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A NEW APPROACH TO SWAINSONINE AND CASTANOSPERMINE ANALOGUES

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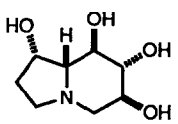
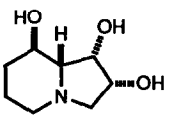
Abstract: (1S, 2R, 7R, 7aR)-1,2,7-Trihydroxypyrrolizidine (**1**) is prepared by elaboration of an erythrose derivative (**4**) via an asymmetric allylation reaction; this approach promises to be widely applicable to syntheses of polyhydroxylated indolizidine and pyrrolizidine alkaloids.

Swainsonine and castanospermine are naturally occurring amino sugar derivatives. These and related compounds are potent inhibitors of certain glycosidase enzymes[1,2] and, perhaps as a consequence of this,[3] some have activity against HIV-1 in cell cultures.[4] More data is required to correlate molecular structures of these polyhydroxylated indolizidine and pyrrolizidine alkaloids with their specific roles as glycosidase inhibitors but only a few analogues of castanospermine and swainsonine have been isolated from natural sources. Consequently, progress in this area appears to be limited by development of synthetic routes to analogues which are not naturally occurring.

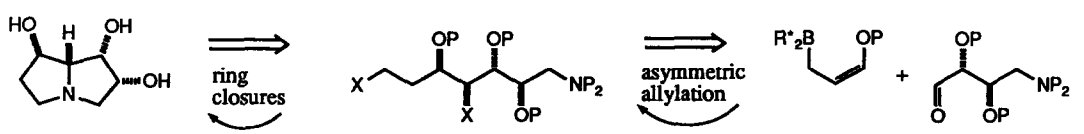


castanospermine



swainsonine

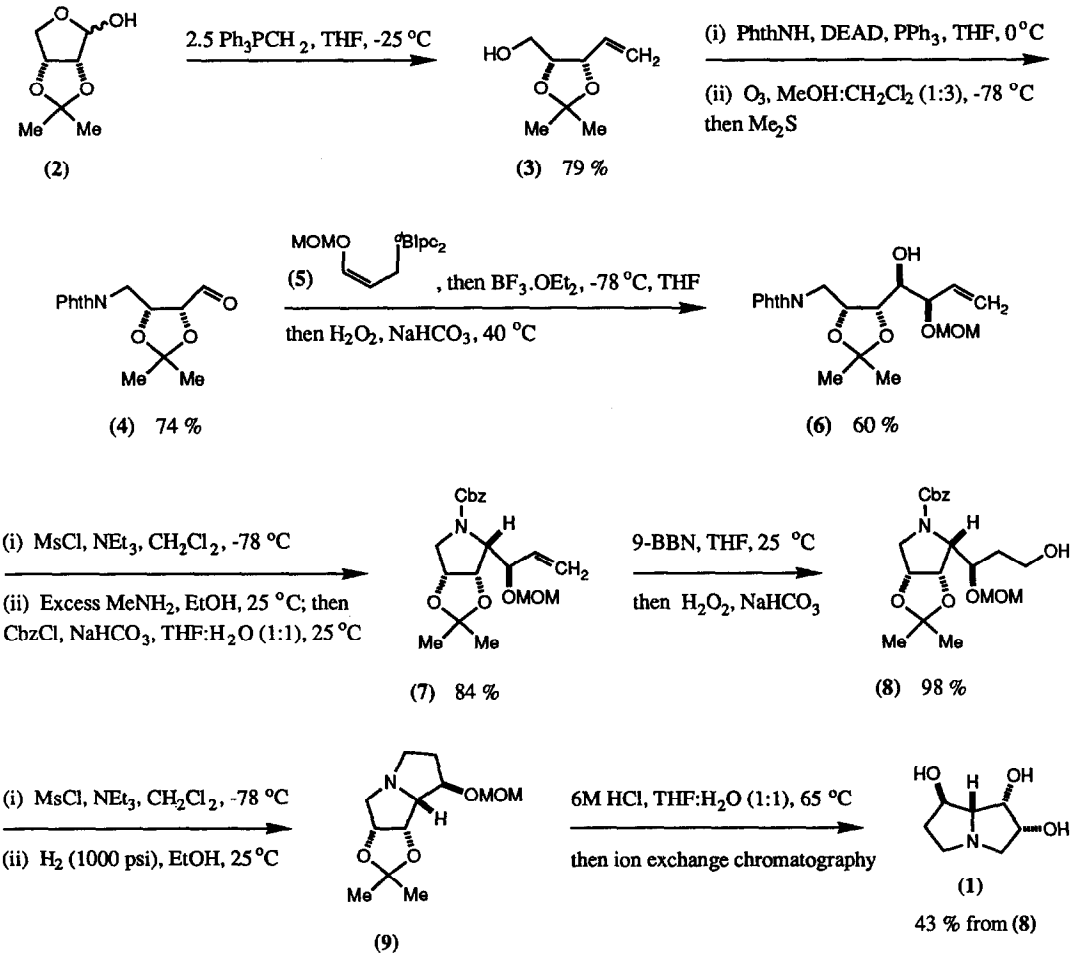
Most of the syntheses of polyhydroxylated indolizidine and pyrrolizidine alkaloids reported to date are based upon manipulation of carbohydrates, methods in which most stereochemical features of the product originate from chirality of the starting material. The emphasis of this project is use of contemporary allylation techniques to construct monochiral acyclic intermediates for cyclization in a late stage of the synthesis; a concept illustrated here in a preparation of the ring contracted swainsonine derivative (**1**).



(1)

P = protecting group; X = leaving group

Our synthesis began with 2,3-*O*-isopropylidene D-erythrose (**2**), a chiron which is conveniently available from D-isoascorbic acid (two steps).[5] This lactol was readily opened via a Wittig reaction giving alkene (**3**), which was then subjected to Mitsunobu displacement with phthalimide,[6] followed by ozonolysis affording N-protected 1,4-amino aldehyde (**4**), a substrate for the pivotal homologation reaction. Asymmetric allylation with [(Z)-γ-(methoxymethoxy)allyl]diisopinocampheylborane (**5**) from (+)-pinene, a reagent developed by H. C. Brown and co-workers,[7,8] transformed this aldehyde into alcohol (**6**). A carbon-carbon bond and two new asymmetric centers are formed in this transformation; furthermore, we were unable to detect diastereomeric impurities (HPLC, GC, and NMR) hence this allylation proceeds with exceptionally high stereocontrol.

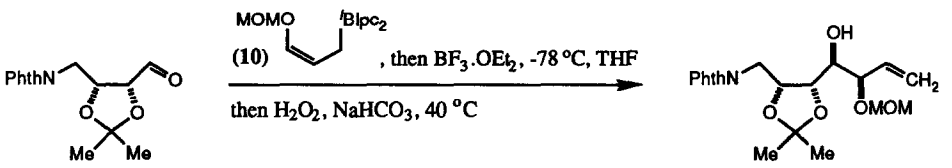


Subsequent steps in this synthesis centered around ring-closures and manipulation of protecting groups. Thus mesylation of alcohol (**6**) followed by deprotection of the terminal amine brought about cyclization to give a pyrrolidine which was immediately N-protected as an O-benzyl carbamate (**7**). In preliminary

experiments hydrazine was used to remove the phthalyl group but this also resulted in appreciable reduction of the alkene, presumably due to formation of diimide *in situ*; this problem was overcome using methyl amine as an unmasking reagent.[9]

Cyclization to form the second ring was achieved using an approach similar to that used in the first ring closure; hydroboration of alkene (**7**), oxidation to alcohol (**8**), mesylation and reductive deprotection of the nitrogen, effected cyclization to the protected pyrrolizidine alkaloid (**9**). Removal of the isopropylidene and methoxymethyl O-protecting groups, and routine ion exchange chromatography afforded the desired product. Whilst this work was in progress, an alternative synthesis of product (**1**) was published;[10] physical and spectral data for our sample are in accord with those presented in that paper.

Transformation of aldehyde (**4**) into alcohol (**6**) via the asymmetric allylation depicted above, occurs in a Felkin-Anh[11 - 13] or Cornforth[14] sense; this is also the stereochemistry favored by the asymmetric influence of the borane reagent. Consequently, the stereochemical bias of the substrate and the reagent are paired constructively.[15] To establish this, and to determine which factor is dominant , we reacted the same substrate, aldehyde (**4**), with the enantiomeric allylating agent (**10**), i.e. that formed from (-)-pinene.



(**4**) (**6**) d.e. >93 %

Even when the reagent and substrate are apparently mismatched[15], the same diastereomer (**6**) is formed with high diastereoselectivity; substrate control is so prevalent that alcohol (**6**) is formed predominantly, irrespective of which optical antipode of the allylating reagent is used.[16] This result is consistent with similar observations by Roush and co-workers[14,17] who reported exceptionally high diastereoselectivities in allylations of glyceraldehyde and related aldehydes with prochiral allylboronates. All these aldehydes have α-chiral centers incorporated into acetonide fragments; other work indicates substrate control in these reactions may be subordinate to reagent control when the α-chirality is not part of a cyclic system,[18] hence it may be possible to increase the scope of these reactions by adjusting protecting groups attached to the aldehyde component.

The synthetic protocol described here outlines a concept that may be applicable to many syntheses of stereoisomers and other structural analogues of castanospermine and swainsonine. A disadvantage of using any diastereoselective reaction in syntheses of these targets is that extremely small amounts of stereoisomeric impurities can skew results obtained in biological assays. This is a problem that can occur when samples are prepared via any route, e.g. conventional carbohydrate chemistry involving manipulation of chiral centers, or syntheses such as the one above where several chiral centers are formed via asymmetric induction. However, asymmetric allylations of other aldehydes available from the chiral pool potentially could be used to prepare many different analogues via similar sequences; this is an advantage because biological results can be

interpreted with certainty if all the stereoisomers that could result from a given synthetic sequence are available. Consequently, our current efforts are focused on establishing the flexibility of this approach.

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8 In retrospect, for this particular synthesis an achiral borane may have been equally suitable; the issue of reagent versus substrate control is of critical importance when examining the general applicability of this methodology.

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