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Total synthesis of (±)-6-deoxycastanospermine: an application of the addition of organoboronates to *N*-acyliminium ions

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Abstract

An efficient synthesis of (±)-6-deoxycastanospermine is reported, using a diastereoselective coupling of organoboronates with *N*-acyliminium ions as the key step. The construction of the indolizidine ring system is completed using a subsequent reductive amination reaction. © 2000 Elsevier Science Ltd. All rights reserved.

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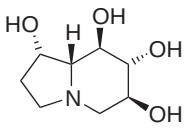
The powerful glycosidase activity of the polyhydroxylated indolizidines has lead to widespread interest in their synthesis. Among such compounds, castanospermine **1** is a prominent target, since its potent glucosidase inhibition has made it a candidate for treatment of various diseases, including cancer, malaria and obesity. While castanospermine has remained a popular target for synthesis, it is readily available in multikilogram quantities from natural sources.[1] The synthesis of rare or totally synthetic polyhydroxylated indolizidines is of significant interest, both because of the challenge inherent with the stereoselective formation of densely functionalized *N*-heterocycles,[2] and because such compounds may possess significant glycosidase activity or other useful biological activity. One such target is (+)-6-deoxycastanospermine, of which there are two reported syntheses,[3] both achieved with relatively low overall yields (5% from literature intermediates). We report herein an efficient synthesis of (±)-6-deoxycastanospermine, which uses as its key step the highly stereocontrolled addition of an organoboron compound to an *N*-acyliminium ion.



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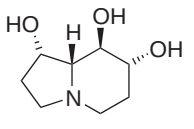

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Petasis and co-workers have shown that boronic acids act as mild nucleophiles in Mannich reactions, leading to allylamines, α-amino acids and β-amino alcohols.[4] We recently extended this concept, demonstrating that alkenyl and arylboronates undergo addition reactions with certain in situ generated *N*-acyliminium ions. For instance in the case of pyrrolidine substrates bearing an oxygen atom at the 3-position, additions proceed in high yield and diastereoselectivity, favoring the *cis*-2,3-substituted products.[5] The relatively mild conditions employed for this reaction, and the ready accessibility of functionalized alkenylboronates and appropriately substituted *N*-acyliminium ion precursors, led us to envisage this reaction as the key step in a general approach to indolizidine and pyrrolizidine alkaloids. This strategy is demonstrated for 6-deoxycastanospermine **2** (Fig. 1). Retrosynthetic disconnection of the indolizidine ring of **2** leads to intermediate **3**, which could in turn be obtained via *syn*-dihydroxylation of **4**. Ring closure of **3** could be anticipated to occur either through an S_N2 displacement, reductive amination or lactamization, depending upon the oxidation state of the terminal carbon of the 4-carbon substituent. Introduction of the butenyl fragment of **4** was envisaged using the stereoselective coupling of an *N*-acyliminium precursor **5** with an *E*-alkenylboronate **6**. In turn, these precursors would be accessible from a protected 2-pyrroline derivative **7** and homopropargyl alcohol.

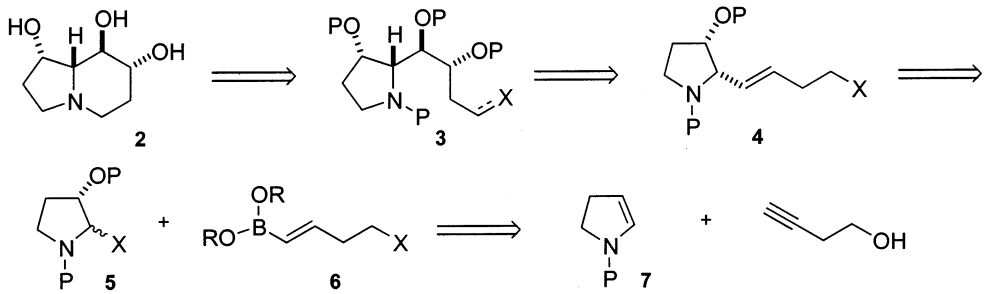
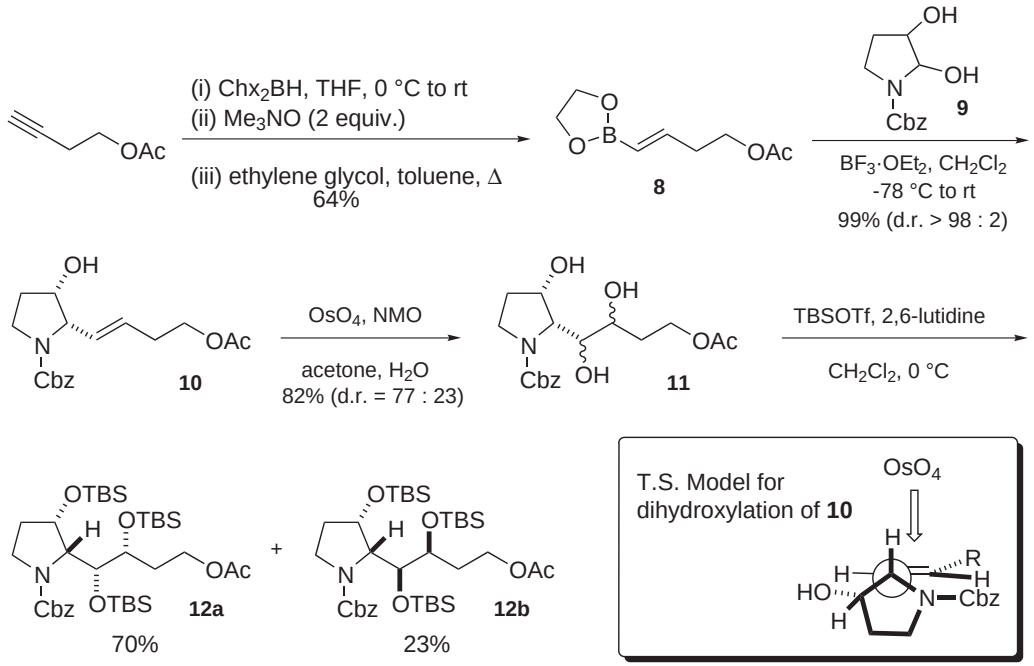


Figure 1. Retrosynthesis of 6-deoxycastanospermine

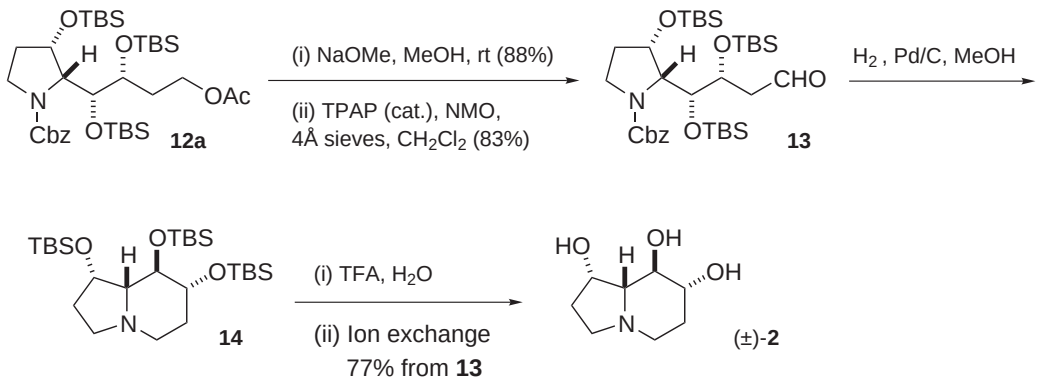
This strategy was realized through the addition of alkenylboronate **8** (1.1 equiv.) to the *N*-acyliminium ion derived from **9** (Scheme 1). This reaction proceeded as anticipated with excellent diastereoselectivity, and, in quantitative yield, on small or multigram scale. Boronate **8** was prepared from 1-acetoxybut-3-yne using a general one-pot procedure developed for producing ethylene glycol boronates, which was modified from known literature procedures for alkenylboronic acid and ethylene glycol boronate synthesis.[6] Diol **9** was synthesized in two steps from pyrrolidine via OsO_4 catalyzed dihydroxylation of Cbz protected 2-pyrroline.[5] With all of the carbons of the indolizidine skeleton in place, introduction of the requisite hydroxyl groups was achieved through dihydroxylation of **10** using 1 mol% OsO_4 and NMO in wet acetone. Triol **11** was formed as an inseparable mixture in 82% yield, with modest diastereoselectivity (3.3:1 as determined by crude NMR).[7] Protection of all three hydroxyl groups was not successful with TBSCl/imidazole, but proceeded readily using TBSOTf/2,6-lutidine and allowed the ready separation of major diastereomer **12a** and minor diastereomer **12b**. The major diastereomer **12a** has the correct stereochemical relationship for conversion to 6-deoxycastanospermine. The preferential formation of **12a** can be rationalized by Vedejs' model for the dihydroxylation of *E*-alkenes,[8] in which OsO_4 approaches the most sterically accessible face of the alkene (Scheme 1 inset). The conformation of the T.S. is such that the allylic C–H is orthogonal to the C=C

bond, with the more sterically demanding CHOH group adopting an anticlinal position and the N-Cbz group a synclinal position with respect to the alkene.



Scheme 1.

The orthogonally protected intermediate **12a** was selectively deprotected to give the primary alcohol, in 88% yield by acetate hydrolysis using NaOMe/MeOH at room temperature for 20 min (Scheme 2). Oxidation of the primary alcohol was sluggish using Dess–Martin reagent,[9] affording 63% yield of aldehyde **13** with 17% recovered starting material. By contrast, catalytic TPAP oxidation[10] to **13** was faster and high yielding. Hydrogenation of **13** removed the Cbz group, with concomitant ring-closing reductive amination to afford the indolizidine ring system **14**. Direct deprotection of **14** with TFA/H_2O[11] followed by purification by cation-exchange chromatography (Varian SCX resin, MeOH–2 M NH_3 in MeOH) gave (±)-6-deoxycastanospermine.[12]



Scheme 2.

The synthesis of (±)-6-deoxycastanospermine has been achieved in seven chemical steps from diol **9**, in 32% overall yield. The foundations of the synthesis are the stereoselective coupling of an alkenylboronic ester with an *N*-acyliminium ion, alkene dihydroxylation, and ring-closing reductive amination. Most significantly the generality of this approach should allow for the synthesis of other natural and unnatural polyhydroxylated indolizidines and pyrrolizidines. Further studies on the utility of nucleophilic organoboron additions to *N*-acyliminium ions will be reported in due course.

Acknowledgements

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References

1. See: Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1994**, *50*, 2131–2160, and references cited therein.
2. For approaches to synthetic analogues of castanospermine, see: Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045–4066. For approaches to polyhydroxylated alkaloids, see: Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev*. **1995**, *95*, 1677–1716. For recent approaches to indolizidine synthesis, see: Michael, J. P. *Nat. Prod. Rep*. **1999**, *16*, 675–696.
3. (a) Reymond, J.-L.; Vogel, P. *J. Chem. Soc., Chem. Commun*. **1990**, 1070–1072. (b) Reymond, J.-L.; Pinkerton, A. A.; Vogel, P. *J. Org. Chem*. **1991**, *56*, 2128–2136. (c) Bhide, R.; Martezaei, R.; Scilimati, A.; Sih, C. *Tetrahedron Lett*. **1990**, *31*, 4827–4830.
4. (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett*. **1993**, *34*, 583–586. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1997**, *119*, 445–446. (c) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463–16470. (d) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1998**, *120*, 11798–11799.
5. Batey, R. A.; MacKay, D. B.; Santhakumar, V. *J. Am. Chem. Soc*. **1999**, *121*, 5075–5076.
6. Hydroboration/oxidation: Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, 103–105. Boronate transesterification: Douglass, J. E. *J. Am. Chem. Soc*. **1964**, *86*, 5431–5433.
7. Control of the diastereoselectivity of dihydroxylation by acyclic alkenes with allylic nitrogen substituents is known, although the facial selectivity is less predictable than for induction by allylic oxygen substituents, see; Cha, J. K.; Kim, N.-S. *Chem. Rev*. **1995**, *95*, 1761–1795. It is also known that the diastereoselectivity can be solvent dependent; see: Krysan, D. J.; Rockway, T. W.; Haight, A. R. *Tetrahedron: Asymmetry*. **1994**, *5*, 625–632.
8. Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc*. **1986**, *108*, 1094–1096.
9. Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4156–4158.
10. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun*. **1987**, 1625–1627.
11. Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem*. **1993**, *58*, 7096–7099.
12. (±)-6-Deoxycastanospermine: IR (neat) 3392 (br), 2941, 2801, 1441, 1372, 1328, 1114, 1060, 837 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.22 (ddd, $J=6.5$, 4.5, 2.0 Hz, 1H), 3.35 (m, 2H), 2.88 (dt, $J=9.0$, 2.0 Hz, 1H), 2.81 (ddd, $J=12.0$, 4.5, 2.5 Hz, 1H), 2.13 (m, 1H), 2.01–1.89 (m, 2H), 1.82–1.71 (m, 2H), 1.50 (ddt, $J=14.5$, 8.5, 2.0 Hz, 1H), 1.39–1.33 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 74.64, 72.46, 71.97, 70.55, 52.53, 49.89, 33.50, 32.24; HRMS (EI) calcd for $C_8H_{15}NO_3$ (M^+) 173.1052, found 173.1055.

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