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A Synthesis of Indolizidines Related to Castanospermine and Swainsonine.

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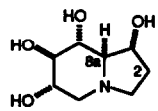
Abstract: *A general synthetic route to indolizidine alkaloids which are structurally similar to castanospermine and swainsonine is described. The described route uses modified pentose sugars and chiral reagents to control the absolute configuration at each asymmetric center.*

Indolizidine alkaloids including castanospermine (1) and swainsonine (2) have attracted a considerable amount of attention due to their biological activity.[1] These compounds and structurally related indolizidines act as glucosidase inhibitors[2] and anticancer[3] compounds. Among the structural differences between indolizidines 1 and 2 are the epimeric C-8a center and the additional C-2 α -hydroxyl of Swainsonine. A synthetic route in which the structural features of these two classes of indolizidines could be combined and examined was required to develop structure vs. activity relationships.[4] We also required a synthesis in which the absolute configuration of each asymmetric center could be manipulated in a predictable and controlled manner. Toward this end, asymmetric reagents were chosen to control the stereochemical outcome at each newly formed center. We would like to report our effort resulting in a general route for the synthesis of indolizidines of structural type 3.



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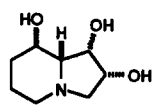

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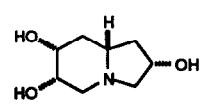
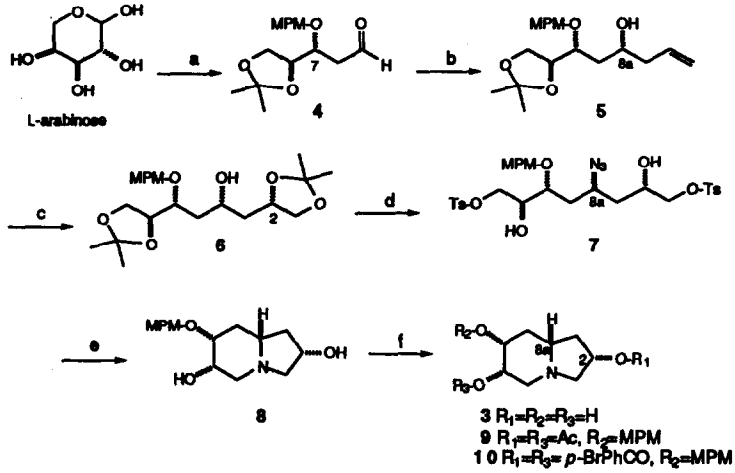


3

The synthesis of indolizidine 3 commenced from aldehyde 4 (Scheme I). This intermediate contains the C-6 and C-7 stereocenters (indolizidine ring numbering) with the remaining functionality in a suitably protected form. Multigram quantities of aldehyde 4 were prepared in six-steps using slight modifications of Kishi's facile route for the 2-deoxypentanoic acids.[5] Asymmetric allylation was used to establish the C-8a stereocenter, this transformation was best carried out using Brown's B-allylbis(4-isocaranyl)borane reagent to give homoallylic alcohol 5 in 95% yield as a 78:8 mixture of diastereomers.[6,7] Asymmetric induction was measured by formation of the Mosher[8] esters of 5 and integration of the corresponding ^{19}F-NMR ($CDCl_3/CFCl_3$ 0 ppm, C_6F_6 -162.9 ppm) signals at δ -71.99 and -72.26 ppm, respectively. Transformation of homoallylic alcohol 5 into alcohol 6 was accomplished by protection of the C-8a hydroxyl as the TBDMS-silyl ether, and conducting Sharpless asymmetric dihydroxylation using the hydroquinine 9-phenanthryl ether ligand.[9] This gave a 4:1 mixture of C-2 diastereomers which were carried on to the next step. Acetonide formation and removal of the TBDMS-silyl ether gave alcohol 6. The requisite nitrogen was introduced into alcohol 6 by inversion of the mesylate at C-8a with sodium azide, removal of the acetonides, and formation of the (bis)primary tosylate to give azide 7. Azide 7 was reduced with Lindlar's catalyst, and the nascent amine was cyclized to indolizidine 8 by stirring in slightly basic ethanol. Treatment of 8 with DDQ[10] followed by acid, hydrogenation (Pd/C), or strongly acidic conditions all resulted in removal of the MPM group to give indolizidine 3.

The indolizidine was converted to the (bis)acetate 9 for NMR characterization. The connectivity and substitution pattern of 9 was assigned by ^{13}C, DEPT and HMQC correlation. However, an unambiguous conclusion could not be reached as to the relative

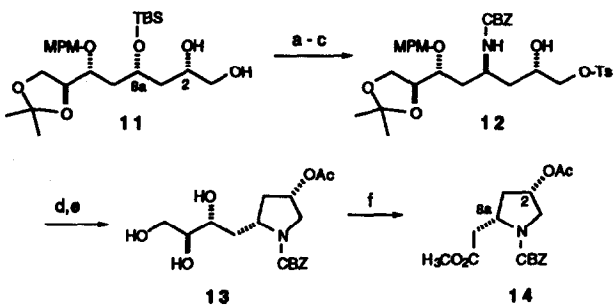
configuration at C-8a. In addition, both the (bis)acetate **9** and the (bis)*p*-bromobenzoyl ester **10** did not give suitable crystals for an x-ray determination.



Scheme I: Reagents and Reaction Conditions.

a. i. EtSH, conc HCl, 0°C to RT. ii. $(CH_3)_2C(OCH_3)_2$, *p*-TSA. iii. *t*-BuOK, DMSO, 0°C to RT. iv. LAH, THF, 0°C to RT. v. KH, MPM-Br, THF, 0°C. vi. I_2, $NaHCO_3$, acetone/water. (40% overall yield). b. $Ipc_2B\text{-}CH_2CH{=}CH_2$, ether, -78°C, 95% yield (78:8 diastereoselectivity). c. i. TBDMS-Cl, DMF, imidazole. ii. Hydroquinine 9-phenanthryl ether, $K_3Fe(CN)_6$, $K_2OsO_4\text{-}(H_2O)_2$, 95% chemical yield (4: 1 diastereoselectivity). iii. $(CH_3)_2C(OCH_3)_2$, *p*-TSA. iv. TBAF, THF. 90% chemical yield over 4 steps. d. i. Ms-Cl, Et_3N, CH_2Cl_2. ii. NaN_3, DMF. iii. Dowex-50, MeOH, 40°C. iv. Ts-Cl, pyridine, 0°C. 43% yield over 4 steps. e. i. H_2, $Pd/CaCO_3$ poisoned with Pb, EtOH. ii. K_2CO_3, EtOH, 50°C. 86% over 2 steps. f. DDQ, CH_2Cl_2/H_2O (20:1), then MeOH 6 N HCl quantitative for 3.

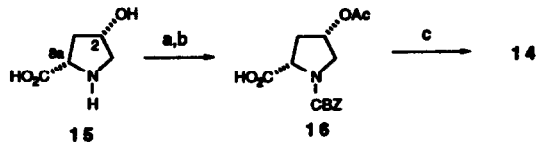
Unambiguous confirmation of the C-8a and C-2 stereocenters was established by correlation to the carbon homologue of *cis*-4-hydroxy-L-proline. Intermediate diol **11** (Scheme II) contains the C-8a and C-2 stereocenters that were introduced using chiral reagents. Diol **11** was protected as the anisylidene, the C-8a nitrogen was introduced, the anisylidene selectively removed, and converted to the primary tosylate to give carbamate **12**. The carbamate was cyclized and the 1,2,3-triol functional array was deprotected to give triol **13**. The triol was cleaved to the aldehyde, oxidized to the acid, and esterified to give the protected *cis*-4-hydroxy-L-proline carbon homologue, methyl ester **14**.



Scheme II: Reagents and Reaction Conditions.

a. i. *p*-MeOPhCH(OMe)$_2$, PPTS, THF. ii. TBAF, THF, 0°C. b. i. MsCl, Et_3N, Et_2O. ii. NaN_3, DMF, 50°C. iii. H_2, $Pd/CaCO_3$ poisoned with Pb, EtOH. iv. CBZ-Cl, $NaHCO_3$, H_2O, EtOAc, 0°C. c. i. 20% aq AcOH, THF. ii. Ts-Cl, Et_3N, CH_2Cl_2, DMAP. (39% yield over 8 steps) d. i. Ac_2O, pyridine, DMAP. ii. NaH, THF, reflux. iii. Ac_2O, pyridine, DMAP. (88% yield over 3 steps) e. i. DDQ, pH 7 buffer, CH_2Cl_2, 0°C. ii. p-TSA, MeOH. (85% yield over 2 steps) f. i. $NaIO_4$, MeOH, H_2O. ii. $NaClO_2$, NaH_2PO_4, H_2O, *t*-BuOH, 2-methyl-2-butene, 0°C. iii. CH_2N_2, THF, Et_2O.

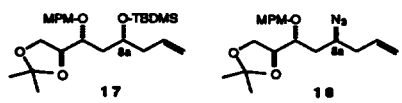
The C-8a and C-2 stereocenters (Scheme III) were also obtained from commercial *cis*-4-hydroxy-L-proline (15). Protection as the N-CBZ derivative followed by formation of the C-2 acetate gave acid 16. Acid 16 was homologated by a modified Arndt-Eistert procedure,[11] involving formation of the α-diazo ketone followed by Wolff rearrangement in methanol, gave the carbon homologue 14. Compound 14, obtained by either route was identical under all methods of examination.[12]



15 16

Scheme III: Reagents and Reaction Conditions.
a. CBZ-Cl, $NaHCO_3$, H_2O, EtOAc, 0°C. b. Ac_2O, pyridine. (97% yield over 2 steps) c. i. iso-butyl chloroformate, N-methylmorpholine, 0°C. ii. CH_2N_2, Et_2O. iii. BzOAg, MeOH, 40°C. (80% yield).

Synthesis of indolizidine 3 centered on the use of chiral reagents to generate the asymmetric centers at C-8a and C-2. Apparently the chiral nature of aldehyde 4 did not significantly influence the anticipated diastereoselectivity (78:8) using the $Icr_2BCH_2CH{=}CH_2$ allylating reagent. In addition, the chiral nature of TBDMS-silyl ether 17 did not reverse the anticipated absolute stereochemical outcome for diol 11. Asymmetric dihydroxylation of the azide 18[13] resulted in a slight erosion in diastereoselectivity[14] (5:2) as compared to the TBDMS-silyl ether case. Use of the 1,4-(bis)-dihydroquinine phthalazine ligand during the asymmetric dihydroxylation of 17 also gave a lower diastereoselectivity[14] (2:1).



17 18

Using this synthetic route with D- or L-xylose and D-arabinose as starting materials allows the systematic preparation of all possible stereoisomers of 3. The biological activity of polyhydroxylated indolizidine analogs of 3 produced by this route will be reported in due course.

Acknowledgment: We would like to thank Dr. R. Tsao and Ms. H. Feng for mass spectral data. Dr. J. Ashcroft for his expert NMR advice and obtaining the ^{13}C, DEPT, HMQC, COSY, NOESY spectra, Mr. George Morton for obtaining the elevated temperature spectra, and the Analytical Support Group at American Cyanamid for the additional spectral data and elemental analysis.

References and Notes:

1. Burgess, K; Henderson, I. *Tetrahedron* **1992**, *48*, 4045 and references therein.

2. Elbein, A.D. *Crit. Rev. Biochem.* **1984**, *16*, 21. Burgess, K.; Chaplin, D.A.; Henderson, I.; Pan, Y.T.; Elbein, A.D. *J. Org. Chem.* **1992**, *57*, 1103.

3. Ostrander, G.K.; Scribner, N.K.; Rohrschneider, L.R. *Cancer Res.* **1988**, *48*, 1091.

4. For an SAR of some polyhydroxylated indolizidines as enzyme inhibitors see: Robinson, K.M.; Rhinehart, B.L.; Ducep, J.-B.; Danzin, C. *Drugs Future* **1992**, *17*, 705.

5. Park, P-u.; Broka, C.A.; Johnson, B.F.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 6205.

6. All compounds gave appropriate spectral data [IR, NMR (^1H and ^{13}C), HRMS(EI) or LRMS(FAB) or combustion analysis and α_D where appropriate], selected spectral data is given: 4: ^1H-NMR (300 MHz, $CDCl_3$) 1.34 ppm (3H, s), 1.40 (3H, s), 2.72 (2H, dd, *J*= 2.2, 5.4 Hz), 3.79 (3H, s), 3.81 (1H, dd, *J*= 5.4, 7.9 Hz), 3.94 (1H, dd, *J*= 5.6, 11.6 Hz), 4.08 (1H, ddd, *J*= 5.6, 6.3, 7.9 Hz), 4.11 (1H, dd, *J*= 6.3, 11.6 Hz), 4.51 (1H, d, *J*= 11.1 Hz), 4.56 (1H, d, *J*= 11.1 Hz), 6.87 (2H), 7.23 (2H). HRMS(EI) 294.1468(-0.1 mmu) $C_{16}H_{22}O_5$ calc 294.1467. FT-IR (oil) 2937 cm^{-1}, 1724, 1515, 1303, 1073,

909, 848, 824, 741. **5**: ^{1}H-NMR (300 MHz, $CDCl_3$) 1.33 (3H, s), 1.45 (3H, s), 1.60-1.74 (2H, m), 2.21 (2H, dt, *J*= 1.0, 6.2 Hz), 3.14 (1H, bs), 3.79 (3H, s), 3.81- 3.92 (3H), 4.05 (1H, ddd, *J*= 2.9, 7.5, 14.2), 4.16 (1H, m), 4.55 (1H, d, *J*= 11 Hz), 4.70 (1H, d, *J*= 11 Hz), 5.05-5.18 (2H), 5.93 (1H, m), 6.89 (2H, m), 7.28 (2H,m). ^{13}C-NMR (75 MHz, $CDCl_3$) 25.1, 26.4, 37.8, 42.0, 55.2, 65.9, 69.4, 72.6, 78.0, 78.2, 109.2, 113.9, 117.5, 129.7, 129.9, 134.7, 159.4. $[\alpha]_D$=-4±1° (c=1.3%, $CHCl_3$). HRMS(EI) 336.1941(-0.4 mmu) $C_{19}H_{28}O_5$ calc 336.1937. **6**: ^{1}H-NMR (300 MHz, $CDCl_3$) 1.35 (3H, s), 1.36 (3H, s), 1.40 (3H, s), 1.45 (3H, s), 1.52-1.62 (2H), 1.66-1.74 (2H), 3.48-3.55 (2H), 3.75 (1H, m), 3.80 (3H, s), 3.86-3.93 (2H), 4.05 (2H, dd, *J*=6.2, 8.0 Hz), 4.18 (2H, m), 4.55 (1H, d, *J*=11 Hz), 4.65 (1H, d, *J*=11 Hz), 6.87 (2H), 7.25 (2H). ^{13}C-NMR(75 MHz, $CDCl_3$) 25.1, 25.2, 25.8, 26.4, 26.9, 38.6, 40.4, 55.3, 65.9, 68.2, 69.6, 72.4, 74.6, 78.1, 78.2, 109.2, 113.8, 113.9, 129.6, 129.7. HRMS(EI) 410.2316(-1.1 mmu) $C_{22}H_{34}O_7$ calc 410.2305. **8**: ^{1}H-NMR (300 MHz, $CDCl_3$) 1.47 (1H, m), 1.71 (1H, m), 1.84 (1H, m), 2.06 (1H, dd, *J*= 1.0, 11.9 Hz), 2.23 (1H, dd, *J*=5.6, 10.2 Hz), 2.37 (1H, m), 2.94 (1H, d, *J*= 10.3 Hz), 3.21 (1H, dd, *J*= 3.0, 12.0 Hz), 3.35 (1H, m), 3.81 (3H, s), 3.92 (2H, bs), 4.23 (1H, m), 4.53 (2H, m), 6.88 (2H, m), 2.28 (2H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) 31.5, 42.2, 55.3, 62.1, 63.1, 66.1, 69.8, 70.5, 66.9, 113.9, 129.4, 130.3, 159.3. HRMS(EI) 293.1614(+1.3 mmu) $C_{16}H_{23}NO_4$ calc 293.1627. **3**: ^{1}H-NMR (300 MHz, CD_3OD) 1.35 (1H, m), 1.56 (1H, m), 1.75 (1H, m), 1.82 (1H, m), 2.05 (1H, m), 2.17 (1H, dd, *J*=1.5, 12.0 Hz), 2.25-2.40 (2H), 2.84 (1H, d, *J*=10.1 Hz), 3.09 (1H, dd, *J*=3.2, 11.9 Hz), 3.55 (1H,m), 3.77 (1H, m). $C_8H_{15}NO_3$ 173 (M^+ 65%), 156 (45), 129 (100) calc 173. **9**: ^{13}C ppm (DEPT, HMQC ^{1}H ppm, assignment): 171.2 (C=O), 171.1 (C=O), 159.3 (Ar H), 130.2 (Ar H), 129.3 (CH, 7.23, Ar H), 113.9 (CH, 6.86, Ar H), 75.7 (CH, 3.38, C-5 H), 72.8 (CH, 5.10, C-2 H), 70.1 (CH_2, 4.58, 4.39, A1, A1'), 66.5 (CH, 5.37, C-8 H), 62.0 (CH, 1.91, C-8a H), 59.8 (CH_2, 3.04, 2.34 C-3 H, C-3 H'), 55.3 (CH_3, 3.79, O-CH_3), 53.6 (CH_2, 2.14, 3.20, C-5 H, C-5 H'), 38.4 (CH_2, 2.37, 1.58, C-1 H, C-1 H'), 32.1 (CH_2, 1.91, 1.78, C-8 H, C-8 H'), 21.5 (CH_3, 2.16, CO-CH_3 at C-5), 21.2 (CH_3, 2.04, CO-CH_3 at C-2) this was also confirmed in the COSY and NOESY spectra.

7. Brown, H.C.; Randad, R.S.; Bhat, K.S.; Zaidlewicz, M.; Racherla, U.S. *J. Am. Chem. Soc.* **1990**, *112*, 2389. Other asymmetric allylation reagents (Roush, W.R.; Walts, A.E.; Hoong, L.K. *J. Am. Chem. Soc.* **1985**, *107*, 8186) were also investigated in this system. Simple allylation of **4** (CH_2=$CHCH_2MgBr$, -78°C) gave a 1:1 mixture of C-8a diastereomers.

8. Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512. Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.

9. Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K-S.; Kwong, H-L.; Morikawa, K.; Wang, Z-M.; Xu, D.; Zhang, X-L. *J. Org. Chem.* **1992**, *57*, 2768 and references therein.

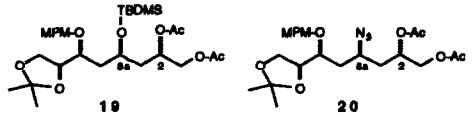
10. Treatment of **8** with DDQ produced the C.6-C.7 anisylidene of **8** which was removed uneventfully with acid. This gave the hydrochloride salt of **3** directly.

11. Coppola, G.M.; Schuster, H.F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids* Wiley Interscience, New York, 1987 pp. 333-336. Rueger, H.; Benn, M.H. *Heterocycles* **1982**, *19*, 23.

12. Compound **14** exists as a 3:2 mixture of rotamers at room temperature in $CDCl_3$. The rotameric resonance observed in the ^{1}H and ^{13}C NMR spectra coalesced at 65° C. The coalesced spectra are reported. ^{1}H-NMR (300 MHz, 65° C in $CDCl_3$) 1.99 ppm (1H, m), 2.04 (3H, s), 2.33 (1H, ddd, *J*= 5.7, 8.5, 14.6 Hz), 3.10 (1H, m), 3.51 (1H, bd, *J*= 12.8 Hz), 3.65 (3H, s), 3.74 (1H, dd, *J*= 5.4, 12.8 Hz), 4.34 (1H, m), 5.13 (2H, s), 5.26 (1H, m), 7.30-7.35 (4H). ^{13}C-NMR (75 MHz, 65° C in $CDCl_3$) 21.0 ppm, 36.4, 39.1, 51.4, 52.5, 53.8, 67.1, 72.9, 127.9, 128.0, 128.5, 136.7, 154.4, 170.0, 171.5. **14** obtained from Scheme II: $[\alpha]_D$=-21±1° (c=1.3%, $CHCl_3$). LRMS(CI) M/z 336 (M^+H, 100%), 292 (75%) $C_{17}H_{21}NO_6$, calc 335 **14** obtained from Scheme III: $[\alpha]_D$=-27±1° (c=1.3%, $CHCl_3$), HRMS(EI) 335.1369(-0.0 mmu) $C_{17}H_{21}O_6$ calc 335.1369. Comparison of TLC behavior in five unrelated solvent systems was identical. FT-IR was identical.

13. Conversion of **5** to azide **18** is a more direct route to **3**, however a lower overall chemical yield was obtained when the azide was introduced at this point in the synthesis and a similar sequence to Scheme I was executed.

14. When the dihydroxylation reaction was run in the absence of a chiral ligand with **17** as the substrate a 1:1 mixture of C-2 diastereomers resulted. Diastereoselectivity at C.2 in the asymmetric dihydroxylation reaction of **17** and **18** was measured by formation of the (bis)acetates **19** and **20**, and integration of the ^{1}H-NMR signal corresponding to the acyl methyl groups.



19 **20**

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