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Synthesis of the putative structures of homopumiliotoxins 235C and 233F

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Abstract—A novel approach to diene based quinolizidines, using an intramolecular Heck reaction in which the vinyl bromide double bond undergoes inversion of configuration, is reported. These quinolizidines have previously been proposed as tentative structures for homopumiliotoxin alkaloids **233F** and **235C**. The mass spectral data of the synthetic materials were different to those of the natural products confirming that the original structures need to be revised.

Pumiliotoxin alkaloids, originally isolated from the defensive skin secretions of the *Dendrobates* frogs, are indolizidines with a 6*Z*-alkylidine substituent.[1,2] There are a number of sub-classes, depending on the oxidation level at C-7 and C-8 of the indolizidine core. Variation in each sub-class is due to the nature of the alkylidene unit. The vast majority of pumiliotoxins have a tertiary alcohol at C-8, exemplified by pumiliotoxin **307A′**[1] (Fig. 1). The allopumiliotoxins possess an additional hydroxyl group at C-7, for example, allopumiliotoxin **339B**[3] (Fig. 1). Deoxypumiliotoxins, devoid of the hydroxyl group at C-8, are rare and to date only one member of this class deoxypumiliotoxin **251H** (Fig. 1) has been isolated.[4] These alkaloids are essentially unavailable from the natural source and this scarcity of material coupled with intriguing biological activity make pumiliotoxins ideal targets for synthesis and for developing new synthetic methodologies.[5] Of particular note was the development of iminium ion chemistry,[6–8] organonickel chemistry,[9,10] organopalladium chemistry,[11,12] organochromium chemistry[13,14] and organotitanium chemistry[15] for the synthesis of these alkaloids.

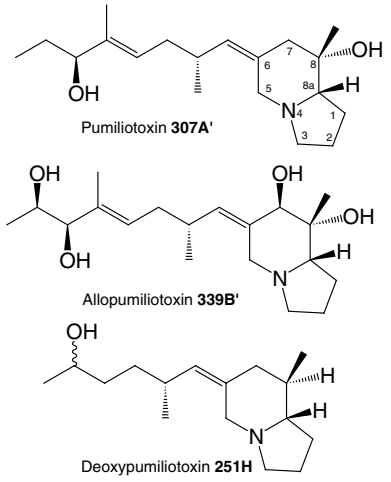

Figure 1. Representative examples of pumiliotoxin alkaloids together with their numbering system.

Homopumiliotoxins contain a quinolizidine core[16] and are much less widespread in distribution than the pumiliotoxins, and have been the subject of some synthetic studies.[13,17] Recently a new class of diene based homopumiliotoxin alkaloid has been isolated from Madagascan frogs of the genus *Mantella*[18] (Fig. 2). Due to the scarcity of material, the structures of these compounds were originally tentatively assigned solely by a combination of GLC/MS and GLC/IR. The C-7 alkylidene side chain was assumed to have a *Z*-geometry and the absolute configuration at C-9a was assumed to be *S* by analogy to C-8a of the pumiliotoxins. To date no

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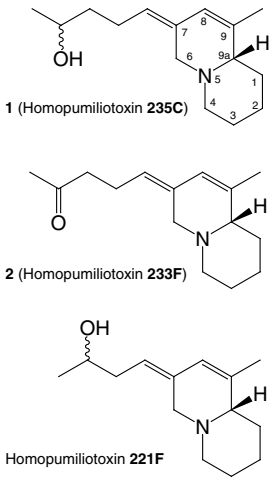
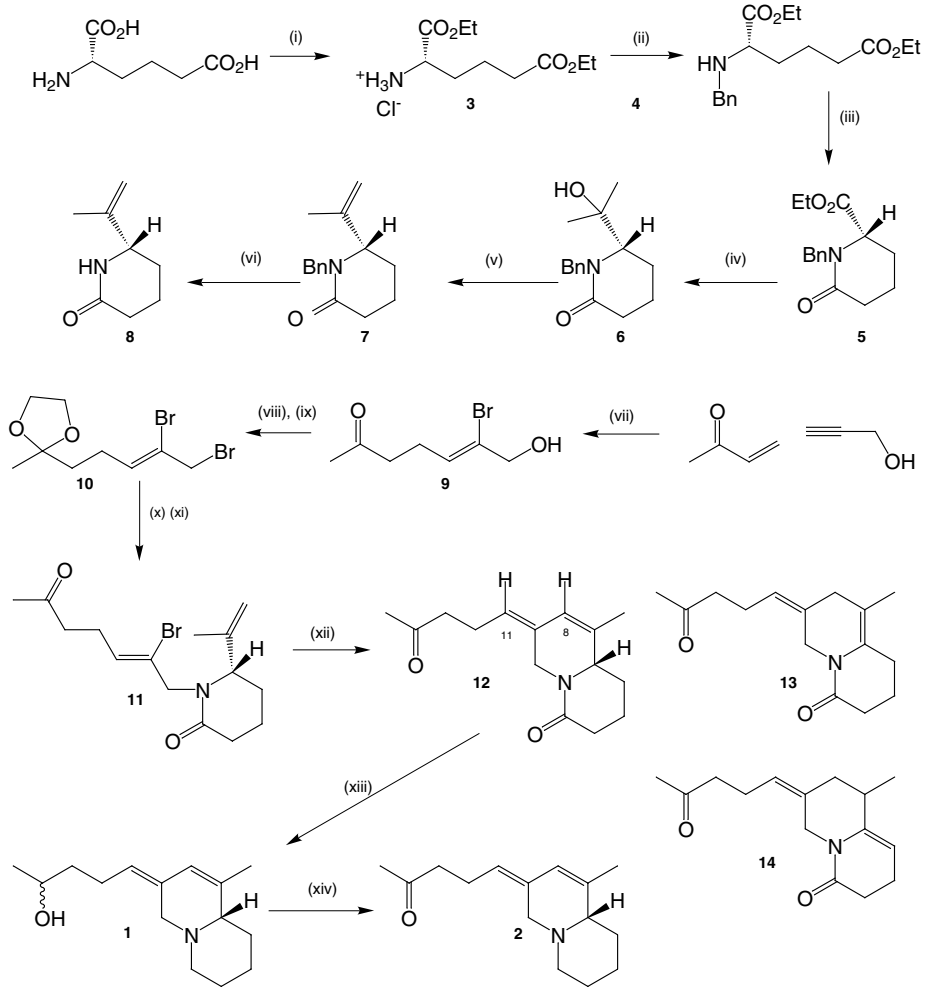


Figure 2. Tentative structures of diene based homopumiliotoxins isolated from *Mantella* frogs.

synthetic work has been reported on these novel diene based quinolizidine alkaloids.

Recently, we have been investigating palladium-catalysed Heck cyclisations of vinyl bromides as potential routes to diene based indolizidines.[19,20] We now report that this chemistry can be extended to give diene based quinolizidines and ultimately the structures, which have tentatively been assigned to homopumiliotoxin alkaloids **233F** and **235C** (Scheme 1). Tertiary amines are problematic substrates for palladium-catalysed reactions so amide precursor **11** was employed. The carbonyl group was strategically placed in the first formed ring to provide optimum bond angles for the palladium-catalysed cyclisation. The lactam moiety of the key cyclisation substrate **11** was readily available from commercially available (*S*)-2-aminoadipic acid. This amino acid was converted to the diester hydrochloride salt **3** in 90% yield by reaction with thionyl chloride in ethanol.[21] The corresponding free base proved to be much too water soluble for isolation but could be generated in ethanol by reaction with sodium ethoxide. Reductive amination with benzaldehyde and sodium borohydride using a standard procedure[22] provided *N*-benzyl amino acid diester **4**. The overall yield for the *N*-benzylation of **3**



Scheme 1. Reagents and conditions: (i) $SOCl_2$, EtOH, 90%; (ii) NaOEt, EtOH then PhCHO then $NaBH_4$, 68%; (iii) EtOH, AcOH, reflux, 4 days, 86%; (iv) CH_3MgI, THF, rt, 91%; (v) $SOCl_2$, Et_3N, THF, −78 °C → rt, 82%; (vi) Na, NH_3(l), EtOH, 81%; (vii) $[CpRu(MeCN)_3]PF_6$, $SnBr_4$, LiBr, acetone, reflux, 43%; (viii) PBr_3, ether, −20 °C, 76%; (ix) ethylene glycol, *p*-TsOH, benzene, reflux, 95%; (x) $KN(SiMe_3)_2$, **8**, THF, 0 °C → rt, 47%; (xi) 2 M aq HCl, THF, rt, 95%; (xii) $Pd(OAc)_2$, PPh_3, K_2CO_3, toluene, reflux, 48 h; (xiii) $LiAlH_4$, $AlCl_3$, THF, 62%; (xiv) Dess–Martin periodinane, CH_2Cl_2, rt.

was 68%. Conversion of secondary amine **4** to δ-lactam **5** proved to be much more difficult than the corresponding reaction in the pyrrolidinone series, in which cyclisation occurred on standing at room temperature.[19] Literature precedent indicated that cyclisation to a δ-lactam was acid catalysed[23] and experimentation showed the cyclisation could be effected in 86% yield by refluxing an ethanolic solution of amine **4**, containing a few drops of acetic acid, for four days. Reaction of ester **5** with a threefold excess of methylmagnesium iodide gave the tertiary alcohol **6** in 91% yield. Dehydration of tertiary alcohol **6** using a standard procedure[6] gave 1,1-disubstituted alkene **7** in 82% yield with none of the regioisomeric dehydration product being observed. Finally *N*-debenzylation using sodium in liquid ammonia[24] gave lactam **8** in 81% yield. The optical purity of compound **8** was measured by making diastereomeric urea derivatives with (*R*)- and (*S*)-α-methylbenzylisocyanate, and the ee was found to be 86%.[25] The advantage of these urea derivatives is that intramolecular hydrogen bonding leads to sharp signals in the proton NMR spectra aiding quantification.

Vinyl bromide **9**, containing all the carbon atoms of the alkylidene sub-unit, was rapidly assembled using the three component ruthenium catalysed cross coupling reaction recently developed by Trost.[26,27] Addition of propargyl alcohol to methyl vinyl ketone in the presence of lithium bromide and 10 mol% $[CpRu(MeCN)_3]PF_6$ in refluxing acetone gave a 10:1 mixture of *Z*:*E*-vinyl bromide isomers from which the pure required *Z*-isomer **9** could be isolated in 43% yield. The moderate yield may be attributed to the volatility of both starting materials and product. Despite the moderate yield, this reaction allowed rapid stereoselective assembly of the desired vinyl bromide in 0.5 g batches. Conversion of alcohol **9** to the corresponding allyl bromide followed by protection of the ketone as a dioxolane gave **10** in 72% yield for the two steps. N-Alkylation of lactam **8** with allylic bromide **10** using a standard procedure[28] but substituting sodium hydride for potassium hexamethyldisilazane as base gave the N-alkylated product **11** in 47% yield. Despite extensive experimentation, the yield for this alkylation could not be improved and we note that the *Z*-vinyl bromides are much more problematic substrates for N-alkylation than the corresponding *E*-vinyl bromides. Model studies on the indolizidinone series revealed that the bulky ketone protecting group retarded the Heck cyclisation. Therefore the acetal group was removed to afford ketone **11** in 95% yield.

We have previously demonstrated that *Z*-vinyl bromides undergo cyclisation with inversion of alkene stereochemistry to give indolizidines with the conjugated diene as the sole product.[19] However, the corresponding chemistry with the quinolizidines proved much more difficult and the conditions developed for the indolizidines were not effective in the quinolizidine series. Much more forcing conditions (toluene reflux compared to acetonitrile reflux) and longer reaction times (48 h, compared to 16 h) were required. On the first cyclisation run, two compounds **12** and **13** were isolated in yields of 41% and 17%, respectively. The stereochemistry of the exocyclic double bond of major compound **12** was confirmed to be *Z*, as shown (Scheme 1), by NOE difference spectroscopy. Saturation of proton H-11 gave a 9.7% enhancement to proton H-8 leaving no doubt that the vinyl bromide had indeed undergone stereochemical inversion on the formal 6-*endo-trig* cyclisation. From the previous model study on the indolizidinone series, formation of double bond isomer **13** was disappointing and unexpected. It is not clear if it is the more forcing conditions that were responsible for the formation of **13** or did a conformation difference between the indolizidine and quinolizidine series determine the final double bond position. On a second run, under apparently identical conditions, an additional diene isomer **14** was isolated in 15% yield. Of particular note were the methyl doublet and the additional triplet in the olefinic region of the proton NMR spectrum confirming the structure of **14**. However, this compound proved to be very unstable and on standing in deuteriochloroform for two days it was quantitatively converted to the alternative enamide isomer **13**. This rapid isomerisation may well explain why compound **14** was not observed in the first run. Simultaneous reduction of the amide and the ketone carbonyl groups of compound **12** gave quinolizidine **1** in 62% yield as a 1:1 mixture of secondary alcohol diastereoisomers. Interestingly, the natural product was isolated as a mixture of diastereoisomers at the secondary alcohol centre. Finally Dess–Martin oxidation[29] gave a sample of diene **2**.

Comparison of the mass spectral data of the synthetic materials **1** and **2** with the data reported for the natural products revealed that the molecular weights were indeed the same at 235 and 233, respectively. However, the fragmentation patterns were very different, suggesting that the originally proposed structures for these alkaloids are incorrect.[30]

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References and notes

1. Daly, J.; Myers, C. *Science* **1967**, *156*, 970–973.
2. Daly, J.; Garraffo, H.; Spande, T. Amphibian alkaloids. In *The Alkaloids*; Cordell, G., Ed.; Academic: New York, 1993; Vol. 43, p 185 (Chapter 3).
3. Tokuyama, T.; Daly, J. W.; Highet, R. J. *Tetrahedron* **1984**, *40*, 1183–1190.
4. Jain, P.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **1995**, *58*, 100–104.
5. Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505–522.
6. Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851–1853.
7. Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192–4201.

8. Lin, N. H.; Overman, L. E.; Rabinovitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062–9072.
9. Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098–6099.
10. Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950–6954.
11. Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988–4990.
12. Kibayashi, C.; Aoyagi, S. *J. Organomet. Chem.* **2002**, *653*, 229–233.
13. Aoyagi, S.; Hasegawa, Y.; Hirashima, S.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 2149–2152.
14. Aoyagi, S.; Wang, T. C.; Kibayashi, C. *J. Am. Chem. Soc.* **1992**, *114*, 10653–10655.
15. Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984–6990.
16. Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643–652.
17. Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6999–7001.
18. Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016–1038.
19. Feutren, S.; McAlonan, H.; Montgomery, D.; Stevenson, P. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1129–1137.
20. McAlonan, H.; Montgomery, D.; Stevenson, P. J. *Tetrahedron Lett.* **1996**, *37*, 7151–7154.
21. Chauvel, E. N.; Llorenscortes, C.; Coric, P.; Wilk, S.; Roques, B. P.; Fourniezaluski, M. C. *J. Med. Chem.* **1994**, *37*, 2950–2957.
22. Rosowsky, A.; Forsch, R. *J. Med. Chem.* **1982**, *25*, 1454–1459.
23. Kubo, A.; Nakai, T.; Koizumi, Y.; Saito, N.; Mikami, Y.; Yazawa, K.; Jun, U. *Heterocycles* **1992**, *34*, 1201–1211.
24. Hodgson, S. T.; Hollinshead, D. M.; Ley, S. V. *Tetrahedron* **1985**, *41*, 5871–5878.
25. Pirkle, W. H.; Robertson, M. R.; Hyun, M. H. *J. Org. Chem.* **1984**, *49*, 2433–2437.
26. Trost, B. M.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 360–362.
27. Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 7376–7389.
28. Harkin, S. A.; Singh, O.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1489–1499.
29. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
30. There is a brief mention in a recent publication that the structures of diene based homopumiliotoxins may need to be revised see: Daly, J. W. *J. Med. Chem.* **2003**, *46*, 445–452.