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

Marek Majewski,* Jianxing Shao, Ken Nelson, Pawel Nowak and Nicholas M. Irvine Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, SK, S7N 5C9, Canada

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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. © 1998 Elsevier Science Ltd. All rights reserved.

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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}



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 reactions⁴ 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 pyrrolime 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.



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 procedure⁷ 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).



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.



Stereochemical assignments: Analysis of relative stereochemistry in compounds 7, 13 and 14 is nontrivial. 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

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- Coupling procedure: Compound 3 (0.239 g, 1.4 mmol) dissolved in Et₂O (2 mL) was added dropwise to a mixture of sparteine (0.439 g, 1.9 mmol), s-BuLi (1.8 mmol) and Et₂O (10 mL) at -78 °C. After stirring for 4h at -78 °C, the aldehyde L-6 (0.516 g, 2.1 mmol) in Et₂O (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 Et₂O and the product was purified by flash chromatography (SiO₂, CH₂Cl₂:hexane:AcOEt, 7:2:4) which yielded compound 7 (0.251 g, 43%). Properties: [α]_D²⁵ -17 (c 1.8, CHCl₃); ¹H-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 C₂₃H₃₅NO₆: C, 65.56; H, 8.31; N, 3.33. Found: C, 65.63; H, 8.42; N, 3.01.
- 9. Compound 11: [α]_D²⁵ +25 (c 1.2, CHCl₃); ¹H-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: [α]_D²⁵ 49 (c 1.2, CHCl₃); ¹H-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: [α]_D²⁵ +9.1 (c 1.0, CHCl₃); ¹H-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).
- 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).