Tetrahedron Letters, Vol. 33, No. 41, pp. 6077-6080, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

An Asymmetric Synthesis of D-1,6-Diepicastanospermine

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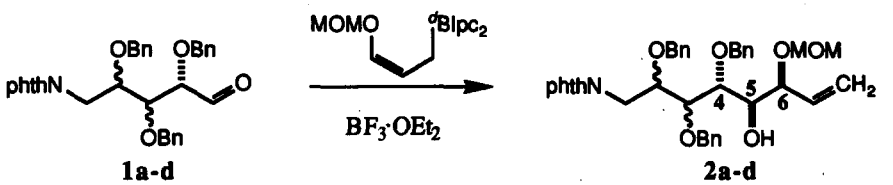
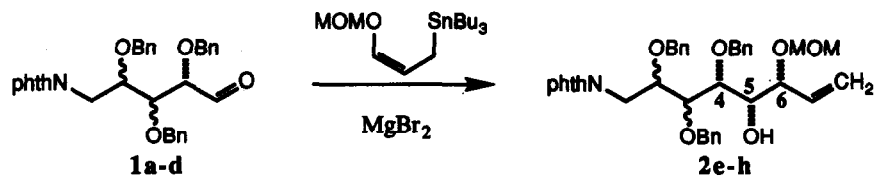
Key Words: castanospermine, 1,6,7,8-tetrahydroxyindolizidine, glucosidase inhibitor.

Abstract: D-1,6-Diepicastanospermine has been prepared via reaction of an allylstannane with the arabinose derivative **1a**. This reaction was almost 100 % stereoselective, but the corresponding allylations of aldehydes **1b** - **d** gave mixtures of isomers. Variable stereodifferentiation in these reactions can be attributed to the influence of the distal (γ) chiral center.

Castanospermine and its stereoisomers are worthwhile synthetic targets due to their proven[1-12] and potential biological activities, particularly with respect to chemotherapy of AIDS, cancer, and diabetes. Nevertheless, most of the thirty-one stereoisomers of castanospermine have yet to be prepared or isolated, despite the efforts of several research groups.[13] Our response to obtaining samples for testing has been to design syntheses that can be readily adapted to give several stereoisomeric products without significant changes in the experimental protocol used for most of the steps. So far, we have shown eight castanospermine stereoisomers can, in principle, be prepared using the reaction shown in equation 1.[14] The allylation methodology used in this transformation[15] is confined to preparations of intermediates with the 4,5-*anti*, 5,6-*syn* relative stereochemistry, *eg* **2a-d**, as shown. This paper describes efforts to prepare the 4,5-*syn*, 5,6-*syn* isomers **2e-h**, and an asymmetric synthesis of D-1,6-diepicastanospermine.

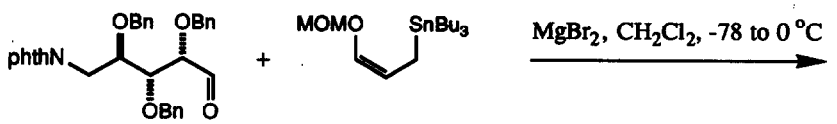


1a-d **2a-d** (1)

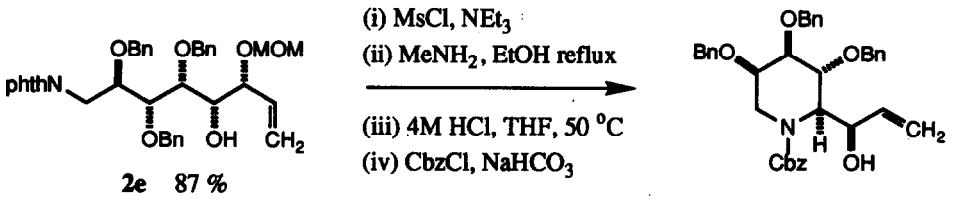


1a-d **2e-h** (2)

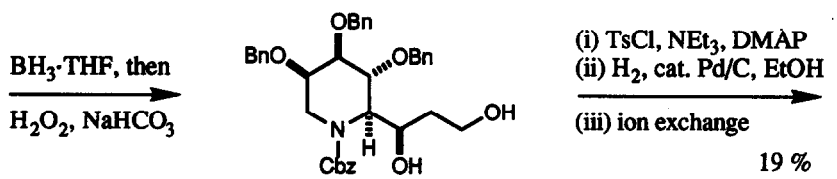
Anti stereochemistry about the 4,5-junction in compounds **2a-d** (eq. 1) corresponds to allylation of the substrates **1** in a Felkin-Anh sense.[16] We sought to overcome this preference using a chelation controlled,[17] *syn* selective attack with an allylstannane reagent (eq. 2).[18-20] Fortunately, this worked very well for the arabinose derivative **1a**; only one diastereomer of the product was detected by $^{1}H/^{13}C$ NMR, and the HPLC trace of the crude reaction mixture was relatively clean.



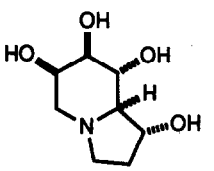
1a **3**



2e 87 % **4** 59 %



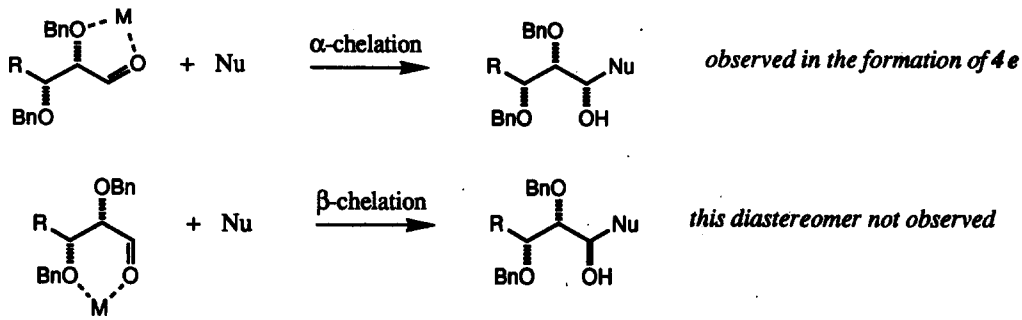
5 67 %



D-1,6-diepicastanospermine

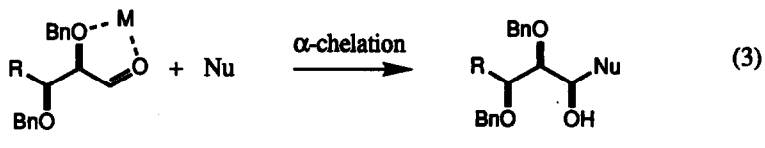
Assignment of stereochemistries for products **2** is non-trivial, especially when they are formed via a reaction which generates two asymmetric centers simultaneously. In the event, stereochemical characterization of compound **2e** was performed by completing the synthesis; the product obtained was spectroscopically identical to a sample of D-1,6-diepicastanospermine prepared via another route.[21,22] Apart

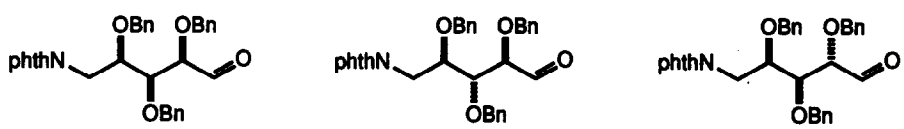
from the allylation reaction, each step in this synthesis is very similar to the analogous transformations described in our first paper on syntheses of castanospermine stereoisomers.[13,23] Substrates **2** are capable of coordinating to $MgBr_2$ via the α, β, and possibly, the γ-benzyloxy groups; one might anticipate coordination to the α and β-groups to be the most significant. In terms of substrate-controlled diastereoselectivity, the α and β-asymmetric centers are mismatched for chelation controlled processes (as illustrated below).



(R = chiral group)

The allylation of **1a** in our synthesis of 1,6-diepicastanospermine is consistent with attack on an α-benzyloxy-chelated intermediate, and not with coordination of the β-benzyloxy substituent. This over-simplistic model implies the stereochemistry at the β-center is irrelevant and allylations of substrates with other relative α/β-configurations should also react with good selectivity, as depicted in equation (3).





In practice, however, allylations of aldehydes **1b-d** with allylstannane **3** gave a mixture of diastereomers in each case (**1b**, 79:13:8:<1; **1c**, 77:23:<1:<1; **1d**, 90:10:<1:<1; stereochemistries not assigned). Qualitative differences in reaction rates were also observed, the arabinose derivative **1a** being the most reactive.

It would be extremely inconvenient to prepare castanospermine stereoisomers via allylations of aldehydes **1b-d**. This work does, however, provide an excellent illustration of the potential influence of distal chiral

centers in substrate-controlled diastereoselectivity. This type of phenomenon has been reported for other reaction types,[24,25] and more will undoubtedly emerge as the field of asymmetric synthesis expands.

Acknowledgments

We thank Dr G. W. Fleet for helpful discussions, Terry Marriot for assistance with the mass spectral analyses, and Dr Alan Kook for help with the two dimensional NMR work. Financial support for this work was obtained from the National Institutes of Health (AI28204A). KB is a recipient of a NIH Research Career Development Award, 1992-7.

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(Received in USA 1 June 1992; accepted 22 July 1992)