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Enantiospecific Synthesis of Functionalised Indolizidines. Synthesis of (8*S*, 8a*R*)-6,7-Dehydro-8-hydroxyindolizidine.

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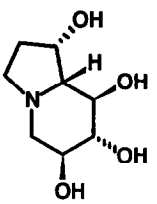
Key Words: *L-Proline; indolizidines; enantiospecific synthesis; glycosidase inhibitors.*

Abstract: *A stereocontrolled route for the title compound has been realised using L-proline as starting material. The route is amenable to modifications to provide a variety of stereoisomers of glycosidase inhibitors.*

Polyhydroxylated indolizidines have recently gained considerable synthetic interest as possible candidates for glycosidase inhibitor design. A major driving force is attributable to the fact that castanospermine ***1***, isolated in 1981,[2] is a potent α-glucosidase-I inhibitor capable of inhibiting HIV infections.[3] Several analogues of castanospermine are currently being evaluated for their ability to intercept the HIV infection, and recently some more hydrophobic derivatives have been shown to be more potent *in vivo* and *in vitro*.[4]



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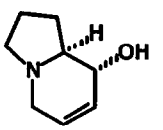

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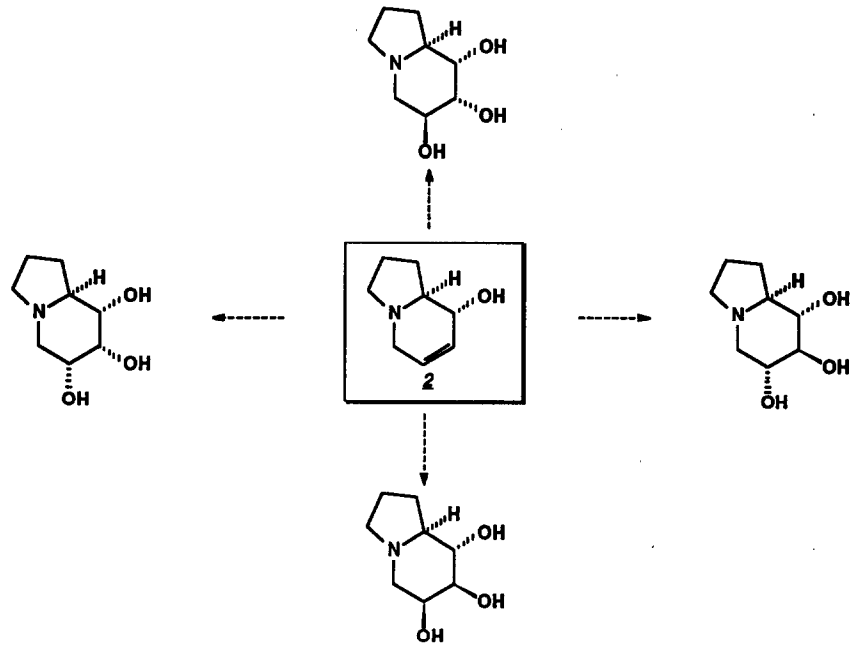
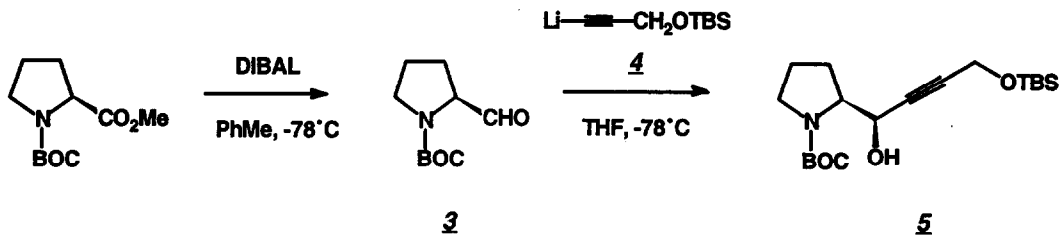
Compounds of this general class have also other pharmacological functions such as antidiabetic,[5] antimetastatic[6] and anti-tumor proliferative[7] actions. It is interesting to note that only two groups have used non-carbohydrate starting materials.[8] Many of the possible stereoisomers are currently not available, because they are either not naturally occurring or synthetic access to these compounds is not yet available. Structure-activity relationships have been studied,[9] but recent reports clearly indicate that much more work needs to done before the SAR picture becomes clear.[10]

In this Letter, we present a rapid stereocontrolled route to (8*S*, 8a*R*)-6,7-dehydro-8-hydroxyindolizidine **2**, a potential precursor to a number of polyhydroxyindolizidines, as shown in the scheme below.



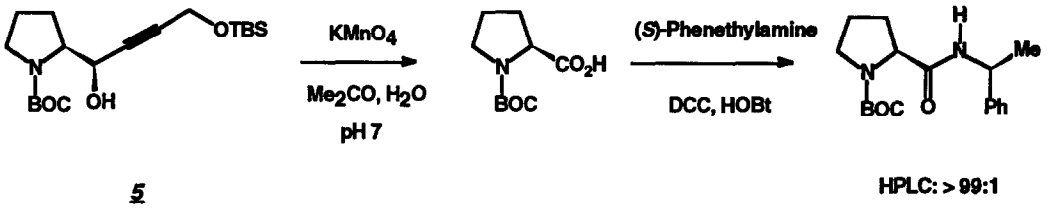
BOC-Proline methyl ester was reduced (DIBAL, toluene, -78 °C) to the corresponding BOC-prolinal **3**.[11,12] Due to its expected lability towards racemization,[13] we decided to carry it forward in the synthesis without purification. Treatment of **3** with the lithio compound **4** of propargyl alcohol TBS ether proceeded cleanly to give the carbinol **5** and its diastereomer (7:1 ratio, 54 % yield).



3 **5**

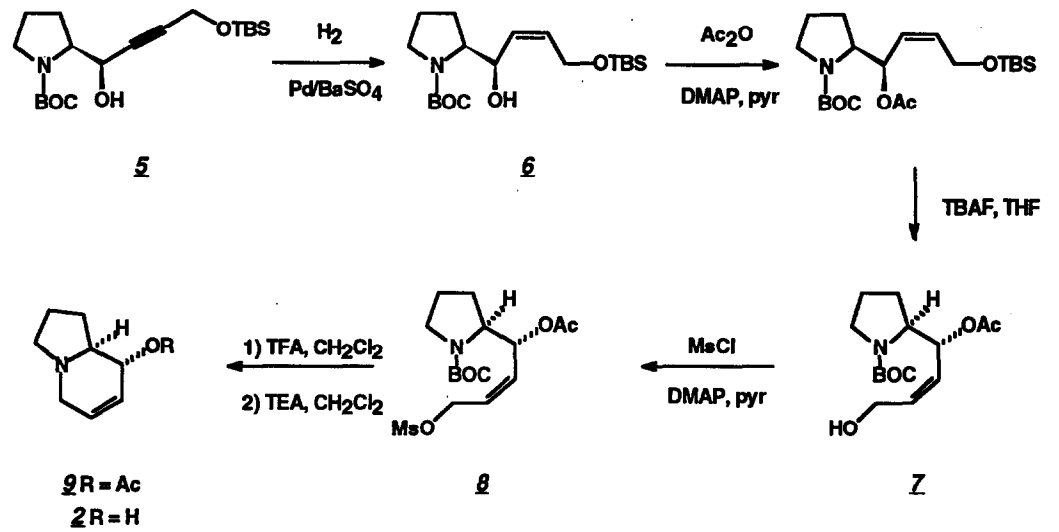
At this stage, we decided to confirm the optical integrity of the route. This was done by exhaustive oxidation ($KMnO_4$) of the propargyl alcohol **5** to BOC-proline, which was coupled with (*S*)-a-methylbenzylamine, and the product was assayed by HPLC. Comparison with the trace from an authentic

mixture of diastereomers led to the conclusion that less than 0.5 % epimerization had occurred during these stages of the synthesis.



5 HPLC: > 99:1

Our next stage called for *cis*-selective partial hydrogenation of the triple bond to the allyl alcohol 6, which was realised in high yield and high selectivity (H_2, $Pd/BaSO_4$, quinoline, rt, 15 min, quant, >95:5 ratio). The alcohol was protected (Ac_2O, pyr, DMAP, 85 %)[14] and the TBS ether was cleaved (n-Bu_4NF, THF, rt, quant.)[15] to give the terminal alcohol 7. In preparation for the cyclization, the terminal alcohol was converted to the mesylate 8 (MsCl, Et_3N, CH_2Cl_2). The BOC protection was removed (TFA, CH_2Cl_2) to give the secondary amine, whose cyclization was effected by treatment with base (Et_3N, CH_2Cl_2) to give the protected target compound 9 in 60 % overall yield from 7. Cleavage of the acetate (LiOH, aq. THF) gave the target compound 2.



5 6 7 8 9 R = Ac 2 R = H

In summary, we have developed a route to provide access to a highly functionalised indolizidine derivative allowing entry to several glucosidase inhibitor analogues. A major disadvantage of the route is the inaccessibility of the other diastereomeric series, a problem whose solution and the synthesis of polyhydroxylated indolizidines will be the subject of a later publication.

References and Notes:

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