

## Stereoselective synthesis of the indolizidine core of the allopumiliotoxins

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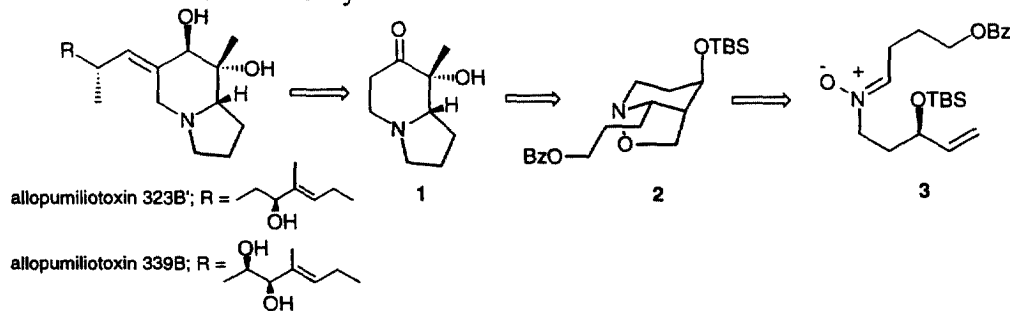
### Abstract

The common indolizidine core leading to the allopumiliotoxins was synthesized using an intramolecular (*Z*)-*N*-4-alkenylnitronc cycloaddition reaction as the key step. The synthesis began with (*R*)-*tert*-butyl-3-hydroxy-pent-4-enoate which was obtained *via* enzymatic resolution using Amano PS lipase. © 1999 Elsevier Science Ltd.

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Indolizidine and quinolizidine alkaloids have been the subject of considerable synthetic effort during recent years [1,2] owing to their interesting and significant biological activities. The toxic skin secretions of the neotropical poison-dart frogs of the family *Dendrobatidae* are rich sources of these alkaloids [3] which include the pumiliotoxin-A class carrying an (*E*)-alkylidene side chain. These alkaloids are divided into three subclasses, the pumiliotoxins, the allopumiliotoxins and the homopumiliotoxins [4], all of which exhibit myotonic and cardiotoxic activity.

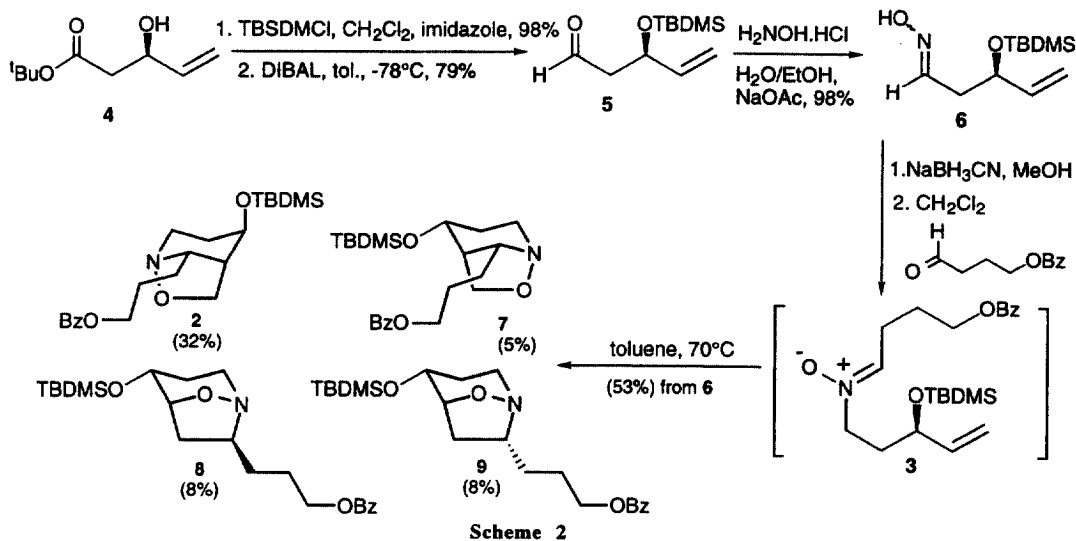


Scheme 1

Several syntheses of the allopumiliotoxins [5] have been reported which use proline or a proline derivative as the starting material. Searching for an alternative route to these interesting molecules, we realised that the indolizidine core 1 can be synthesized from the isoxazolidine 2, in turn derived from the *N*-alkenylnitronc 3 (Scheme 1). We have

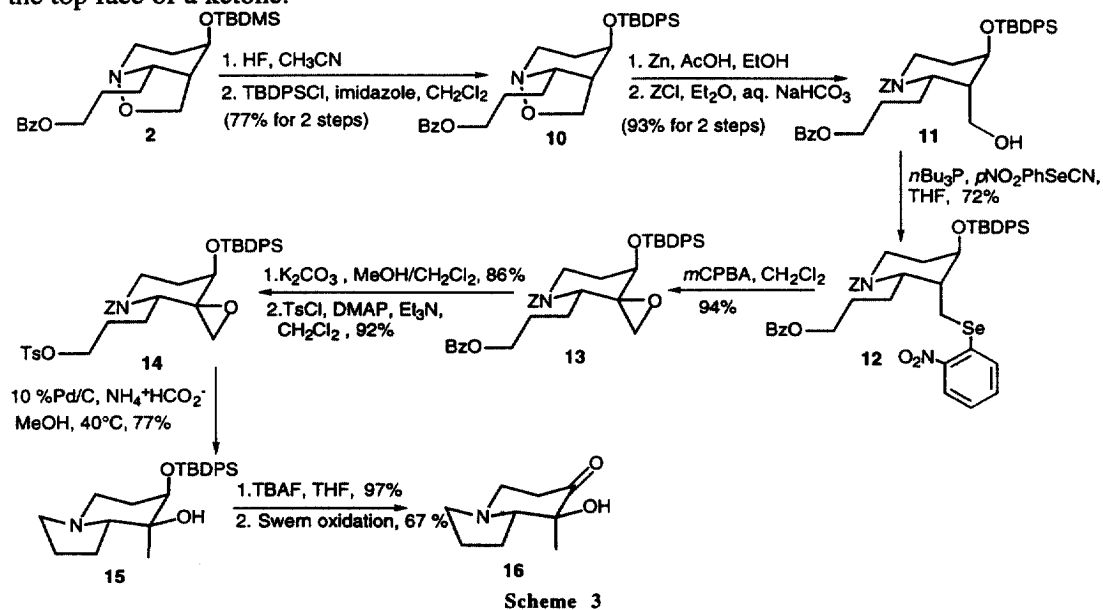
previously used similar *N*-alkenylnitrones in the syntheses of indolizidines 167B, 205A, 207A, 209B [6] and deoxynojirimycin [7].

The aldol reaction of the lithium enolate of *tert*-butyl acetate with acrolein afforded a  $\beta$ -hydroxy ester which was resolved using Amano PS lipase to give **4** (Scheme 2) [8,9]. The (*R*)- $\beta$ -hydroxy ester **4** was protected as its TBDMS ether. Reduction with diisobutylaluminium hydride at low temperature gave the aldehyde **5** which was transformed into the oxime **6** in high yield using aqueous hydroxylamine. The oxime was subsequently subjected to a two-step reduction-condensation procedure affording the nitrone **3**. Without further purification, a dilute solution of **3** was heated for 18 h at 70 °C to give four isoxazolidines **2**, **7**, **8** and **9** (32:5:8:8) in a combined yield of 53% from **6**, with the major product being **2** as shown by <sup>1</sup>H NMR, NOE studies and X-ray crystallographic analysis. Clearly the cycloaddition reaction exhibits a regiochemical preference for incorporation of the newly formed C-C bond in a 6-membered ring [10] in a chair-like transition state which places the OTBDMS group in an axial orientation [11].



Owing to the labile nature of the TBDMS protecting group under the acidic conditions used for N-O bond cleavage, it was exchanged for the more robust TBDPS group (Scheme 3). Treatment of the TBDPS derivative **10** with Zn/AcOH at 65 °C for two hours effected the ring opening, and the resulting free amino group was protected using benzyl chloroformate (ZCl) to give **11**. The alcohol **11** was converted into the selenide **12** using *o*-nitrophenylselenocyanate and *n*-tributylphosphine [12]. On exposure to *m*-CPBA rapid oxidation of the selenide **12** occurred to give a selenoxide intermediate which underwent elimination to provide the corresponding alkene. This alkene was epoxidised *in situ* by the excess *m*-CPBA to give the epoxide **13** as a single stereoisomer. Removal of the benzoyl group was achieved under mildly basic conditions (K<sub>2</sub>CO<sub>3</sub>/MeOH), and the resulting alcohol was converted into the tosylate **14** in high yield. The indolizidine **15** was obtained by subjecting **14** to catalytic transfer hydrogenation using 10% Pd/C with ammonium formate

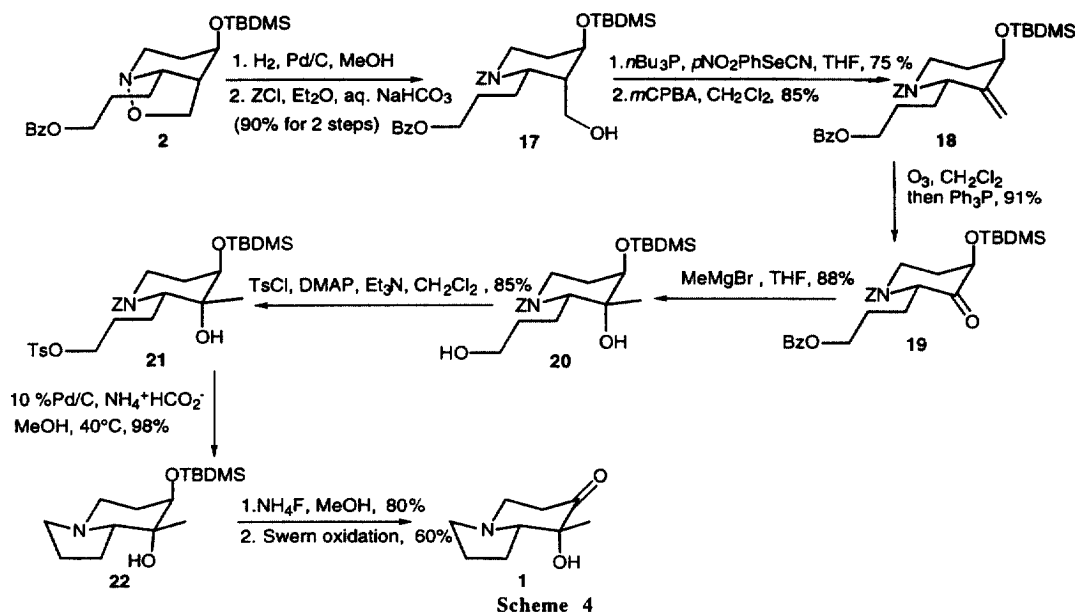
as the hydrogen source [13,14]. Under these conditions, the Z protecting group was removed, and the resulting free amino group displaced the tosylate group to form the indolizidine. Simultaneously, regioselective opening of the epoxide occurred at the less hindered carbon to give the tertiary alcohol 15. Finally, removal of the silyl protecting group and oxidation of the resulting hydroxy group yielded the indolizidine 16. Unfortunately, an X-ray crystallographic analysis<sup>1</sup> of indolizidine 16 revealed the undesired  $\beta$ -orientation of the alcohol and thus indicated that the epoxide 13 was formed by peracid attack on the upper face of the alkene derived from 12. In order to correct the stereochemistry of the tertiary alcohol it was necessary to add a methyl Grignard reagent to the top face of a ketone.



Hydrogenolysis of the oxazolidine 2 and benzyloxycarbonylation of the resulting amine gave 17 (Scheme 4). Formation of the selenide and oxidation with one equivalent of *m*-CPBA gave alkene 18 in good yield. This was ozonolysed to give the ketone 19. Nucleophilic addition with an excess of methyl magnesium bromide gave the tertiary alcohol 20 with the correct relative stereochemistry, and concomitant removal of the benzoyl group. Tosylation gave 21 and catalytic transfer hydrogenation yielded the indolizidine 22. Finally, the silyl protecting group was removed using methanolic ammonium fluoride [15], and the resulting alcohol was oxidised to the indolizidine core 1, which is identical in all respects with the data reported by Overman [16].<sup>2</sup>

<sup>1</sup> Crystal data : monoclinic; C2/c;  $a = 5.655(3) \text{ \AA}$ ,  $b = 12.429(3) \text{ \AA}$ ,  $c = 24.953(2) \text{ \AA}$ ,  $\alpha = 90^\circ$ ,  $\beta = 90.74(3)^\circ$ ,  $\gamma = 90^\circ$ ;  $Z = 8$ ; goodness-of-fit on  $F^2$  1.076; final  $R$  indices [ $I > 2\sigma(I)$ ]  $R1 = 0.0526$ ,  $wR2 = 0.1334$ ;  $R$  indices (all data)  $R1 = 0.0666$ ,  $wR2 = 0.1465$ . mp 72-73 °C. Data deposited in the Cambridge Crystallographic Database.

<sup>2</sup> All new compounds exhibit spectroscopic and analytic/ HRMS data consistent with the assigned structure.



In conclusion, the stereoselective synthesis of the indolizidine core of the allopumiliotoxins was achieved using an *N*-alkenylnitronone-based route. The avoidance of use of proline as a starting material allows this methodology to be generalised and extended to the synthesis of related alkaloids.

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