Exploiting multiple nucleophilic sites on pyrrole for the assembly of polyheterocyclic frameworks: application to a formal total synthesis of (±)-aspidospermidine

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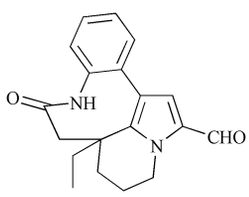
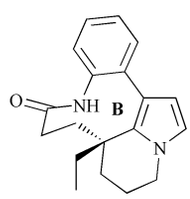
The tricyclic ketone **19**, an advanced intermediate in Aubé's recently reported synthesis of aspidospermidine (**4**), is prepared in twelve steps from pyrrole (**3**). The key transformations involve a previously described intramolecular Michael addition reaction of pyrrole **10** and intramolecular Friedel–Crafts type cyclisation of the derived carboxylic acid **15** to ketone **16**. Careful hydrogenation of this last compound afforded the fully saturated alcohol **17** which was readily oxidised to the target ketone **19**.

Introduction

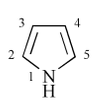
In connection with a general program directed towards the synthesis of pyrrole-containing natural products now underway in these laboratories[1] we have begun to more fully appreciate the manifold nucleophilic properties of this readily available five-membered aromatic heterocycle.[2] Such properties have been exploited in our recently described syntheses of the marine alkaloid longamide B[3] and (±)-B-norrhazinal (**1**),[4] a biologically active analogue of the terrestrial natural product (−)-rhazinilam (**2**) which possesses intriguing anti-mitotic properties.[5] Our synthesis of compound **1** exploited the nucleophilic character of both *N*-1 and *C*-2 of pyrrole (**3**), with the former centre participating in an intermolecular alkylation reaction and the latter in a facile intramolecular Michael addition to a tethered acrylate. Herein we report extension of such chemistries to a formal total synthesis of the alkaloid (±)-aspidospermidine [(±)-**4**] wherein the nucleophilic character of *N*-1, *C*-2 and *C*-3 of pyrrole are all engaged in the course of assembling an advanced precursor to this target molecule. Thus, our synthesis starts from abundant pyrrole, employs simple reagents throughout and, in keeping with the majority of previous routes, proceeds *via* a hydrolilolidone precursor (incorporating the CDE-ring substructure of target **4**) which can be subjected to a "one-pot" Fischer indolization reaction to complete the synthesis. Whilst aspidospermidine (**4**) is biologically inactive it embodies the pentacyclic framework associated with a number of pharmacologically significant *Aspidosperma* alkaloids including vindoline and the related "dimers" vinblastine and vincristine.[6] As such, compound **4** has been a popular synthetic target for "showcasing" new methodologies. It was first prepared by Stork and Dolfini in 1963[7] and since this time numerous additional and ingenious approaches have been described[8] including several more recent ones employing novel radical or ionic cyclisation sequences and another exploiting an intramolecular Schimdt reaction.



(±)-B-norrhazinal (**1**)



(−)-rhazinilam (**2**)



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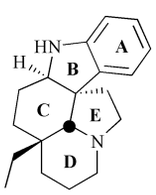

(−)-aspidospermidine (**4**)

Results and discussion

The reaction sequence leading from the readily prepared potassium salt, **5**, of pyrrole to target **4** is shown in Scheme 1. Thus, following on from our work[4] on the synthesis of (±)-B-norrhazinal, salt **5** was reacted with γ-butyrolactone (**6**) under the conditions defined by Synder[9] to give, after acidic work-up, the *N*-1 alkylation product **7** (90%). This last compound was then converted, in one-pot, into the corresponding Weinreb amide **8** (87%) by using our recently described[10] adaptation of the Mukaiyama amide synthesis. Reaction of amide **8** with ethyl magnesium bromide then afforded, after work-up at −40 °C (in order to avoid formation of unwanted products of cyclisation between the carbonyl carbon and C-2 of the pyrrole), the ethyl ketone **9** (100%). Wadsworth–Emmons olefination of the latter compound using the anion derived from methyl diethylphosphonoacetate then afforded the β,β-disubstituted acrylate **10** (77%). The use of methyl diethylphosphonoacetate is preferred for this olefination as the sodium salt is soluble in THF, unlike the salts of the triethyl and trimethyl phosphonoacetates. The acrylate **10** was obtained as a 1:1 mixture of geometric isomers which were separated chromatographically for the purposes of independent characterization. In keeping with the behaviour of other acrylates incorporating tethered nucleophiles,[11] compound **10** engaged in a Lewis-acid (in this case $AlCl_3$) mediated intramolecular Michael addition reaction wherein C-2 of the tethered pyrrole acts as the nucleophilic centre and in this way the indolizidine **11** was obtained in 83% yield. Whilst the intermolecular reaction of acrylates and related species with pyrroles is well

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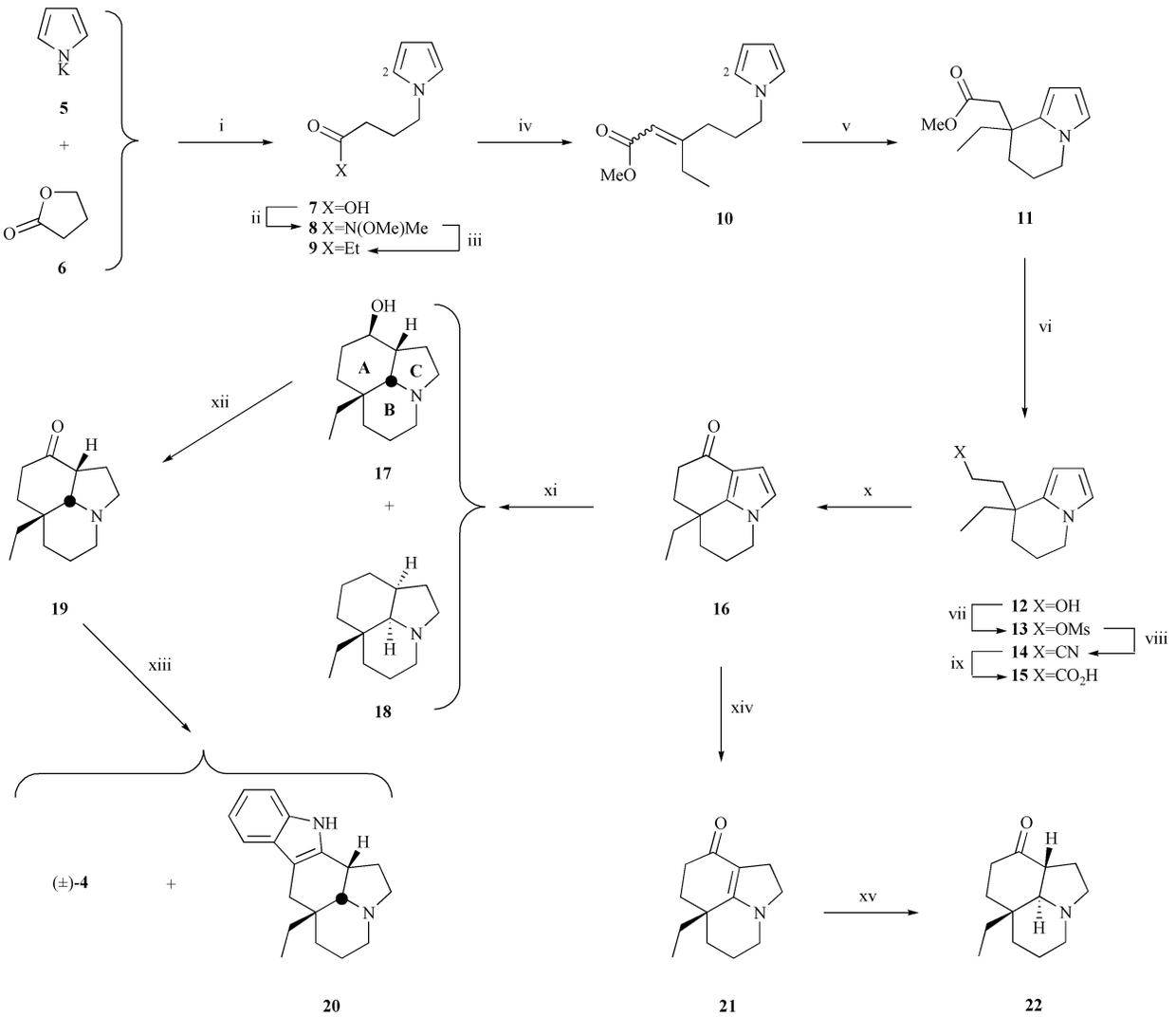

Scheme 1 *Reagents and conditions*: (i) 160 °C, 2 h; (ii) $H_3CNHOCH_3$·HCl (1.2 mole equiv.), Et_3N (1.2 mole equiv.), pyridine *N*-oxide disulfide (1.5 mole equiv.), Bu_3P (1.5 mole equiv.), CH_2Cl_2, 18 °C, 16 h; (iii) (a) EtMgBr (1.7 mole equiv.), Et_2O, 18 °C, 1 h then (b) 0.3 M aq. $KHSO_4$ (excess), −40 °C, 0.1 h then (c) $NaHCO_3$ (excess), −40 °C to 18 °C; (iv) NaH (2 mole equiv.), $(EtO)_2POCH_2CO_2Me$ (2 mole equiv.), THF, 18 °C, 48 h; (v) $AlCl_3$ (5 mole equiv.), Et_2O, 18 °C, 5 h; (vi) DIBAL-H (2 mole equiv.), CH_2Cl_2, −78 °C, 0.16 h; (vii) $MeSO_2Cl$ (1 mole equiv.), Et_3N (1 mole equiv.), CH_2Cl_2, 0–18 °C, 1.0 h; (viii) NaCN (5 mole equiv.), DMPU, 18 °C, 48 h; (ix) KOH (26 mole equiv.), H_2O–MeOH, reflux, 16 h then aq. HCl; (x) HCl (excess of a 5 M aqueous solution), 18 °C, 1 h; (xi) H_2 (1 atm.), PtO_2 (cat.), AcOH, 18 °C, 18 h; (xii) Dess–Martin periodinane (3 mole equiv.), CH_2Cl_2, 0–18 °C, 1.0 h; (xiii) see reference 8*o*; (xiv) H_2 (1 atm.), 5% Rh on Al_2O_3 (cat.), AcOH–EtOH, 18 °C, 18 h; (xv) $LiAlH_4$ (excess), THF, 66 °C, 1.5 h.

known,[12] to the best of our knowledge the conversion **10** ⟶ **11** represents the first example of the equivalent intramolecular process. As a necessary prelude to construction of the six-membered C-ring of target **4**, which was to be carried out *via* intramolecular acylation at C-3 of the pyrrole backbone, one-carbon homologation of ester **11** was required. To this end rather traditional methods were employed involving initial DIBAL-H-mediated reduction to the 1°-alcohol **12** (75%) which was immediately subject to mesylation under the Crossland–Servis conditions.[13] The resulting mesylate **13** (95%) was then subject to reaction with a five-fold excess of sodium cyanide in *N*,*N*′-dimethylpropyleneurea (DMPU)[14] and in this manner the target nitrile **14** (91%) was readily obtained. In principle, compound **14** could participate in the foreshadowed intramolecular acylation reaction to give the target tricyclic ketone **16**. In practice, however, such a conversion could not be achieved so the nitrile was hydrolysed to the corresponding acid **15** (88%) under standard conditions. The latter compound readily engaged in the required Friedel–Crafts reaction upon exposure to 5 M aqueous HCl so as to form ketone **16** (72%) which incorporates the CDE-ring substructure associated with the monomeric aspidospermidine alkaloids including **4**.

With the *bis*-annulated pyrrole **16** in hand the completion of the synthesis of compound **4** required its reduction to any one of the several possible stereoisomeric tetrahydro-derivatives since each of these should, in principle, engage in a Fisher-indolization reaction with phenylhydrazine so as to give, after "reductive work-up", (±)-aspidospermidine.[7,8*o*] In the event, reaction of an acetic acid solution of compound **16** with dihydrogen in the presence of PtO_2 at 18 °C for 18 h afforded a *ca*. 1:1 mixture of what are tentatively assigned as alcohol **17** and the deoxygenated congener **18**. The stereochemistries assigned to these reduction products can be rationalized (Fig. 1) on the basis that initial hydrogenation of substrate **16** occurs at the pyrrole double bond remote from the carbonyl group to give compound **21**. This suggestion is supported by the observation (*vide infra*) that hydrogenation of pyrrole **16** under milder conditions (5% Rh on Al_2O_3) does indeed give the dihydro-derivative **21**. Reduction of the latter compound then occurs at the carbonyl group and on the opposite face to the sterically demanding and angular ethyl group to afford the allylic alcohol **23**. Compound **23**, in turn, engages in a hydroxy-group directed hydrogenation of the remaining double bond to deliver the observed saturated alcohol **17** incorporating an all-*cis* arrangement of the angular substituents. An alternate mode of reaction of intermediate **23** could involve hydrogenolytic removal of the OH group (a process which may well be facilitated by the ring nitrogen) then reduction of the resulting

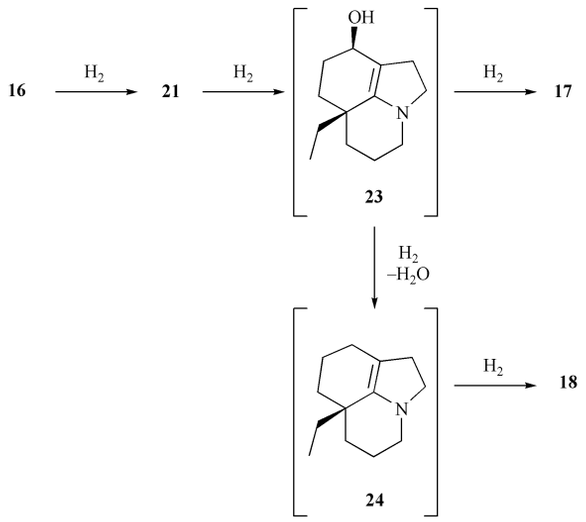

Fig. 1 Intermediates associated with the 5% PtO_2-catalysed reduction of compound **16** to products **17** and **18**.

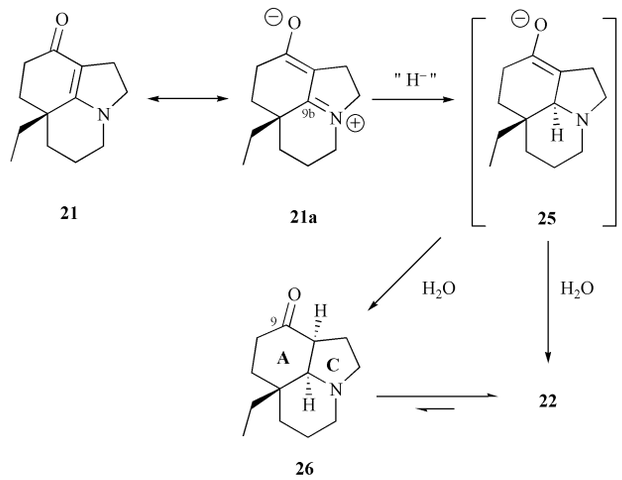

Fig. 2 Intermediates associated with the $LiAlH_4$-promoted reduction of compound **21** to product **22**.

enamine (**24**) wherein hydrogen is delivered to the α-face (*i.e.* opposite the angular ethyl group) thereby affording the deoxygenated product **18**. The structure of compound **17** follows from the observation that subjection of the mixture of this compound and co-product **18** to reaction with the Dess–Martin periodinane[15] gave the known ketone **19**[8o] (28% from **16**) which could, at this stage, be readily separated from the saturated amine (**18**) by flash chromatography. After allowance is made for changes in chemical shift induced by varying pH (due to differing amounts of DCl present in the solvent) the ^1H and ^{13}C NMR spectral data derived from amino ketone **19** were judged to be in good agreement with those reported by Aubé[8o] for the corresponding enantiomerically pure material. In particular, the profiles of the complex proton envelopes observed in the ^1H NMR spectra of the two samples represent a very good match indeed. In contrast, the equivalent spectrum of isomer **22** (see below) looks distinctly different. The acquisition of ketone **19** constitutes a formal total synthesis of (±)-aspidospermidine (**4**) since Aubé[8o] has converted, in a one-pot process, the former compound into the latter (accompanied by small amounts of isomer **20**) using Stork's original Fischer indolization strategy.

In an effort to provide a higher yielding route to a CDE-ring precursor of aspidospermidine, alternate methods for the reduction of pyrrole **16** were examined but with limited success. Thus, exposure of an ethanol–acetic acid solution of compound **16** to dihydrogen in the presence of rhodium on alumina afforded the ketoenamine **21** (80% at 50% conversion) which could be reduced to the fully saturated ketone **22** (65%) on treatment with lithium aluminium hydride. The illustrated stereochemistry for amino ketone **22** follows from mechanistic considerations and by analogy with the production of the same and a closely related compound as described by Ban[16] and Saxton,[17] respectively. Thus, the reduction of compound **21** is probably best interpreted (Fig. 2) as involving initial α-face selective hydride delivery to the iminium type-carbon C-9b highlighted in the zwitterionic resonance contributing form (**21a**) of the substrate. The ensuing enolate **25** would then be quenched, upon aqueous work up, to give ketone **22** and/or isomer **26**. Our molecular mechanics calculations as well as work by both Ban and Saxton suggests that compounds such as **26** which incorporate a *cis* A/C ring junction and ketone carbonyl at C-9 are more strained (by several kcal mol^{-1}) than the epimer (*e.g.* **22**) possessing the equivalent *trans* ring junction and that under conditions of thermodynamic control production of the latter system will be favoured. Unfortunately, whilst compound **22** has been described previously[16] there are no spectral data available in the literature for comparison with our own. Nevertheless, our data (see Experimental) are fully consistent with the assigned structure. In particular, the infrared spectrum shows a carbonyl stretching band at 1717 cm^{-1} which is indicative[16,17] of hydrolilolidones embodying the illustrated ABC ring junction stereochemistries (*cf.* an absorption at 1708 cm^{-1} for ketone **19**). Unfortunately, all attempts (including those involving application of the conditions defined by Aubé for the conversion **19** ⟶ **4**) to engage this material in the Fischer indolisation reaction so as to produce aspidosperimidine (**4**) have failed thus far. This disappointing result is not entirely surprising as it has been noted[8o] that application of the Fischer indolisation process to the synthesis of *Aspidosperma* alkaloids from precursors such as **19** and **22** can be capricious especially when carried out on a small scale.

Conclusions

The work described here demonstrates the potential for exploitation, in both inter- and intra-molecular reactions, of the three distinct nucleophilic centres (*viz*. *N*-1, *C*-2 and *C*-3) associated with pyrrole (**3**) in the construction of polyheterocyclic frameworks. Appropriate combinations of such processes when used in conjunction with differing tethers for connection of the reacting centres should allow for the rapid assembly of a diverse array of multiply-fused pyrroles and pyrrolidines. In addition, the development of enantioselective variants of conversions such as **10** ⟶ **11** would serve to further enhance the value of the strategies described here. Recent work by McMillan[18] on enantioselective and intermolecular Friedel–Crafts alkylations of pyrroles suggests that such variants are possible and these are being pursued in our laboratories at present. Results will be reported in due course.

Experimental

General

Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 or Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75.4 MHz for carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterochloroform ($CDCl_3$) at 20 °C unless otherwise stated. For ^1H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference. ^1H NMR data are recorded as follows: chemical shift (δ) [relative integral, multiplicity, coupling constant(s) *J* (Hz), assignment (where possible)] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet or

combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ triplet was used as the reference for proton-decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra the data are given as: chemical shift (δ) (protonicity), where protonicity is defined as: C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl; C or CH_2 = quaternary or methylene; CH or CH_3 = methine or methyl. The assignments of signals observed in various NMR spectra were often assisted by conducting attached proton test (APT), homonuclear ($^1H/^1H$) correlation spectroscopy (COSY), nuclear Overhauser effect (NOE), and/or heteronuclear ($^1H/^{13}C$) correlation spectroscopy (HETCOR) experiments.

Infrared spectra (ν_{max}) were recorded on either a Perkin–Elmer 1800 Fourier Transform Infrared Spectrophotometer or a Perkin–Elmer Spectrum *One* instrument as thin films on KBr plates.

Analytical thin layer chromatography (TLC) was conducted on glass-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the chromatograms were visualised under a 254 nm UV lamp and/or by treatment with an alkaline potassium permanganate dip (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% aqueous NaOH, 300 mL water) or a phosphomolybdic acid–ceric sulfate–sulfuric acid–water dip (37.5 g:7.5 g:37.5 mL:720 mL) followed by heating. The retention factor (R_f) quoted is rounded to the nearest 0.1. Flash chromatography was conducted according to the method of Still and co-workers [19] using silica gel 60 (mesh size 0.040–0.063 mm) as the stationary phase and the analytical reagent (AR) grade solvents indicated.

Many starting materials and reagents were available from the Aldrich Chemical Company or EGA-Chemie and were used as supplied or simply distilled. Drying agents and other inorganic salts were purchased from AJAX or BDH Chemicals. Reactions employing air- and/or moisture-sensitive reagents and intermediates were carried out under an atmosphere of dry, oxygen-free nitrogen.

Tetrahydrofuran and diethyl ether were dried using sodium metal and then distilled, as required, from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride.

Organic solutions obtained from work-up of reaction mixtures were dried with magnesium sulfate ($MgSO_4$). Organic solutions were concentrated under reduced pressure on a rotary evaporator with the water bath generally not exceeding 40 °C.

N-Methoxy-*N*-methyl-4-(1*H*-pyrrol-1-yl)butanamide (8)

Triethylamine (7.08 g, 70 mmol) was added slowly to a magnetically stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (6.825 g, 70 mmol) in CH_2Cl_2 (150 mL) maintained at 0 °C under a nitrogen atmosphere. The cooling bath was then removed and after 15 min acid **7**[9] (10.0 g, 65.3 mmol) and pyridine *N*-oxide disulfide (24.57 g, 97.5 mmol) were added. The reaction mixture was re-cooled to 0 °C then, whilst protected from light, tributylphosphine (19.73 g, 97.5 mmol) was added slowly. The ensuing mixture was allowed to warm to 18 °C, stirred at this temperature for 16 h then concentrated under reduced pressure. The residue was diluted with ethyl acetate (200 mL), washed with potassium hydrogensulfate (2 × 50 mL of a 0.3 M aqueous solution), sodium bicarbonate (2 × 50 mL of a 2 M aqueous solution) then dried, filtered and concentrated under reduced pressure to give a light-yellow oil. This material was passed down a short column of silica gel (3:7 v/v ethyl acetate–hexane elution) to give, after concentration of the filtrate, compound **8**[4,10] (11.1 g, 87%) as a clear, colourless oil (Found: $M^{+\bullet}$, 196.1211. $C_{10}H_{16}N_2O_2$ requires $M^{+\bullet}$, 196.1212); ν_{max} (KBr, neat) 1660 cm^{-1}; δ_H 2.09 (2H, quin, *J* 7), 2.36 (2H, t, *J* 7), 3.16 (3H, s), 3.60 (3H, s), 3.96 (2H, t, *J* 7), 6.13 (2H, t, *J* 2.1), 6.65 (2H, t, *J* 2.1); δ_C 26.1, 28.3, 31.9, 48.5, 61.0, 107.9, 120.5, 173.4; *m*/*z* 196 (M^+, 70%), 165 (30), 136 (100), 118 (30), 106 (35), 80 (60).

6-(1*H*-Pyrrol-1-yl)hexan-3-one (9)

Ethyl magnesium bromide (13.33 mL of a 3 M solution in diethyl ether, 40 mmol) was slowly added to a magnetically stirred solution of amide **8** (5.00 g, 24 mmol) in diethyl ether (150 mL) maintained at 0 °C under a nitrogen atmosphere. The cooling bath was then removed and the reaction mixture stirred at 18 °C for 2 h before being cooled to −40 °C and treated, dropwise, with potassium hydrogensulfate (10 mL of a 0.3 M aqueous solution). After 5 min sodium bicarbonate (10 mL of a 2 M aqueous solution) was slowly added and the resulting mixture warmed to 18 °C then diluted with brine (50 mL). The separated aqueous phase was extracted with ether (2 × 25 mL) and the combined organic phases then dried, filtered and concentrated under reduced pressure to give the title ketone **9**[4] (3.96 g, 100%) as a clear colourless oil. ν_{max} (KBr, neat) 1713 cm^{-1}; δ_H (CD_3COCD_3) 1.07 (3H, t, *J* 7), 2.07 (2H, quin, *J* 7), 2.50, (4H, m), 4.02, (2H, t, *J* 7), 6.14 (2H, m), 6.62 (2H, m); *m*/*z* 165 (M^+, 100%), 148 (15), 136 (30), 108 (35), 99 (45), 81 (55). This unstable material was used immediately in the next step of the reaction sequence as described in the following paragraph.

Methyl 3-ethyl-6-(1*H*-pyrrol-1-yl)hex-2-enoate (10)

Methyl diethylphosphonoacetate (4.10 g, 22.5 mmol) was added dropwise to a magnetically stirred suspension of NaH (612 mg, 25.5 mmol) in THF (30 mL) maintained at 0 °C under a nitrogen atmosphere. The cooling bath was then removed and the ensuing mixture stirred for 15 min at 18 °C then treated, dropwise, with a solution of ketone **9** (2.10 g, 12.75 mmol) in THF (5 mL). The reaction mixture was stirred at 18 °C for 48 h then diluted with brine (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 1:9 v/v ethyl acetate–hexane elution) gave, after concentration of the appropriate fractions, the title compound **10**[4] (2.17 g, 77%) as a clear colourless oil and which was comprised of a *ca*. 1:1 mixture of *E*/*Z* isomers as judged by ^1H NMR analysis. This material was used directly in the next step of the reaction sequence.

For the purposes of characterization, a small sample of compound **10** was subject flash chromatography (silica gel, 5:95 v/v ethyl acetate–hexane elution) and in this way two fractions, A and B, were obtained.

Concentration of fraction A (R_f 0.3 in 1:9 v/v ethyl acetate–hexane) afforded (*E*)-**10** as a clear colourless oil (Found: $M^{+\bullet}$, 221.1414. $C_{13}H_{19}NO_2$ requires $M^{+\bullet}$, 221.1416); ν_{max} (KBr, neat) 3100, 2968, 1714, 1644, 1164, 723 cm^{-1}; δ_H 1.07 (3H, t, *J* 7), 1.93 (2H, m), 2.16 (2H, dq, *J* 7 and 1.4), 2.61 (2H, m), 3.69 (3H, s), 3.94 (2H, t, *J* 7), 5.68 (1H, s), 6.15 (2H, t, *J* 2), 6.68 (2H, t, *J* 2); δ_C 12.0, 29.7, 30.5, 31.1, 49.6, 50.9, 107.9, 114.5, 120.4, 164.7, 166.9; *m*/*z* 221 (M^+, 35%), 206 (27), 190 (45), 162 (80), 160 (42), 148 (45), 94 (43), 81 (100).

Concentration of fraction B (R_f 0.25 in 1:9 v/v ethyl acetate–hexane) afforded (*Z*)-**10** as a clear colourless oil (Found $M^{+\bullet}$, 221.1415. $C_{13}H_{19}NO_2$ requires $M^{+\bullet}$, 221.1416); ν_{max} (KBr, neat) 3100, 2948, 1716, 1644, 1149, 724 cm^{-1}; δ_H 1.06 (3H, t, *J* 7.5), 1.95 (2H, m), 2.14 (2H, m), 2.62 (2H, q, *J* 7.5), 3.69 (3H, s), 3.90 (2H, t, *J* 6.9), 5.62 (1H, s), 6.06 (2H, t, *J* 2.1), 6.65 (2H, t, *J* 2.1); δ_C 13.0, 25.2, 29.2, 34.7, 48.8, 50.9, 108.1, 114.9, 120.4, 164.5, 166.6; *m*/*z* 221 (M^+, 30%), 206 (5), 192 (25), 162 (65), 148 (50), 94(38), 81 (100).

Methyl 8-ethyl-5,6,7,8-tetrahydroindolizine-8-acetate (11)

Anhydrous aluminium chloride (815 mg, 6.1 mmol) was added, in small portions, to a magnetically stirred solution of the α,β-unsaturated ester **10** (270 mg, 1.22 mmol) in diethyl ether (20 mL) maintained at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred at 18 °C for 5 h then re-cooled to

0 °C and slowly treated (CAUTION) with water (10 mL) followed by sulfuric acid (20 mL of a 0.5 M aqueous solution). The separated aqueous phase was extracted with diethyl ether (1 × 20 mL) and the combined organic phases then dried, filtered and concentrated under reduced pressure to give compound **11**[4] (223 mg, 83%) as a clear colourless oil (Found: $M^{+\bullet}$, 221.1414. $C_{13}H_{19}NO_2$ requires $M^{+\bullet}$, 221.1416); ν_{max} (KBr, neat) 2942, 1732, 706 cm^{-1}; δ_H (CD_3COCD_3) 0.94 (3H, t, *J* 7.5), 1.81–1.96 (3H, complex m), 2.04–2.15 (3H, complex m), 2.67 (2H, m), 3.66, (3H, s), 3.99 (2H, m), 5.90 (1H, dd, *J* 3.7 and 1.7), 6.06 (1H, m), 6.57 (1H, m); δ_C (CD_3COCD_3) 8.6, 20.2, 30.5, 33.0, 37.6, 44.6, 45.1, 50.6, 103.9, 107.2, 118.7, 134.1, 171.5; *m*/*z* 221 (M^+, 43%), 206 (6), 192 (70), 160 (8), 148 (100), 132 (82), 118 (17).

2-(8-Ethyl-5,6,7,8-tetrahydroindolizin-8-yl)ethanol (12)

DIBAL-H (1.95 mL of a 1 M solution in hexane, 1.95 mmol) was added, dropwise, to a magnetically stirred solution of ester **11** (180 mg, 0.84 mmol) in CH_2Cl_2 (10 mL) and maintained at −78 °C under a nitrogen atmosphere. The resulting solution was stirred at −78 °C for a further 30 min, warmed to 0 °C, stirred at this temperature for 1 h then quenched with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried, filtered and concentrated under reduced pressure to give a light-yellow oil. This material was subject to flash chromatography (silica gel, 2:3 v/v ethyl acetate–hexane elution) and concentration of the appropriate fractions afforded the alcohol **12** (122 mg, 75%) as a clear, colourless oil (Found: $M^{+\bullet}$, 193.1468. $C_{12}H_{19}NO$ requires $M^{+\bullet}$, 193.1467); ν_{max} (KBr, neat) 3367, 2936, 1462, 1325, 1028, 707 cm^{-1}; δ_H (CD_3OD) 0.82 (3H, t, *J* 7.5), 1.60 (2H, m), 1.71 (2H, m), 1.81 (2H, m), 1.94 (2H, m), 3.53 (2H, m), 3.84 (2H, dt, *J* 6.0 and 1.8), 5.78 (1H, dd, *J* 3.6 and 1.8), 5.99 (1H, dd, *J* 3.6 and 2.7), 6.45 (1H, dd, *J* 2.7 and 1.8); δ_C 8.6, 20.1, 31.0, 33.8, 36.7, 42.4, 45.3, 59.7, 103.5, 107.3, 118.8, 135.4; *m*/*z* 193 (M^+, 50%), 164 (100), 148 (90), 134 (40), 118 (25).

2-(8-Ethyl-5,6,7,8-tetrahydroindolizin-8-yl)ethyl methanesulfonate (13)

Methanesulfonyl chloride (687 mg, 6 mmol) was added, dropwise, to a magnetically stirred solution of alcohol **12** (1.124 g, 5.79 mmol) and triethylamine (607 mg, 6 mmol) in CH_2Cl_2 (50 mL) maintained at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 5 min at 0 °C, for 45 min at 18 °C then washed with Na_2CO_3 (2 × 50 mL of a 2 M aqueous solution) and HCl (2 × 50 mL of 2 M aqueous solution) before being dried, filtered and concentrated under reduced pressure to give the mesylate **13** (1.491 g, 95%) as a light-yellow oil (Found: $M^{+\bullet}$, 271.1241. $C_{13}H_{21}NO_3S$ requires $M^{+\bullet}$, 271.1242); ν_{max} (KBr, neat) 2938, 1696, 1353, 1173, 950 cm^{-1}; δ_H 0.86 (3H, t, *J* 7.3), 1.58–1.76 (4H, complex m), 1.94–2.07 (4H, complex m), 2.93 (3H, s), 3.88 (2H, t, *J* 6.0), 4.23 (2H, m), 5.86 (1H, dd, *J* 3.6 and 1.8), 6.10 (1H, dd, *J* 3.6 and 2.7), 6.49 (1H, dd, *J* 2.7 and 1.8); δ_C 8.6, 20.1, 31.1, 33.8, 36.9, 37.3, 38.5, 45.2, 68.0, 104.2, 107.4, 118.9, 133.7; *m*/*z* 271 (M^+, 40%), 242 (50), 148 (90), 146 (100), 133 (30), 118 (25).

3-(8-Ethyl-5,6,7,8-tetrahydroindolizin-8-yl)propionitrile (14)

Sodium cyanide (1.225 g, 25 mmol) was added to a magnetically stirred solution of the mesylate **13** (1.40 g, 5.16 mmol) in DMPU (10 mL) maintained at 18 °C under a nitrogen atmosphere. The ensuing mixture was stirred at this temperature for 48 h then diluted with water (50 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were then dried, filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 1:4 v/v ethyl acetate–hexane elution) gave, after concentration of the appropriate fractions, nitrile **14** (949 mg, 91%) as a clear colourless oil (Found: $M^{+\bullet}$, 202.1467. $C_{13}H_{18}N_2$ requires $M^{+\bullet}$, 202.1470); ν_{max} (KBr, neat) 2934, 2244, 1459, 714 cm^{-1}; δ_H 0.86 (3H, t, *J* 7.3), 1.58–1.78 (4H, complex m), 1.91–2.04 (4H, complex m), 2.26 (2H, m), 3.89 (2H, t, *J* 6.0), 5.83 (1H, dd, *J* 3.6 and 1.8), 6.12 (1H, dd, *J* 3.6 and 2.7), 6.52 (1H, dd, *J* 2.7 and 1.8); δ_C 8.4, 12.8, 19.9, 30.4, 33.0, 35.2, 37.6, 45.1, 104.2, 107.4, 119.2, 120.4, 133.0; *m*/*z* 202 (M^+, 40%), 173 (100), 148 (70), 133 (45), 118 (20).

3-(8-Ethyl-5,6,7,8-tetrahydroindolizin-8-yl)propionic acid (15)

A magnetically stirred solution nitrile **14** (274 mg, 1.35 mmol) and KOH (2.00 g, 35.6 mmol) in aqueous methanol (7 mL of a 4:3 v/v mixture) was heated at reflux for 16 h. The cooled mixture was then acidified with HCl (conc. aqueous solution) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were then dried, filtered and concentrated under reduced pressure to give the acid **15** (262 mg, 88%) as a light-yellow oil (Found: $M^{+\bullet}$, 221.1417. $C_{13}H_{19}NO_2$ requires $M^{+\bullet}$, 221.1416); ν_{max} (neat) 2942, 1705 cm^{-1}; δ_H 0.86 (3H, t, *J* 7.3), 1.67 (4H, m), 1.91 (2H, m), 1.99 (2H, m), 2.33 (2H, m), 3.89 (2H, t, *J* 6.0), 5.87 (1H, dd, *J* 3.6 and 1.8), 6.12 (1H, dd, *J* 3.6 and 2.7), 6.50 (1H, dd, *J* 2.7 and 1.8), 11.0 (1H, br s); δ_C 8.5, 20.0, 29.8, 30.7, 33.2, 34.2, 37.3, 45.3, 104.2, 107.2, 118.7, 134.5, 180.7; *m*/*z* 221 (M^+, 50%), 192 (90), 174 (15), 148 (100), 133 (35), 118 (25).

6a-Ethyl-4,5,6,6a,7,8-hexahydro-9*H*-pyrrolo[3,2,1-*i*,*j*]quinolin-9-one (16)

A magnetically stirred solution of the acid **15** (189 mg, 0.81 mmol) in HCl (5 mL of a 5 M aqueous solution) was maintained at 18 °C for 1 h then made alkaline by the addition of Na_2CO_3 (saturated aqueous solution) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material flash chromatography (silica gel, ether elution) and concentration of the appropriate fractions afforded ketone **16** (118 mg, 72%) as a clear, colourless oil (Found: $M^{+\bullet}$, 203.1308. $C_{13}H_{17}NO$ requires $M^{+\bullet}$, 203.1310); ν_{max} (KBr, neat) 2942, 1652, 1513, 1466, 1314, 1188 cm^{-1}; δ_H 0.90 (3H, t, *J* 7.2), 1.31 (1H, td, *J* 13.5 and 3.3) 1.71 (3H, m), 1.99–2.01 (1H, complex m), 2.05 (1H, dt, *J* 13.5 and 3.3), 2.11–2.28 (2H, complex m), 2.38 (1H, ddd, *J* 18.0, 4.8 and 2.1), 2.65 (1H, ddd, *J* 18.0, 13.5 and 4.8), 3.77 (1H, td, *J* 11.7 and 6.3), 4.03 (1H, ddd, *J* 12.6, 6.9 and 1.5) 6.50 (2H, apparent q, *J* 2.7); δ_C 8.7, 18.5, 26.8, 28.3, 33.8, 35.0, 43.9, 106.3, 116.9, 121.8, 151.1, 193.8 (one signal due to pyrrolic carbon obscured or overlapping); *m*/*z* 203 (M^+, 40%), 174 (100), 160 (10), 146 (25).

(6a*α*,9a*α*,9b*α*)-6a-Ethyldecahydro-4*H*-pyrrolo[3,2,1-*i*,*j*]quinoline (18) and (6a*α*,9a*β*,9b*β*)-6a-ethyldecahydro-4*H*-pyrrolo[3,2,1-*i*,*j*]-quinolin-9-one (19)

A magnetically stirred solution of ketone **16** (35 mg, 0.172 mmol) in acetic acid (7 mL) and containing PtO_2 (10 mg) was maintained at 18 °C under an atmosphere of hydrogen (balloon) for 18 h. The resulting mixture was filtered through a plug of Celite™ and the filtrate concentrated under reduced pressure. A magnetically stirred solution of the resulting oil (containing alcohol **17** and the corresponding deoxy-analogue **18**) in CH_2Cl_2 (5 mL) was cooled to 0 °C then treated with the Dess–Martin periodinane[15] (220 mg, 0.516 mmol). Stirring was continued at 0 °C for 30 min and at 18 °C for 30 min then the reaction mixture was treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and $Na_2S_2O_3$ (5 mL of a 20% w/v aqueous solution). The ensuing mixture was stirred rapidly at 18 °C for 15 min then the separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (sodium sulfate), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 200:180:19:1 v/v/v/v CH_2Cl_2–$CHCl_3$–MeOH–NH_3 elution) afforded two fractions A and B.

Concentration of fraction A afforded amine **18** (7 mg, 22%) as a clear, colourless oil. ν_{max} (KBr, neat) 1619, 1425 cm^{-1}; δ_H (600 MHz, CD_3OD) 0.84 (3H, t, *J* 7.5), 1.11–1.38 (6H, complex m), 1.45–1.62 (6H, complex m), 1.66–1.92 (4H, complex m), 2.02 (1H, m), 2.08 (1H, m), 3.03 (1H, m), 3.10 (1H, td, *J* 9.0 and 3.3); δ_C (150 MHz, CD_3OD) 7.2, 22.0, 22.8, 26.7, 29.3, 31.0, 31.9, 35.3, 35.4, 35.8, 54.4, 54.5, 73.1; *m*/*z* 193 (M^+, 30%), 192 (100), 178 (5), 164 (35).

Concentration of fraction B afforded ketone **19**[8o] (8 mg, 28%) as a clear, colourless oil [Found: $(M - H^{\bullet})^+$, 206.1547, $C_{13}H_{21}NO$ requires $(M - H^{\bullet})^+$, 206.1545]; ν_{max} (KBr, neat) 2932, 1708 cm^{-1}; δ_H (600 MHz) 0.93 (3H, t, *J* 7.5), 1.10 (1H, m), 1.31 (2H, m), 1.46–1.52 (2H, complex m), 1.59–1.97 (7H, complex m), 2.18–2.48 (3H, complex m), 2.66 (1H, ddd, *J* 9.0, 5.4 and 2.1), 3.00 (2H, m); δ_C (150 MHz) 7.1, 21.3, 26.0, 29.7, 30.1, 32.8, 34.7, 36.8, 48.1, 52.9, 53.2, 73.5, 211.7; *m*/*z* 207 (M^+, 50%), 206 (100), 178 (50), 150 (15), 124 (25), 95 (20), 82 (35).

(±)-6a-Ethyl-1,2,4,5,6,6a,7,8-octahydro-9*H*-pyrrolo[3,2,1-*i*,*j*]-quinolin-9-one (21)

A magnetically stirred solution of ketone **16** (25 mg, 0.123 mmol) in acetic acid–ethanol (20 mL of a 2:98 v/v mixture) containing 5% Rh/Al_2O_3 (~10 mg) was maintained at 18 °C under an atmosphere of hydrogen (balloon) for 18 h. The resulting mixture was filtered through a plug of Celite™ and the filtrate concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, successive elution with 3:2 v/v ethyl acetate–hexane then 180:19:1 v/v/v $CHCl_3$–MeOH–NH_3) afforded two fractions, A and B.

Concentration of fraction A afforded the starting ketone **16** (12 mg, 50% recovery) which was identical, in all respects, with an authentic sample.

Concentration of fraction B afforded compound **21** (10 mg, 80% at 50% conversion) as a clear colourless oil (Found: $M^{+\bullet}$, 205.1465. $C_{13}H_{19}NO$ requires $M^{+\bullet}$, 205.1467); ν_{max} (neat) 2934, 1562, 1515 cm^{-1}; δ_H 0.87 (3H, t, *J* 7.5), 1.12 (1H, td, *J* 13.5 and 3.3), 1.46–2.00 (7H, complex m), 2.25 (1H, ddd, *J* 17.4, 5.4 and 2.1), 2.43 (1H, ddd, *J* 17.4, 13.5 and 4.8), 2.60 (1H, m), 2.78 (2H, m), 3.17 (1H, q, *J* 10.5), 3.28 (1H, dd, *J* 11.4 and 5.4), 3.58 (1H, ddd, *J* 11.4, 10.5 and 4.0); δ_C 7.8, 18.6, 23.9, 25.2, 28.5, 32.4, 33.2, 35.0, 46.9, 54.0, 107.4, 175.8, 190.0; *m*/*z* 205 (M^+, 45%), 177 (90), 162 (100), 148 (17), 135 (16).

(6a*α*,9a*α*,9b*α*)-6a-Ethyldecahydro-4*H*-pyrrolo[3,2,1-*i*,*j*]quinolin-9-one (22)

A solution of the dihydropyrrole **21** (18 mg, 0.09 mmol) in THF (0.5 mL) was slowly added to a magnetically stirred suspension of $LiAlH_4$ (excess) in THF (5 mL) maintained at 18 °C under an nitrogen atmosphere. The resulting mixture was heated at reflux for 1.5 h then cooled, treated with ethyl acetate (2 mL) then water (5 mL) and finally extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (sodium sulfate), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 180 : 19 : 1 v/v/v $CHCl_3$–MeOH–NH_3 elution) afforded, after concentration of the appropriate fractions, ketone **22**[16] (12 mg, 65%) as a clear, colourless oil [Found: $(M - H^{\bullet})^+$, 206.1547, $C_{13}H_{21}NO$ requires $(M - H^{\bullet})^+$, 206.1545]; ν_{max} (KBr, neat) 2933, 1717 cm^{-1}; δ_H 0.73 (1H, m), 0.89 (3H, t, *J* 7.5), 1.12 (1H, tdd, *J* 13.2, 5.1 and 1.5), 1.44–1.84 (7H, complex m), 1.89–2.04 (4H, complex m), 2.21–2.42 (2H, complex m), 2.73 (1H, m), 3.13 (2H, m); δ_C 7.8, 17.6, 19.8, 21.9, 32.9, 34.7, 35.7, 39.0, 48.6, 53.6, 54.2, 76.8, 209.4; *m*/*z* 207 (M^+, 30%), 206 (100), 177 (10).

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