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Palladium-mediated reductive coupling, a stereoselective approach to the 8-dehydropumiliotoxin skeleton

Stephanie A. Feutran, Helena McAlonan, Paul J. Stevenson *, Andrew D. Walker

School of Chemistry and Chemical Engineering, Queen's University, Belfast, BT9 5AG, Northern Ireland, United Kingdom

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ABSTRACT

Reductive cyclisation of an *E*-vinyl bromide with an allylic acetate proceeds under palladium catalysis to give the 8-dehydropumiliotoxin skeleton, a potential advanced precursor to 8-deoxypumiliotoxin alkaloids. Control of the stereochemistry of the *E*-vinyl bromide precursor is achieved readily using the Kogen or Bruckner bromophosphonate reagents and the reductive cyclisation proceeds with retention of the vinyl bromide stereochemistry. The mechanism for the cyclisation involves an in situ conversion of the allylic acetate to an allyl stannane followed by an intramolecular Stille-type coupling.

The pumiliotoxin alkaloids, isolated from the defensive skin secretions of *Dendrobates* frogs have an indolizidine ring with a *Z*-exocyclic alkene at C6.[1–3] Most of these alkaloids have a methyl group at C8 and the different classes are distinguished by the oxygenation pattern on the six-membered ring. The vast majority of pumiliotoxins have a tertiary alcohol at C8 and the allopumiliotoxins have an additional hydroxy group at C7. Recently, a new class of pumiliotoxin, Figure 1, devoid of the tertiary alcohol at C8, was isolated and the structure of deoxypumiliotoxin 251H was assigned by NMR spectroscopy.[4] Since, an additional eleven members of this class have been isolated and their structures tentatively assigned as deoxypumiliotoxins.[5] To date, no syntheses of the deoxypumiliotoxin class of alkaloid have been reported.

The main difficulty in pumiliotoxin alkaloid synthesis is control of the stereochemistry of the exocyclic trisubstituted double bond. Many ingenious solutions have emerged to solve this problem including iminium ion chemistry,[6–10] aldol methodologies,[11–15] Wittig Horner reaction,[16] allylic rearrangement,[17] organonickel[18–20] or titanium[21] chemistry of alkynes and organochromium chemistry of vinyl iodides.[22–24] Recently, we demonstrated that vinyl bromides are versatile substrates for controlling the stereochemistry of the exocyclic trisubstituted alkene in diene-based pumiliotoxins via intramolecular Heck reaction.[25–27] However, this chemistry was complicated by the fact that the vinyl bromide underwent a stereochemical inversion on *endo*-cyclisation and for the desired pumiliotoxin stereochemistry, the less reactive, more problematic *Z*-vinyl bromides were required. Furthermore, the conjugated dienes produced could not be chemoselectively functionalised at the endocyclic alkene.

8-Dehydropumiliotoxins with the double bond exocyclic, although not naturally occurring, are likely candidates for the synthesis of 8-deoxypumiliotoxins. Since the two alkenes have different substitution patterns, the 8-methylene group should reduce faster under catalytic hydrogenation conditions than the 6-trisubstituted double bond. Given that we have already shown, in similar systems, that catalytic hydrogenation and oxidation preferentially occur from the concave face,[28,29] these substrates are thus ideal intermediates for 8-deoxypumiliotoxin synthesis with the desired *R*-configuration at C8.

We now report a robust approach to the 8-dehydropumiliotoxin skeleton **8**, based on an intramolecular reductive coupling reaction of an *E*-vinyl bromide, **5**, with an allylic acetate, which proceeded with retention of vinyl bromide stereochemistry, Scheme 1.

The starting diene **3** was prepared as previously described[25] with the variation that Wittig Horner-type reactions of α-bromophosphonates **1a–c** were used to prepare the *E*-α-bromoacrylates, **2**, Scheme 2. The McKenna bromophosphonate, **1a**,[30] favoured formation of the *Z*-α-bromoacrylate with low de. In order

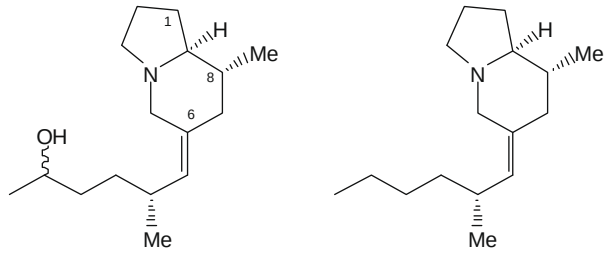

Figure 1. Structure of deoxypumiliotoxins 251H and 235V.

* Corresponding author. Tel.: +44 2890974426.
E-mail address: p.stevenson@qub.ac.uk (P.J. Stevenson).

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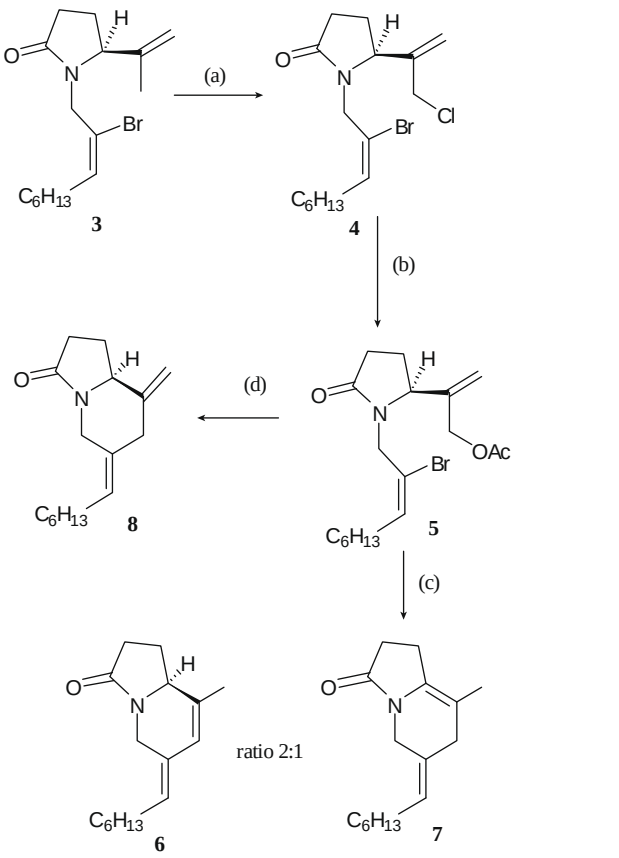
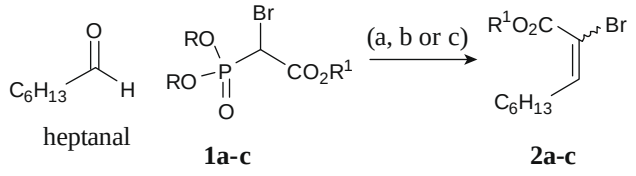


Scheme 1. Reagents and conditions: (a) $Ca(oCl)_2$, $CO_2(s)$, CH_2Cl_2/H_2O 5:1, 30 min (62%); (b) KOAc, DMF, 120 °C, 1 h (66%); (c) $(Bu_3Sn)_2$, BuLi, Et_2AlCl, $Pd_2(dba)_3CHCl_3$, Ph_3P, THF, 4 h, 60 °C, then 10 h, 105 °C (60%); (d) $(Bu_3Sn)_2$, BuLi, Et_2AlCl, $Pd_2(dba)_3CHCl_3$, Ph_3P, THF, 6 h, 60 °C (65%).



Scheme 2. Reagents and conditions: (a) **1a** R = R^1 = Et, McKenna's reagent, THF, NaH, 0 °C, 1 h (85%), de 20% *Z*-alkene; (b) **1b** R = CF_3CH_2, R^1 = Me, Kogen's reagent, ^{t}BuOK, 18-crown-6, −78 °C, 2 h (95%), only *E*-isomer detected by NMR (c) **1c**, R = Ph, R^1 = Et, Bruckner's reagent, NaHMDS, THF, 0 °C, 30 min (96%), de 88% *E*-alkene.

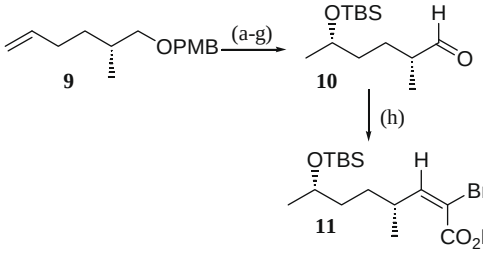
to achieve high *E*-selectivity it was necessary to place electron-withdrawing groups on the phosphonate ester. Two reagents, the trifluoroethyl and diphenyl esters, **1b** and **1c**, respectively, have recently been developed by Kogen[31–33] and Bruckner[34] to accomplish this transformation with high *E*-selectivity. These reagents are merely bromo analogues of the Still–Gennari[35] and Ando[36] reagents, respectively, routinely used for preparing *Z*-acrylates.

Reaction of heptanal with the Kogen reagent, **1b**, gave exclusively the desired *E*-bromoacrylate, **2b**, in 95% yield as a single diastereoisomer. Unfortunately, in our hands, there was difficulty in reproducibly preparing this reagent and at best, the yield was always low, and the purification tedious. In situ methods for generating this reagent are known,[37,38] but our preference was to use an isolated reagent, which was pure by ^{31}P NMR spectroscopy. Attention was next turned to the Bruckner reagent **1c**. This was initially prepared as a 2:1 mixture of mono and dibromophosphonates (by ^{31}P NMR spectroscopy) as reported. This mixture reportedly converts aldehydes to *E*-bromoacrylates in high yield. However, our preference was to use a single component reagent and on further experimentation, conditions were found to reduce selectively the dibromide component to the monobromide which gave a homogeneous reagent, **1c**. This was achieved by titrating a solution of tin(II) chloride into the crude mixture of mono and dibromophosphonates and by monitoring the instantaneous reduction by ^{31}P NMR spectroscopy. An end-point was readily found where the dibromophosphonate contaminant was selectively reduced to the desired monobromophosphonate, with no over reduction. Using Bruckner's conditions, with pure monobromophosphonate **1c**, gave the required bromoacrylate, **2c**, in 96% crude yield with 94:6 selectivity in favour of the *E*-isomer.

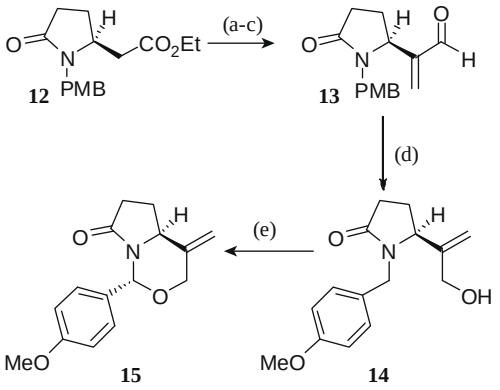
The *E*-α-bromoacrylate **2c** was converted into the enantioenriched diene **3** as previously reported.[25] Functionalisation of the allylic methyl group was achieved in moderate yield using Wolinsky's conditions to give the allylic chloride **4**.[39,40] Nucleophilic substitution with acetate gave the prerequisite allylic acetate **5**. Although this reaction sequence was convenient, in that it gave the desired material from a known diene, purification following the chlorination step was difficult and a new procedure for generating the allylic alcohol was desirable. The key reductive cyclisation employed chemistry pioneered by Trost,[41] which surprisingly to date, has seen very little use in synthesis. This involved an in situ conversion of an allylic acetate to an allylstannane, using (tri-*n*-butylstanny1)diethylalane, under palladium catalysis, followed by an intramolecular Stille-type cyclisation using the same catalyst. This sequence was convenient in that there was no need to isolate the intermediate allylstannane reagent. Using Trost's conditions, compound **5** cyclised to give a 2:1 mixture of dienes **6** and **7**, in 60% yield, plus other unidentified products. It was reasoned that the cyclisation had proceeded as planned, but that the exocyclic alkene **8** had isomerised to the thermodynamically more stable endocyclic alkenes **6** and **7** under the reaction conditions. In the original paper the initial heating period, at 60 °C, was required to convert the acetate to the stannane and the higher temperature, 105 °C, was required for the cyclisation. By varying the temperature it was found that the cyclisation also proceeded at 60 °C and gave the desired bis-exocyclic diene **8** in 65% isolated yield. Interestingly no products of intramolecular Heck reaction were detected, even though we have demonstrated that diene **3** undergoes intramolecular Heck reaction at room temperature.[25]

With the crucial cyclisation accomplished, in a simple model system, efforts were directed towards preparing more alkaloid-like side chains and to make the route more convergent. This necessitated early introduction of the allylic alcohol functionality into the pyrrolidinone before attachment of the vinyl bromide.

Scheme 3 outlines how the side chain **11**, for deoxypumiliotoxin 251H was assembled. Sharpless asymmetric dihydroxylation,[42] of



Scheme 3. Reagents and conditions: (a) AD-mix-β, ^{t}BuOH/H_2O, 0 °C, 12 h (97%); (b) TsCl, Et_3N, Bu_2SnO, DCM, rt, 16 h (98%); (c) Amberlite IRA-400(OH), EtOH, 48 h, rt (100%); (d) Red-Al, THF, 0 °C–rt, 16 h (85%); (e) TBSCl, imidazole, DMF, −10 °C, 6 h (91%); (f) DDQ, CH_2Cl_2/H_2O, rt, 2 h (82%); (g) Dess Martin periodinane, rt, 2 h (88%); (h) KHMDS, THF, bromophosphonate **1c**, 0 °C, 3h (47%).



Scheme 4. Reagents and conditions: (a) $NaBH_4$, EtOH, 4 h, 45 °C (98%); (b) Dess Martin periodinane, CH_2Cl_2, 18 h, rt (79 %); (c) Eschenmoser's salt, Et_3N, CH_2Cl_2, rt, 18 h (86%); (d) $NaBH_4$, $CeCl_3$, EtOH, 0 °C, 1 h (67%); (e) CAN, $MeCN/H_2O$ 1:1, rt, 1 h (56%).

the known alkene **9**[43] gave a diol with 87% de. Selective tosylation of the primary alcohol, followed by treatment with a basic ion exchange resin gave an epoxide. Reduction of the epoxide with Red-Al gave a secondary alcohol, which was protected as the TBS ether. Oxidative removal of the PMB group gave a primary alcohol, which was oxidised to the aldehyde **10**. Gratifyingly, reaction of aldehyde **10** with the Bruckner bromophosphonate **1c** gave exclusively the *E*-bromoacrylate **11**. Branching at the α-carbon clearly improves the *E*-stereoselectivity, albeit with a substantial reduction in yield.

Scheme 4 outlines an approach to the key enantiomerically enriched pyroglutamate allylic alcohol starting from the known ester **12**.[44] Sodium borohydride reduction of the ester, followed by Dess Martin oxidation[45,46] gave an aldehyde, which on aldol condensation with Eschenmoser's salt[47] gave the α,β-unsaturated aldehyde **13**. Luche reduction[48] of the aldehyde gave the desired allylic alcohol **14**. Attempted oxidative cleavage of the *N*-PMB, group using ceric ammonium nitrate, was complicated in that the major product of the reaction was the *N,O*-acetal **15**, isolated as a single diastereoisomer.

Work is currently in progress on hydrolysing *N,O*-acetal **15** and completing the synthesis of deoxypumiliotoxin 251H.

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