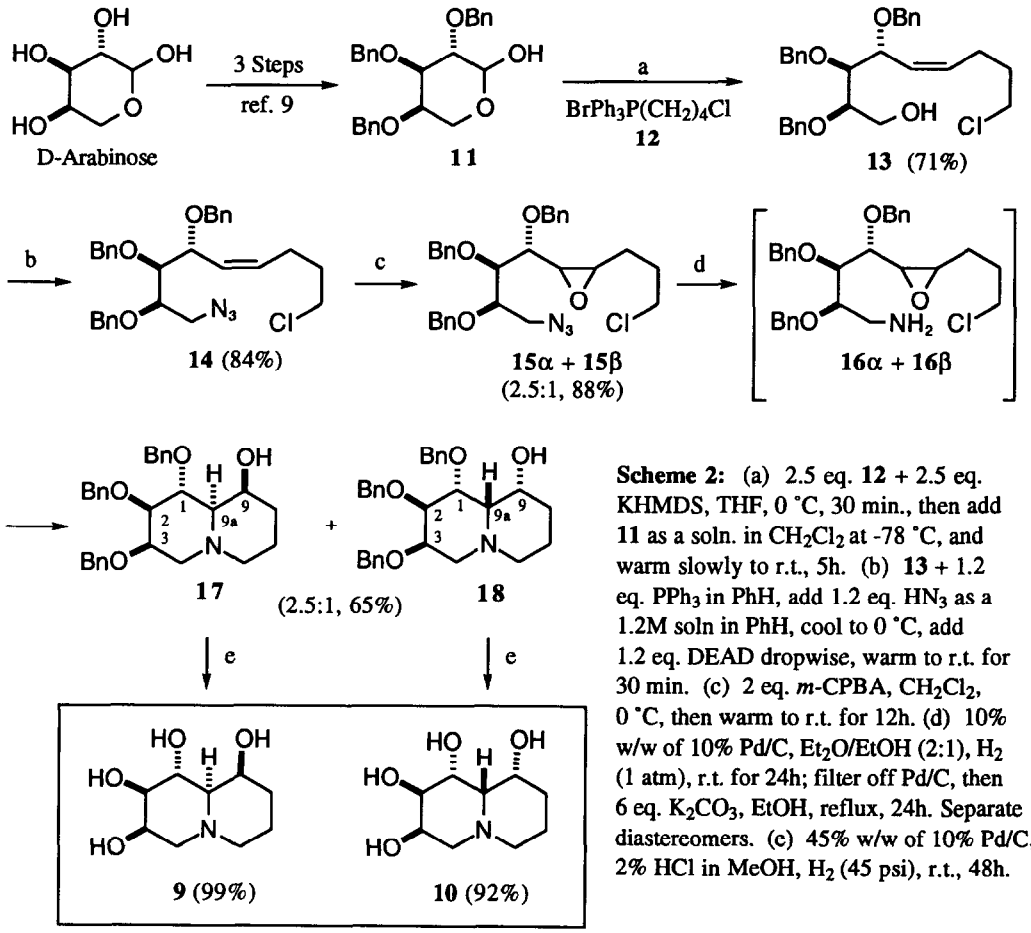


Scheme 1

Our synthesis began with 2,3,4-tri-O-benzyl-D-arabinopyranose **11**, which was prepared from D-arabinose in three steps according to Fletcher's procedure (Scheme 2).[9] Wittig olefination of **11** with the chloro-substituted phosphonium salt **12**[10] selectively yielded the (*Z*)-chloroalkenol **13** in 71% yield, which was then converted to azide **14** in 84% yield using the Mitsunobu method.[11] Epoxidation of **14** with *m*-CPBA produced an inseparable mixture of epoxides **15**α and **15**β (2.5 : 1) in 88% (α and β refer to the orientation of

the epoxide oxygen). Reduction of the mixture of azido-epoxides **15α/15β** to amino-epoxides **16α/16β** without debenzylation was accomplished under mild Pd-catalyzed hydrogenolysis conditions. The amino compounds **16α/16β** were not purified, but were heated in refluxing ethanol containing K_2CO_3 to produce a mixture of quinolizidines **17** and **18** (2.5 : 1) in 65% from **15α/15β**. Compounds **17** and **18** separated (SiO_2) and their stereochemistries were assigned by examination of ^1H NMR coupling constants.[12] The stereochemistry of the major isomer **17** implies that **15α** is the major product of the epoxidation reaction. Debenzylation of **17** and **18** was carried out under more rigorous Pd-catalyzed hydrogenolysis conditions to yield respectively (1*R*,2*R*,3*R*,9*S*,9a*R*)-1,2,3,9-tetrahydroxyquinolizidine **9** in 99% and (1*R*,2*R*,3*R*,9*R*, 9a*S*)-1,2,3,9-tetrahydroxy-quinolizidine **10** in 92%.[13]

Screening for glycosidase inhibitory activity is underway and will be reported with a full account of this work.



Scheme 2: (a) 2.5 eq. **12** + 2.5 eq. KHMDS, THF, 0 °C, 30 min., then add **11** as a soln. in CH_2Cl_2 at -78 °C, and warm slowly to r.t., 5h. (b) **13** + 1.2 eq. PPh_3 in PhH, add 1.2 eq. HN_3 as a 1.2M soln in PhH, cool to 0 °C, add 1.2 eq. DEAD dropwise, warm to r.t. for 30 min. (c) 2 eq. *m*-CPBA, CH_2Cl_2, 0 °C, then warm to r.t. for 12h. (d) 10% w/w of 10% Pd/C, Et_2O/EtOH (2:1), H_2 (1 atm), r.t. for 24h; filter off Pd/C, then 6 eq. K_2CO_3, EtOH, reflux, 24h. Separate diastereomers. (e) 45% w/w of 10% Pd/C, 2% HCl in MeOH, H_2 (45 psi), r.t., 48h.

Acknowledgement We thank the National Institutes of Health (GM-35572) for support of this research.

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12. The two isomers can be differentiated by the ^1H coupling constants between H9-H9a, H1-H9a and H1-H2. Neither isomer shows an axial-axial coupling between H9-H9a indicating that these hydrogens are cis and that H9 is equatorial in both structures. The major isomer **17** shows axial-axial coupling between both H1-H9a and H1-H2 ($J_{1,9a}$= $J_{1,2}$ = 9.5 Hz), while the minor isomer **18** shows an axial-equatorial coupling between H1-H9a ($J_{1,9a}$= 2.4 Hz), and an equatorial-equatorial coupling between H1-H2, ($J_{1,2}$= 3.4 Hz).
13. Representative spectral data: **9**: ^1H NMR (D_2O, 300 MHz) δ3.98 (broad s, 1H), 3.79 (broad s, 1H), 3.61 (t, J = 9.8 Hz, 1H), 3.32 (dd, J = 3.5, 9.8 Hz, 1H), 2.72 (dd, J = 2.9, 13.0 Hz, 1H), 2.65 (broad d, J = 11.5 Hz, 1H), 2.16 (d, J = 12.9 Hz, 1H), 1.94 (broad t, J = 11.5 Hz, 1H), 1.6-1.8 (m, 3H), 1.25-1.45 (m, 2H). ^{13}C NMR (D_2O, $CDCl_3$ ext std. 90 MHz, JMOD) δ74.44 (+), 67.99 (+), 67.77 (+), 67.21 (+), 58.92 (-), 54.85 (-), 29.87 (-), 18.48 (-). **10**: ^1H NMR (D_2O, 300 MHz) δ3.98 (d, J =1.6 Hz, 1H), 3.93 (ddd, J = 3.2, 4.9, 11.6 Hz, 1H), 3.88 (dd, J = 1.8, 3.7 Hz, 1H), 3.70 (t, J = 3.3 Hz, 1H), 2.66 (broad d, J = 11.6 Hz, 1H), 2.49 (dd, J = 4.9, 10.9 Hz, 1H), 2.12 (t, J =11.2 Hz, 1H), 2.09 (broad s, 1H), 1.98 (m, 1H), 1.71 (dt, J = 3.7, 12.8 Hz, 1H), 1.62 (broad d, J = 13.9 Hz, 1H), 1.41 (ddd, J = 2.5, 3.0, 13.5 Hz, 1H), 1.31 (m, 1H). ^{13}C NMR (D_2O, $CDCl_3$ ext std, 90 MHz) δ76.72, 72.84, 72.02, 67.35, 61.86, 58.42, 57.43, 33.78, 21.24.

(Received in USA 3 September 1993; accepted 11 October 1993)