Palladium catalysed formal 6-*endo-trig* approaches to pumiliotoxin alkaloids: interception of the elusive cyclopropyl intermediate

Stephanie Feutren, Helena McAlonan, David Montgomery and Paul J. Stevenson *

School of Chemistry, The Queen's University of Belfast, Belfast, UK BT9 5AG

Received (in Cambridge, UK) 13th December 1999, Accepted 28th February 2000

Intramolecular Heck cyclisation of (*E*)-vinyl bromides leads to indolizidines, related to pumiliotoxin alkaloids, in which the stereochemistry of the trisubstituted double bond undergoes inversion. A cyclopropyl intermediate, which is believed to be responsible for the double bond inversion, has been intercepted by forcing an 'early' β-hydride elimination on this species. The relative stereochemistry of this cyclopropyl intermediate determines the regioselectivity of the final β-hydride elimination. In this case all three β-hydride eliminations were stereochemically permitted, giving rise to a mixture of three isomeric products, differing in the position of a double bond. (*Z*)-Vinyl bromides were found to be less reactive than (*E*)-vinyl bromides, but on cyclisation gave the required conjugated diene, with inversion of the vinyl bromide stereochemistry, as the sole reaction product. This methodology will allow rapid stereoselective access to the diene-based pumiliotoxin alkaloids.

Introduction

The pumiliotoxin alkaloids, isolated from defensive skin secretions of amphibians, comprise an indolizidine skeleton with a (*Z*)-alkylidene side chain (Fig. 1).[1] Pumiliotoxin 307A was first discovered as one of the three major alkaloids in the Panamanian poison frog *Dendrobates pumilio*.[2] Since then many other members of this class of alkaloid, at present over forty, with variation in the alkyl side chain have been isolated and characterised. The vast majority of pumiliotoxins bear a tertiary hydroxy group at C8 and the allopumiliotoxins bear an additional hydroxy group at C7.[3] Recently, a pumiliotoxin devoid of a C8 hydroxy group, deoxypumiliotoxin 251H, has been isolated as a minor component from the Ecuadorean frog *Epipedobates tricolor*.[4] Diene-based quinolizidines, for example homopumiliotoxin 221F, have been isolated from the Madagascar frog *Mantella*, in which the tertiary alcohol at C8 is replaced with a double bond.[5] Due to the small amounts of quinolizidines isolated these structures remain tentative, but it is assumed that the trisubstituted double bond stereochemistry is the same as in the pumiliotoxins.[6] Due to the scarcity of pumiliotoxins from the natural source and their biological activity, there has been intense interest in the synthesis of these compounds, and this has been the subject of a review.[7] To date, most biological studies on the pumiliotoxin alkaloids have been performed with synthetic material.[8]

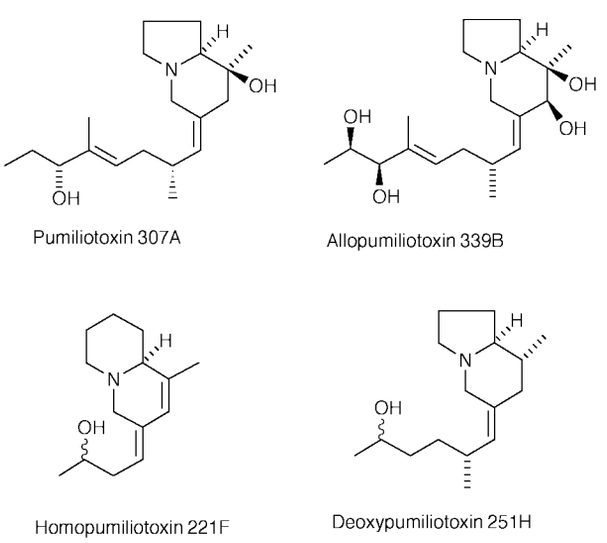


Fig. 1 Representative examples of the different classes of pumiliotoxin alkaloids.

The major problem in pumiliotoxin synthesis is control of the stereochemistry at the trisubstituted, exocyclic double bond. A number of ingenious solutions to this problem have emerged based on iminium ion chemistry,[9] aldol chemistry,[10] organochromium chemistry,[11] organopalladium chemistry[12] and recently, for the allopumiliotoxins, reductive cyclisation of ynals.[13]

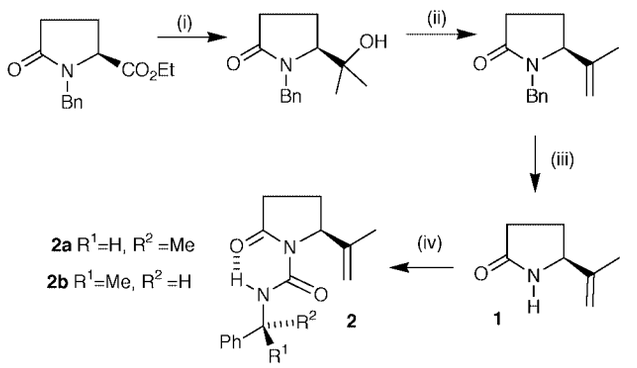
Recently we became interested in the application of intramolecular Heck chemistry to assemble the (*Z*)-trisubstituted double bond, found in the pumiliotoxins and homopumiliotoxins, Fig. 1. The diene analogues of the natural pumiliotoxins are interesting substrates to probe the effect of the hindered C8 hydroxy group on the biological activity. Alternatively, selective functionalisation of the endocyclic double bond could in principle lead to natural pumiliotoxins or allopumiliotoxins.

Results and discussion

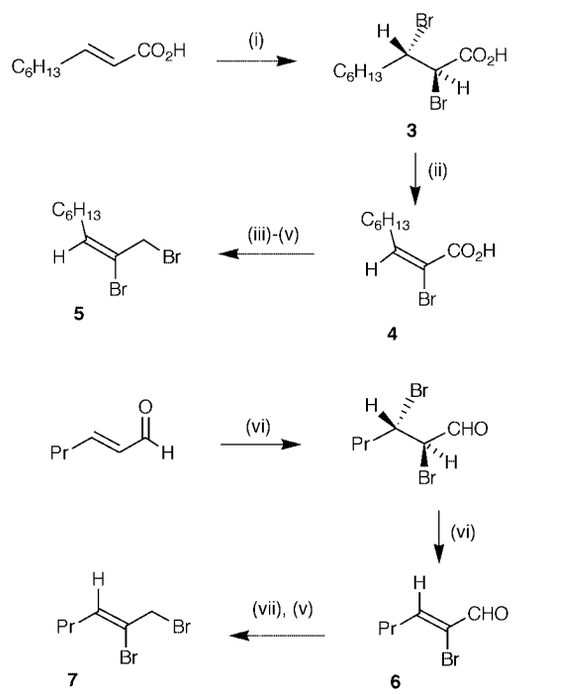
The aim of this study was to investigate whether the indolizidine pumiliotoxin skeleton, could be stereoselectively assembled by cyclisation of vinyl bromide **8**. The synthesis of the starting material for this investigation is summarised in Schemes 1 and 2.

Tertiary amines are notoriously difficult compounds to handle so internal amine protection was sought. This was readily accomplished by employing pyroglutamates as precursors. The advantage of having the carbonyl group contained in the five membered ring is that it eliminates hindered rotation and makes the proton NMR spectra simple and easy to interpret. The synthesis of the pyrrolidinone fragment **1** is detailed in Scheme 1. *N*-Benzyl pyroglutamic acid ethyl ester is available from glutamic acid using Rapoport's procedure,[14] and was the starting point for this study. Introduction of the 5-isopropenyl group was readily achieved by reaction of the ester with two equivalents of methylmagnesium iodide followed by dehydration. Reductive removal of the *N*-benzyl group using sodium in

DOI: 10.1039/a909774k



Scheme 1 *Reagents and conditions*: (i) MeMgI, THF–Et_2O; (ii) thionyl chloride, THF, −78 °C; (iii) Na, NH_3; (iv) α-methylbenzyl isocyanate, toluene, 108 °C.



Scheme 2 *Reagents and conditions*: (i) Br_2, CH_2Cl_2, 25 °C; (ii) NaOH, H_2O, 40 °C; (iii) NaOH, H_2O, DMSO, MeI; (iv) DIBAL-H, toluene, −78 °C; (v) Ph_3P, Br_2, CH_3CN; (vi) Br_2, CH_2Cl_2, 0 °C then Et_3N; (vii) $NaBH_4$, EtOH.

liquid ammonia gave the key intermediate **1** in 50% overall yield for the three steps. The optical purity of this material was determined to be at least 96% ee by making urethane derivatives **2a**,**b** with both (*R*)- and (*S*)-α-methylbenzyl isocyanate, and measuring the relative amounts of diastereoisomers present.[15] It is assumed that the isocyanate supplied by the Aldrich Chemical Company was optically pure. These urethanes are ideal derivatives for measuring the optical purity of cyclic amides because the hydrogen bond between the *N*H and ring carbonyl group freezes out one conformation and gives rise to sharp signals in proton NMR spectra.

Since this was merely a feasibility study, a hydrophobic, stereochemically pure (*E*)-vinyl bromide was sought. The required vinyl bromide precursor was readily available by bromination dehydrobromination of nonenoic acid (Scheme 2). The role of the carbonyl group was to ensure that the dehydrobromination reaction was completely regioselective, giving only the 2-bromoalkene on elimination. When dibromide **3** was treated with aqueous sodium hydroxide according to James's original procedure,[16] the steroselectivity of the elimination reaction was moderate, giving a 5.7:1 mixture of (*E*)- and (*Z*)-double bond isomers **4** in 68% overall yield for the two steps. The production of the (*E*)-vinyl bromide as the major

Table 1 Products of intramolecular Heck cyclisations of compound **8**

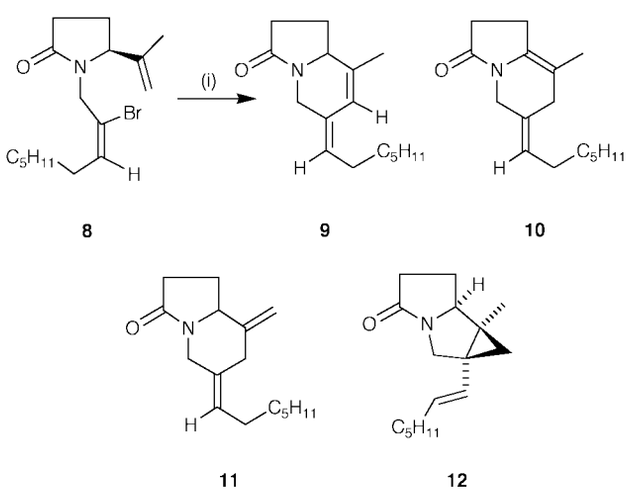
Amount of products formed (%)				
9	**10**	**11**	**12**	Conditions
30	55	15	0	1 h, 80 °C
28	46	26	0	RT, 18 h, Et_4NCl
17	14	14	41	RT, 56 h, TlOAc

product is consistent with a stereoselective antiperiplanar elimination of hydrogen bromide.

Alkene stereochemistry was readily assigned by proton NMR spectroscopy. Hence, the vinyl proton in the (*Z*)-isomer is predicted to have a higher chemical shift than that of the corresponding proton in the (*E*)-isomer because it is *cis* to the carboxy group. In the event the chemical shift values of the (*E*)- and (*Z*)-isomers were found to be 7.52 ppm and 6.88 ppm respectively, close to the empirically calculated values of 7.66 ppm and 6.73 ppm respectively.[17]

Esterification under mildly basic conditions gave the corresponding methyl esters with no scrambling of the double bond stereochemistry. At this stage the stereoisomers were separated by flash chromatography, aided by the (*E*)-isomer having a higher R_f value than the (*Z*)-isomer. Reduction of the ester to the alcohol and conversion of the alcohol to bromide **5** proceeded smoothly. Some batches of allylic bromide **5** were configurationally unstable and could not be stored, whilst other batches were stable. It is therefore recommended that this compound is used as soon as it is made. Finally, coupling of amide **1** to bromide **5**, was effected using sodium hydride as base in anhydrous THF as solvent and gave the starting material **8**, in 85% yield, for the cyclisation study.

The results of the intramolecular Heck cyclisations on substrate **8** are summarised in Scheme 3 and Table 1.



Scheme 3 *Reagents and conditions*: (i) $Pd(OAc)_2$, Ph_3P, K_2CO_3, CH_3CN.

On heating substrate **8** under normal Heck conditions, three cyclic compounds **9**–**11** were formed in 55% combined yield. The conjugated diene **9** was assigned by the presence of a singlet in the vinyl region at δ 6.21 ppm in the proton NMR spectrum. The structure of the major product **10** was confirmed by the simplicity of its proton NMR spectrum arising from the loss of chirality. Structure **11** was readily assigned by the presence of the alkene methylene signals at δ 4.81 ppm and 4.92 ppm and the methylene group between the two alkenes coming as an AB multiplet centred at δ 2.92 ppm in the proton NMR spectrum.

It was somewhat surprising to see how little of the conjugated diene **9** (30%) was formed, the unconjugated isomer **10**

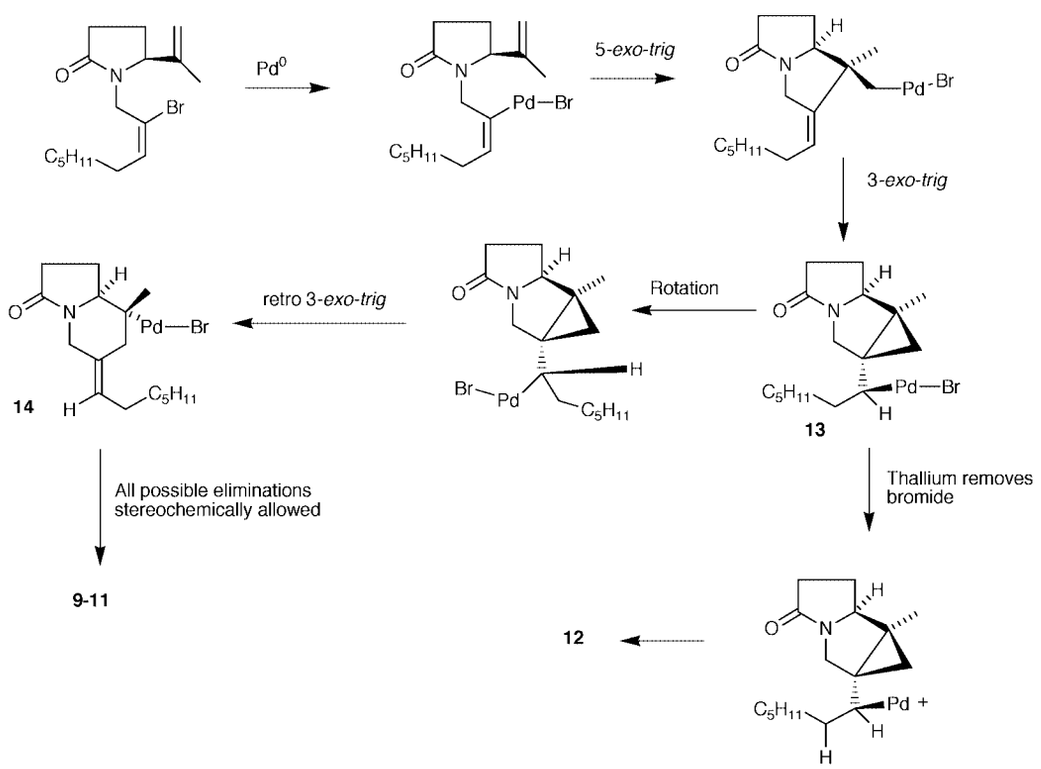
being the major product (Table 1, entry 1). However, it is conceivable that β-hydride elimination to give **9** is retarded as the hydrogen on the newly formed alkene and the pendent alkyl group approach each other as the system becomes planar. Formation of bis-exocyclic alkene **11** was completely unexpected and suggested that the final β-hydride elimination into the ring was difficult. Exocyclic β-hydride eliminations have previously been observed in sterically constrained systems, so this reaction is not without precedent.[18] Formation of **10** as the major product is interesting and has implications for the relative stereochemistry of the intermediate organopalladium species **14**. β-Hydride elimination can only take place when the palladium and hydrogen are *cis*. In principle there are two possible diastereoisomeric organopalladium intermediates, and the formation of **10** indicates that the intermediate diastereoisomer **14** is the one in which the hydrogen and palladium are *cis*. However this argument is not totally conclusive as **10** could arise from a subsequent isomerisation of **9** or **11**.

Tetraalkylammonium halides can have a dramatic effect on the outcome of Heck reactions.[19] The result of addition of one equivalent of tetraethylammonium chloride to the reaction mixture is summarised (Table 1, entry 2). The same products, **9**–**11**, were formed as before, but in different amounts. In particular the relative amount of **11** is up, mainly at the expense of **10**, suggesting **11** may be a kinetic product of the reaction. Heating the reaction mixture for one hour after consumption of starting material, gave the same isomer mixture as entry 1 Table 1, strongly suggesting that **11** may be a kinetic product.

The reaction mixtures were complex due to all three possible β-hydride eliminations taking place, with poor selectivity. Thallium salts are capable of having a profound influence in the direction of β-hydride elimination.[20] It is believed that the thallium removes the halide from the intermediate organopalladium species, facilitating elimination, and often giving only one isomer. One equivalent of thallium acetate was introduced into the reaction with a view to increasing the selectivity of β-hydride elimination (Table 1, entry 3). The outcome of this reaction was completely unprecedented, with the major product now being the vinylcyclopropane **12**. The gross structure of this adduct was readily assigned based on the diastereotopic hydrogens within the cyclopropane methylene group appearing as an AB multiplet in the proton NMR spectrum at δ 0.46 ppm and 0.56 ppm, J = 5.6 Hz. Cyclopropane **12** was formed as a single diastereoisomer with complete stereocontrol at the two newly created chiral centres and as only the (*E*)-alkene. The relative stereochemistry of **12** was determined by NOE difference spectroscopy. Hence, saturation of the methyl group adjacent to the cyclopropane ring gave a 7.6% NOE to the adjacent methine proton and a 6.1% NOE enhancement to the vinyl proton, supporting the stereochemistry postulated. This is the first example of an intramolecular Heck reaction leading to a vinylcyclopropane product in a conformationally flexible system.

The stereochemistry of compounds **9**–**11** was assigned by irradiating the alkene triplets in the proton NMR spectra and observing strong NOE enhancements to the NCH_2 protons of 5.0–6.8%. To our surprise this suggested that the trisubstituted double bond had undergone inversion on cyclisation. Although vinylpalladium species are configurationally stable, reports of inversion of configuration on cyclisation have previously been noted,[21] and a mechanism involving cyclopropane intermediates has been proposed.[22] It should also be noted that formal 6-*endo-trig* cyclisation of a vinyl radical also proceeds *via* a cyclopropyl intermediate.[23]

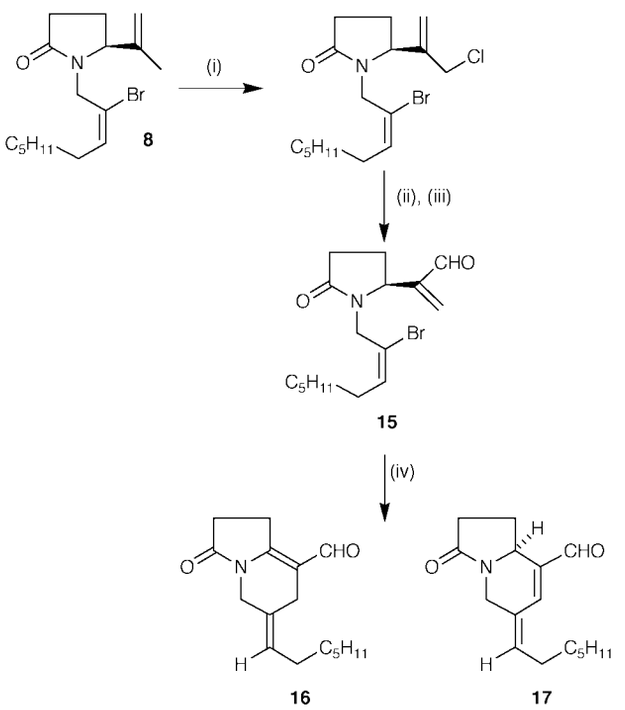
A unifying mechanism for the formation of products **9**–**12** is outlined in Scheme 4. 5-*exo-trig* followed by a consecutive 3-*exo-trig* cyclisation gave the key cyclopropyl intermediate **13**. In the presence of thallium acetate, bromide is removed from this intermediate and this triggers a β-hydride elimination and gave tricyclic compound **12** as the major product. Isolation of product **12** allows an unambiguous assignment of stereochemistry in intermediate **13**, at the two newly formed chiral centres, and confirms that cyclopropanes will readily form under these reaction conditions. Although vinylcyclopropanes have previously been observed in intramolecular Heck reactions,[24] their presence was limited to conformationally inflexible systems in which the alkylpalladium was generated inside a ring before the final β-hydride elimination. In the absence of thallium acetate, cyclopropyl intermediate **13** undergoes rotation around the *exo* σ-bond to give the correct conform-



Scheme 4

ation for a fragmentation which leads to **14** with inversion of alkene stereochemistry. The fragmentation, which is the reverse of 3-*exo-trig* cyclisation, is highly stereoselective giving (*R*)-configuration at the newly generated chiral centre bearing palladium. Interestingly, with this diastereoisomer all three β-hydride eliminations are stereochemically permissible and it is gratifying that all products **9**–**11** are produced.

The corresponding cyclisation with an electron withdrawing group on the alkene double bond was next investigated (Scheme 5). This should electronically encourage direct 6-*endo-trig*



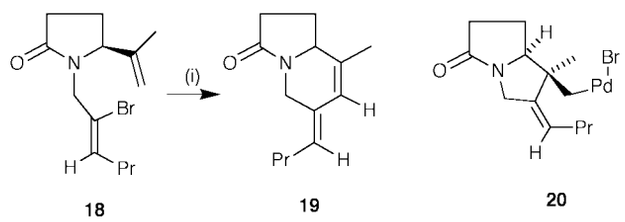
Scheme 5 *Reagents and conditions*: (i) CaOCl, CO_2, H_2O–CH_2Cl_2; (ii) dioxane, H_2O, $NaHCO_3$, 105 °C; (iii) TPAP, *N*-methylmorpholine *N*-oxide, CH_2Cl_2, 0 °C; (iv) $Pd(OAc)_2$, Ph_3P, K_2CO_3, CH_3CN, 80 °C.

cyclisation with preservation of the vinyl bromide stereochemistry. The starting material for this study, **15**, was readily available from allylic chlorination of substrate **8**,[25] conversion of the chloride to the alcohol and oxidation to aldehyde **15**. The overall yield for the three stage sequence was 40%, with the poorest yield being for the allylic chlorination at 62%.

Substrate **15** cyclised in boiling acetonitrile under standard Heck conditions and gave **16** and **17** as a 2 : 1 mixture of double bond isomers. If heating was continued for a further hour then the isomer ratio changed to 94 : 6, confirming equilibration of **17** to **16**. The fact that so little of the conjugated diene, **17**, formed, immediately suggested that the double bond had indeed undergone inversion on cyclisation. This was confirmed by NOE difference spectroscopy where irradiation of the triplet at δ 5.89 ppm in substrate **17** gave a strong enhancement of 6.3% of one of the diastereotopic protons at δ 4.71 ppm of the NCH_2 group and no enhancement of the other vinyl signal at δ 7.34 ppm. Isomer **16** displayed two singlets at δ 4.08 and 3.06 respectively in the proton NMR spectrum corresponding to $NCH_2C{=}C$ and $N{=}C{-}CH_2{-}C{=}C$ groups respectively. Again, the spectrum was simple because chirality was lost during the elimination. Irradiation of the vinyl triplet at δ 5.57 ppm gave a NOE of 6.8% to the singlet at δ 4.08 ppm, confirming inversion of the trisubstituted double bond on cyclisation. Even with electron deficient alkenes the initial attack is at the α-carbon.

In order to gain access to the pumiliotoxin skeleton with the correct trisubstituted (*Z*)-double bond stereochemistry a substrate containing a (*Z*)-vinyl bromide was required (Scheme 2). A similar strategy to that adopted for the synthesis of **5** was adopted but the base for the dehydrobromination was changed to triethylamine since tertiary amines are known to give predominantly (*Z*)-vinyl bromides predominately on elimination.[26] An aldehyde was used instead of a carboxylic acid to circumvent the known ready decarboxylation of these substrates.[27] Hence, bromination of hex-2-enal at 0 °C followed by immediate dehydrobromination using triethylamine gave only the (*Z*)-vinyl bromide isomer **6** in 99% crude yield for the one pot procedure.[28] The corresponding (*E*)-isomer could not be detected by ^{13}C NMR spectroscopy of the crude reaction mixture. It is suspected that the (*E*)-alkene is equilibrating to give exclusively the (*Z*)-alkene under the reaction conditions. To test this hypothesis a sample of an (*E*)-2-bromoalk-2-enal was required. However attempts to oxidise (*E*)-2-bromonon-2-en-1-ol with the Dess–Martin periodinane gave exclusively (*Z*)-2-bromonon-2-enal. Although this was not what was required it does demonstrate that the isomerisation of (*E*)-2-bromonon-2-enal to (*Z*)-2-bromonon-2-enal is very facile indeed.

Reduction of the aldehyde **6** gave an allylic alcohol which was converted to **18** *via* the dibromide **7** as previously described for **8**.



Scheme 6 *Reagents and conditions*: (i) $Pd(OAc)_2$, Ph_3P, K_2CO_3, CH_3CN, 12 h, 80 °C.

The cyclisation of **18** was much slower that that of substrate **8** requiring a 12 h reflux to go to completion, but it gave exclusively the conjugated diene **19** as the sole reaction product in 56% isolated yield (Scheme 6). Again, the stereochemistry of the exocyclic trisubstituted double bond was assigned by NOE difference spectroscopy. Saturation of the vinyl singlet at δ 5.88 ppm gave an enhancement of 4.7% to the triplet at δ 5.31 ppm confirming the vinyl bromide changed stereochemistry on cyclisation. With the alkyl group on the opposite side of the exocyclic double bond, the final β-hydride elimination to give the endocyclic conjugated double bond is now favoured. There are a number of reasons why the cyclisation is slower than with the corresponding (*E*)-vinyl bromide. Firstly, the pendent alkyl group is now *cis* to the bromide and it would be expected that the initial oxidative addition is not as facile as it was with the corresponding (*E*)-isomer. Secondly, it is likely that in formation of the tricyclic intermediate **20**, by a 5-*exo-trig* pathway, interaction between the propyl group and the palladium retards the rate of this reaction. The same interaction would also retard the subsequent 3-*exo-trig* cyclisation of **20**. It is difficult to quantify which of the above factors is more influential but clearly there will be a cumulative effect leading to an overall slower rate for cyclisation.

In conclusion, the palladium chemistry studied proved much more subtle and complex than initially envisaged and a number of valuable mechanistic insights have been gleaned. This methodology is currently being applied to the synthesis of the tentatively assigned homopumiliotoxin 221F (Fig. 1).

Experimental

General

Melting points were recorded using a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 983G instrument coupled to a Perkin-Elmer 3700 Data Station as potassium bromide (KBr) disks, or films

(liquids). Proton nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz and 500 MHz using General Electric QE 300, Bruker DPX 300 and DRX 500 NMR spectrometers. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard and coupling constants are given in hertz. The following abbreviations are used: s singlet, d doublet, t triplet, q quartet, m multiplet and br broad. Mass spectra were recorded using Double Focusing Triple Sector VG Auto Spec and accurate molecular masses were determined by the peak matching method using perfluorokerosene as standard reference and were accurate to within ±0.006 amu. Microanalyses were obtained using a Perkin-Elmer 2400 CHN elemental analyser. Optical rotations were determined on a Perkin-Elmer precision polarimeter Model 241, using specified solvent and concentration at the D-line 589 nm and at ambient temperature. Analytical TLC was carried out on Merck Kieselgel 60_{254} plates and the spots visualised using a Hanovia Chromatolite UV lamp. Flash chromatography was effected using Merck Kielselgel 60 (230–400 mesh). The solvents for which the R_f values are quoted are the same that were used for any subsequent chromatography.

(*S*)-(+)-1-Benzyl-5-(1-hydroxy-1-methylethyl)pyrrolidin-2-one

Methyl iodide (24.4 g, 170.4 mmol) in ether (50 ml) was added dropwise over 30 minutes to a suspension of magnesium (4.1 g, 170.4 mmol) in ether (100 ml), with ice cooling. When the initial vigorous reaction had subsided, (*S*)-(+)-1-benzyl-5-ethoxycarbonylpyrrolidin-2-one (12.03 g, 48.7 mmol)[18] in ether (200 ml) was added dropwise over 40 minutes (the addition was such as to maintain a steady reflux). The resulting mixture was mechanically stirred at room temperature for 3 hours. Saturated ammonium chloride (100 ml) was added dropwise, followed by extraction with ether (3 × 100 ml). The combined ether fractions were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (60% ethyl acetate–hexane) gave (*S*)-(+)-1-benzyl-5-(1-hydroxy-1-methylethyl)pyrrolidin-2-one (9.5 g, 83.7%) as a colourless oil, R_f 0.34 ($C_{14}H_{19}NO_2$ requires: C, 72.1; H, 8.2; N, 6.0%. Found: C, 71.8; H, 8.5; N, 6.0%); $[a]_D$ = +131.7 (*c* 2.81, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3395, 3080, 3024, 1659, 1581, 1490, 1445, 1418; δ_H (300 MHz, $CDCl_3$) 1.16 (3H, s, CCH_3CH_3OH), 1.21 (3H, s, CCH_3CH_3OH), 1.55 (1H, br, OH), 1.73 (1H, ddt, *J* 14.2, 9.7, 3.9, NCHC*H*H), 2.0 (1H, m, NCHCH*H*), 2.38 (1H, ddd, *J* 16.9, 10.0, 5.2, NCOC*H*H), 2.55 (1H, ddd, *J* 17.1, 9.8, 7.1, NCOCH*H*), 3.34 (1H, dd, *J* 9.1, 3.5, NC*H*), 4.53 and 5.21 (2 × 1H, 2 × d, *J* 14.7, NCH_2Ph), 7.24–7.35 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 21.06, 22.99, 27.57, 29.88, 46.03, 65.00, 74.02, 126.78, 127.88, 128.07, 137.00, 176.32; *m*/*z*(%) 233 (M^+, 0.6), 175 (44.3), 174 (77.7), 91 (100.0).

(*S*)-(+)-1-Benzyl-5-isopropenylpyrrolidin-2-one

Thionyl chloride (6.0 ml, 82 mmol) was added dropwise, over 20 minutes, to a magnetically stirred solution of (*S*)-(+)-1-benzyl-5-(1-hydroxy-1-methylethyl)pyrrolidin-2-one (9.07 g, 38.9 mmol) in THF (250 ml), at −78 °C. The mixture was stirred at this temperature for 2.5 hours before the dropwise addition of triethylamine (95 ml, 0.66 mol) at −78 °C, over 30 minutes. The solvent was then removed under reduced pressure, extracted with dichloromethane (3 × 50 ml) and washed with water (3 × 100 ml). Drying over magnesium sulfate and concentration under reduced pressure, followed by vacuum distillation gave (*S*)-(+)-1-benzyl-5-isopropenylpyrrolidin-2-one (6.79 g, 81%) as a colourless oil, bp 111–115 °C (0.001 mmHg); $[a]_D$ = +195.6 (*c* 2.01, $CHCl_3$) ($C_{14}H_{17}NO$ requires: C, 78.1; H, 8.0; N, 6.5%. Found: C, 78.4; H, 8.0; N, 6.8%); ν_{max} (KBr)/cm^{-1} 3057, 3024, 1685, 1647, 1600, 1581, 1491, 1451; δ_H (300 MHz, $CDCl_3$) 1.63 (3H, s, $=CCH_3$), 1.73 (1H, ddd, *J* 17.0, 9.7, 7.1, NCHC*H*H), 2.12 (1H, m, NCHCH*H*), 2.49 (2 × 1H, m, $NCOCH_2$), 3.63 and 5.07 (2 × 1H, 2 × d, *J* 14.5, NCH_2Ph), 3.90 (1H, dd, *J* 8.7, 4.1, NC*H*), 4.85 and 4.96 (2 × 1H, 2 × s, $=CH_2$), 7.21–7.38 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 16.92, 23.13, 30.04, 44.14, 62.62, 114.17, 127.39, 128.43, 128.47, 136.59, 143.13, 175.11; *m*/*z*(%) 216 ($M + 1^+$, 15.7), 215 (M^+, 88.2), 174 (28.3), 146 (29.0), 91 (100.0).

(*S*)-(+)-5-Isopropenylpyrrolidin-2-one 1

Sodium (1.45 g, 63.0 mmol) was cautiously added in small pieces to a stirred solution of (*S*)-(+)-1-benzyl-5-isopropenylpyrrolidin-2-one (2.6 g, 12.1 mmol) in liquid ammonia (100 ml). Initially, the blue colour around the sodium discharged but persisted after 30 minutes. The ammonia was allowed to evaporate over 4 hours. Methanol (30 ml) was cautiously added, followed by concentration under reduced pressure. The residue was extracted with dichloromethane (2 × 150 ml), washed with water (3 × 60 ml), dried over magnesium sulfate and concentrated. Purification by flash chromatography (4:1 ether–petroleum ether) gave (*S*)-(+)-5-isopropenylpyrrolidin-2-one (**1**, 1.1 g, 74%) as a lightly coloured solid, mp 49–50 °C. Vacuum distillation bp 125 °C (0.5 mmHg) gave **1** which solidified on cooling as white platelets, mp 49–50 °C; $[a]_D$ = +0.6 (*c* 0.81, $CHCl_3$) ($C_7H_{11}NO$ requires: C, 67.2; H, 8.9; N, 11.2%. Found: C, 67.1; H, 8.9; N, 11.1%); ν_{max} (KBr)/cm^{-1} 3400, 1701, 1455; δ_H (300 MHz, $CDCl_3$), 1.73 (3H, s, $=CCH_3$), 1.88 (1H, ddt, *J* 16.8, 9.9, 3.4, NCHC*H*H), 2.28–2.42 (3 × 1H, 3 × m, $NCHCHHCH_2$), 4.13 (1H, m, NC*H*), 4.84 and 4.94 (2 × 1H, 2 × s, $=CH_2$), 6.38 (1H, br, N*H*); δ_C (75 MHz, $CDCl_3$) 27.29, 29.99, 56.19, 63.14, 110.80, 148.84, 179.07; *m*/*z*(%) 125 (M^+, 6.4), 110 (39.4), 84 (66.9), 67 (23.8), 41 (100.0).

Reaction of (*S*)-(+)-5-isopropenylpyrrolidin-2-one 1 with (*R*)-(+)- and (*S*)-(−)-α-methylbenzyl isocyanate

A solution of α-methylbenzyl isocyanate (11.8 mg, 0.08 mmol) and (*S*)-(+)-5-isopropenylpyrrolidin-2-one (10 mg, 0.08 mmol) in toluene (2 ml) was refluxed overnight. The solvent was removed under reduced pressure, and NMR spectra of the two diastereoisomeric urethane derivatives were recorded. For (*R*)-(+)-α-methylbenzyl isocyanate adduct δ_H (300 MHz, $CDCl_3$) 1.52 (3H, d, *J* 7.0, $NCHPhCH_3$), 1.75 (3H, s, $=CCH_3$), 1.81 (1H, m, NCHC*H*H), 2.21 (1H, m, NCHCH*H*), 2.50 (1H, m, NCOC*H*H), 2.64 (1H, m, NCOCH*H*), 4.65 and 4.81 (2 × 1H, 2 × s, $=CH_2$), 4.75 (1H, m, NC*H*), 5.05 (1H, quintet, *J* 6.7, $NHCHCH_3$), 7.25–7.43 (5H, m, Ar*H*), 8.59 (1H, d, *J* 6.9, N*H*). For (*S*)-(−)-α-methylbenzyl isocyanate adduct δ_H (300 MHz, $CDCl_3$) 1.53 (3H, d, *J* 7.0, $NCHPhCH_3$), 1.78 (3H, s, $=CCH_3$), 1.80 (1H, m, NCHC*H*H), 2.18 (1H, m, NCHCH*H*), 2.40 (1H, m, NCOC*H*H), 2.70 (1H, m, NCOCH*H*), 4.77 and 4.88 (2 × 1H, 2 × s, $=CH_2$), 4.70 (1H, m, CONC*H*), 5.11 (1H, quintet, *J* 6.9, $NHCHCH_3$), 7.24–7.39 (5H, m, Ar), 8.63 (1H, d, *J* 7.0, N*H*).

Using the resonance for the vinylic protons at δ 4.65 ppm and 4.77 ppm for each of the two diastereoisomers the two samples independently showed a 98:2 and a 2:98 ratio of two diastereoisomers. This translates to an ee of 96% for the pyrrolidinone **1**.

2,3-Dibromononanoic acid 3

Dry bromine (5.8 ml, 112 mmol) was added to a stirred solution of non-2-enoic acid (16.03 g, 102 mmol) in dry dichloromethane (100 ml). After the initial exothermic reaction had subsided the mixture was stirred at room temperature overnight. The resulting mixture was washed with 1 M sodium thiosulfate (2 × 25 ml) and brine (2 × 30 ml), dried over magnesium sulfate and concentrated under reduced pressure and gave 2,3-dibromononanoic acid (30.97 g, 96%) as a yellow oil which solidified upon pumping, mp 32–36 °C. This material was used without purification for the next stage. ν_{max} (KBr)/cm^{-1} 3600, 2950, 1712, 1461, 1424 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.80 (3H,

m, CH_3), 1.10–1.70 (8H, 8 × m, (CH_2)$_4$CH$_3$), 1.82 (1H, m, CHHCHBr), 2.25 (1H, m, CHHCHBr), 4.32–4.46 (2 × 1H, 2 × m, CHBrCHBrCO$_2$), 7.88 (1H, br, COOH); *m*/*z*(%) 318 ($M_{2^{81}Br}^+$, 0.02), 316 ($M_{^{79}Br^{81}Br}^+$, 0.04), 314 ($M_{2^{79}Br}^+$, 0.03), 237 (71.1), 235 (73.2), 255 (57.7), 109 (100.0).

(*E*/*Z*)-2-Bromonon-2-enoic acid 4

A solution of 1 M potassium hydroxide (150 ml) was added to 2,3-dibrononanoic acid (21.50 g, 68 mmol) and this was heated at 35–40 °C for 56 hours. The solution was acidified with concentrated hydrochloric acid (18 ml, 219 mmol) and extracted with ether (1 × 50 ml). The organic layer was washed with brine (2 × 20 ml), dried over magnesium sulfate and concentrated under reduced pressure. Vacuum distillation gave 2-bromonon-2-enoic acid (11.31 g, 71%), as clear liquid, bp 90–92 °C (2 mmHg) as a mixture of (*E*)- and (*Z*)-isomers ratio 5.7 : 1 ($C_9H_{15}BrO_2$ requires: C, 46.0; H, 6.4%. Found: C, 45.6; H, 6.2%); ν_{max} (KBr)/cm^{-1} 3919, 3735, 1689, 1601, 1462, 1453, 1418; δ_H (300 MHz, $CDCl_3$, (*E*)-isomer) 0.89 (3H, t, *J* 6.9, CH_3), 1.20–1.46 (8H, overlapping m, (CH_2)$_4$CH$_3$), 2.57 (2H, q, *J* 7.5, =CHCH_2), 6.88 (1H, t, *J* 7.8H, CBr=CH); *m*/*z*(%) 236 ($M_{^{81}Br}^+$, 3.4), 234 ($M_{^{79}Br}^+$, 2.9), 179 (26.9), 177 (26.4), 155 (60.6).

(*E*)-2-Bromonon-2-enoic acid methyl ester

DMSO (75 ml), followed by iodomethane (5.0 ml, 80 mmol) was added to a stirred solution of the previously prepared 2-bromonon-2-enoic acid (5.0 g, 21.3 mmol) in potassium hydroxide solution (15 ml) [2.0 g in water (15 ml)]. The clear yellow solution became cloudy and was stirred at room temperature for 20 hours. Water (100 ml) was added and the resulting mixture was extracted with ether (3 × 50 ml). The combined ethereal extracts were washed with water (3 × 30 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (1 : 99 ether–petroleum ether) gave pure (*E*)-2-bromonon-2-enoic acid methyl ester (3.18 g, 60%) as a colourless oil. (*E*)-isomer, R_f 0.6; (*Z*)-isomer, R_f 0.5; bp 80–85 °C (1 mmHg) ($C_{10}H_{17}BrO_2$ requires: C, 48.2, H, 6.9%. Found: C, 48.2; H, 6.6%); ν_{max} (KBr)/cm^{-1} 1729, 1647, 1619, 1452, 1432; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0, CH_2CH_3), 1.20–1.50 (8H, overlapping m, (CH_2)$_4$CH$_3$), 2.47 (2H, q, *J* 7.7, =CHCH_2), 3.81 (3H, s, OCH_3), 6.69 (1H, t, *J* 7.7, =CH); δ_C (125 MHz, $CDCl_3$) 14.67, 23.17, 29.34, 29.47, 32.16, 32.18, 53.39, 111.04, 150.16, 163.95; *m*/*z*(%) 250 ($M_{^{81}Br}^+$, 4.0), 248 ($M_{^{79}Br}^+$, 5.6), 193 (15.2), 191 (13.9), 169 (96.5), 167 (88.0), 109 (100.0).

(*E*)-2-Bromonon-2-en-1-ol

DIBAL-H 1 M (16 ml, 24 mmol) was added dropwise, over 40 minutes, to a stirred solution of (*E*)-2-bromonon-2-enoic acid methyl ester (2.6 g, 10.4 mmol) in ether (80 ml), at −78 °C, whilst maintaining the temperature below −65 °C during the addition. The mixture was then allowed to warm to 0 °C slowly over 2 hours, water (1 ml) was cautiously added dropwise, followed by the dropwise addition of a hydrochloric acid solution (25 ml) [concentrated acid (5 ml) in water (20 ml)]. The two-phase mixture was stirred vigorously at room temperature for 2 hours to dissolve the solids. The aqueous layer was extracted with ether (2 × 30 ml) and the combined organic extracts were washed with water (2 × 30 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by vacuum distillation gave (*E*)-2-bromonon-2-en-1-ol (2.1 g, 82%) as a colourless oil, bp 80–82.5 °C (1 mmHg) ($C_9H_{17}BrO$ requires: C, 49.3; H, 7.7%. Found: C, 49.6; H, 7.5%); ν_{max} (KBr)/cm^{-1} 3350, 1641, 1452; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 5.8, CH_2CH_3), 1.27–1.45 (8H, overlapping m, (CH_2)$_4$CH$_3$), 1.95 (1H, br, OH), 2.11 (2H, q, *J* 7.3, =CHCH_2), 4.30 (2H, s, CH_2OH), 6.02 (1H, t, *J* 7.8, CBr=CH); δ_C (75 MHz, $CDCl_3$) 14.21, 22.37, 25.14, 26.60, 28.77, 31.62, 46.67, 122.89, 142.16; *m*/*z*(%) 222 ($M_{^{81}Br}^+$, 12.3), 220 ($M_{^{79}Br}^+$, 11.9), 204 (100.0), 202 (96.0), 123 (42.3).

(*E*)-1,2-Dibromonon-2-ene 5

Dry bromine (1.44 g, 9.0 mmol) in dry acetonitrile (5 ml) was added dropwise over 10 minutes to a stirred suspension of triphenylphosphine (2.36 g, 9.0 ml) in acetonitrile (15 ml), at 0 °C. (*E*)-2-Bromonon-2-en-1-ol (1.81 g, 8.14 mmol) was added to the solution at 0 °C and allowed to warm to room temperature, whereupon it became homogeneous. The mixture was stirred for three hours, the acetonitrile was removed under reduced pressure and petroleum ether (100 ml) added to the residue. The suspension was stirred for 20 minutes, the solids filtered and washed with a further portion of petroleum ether (30 ml). The petroleum ether fractions were combined, dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether) gave (*E*)-1,2-dibromonon-2-ene (1.9 g, 83%) as a colourless oil. An analytical sample was obtained by vacuum distillation, bp 89–92 °C (10 mmHg), R_f 0.7 (hexane) ($C_9H_{16}Br_2$ requires: C, 38.1; H, 5.7%. Found: C, 38.2, H, 5.9%); ν_{max} (KBr)/cm^{-1} 1638, 1626, 1611, 1466, 1452; δ_H (300 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.5, CH_3), 1.50 (8H, overlapping m, (CH_2)$_4$CH$_3$), 2.10 (2H, q, *J* 7.4, =CHCH_2), 4.25 (2H, s, CH_2Br), 6.05 (1H, t, *J* 7.4, =CH); *m*/*z*(%) 286 ($M_{2^{81}Br}^+$, 7.2), 284 ($M_{^{81}Br^{79}Br}^+$, 13.5), 282 ($M_{2^{79}Br}$, 11.3), 124 (11.3), 123 (100.0).

(*Z*)-2-Bromohex-2-enal 6

Bromine (8.16 g, 51.1 mmol) was added dropwise over two hours to a solution of (*E*)-hex-2-enal (5.0 g, 51.1 mmol) in dichloromethane (30 ml) at 0 °C. The temperature was always maintained below 5 °C. Two hours after final addition triethylamine (7.70 g, 76.2 mmol) was added dropwise to the mixture and the resulting solution was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure and ether (35 ml) added, and this was washed with water (3 × 15 ml) and brine (15 ml). The organic layer was dried over magnesium sulfate and concentrated to give (*Z*)-2-bromohex-2-enal as a yellow oil (9.0 g, 99% crude). The crude product was deemed pure enough to be used for the next step. The corresponding (*E*)-isomer could not be detected in the crude mix by ^{13}C NMR spectroscopy. ν_{max} (KBr)/cm^{-1} 2964, 2934, 1702, 668; δ_H (500 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.4, CH_3), 1.62 (2H, septet, *J* 7.4, CH_2CH$_3$), 2.52 (2H, q, *J* 7.4, CH_2CH), 7.17 (1H, t, *J* 7.4, CH=), 9.21 (1H, s, CHO); δ_C (75 MHz, $CDCl_3$) 14.20, 21.34, 34.34, 129.29, 156.08, 186.58; *m*/*z*(%) 177 (11.5), 97 (39.5), 67 (41.5), 43 (31.0), 39 (100.0).

(*Z*)-2-Bromohex-2-en-1-ol

Sodium borohydride (0.2 g, 5.3 mmol) was added in small portions to a solution of (*Z*)-2-bromohex-2-enal (2.0 g, 11.2 mmol) in ethanol (20 ml) and the resulting solution was stirred for 2 hours. The solvent was then removed under reduced pressure and the residue was taken up with dichloromethane (50 ml) and washed with water (3 × 20 ml), dried over magnesium sulfate and concentrated. Distillation of the crude yellow oil gave (*Z*)-2-bromohex-2-en-1-ol as a colourless oil (1.15 g, 56.9%), bp 48 °C (3 mmHg) ($C_6H_{11}OBr$ requires: C, 40.2; H, 6.2%. Found: C, 39.9; H, 6.3%); ν_{max} (KBr)/cm^{-1} 3341, 2961, 2872, 1656, 684; δ_H (500 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.4, CH_3), 1.45 (2H, sextet, *J* 7.4, CH_2CH$_3$), 2.18 (2H, q, *J* 7.4, CH_2CH=), 2.28 (1H, br s, OH), 4.24 (2H, s, CH_2OH), 6.00 (1H, t, *J* 7.4, C=CH); δ_C (75 MHz, $CDCl_3$) 14.49, 22.30, 33.55, 69.20, 127.43, 131.07; *m*/*z*(%) 180 (10.3), 178 (10.3), 99 (7.2), 81 (69.0), 79 (19.0), 57 (100.0).

(*Z*)-1,2-Dibromohex-2-ene 7

Phosphorus tribromide (0.15 ml, 1.58 mmol) was added to a solution of (*Z*)-2-bromohex-2-en-1-ol (0.85 g, 4.75 mmol) in

dry ether (12 ml) at −20 °C under an atmosphere of dry nitrogen. The reaction mixture was then allowed to warm to room temperature and stirred for a further hour. The reaction was quenched with saturated sodium carbonate (15 ml) and extracted with ether (3 × 10 ml). The combined organic layers were washed with brine (10 ml), dried over magnesium sulfate and concentrated. The crude material (0.29 g, 64%) was deemed pure enough to be used for the next step. δ_H (300 MHz, $CDCl_3$) 0.79 (3H, t, *J* 7.3, C*H*$_3$), 1.31 (2H, sextet, *J* 7.3, C*H*$_2$CH$_3$), 2.01 (2H, q, *J* 7.3, C*H*$_2$CH), 4.10 (2H, s, C*H*$_2$Br), 5.96 (1H, t, *J* 7.3, C*H*=); δ_C (75 MHz, $CDCl_3$) 14.11, 21.71, 33.96, 39.41, 122.89, 135.22.

(*S*)-(+)-1-[(*E*)-2-Bromonon-2-enyl]-5-isopropenylpyrrolidin-2-one 8

(*S*)-(+)-5-Isopropenylpyrrolidin-2-one (0.30 g, 2.40 mmol) in THF (2 ml) was added dropwise, over 10 minutes, to a suspension of 60% sodium hydride (0.46 g, 2.76 mmol) in THF (18 ml), with ice cooling. (*E*)-1,2-Dibromonon-2-ene (0.68 g, 2.40 mmol) was added dropwise over 15 minutes, and the resulting mixture was stirred overnight at room temperature. The THF was removed under reduced pressure, the remaining residue was taken up in ether (50 ml), washed with water (2 × 40 ml), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (50% ether–petroleum ether) gave (*S*)-(+)-1-[(*E*)-2-bromonon-2-enyl]-5-isopropenylpyrrolidin-2-one (**8**, 0.67 g, 85%) as a colourless oil, R_f 0.41 (50% ether–petroleum ether); $[\alpha]_D$ = +4.5 (*c* 1.04, $CHCl_3$) ($C_{16}H_{26}BrNO$ requires: C, 58.5; H, 8.0; N, 4.3%. Found: C, 58.5; H, 7.6; N, 4.2%); ν_{max} (KBr)/cm^{-1} 3070, 1697, 1646, 1553, 1501, 1452; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.3, CH_2CH_3), 1.21–1.37 (8H, overlapping m, $(CH_2)_4CH_3$), 1.67 (3H, s, =CCH_3), 1.81 (1H, ddd, *J* 14.7, 6.9, 4.4, NCHC*H*H), 2.03–2.08 (2 × 1H, 2 × m, =CHCH_2), 2.24 (1H, ddd, *J* 13.9, 8.7, 4.6, NCHCH*H*), 2.43–2.49 (2 × 1H, 2 × m, OCCH_2), 3.62 and 4.62 (2 × 1H, 2 × d, *J* 14.8, NC*HH*CBr), 4.10 (1H, dd, *J* 8.7, 4.3, NC*H*), 4.85 and 4.94 (2 × 1H, 2 × s, =CH_2), 6.06 (1H, t, *J* 7.0, CBr=C*H*); δ_C (75 MHz, $CDCl_3$) 14.03, 17.56, 22.53, 23.51, 28.75, 29.06, 29.72, 29.84, 31.58, 42.62, 62.37, 113.39, 119.18, 137.35, 143.32, 175.38; *m*/*z*(%) 329 ($M_{^{81}Br}^+$, 0.5), 327 ($M_{^{79}Br}^+$, 0.5), 248 (100.0), 247 (24.2), 138 (22.1).

(*S*)-(+)-1-[(*Z*)-2-Bromohex-2-enyl]-5-isopropenylpyrrolidin-2-one 18

Sodium hydride (previously washed with hexane) (53 mg, 2.20 mmol) was carefully added to a solution of (*S*)-(+)-5-isopropenylpyrrolidin-2-one (0.25 g, 1.99 mmol) in dry THF (10 ml) at 0 °C. When hydrogen evolution ceased, (*Z*)-1,2-dibromohex-2-ene (0.58 g, 2.40 mmol) was added dropwise. The cold bath was removed and the reaction stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue taken up with ether (10 ml), washed with water (2 × 4 ml) and brine (4 ml). The aqueous layers were washed with ether (5 ml). The combined ethereal layers were dried over magnesium sulfate and concentrated. Purification by flash chromatography (ether) gave (*S*)-(+)-1-[(*Z*)-2-bromohex-2-enyl]-5-isopropenylpyrrolidin-2-one as a colourless oil (0.21 g, 37%). R_f 0.35; $[\alpha]_D$ = +146.3 (*c* 4.0, $CHCl_3$) ($C_{13}H_{20}BrNO$ requires: M^+, 285.073. Found: M^+, 285.073); ν_{max} (KBr)/cm^{-1} 3078, 2961, 2872, 1701, 1414, 903, 611; δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.3, CH_2CH_3), 1.43 (2H, sextet, *J* 7.3, CH_2CH_3), 1.65 (3H, s, =CCH_3), 1.76–1.86 (1H, m, NCOCH$_2$C*H*H), 2.12–2.29 (3H, m, NCOCH$_2$CH*H* and =CCHCH_2), 2.43–2.49 (2H, m, NCOCH_2), 3.43 (1H, d, *J* 14.9, NCH*H*), 4.08 (1H, dd, *J* 8.7, 4.3, CH$_2$C*H*), 4.73 (1H, d, *J* 14.9, NC*H*H), 4.89 (2H, d, *J* 25.4, =CH_2), 5.83 (1H, t, *J* 6.8, C=C*H*CH$_2$); δ_C (75 MHz, $CDCl_3$) 14.13, 17.61, 21.95, 23.69, 30.39, 33.43, 49.19, 62.85, 114.29, 122.17, 133.45, 143.47, 175.71; *m*/*z*(%) 286 (M^+, 13.5), 206 (100.0), 190 (5.4), 138 (46.8).

(*S*)-1-[(*E*)-2-Bromonon-2-enyl]-5-(1-chloromethylvinyl)-pyrrolidin-2-one

Calcium hypochlorite (790 mg, 6.7 mmol) was dissolved in water (7 ml) and this was added to (*S*)-1-[(*E*)-2-bromonon-2-enyl]-5-isopropenylpyrrolidin-2-one (1.85 g, 5.61 mmol), in dichloromethane (30 ml) and the two phase solution was vigorously stirred. Dry ice (10 mmol) was added in small pieces over half an hour. The resulting mixture was stirred for 45 minutes and saturated sodium bicarbonate (50 ml) was added. The dichloromethane layer was separated and the aqueous layer extracted with further dichloromethane (2 × 40 ml). The combined dichloromethane extracts were dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (60% ether–hexane) gave (*S*)-1-[(*E*)-2-bromonon-2-enyl]-5-(1-chloromethylvinyl)pyrrolidin-2-one (1.26 g, 62%) as a yellow oil, R_f 0.32 (80% ether–hexane) ($C_{16}H_{25}BrNOCl$ requires: $M - Br^+$, 282.154. Found: $M - Br^+$, 282.153); ν_{max} (KBr)/cm^{-1} 3080, 1693, 1553, 1502, 1451, 1411, 1234; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, CH_2CH_3), 1.19–1.38 (8H, br m, $(CH_2)_4CH_3$), 1.83 (1H, m, NCHC*H*H), 2.03 (2H, m, =CHCH_2), 2.31–2.55 (3H, 3 × m, NCHCH*HC*H_2), 3.69 (1H, d, *J* 15.0, NC*H*H), 4.04 (2H, s, CH_2Cl), 4.31 (1H, dd, *J* 8.3, 3.5, NC*H*), 4.65 (1H, d, *J* 15.0, NCH*H*), 5.10 and 5.39 (2 × 1H, 2 × s, =CH_2), 6.09 (1H, t, *J* 7.9, CBr=C*H*); δ_C (75 MHz, $CDCl_3$) 14.13, 22.51, 25.03, 26.69, 28.94, 29.69, 30.16, 42.77, 44.72, 59.16, 116.31, 118.77, 137.72, 143.58, 175.44; *m*/*z*(%) 365 ($M_{^{37}Cl^{81}Br}^+$, 0.02), 363 (M^+, 0.06), 361 ($M_{Cl^{35}Br^{79}}^+$, 0.05), 345 (0.45), 298 (1.0), 282 ($M - Br^+$, 1.4), 265 (23.9), 264 (100.0).

(*S*)-(+)-1-[(*E*)-2-Bromonon-2-enyl]-5-(1-hydroxymethylvinyl)-pyrrolidin-2-one

(*S*)-(+)-1-[(*E*)-2-Bromonon-2-enyl)-5-(1-chloromethylvinyl)-pyrrolidin-2-one (1.19 g, 3.27 mmol) was dissolved in 25% aqueous dioxane (35 ml) containing sodium bicarbonate (0.65 g, 7.76 mmol) and the resulting mixture was boiled under reflux for 4 days. The dioxane was removed under reduced pressure and the residue was extracted with dichloromethane (3 × 20 ml), dried over magnesium sulfate and concentrated. Flash chromatography (100% ether) gave (*S*)-(+)-1-[(*E*)-2-bromonon-2-enyl]-5-(1-hydroxymethylvinyl)pyrrolidin-2-one (0.89 g, 85%) as a colourless oil, R_f 0.28; $[\alpha]_D$ = +2.7 (*c* 0.49, $CHCl_3$) ($C_{16}H_{26}BrNO_2$ requires: C, 55.8; H, 7.6; N, 4.1%. Found: C, 56.3; H, 7.6; N, 4.0%); ν_{max} (KBr)/cm^{-1} 3406, 1671, 1553, 1451, 1432, 1415; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.7, CH_2CH_3), 1.21–1.39 (8H, br m, $(CH_2)_4CH_3$), 1.89 (1H, ddt, *J* 16.4, 9.9, 3.5, NCHC*H*H), 1.96–2.12 (2 × 1H, m, =CHCH_2), 2.26–2.55 (3H, 3 × m, NCHCH*HC*H_2), 3.71 (1H, d, *J* 15.0, NC*H*H), 4.12 (2H, s, CH_2OH), 4.22 (1H, dd, *J* 8.7, 3.8, NC*H*), 4.62 (1H, d, *J* 15.0, NCH*H*), 4.98 and 5.29 (2 × 1H, 2 × s, =CH_2), 6.07 (1H, t, *J* 7.7, CBr=C*H*); δ_C (75 MHz, $CDCl_3$) 13.97, 22.45, 24.79, 28.66, 28.99, 29.56, 29.64, 31.51, 42.76, 59.42, 62.77, 112.16, 118.86, 137.55, 146.94, 175.70; *m*/*z*(%) 345 ($M_{^{81}Br}^+$, 0.4), 343 ($M_{^{79}Br}^+$, 0.4), 298 (1.0), 282 (1.3), 264 (100.0).

(*S*)-(+)-2-{1-[(*E*)-2-Bromonon-2-enyl]-5-oxopyrrolidin-2-yl}propenal 15

A mixture of (*S*)-(+)-1-[(*E*)-2-bromonon-2-enyl]-5-(1-hydroxymethylvinyl)pyrrolidin-2-one (60 mg, 0.17 mmol), *N*-methylmorpholine *N*-oxide (45.9 mg, 0.46 mmol) and crushed activated molecular sieves (40 mg), in dichloromethane (1.5 ml) was cooled to 0 °C. Tetrapropylammonium perruthenate (10.9 mg, 0.03 mmol) was added and the mixture was allowed to reach room temperature and stirred for a further 24 hours. The reaction mixture was purified directly by flash chromatography (100% chloroform) and gave (*S*)-(+)-2-{1-[(*E*)-2-bromonon-2-enyl]-5-oxopyrrolidin-2-yl}propenal (50 mg, 85%) as a

heavy colourless oil, R_f 0.19; $[\alpha]_D = +2.9$ (*c* 0.40, $CHCl_3$) ($C_{16}H_{24}NO_2Br$ requires: M^+, 341.099. Found: M^+, 341.100); ν_{max} (KBr)/cm^{-1} 1684, 1553, 1534, 1501, 1452, 1410, 1277; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9, CH_3), 1.15–1.38 (8H, br m, $(CH_2)_4CH_3$), 1.72 (1H, ddt, *J* 13.2, 9.8, 3.7, NCHC*H*H), 1.90–2.05 (2H, m, =CHCH_2), 2.30–2.47 (3H, 3 × m, NCHCH-*H*CH_2), 3.62 (1H, d, *J* 15.0, NC*H*H), 4.62–4.71 (2 × 1H, 2 × m, NCH*H* and NC*H*), 6.06 (1H, t, *J* 7.7, CBr=C*H*), 6.20 and 6.22 (2 × 1H, 2 × s, C=CH_2), 9.66 (1H, s, C*H*O); δ_C (125 MHz, $CDCl_3$) 14.72, 23.18, 26.16, 29.41, 29.67, 30.39, 32.22, 43.68, 55.17, 119.01, 133.88, 138.60, 149.16, 176.35, 193.59; *m*/*z*(%) 343 ($M_{^{81}Br}^+$, 0.2), 341 ($M_{^{79}Br}^+$, 0.2), 328 (0.2), 325 (0.3), 288 (0.7), 286 (1.0), 262 (100.0), 206 (2.3).

Palladium catalysed cyclisation reactions

Standard Heck conditions. Potassium carbonate (250 mg, 1.8 mmol) was added to a solution of (*S*)-(+)-1-[(*E*)-2-bromonon-2-enyl]-5-isopropenylpyrrolidin-2-one (502 mg, 1.52 mmol), palladium acetate (36 mg, 0.16 mmol) and triphenylphosphine (77 mg, 0.30 mmol) in acetonitrile 25 ml under a nitrogen atmosphere and the mixture was boiled under reflux for 1 h. The solvent was removed under reduced pressure, water (10 ml) added and the product was extracted with dichloromethane (2 × 20 ml), dried over magnesium sulfate and concentrated under reduced pressure. The ratio of the isomers **9**, **10** and **11** was determined by integrating the triplets at δ 5.24 ppm, 5.47 ppm and 5.37 ppm respectively in the proton NMR spectrum. Flash chromatography gave a mixture of the three isomers (222 mg, 59% combined yield). The individual components of the mixture were separated by multiple elution (× 14) preparative TLC using ether–petroleum ether 9 : 1 as solvent and cutting the top and bottom of bands and discarding the middle. This eventually gave compounds **9**–**11** pure but the recovery in all cases was very poor.

Jeffery conditions. Same as above except that tetraethylammonium chloride (252 mg, 1.53 mmol) was added and 24 h at room temperature were required for consumption of vinyl bromide starting materials.

Thallium acetate conditions. Same as standard Heck conditions with substitution of thallium acetate (370 mg, 1.4 mmol) for potassium carbonate. 48 h were required for consumption of vinyl bromide starting material.

(*S*)-(+)-6-(*E*)-Heptylidene-8-methyl-1,5,6,8a-tetrahydroindolizin-3(2*H*)-one 9. $[\alpha]_D = +0.7$ (*c* 1.1, $CHCl_3$) ($C_{16}H_{25}NO$ requires: M^+, 247.194. Found: M^+, 247.193); ν_{max} (KBr)/cm^{-1} 1689, 1590, 1535, 1452, 1431, 1414; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.6, CH_2CH_3), 1.23–1.38 (8H, 8 × m, $(CH_2)_4CH_3$), 1.62 (1H, m, NCHC*H*H), 1.79 (3H, s, =CCH_3), 2.10 (2H, q, *J* 7.3, =CHCH_2), 2.32 (1H, m, NCHCH*H*), 2.45 (2 × 1H, m, NCOCH_2), 3.47 (1H, d, *J* 15.0, NC*H*H), 4.09 (1H, m, NC*H*), 4.49 (1H, d, *J* 14.8, NCH*H*), 5.24 (1H, t, *J* 7.7, C=C*H*CH_2), 6.21 (1H, s, MeC=C*H*); saturation of signal at δ 6.21 gave a 5.5% NOE at δ 4.09 ppm; δ_C (125 MHz, $CDCl_3$) 14.77, 19.28, 23.28, 26.22, 27.45, 29.64, 30.26, 32.34, 32.38, 43.54, 59.24, 119.79, 127.04, 128.40, 136.60, 173.24; *m*/*z*(%) 247 (M^+, 78.5), 232 (100.0), 176 (68.5), 162 (43.1), 148 (43.6).

6-(*E*)-Heptylidene-8-methyl-1,5,6,7-tetrahydroindolizin-3(2*H*)-one 10. ($C_{16}H_{25}NO$ requires: C, 77.7; H, 10.2; N, 5.7%. Found: C, 77.2; H, 10.3; N, 5.6%) (Found: $M - CH_2^+$, 233.178. $C_{15}H_{23}NO$ requires: $M - CH_2^+$, 233.178); ν_{max} (KBr)/cm^{-1} 1679, 1591, 1451, 1409, 1374, 1257; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, CH_2CH_3), 1.22–1.40 (8H, overlapping m, $(CH_2)_4CH_3$), 1.65 (3H, s, =CCH_3), 2.03 (2H, m, =CHCH_2), 2.48 and 2.58 (2 × 2H, 2 × m, NCOCH_2CH_2), 2.72 (2H, s, =C–CH_2–C=), 3.97 (2H, s, NCH_2), 5.47 (1H, t, *J* 7.1, =C*H*CH_2); saturation at δ 5.47 ppm gave a 6.8% NOE at δ 3.97 ppm; δ_C (75 MHz, $CDCl_3$) 14.5, 16.91, 21.20, 22.60, 27.91, 28.92, 29.34, 29.60, 30.39, 31.67, 46.21, 103.71, 127.28, 127.39, 131.71, 173.64; *m*/*z*(%) 249 (M + 2^+, 8.5), 247 (M^+, 1.3), 233 (M − 14^+, 26.2), 163 (41.6), 148 (30.9), 43 (100.0).

(*S*)-(+)-6-(*E*)-Heptylidene-8-methylenehexahydroindolizin-3(2*H*)-one 11. $[\alpha]_D = +0.5$ (*c* 2.1, $CHCl_3$) ($C_{16}H_{25}NO$ requires: M^+, 247.194. Found: M^+, 247.195); ν_{max} (KBr)/cm^{-1} 2926, 2853, 1589, 1483, 1458, 1432; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9, CH_2CH_3), 1.22–1.39 (8H, br m, $CH_3(CH_2)_4$), 1.98–2.04 (3H, 3 × m, NCHC*H*H and =CHCH_2), 2.26 (1H, m, NCH-CH*H*), 2.40 (2 × 1H, 2 × m, NCOCH_2), 2.90 and 2.95 (2 × 1H, 2 × d, *J* 13.9, =C–CH_2–C=), 3.45 (1H, d, *J* 14.3, NC*H*H), 4.09 (1H, m, NC*H*), 4.43 (1H, d, *J* 14.3, NCH*H*), 4.81 and 4.92 (2 × 1H, 2 × s, =CH_2), 5.37 (1H, t, *J* 7.6, =C*H*CH_2); saturation at δ 5.37 ppm gave a 5.0% NOE enhancement to multiplet at δ 3.45 ppm; δ_C (125 MHz, $CDCl_3$) 14.77, 23.18, 23.66, 27.70, 28.46, 29.56, 30.03, 31.53, 35.84, 47.65, 60.12, 108.94, 126.83, 127.15, 145.29, 173.32; *m*/*z*(%) 247 (M^+, 77.5), 232 (13.9), 176 (100.0), 162 (77.2), 148 (42.2), 41 (66.4).

5a-(*E*)-Hept-1-enyl-1a-methylhexahydro-4a-azacyclopropa-[*a*]pentalen-4-one 12. Yellow oil, $[\alpha]_D = +1.5$ (*c* 0.55, $CHCl_3$) ($C_{16}H_{25}NO$ requires: M^+ 247.194. Found: M^+ 247.193); ν_{max} (KBr)/cm^{-1} 1694, 1453, 1403, 1293, 1262; δ_H (500 MHz, $CDCl_3$) 0.46 and 0.56 (2 × 1H, 2 × d, *J* 5.9, cyclopropane CH_2), 0.87 (3H, t, *J* 6.9, CH_2CH_3), 1.09 (3H, s, CH_3), 1.22–1.31 (6H, 6 × m, $CH_3(CH_2)_3$), 1.74 (1H, m, NCOCH$_2$C*H*H), 2.03 (2H, q, *J* 6.9, CHCH_2), 2.18 (1H, m, NCOCH$_2$CH*H*), 2.38 (1H, ddd, *J* 2.1, 10.0, 16.9, NCOC*H*H), 2.62 (1H, m, NCOCH*H*), 3.11 and 3.72 (2 × 1H, 2 × d, *J* 11.4, NCH_2), 3.93 (1H, t, *J* 7.2, NC*H*CH_2), 5.32 (1H, d, *J* 15.5, C*H*=CHCH_2), 5.43 (1H, dt, *J* 15.5, 6.6, CH=C*H*CH_2); saturation at δ 1.09 ppm gave NOE enhancements at δ 3.93 ppm of 7.6% and at δ 5.32 ppm of 6.1%; δ_C (75 MHz, $CDCl_3$) 14.58, 14.71, 17.19, 23.14, 24.14, 29.87, 33.40, 33.84, 35.08, 28.24, 67.29, 127.48, 132.34, 175.89; *m*/*z*(%) 248 (M + 1, 11.41), 247 (M^+, 63.09), 232 (10.1), 190 (32.2), 107 (45.6), 93 (100).

Cyclisation of (*S*)-(+)-2-{1-[(*E*)-2-bromonon-2-enyl]-5-oxopyrrolidin-2-yl}propenal 15

A solution of (*S*)-2-{1-[(*E*)-2-bromonon-2-enyl]-5-oxopyrrolidin-2-yl}propenal (40 mg, 0.122 mmol), potassium carbonate (1.83 mg, 0.013 mmol), palladium(II) acetate (3 mg, 0.012 mmol) and triphenylphosphine (6.4 mg, 0.024 mmol) in anhydrous acetonitrile (2 ml) was stirred at room temperature for 24 hours. The crude proton NMR spectrum suggested incomplete reaction so the solution was refluxed for a further 30 minutes. The acetonitrile was removed under reduced pressure and the resulting residue extracted with ether (2 × 30 ml), dried over magnesium sulfate and concentrated under reduced pressure. Flash chromatography (solvent diethyl ether) gave **16** and **17** as an inseparable mixture (25 mg, 59%). The products **16** and **17** were separated by multiple elution TLC (100% ether).

(*S*)-6-(*E*)-Heptylidene-3-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carbaldehyde 16. The title product was obtained pure from multiple elution preparative TLC as a yellow oil, R_f 0.21 ($C_{16}H_{23}NO_2$ requires: M^+, 261.173. Found: M^+, 261.173); ν_{max} (KBr)/cm^{-1} 1673, 1661, 1548, 1452, 1413; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.7, CH_2CH_3), 1.16–1.43 (8H, br m, $(CH_2)_4CH_3$), 2.06 (2H, q, *J* 7.1, =CHCH_2), 2.64–2.68 (2H, m, NCOCH$_2$CH_2), 3.06 (2H, s, =C–CH_2–C=), 3.22 (2H, m, NCOCH_2), 4.08 (2H, s, NCH_2), 5.57 (1H, t, *J* 6.9, =C*H*CH_2), 9.74 (1H, s, C*H*O); saturation at δ 5.57 ppm gave an NOE enhancement of 6.8% at δ 4.08 ppm; δ_C (75 MHz, $CDCl_3$) 14.72, 21.83, 23.36, 25.67, 28.43, 29.57, 30.24, 31.08, 32.37, 45.68, 105.39, 127.28, 127.40,

131.84, 174.02, 201.57; *m*/*z*(%) 261 (M^+, 24.8), 246 (100.0), 232 (12.7), 176 (41.9).

6-(*E*)-Heptylidene-3-oxo-1,2,3,5,6,8a-hexahydroindolizine-8-carbaldehyde 17. Again the title product was obtained pure from multiple elution preparative TLC as a yellow oil R_f 0.24 ($C_{16}H_{23}NO_2$ requires: M^+, 261.189. Found: M^+, 261.191); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7, CH_2CH_3), 1.33 (8H, br m, $(CH_2)_4CH_3$), 1.57 (1H, ddt, *J* 16.9, 9.7, 3.5, NCHCHH), 2.12 (2H, q, =CHCH_2), 2.30 (1H, m, NCHCHH), 2.48 (2H, m, NCOCH_2), 3.46 (1H, d, *J* 14.8, NCHH), 4.23 (1H, m, NCH), 4.71 (1H, d, *J* 15.1, NCHH), 5.89 (1H, t, *J* 7.6, =CHCH$_2$), 7.34 (1H, s, =CH), 9.53 (1H, s, CHO); saturation at δ 5.89 ppm gave a 6.3% NOE at δ 4.71 ppm; *m*/*z*(%) 261 (M^+, 2.3), 246 (87.4), 176 (21.4).

(*S*)-(−)-6-(*Z*)-Butylidene-8-methyl-1,5,6,8a-tetrahydro-indolizin-3(2*H*)-one 19. Potassium carbonate (97 mg, 0.70 mmol) was added to a solution of (*S*)-1-[(*Z*)-2-bromohex-2-enyl]-5-isopropenylpyrrolidin-2-one (200 mg, 0.70 mmol), palladium acetate (15.7 mg, 0.07 mmol) and triphenylphosphine (37 mg, 0.14 mmol) in dry acetonitile (15 ml) under a nitrogen atmosphere and the mixture was refluxed overnight. The solvent was removed under reduced pressure and the residue extracted with ether (3 × 10 ml). The combined organic layers were dried over magnesium sulfate and concentrated to give a brown oil. Purification by flash chromatography column (ether) gave (*S*)-(−)-6-(*Z*)-butylidene-8-methyl-1,5,6,8a-tetrahydro-indolizin-3(2*H*)-one as a colourless oil (80 mg, 56%), R_f 0.20; $[\alpha]_D = -10.4$ (*c* 4.3, $CHCl_3$) ($C_{13}H_{19}NO$ requires: M^+ 205.147. Found: M^+ 205.146); ν_{max} (KBr)/cm^{-1} 2961, 1694, 1419, 1303, 896; δ_H (500 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.4, CH_3CH_2), 1.36–1.44 (2H, m, CH_3CH_2), 1.62 (1H, tt, *J* 11.8, 9.7, $COCH_2CH$), 1.75 (3H, s, =CCH_3), 2.09–2.16 (2 × 1H, 2 × m, C=CHCH_2), 2.30 (1H, m, $COCH_2CH$), 2.38–2.51 (2 × 1H, m, C=CHCH_2), 3.35 (1 H, d, *J* 16.0, NCHH), 4.09 (1 H, t, *J* 8.2, NCH), 4.90 (1 H, d, *J* 16.0, NCHH), 5.30 (1 H, t, *J* 7.44, =CCHCH$_2$), 5.88 (1 H, s, CH_3C=CH); saturation at δ 5.88 ppm gave a 4.7% NOE at δ 5.30 ppm; δ_C (125 MHz, $CDCl_3$) 14.20, 18.42, 23.00, 25.76, 30.00, 32.04, 38.32, 58.34, 125.43, 128.19, 129.99, 133.64, 175.35; *m*/*z*(%) 205 (M^+, 82.5), 190 (100), 176 (43.1), 162 (12.5), 148 (29.6).

Acknowledgements

We would like to thank the Department of Education, N. Ireland D.E.N.I. for studentships (D. M. and H. McA.), European Social Fund ESF and Queens University (S. F.) for support.

References

1 J. W. Daly, H. M. Garraffo and T. F. Spande, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, New York, 1993, vol. 43, p. 185.
2 J. W. Daly and C. W. Myers, *Science*, 1967, **156**, 970.
3 T. Tokuyama, J. W. Daly and R. J. Highet, *Tetrahedron*, 1984, **40**, 1183.
4 J. P. Michael *Nat. Prod. Rep.*, 1997, **14**, 21; P. Jain, H. M. Garraffo, T. F. Spande, H. J. C. Yeh and J. W. Daly, *J. Nat. Prod.*, 1995, **58**, 100.
5 H. M. Garraffo, J. Caceres, J. W. Daly and T. F. Spande, *J. Nat. Prod.*, 1993, **56**, 1016
6 J. W. Daly, personal communication, November 1994.
7 L. E. Overman and A. S. Franklin, *Chem. Rev.*, 1996, **96**, 505.
8 J. W. Daly, E. McNeal, F. Gusovsky, F. Ito and L. E. Overman, *J. Med. Chem.*, 1988, **31**, 477.
9 L. E. Overman and K. L. Bell, *J. Am. Chem. Soc.*, 1981, **103**, 1851; L. E. Overman and M. J. Sharp, *Tetrahedron Lett.*, 1988, **29**, 901.
10 L. E. Overman and S. W. Goldstein, *J. Am. Chem. Soc.*, 1984, **106**, 5360; D. N. A. Fox, D. Lathbury, M. F. Mahon, K. C. Molloy and T. Gallagher, *J. Am. Chem. Soc.*, 1991, **113**, 2652; A. G. M. Barrett and F. Damiani, *J. Org. Chem.*, 1999, **64**, 1410.
11 S. Aoyagi, T. C. Wang and C. Kibayashi, *J. Am. Chem. Soc.*, 1993, **115**, 11393; D. Montgomery, K. Reynolds and P. J. Stevenson, *J. Chem. Soc., Chem. Commun.*, 1993, 363.
12 B. M. Trost and T. S. Scanlan, *J. Am. Chem. Soc.*, 1989, **111**, 4988; H. McAlonan, D. Montgomery and P. J. Stevenson, *Tetrahedron Lett.*, 1996, **37**, 7151; S. Aoyagi, Y. Hasegawa, S. Hirashima and C. Kibayashi, *Tetrahedron Lett.*, 1998, **39**, 2149.
13 X. Q. Tang and J. Montgomery, *J. Am. Chem. Soc.*, 1999, **121**, 6098; S. Okamoto, M. Iwakubo, K. Kobayashi and F. Sato, *J. Am. Chem. Soc.*, 1997, **119**, 6984.
14 H. Rapoport, J. S. Petersen and F. Gregor, *J. Am. Chem. Soc.*, 1984, **106**, 4539.
15 W. H. Pirkle, M. R. Robertson and M. Hyun, *J. Org. Chem.*, 1984, **49**, 2433.
16 T. C. James, *J. Chem. Soc.*, 1910, 1565.
17 R. J. Abraham, J. Fisher and P. Loftus, *Introduction to NMR Spectroscopy*, Wiley, Chichester, 1988, 18.
18 R. Grigg, V. Santhakumar, V. Sridharan, P. Stevenson, A. Teasdale, M. Thornton-Pett and T. Workun, *Tetrahedron*, 1991, **47**, 9703.
19 J. H. Rigby, *J. Am. Chem. Soc.*, 1995, **117**, 7834; T. Jeffrey, *Tetrahedron Lett.*, 1991, **32**, 2121.
20 R. Grigg and V. Sridharan, *Tetrahedron Lett.*, 1993, **34**, 7471; R. Grigg, V. Loganathan, S. Sukirthalingam and V. Sridharan, *Tetrahedron Lett.*, 1990, **31**, 6573.
21 V. H. Rawal and C. Michoud, *J. Org. Chem.*, 1993, **58**, 5583.
22 Z. Owczarczyk, F. Lumaty, E. J. Vawter and E. Negishi, *J. Am. Chem. Soc.*, 1992, **114**, 10091.
23 A. L. J. Beckwith and D. M. O'Shea, *Tetrahedron Lett.*, 1986, **27**, 4525; G. Stork and R. Mook, *Tetrahedron Lett.*, 1986, **27**, 4529; D. Critch, J. Hwang and H. Liu, *Tetrahedron Lett.*, 1996, **37**, 3105.
24 A. Brown, R. Grigg, T. Rasvishankar and M. Thorton-Pett, *Tetrahedron Lett.*, 1994, **35**, 2753; L. E. Overman, M. M. Abelman, D. J. Kucera, V. D. Tran and D. J. Ricca, *Pure Appl. Chem.*, 1992, **64**, 1813.
25 J. Wolinsky and S. G. Hedge, *J. Org. Chem.*, 1982, **47**, 3148.
26 B. Bachman, *J. Am. Chem. Soc.*, 1933, **55**, 4279.
27 C. E. Fuller and D. G. Walker, *J. Org. Chem.*, 1991, **56**, 4066.
28 M. J. Rozema, C. Eisenberg, H. Lutjens, R. Ostwald, K. Belyk and P. Knochel, *Tetrahedron Lett.*, 1993, **34**, 3115.

Paper a909774k