Total synthesis of two novel 5,6,7,8-tetrahydroindolizine alkaloids, polygonatines A and B

Andrew Dinsmore, Karen Mandy and Joseph P. Michael*

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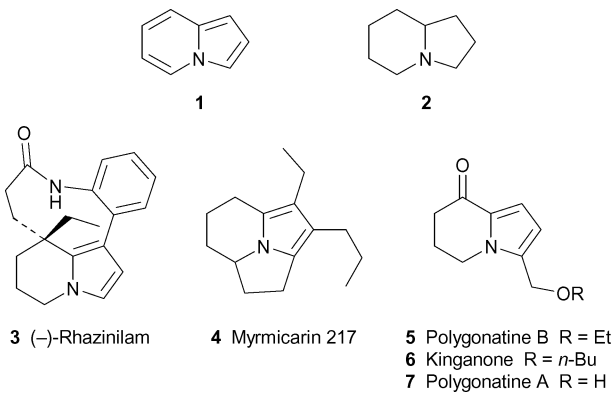
The structures of polygonatines A and B, two simple but structurally novel alkaloids, have been substantiated by synthesis. Cyclisation of 4-(1*H*-pyrrol-1-yl)butanoic acid or its ethyl ester produced 6,7-dihydroindolizin-8(5*H*)-one **10**, formylation of which at C-3 followed by reduction afforded polygonatine A **7**. Acetylation of this alkaloid followed by displacement of the acetate with ethanol yielded polygonatine B **5**, possibly *via* an azafulvenium cation.

Introduction

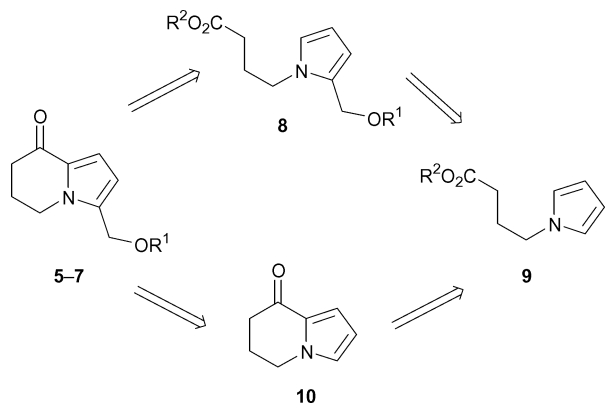
Alkaloids containing isolated pyrrole rings occur as secondary metabolites in a variety of sources, including plants, invertebrates, fungi and bacteria.[1] Especially prolific are those natural products in which the pyrrole ring forms part of a fused bicyclic or polycyclic system; in particular, the number of alkaloids containing indole, carbazole or β-carboline substructures is enormous.[2] However, the simple indolizine ring system **1** has not yet been found in a natural product, even though the saturated analogue, indolizidine **2**, is extremely well represented in alkaloid chemistry.[3,4] Even partially reduced indolizines are rare in nature; and naturally-occurring 5,6,7,8-tetrahydroindolizines, in which the pyrrole ring remains intact, have until recently been found only as part of more complex cyclic arrays, *e.g.*, in the anticancer alkaloid (−)-rhazinilam **3**[5,6] and the ant alkaloid myrmicarin 217 **4**.[7] The first simple bicyclic 5,6,7,8-tetrahydroindolizine alkaloid was reported in 1997 in the relatively inaccessible Chinese literature as a metabolite of *Polygonatum sibiricum*.[8] This unnamed compound, to which the structure **5** was assigned, caught our attention because of its unusual ring system, its curious ethoxymethyl substituent, and the fact that it was found in a plant family (the Liliaceae) from which indolizine derivatives (and, indeed, pyrrole alkaloids) had never previously been isolated. However, the same compound turned up some time later in an extract from the rhizomes of a related plant, *P. kingianum*, together with the butoxymethyl homologue **6**, to which the name kinganone was given.[9] Both alkaloids showed moderate antimicrobial activity against a range of microorganisms, thus lending credence to the traditional uses of the plant in treating lung diseases. Very recently, the original authors confirmed the presence of **5** – now given the name polygonatine B – in an alcoholic extract from the rhizomes of *P. sibiricum*, which was also shown to contain polygonatine A **7**, the hydroxymethyl parent of both **5** and **6**.[10] Although the spectroscopic evidence for these compounds seemed unambiguous, we felt that their simple but unprecedented structures merited substantiation by synthesis. In this article we report the total synthesis of polygonatines A and B.

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Johannesburg, P.O. Wits 2050, South Africa E-mail: jmichael@aurum.wits.ac.za; Fax: +27 (0)11 717-6749; Tel: +27 (0)11 717-6753



Results and discussion

Two complementary strategies for preparing the target alkaloids were considered (Scheme 1). In the first, a late-stage intramolecular cycloacylation on to the nucleophilic 5-position of a suitably *N*-alkylated pyrrole **8** already bearing the alkoxymethyl or hydroxymethyl substituent at C-2 was envisaged, the C-2 substituent arising in turn by alkylation of a 4-(1*H*-pyrrol-1-yl)butanoic acid derivative **9**. In the second approach, the order of the sequence was reversed; that is, alkoxymethylation was planned as the final process in a sequence involving initial formation of the known[11–17]



Scheme 1

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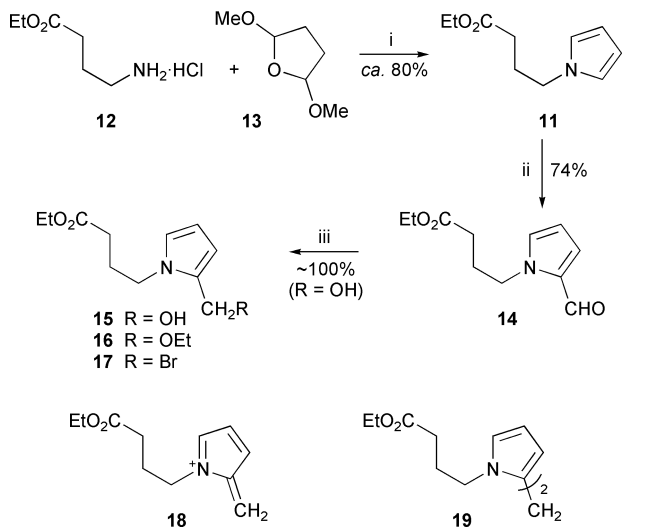
6,7-dihydroindolizin-8(5*H*)-one **10**. This intermediate is itself also accessible in principle from the generalised *N*-alkylpyrrole **9**.

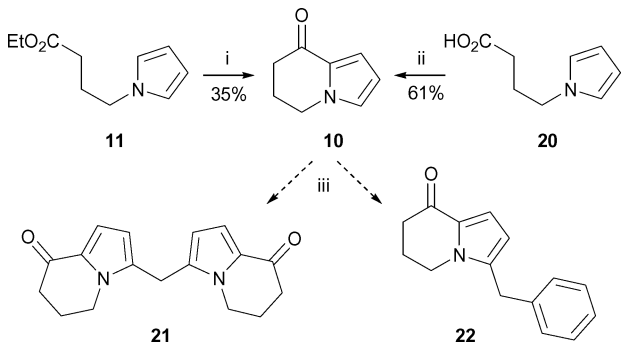
Our precursor of choice, ethyl 4-(1*H*-pyrrol-1-yl)butanoate **11**, was prepared in consistent yields of *ca.* 80% by reaction of ethyl 4-aminobutyrate hydrochloride **12** with 2,5-dimethoxytetrahydrofuran **13** in a vigorously stirred mixture of acetic acid, sodium acetate, water and 1,2-dichloroethane at 90 °C (Scheme 2). This is a modification of a procedure developed by Müller and Polleux, who prepared the corresponding methyl ester by this method.[18] For the realisation of the first strategy, the next step was the attachment of the ethoxymethyl substituent, which we initially chose to introduce by formylation, reduction and *O*-alkylation. Heaney and co-workers reported that the position of formylation of *N*-substituted pyrroles depends on the size of the substituent, the proportion of 3-formyl product increasing as a function of the steric demand of the attached group.[19] In the event, standard Vilsmeier–Haack formylation of **11** with *N*,*N*-dimethylformamide and phosphoryl chloride in boiling toluene gave the 2-formylpyrrole **14** in 74% yield; none of the 3-formyl product was detected. Reduction of **14** to the hydroxymethyl product **15** was achieved quantitatively with sodium borohydride in ethanol at room temperature. However, at this point problems began to appear. The alcohol **15** decomposed rapidly, especially upon attempted chromatography. Attempts to convert it immediately into the desired ethoxymethyl product **16** by treatment with various bases and iodoethane gave only unidentifiable products; and one attempt to convert **15** into the corresponding bromide **17** prior to treatment with ethanol gave an even less stable intermediate. It is highly probable that decomposition proceeds through ready expulsion of the leaving group in the 'benzylic' position to give an azafulvenium ion intermediate **18**,[20,21] which can decompose by a variety of pathways, including polymerisation.



Scheme 2 *Reagents and conditions*: i, NaOAc, H_2O–AcOH–$(CH_2Cl)_2$, 90 °C, 16 h; ii, DMF, $POCl_3$, 0 °C, then add **11**, toluene, reflux, 3 h; iii, $NaBH_4$, EtOH, rt, 1 h.

An alternative attempt to introduce the ethoxymethyl substituent directly into **11** by Friedel–Crafts alkylation with chloromethyl ethyl ether was also unpromising. When the reactants were heated together in toluene in the absence of a Lewis acid, the dark tar isolated from the reaction contained only traces of the desired product **16**, as indicated by mass spectrometry (M^+, 239). Another attempt in the presence of the mild Lewis acid stannic chloride at low temperature also produced only traces of **16**, but the presence of a dimer (M^+, 374) in the crude product, perhaps having structure **19**, supports the notion of interference by azafulvenium ion formation after the initial alkylation process.

Not surprisingly, the π-excessive nature of the pyrrole ring appears to be the problematic feature of our first strategy. By contrast, the alternative approach (Scheme 1) involves the intermediacy of a system **10** in which the pyrrole is substituted at C-2 by an electron-withdrawing carbonyl group that should deactivate it, thereby making it less susceptible to unfavourable side reactions during the subsequent alkylation. The first task was thus to effect cyclisation of **11** to the indolizinone **10**. Following a method introduced by Jefford *et al.* for the cyclisation of a similar ester-containing pyrrole with boron tribromide in dichloromethane,[22] Smith and co-workers were able to prepare **10** in 91% yield from the methyl ester **9** (R = Me).[17] We succeeded in cyclising the ethyl ester **11** under the same conditions, but we could not raise the yield of the desired bicyclic product **10** above 35% even by optimising the reaction time and temperature (Scheme 3). Relevant alternative routes to **10** reported in the literature have been by cyclisation of 4-(pyrrol-1-yl)butanenitrile[11,12] or 4-(pyrrol-1-yl)butanoic acid **20**,[14] the latter undergoing ready ring closure upon treatment with hydrogen chloride gas in dry methanol. In following the latter route, we prepared the acid **20**[23] in 90% yield by treating 2,5-dimethoxytetrahydrofuran **13** with 4-aminobutyric acid under our modified Müller–Polleux conditions – an improvement over the reported yield of 50%. However, cyclisation in the recommended acidic medium produced **10** in a disappointingly low yield (16%). Fortunately, cyclisation in polyphosphoric acid at room temperature under conditions described by Barton *et al.* for similar systems[15] afforded **10** in a workable yield of 61%. The spectroscopic data for this product agreed with those reported in the literature.[16,17]

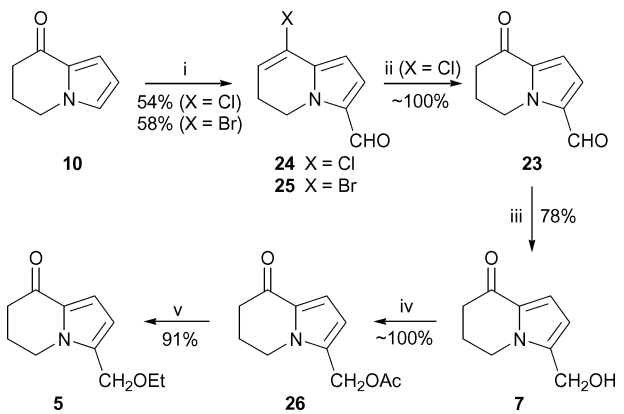


Scheme 3 *Reagents and conditions*: i, BBr_3, CH_2Cl_2, 5 °C, 20 min; ii, PPA, rt, 16 h; iii, $EtOCH_2Cl$, $SnCl_4$, C_6H_6, 0 °C, 15 min.

The attempted Friedel–Crafts alkylation of **10** with chloromethyl ethyl ether and stannic chloride in a variety of solvents produced intractable products containing only traces of the expected alkaloid polygonatine B **5**. However, when the reaction was performed in dry benzene, mass spectrometry of the crude product showed the presence of traces of **5** as well as the dimer **21** (M^+, 282) and the benzyl-substituted product **22** (M^+, 225), in which the solvent has participated in the reaction. These observations once again suggest that, under the reaction

conditions, the initially formed ethoxymethyl product readily forms an azafulvenium ion, which can be intercepted by a second equivalent of **10** or by the solvent.

This result, although undesirable in itself, suggested that if we could control the formation of the putative azafulvenium ion, we might be able to trap it with suitable nucleophiles such as ethanol. The plan was thus to formylate **10** under Vilsmeier–Haack conditions, then to reduce the aldehyde to a hydroxymethyl group (thus giving polygonatine A **7** directly) before taking advantage of azafulvenium ion formation from this product in order to introduce other nucleophiles. However, when **10** was treated with *N*,*N*-dimethylformamide and phosphoryl chloride in toluene at reflux, the product obtained, in 54% yield, was not the keto aldehyde **23**, but the vinyl chloride **24**, in which the ketone had itself reacted with phosphoryl chloride (Scheme 4). Replacing phosphoryl chloride with phosphoryl bromide gave the bromo analogue **25** in comparable yield (58%). The formation of vinyl chloride **24** was not a major setback since, after some experimentation, we were able to hydrolyse it to **23** quantitatively with a mixture of concentrated perchloric acid and formic acid (1 : 10) at 80 °C.[24] Other reported methods for hydrolysing vinyl chlorides to ketones were less successful; for instance, with concentrated sulfuric acid at room temperature,[25] the yield of **23** was 20%; while hydrolysis with titanium tetrachloride in a water–methanol–acetone mixture[26] gave only a 15% yield.



Scheme 4 *Reagents and conditions*: i, DMF, POX_3, (X = Cl or Br), 0 °C, then add **10**, toluene, reflux, 3 h; ii, aq. $HClO_4$ (60%)–HCO_2H (1 : 10), 80 °C, 1.5 h; iii, $Zn(BH_4)_2$, THF, −10 °C, 0.5 h; iv, Ac_2O, pyridine, 80 °C, 2 h; v, EtOH, reflux, 2 days.

The chemoselective reduction of the aldehyde functional group in **23** was easily accomplished with freshly prepared zinc borohydride.[27] This afforded polygonatine A **7** in 78% yield. The spectra obtained on this synthetic sample closely matched those obtained on the natural product;[10] in particular, all but one of the ^{13}C NMR signals were within ±0.7 ppm of those reported. Interestingly enough, this compound has also been reported by Allin *et al.*, who obtained it in 65% yield as the unexpected product of acyl radical cyclisation from the reaction between *Se*-phenyl 3-(2-formyl-1*H*-pyrrol-1-yl)propaneselenoate and tributyltin hydride.[28]

The envisaged conversion of **7** into polygonatine B **5** *via* an azafulvenium ion intermediate was then attempted by stirring the former in ethanol with a catalytic amount of hydrochloric acid at room temperature. Although **5** was indeed produced, the degree of conversion was modest (43%) even after 16 hours, and decomposition was again apparent. This result necessitated the conversion of the alcohol into a better leaving group. Accordingly, acetylation of **7** with acetic anhydride and pyridine at 80 °C quantitatively afforded the acetoxy product **26**. When this compound was heated with ethanol under reflux, the nucleophilic substitution proved to be slow but efficient, giving polygonatine B **5** in 91% yield. Once again, the spectroscopic data were in full agreement with those reported for the natural product (^1H signals ±0.02 ppm; ^{13}C signals ±0.1 ppm),[10] thereby substantiating the assigned structure. We have thus completed total syntheses of two novel natural products and confirmed their unusual structures. Presumably, analogous treatment of the acetate **26** with *n*-butanol would give kinganone **6**.

One final comment about the novel alkaloids is worth making. In view of the unusual ethoxy and butoxy substituents in polygonatine B **5** and kinganone **6**, respectively, we doubt whether these compounds are 'natural' products. We suspect that they may actually be artifacts of the isolation procedure in view of the relative reactivity of 2-hydroxymethyl or 2-acyloxypyrroles towards nucleophiles. To support our contention, we note that ethanol was in fact used in the extraction of **5** from the rhizomes of *Polygonatum sibiricum*,[8,10] while both ethanol and *n*-butanol were used in extracting **5** and **6** from *P. kingianum*.[9] Since both 2-acyl-5-hydroxymethylpyrroles and 2-acyl-5-acyloxymethylpyrroles occur in nature,[29] the free hydroxymethyl-containing compound polygonatine A **7**, or an ester thereof, is more likely to be the naturally occurring metabolite.

Experimental

All solvents used for reactions and chromatography were distilled before use. Tetrahydrofuran (THF) was distilled from Na/benzophenone; acetonitrile, *N*,*N*-dimethylformamide (DMF), dichloromethane, 1,2-dichloroethane and triethylamine from CaH_2; pyridine from potassium hydroxide; and toluene from Na metal. Commercially available chemicals were used as received. Melting points, recorded on a Reichert hot-stage microscope apparatus, are uncorrected. TLC was performed on aluminium-backed Alugram Sil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60. Column chromatography was carried out on silica gel 60, particle size 0.063–0.200 mm (conventional columns). FTIR spectra were recorded on a Bruker Vector 22 spectrometer. NMR spectra were recorded on Bruker AC-200 (200.13 MHz for ^1H, 50.32 MHz for ^{13}C), Bruker 300 (300.139 MHz for ^1H, 75.035 MHz for ^{13}C) or Bruker DRX 400 (400.132 MHz for ^1H, 100.625 MHz for ^{13}C) spectrometers. $CDCl_3$ was used as solvent and TMS as internal standard. DEPT and CH-correlated spectra were routinely used for assignment of signals. *J* values are given in Hz. High-resolution mass spectra were recorded at 70 eV on a VG 70 SEQ mass spectrometer with a MASPEC II data system.

Ethyl 4-(pyrrol-1-yl)butanoate 11

This compound was prepared by an adaptation of the method of Müller and Polleux.[18] Ethyl 4-aminobutyrate hydrochloride **12** (6.70 g, 40 mmol), H_2O (60 cm^3), NaOAc (3.28 g, 40 mmol), AcOH (20 cm^3) and 1,2-dichloroethane (60 cm^3) were heated

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together to 80 °C. 2,5-Dimethoxytetrahydrofuran **13** (5.20 cm^3, 5.30 g, 40.1 mmol) was added to the mixture, which was stirred vigorously at 90 °C for 16 h. The mixture was cooled, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic extracts were washed with water (2 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with EtOAc–hexane (3 : 17) as eluent to give *ethyl 4-(pyrrol-1-yl)butanoate* **11** (5.85 g, 81%) as a yellow oil; R_f 0.31 (EtOAc–hexane, 3 : 17); ν_{max}(film)/cm^{-1} 3101 (w), 2980 (m), 2925 (m), 1733 (s, C=O), 1501 (m), 1447 (m), 1375 (m), 1282 (m), 1185 (m), 1159 (m), 1090 (m), 1030 (m) and 736 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.62 (2H, t, *J* 2.1, pyrrole 2-H, 5-H), 6.13 (2H, t, *J* 2.1, pyrrole 3-H, 4-H), 4.12 (2H, q, *J* 7.1, OCH_2CH_3), 3.92 (2H, t, *J* 6.7, NCH_2), 2.24 (2H, t with further fine coupling, *J ca.* 7.0, CH_2CO_2Et), 2.06 (2H, quintet with further fine coupling, *J ca.* 7.0, $CH_2CH_2CO_2Et$) and 1.24 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 172.6 (*C*=O), 120.4 (pyrrole C-2, C-5) 108.0 (pyrrole C-3, C-4), 60.3 (OCH_2CH_3), 48.3 (NCH_2), 30.9 (CH_2CO_2Et), 26.6 ($CH_2CH_2CO_2Et$) and 14.1 (OCH_2CH_3); *m/z* 181 (M^+, 100%), 136 (83), 130 (19), 108 (15), 94 (50), 93 25), 81 (89), 80 (64), 67 (10) and 53 (23) (Found: M^+, 181.1105. $C_{10}H_{15}NO_2$ requires 181.1103).

Ethyl 4-(2-formyl-1*H*-pyrrol-1-yl)butanoate 14

A mixture of DMF (1.14 cm^3, 1.08 g, 14.8 mmol) and $POCl_3$ (1.56 cm^3, 2.57 g, 16.8 mmol) was briefly stirred at 0 °C in order to form the Vilsmeier salt. The mixture was warmed to rt, after which a solution of ethyl 4-(pyrrol-1-yl)butyrate **11** (2.00 g, 11.0 mmol) in dry toluene (2 cm^3) was added. The reaction mixture was heated at reflux for 3 h, then cooled to rt and quenched with saturated aqueous $NaHCO_3$ solution. The resulting solution was extracted with CH_2Cl_2 (3 × 20 cm^3). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with CH_2Cl_2–EtOAc (98 : 2) as eluent to give *ethyl 4-(2-formyl-1*H*-pyrrol-1-yl)butanoate* **14** (1.70 g, 74%) as a yellow oil; R_f 0.58 (CH_2Cl_2–EtOAc, 98 : 2); ν_{max} (film)/cm^{-1} 3110 (w), 2980 (w), 1732 (s, C=O), 1665 (s, C=O), 1481 (m), 1371 (m), 1324 (m), 1186 (m) and 764 (m); δ_H (300 MHz; $CDCl_3$; Me_4Si) 9.52 (1H, d, *J* 0.9, C*H*O), 6.96–6.92 (2H, m, pyrrole 3-H, 5-H), 6.22 (1H, dd, *J* 4.0 and 2.5, pyrrole 4-H), 4.38 (2H, t, *J* 7.0, NCH_2), 4.12 (2H, q, *J* 7.1, OCH_2CH_3), 2.28 (2H, t with further fine coupling, *J ca.* 7.2, CH_2CO_2Et), 2.08 (2H, quintet with further fine coupling, *J ca.* 7.1, $CH_2CH_2CO_2Et$) and 1.25 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 179.0 (*C*HO), 172.5 (*C*=O), 131.3 (overlapping pyrrole C-2, C-5), 124.7 (pyrrole C-3), 109.5 (pyrrole C-4), 60.2 (OCH_2CH_3), 47.7 (NCH_2), 30.6 (CH_2CO_2Et), 26.2 ($CH_2CH_2CO_2Et$) and 14.0 (OCH_2CH_3); *m/z* 209 (M^+, 37%), 181 (67), 152 (5), 136 (100), 122 (72), 121 (15), 108 (26), 106 (13), 94 (19), 81 (29), 80 (21) and 53 (17) (Found: M^+, 209.1065. $C_{11}H_{15}NO_3$ requires 209.1052).

Ethyl 4-(2-hydroxymethyl-1*H*-pyrrol-1-yl)butanoate 15

A suspension of $NaBH_4$ (77 mg, 2.04 mmol) was stirred at rt in EtOH (2 cm^3) under a nitrogen atmosphere. Ethyl 4-(2-formyl-1*H*-pyrrol-1-yl)butanoate **14** (388 mg, 1.85 mmol) in EtOH (2 cm^3) was slowly added through a dropping funnel. After addition was complete, the reaction mixture was stirred at rt for 1 h. The mixture was quenched with water and extracted into CH_2Cl_2 (3 × 10 cm^3) and EtOAc (2 × 10 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give *ethyl 4-(2-hydroxymethyl-1*H*-pyrrol-1-yl)butanoate* **15** (390 mg, *ca.* 100%) as a brown oil that decomposed rapidly, making full characterization impossible; R_f 0.61 (MeOH–CH_2Cl_2, 19 : 1); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.65 (1H, apparent t, *J* 2.4, pyrrole 5-H), 6.08–6.03 (2H, m, pyrrole 3-H, 4-H), 4.55 (2H, s, CH_2OH), 4.10 (2H, q, *J* 7.1, OCH_2CH_3), 3.99 (2H, t, *J* 7.1, NCH_2), 2.31 (2H, br t, *J ca.* 7.0, CH_2CO_2Et), 2.11 (3H, m, $CH_2CH_2CO_2Et$ and O*H*) and 1.24 (3H, t, *J* 7.1, OCH_2CH_3), δ_C (50 MHz; $CDCl_3$) 173.0 (*C*=O), 131.6 (pyrrole C-2), 122.0 (pyrrole C-5), 108.9 and 107.1 (pyrrole C-3, C-4), 60.5 (OCH_2CH_3), 56.3 (CH_2OH), 45.6 (NCH_2), 31.0 (CH_2CO_2Et), 26.5 ($CH_2CH_2CO_2Et$) and 14.1 (OCH_2CH_3).

4-(Pyrrol-1-yl)butanoic acid 20

4-Aminobutyric acid (10.0 g, 97.0 mmol), H_2O (144 cm^3), NaOAc (8.0 g, 97.5 mmol), AcOH (48 cm^3) and 1,2-dichloroethane (144 cm^3) were heated together at 90 °C. 2,5-Dimethoxytetrahydrofuran **13** (12.6 cm^3, 12.85 g, 97.2 mmol) was added to the mixture, which was stirred vigorously at 90 °C for 16 h. The mixture was cooled, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were washed with water (2 × 200 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (20 cm^3) and extracted repeatedly with saturated aqueous $NaHCO_3$ solution. The combined basic extracts were made acidic with aqueous HCl solution and extracted with CH_2Cl_2 (3 × 20 cm^3). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give chromatographically homogeneous *4-(pyrrol-1-yl)butanoic acid* **20** (13.3 g, 90%) as a yellow oil; R_f 0.74 (CH_2Cl_2–EtOAc, 98 : 2); ν_{max} (film)/cm^{-1} 3300–2600 (br, OH), 1708 (s, C=O), 1501 (m), 1450 (m), 1425 (m), 1282 (m), 1245 (m), 1090 (m), 728 (s) and 618 (m); δ_H (300 MHz; $CDCl_3$; Me_4Si) 10.5–9.5 (1H, br s, O*H*), 6.64 (2H, t, *J* 2.1, pyrrole 2-H, 5-H), 6.14 (2H, t, *J* 2.1, pyrrole 3-H, 4-H), 3.95 (2H, t, *J* 6.8, NCH_2), 2.32 (2H, t, *J* 7.1, CH_2CO_2H) and 2.08 (2H, quintet, *J* 7.0, $CH_2CH_2CO_2H$); δ_C (75 MHz; $CDCl_3$) 179.1 (*C*=O), 120.5 (pyrrole C-2, C-5) 108.3 (pyrrole C-3, C-4), 48.3 (NCH_2), 30.7 (CH_2CO_2H) and 26.4 ($CH_2CH_2CO_2H$); *m/z* 153 (M^+, 82%), 108 (12), 94 (15), 93 (14), 81 (100), 80 (89), 67 (20) and 53 (21) (Found: M^+, 153.0787. $C_8H_{11}NO_2$ requires 153.0790). The spectra agree with those previously reported.[23]

6,7-Dihydroindolizin-8(5*H*)-one 10

(a) BBr_3 (0.57 cm^3, 1.51 g, 6.03 mmol) in CH_2Cl_2 (4 cm^3) was added dropwise to a solution of ethyl 4-(pyrrol-1-yl)butanoate **11** (1.00 g, 5.52 mmol) in dry CH_2Cl_2 (60 cm^3) at 5 °C. The solution was stirred for an additional 20 min while warming to ambient temperature, then quenched with saturated aqueous $NaHCO_3$ solution (20 cm^3) with cooling, and vigorously stirred for a few min. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was

purified by column chromatography on silica gel with CH_2Cl_2–EtOAc (19 : 1) as eluent to give *6,7-dihydroindolizin-8(5*H*)-one* **10** (258 mg, 35%) as a brownish oil; see below for characterisation.

(b) 4-(Pyrrol-1-yl)butanoic acid **20** (1.00 g, 6.53 mmol) was stirred in PPA (5.0 cm^3) at rt for 16 h. The reaction mixture was quenched with water (*ca.* 50 cm^3), and the resulting solution was extracted with CH_2Cl_2 (3 × 50 cm^3). The organic phases were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified using column chromatography on silica gel using 95% CH_2Cl_2–EtOAc (19 : 1) as eluent (R_f 0.29) to give *6,7-dihydroindolizin-8(5*H*)-one* **10** (0.54 g, 61%) as a brownish oil; ν_{max} (film)/cm^{-1} 3108 (w), 2956 (w), 2885 (w), 1653 (s, C=O), 1530 (m), 1484 (m), 1391 (m), 1339 (m) and 749 (m); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.00 (1H, dd, *J* 4.0 and 1.4, 3-H), 6.86 (1H, apparent t, *J* 1.8, 1-H), 6.25 (1H, dd, *J* 4.0 and 2.4, 2-H), 4.12 (2H, t, *J* 5.8, NCH_2), 2.58 (2H, t with further fine coupling, *J ca.* 6.4, CH_2C=O) and 2.27 (2H, quintet with further fine coupling, *J ca.* 6.1, C$H_2$$CH_2$C=O); δ_C (75 MHz; $CDCl_3$) 187 (C=O), 131.0 and 125.8 (C-3, C-8a), 113.8 and 110.2 (C-1, C-2), 45.0 (C-5), 36.0 (C-7) and 23.4 (C-6); *m/z* 136 (M^+ + 1, 9%), 135 (M^+, 100), 107 (18), 106 (33), 93 (5), 80 (12), 79 (49), 65 (5) and 52 (14) (Found: M^+, 135.0688. C_8H_9NO requires 135.0684). The NMR spectra agree with those previously reported.[16,17]

8-Chloro-5,6-dihydroindolizine-3-carbaldehyde 24

A mixture of DMF (0.37 cm^3, 352 mg, 4.81 mmol) and $POCl_3$ (0.67 cm^3, 1.10 g, 7.17 mmol) was briefly stirred at 0 °C in order to form the Vilsmeier salt. The mixture was warmed to rt, after which a solution of 6,7-dihydroindolizin-8(5*H*)-one **10** (0.65 g, 4.81 mmol) in dry toluene (1 cm^3) was added. The mixture was heated at reflux for 2 h, then cooled to rt and quenched with a saturated aqueous $NaHCO_3$ solution. The resulting solution was extracted with CH_2Cl_2 (3 × 20 cm^3). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with CH_2Cl_2–EtOAc (98 : 2) as eluent to give *8-chloro-5,6-dihydroindolizine-3-carbaldehyde* **24** (0.47 g, 54%) as a solid that darkened immediately upon isolation; R_f 0.50 (CH_2Cl_2–EtOAc, 98 : 2); ν_{max} (KBr)/cm^{-1} 1637 (s, C=O), 1513 (m), 1474 (m), 1401 (m), 1314 (m) and 1232 (m); δ_H (400 MHz; $CDCl_3$; Me_4Si) 9.54 (1H, s, C*H*O), 6.89 (1H, d, *J* 4.1, pyrrole-H), 6.41 (1H, d, *J* 4.1, pyrrole-H), 6.06 (1H, t, *J* 4.9, C*H*=C), 4.52 (2H, t, *J* 7.6, NCH_2) and 2.63 (2H, td, *J* 7.6 and 4.9, CH_2CH=C); δ_C (100 MHz; $CDCl_3$) 180.0 (*C*HO), 135.7 and 132.2 (C-3, C-8a), 123.7, 122.7 and 122.3 (C-2, C-7, C-8), 108.5 (C-1), 41.5 (C-5) and 25.1 (C-6); *m/z* 183 (^{37}Cl–M^+, 24%), 182 (33) 181 (^{35}Cl–M^+, 75), 180 (100), 152 (7), 146 (12), 145 (21), 118 (11), 117 (31), 116 (8), 89 (10) and 63 (9) (Found: ^{35}Cl–M^+, 181.0288. $C_9H_8{}^{35}ClNO$ requires 181.0294).

8-Bromo-5,6-dihydroindolizine-3-carbaldehyde 25

The title compound was prepared in a similar manner from DMF (0.31 cm^3, 295 mg, 4.02 mmol), $POBr_3$ (1.72 g, 6.00 mmol) and a solution of 6,7-dihydroindolizin-8(5*H*)-one **10** (0.54 g, 4.00 mmol) in dry toluene (1 cm^3). Column chromatography on silica gel with CH_2Cl_2–EtOAc (98:2) as eluent gave *8-bromo-5,6-dihydroindolizine-3-carbaldehyde* **25** (0.52 g, 58%) as a solid that darkened immediately upon isolation; R_f 0.47 (CH_2Cl_2–EtOAc, 98 : 2); ν_{max} (KBr)/cm^{-1} 1637 (s, C=O); δ_H (200 MHz; $CDCl_3$; Me_4Si) 9.53 (1H, s, C*H*O), 6.88 (1H, d, *J* 4.1, pyrrole-H), 6.39 (1H, d, *J* 4.1, pyrrole-H), 6.29 (1H, t, *J* 4.9, C*H*=C), 4.53 (2H, t, *J* 7.6, NCH_2) and 2.59 (1H, td, *J* 7.6 and 4.9, CH_2CH=C); δ_C (50 MHz; $CDCl_3$) 180.1 (*C*HO), 136.4 and 132.2 (C-3, C-8a), 126.7 and 124.5 (C-2, C-7), 110.6 and 110.2 (C-1, C-8), 41.4 (C-5) and 26.2 (C-6); *m/z* 227 (^{81}Br–M^+, 5%), 226 (12), 225 (^{79}Br–M^+, 7), 224 (10), 149 (8), 82 (98), 81 (34), 80 (100), 79 (34) and 57 (60) (Found: ^{79}Br–M^+, 224.9800. $C_9H_8{}^{79}BrNO$ requires 224.9789).

8-Oxo-5,6,7,8-tetrahydroindolizine-3-carbaldehyde 23

8-Chloro-5,6-dihydroindolizine-3-carbaldehyde **24** (21 mg, 0.12 mmol) was stirred at 80 °C in a mixture of 60% $HClO_4$ and HCO_2H (1 : 10 v/v; 1.0 cm^3) for 1.5 h. The reaction mixture was cooled to rt and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (20 cm^3) and water (20 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give *8-oxo-5,6,7,8-tetrahydroindolizine-3-carbaldehyde* **23** (19 mg, *ca.* 100%) as a colourless solid; mp 105–107 °C; R_f 0.55 (CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3115 (w), 2870 (w), 1660 (s, C=O), 1479 (m), 1434 (m), 1403 (m), 1370 (m), 1350 (m), 1190 (m), 1173 (m) and 783 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 9.76 (1H, s, C*H*O), 7.00 and 6.95 (2H, AB system, *J* 4.3, 2 × pyrrole-H), 4.59 (2H, apparent t, *J ca.* 5.9, NCH_2), 2.68 (2H, apparent t, *J ca.* 6.5, CH_2C=O) and 2.42–2.27 (2H, m, C$H_2$$CH_2$C=O); δ_C (75 MHz; $CDCl_3$) 189.1 (*C*=O), 181.7 (*C*HO), 135.6 and 133.4 (C-3, C-8a), 122.2 (C-2), 113.1 (C-1), 44.7 (C-5), 36.5 (C-7) and 23.2 (C-6); *m/z* 164 (M^+ + 1, 13%), 163 (M^+, 100), 162 (17), 135 (11), 134 (57), 107 (30), 106 (19), 78 (12) and 77 (10) (Found: M^+, 163.0635. $C_9H_9NO_2$ requires 163.0633).

3-(Hydroxymethyl)-6,7-dihydroindolizin-8(5*H*)-one (polygonatine A) 7

To a solution of 8-oxo-5,6,7,8-tetrahydroindolizine-3-carbaldehyde **23** (19 mg, 0.116 mmol) in dry THF (0.1 cm^3) at −10 °C was added a freshly prepared solution of $Zn(BH_4)_2$ in THF[27] (0.15 M; 0.80 cm^3, 0.12 mmol). The reaction mixture was stirred at −10 °C for 0.5 h, then quenched by the addition of water and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give *polygonatine A* **7** (15 mg, 78%) as an off-white solid; mp. 98–99 °C (lit.,[10] 101–103 °C); R_f 0.16 (CH_2Cl_2–MeOH, 19 : 1); ν_{max} (KBr)/cm^{-1} 3378 (br, OH), 2927 (w), 1624 (s, C=O), 1534 (m), 1487 (m), 1433 (m), 1341 (m), 1018 (m), 794 (m) and 756 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.87 (1H, d, *J* 4.0, pyrrole-H), 6.15 (1H, d, *J* 4.0, pyrrole-H), 4.59 (2H, s, CH_2OH), 4.10 (2H, apparent t, *J ca.* 5.8, NCH_2), 3.80 (1H, br s, O*H*), 2.68 (2H, apparent t, *J ca.* 6.5, CH_2C=O) and 2.29–2.10 (2H, m, C$H_2$$CH_2$C=O), δ_C (75 MHz; $CDCl_3$) 187.7 (*C*=O), 136.8 and 131.6 (C-3, C-8a), 113.3 and 110.5 (C-1, C-2), 56.6 (*C*H_2OH), 42.5 (C-5), 35.9 (C-7) and 23.3 (C-6); *m/z* 166 (M^+ + 1, 9%), 165 (M^+, 89), 164 (15), 149 (11), 148 (100), 136 (16), 120 (20), 109 (12), 106 (8), 80 (13) and 78 (10) (Found: M^+, 165.0787. $C_9H_{11}NO_2$ requires 165.0790).

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(8-Oxo-5,6,7,8-tetrahydro-3-indolizinyl)methyl acetate 26

Polygonatine A **7** (9 mg, 0.054 mmol), Ac_2O (11.0 μL, 0.116 mmol) and pyridine (0.5 cm^3) were stirred at 80 °C for 2 h. The mixture was cooled to rt, made acidic with conc. HCl, diluted with water and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were washed further with water to remove the pyridinium salt. The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give *(8-oxo-5,6,7,8-tetrahydro-3-indolizinyl)methyl acetate* **26** (12 mg, *ca.* 100%) as a brown oil; R_f 0.67 (CH_2Cl_2–MeOH, 19 : 1); ν_{max} (thin film)/cm^{-1} 2923 (w), 1729 (s, C=O), 1661 (s, C=O), 1539 (m), 1434 (m), 1337 (m), 1236 (m), 1036 (m) and 789 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.99 (1H, d, *J* 4.1, pyrrole-H), 6.33 (1H, d, *J* 4.1, pyrrole-H), 5.10 (2H, s, C*H*$_2$OAc), 4.09 (2H, t, *J* 5.9, NC*H*$_2$), 2.61 (2H, apparent t, *J ca.* 6.5, C*H*$_2$C=O), 2.32 (2H, apparent quintet, *J ca.* 6.1, C*H*$_2$CH$_2$C=O) and 2.09 (3H, s, COC*H*$_3$), δ_C (75 MHz; $CDCl_3$) 187.4 (*C*=O), 170.5 (O*C*=O), 132.0 and 131.6 (C-3, C-8a), 113.4 and 112.6 (C-1, C-2), 57.1 (*C*H$_2$OAc), 42.5 (C-5), 35.9 (C-7), 23.2 (C-6) and 20.8 (CO*C*H$_3$); *m/z* 208 (M^+ + 1, 7%), 207 (M^+, 52), 166 (7), 165 (9), 149 (10), 148 (100), 147 (8), 120 (9), 106 (5) and 78 (5) (Found: M^+, 207.0898. $C_{11}H_{13}NO_3$ requires 207.0895).

3-Ethoxymethyl-6,7-dihydroindolizin-8(5*H*)-one (polygonatine B) 5

(a) Polygonatine A **7** (66 mg, 0.40 mmol) was stirred in EtOH (5 cm^3) with a catalytic amount of conc. HCl (1 drop) for 16 h at rt. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 cm^3) and washed with water (2 × 10 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give chromatographically homogeneous *polygonatine B* **5** (33 mg, 43%); see below for characterisation.

(b) (8-Oxo-5,6,7,8-tetrahydro-3-indolizinyl)methyl acetate **26** (13.3 mg, 0.064 mmol) was heated under reflux in EtOH (5 cm^3) for 2 days. The mixture was cooled to rt and the solvent was evaporated under reduced pressure to give *polygonatine B* **5** (11.3 mg, 91%) as a yellow oil; R_f 0.30 (CH_2Cl_2–MeOH, 19 : 1); ν_{max} (thin film)/cm^{-1} 2975 (w), 2928 (w), 2870 (w), 1658 (s, C=O), 1538 (m), 1480 (m), 1435 (m), 1338 (m), 1120 (m), 1089 (m) and 787 (w); δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.97 (1H, d, *J* 4.0, 1-H), 6.22 (1H, d, *J* 4.0, 2-H), 4.48 (2H, s, C*H*$_2$OEt), 4.11 (2H, t, *J* 5.9, NC*H*$_2$), 3.51 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 2.59 (2H, t, *J* 6.4, C*H*$_2$C=O), 2.30 (2H, apparent quintet, *J ca.* 6.1, C*H*$_2$CH$_2$C=O) and 1.22 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 187.5 (*C*=O), 134.3 and 131.8 (C-3, C-8a), 113.1 and 111.6 (C-1, C-2), 65.5 (O*C*H$_2$CH$_3$), 63.9 (*C*H$_2$OEt), 42.5 (C-5), 36.0 (C-7), 23.3 (C-6) and 15.1 (OCH$_2$*C*H$_3$); *m/z* 193 (M^+, 37%), 164 (3), 149 (12), 148 (100), 136 (3), 120 (10), 106 (4) and 78 (4) (Found: M^+, 193.1104. $C_{11}H_{15}NO_2$ requires 193.1103).

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