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Potentially General Synthesis of Polyhydroxyindolizidines

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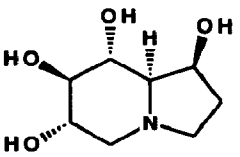
Summary: Allylboration of pentose derivatives with (Z)-3-(methoxy)methoxyallyldiisopinocampheylboranes provides octose derivatives with excellent diastereoselectivity. These intermediates are efficiently utilized for the synthesis of polyhydroxyindolizidines.

Castanospermine[1] **1**, 6-*epi*-castanospermine[2] **2** , and swainsonine[3] **3** are polyhydroxyindolizine alkaloids isolated from natural products. These alkaloids are potent inhibitors of glycohydrolases[4] and show promising antidiabetic,[5] anticancer,[6] antiviral,[7] and anti-AIDS activities.[8] Several elegant approaches for the synthesis of various polyhydroxyindolizidines have been reported.[9]



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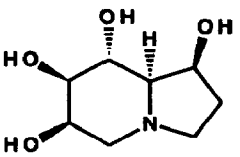

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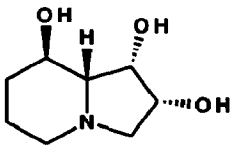

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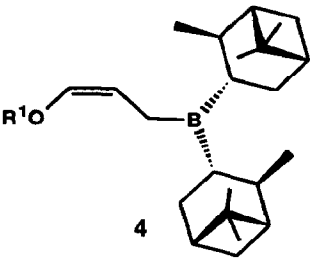
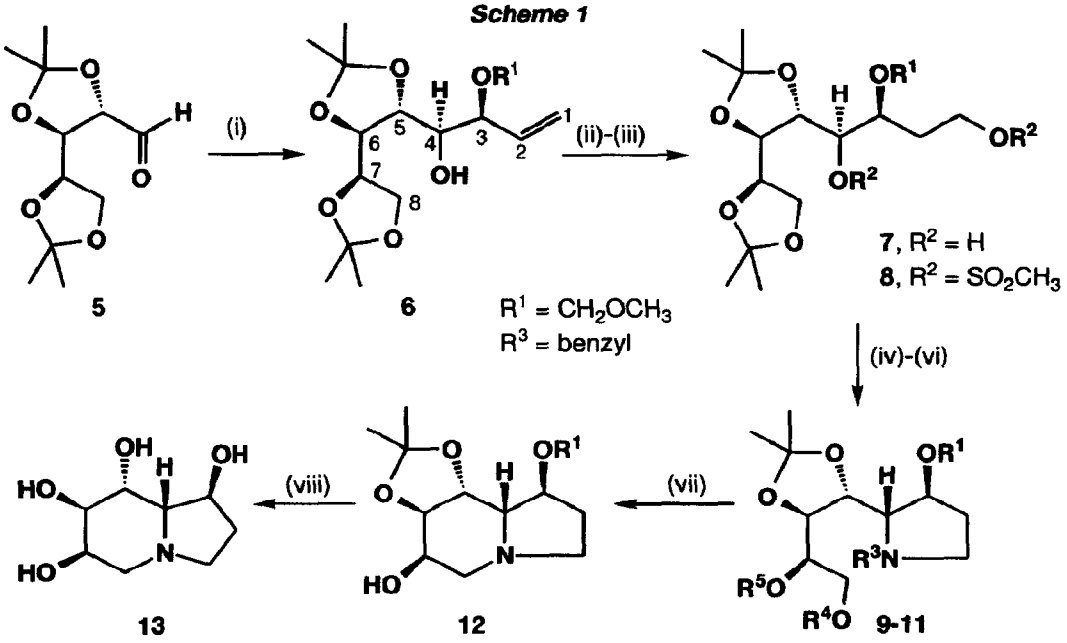


4

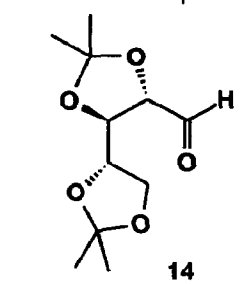
In this communication we report a highly stereoselective and potentially general synthesis of polyhydroxyindolizidine. Allylboration using allyldiisopinocampheylboranes[10] has proved to be a very powerful asymmetric carbon-carbon bond forming reaction. (*Z*)-3-(Methoxy)methoxy allyldiisopinocampheylborane[10g] **4** is a useful allylboration reagent for enantio- and diastereoselective synthesis of *threo* diols. We thought that the addition of **4** to pentose derivatives would generate octose derivatives with five well defined contiguous chiral centers. These acyclic octose derivatives then can be cyclized to bicyclic polyhydroxyindolizidines. Since all the possible isomers of pentoses (viz. D- and L-xylose, ribose, lyxose and arabinose) are commercially available, our strategy has a potential to generate all 32 isomers of polyhydroxyindolizidines by the combination of the appropriate pentose derivative with the allylborane.

Scheme 1



9, R^4, R^5 = -$C(CH_3)_2$-; **10**, R^4 = R^5 = H; **11**, R^4 = p-toluenesulfonyl, R^5 = H

(i) reagent **4** at -78 ^{0}C then NaOAc/ H_2O_2, yield 79%; (ii) dicyclohexylborane then NaOAc/ H_2O_2 (iii) CH_3SO_2Cl/ pyridine, overall yield 64% in two steps from **6**; (iv) benzylamine (neat), 70 ^{0}C/ 18h, yield 88%; (v) 50% aq. CF_3COOH, 0 ^{0}C/ 2h/ yield 94%; (vi) p-toluenesulfonyl chloride/ pyridine, yield 74%; (vii) Pd on C/ DABCO/ EtOH, yield 58%, (viii) Bio-Rad AG-50W-X8 H^+ resin/ 50% aq. EtOH/ 70 ^{0}C/ 3h, yield 80%



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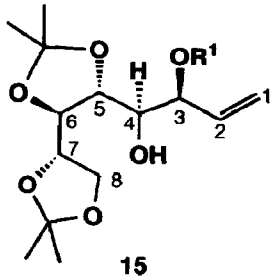

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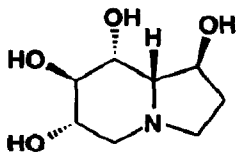

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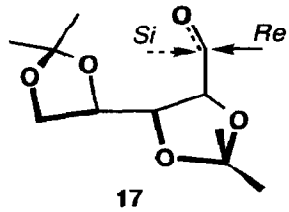

17

We selected the readily available D-arabinose derivative[11] **5** to demonstrate our strategy. Thus, allylboration of **5** with (*Z*)-3-(methoxy)methoxyallyldiisopinocampheylborane **4** followed by oxidative workup provided octose derivative **6** in >80% yield and with >99% diastereoselectivity. In the case of polyhydroxy derivatives several protection-deprotection steps are needed to unmask a desired hydroxyl group. Fortuitously, all the hydroxyl groups in **6** are protected except the one at C-4 that needs to be displaced with a nitrogen nucleophile.

The octose derivative **6** was used as an intermediate in the synthesis of 6,8a-*diepi*-castanospermine (*Scheme1*). Thus hydroboration of **6** with dicyclohexylborane followed by oxidation yielded the diol **7**. The dimethanesulfonate derivative **8** on treatment with benzylamine provided pyrrolidine derivative **9**. Displacement of methanesulfonate at C-4 in **9** occurs with complete inversion of configuration. Initial attempts to selectively remove one acetonide moiety with the cation exchange resin (H^+ form) resulted in loss of both the MOM and the acetonide protecting groups and provided a highly hygroscopic pentahydroxypyrrolidine derivative. This difficulty was readily overcome by the selective removal of one acetonide group under milder conditions (50% aqueous trifluoroacetic acid). The resulting monoacetonide **10** on treatment with p-toluenesulfonyl chloride in pyridine provided monotosylate **11**. Hydrogenolytic removal of the N-benzyl group with Palladium black followed by *in-situ* displacement of tosylate furnished the indolizidine[12] derivative **12**. The desired 6,8a-*diepi*-castanospermine **13** was obtained by deprotection of **12** with the cation exchange resin (H^+ form). Similarly, L-xylose derivative[13] **14** on treatment with (*Z*)-3-(methoxy)methoxyallyldiisopinocampheylboranes **4** provided the octose derivative **15** in 60% yield and 99% diastereomeric purity. Further transformation of **15** into 8a-*epi*-castanospermine **16** was achieved following a similar sequence of reactions as outlined in *Scheme 1*.

The minimum energy conformation[14] of **5** where the aldehyde group is anti-periplanar to the oxygen on the neighboring carbon (dipole-dipole interaction) can be used to explain the high level of distereoselectivity observed in the allylboration reaction. The *Re* face attack as shown in **17** is favored over the *Si* facial attack due to steric hindrance. The 4,5-O-Isopropylidene ring blocks the coordination of the aldehyde to the hindered borane **4** from *Si* face. Consequently, the complexation of the allylborane followed by allyl transfer takes place preferentially from the less hindered *Re* face.

In conclusion, allylboration of pentose derivatives with (*Z*)-3-(methoxy)methoxyallyldiisopinocampheylborane **4** provides octose derivatives with excellent diastereomeric purity. We have demonstrated in two cases that these octose derivatives can be used for the synthesis of polyhydroxyindolizidines. The approach outlined here has a potential to be very general.

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12. All new compounds reported were fully characterized by ^{1}H and ^{13}C NMR, IR and HRMS spectrometry.
13. L-Xylose aldehyde **14** was prepared using the procedure described for the synthesis of **5**.
14. The minimum energy conformation of aldehyde **5** was determined as follows: The Cambridge Crystal Database was searched for X-ray structures of the compounds containing two isopropylidene rings with the same absolute configuration as **5**. A representative X-ray structure[15] was imported into Sybyl[16] and was used to build aldehyde **5**. Charges (Gasteiger-Huckel) were assigned and the structure minimized until it converged. After energy minimization the conformation of the two isopropylidene rings in **5** was identical to the starting X-ray conformation.
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16. Sybyl® a Molecular Modeling Software is available from Tripos Associates, Inc., St. Louis MO 63144-2913.

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