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Approaches to Diene Based Homopumiliotoxin Alkaloids.

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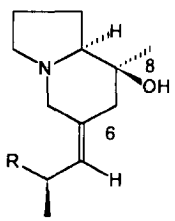
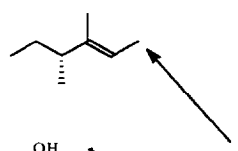
Abstract. Palladium catalysed reductive cyclisation of a 1,1-dibromoalkene to an acetylene gives the core unit of the quinolizidine based diene homopumiliotoxin alkaloids with complete control of stereochemistry of the exocyclic double bond. Copyright © 1996 Elsevier Science Ltd

Pumiliotoxins (A) and (B) were first discovered as two of the three major alkaloids in the Panamanian poison frog Dendrobates pumilo[1]. Since then many other members of this class of alkaloid with variation in the alkyl side chain have been shown to have a wide distribution in amphibians[2]. Pumiliotoxins A and B are characterised by an indolizidine ring system with a 6-alkylidene side chain and usually a tertiary alcohol at C8. Due to the scarcity of these alkaloids from the natural source, their profound biological activity and their molecular complexity there has been intense interest in the synthesis of these materials and this has been the subject of a recent review[3]. Control of the stereochemistry of the 6-alkylidene bond is crucial in pumiliotoxin synthesis and many ingenious solutions to this problem have been reported. Iminium ion cyclisation of vinyl silanes[4a] and alkynes[4b] have being used to great effect by Overman, Aldol based strategies have being employed both by Overman[4c] and Gallagher,[4d] chromium mediated cyclisation of vinyl iodides to aldehydes has being used by Kibayashi[4e] and Trost[4f] has employed an S_N2' reaction of a vinyl epoxide to stereoselectively create the exocyclic double bond.



Pumiliotoxin A R=



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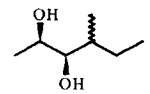
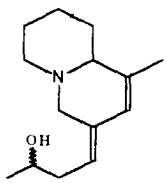
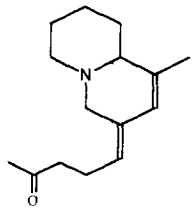


point of attachment

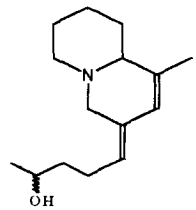
Homopumiliotoxin alkaloids contain a quinolizidine skeleton as their central nucleus and occurrence is much rarer than the pumiliotoxins. Recently homopumiliotoxins 221F, 233F and 235C have been isolated from the Madagascar frog Mantella in which the tertiary alcohol is no longer present at C8 but is replaced with a double bond[5]. Scarcity of material precluded determination of the exocyclic double bond stereochemistry but it is assumed that it is the same as the pumiliotoxins[6].



Homopumiliotoxin 221F

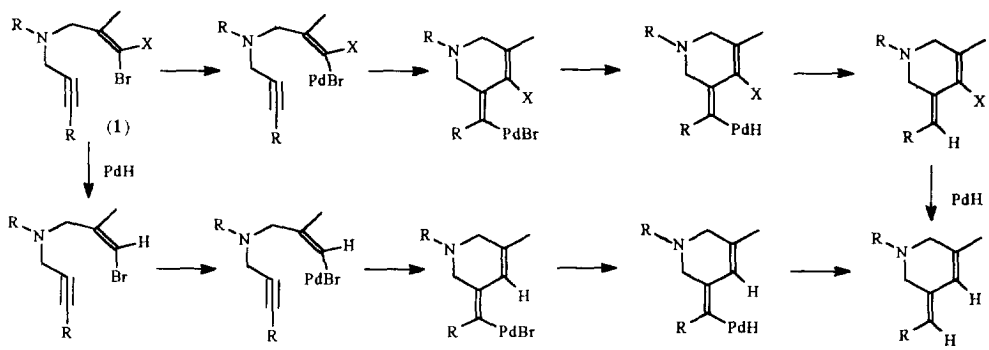


Homopumiliotoxin 233F



Homopumiliotoxin 235C

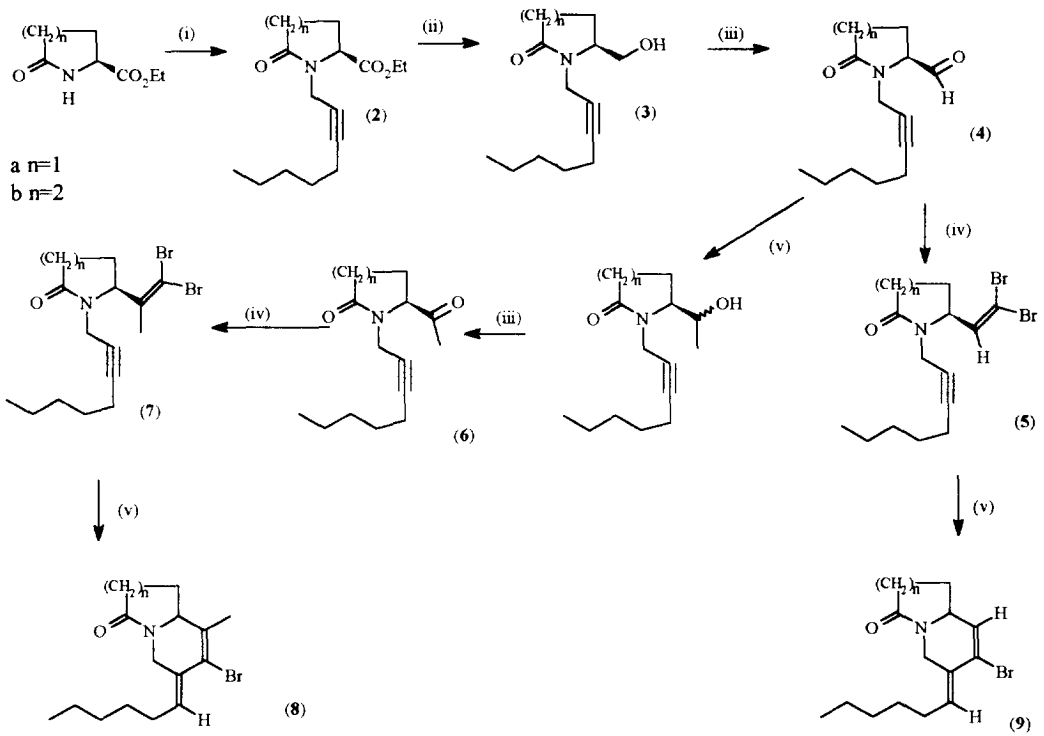
One conceptually simple stereoselective approach to the diene moiety in homopumiliotoxins 221F, 233F and 235C would be a palladium catalysed cyclisation of a vinyl bromide onto an acetylene, followed by reduction of the vinyl palladium with hydride ion, **Scheme 1**. Intermolecular versions of this reaction are well known[7] and recently intramolecular versions have appeared using both aryl and vinyl halides as substrates, and formic acid and piperidine as a source of hydride[8]. It was envisaged that if a 1,1-dibromoalkene was used as substrate (**1**, X=Br) and if the final cyclic product did not contain bromine, then because there are two different pathways for forming cyclic material, pre-formed stereo-controlled synthesis of a Z-trisubstituted vinyl bromide would be unnecessary. **Scheme 2** outlines our model studies designed to test this chemistry as applied to indolizidines (n=1) and quinolizidines (n=2).



Scheme 1

Amide precursors were chosen, as previous experience has shown that tertiary amines can be problematic substrates for transition metal catalysed reactions. Alkylation of commercially available ethyl-(S)-(+)-2-pyrollidinone-5-carboxylate (1a) with 2-octyn-1-mesylate proceeded smoothly to give tertiary amide (**2a**, 55%)[9]. Reduction of the carboethoxy group was accomplished with sodium borohydride in ethanol to give (**3a**, 79%). Swern oxidation of the primary alcohol gave the unstable aldehyde (**4a**, 69%) which was converted to the required dibromoalkene (**5a**, 17%) using the Corey-Fuchs protocol[10] by reaction of carbon tetrabromide and triphenylphosphine. To introduce the methyl group at C8 the aldehyde (**4a**) was reacted with methyl magnesium bromide followed by Swern oxidation to give the ketone (**6a**) 59% overall yield from aldehyde (**4a**). Ketone (**6a**) was converted to the 1,1-dibromoalkene (**7a**, 25%) again by reaction with triphenylphosphine and carbon

tetrabromide. Although the yields for converting the carbonyl compounds to the 1,1-dibromoalkenes are poor, this chemistry rapidly gives precursors to the indolizidines from readily available precursors.



Reagents: (i) Sodium hydride then 2-octyn-1-mesylate, (ii) sodium borohydride in ethanol, (iii) oxalyl chloride/DMF/triethylamine -40°C, (iv) triphenylphosphine carbon tetrabromide, (v)palladium acetate 2mol%, triphenylphosphine 4mol% , ammonium formate 2mol in acetonitrile.

Scheme 2

Treatment of (**7a**) with palladium acetate triphenylphosphine and ammonium acetate in boiling acetonitrile cleanly gave cyclic material (**8a**, 61%) as a single diastereoisomer (by ^{1}H nmr spectroscopy). The product always retained one bromine atom regardless of what excess of reducing agent was used. One possible explanation of this result, is that the more sterically hindered Z-vinyl bromide is being activated to oxidative addition to palladium by prior co-ordination of the acetylene moiety and that the cyclic tetra-substituted vinyl bromide formed is inert to further reduction under these reaction conditions. This would explain the yield of cyclic material being greater 50%. At this stage we can not rule out oxidative addition of the E-vinyl bromide to palladium leading to decomposition products, as this would explain the modest yield of cyclic material. It is indeed an added bonus that one bromine is retained as this gives a handle to distinguish between the two double bonds of the diene. Selective functionalisation of the endocyclic double bond to give pumiliotoxins or

allopumiliotoxins may be possible. Dibromide (**5**) cyclised under similar condition gave (**9**, 48%) but the yield was lower and another unidentified product was present in the crude reaction mixture.

With these encouraging results we next turned our attention to the quinolizidine based homopumiliotoxins **Scheme 2**, b series, n=2. Commercially available racemic 2-aminoadipic acid[11] was converted to (**1b**, 58%) by conversion to the diethyl ester and subsequent cyclisation by heating in xylene. Compound (**1b**) was converted to (**7b**) with overall yield 2.5%, using the previously described chemistry for n=1. As expected (**7b**) cleanly cyclised to indolizidine (8b, 54%) when treated with palladium acetate, triphenylphosphine and ammonium formate.

In conclusion, we have developed a divergent stereoselective route to the basic quinolizidine diene skeleton of the homopumiliotoxins and potential precursors to indolizidine based pumiliotoxins, allopumiliotoxin alkaloids. Studies are currently at hand to make this chemistry convergent and apply the methodology towards the synthesis of homopumiliotoxins 221F, 233F and 235C.

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Notes and References.

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