An Expeditious Synthesis of the Dendrobatid Indolizidine Alkaloid 167B

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The synthesis of the racemic title alkaloid **1** has been accomplished in eight steps and 7.2% overall yield from pyrrolidine-2-thione (**5**) and ethyl hex-2-enoate (**6**). Key steps include a ring closure that takes advantage of the nucleophilicity of a vinylogous urethane **8**, and stereoselective reduction of the C=C double bond of a bicyclic vinylogous amide **12**.

Indolizidine alkaloids are common constituents of the skin secretions of neotropical frogs of the family Dendrobatidae, which is native to Central and South America[1]. Amongst the best known examples are the potently neurotoxic pumiliotoxins and allopumiliotoxins, the complex structures of which continue to provide formidable challenges for synthesis[2]. The simpler frog alkylindolizidine alkaloids, which include 5-alkylindolizidines, 3,5- and 5,8-dialkylindolizidines, and the recently discovered 5,6,8-trialkylindolizidines[3], are also attractive synthetic targets for several reasons. Firstly, synthetic studies are helping to resolve structural and stereochemical ambiguities in many of these compounds, which are frequently found in concentrations too low to allow complete structural elucidation. Secondly, some of the alkaloids are non-competitive blockers of nicotinic acetylcholine receptor channels in muscle and ganglia membranes, making them potentially useful compounds for studying the mechanisms of neuromuscular transmission[4][5]. Finally, because of their comparatively simple structures, the compounds provide convenient targets for probing the scope and limitations of new synthetic strategies.

Indolizidine 167B, one of the simplest amphibian indolizidine alkaloids, was originally found as a trace component in the skin secretions of an unidentified frog belonging to the genus *Dendrobates* captured on the Isla Colón, Panama, and later identified in a single population of *D. speciosus*, also from Panama[6]. So little material was obtained that its tentative identification was based solely on GC-MS analysis. The structure and relative stereochemistry shown in **1** (which also shows the conventional numbering of the indolizidine system) are now accepted as correct, although the absolute configuration of the natural product remains uncertain. The alkaloid is a popular synthetic target, and syntheses of the racemic compound[7][8][9][10], the (5*R*,9*R*)-(−) enantiomer **1**[11][12][13][14][15][16][17] and the (5*S*,9*S*)-(+) enantiomer *ent*-**1**[18] have been published. The diastereoisomer **2** has also been synthesised as the racemate[8] and as the (5*S*,9*R*)-(−) enantiomer[11]. A synthesis of 5-propylindolizidine dating from 1940[19] has been cited by some later authors, but the citation is incorrect since a later reference[12] to the contents of this early work, which actually reports the synthesis of the 5-isopropyl isomer, has apparently been misunderstood.

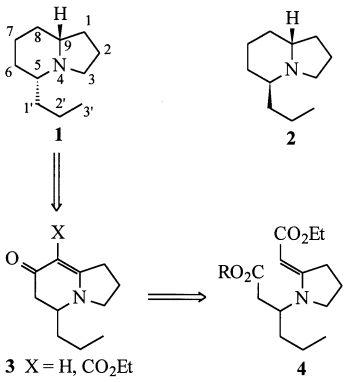
We have for some years now been exploring the use of vinylogous urethanes as versatile intermediates en route to alkaloids and other biologically interesting nitrogen heterocycles[20]. These useful compounds are easy to make, comparatively stable and, most importantly, can show ambident reactivity either as nucleophiles or as electrophiles. Indolizidine 167B offered an opportunity not only for extending our generalised synthetic approach to include a topical natural product, but also for probing stereocontrol in the manipulation of an enaminone intermediate. Scheme 1 shows in retrosynthetic mode the relationship of alkaloid **1** to enaminone intermediates envisaged as central to the current study. Clearly, the corresponding synthesis has to incorporate three pivotal features: efficient cyclisation of a vinylogous urethane similar to **4**, stereocontrolled reduction of the endocyclic C=C bond of bicyclic enaminones such as **3** (X = H) in order to set up the correct relative stereochemistry for the alkaloid, and appropriate removal of residual functional groups once they have fulfilled their purpose[21].

Results and Discussion

The synthesis of a vinylogous urethane akin to **4** commenced with the conjugate addition of pyrrolidine-2-thione (**5**)[22] to ethyl hex-2-enoate (**6**) [a 9:1 (*E*/*Z*) mixture made by Wittig reaction between butanal and ethoxycarbonyltriphenylphosphorane] (Scheme 2). This reaction took place in boiling THF in the presence of a catalytic quantity of sodium hydroxide. The rather modest yield of *rac*-pyrrolidine-2-thione **7** (46%) could not be improved by varying the reaction conditions. However, recovery of unconverted starting materials suggested that the reaction was reaching equilibrium, a suggestion we corroborated by showing the

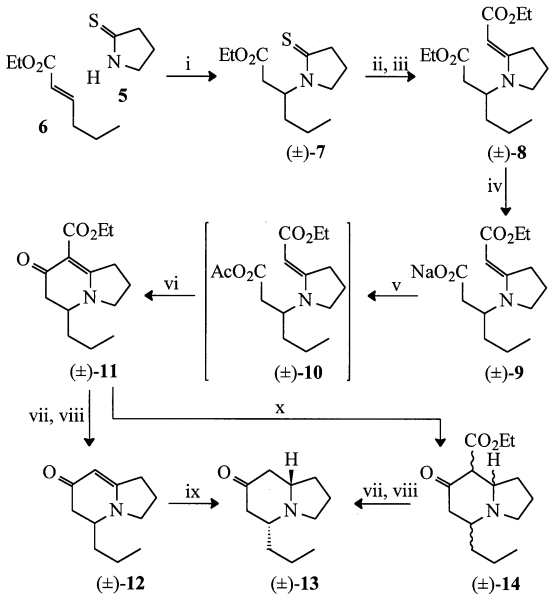
  1434−193X/98/0505−0865 $ 17.50+.50/0

Scheme 1



disproportionation of the pentyl analogue of **7** in the presence of sodium hydroxide. Eschenmoser sulfide contraction[23] on the salt formed by reaction between **7** and ethyl bromoacetate then yielded exclusively the *rac*-(*E*)-β-aminoacrylate **8** (99%). The geometry of this key intermediate was inferred from the chemical shift of the hydrogen atoms on C-3 of the pyrrolidine ring (δ = 3.15), the downfield shift of about 0.5 ppm relative to cognate (*Z*)-β-aminoacrylates[23a][24] being due to the anisotropic deshielding effect of the carbonyl group.

Scheme 2



i: NaOH (cat.), THF, reflux. − ii: $BrCH_2CO_2Et$, MeCN, room temp. − iii: PPh_3, NEt_3, MeCN, room temp. − iv: NaOH, H_2O, reflux. − v: Ac_2O, MeCN, room temp. − vi: MeCN, reflux. − vii: KOH, H_2O, reflux. − viii: HCl. − ix: $LiAlH_4$, THF, 0°C. − x: $LiAlH_4$, THF, −70°C to −50°C.

As is apparent from Scheme 2, the desired cyclisation of **8** takes advantage of its enamine-like nucleophilicity. Once this property has been exploited, the ester group of the vinylogous urethane becomes redundant, since C-8 in the target alkaloid is unsubstituted. An acylative cyclisation of the type illustrated will yield a β-oxo ester system, which will facilitate the removal of the unwanted ester group by hydrolysis and decarboxylation. Unfortunately, intermediate **8** itself could not be induced to undergo cyclisation; the saturated ester is not a sufficiently reactive acylating agent for a β-aminoacrylate, as we have previously shown[25][26][27]. However, in line with the cited precedents, a mixed anhydride was expected to be a suitable electrophilic partner for an efficient cyclisation. Transforming the saturated ester group of **8** into the more reactive anhydride required an initial chemoselective hydrolysis, which was achieved in refluxing aqueous solution with one equivalent of sodium hydroxide. The β-aminoacrylate is remarkably robust under these conditions, and withstands hydrolysis. The scrupulously dried *rac*-carboxylate salt **9** was converted in situ into the mixed *rac*-anhydride **10** by treatment with acetic anhydride in dry acetonitrile at ambient temperature. Cyclisation of **10** was spontaneous when the temperature was increased to reflux, and the *rac*-indolizidinone **11** was obtained in an overall yield of 89% based on **8**. The ester group in this bicyclic compound is now part of a β-oxo ester system, and is labile enough to be removed by hydrolysis and decarboxylation. Heating **11** under reflux with aqueous potassium hydroxide solution, followed by concentrated hydrochloric acid afforded the new bicyclic enaminone *rac*-**12** in 91% yield.

Completing the synthesis of racemic indolizidine 167B requires reduction of the C=C bond of **12** as well as defunctionalisation of its carbonyl group. We have shown for vinylogous amides that the former task can be performed chemoselectively with lithium aluminium hydride if one takes care to avoid an excess of the reagent[20a]. When **12** was treated with the reductant in dry THF, the principal product was the volatile (±)-(5*R**,9*S**)-indolizidinone **13** (56%); no more than a trace of a minor by-product, possibly the other diastereoisomer, was isolated. The presence of Bohlmann bands[28] at 2780 and 2700 cm^{-1} in the FTIR spectrum of **13** strongly supported the *trans*-diaxial disposition of the hydrogen atoms at C-5 and C-9 relative to the lone electron pair on the nitrogen atom, although unambiguous confirmation of this relative stereochemistry had to await completion of the synthesis of the target alkaloid. The most deshielded signal in the ^{1}H-NMR spectrum of **13** is due to the pseudo-equatorial methylene hydrogen atom on C-3 (δ = 3.29), which appears as a triplet of doublets ($J \approx 8.4$, 2.6 Hz). This hydrogen atom is deshielded more than the methine hydrogen atoms adjacent to the nitrogen atom by its proximity to the lone pair. The corresponding pseudo-axial proton at C-3, a four-line signal with equal coupling constants ($J \approx 8.6$ Hz) for the geminal and the two vicinal interactions, is observed at δ = 2.13, a noteworthy relative shielding difference of 1.16 ppm. This pattern for the methylene group at C-3 is consistent with literature precedents for the indolizidine system[15], and is also observed in the indolizidines obtained by further transformations of **13** (see below).

The origin of the stereoselectivity in the reduction of **12** to **13** is not clear. A simple steric preference (equatorial predisposition of the propyl group, with hydride delivery on to the more remote face of the C=C bond) provides a possible but glib rationalisation. The attractive stereoelectronic prin-

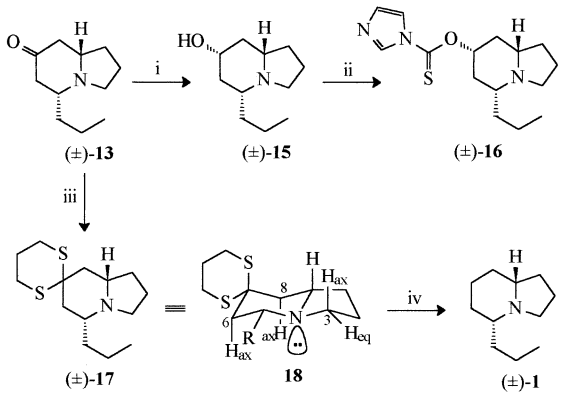
ciples of Stevens[29] do not seem applicable here since it is hard to envisage the formation of an intermediate iminium ion as the reactive form of the substrate.

In order to test whether any advantages would accrue by reversing the order of decarboxylation and double-bond reduction of indolizidinone **11**, this compound was treated with lithium aluminium hydride in dry THF at reduced temperature. In this case reduction was not diastereoselective, and a mixture of products **14** was isolated (69% combined yield). The mixture was not considered problematic, since hydrolysis and decarboxylation would remove the stereogenic centre at C-8 and reduce the number of products. When the mixture of diastereoisomers **14** was hydrolysed and decarboxylated as described previously, one major and one relatively minor product were obtained. Flash chromatography afforded a set of fractions containing the desired product **13** in a modest 53% yield. Comparison of the two routes shows that decarboxylation prior to reduction of the double bond is to be preferred (51% versus 37% yield over the two steps).

With indolizidinone **13** in hand, one of the options considered for completing the synthesis of indolizidine 167B was deoxygenation via the derived alcohol. Reduction of the ketone **13** was readily achieved with lithium aluminium hydride, and yielded *rac*-indolizidinol **15** (97%) as a single stereoisomer. Once again, Bohlmann bands at 2785 and 2695 cm^{-1} attested to the *trans*-diaxial relationship of the hydrogen atoms at C-5 and C-9 relative to the lone electron pair on the nitrogen atom. More importantly, the signal of the methine proton geminal with the hydroxy group appeared as a triple triplet at $\delta = 3.68$ with coupling constants of 11.0 and 4.6 Hz. The former value is consistent with an axial disposition of 7-H, and *trans*-diaxial relationships with the neighbouring protons 6-H and 8-H; it follows that the hydroxy group must occupy an equatorial position. In effect, this stereocontrolled reduction merely corroborates the extremely well precedented stereoselectivity with which the reduction of cyclohexanones is known to occur[30]. Unfortunately, deoxygenation of indolizidinol **15** by way of derivatives known to undergo radical-mediated defunctionalisation proved to be unworkable. For example, although the *rac*-thiocarbonylimidazolide **16** was readily prepared in 78% yield from **15** and *N*,*N*′-thiocarbonyldiimidazole[31], attempts to remove it with tributyltin hydride yielded only a complex mixture of products. Attempted replacement of the hydroxy group by bromide was also unproductive, possibly because intramolecular participation by the nucleophilic tertiary amine group leads to rapid decomposition of the halide as it is formed. The poor results obtained prompted us to pay more attention to removing the oxygen functionality at the carbonyl oxidation level, i.e. from indolizidinone **13** itself.

The final defunctionalisation was achieved via *rac*-propylene dithioketal **17**, made in 94% yield by treating **13** with propane-1,3-dithiol in trifluoroacetic acid in the presence of a catalytic quantity of boron trifluoride–diethyl ether (Scheme 3). This compound showed the expected Bohlmann bands in the FTIR spectrum, and a complex ^{1}H-NMR spectrum consistent with a preferred conformation as shown in **18**. COSY and *J*-resolved NMR spectra permitted the assignment of most signals and extraction of several of the coupling constants. Once again, the most deshielded signal ($\delta = 3.21$, td, $J = 8.4$, 2.7 Hz) is due to the pseudo-equatorial methylene hydrogen atom on C-3, its pseudo-axial partner resonating at $\delta = 2.13$. Similarly, the axial lone pair on the nitrogen atom is responsible for substantial deshielding of the signal for the axial protons 6-H and 8-H ($\delta = 2.38$, 2.51) relative to their equatorial counterparts ($\delta = 1.62$, 1.63).

Scheme 3



i: $LiAlH_4$, THF, 0°C to room temp. – ii: $Im_2C{=}S$, THF, reflux. – iii: $HS[CH_2]_3SH$, $BF_3{\cdot}Et_2O$, CF_3CO_2H, room temp. – iv: Raney Ni W-2, EtOH, reflux.

Hydrogenolysis of (±)-**17** to (±)-indolizidine 167B (**1**) was achieved with Raney nickel in boiling ethanol. However, the isolated yield was modest (37%), almost certainly because the product is very volatile, as several authors have pointed out; Holmes and co-workers, for example, chose to isolate the alkaloid as its hydrochloride salt[7]. More to the point, the NMR spectra recorded on our product were in perfect agreement with those reported in the literature for indolizidine 167B[9][11][12][15][17], and the ^{13}C-NMR spectrum in particular was quite different from that reported for the alternative diastereoisomer[11].

In summary, we have achieved a short (eight-step) synthesis of (±)-*rel*-(5*R*,9*R*)-indolizidine 167B (**1**) in an overall yield of 7.2% based on pyrrolidine-2-thione (**5**). The reported route has the advantage of operational simplicity, and uses readily available and comparatively cheap precursors and reagents as well as straightforward chemical transformations. It is not only diastereoselective, but also shorter than all but three[9][11][12] of the published routes to indolizidine 167B. While it is not enantioselective, it can easily be made so by using an enantiomerically pure 3-aminohexanoate as chiral starting compound. We are currently investigating this approach, as well as applications to related frog skin alkaloids[21].

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Experimental Section

General: All solvents used for reactions and chromatography were distilled before use. Tetrahydrofuran (THF) and diethyl ether were distilled from Na/benzophenone, CH_2Cl_2, acetonitrile and triethylamine from CaH_2, and benzene and toluene from Na. Commercially available chemicals were used as received. − TLC: Aluminium-backed Alugram Sil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60. − Column chromatography: Silica gel 60, particle size 0.063−0.200 mm (conventional column chromatography), Whatman Partisil Prep 40, particle size 0.040−0.063 mm (flash chromatography). − GC: Hewlett Packard 5890A, equipped with an HP-1 methylsilicone gum column (5 m × 0.53 mm, film thickness 2.65 μm). − IR: Jasco IR Report-100, Bruker IFS 25. − NMR: Bruker AC-200 (200.13 MHz for ^{1}H; 50.32 MHz for ^{13}C). $CDCl_3$ was used as solvent and TMS as internal standard, and DEPT and CH-correlated spectra were routinely used for complete assignment of signals. − Melting point: Reichert hot-stage microscope. − MS: Kratos MS 902/50 (70 eV), Mass Spectrometry Unit of the *Cape Technikon* (with thanks to Dr. *P. R. Boshoff*).

(±)-Ethyl 3-(2-Thioxopyrrolidin-1-yl)hexanoate (**7**): Pyrrolidine-2-thione (**5**)[22] (2.94 g, 29.1 mmol) and ethyl hex-2-enoate (**6**) [4.14 g, 29.1 mmol, prepared as a 9:1 mixture of (*E*/*Z*) isomers by Wittig reaction of ethoxycarbonyltriphenylphosphorane with butanal] were heated under reflux in dry THF (30 ml) in the presence of a catalytic quantity of sodium hydroxide for 48 h. Evaporation of the solvent yielded an oil (5.99 g), which was purified by column chromatography with ethyl acetate/hexane mixtures (17−33%) to yield **7** as a pale yellow oil (3.28 g, 46%); R_f = 0.72 (ethyl acetate/hexane, 1:1). − IR (liquid film): $\tilde{\nu}$ = 2955 cm^{-1} (s, C−H), 2925 (s, C−H), 2860 (s, C−H), 1730 (s, C=O), 1487 (s), 1450 (s), 1365 (m), 1300 (s), 1240 (m), 1185 (m, C−O), 1123 (m), 1032 (m). − ^{1}H NMR: δ = 5.38 (tt, *J* = 8.1, 6.8 Hz, 1 H, C*H*N), 4.11 (q, *J* = 7.2 Hz, 2 H, OCH_2CH$_3$), 3.76−3.52 (m, 2 H, CH_2NC=S), 3.01 (t, *J* = 7.9 Hz, 2 H, CH_2C=S), 2.57 (AB system, *J* = 14.5 Hz, further split into d, *J* = 6.4 Hz, 2 H, CH_2CO$_2$Et), 2.04 (quint, *J* = 7.4 Hz, 2 H, ring CH$_2$CH_2CH$_2$), 1.70−1.58 (m, 2 H, CHCH_2CH$_2$), 1.42−1.26 (m, 2 H, CH$_2$CH_2CH$_e$), 1.25 (t, *J* = 7.1 Hz, 3 H, OCH$_2$CH_3), 0.95 (t, *J* = 7.2 Hz, 3 H, CH$_2$CH$_2$CH_3). − ^{13}C NMR: δ = 202.07 (*C*=S), 170.28 (*C*=O), 60.74 (O*C*H$_2$CH$_3$), 52.89 (*C*HN), 49.14 (*C*H$_2$NC=S), 45.02 (*C*H$_2$C=S), 37.09 (*C*H$_2$C=O), 34.12 (CH*C*H$_2$CH$_2$), 19.96 (ring CH$_2$*C*H$_2$CH$_2$), 19.11 (CH$_2$*C*H$_2$CH$_3$), 13.97 (OCH$_2$*C*H$_3$), 13.69 (CH$_2$CH$_2$*C*H$_3$). − MS; *m*/*z* (%): 243 (38) [M$^+$], 210 (42), 201 (15), 172 (20), 168 (26), 156 (18), 142 (12), 129 (24), 128 (57), 126 (21), 102 (100), 101 (31), 85 (48), 69 (21). − $C_{12}H_{21}NO_2S$: calcd. for [M$^+$] 243.1293; found 243.1301 (HRMS).

(±)-Ethyl 3-[(2E)-2-Ethoxycarbonylmethylenepyrrolidin-1-yl]hexanoate (**8**): Thiolactam **7** (3.28 g, 13.5 mmol) and ethyl bromoacetate (1.49 ml, 13.5 mmol) were stirred together in dry acetonitrile (20 ml) for 17 h at ambient temperature. Triphenylphosphane (3.89 g, 14.8 mmol) and dry triethylamine (2.07 ml, 14.8 mmol) were added, and stirring was continued for 4 h. The resulting suspension was filtered to remove triethylammonium bromide. The solids were washed with ethyl acetate/hexane (1:1). The combined organic phases were concentrated in vacuo. The resulting product was dissolved in CH_2Cl_2 (100 ml) and washed with water (2 × 100 ml). The aqueous layers were back-extracted with CH_2Cl_2 (2 × 50 ml). The organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo, after which the crude product was purified by flash column chromatography with ethyl acetate/hexane (1:4) as eluant to give vinylogous urethane **8** as a pale yellow oil (3.98 g, 99%); R_f = 0.64 (ethyl acetate/hexane, 1:1). − IR (liquid film): $\tilde{\nu}$ = 2970 cm^{-1} (s, C−H), 2930 (s, C−H), 2860 (m, C−H), 1730 (s, saturated ester C=O), 1680 (s, unsaturated ester C=O), 1585 (s, C=C), 1370 (m), 1285 (m), 1198 (m), 1135 (s, C−O), 1060 (s), 785 (m). − ^{1}H NMR: δ = 4.67 (s, 1 H, =C*H*), 4.15−4.02 (m, 5 H, C*H*N and 2 × OCH_2CH$_3$), 3.26 (td, *J* = 6.9, 1.5 Hz, 2 H, CH_2N), 3.15 (t, *J* = 7.9 Hz, with further fine coupling, *J* ≈ 1.6 Hz, 2 H, CH_2C=), 2.59 (AB system, *J* = 14.6 Hz, further split into d, *J* = 7.3 Hz, 2 H, CH_2CO$_2$Et), 1.89 (quint, *J* = 7.4 Hz, 2 H, ring CH$_2$CH_2CH$_2$), 1.66−1.42 (m, 2 H, NCHCH_2CH$_2$), 1.36−1.14 superimposed on 1.24 (m, superimposed on 2 × t, *J* = 7.2 Hz, 8 H, CH$_2$CH_2CH$_3$ and 2 × OCH$_2$CH_3), 0.92 (t, *J* = 7.2 Hz, 3 H, CH$_2$CH$_2$CH_3). − ^{13}C NMR: δ = 170.85 (*C*=O of saturated ester), 169.66 (*C*=O of unsaturated ester), 165.13 (HC=*C*N), 78.75 (H*C*=CN), 60.76 (O*C*H$_2$CH$_3$ of saturated ester), 58.22 (O*C*H$_2$CH$_3$ of unsaturated ester), 51.35 (*C*HN), 45.98 (CH_2N), 37.42 (*C*H$_2$C=O), 34.31 (NCH*C*H$_2$CH$_2$), 32.68 (*C*H$_2$C=), 21.03 (ring CH$_2$*C*H$_2$CH$_2$), 19.46 (CH$_2$*C*H$_2$CH$_3$), 14.70 (OCH$_2$*C*H$_3$ of saturated ester), 14.06 (OCH$_2$*C*H$_3$ of unsaturated ester), 13.79 (CH$_2$CH$_2$*C*H$_3$). − MS; *m*/*z* (%): 297 (22) [M$^+$], 255 (19), 252 (51), 224 (28), 210 (100), 182 (74), 156 (41), 136 (15), 110 (37). − $C_{16}H_{27}NO_4$: calcd. for [M$^+$] 297.1940; found 297.1957 (HRMS).

(±)-Ethyl 7-Oxo-5-propyl-Δ^8-indolizidine-8-carboxylate (**11**): NaOH (0.20 g, 5.00 mmol) and vinylogous urethane **8** (1.49 g, 5.01 mmol) were heated under reflux in water (5 ml) until the solution became homogeneous and thin-layer chromatography revealed no starting material. The solvents were evaporated in vacuo and the carboxylate salt **9** thus obtained was dried overnight (ca. 1 Torr, 60°C). When thoroughly dry, the brownish solid was crushed and stirred with freshly distilled acetic anhydride (0.94 ml, 10 mmol) in dry acetonitrile (5 ml) at room temperature for 3 h and then under reflux for 3 h. The solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (50 ml) and washed with saturated $NaHCO_3$ solution (50 ml). The aqueous layer was back-extracted with CH_2Cl_2 (3 × 25 ml), after which the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an orange oil (1.37 g). Purification by column chromatography with ethyl acetate/methanol (7:1) as eluant afforded bicyclic enaminone **11** as a viscous orange oil (1.12 g, 89%); R_f = 0.36 (ethyl acetate/methanol, 7:1). − IR (liquid film): $\tilde{\nu}$ = 2955 cm^{-1} (s, C−H), 2925 (s, C−H), 2865 (s, C−H), 1705 (s, ester C=O), 1650 (s, ketone C=O), 1557 (s, C=C), 1475 (s), 1455 (s), 1417 (m), 1370 (s), 1237 (s), 1153 (s), 1095 (s). − ^{1}H NMR: δ = 4.21 (q, *J* = 7.1 Hz, 2 H, OCH_2CH$_3$), 3.75 (dt, *J* = 10.4, 7.5 Hz, 1 H, 3a-H), 3.65−3.55 (m, 1 H, 5-H), 3.54 (dt, *J* = 10.3 Hz, *J* = 7.1 Hz, 1 H, 3b-H), 3.29 (m, 2 H, 1-H), 2.75 (dd, *J* = 15.9, 6.5 Hz, 1 H, 6a-H), 2.41 (dd, *J* = 15.9, 5.1 Hz, 1 H, 6b-H), 2.12 (quint, *J* = 7.6 Hz, 2 H, 2-H), 1.64 (dt, *J* = 8.6, 7.2 Hz, 2 H, 1′-H), 1.32 superimposed on 1.55−1.20 (t, *J* = 7.1 Hz, overlapping with m; 5 H, OCH$_2$CH_3 and 2′-H), 0.93 (t, *J* = 7.2 Hz, 3 H, 3′-H). − ^{13}C NMR: δ = 186.99 (ketone *C*=O), 172.10 (ester *C*=O), 165.80 (C-9), 97.60 (C-8), 59.06 (O*C*H$_2$CH$_3$), 54.32 (C-5), 52.34 (C-3), 39.96 (C-6), 34.73, 32.04 (C-1, C-1′), 20.70 (C-2), 18.20 (C-2′), 14.23 (OCH$_2$*C*H$_3$), 13.56 (C-3′). − MS; *m*/*z* (%): 251 (10) [M$^+$], 208 (9), 206 (15), 179 (12), 178 (9), 162 (47), 137 (17), 136 (100), 108 (19), 106 (19). − $C_{14}H_{21}NO_3$: calcd. for [M$^+$] 251.1521; found 251.1491 (HRMS).

(±)-5-Propyl-Δ^8-indolizidin-7-one (**12**): An aqueous solution of KOH (1 M, 66 ml) was deaerated by bubbling nitrogen through it overnight. The oxo ester **11** (1.12 g, 4.46 mmol) was added and the solution was heated under reflux for 1 h. After being cooled to room temperature, the mixture was acidified (concentrated hydrochloric acid), stirred at room temperature for 0.5 h, made basic (25% ammonia) and extracted with dichloromethane (50 ml, 2 × 25 ml). The combined organic extracts were dried ($MgSO_4$), fil-

tered, and concentrated in vacuo to afford the unsaturated indolizidinone **12** as a chromatographically pure, viscous orange oil (0.73 g, 91%); R_f = 0.29 (ethyl acetate/methanol, 7:1). − IR (liquid film): $\tilde{\nu}$ = 2950 cm^{-1} (m, C−H), 2925 (m, C−H), 2865 (m, C−H), 1623 (s, C=O), 1568 (s, C=C), 1460 (w), 1255 (w), 1225 (w). − ^{1}H NMR: δ = 4.94 (s, 1 H, 8-H), 3.59 superimposed on 3.52 (ddd, J = 9.6, 7.3, 5.5 Hz, overlapping with m; 2 H, 3a-H and 5-H, respectively), 3.27 (dt, J = 9.6, 7.4 Hz, 1 H, 3b-H), 2.69 (br. t, $J \approx$ 7.6 Hz, 2 H, 1-H), 2.56 (dd, J = 16.3, 6.1 Hz, 1 H, 6a-H), 2.32 (dd, J = 16.3, 9.3 Hz, 1 H, 6b-H), 2.11−1.96 (m, 2 H, 2-H), 1.71−1.60 (m, 2 H, 1′-H), 1.48−1.24 (m, 2 H, 2′-H), 0.95 (t, J = 7.2 Hz, 3 H, 3′-H). − ^{13}C NMR: δ = 190.44 (*C*=O at C-7), 168.18 (C-9), 92.34 (C-8), 55.33 (C-5), 50.32 (C-3), 39.49 (C-6), 32.79 (C-1′), 31.77 (C-1), 20.65 (C-2), 17.92 (C-2′), 13.70 (C-3′). − MS; *m/z* (%): 179 (18) [M^+], 137 (27), 136 (100), 109 (33), 108 (44), 81 (13), 80 (14). − $C_{11}H_{17}NO$: calcd. for [M^+] 179.1308; found 179.1310 (HRMS).

(±)-(5R,9S*)-5-Propylindolizidin-7-one* (**13**): Lithium aluminium hydride (93 mg, 2.45 mmol, 0.75 equiv.) was added to a stirred solution of enaminone **12** (582 mg, 3.25 mmol) in dry THF (30 ml) at 0°C. The mixture was allowed to warm to room temperature and then stirred for a further 14 h. The reaction was quenched by the sequential addition of water (0.1 ml), NaOH solution (15% w/v, 0.1 ml) and water (0.3 ml). The precipitated solids were filtered and washed with CH_2Cl_2. The filtrate was dried ($MgSO_4$), filtered again, and concentrrated in vacuo to afford an oil (574 mg), which was purified by flash chromatography with 18% methanol/ethyl acetate as eluant. A pure fraction of the indolizidinone **13** was obtained as a mobile, pale yellow oil (328 mg, 56%); R_f = 0.46 (ethyl acetate/methanol, 4:1). − IR (liquid film): $\tilde{\nu}$ = 2955 cm^{-1} (s, C−H), 2865 (s, C−H), 2780 (s, Bohlmann band), 2700 (w, Bohlmann band), 1718 (s, C=O), 1457 (m), 1405 (m), 1372 (m), 1308 (m), 1245 (m), 1190 (m), 1178 (m). − ^{1}H NMR: δ = 3.29 (td, J = 8.4, 2.6 Hz, 1 H, 3-H_{eq}), 2.13 superimposed on 2.53−1.12 (4-line pattern, $J \approx$ 8.6 Hz, 3-H_{ax}, overlapping with m, total 14 H), 0.93 (t, J = 7.1 Hz, 3 H, 3′-H). − ^{13}C NMR: δ = 209.40 (*C*=O), 63.82 (C-9), 60.92 (C-5), 50.13 (C-3), 47.07 (C-8), 45.54 (C-6), 36.96 (C-1′), 30.70 (C-1), 21.34 (C-2), 18.08 (C-2′), 14.19 (C-3′). − MS; *m/z* (%): 181 (< 1) [M^+], 141 (8), 140 (100), 138 (5), 124 (8), 122 (11), 110 (6), 97 (7), 96 (73), 70 (27), 68 (11). − $C_{11}H_{19}NO$: calcd. for [M^+] 181.1467; found 181.1452 (HRMS). − A second fraction (31 mg, ca. 5%) proved to be a mixture of **13** and a compound that is probably its diastereoisomer in the ratio 0.58:1.00 (by glc); a trace of starting material **12** was also present.

Alternative Synthesis of (±)-(5R,9S*)-5-Propylindolizidin-7-one* (**13**): Lithium aluminium hydride (213 mg, 5.61 mmol) and unsaturated indolizidinone **11** (941 mg, 3.74 mmol) were stirred together in dry THF (37 ml) for 1 h at −70°C and for 1 h at −50°C. The reaction was quenched by the sequential addition of water (0.2 ml), NaOH solution (15% w/v, 0.2 ml) and finally water (0.6 ml). The precipitated solids were removed by filtration, washed with CH_2Cl_2 and ethyl acetate, and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated to give a viscous yellow oil (833 mg). Chromatography with hexane/ethyl acetate (4:1) as eluant yielded a small quantity of yellow oil (46 mg) followed by a mixture of diastereoisomers of **14** (652 mg, 69%); R_f = 0.27 (ethyl acetate/hexane, 1:1). Without further purification, a suspension of oxo ester **14** (651 mg, 2.57 mmol) in an aqueous solution of KOH (1 M, 40 ml) was heated under reflux in a nitrogen atmosphere for 1 h. After cooling to room temperature, the mixture was acidified (concentrated hydrochloric acid), refluxed for 1 h, made basic (25% ammonia) and extracted with dichloromethane (3 × 25 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give a viscous orange oil (373 mg). Chromatography with hexane/ethyl acetate (7:1) as eluant yielded the indolizidinone **13** (246 mg, 53%; 37% over both steps); characterisation as described previously.

(±)-(5R,7S*,9S*)-5-Propylindolizidin-7-ol* (**15**): Lithium aluminium hydride (76 mg, 2.0 mmol) and indolizidinone **13** (362 mg, 2.00 mmol) were stirred together in dry THF (20 ml) for 0.5 h at 0°C and then at ambient temperature until the starting material had been consumed. The reaction was quenched by the sequential addition of water (0.08 ml), NaOH solution (15% w/v, 0.08 ml) and finally water (0.24 ml). The precipitated solids were removed by filtration, washed with CH_2Cl_2, ethyl acetate and methanol, and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated to give chromatographically pure indolizidinol **15** as a viscous, colourless oil (354 mg, 97%); R_f = 0.31 (ethyl acetate/methanol, 4:1). − IR (liquid film): $\tilde{\nu}$ = 3360 cm^{-1} (br., s, O−H), 2955 (s, C−H), 2935 (s, C−H), 2865 (s, C−H), 2785 (s, Bohlmann band), 2695 (m, Bohlmann band), 1660 (br., w), 1456 (m), 1380 (m), 1357 (m), 1325 (m), 1123 (w), 1097 (w), 1031 (m). − ^{1}H NMR: δ = 3.68 (tt, J = 11.0, 4.6 Hz, 1 H, 7-H), 3.25 (td, J = 8.5, 2.4 Hz, 1 H, 3-H_{eq}), 2.93 (br. s, 1 H, O*H*), 2.20−1.15 (m, 15 H), 0.92 (t, J = 6.9 Hz, 3 H, 3′-H). − ^{13}C NMR: δ = 69.30 (C-7), 63.12 (C-9), 60.50 (C-5), 50.30 (C-3), 39.69 (C-6, C-8), 36.21 (C-1′), 29.66 (C-1), 21.03 (C-2), 18.82 (C-2′), 14.31 (C-3′). − MS; *m/z* (%): 183 (3) [M^+], 141 (9), 140 (100), 124 (5), 122 (6), 110 (3), 97 (4), 96 (37), 70 (9). − $C_{11}H_{21}NO$: calcd. for [M^+] 183.1623; found 183.1620 (HRMS).

(±)-O-[(5R,7S*,9S*)-5-Propylindolizidin-7-yl] 1-Imidazolecarbothioate* (**16**): A mixture of (±)-indolizidinol **15** (354 mg, 1.93 mmol) and *N*,*N*′-thiocarbonyldiimidazole (751 mg, 4.21 mmol) in dry THF (7 ml) was heated under reflux for 4 h, after which the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (25 ml) and washed with saturated $NaHCO_3$ solution (25 ml). The aqueous layer was back-extracted with CH_2Cl_2 (3 × 25 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to afford a dark red oil (1.026 g). Flash chromatography (40% hexane/ethyl acetate followed by 11% methanol/ethyl acetate) afforded fractions containing imidazole by-products followed by the desired thiocarbonylimidazolide **16** as a viscous orange oil (442 mg, 78%); R_f = 0.28 (ethyl acetate/methanol, 1:1). − IR (liquid film): $\tilde{\nu}$ = 3120 cm^{-1} (w, =C−H), 2952 (s, C−H), 2860 (m, C−H), 2788 (m, Bohlmann band), 2700 (w, Bohlmann band), 1526 (w, C=N), 1460 (m), 1383 (s), 1325 (s), 1282 (s), 1230 (s), 1182 (w), 1120 (m), 1098 (m, C=S), 1042 (w), 978 (s). − ^{1}H NMR: δ = 8.33 (t, $J \approx$ 1 Hz, 1 H, imidazole 2-H), 7.62 (t, $J \approx$ 1.5 Hz, 1 H, imidazole 5-H), 7.02 (dd, J = 1.7, 0.9 Hz, 1 H, imidazole 4-H), 5.50 (tt, J = 11.3, 4.9 Hz, 1 H, 7-H), 3.23 (td, J = 8.1, 2.5 Hz, 1 H, 3-H_{eq}), 2.47−1.20 (m, 15 H), 0.93 (t, J = 7.0 Hz, 3 H, 3′-H). − ^{13}C NMR: δ = 183.23 (*C*=S), 136.66 (imidazole C-2), 130.57 (imidazole C-4), 117.65 (imidazole C-5), 81.57 (C-7), 62.04 (C-9), 59.74 (C-5), 50.19 (C-3), 36.35, 35.37, 35.06 (C-6, C-8, C-1′), 29.79 (C-1), 21.04 (C-2), 18.48 (C-2′), 14.23 (C-3′). − MS; *m/z* (%): 293 (6) [M^+], 250 (24), 166 (43), 124 (30), 122 (100), 70 (37). − $C_{15}H_{23}N_3OS$: calcd. for [M^+] 293.1562; found 293.1560 (HRMS).

(±)-(5R,9S*)-5-Propylindolizidin-7-one Propylene Dithioketal* (**17**): Indolizidinone **13** (96 mg, 0.53 mmol), boron trifluoride−diethyl ether (0.085 ml, 0.70 mmol), and propane-1,3-dithiol (0.10 ml, 1.0 mmol) were stirred at ambient temperature in trifluoroacetic acid (1 ml) for 29 h. Ethyl acetate (100 ml) and water (100 ml) were added, and the resulting solution was made basic with NH_4OH solution (25%). The organic layer was separated, dried

($MgSO_4$), filtered, and concentrated in vacuo to afford an oil (649 mg). Flash chromatography (5% methanol/ethyl acetate) afforded dithioketal **17** as a colourless, very viscous oil (135 mg, 94%); R_f = 0.31 (ethyl acetate). − IR (liquid film): $\tilde{\nu}$ = 2956 cm^{-1} (s, C−H), 2936 (s, C−H), 2910 (s, C−H), 2870 (m, C−H), 2798 (m, Bohlmann band), 1458 (m), 1424 (m), 1382 (m), 1276 (m), 1182 (m). − ^1H NMR: δ = 3.21 (td, J = 8.4, 2.7 Hz, 1 H, 3-H_{eq}), 2.95−2.86 (m, 2 H, SCH_2), 2.81−2.72 (m, 2 H, SCH_2), 2.51 and 2.38 superimposed on 2.53−2.35 (dt, J = 13.7, 2.5 Hz; dt, J = 13.6 Hz, J = 2.5 Hz; overlapping with m; 4 H, 6-H_{ax}, 8-H_{ax}, overlapping with 5-H, 9-H), 2.13 (4-line pattern, $J \approx$ 8.8 Hz, 1 H, 3-H_{ax}), 2.11−1.91 (m, 2 H, SCH_2CH_2), 1.63, 1.62 superimposed on 1.89−1.20 (m, 10 H, former two signals are due to 6-H_{eq}, 8-H_{eq},), 0.92 (t, J = 6.9 Hz, 3 H, 3′-H). − ^{13}C NMR: δ = 59.34 (C-9), 57.84 (C-5), 50.49 (C-3), 49.07 (C-7), 42.69, 42.21 (C-6, C-8), 36.00 (C-1′), 29.69 (C-1), 26.25 (SCH_2), 25.90 (SCH_2CH_2), 25.55 (SCH_2), 20.62 (C-2), 18.71 (C-2′), 14.29 (C-3′). − MS; *m/z* (%): 271 (7) [M^+], 228 (24), 196 (8), 164 (8), 138 (7), 125 (68), 124 (20), 122 (20), 97 (15), 96 (100), 70 (14). − $C_{14}H_{25}NS_2$: calcd. for [M^+] 271.1428; found 271.1440 (HRMS).

(±)-Indolizidine 167B (**1**): Raney nickel catalyst, prepared according to the method of Covert and Adkins[32] (W-2 activity, suspension in absolute EtOH, about 500 mg), was added to dithioketal **17** (95 mg, 0.35 mmol) in absolute EtOH (20 ml), and the mixture was stirred under reflux for 3 h. The reaction mixture was cooled to room temperature and filtered through Celite. The solids were washed with ethyl acetate and CH_2Cl_2. The combined organic phases were concentrated in vacuo to yield chromatographically pure **1** as a pale yellow mobile oil (21.5 mg, 37%); R_f = 0.07 (ethyl acetate). − IR (liquid film): $\tilde{\nu}$ = 2958 cm^{-1} (s, C−H), 2934 (s, C−H), 2872 (s, C−H), 2784 (s, Bohlmann band), 1458 (m), 1380 (m), 1198 (m), 1182 (m), 1130 (w). − ^1H NMR: δ = 3.26 (td, J = 8.4, 2.4 Hz, 1 H, 3-H_{eq}), 1.97 superimposed on 2.05−1.60 and 1.60−1.09 (4-line pattern, $J \approx$ 8.8 Hz, 3-H_{ax}, overlapping with 2 × m, 17 H), 0.91 (t, J = 7.1 Hz, 3 H, 3′-H). − ^{13}C NMR: δ = 64.98 (C-9), 63.66 (C-5), 51.49 (C-3), 36.84 (C-1′), 30.93 (C-8), 30.76 (C-6), 30.49 (C-1), 24.64 (C-7), 20.35 (C-2), 19.06 (C-2′), 14.48 (C-3′). − MS; *m/z* (%): 167 (12) [M^+], 166 (16), 125 (28), 124 (100), 97 (45), 96 (29), 85 (38), 83 (42), 71 (48), 70 (24), 69 (42), 57 (75), 55 (40). − $C_{11}H_{21}N$: calcd. for [M^+] 167.1674; found 167.1677 (HRMS).

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