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# Stereoselective Synthesis of Hydroxyindolizidines via Sparteine-Assisted Deprotonation of N-Boc-Pyrrolidine

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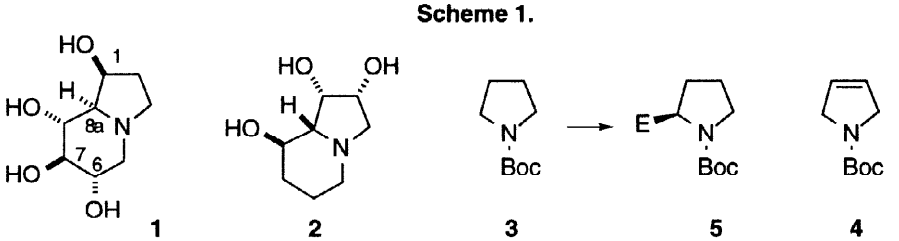
**Abstract:** Three diastereoisomers of 1-deoxycastanospermine were synthesized in enantiomerically pure form. The key step in the synthesis involved reaction of lithiated N-Boc-pyrrolidine in the presence of sparteine with a chiral building block derived from tartaric acid. 

**Keywords:** alkaloids; indolizidines; enantioselective deprotonation

Hydroxylated indolizidines comprise a group of alkaloids containing the 1-azabicyclo[4.3.0]nonane skeleton decorated with a number of hydroxy substituents on both rings.[1] Several of these natural products, e.g., swainsonine (**2**), castanospermine (**1**) and its 6-epi- and 6,7-diepi-isomers act as competitive and reversible glucosidase inhibitors and show potential in treatment of diabetes, obesity, cancer and viral infections.[2] Not surprisingly, the synthesis of these alkaloids, and also of their analogs and derivatives, in enantiomerically pure form, attracted a lot of attention.[2,3]

**Scheme 1.**




A brief analysis of the structure of castanospermine (**1**) indicates that the stereoselective construction of the stereogenic center at the ring junction (C-8a, Scheme 1) is crucial to a successful synthesis. The three hydroxy groups at C-6, C-7 and C-8 are all equatorial and the hydroxy group at C-1 lies inside the concave face of the molecule making it accessible by a carbonyl reduction. We decided to develop a synthesis of polyhydroxyindolizidines based on construction of the C-8a stereocenter as the key step. Our interest in stereoselective deprotonation reactions[4] led us to explore the enantioselective deprotonation of t-Boc-protected pyrrolidine (**3**), developed by Beak,[5] as the means to construct this key element of stereochemistry. Enantioselective deprotonation of Boc-protected pyrroline **4**, using chiral lithium amides, should provide a method to synthesize unsaturated analogs of compound **5**, having the double bond suitably positioned for the later introduction of the hydroxy group(s) present in the five-membered ring of the natural product. As far as the stereogenic centers present at C-6 and C-7 are concerned, we envisaged that they could be delivered by a reagent derived from tartaric acid.

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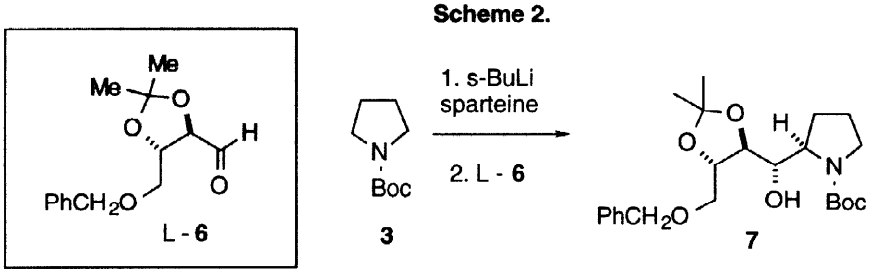
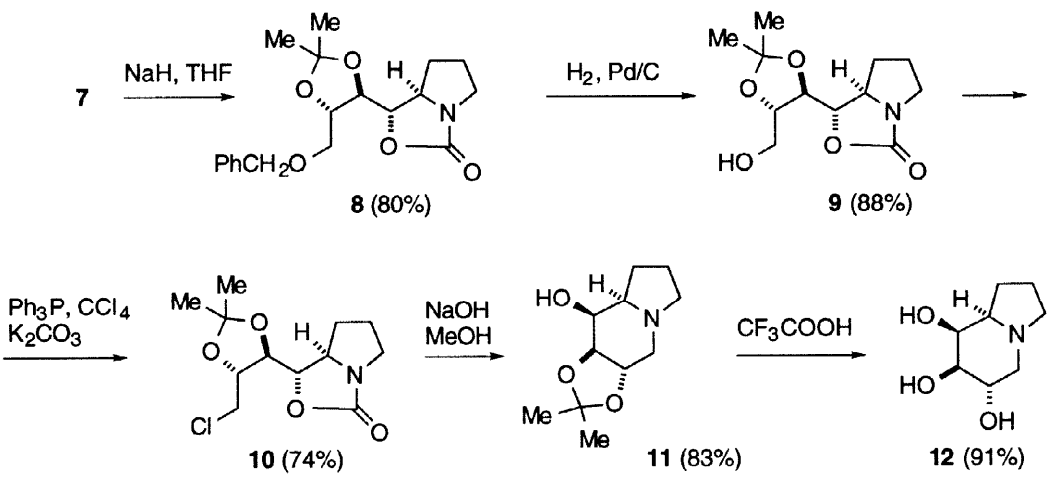
**Scheme 2.**



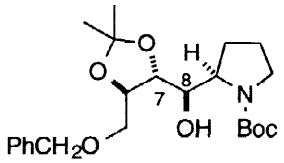

A number of electrophilic reagents derived from tartaric acid is known.[6] Of these, an aldehyde seemed most suitable due to the presence of the OH at C-8 in the target structure. We decided to utilize 4-O-benzyl-2,3-O-isopropylidenethreose (**6**), a known building block,[7] readily available as either enantiomer. Some reactions of this compound with carbanions had been investigated by Mukayiama.[7a] The L isomer of **6** was synthesized from L-tartaric acid by a known 4 step procedure[7] in 40% overall yield. The protected pyrrolidine **3** was lithiated with s-BuLi in the presence of sparteine, using a modified procedure of Beak,[8] and the resulting organolithium species was treated with the aldehyde **6** (Scheme 2). Two diastereoisomeric compounds (out of possible 4), in a ratio of 9:1 (by NMR) were detected in the crude product. Column chromatography yielded the pure compound **7** in 45% yield. The stereochemistry of the two newly created stereocenters in **7** was assigned later upon analyzing the structure of the corresponding trihydroxyindolizidine (vide infra).

**Scheme 3.**

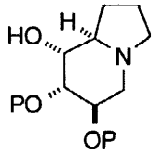



At this point it seemed that the closure of the six-membered ring to form the 1-azabicyclo[4.3.0]nonane skeleton should be relatively straightforward: we envisaged removal of the benzyl group protecting the primary OH, removal of the Boc group and conversion of the OH into a better leaving group as a prelude to cyclization via an intramolecular nucleophilic displacement. However, the removal of the Boc group proved surprisingly difficult. In the end, we observed that treatment of compound **7** with NaH in THF resulted in a facile formation of the cyclic carbamate **8** (Scheme 3). The benzyl group was now easily removed by hydrogenolysis and the resulting alcohol **9** was converted into the corresponding chloride **10** under standard conditions.[3h] Hydrolysis of the carbamate **10** proceeded with concomitant cyclization to give the partially protected indolizidine triol **11**. Removal of the isopropylidene protecting group yielded the triol **12** (8-epi-1-deoxycastanospermine).

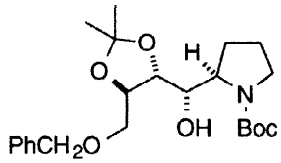
An analogous sequence of transformations involving the other enantiomer of the threose reagent, compound D-**6**, afforded another two diastereoisomers of trihydroxyindolizidine. Thus the coupling of D-**6** with lithiated Boc-pyrrolidine in the presence of sparteine gave two diasteroisomeric products **13** (major) and **14** (minor) in a ratio of 4 : 1 (77% overall yield). Each of these products was converted into the corresponding trihydroxyindolizidine: **15** was obtained from **13** in 41% overall yield, and **16** was obtained from **14** in 27% overall yield, by the 5 step sequence of reactions analogous to the one described above.



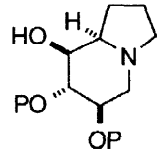

**13**




**15a:** P = $CMe_2$
**15b:** P = H




**14**




**16a:** P = $CMe_2$
**16b:** P = H

*Stereochemical assignments:* Analysis of relative stereochemistry in compounds **7**, **13** and **14** is non-trivial. It is known that the sparteine assisted lithiation of t-Boc-pyrrolidine, followed by a reaction with an electrophile, leads usually to one of the $H_S$ protons being replaced by the electrophile leading to the product having the absolute stereochemistry as drawn in Scheme 1 (structure **5**).[5] As far as the threose reagent **6** is concerned, Mukayiama had established that the diastereotopic face selectivity of this compound in reactions involving lithiated species is relatively small in favor of the anti products[7a] (the syn-anti nomenclature refers to the relative stereochemistry at C-7 and C-8, castanospermine numbering, c.f., **13**). This stereoselectivity was rationalized by Mukayiama on the basis of the chelated Felkin-Ahn model. On this basis one could expect that compound **13**, which is anti, should predominate over **14**, which is syn, and **7** should predominate over the corresponding syn epimer. We have confirmed these structural assignments by careful analysis of the NMR and optical rotation data of compound **11** and it's diastereoisomers **15a** and **16a**.[9] Spectral data for these compounds had been published by other authors, and, after some controversy,[10] provide a solid background for the assignments.

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## References and Notes

1. Takahata, H.; Momose, T. *The Alkaloids* **1993**, *44*, 189.

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

3. Selected recent syntheses of castanospermine and related compounds: a) Jadhav, P. K.; Woerner, F. J. *Tetrahedron Lett.* **1994**, *48*, 8973. b) Martin, S. F.; Chen, H.-J.; Lynch, V. M. *J. Org. Chem.* **1995**, *60*, 276. c) Leeper, F. J.; Howard, S. *Tetrahedron Lett.* **1995**, *36*, 2335. d) Carretero, J. C.; Arrayas, R. G. *J. Org. Chem.* **1995**, *60*, 6000. e) Overkleeft, H. S.; Pandit, U. K.; *Tetrahedron Lett.* **1996**, *37*, 547. f) Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748. g) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546. h) St-Denis Y.; Chan, T.-H. *J. Org. Chem.* **1992**, *57*,

3078. i) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1997**, *53*, 245. *Swainsonine*: j) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112. k) Zhou, W.-S.; Xie, W.-G.; Lu, Z.-H.; Pan, X.-F. *Tetrahedron Lett.* **1995**, *36*, 1291. l) Kang, S. H.; Kim, G. T. *Tetrahedron Lett.* **1995**, *36*, 5049. m) Knight, D. W.; Sibley, A. W. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2179. n) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217 and 5537.

4. Majewski, M.; Lazny, R.; Ulaczyk, A. *Can. J. Chem.* **1997**, *75*, 754 and references therein.

5. a) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. b) Beak, P.; Basu, A. Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. c) Hoppe, D.; Hense, T. *Angew, Chem. Int. Ed. Engl.* **1997**, *36*, 2282.

6. Seebach, D.; Hungerbuhler, E. in *Modern Synthetic Methods 1980*, Scheffold, R. , Ed.; Salle (Frankfurt) and Sauerlander (Aarau), 1980.

7. a) Mukayiama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265. b) Pak, C. S.; Lee, E.; Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523. c) Achmatowicz, B.; Wicha, J. *Tetrahedron Lett.* **1987**, *28*, 2999. d) Saito, S.; Morikawa, Y.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5424.

8. Coupling procedure: Compound **3** (0.239 g, 1.4 mmol) dissolved in $Et_2O$ (2 mL) was added dropwise to a mixture of sparteine (0.439 g, 1.9 mmol), s-BuLi (1.8 mmol) and $Et_2O$ (10 mL) at –78 °C. After stirring for 4h at –78 °C, the aldehyde **L-6** (0.516 g, 2.1 mmol) in $Et_2O$ (1.5 mL) was added dropwise and the resulting solution was stirred for further 15 min. at –78 °C, quenched with AcOH (0.16 mL) and the mixture was warmed to rt for 15 min. Brine was added (10 mL), the mixture was extracted with $Et_2O$ and the product was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:hexane:AcOEt, 7:2:4) which yielded compound **7** (0.251 g, 43%). Properties: $[\alpha]_D^{25}$ –17 (*c* 1.8, $CHCl_3$); $^1$H-NMR: 7.34-7.26 (m, 5H), 5.14 (br, 1H), 4.60 (s, 2H), 4.31 (m, 1H), 3.89 (dd, J=2.7, 10.3 Hz, 1H), 3.69 (t, J=7.8 Hz, 1H), 3.61 (dd, J=6.1, 6.0 Hz, 1H), 3.52 (T, J=8.3 Hz, 1H), 3.48-3.30 (m, 2H), 2.16 (br, 1H), 1.87-1.77 (m, 4H), 1.45 (s, 9H), 1.40 (s, 3H), 1.38 (s, 3H); IR: 3438, 1690 $cm^{-1}$; Analysis: calcd. for $C_{23}H_{35}NO_6$: C, 65.56; H, 8.31; N, 3.33. Found: C, 65.63; H, 8.42; N, 3.01.

9. Compound **11**: $[\alpha]_D^{25}$ +25 (*c* 1.2, $CHCl_3$); $^1$H-NMR: 4.14 (br s, 1H), 4.07-3.99 (dt, J=4.2, 10.0 Hz, 1H), 3.42-3.37 (m, 2H), 3.07-3.02 (m, 1H), 2.36-2.21 (m, 4H), 1.94-1.69 (m, 4H), 1.45 (s, 3H), 1.43 (s, 3H); compound **15a**: $[\alpha]_D^{25}$ – 49 (*c* 1.2, $CHCl_3$); $^1$H-NMR: 4.23 (t, J=3.2 Hz, 1H), 4.17-4.15 (m, 1H), 3.78 (dd, J=9.6, 3.9, 1H), 3.21 (br s, 1H), 3.05-2.96 (m, 3H), 2.79 (t, J=9.6, 1H), 2.62 (q, J=9.7, 1H), 2.00-1.92 (m, 2H), 1.75 (m, 1H), 1.55 (m, 1H), 1.47 (s, 6H); compound **16a**: $[\alpha]_D^{25}$ +9.1 (*c* 1.0, $CHCl_3$); $^1$H-NMR: 4.19 (dd, J=6.1, 8.0, 1H), 3.73-3.67 (m, 2H), 3.24 (dd, J=7.5, 6.2, 1H), 3.05-2.92 (m, 2H), 2.80-2.69 (m, 2H), 1.97-1.74 (m, 5H) 1.45 (s, 6H).

10. Apparently some structural assignments in reference 3h were incorrect. Structure labelled **21aa** on page 3081 in this reference should be **21ba** (and vice versa) and structure **21bb** should be exchanged with **21ab**. We thank Professor Chan for this information and for the copies of relevant spectra (see also ref. 3b, footnote 6).