ARTICLE

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Total synthesis of (±)-rhazinal, an alkaloidal spindle toxin from *Kopsia teoi*

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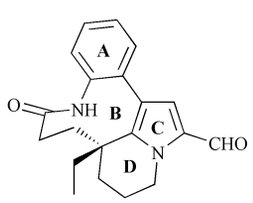
The title alkaloid **1** and its B-nor-congener **3**, both of which display potent and unusual anti-mitotic properties, have been synthesized in racemic form and characterised by single-crystal X-ray analysis.

Introduction

In 1998 Kam and co-workers reported on the isolation of the alkaloid (−)-rhazinal (**1**) from the stem extracts of a Malayan *Kopsia* species.[1] The compound had also been prepared by Vilsmeier–Haack formylation[2] of the closely related alkaloid (−)-rhazinilam (**2**), first isolated in 1965 from *Melodinus australia*,[3] then again in 1970 from *Rhazya stricta* (Apocynaceae)[4] and most recently (1987) from the Malaysian plant *Kopsia singapurensis* (Ridlay).[5] Compound **2**, at least, is an artefact of the isolation process, and the natural precursor is 5,21-dihydrorhazinilam.[6] Rhazinilam, which can be prepared from the natural product vincadifformine,[7,8] has been the subject of three successful total syntheses, the first by Smith[7,8] in 1973 then by Sames (2000)[9] and Magnus (2001).[10] In contrast, rhazinal has not, hitherto, been prepared by total synthesis.



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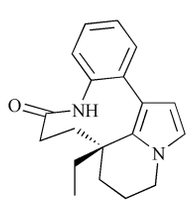

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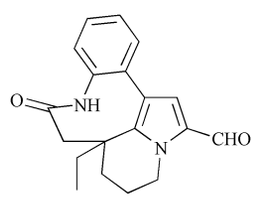
The above-mentioned conversion **2** ⟶ **1** was undertaken as part of an extensive analoguing program carried out around rhazinilam after it was reported that this alkaloid mimics the effects of both vinblastine and Taxol™ by inducing a non-reversible assembly (spiralisation) of tubulin (a vinblastine-type effect) AND by inhibiting the cold-induced disassembly of microtubules (a Taxol™-like property).[2,5,11] In an even more striking similarity to Taxol™, rhazinilam has the ability to induce formation of asters in mitotic cells and microtubule bundles in interphase cells.[11] Such observations account for the renewed interest in compound **2**[12] and prompted the two recently reported total syntheses[9,10] as well as the production of numerous series of structurally simpler analogues.[2,13–17]

As part of a continuing program[18] in this laboratory directed towards the synthesis of pyrrole-containing natural products, we now report the first total synthesis of rhazinal (**1**) and also provide full details of a previously communicated[19] and related synthesis of its lower homologue (±)-B-norrhazinal (**3**). A key feature associated with these syntheses is the use of an intramolecular Michael addition of the C2 of pyrrole to an N1-tethered acrylate thereby allowing for construction of the D-ring of targets **1** and **3**. To the best of our knowledge the present work provides the first examples of such a process,[20] which we believe holds considerable potential for the construction of a wide-range of other annulated pyrroles.



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Results and discussion

(a) Preliminary synthetic approaches involving cyclopropane chemistry

In broad terms, our approach to rhazinal was to involve a late stage lactamisation reaction so as to establish the B-ring and with the early chemistry focused on exploiting regioselective electrophilic substitution reactions that can be carried out on pyrrole.[21] The initial version of this strategy (Fig. 1) was aimed at engaging *gem*-dibromocyclopropane **4** in an electrocyclic ring-opening reaction in the expectation that the resulting π-allyl cation would be captured by C2 of the tethered pyrrole so as to form bromoalkene **5**.[22] Reaction of this latter compound with an excess of strong base should effect dehydrobromination then deprotonation to give the corresponding alkynyl anion which could be captured with methyl chloroformate to deliver propiolate **6**. Hydrogenation of this last compound should then provide the requisite substrate for the foreshadowed lactamisation process which would deliver target (±)-**1**.

The preliminary steps associated with attempts to implement such an approach are shown in Scheme 1. Thus, the synthesis of the potential cyclisation substrate, compound **4** (X = NO_2, Y = CO_2Me), started with Michael addition of the anion derived from nitropropane (**7**) to methyl acrylate (**8**) thus forming conjugate **9**[23] (65%). Subjection of the last compound to a Nef reaction using Oxone[24] then afforded the corresponding ketone **10**[25] (95%). Wittig methylenation of compound **10** afforded the alkene **11**[26] (30%) which was immediately reduced to the corresponding alcohol **12**[27] (57%) using $LiAlH_4$. The

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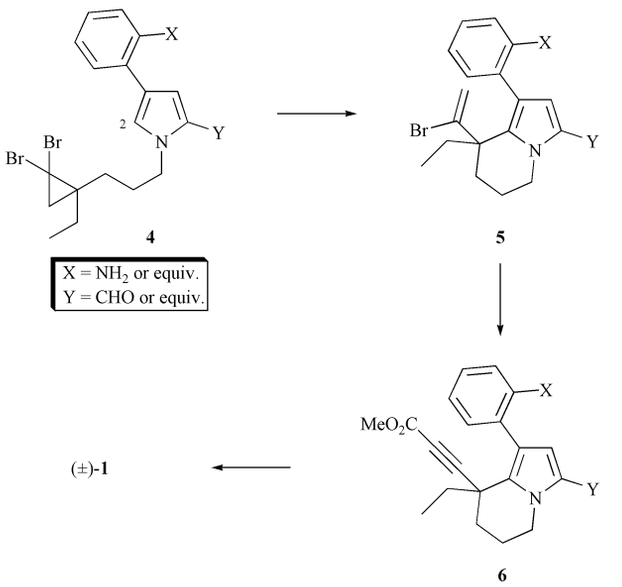
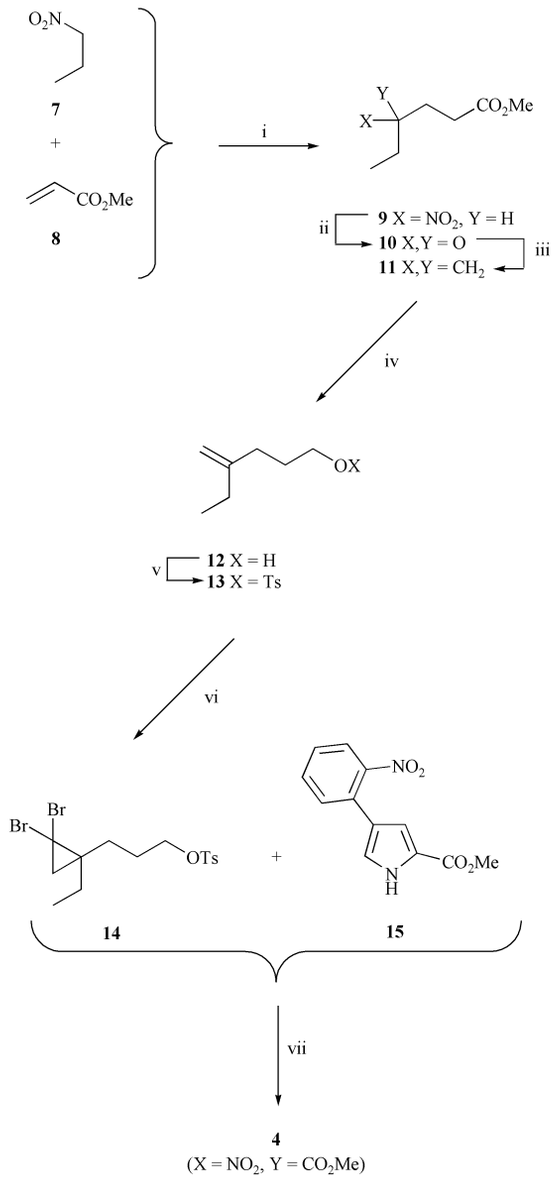


Fig. 1

readily derived tosylate **13** (76%) was then subjected to dibromocarbene addition under phase transfer conditions and in this manner the *gem*-dibromocyclopropane **14** was obtained in 70% yield. Reaction of this last compound under solvent free conditions with the sodium salt of 2-nitrophenylated pyrrole **15**,[7] readily derived *via* a Pd[0]-catalysed Ullmann cross-coupling[28] of *o*-nitrobromobenzene with methyl 4-iodo-1*H*-pyrrole-2-carboxylate,[29] then afforded the target substrate **4** (X = NO_2, Y = CO_2Me) (quantitative) required for examination of the pivotal cyclisation step. In the event, all attempts, including those involving the use of silver salts and/or the application of heat, failed to effect electrocyclic ring-opening of cyclopropane **4** (X = NO_2, Y = CO_2Me) and consequent formation of target **5**. Either starting material was recovered or, under more forcing conditions, its complete decomposition was observed. The reluctance of this substrate to engage in the desired ring-opening/nucleophilic trapping sequence is attributed to the low degree of substitution and consequent smaller than usual degree of strain associated with the *gem*-dibromocyclopropyl moiety within compound **4** (X = NO_2, Y = CO_2Me).

In an attempt to persist with the sort of approach described above, "Danishefsky-type" electrophilic cyclopropanes[30] tethered to pyrroles were sought. It was hoped that these would engage in intramolecular and homo-Michael type addition reactions to give, in a direct fashion, analogues of compound **6** wherein the C–C triple bond had been replaced by an ethylene unit. To such ends (Scheme 2) the readily prepared *O*-benzyl derivative, **16** (70%), of alcohol **12** was subjected to reaction with ethyl diazoacetate in the presence of rhodium diacetate dimer[31] and the resulting 2 : 1 mixture of epimeric cyclopropane carboxylic acid esters, **17**, debenzylated under the usual conditions to give the corresponding mixture of alcohols **18** (42% from **16**). The readily derived mixture of tosylates **19** (84%) was then reacted with the potassium salt of pyrrole to give the target compound **20** (89%), again as a 2 : 1 mixture of epimers. Unfortunately all attempts to effect the desired nucleophilic ring-opening of this cyclopropyl-containing system failed. On the basis that this disappointing outcome might be due to inadequate activation of the cyclopropyl group within compound **20**, the related and now "doubly-activated" system **24** (Scheme 2) was sought. To these ends alkene **16** was reacted with dimethyl diazomalonate in the presence of rhodium diacetate dimer and the cyclopropane **21** thereby obtained. Hydrogenolytic debenzylation of ether **21**, followed by tosylation of the resulting alcohol, **22** (45% from **20**), then afforded the tosylate **23** (67%), but this last compound failed to react with either pyrrole or its potassium salt and thereby

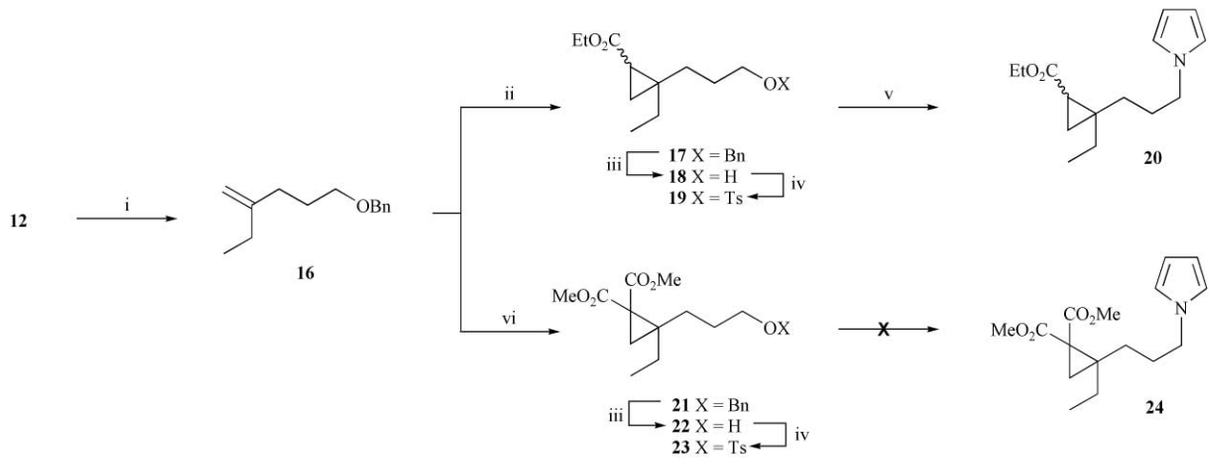


Scheme 1 *Reagents and conditions*: (i) 0.1 M aqueous NaOH, 18 °C, 22 h; (ii) Oxone™ (2.7 mole equiv.), K_2CO_3, $NaHCO_3$, aqueous acetone, 18 °C, 29 h; (iii) $Ph_3P{=}CH_2$ (1.1 mole equiv.), THF, 18 °C, 15 h; (iv) $LiAlH_4$ (2.2 mole equiv.), Et_2O, 37 °C, 0.5 h; (v) *p*-TsCl (1.1 mole equiv.), Et_3N (1.3 mole equiv.), DMAP (cat.), CH_2Cl_2, 4 °C, 48 h; (vi) $CHBr_3$ (1.1 mole equiv.), 50% w/v aqueous NaOH, benzyltriethylammonium chloride (cat.), C_6H_6, 0–18 °C, 16 h; (vii) NaHMDS (1 mole equiv.), THF, 65 °C, 16 h.

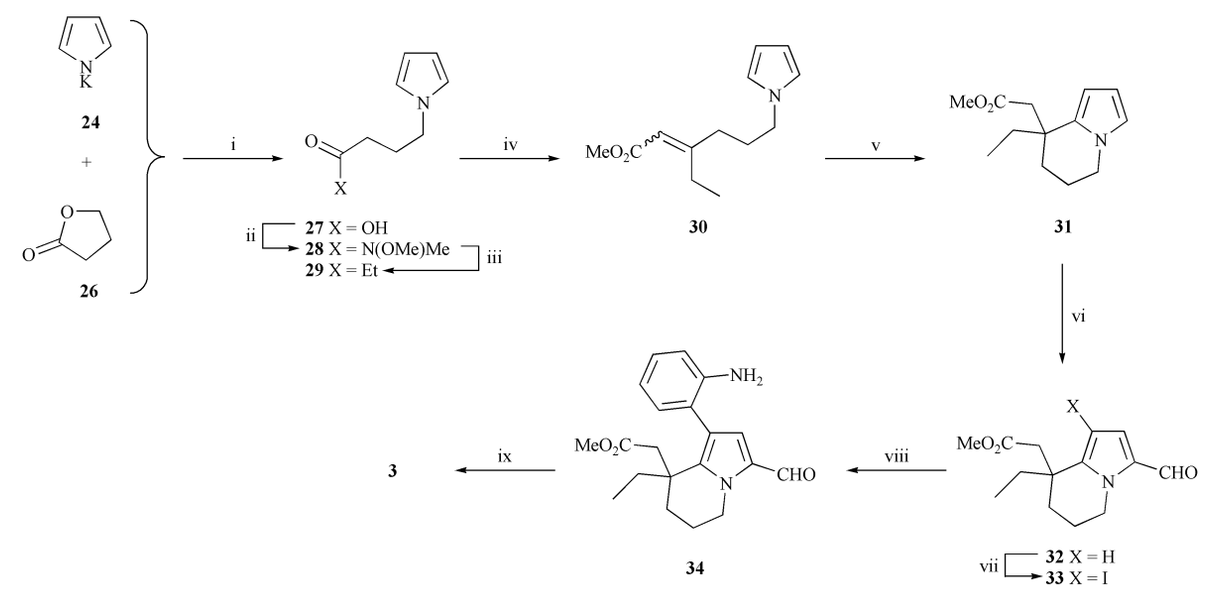
generate the pivotal substrate **24**. As a consequence, this line of investigation came to an end, and alternate means for annulating the rhazinal D-ring to a pyrrole scaffold were sought.

(b) Synthetic approaches involving intramolecular Michael addition chemistry

The intermolecular Michael addition of pyrrole through C2 to acrylates and related electrophiles represents a very effective process,[20] and the intramolecular variant, involving an N1-tethered acrylate, should provide a means for constructing the CD-ring substructure associated with target **1**. Whilst such intramolecular processes appear to be unknown, we were encouraged to attempt implementation of this type of chemistry by virtue of our earlier observation[32] that intramolecular Michael addition of N1 of pyrrole to a C2-tethered acrylate is a facile and efficient process. As a consequence the relevant substrate, **30** (Scheme 3), was targeted and proved remarkably easy to prepare. Thus, reaction of the potassium salt (**24**) of



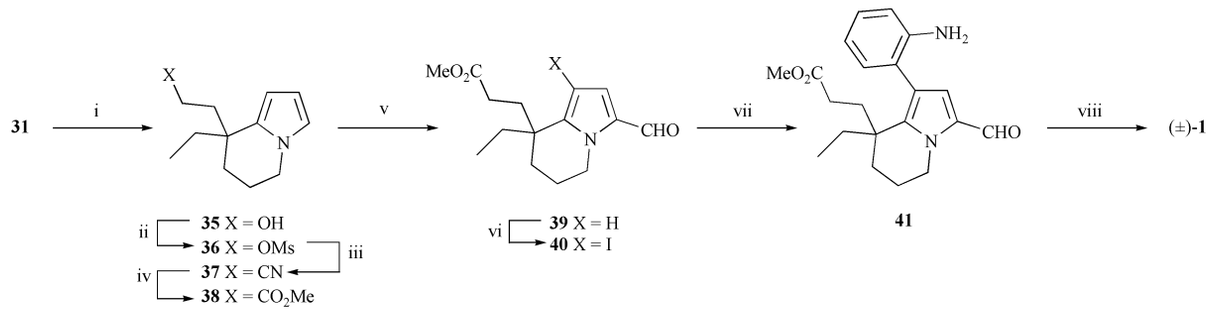
Scheme 2 *Reagents and conditions*: (i) NaH (2 mole equiv.), BnBr (1.1 mole equiv.), NaI (cat.), DMF, 18 °C, 18 h; (ii) N_2CHCO_2Et (3 mole equiv.), $Rh_2(OAc)_4$ (0.6 mole %), CH_2Cl_2, 18 °C, 0.5 h; (iii) H_2 (1 atm.), 5 % Pd on C (cat.), EtOAc–CH_2Cl_2–EtOH, 18 °C, 22 h; (iv) *p*-TsCl (1.1 mole equiv.), Et_3N, DMAP (cat.), CH_2Cl_2, 4 °C, 48 h; (v) pyrrole (2.0 mole equiv.), KH (2.0 mole equiv.), DMF, 18 °C, 1.5 h; (vi) $N_2C(CO_2Me)_2$ (3.0 mole equiv.), $Rh_2(OAc)_4$ (0.6 mole %), CH_2Cl_2, 18 °C, 0.5 h.



Scheme 3 *Reagents and conditions*: (i) 160 °C, 2 h; (ii) MeNHOMe·HCl (1.2 mole equiv.), Et_3N (1.2 mole equiv.), (2-pyridine *N*-oxide)disulfide (1.5 mole equiv.), Bu_3P (1.5 mole equiv.), 18 °C, 16 h; (iii) (a) EtMgBr (3 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.), 18 °C, 48 h; (v) $AlCl_3$ (5 mole equiv.), Et_2O, 18 °C, 5 h; (vi) $POCl_3$ (1.1 mole equiv.), 1 : 33 v/v DMF–Et_2O, 18 °C, 3 h; (vii) I_2 (1.2 mole equiv.), $AgOCOCF_3$ (1.2 mole equiv.), $CHCl_3$, 18 °C, 4 h; (viii) 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine (1.5 mole equiv.), $Pd(PPh_3)_4$ (4 mole %), toluene, 2 M aq. Na_2CO_3 (excess), MeOH, 80 °C, 1.5 h; (ix) KOBu^t (3.0 mole equiv.), HOBu^t, 18 °C, 3 h.

pyrrole with γ-butyrolactone (**26**) at 160 °C according to the procedure of Li and Snyder[33] afforded the previously reported acid **27** (60–90%) which was converted into the corresponding Weinreb amide **28** (87%) using a modified Mukaiyama amide coupling procedure.[34] Treatment of compound **28** with ethylmagnesium bromide followed by careful acidic work up then gave the ketone **29** (≥ 95%), which was immediately subjected to a Wadsworth–Emmons reaction using methyl diethylphosphonoacetate. The resulting 1 : 1 mixture of *E*- and *Z*-acrylates **30** (77%) could only be separated into the constituent isomers on a small scale, so, for preparative purposes, the mixture was used in examining the pivotal intramolecular Michael addition reaction. Gratifyingly, on treating acrylate **30** with *ca*. five molar equivalents of aluminium trichloride in diethyl ether at 18 °C the tetrahydroindolizine **31**[35] was obtained in 83% yield. Thus far it is not clear whether both isomers of compound **30** are engaging, in a direct sense, in this cyclisation process or if only one is with the other being isomerised to its reactive congener under these conditions. Work aimed at clarifying this matter and extending this type of chemistry is currently underway in these laboratories.

In terms of targeting rhazinal (**1**) it is necessary to effect the one-carbon homologation of ester **30**. However, before devising methods for doing this it seemed appropriate to carry the latter compound forward to (±)-B-norrhazinal (**3**), since this conformationally more constrained analogue of the natural product might be expected to display interesting biological properties. To such ends, compound **31** was subjected to Vilsmeier–Haack formylation, and this afforded, in a completely regioselective manner, the aldehyde **32** (95%), which was reacted with iodine/silver trifluoroacetate to give the iodinated derivative **33** (75%) as the exclusive product of the reaction. Suzuki–Miyuara[36] cross-coupling of compound **33** with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine[37] then gave the C4 arylated indolizidine **34** (76%). With this pivotal amino-ester in hand, methods for effecting the foreshadowed lactamisation reaction could be examined. In the first approach, saponification of the ester moiety within compound **34** was carried out using ethanolic potassium hydroxide, and the carboxylate salt thus formed was acidified with mineral acid. The resulting amino acid was not characterised but immediately subjected to reaction with DTMMN, the salt derived from 2-chloro-4,6-



Scheme 4 *Reagents and conditions*: (i) DIBAL-H (2 mole equiv. of a 1 M solution in hexane), hexane, −78 °C, 0.16 h; (ii) $MeSO_2Cl$ (2 mole equiv.), Et_3N, CH_2Cl_2, 0 °C, 0.5 h; (iii) NaCN (20 mole equiv.), DMPU, 18 °C, 24 h; (iv) (a) KOH (26 mole equiv.), H_2O–MeOH, reflux, 16 h then aq. HCl; (b) DCC (2.2 mole equiv.), DMAP (cat.), CH_2Cl_2–MeOH, 18 °C, 3 h; (v) DMF (12 mole equiv.), $POCl_3$ (1.1 mole equiv.), Et_2O, 0 °C, 0.5 h; (vi) I_2 (1.1 mole equiv.), $AgOCOCF_3$ (1.1 mole equiv.), $CHCl_3$, 0–18 °C, 4.5 h; (vii) 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine (1.65 mole equiv.), $Pd(PPh_3)_4$ (10 mole %), toluene, 2 M aq. Na_2CO_3 (excess), MeOH, 80 °C, 1.5 h; (viii) (a) KOH (1000 mole equiv.), EtOH, 18 °C, 3 h then aq. HCl; (b) EDCI (1.4 mole equiv.), DMAP (1.1 mole equiv.), CH_2Cl_2, 18 °C, 3 h.

dimethoxy-1,3,5-triazine and *N*-methylmorpholine,[38] and in this manner the target compound **3** (50%) was obtained. A superior method for effecting lactamisation involved treatment of amino-ester **34** with potassium *tert*-butoxide in *tert*-butanol, and in this manner (±)-B-norrhazinal was formed directly and in 74% yield (at 83% conversion). The spectral data derived from compound **3** were in full accord with the assigned structure, but a single-crystal X-ray analysis, details of which have been communicated previously,[19] provided final confirmation. This analysis revealed, *inter alia*, that the amide unit adopts an *s*-cissoid conformation and that the dihedral angle between the planes of the two aromatic rings is *ca*. 56° (which contrasts with an angle of 96° reported[39] for rhazinilam itself). Details associated with the biological evaluation of compound **3** are provided below.

Encouraged by the successful synthesis of compound **3**, attention was now directed towards rhazinal itself. The most effective means of achieving the necessary one-carbon homologation of ester **31** involved (Scheme 4) its $LiAlH_4$-promoted reduction to alcohol **35** (75%) then displacement of the readily derived mesylate **36** (95%) with cyanide. The resulting nitrile **37** (91%) was hydrolysed to the corresponding acid, which was then esterified with methanol in the presence of DCC–DMAP to give the required homologous ester, **38** (63% from **37**).[40] Completion of the synthesis of rhazinal now involved the same steps as employed in the preparation of congener **3**. Thus, Vilsmeier–Haack formylation provided aldehyde **39** (78%), which was iodinated under previously described conditions to give compound **40** (quantitative). Suzuki–Miyuara cross-coupling of iodide **40** with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine then gave the C4 arylated indolizidine **41** (64%). Lactamisation of this last compound *via* ester hydrolysis, then EDCI–DMAP-promoted coupling of the resulting amino acid afforded racemic rhazinal [(±)-**1**] in 68% yield. The ^1H and ^{13}C NMR spectra derived from this material matched perfectly with those reported[1] for the natural product, and final confirmation of structure followed from a single-crystal X-ray analysis (see Fig. 2 and Experimental). As expected, this analysis reveals that, as with congener **3**, the amide unit adopts an *s*-cissoid conformation and that the dihedral angle between the planes of the two aromatic rings is *ca*. 89° (which compares with an angle of 96° reported[39] for rhazinilam itself).

(c) Results of biological testing

(−)-Rhazinilam (**2**) and (±)-B-norrhazinal (**3**) were evaluated for their cytotoxic effects on the growth of human CA46 Burkitt lymphoma cells, and IC_{50} values of 1 and 3 μM, respectively, were observed. The open-ring amino ester precursor, **34**, of **3** gave an IC_{50} value of 20 μM in the same assay. Both compounds **2** and **3** arrested cells at G2M phase at all concentrations studied (*viz*. 5, 10, 25, 50 and 100 μM). Compound **3** was also examined for its effects on the polymerisation of purified tubulin dependent either on glutamate (Fig. 3) or on microtubule-associated proteins (MAPs) (Fig. 4) and results similar to those described[11] for (−)-rhazinilam were obtained. Such data suggest **3** is about 20–30% as active as rhazinilam and if only one enantiomeric form is active (as is probable) then the difference between the two compounds [*viz*. (+)- or (−)-**3** and (−)-**2**] is essentially the same within experimental error. These results suggest that compound **3** and its derivatives warrant further evaluation as potential anti-mitotic agents. The biological evaluation of (−)-rhazinal (**1**) has been described previously.[2]

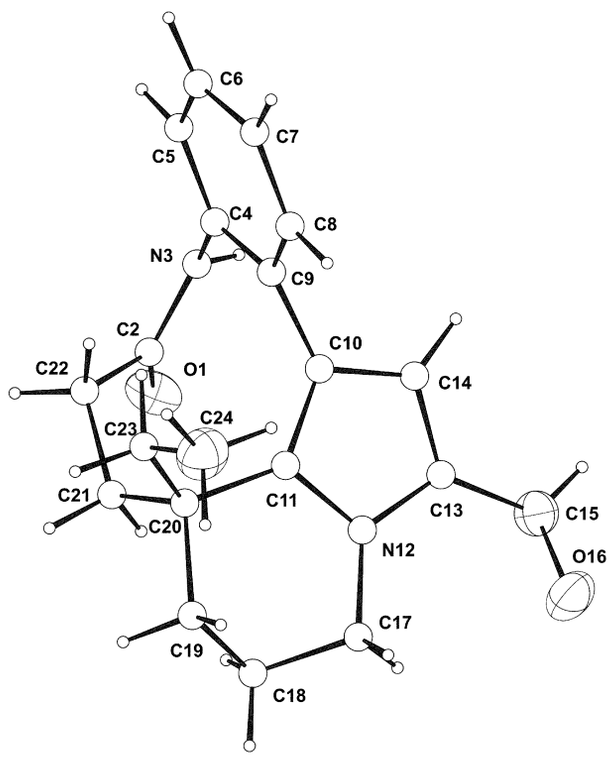


Fig. 2 A molecule of **1** derived from X-ray crystallographic data — anisotropically refined atoms shown with 50% displacement ellipsoids.

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

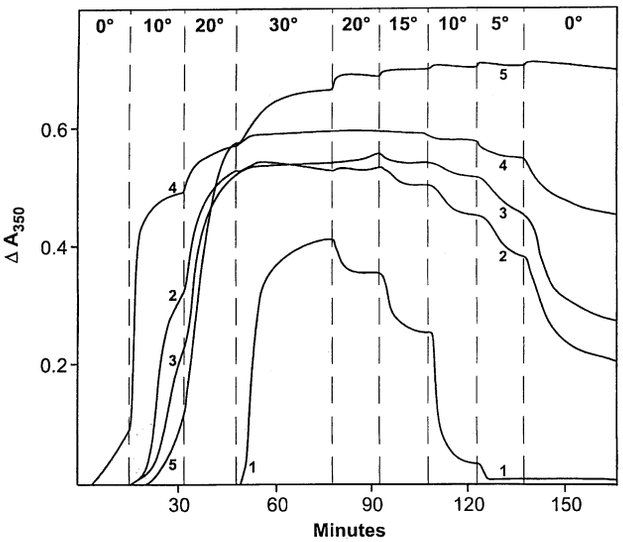


Fig. 3 Effects of compounds **2**, **3**, Taxol™ and vinblastine on the polymerisation of purified tubulin as determined in a reaction sequence measuring glutamate-dependent assembly, followed by cold-induced disassembly. Curve 1 = reaction without drug; Curve 2 = reaction with 20 μM **2**; Curve 3 = reaction with 60 μM **3**; Curve 4 = reaction with 10 μM Taxol™; Curve 5 = reaction with 20 μM vinblastine. *Reaction conditions*: 0.8 M monosodium glutamate (2 M stock adjusted to pH 6.6 with HCl), 0.4 mM GTP, 10 μM tubulin (1 mg mL^{-1}) with DMSO at 4%.

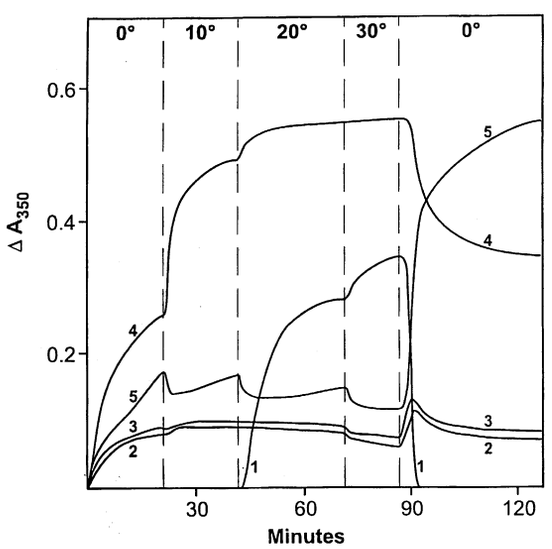


Fig. 4 Effects of compounds **2**, **3**, Taxol™ and vinblastine on the polymerisation of purified tubulin as determined in a reaction sequence measuring MAPs-dependent assembly, followed by cold-induced disassembly. Curve 1 = reaction without drug; Curve 2 = reaction with 20 μM **2**; Curve 3 = reaction with 120 μM **3**; Curve 4 = reaction with 20 μM Taxol™; Curve 5 = reaction with 40 μM vinblastine. *Reaction conditions*: 0.1 M 4-morpholineethanesulfonate (1 M stock adjusted to pH 6.9 with NaOH), 0.5 mM GTP, 0.5 mM $MgCl_2$, 20 μM tubulin (2 mg mL^{-1}), heat-treated MAPs at 1.5 mg mL^{-1} with DMSO at 4%.

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 ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference. ^{1}H 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 (^{1}H/^{1}H) correlation spectroscopy (COSY), nuclear Overhauser effect (nOe), and/or heteronuclear (^{1}H/^{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 (for oils) or as KBr discs (for solids).

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[41] 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 ($MgSO_4$) then filtered and concentrated under reduced pressure on a rotary evaporator with the water bath generally not exceeding 40 °C.

Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected. Elemental analyses were performed by the Australian National University Microanalytical Services Unit based in the Research School of Chemistry, The Australian National University, Canberra, Australia.

Methyl 4-nitrohexanoate (9)

A mixture of methyl acrylate (10 mL, 110 mmol), nitropropane (14.9 mL, 170 mmol) and NaOH (210 mL of a 0.1 M aqueous solution, 21 mmol) was stirred vigorously at 18 °C for 22 h. After this time the reaction mixture was saturated with NaCl (solid), then extracted with diethyl ether (4 × 75 mL). The combined organic phases were dried, filtered and concentrated under reduced pressure. Distillation of the resulting pale yellow residue gave methyl 4-nitrohexanoate (**9**)[23] (12.5 g, 65%) as a clear, colourless liquid, bp 115–117 °C at 1.8 mm Hg (lit.[23] 92 °C at 1 mm Hg). δ_H 0.94 (3H, t, J 7.4), 1.82 (1H, m), 1.92–2.38 (5H, complex m), 3.67 (3H, s), 4.46 (1H, m).

Methyl 4-oxohexanoate (10)

A solution of K_2CO_3 (72.6 g, 0.53 mol) and $NaHCO_3$ (44.2 g, 0.53 mol) in H_2O (280 mL) was added to a solution of nitroalkane **9** (4.60 g, 0.026 mol) in acetone (220 mL) and the resulting mixture stirred vigorously at 18 °C. A solution of Oxone™ (17.80 g, 0.029 mol) in H_2O (140 mL) was then added dropwise and the resulting mixture stirred at 18 °C for 6 h. Additional portions of Oxone™ (17.80 g, 0.029 mol) in H_2O (50 mL) and K_2CO_3 (18.10 g, 130 mmol) in H_2O (50 mL) were then added and stirring continued. After a further 16 h, more

Oxone™ (8.90 g, 0.014 mol) and K_2CO_3 (9.00 g, 0.065 mol) were added, and stirring was continued for another 7 h. The ensuing material was poured into HCl (100 mL of a conc. aqueous solution) containing ice (300 g) and the mixture thus obtained extracted with CH_2Cl_2 (3 × 250 mL). The combined organic phases were washed with H_2O (1 × 200 mL), and brine (1 × 200 mL) then dried and filtered. The filtrate was concentrated under reduced pressure to give keto-ester **10**[25] (3.60 g, 95%) as a pale yellow liquid. δ_H 1.07 (3H, t, *J* 7.4), 2.48 (2H, q, *J* 7.4), 2.61 (2H, m), 2.73 (2H, m), 3.67 (3H, s). This material was used, without purification, in the next step of the reaction sequence.

Methyl 4-methylenehexanoate (11)

NaHMDS (35 mL of a 1 M solution in THF, 35 mmol) was added to a magnetically stirred suspension of Ph_3PMeBr (9.80 g, 28 mmol) in THF (70 mL) maintained at 18 °C under a nitrogen atmosphere. The resulting yellow mixture was stirred at 18 °C for 1.5 h, then a solution of ketone **10** (3.60 g, 25 mmol) in THF (15 mL) was added dropwise. Stirring was continued at 18 °C for 15 h and then the reaction mixture diluted with pentane (100 mL). The resulting precipitate was removed by filtration, the filtrate concentrated under reduced pressure and the residue treated with additional pentane (100 mL). Filtration followed by concentration of the filtrate under reduced pressure afforded alkene **11**[26] (1.07 g, 30%) as a pale yellow and volatile liquid. δ_H 1.05 (3H, t, *J* 7.4), 2.05 (2H, m), 2.37 (2H, m), 2.48 (2H, m), 3.68 (3H, s), 4.71 (1H, broad s), 4.76 (1H, broad s). This material was used, without purification, in the next step of the reaction sequence.

4-Ethylpent-4-en-1-ol (12)

A solution of ester **11** (3.60 g, 25 mmol) in diethyl ether (25 mL) was added dropwise to a magnetically stirred suspension of $LiAlH_4$ (2.10 g, 55 mmol) in diethyl ether (75 mL) maintained at gentle reflux under a nitrogen atmosphere. The ensuing mixture was heated at reflux for a further 0.5 h, cooled, stirred at 18 °C for 1 h, then cooled to 0 °C (ice-bath) and treated, dropwise, with $KHSO_4$ (30 mL of a 2 M aqueous solution). The resulting mixture was heated at reflux for 2 min, then filtered, while still hot, through a pad of Celite, which was washed with ether (2 × 10 mL). The combined organic phases were dried, filtered and concentrated under reduced pressure to give alcohol **12**[27] (1.63 g, 57%) as a clear, colourless liquid. δ_H 1.00 (3H, t, *J* 7.4), 1.52 (1H, broad s), 1.70 (2H, m), 1.99–2.14 (4H, complex m), 3.58 (2H, broad t, *J* 6.7), 4.71 (2H, broad s). This material was used, without purification, in the next step of the reaction sequence.

4-Ethylpent-4-en-1-yl toluene-4-sulfonate (13)

A magnetically stirred solution of alcohol **12** (1.09 g, 9.6 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C, then Et_3N (1.78 mL, 12.48 mmol), DMAP (100 mg, cat.) and *p*-toluenesulfonyl chloride (2.06 g, 10.6 mmol) were added. The resulting solution was stirred under a nitrogen atmosphere at 4 °C for 48 h, then poured onto a mixture of ice (100 g) and HCl (200 mL of a 1 M aqueous solution). This mixture was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic phases washed with $NaHCO_3$ (1 × 200 mL of a saturated aqueous solution) and brine (1 × 200 mL), then dried, filtered and concentrated under reduced pressure to give *tosylate* ***13*** (1.95 g, 76%) as a light yellow oil. δ_H 0.98 (3H, t, *J* 7.4), 1.78 (2H, m), 1.93 (2H, q, *J* 7.4), 2.04 (2H, m), 2.45 (3H, s), 4.02 (2H, t, *J* 7.3), 4.60 (1H, broad s), 4.70 (1H, broad s), 7.34 (2H, d, *J* 8.2), 7.79 (2H, d, *J* 8.2); δ_C 12.2, 21.6, 26.9 28.6, 31.7, 70.2, 108.6, 127.9, 129.8, 144.7, 149.4 (one signal obscured or overlapping). This slightly impure material was used, directly, in the next step of the reaction sequence.

3-(2,2-Dibromo-1-ethylcyclopropyl)propyl toluene-4-sulfonate (14)

Sodium hydroxide (7.0 mL of a 1 : 1 w/v aqueous solution) was added to a vigorously stirred solution of alkene **13** (310 mg, 1.16 mmol), bromoform (3.22 g, 12.7 mmol) and benzyltriethylammonium chloride (50 mg) in benzene (7 mL) maintained at 0 °C (ice-bath). The ensuing mixture was stirred vigorously for 16 h (during which time the bath was allowed to warm to 18 °C), then H_2O (40 mL) was added and the mixture extracted with diethyl ether (2 × 25 mL). The combined extracts were dried, filtered and concentrated under reduced pressure to give a light yellow oil. Subjection of this material to flash chromatography (silica gel, 9 : 1 v/v hexane–ethyl acetate elution) gave, after concentration of the appropriate fractions (R_f 0.3), the *title sulfonate* ***14*** (356 mg, 70%) as a clear, colourless oil [Found: $(M + H)^+$, 438.9569. $C_{15}H_{20}{}^{79}Br_2O_3S$ requires $(M + H)^+$, 438.9578); ν_{max} (neat) 2968, 1360, 1188, 1176 cm^{-1}; δ_H 0.96 (3H, t, *J* 7.2), 1.33 (2H, m), 1.49–1.89 (6H, complex m), 2.44 (3H, s), 4.05 (2H, m), 7.34 (2H, d, *J* 8.1), 7.78 (2H, d, *J* 8.1); δ_C 10.4, 21.6, 25.7, 27.7, 30.3, 33.1, 33.7, 38.6, 70.2, 127.9, 129.9, 133.0, 144.8; *m/z* 443 (5%) 441 (8) 439 (5) [$(M + H)^+$], 327 (5), 242 (17), 240 (35), 238 (19), 189 (78), 187 (85), 173 (25), 155 (40), 107 (85), 82 (100), 67 (45).

Methyl 4-(2-nitrophenyl)-1*H*-pyrrole-2-carboxylate (15)

Copper bronze (512 mg, 8.0 mg-atom) was added to a solution of methyl 4-iodopyrrole-2-carboxylate[29] (252 mg, 1.0 mmol), 2-bromonitrobenzene (882 mg, 3.0 mmol) and $Pd(PPh_3)_3$ (30 mg, 0.03 mmol) in DMF (3 mL) and the resulting mixture subjected to ultrasonication at *ca*. 18 °C for 18 h. After this time the reaction mixture was diluted with ethyl acetate–hexane (50 mL of a 1 : 1 v/v mixture) and the separated organic phase washed with water (3 × 20 mL), ammonia (2 × 10 mL of a 2 M aqueous solution) and then brine (2 × 10 mL). The separated organic layer was dried, filtered and concentrated under reduced pressure to give a light yellow oil. Subjection of this material to flash chromatography (silica gel, 1 : 1 v/v hexane–dichloromethane elution) afforded three fractions, A–C.

Concentration of fraction A afforded 2,2′-dinitrobiphenyl[42] (190 mg, 55%) as a light yellow oil and identical with an authentic sample.

Concentration of fraction B afforded the starting iodopyrrole (132 mg, 52% recovery) as a colourless solid and identical with an authentic sample.

Concentration of fraction C afforded the title pyrrole **15** (110 mg, 88% at 48% conversion) as a yellow crystalline solid, mp 105–108 °C (lit.[7] 114 °C) (Found: $M^{+\bullet}$, 246.0645. $C_{12}H_{10}N_2O_4$ requires $M^{+\bullet}$, 246.0641); ν_{max} (neat) 3290, 1693, 1525, 1445, 1384, 1282, 1214, 1142, 993, 928, 853, 768, 747 cm^{-1}; δ_H 3.84 (3H, s), 6.97 (1H, t, *J* 2.1), 7.11 (1H, dd, *J* 3.0 and 1.8), 7.34 (1H, m), 7.44–7.54 (2H, complex m), 7.65 (1H, dd, *J* 8.1 and 1.2), 10.0 (1H, bs); δ_C 51.7, 114.6, 120.8, 122.0, 123.2, 123.5, 127.2, 128.6, 131.1, 131.8, 148.4, 161.6; *m/z* 246 ($M^{+\bullet}$, 100%), 229 (15), 215 (40), 201 (25), 187 (15), 169 (25), 161 (50), 140 (40), 132 (30), 104 (30).

Methyl 4-(2-nitrophenyl)-1-[3-(2,2-dibromo-1-ethylcyclopropyl]-1*H*-pyrrole-2-carboxylate [4 (X = NO_2, Y = CO_2Me)]

NaHMDS (0.2 mL of a 1 M solution in THF, 0.2 mmol) was added dropwise to a magnetically stirred solution of pyrrole **15** (50 mg, 0.2 mmol) in THF (4 mL) maintained at 0 °C under a nitrogen atmosphere. After 10 min. a solution of tosylate **14** (110 mg, 0.25 mmol) in THF (1 mL) was added dropwise and the resulting mixture heated (oil bath) at 65 °C while a gentle stream of nitrogen was employed to remove the solvent. Heating of the residue was continued for 16 h, and after cooling the reaction mixture was diluted with H_2O (5 mL), then extracted with CH_2Cl_2 (2 × 20 mL) to give the *title compound* ***4*** (X = NO_2, Y = CO_2Me) (111 mg, quantitative) as a clear colour-

less oil contaminated with traces of the tosylate **14** (Found: $M^{+\bullet}$, 511.9938. $C_{20}H_{22}{}^{79}Br_2N_2O_4$ requires $M^{+\bullet}$, 511.9946); ν_{max} (neat) 2966, 1709, 1660, 1526, 1441, 1361, 1176, 1106 cm^{-1}; δ_H 0.97 (3H, t, *J* 7.5), 1.52–2.02 (8H, complex m), 3.82 (3H, s), 4.35 (2H, m), 6.99 (1H, d, *J* 2.0), 7.01 (1H, d, *J* 2.0), 7.35 (1H, m), 7.45 (1H, dd, *J* 7.8 and 1.8), 7.52 (1H, td, *J* 7.8 and 1.2), 7.66 (1H, dd, *J* 7.8 and 1.2); δ_C 10.4, 27.9, 28.1, 31.2, 33.3, 33.8, 39.1, 49.2, 51.2, 117.5, 118.4, 122.4, 123.6, 127.1 (two signals superimposed), 128.6, 131.0, 131.8, 149.0, 161.1; *m/z* 516 (15%) 514 (30) 512 (15) [$M^{+\bullet}$], 403 (40) 401 (40), 353 (35), 283 (60), 269 (45), 259 (100), 107 (40).

4-Ethylpent-4-enyloxymethylbenzene (16)

NaH (1.20 g, 49 mmol) was added in portions to a magnetically stirred and ice-cold solution of alcohol **12** (2.80 g, 25 mmol), benzyl bromide (3.2 mL, 27 mmol) and sodium iodide (200 mg, 1 mmol) in DMF (50 mL) maintained at 18 °C under a nitrogen atmosphere. The resulting mixture was stirred at 18 °C for 18 h, quenched with H_2O (25 mL), then partitioned between diethyl ether (75 mL) and H_2O (150 mL). The separated aqueous phase was extracted with diethyl ether (3 × 75 mL) and the combined organic phases washed with H_2O (3 × 75 mL) and brine (1 × 75 mL), then dried, filtered and concentrated under reduced pressure to give a light brown liquid. Subjection of this material to flash chromatography (silica gel, 97 : 3 v/v hexane–diethyl ether elution) and concentration of the appropriate fractions gave the *title compound* 16 (3.50 g, 70%) as a clear, colourless oil (Found: $M^{+\bullet}$, 204.1517. $C_{14}H_{20}O$ requires $M^{+\bullet}$. 204.1514); ν_{max} (neat) 2936, 2854, 1645, 1453, 1104, 889, 734, 696 cm^{-1}; δ_H 1.02 (3H, t, *J* 7.4), 1.77 (2H, m), 1.97–2.14 (4H, complex m), 3.48 (2H, t, *J* 6.6), 4.51 (2H, s), 4.71 (2H, br s), 7.25–7.34 (5H, complex m); δ_C 12.3 (CH_3) 27.9 (CH_2), 28.8 (CH_2), 32.6 (CH_2), 70.1 (CH_2), 72.9 (CH_2), 107.7 (CH_2), 127.5 (CH), 127.6 (CH), 128.3 (CH), 138.6 (C), 151.0 (C); *m/z* 204 ($M^{+\bullet}$, 1%), 175 (6), 134 (6), 113 (21), 91 (100).

2-(3-Hydroxypropyl)-2-ethylcyclopropanecarboxylic acid ethyl ester (18)

A solution of ethyl diazoacetate (0.8 mL, 7.5 mmol) in CH_2Cl_2 (4 mL) was added, *via* syringe pump at a rate of 2–3 drops per minute, to a magnetically stirred solution of alkene **16** (0.5 g, 2.4 mmol) and $Rh_2(OAc)_4$ (22 mg, 0.6 mol%) in CH_2Cl_2 (3 mL) maintained at 18 °C under a nitrogen atmosphere. On completion of the addition the reaction mixture was filtered through a silica pad and the filtrate concentrated under reduced pressure. The residue, containing the diastereoisomeric cyclopropanes **17**, was dissolved in a mixture of ethyl acetate (20 mL), CH_2Cl_2 (10 mL) and ethanol (10 mL), then 5% Pd/C (10 mg) was added, and the resulting mixture was stirred under a balloon of H_2 for 22 h. The mixture was then filtered through a pad of Celite and the filtrate concentrated under reduced pressure to give a pale orange liquid. Subjection of this material to column chromatography (silica gel, 1 : 1 v/v diethyl ether–hexane elution) and concentration of the appropriate fractions (R_f 0.2) gave a 2 : 1 mixture of the diastereoisomers associated with *alcohol **18*** (210 mg, 42%) as a clear, colourless oil [Found: $(M + H)^+$, 201.1490. $C_{11}H_{20}O_3$ requires $(M+H)^+$, 201.1491]; ν_{max} (neat) 3424, 2962, 2936, 1723, 1176 cm^{-1}; δ_H 0.81–0.94 (4H, complex m), 1.05 (1H, q, *J* 4.7), 1.24 (4H, m), 1.41–1.70 (6H, complex m), 1.70 (1H, broad s), 3.57 (2/3H, t, *J* 6.1), 3.62 (4/3H, t, *J* 6.3), 4.11 (2H, q, *J* 7.2); δ_C 10.8, 11.2, 14.7, 21.0, 21.1, 22.0, 24.9, 26.3, 26.7, 29.8, 30.0, 30.2, 32.0, 32.2, 32.8, 60.6, 60.8, 63.0, 63.1, 173.1, 173.5 (one signal obscured or overlapping); *m/z* (DCI) 201 [$(M + H)^+$, 22%] 155 (100), 137 (38), 109 (58), 99 (92).

2-Ethyl-2-[3-(toluene-4-sulfonyloxy)propyl]cyclopropanecarboxylic acid ethyl ester (19)

A magnetically stirred solution of alcohol **18** (140 mg, 0.70 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, then Et_3N (0.13 mL, 0.91 mmol), DMAP (5 mg, 0.04 mmole) and *p*-toluenesulfonyl chloride (150 mg, 0.77 mmol) were added. The resulting solution was stirred under a nitrogen atmosphere at 4 °C for 48 h, then poured onto a mixture of ice (10 g) and HCl (20 mL of a 1 M aqueous solution). This mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases washed with $NaHCO_3$ (1 × 20 mL of a saturated aqueous solution) and brine (1 × 20 mL), then dried, filtered and concentrated under reduced pressure to give a 2 : 1 mixture of diastereomers associated with *tosylate **19*** (210 mg, 84%) as a pale yellow oil. δ_H 0.82 (1H, m), 0.87 (3H, t, *J* 7.2), 0.99 (1H, t, *J* 4.8), 1.17–1.74 (10H, complex m), 2.45 (3H, s), 3.87 (2H, m), 4.09 (2H, m), 7.34 (2H, d, *J* 8.4), 7.78 (2H, d, *J* 8.4). This material was used, without purification, in the next step of the reaction sequence.

2-Ethyl-2-(3-pyrrol-1-ylpropyl)cyclopropanecarboxylic acid ethyl ester (20)

Pyrrole (31 μL, 0.46 mmol) was added to a magnetically stirred suspension of KH (18 mg, 0.46 mmol) in DMF maintained under a nitrogen atmosphere and the resulting solution stirred at 18 °C for 5 min, then a solution of the tosylate **19** (80 mg, 0.23 mmol) in DMF (2 mL) was added. The resulting mixture was stirred at 18 °C for 1.5 h, then quenched with H_2O (5 mL) and partitioned between ethyl acetate (20 mL) and HCl (5 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL) and the combined organic phases washed with H_2O (3 × 40 mL) and brine (1 × 40 mL), then dried, filtered and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (silica gel, 1 : 1 v/v hexane–diethyl ether elution) and concentration of the appropriate fractions (R_f 0.6) gave a 2 : 1 mixture of diastereomers associated with *pyrrole **20*** (50 mg, 89%) as a clear, colourless oil (Found: $M^{+\bullet}$, 249.1728. $C_{15}H_{23}NO_2$ requires $M^{+\bullet}$, 249.1729); ν_{max} (neat) 2962, 1722, 1449, 1405, 1281, 1174, 1089, 722 cm^{-1}; δ_H 0.86 (4H, m), 1.05 (1H, m), 1.25 (3H, t, *J* 6.9), 1.23–1.95 (7H, complex m), 3.80 (2H, m), 4.07 (2H, q, *J* 6.9), 6.10 (2H, m), 6.61 (2H, m); δ_C 10.4, 10.8, 14.3, 20.4, 20.6, 21.6, 25.7, 25.9, 26.3, 28.3, 28.9, 29.6, 31.3, 31.5, 33.3, 49.4, 49.7, 60.3, 107.9, 108.0, 120.3, 172.4, 172.8 (three peaks obscured or overlapping); *m/z* 249 ($M^{+\bullet}$, 73%), 220 (43), 204 (50), 176 (39), 162 (46), 148 (71), 134 (60), 94 (65), 81 (100), 80 (88).

Dimethyl 2-(3-hydroxypropyl)-2-ethylcyclopropane-1,1-dicarboxylate (22)

A solution of dimethyl diazomalonate[31] (250 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added, *via* syringe pump at a rate of 2–3 drops per minute, to a solution of alkene **16** (100 mg, 0.49 mmol) and $Rh_2(OAc)_4$ (11 mg, 2 mol %) in CH_2Cl_2 (2 mL) maintained at reflux under a nitrogen atmosphere. On completion of the addition the mixture was heated at reflux for 1 h, then cooled and filtered through a pad of silica gel and the filtrate concentrated under reduced pressure to give a light yellow oil. The residue, containing ether **21**, was dissolved in ethyl acetate–methanol (17 mL of a 10 : 7 v/v mixture), 5% Pd/C (10 mg) was added and the resulting mixture stirred magnetically under an atmosphere of H_2 at 18 °C for 22 h. The ensuing mixture was filtered through a pad of Celite and the filtrate concentrated under reduced pressure to give a pale yellow liquid. Subjection of this material to flash chromatography (silica gel, 2 : 1 v/v hexane–diethyl ether elution) and concentration of the appropriate fractions (R_f 0.3) gave the *title cyclopropane **22*** (54 mg, 45%) as a clear, colourless liquid [Found: $(M + H)^+$, 245.1390. $C_{12}H_{20}O_5$ requires $(M + H)^+$, 245.1389); ν_{max} (neat) 3415, 2953, 2878, 1731, 1436, 1289, 1225, 1112, 1061, 897 cm^{-1}; δ_H 0.93 (3H, t, *J* 7.2), 1.22 (1H, m), 1.41–1.78 (8H, complex m), 3.56 (2H, t, *J* 6.3), 3.73 (6H, s); δ_C 10.5,

24.3, 26.3, 26.4, 29.4, 37.8, 39.7, 52.4, 52.5, 62.4, 169.2, 169.5; *m/z* (DCI) 245 [(M + H)$^+$, <1%], 227 (24), 213 (56), 195 (23), 181 (28), 99 (100).

2-Ethyl-2-[3-(toluene-4-sulfonyloxy)propyl]cyclopropane-1,1-dicarboxylic acid dimethyl ester (23)

A magnetically stirred solution of alcohol **22** (50 mg, 0.21 mmol) in pyridine (3 mL) was cooled to 0 °C, then *p*-toluenesulfonyl chloride (43 mg, 0.23 mmol) was added. The resulting solution was stirred under a nitrogen atmosphere at 4 °C for 48 h, then poured onto a mixture of ice (10 g) and HCl (20 mL of a 1 M aqueous solution). This mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases washed with HCl (1 × 20 mL of a 1 M aqueous solution), H_2O (1 × 20 mL) and brine (1 × 20 mL), then dried, filtered and concentrated under reduced pressure to give the *tosylate* ***23*** (55 mg, 67%) as a colourless oil. δ_H 0.87 (3H, t, *J* 7.2), 1.20 (1H, m), 1.35–1.71 (7H, complex m), 2.45 (3H, s), 3.70 (3H, s), 3.71 (3H, s), 3.98 (2H, m), 7.34 (2H, *J* 8.4), 7.78 (2H, d, *J* 8.4). This material was used, without purification, in attempts to prepare compound **24** (see Results and discussion section).

Methyl (±)-8-ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-acetate (32)

Phosphorus oxychloride (70 mg, 0.45 mmol) was added to a magnetically stirred solution of pyrrole **31**[35] (92 mg, 0.42 mmol) and DMF (0.4 mL) in ether (5 mL) maintained at 0 °C. After 0.5 h the ice-bath was removed and the mixture stirred at 18 °C for 3 h before addition of ether (20 mL) and Na_2CO_3 (20 mL of a 2 M aqueous solution). Stirring was continued for a further 10 min then the organic phase was separated and the aqueous phase extracted with diethyl ether (1 × 25 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 : 4 v/v ethyl acetate–hexane elution) gave, after concentration of the appropriate fractions, the 2-formylpyrrole **32** (100 mg, 95%) as a white crystalline solid, mp 69–70 °C (Found: M$^{+\bullet}$, 249.1361. $C_{14}H_{19}NO_3$ requires M$^{+\bullet}$, 249.1365); ν_{max} 2967, 1731, 1659, 1181, 785 cm^{-1}; δ_H 0.83 (3H, t, *J* 7.5), 1.78 (2H, q, *J* 7.5), 1.81 (1H, m), 1.96 (3H, m), 2.61 (2H, m), 3.58 (3H, s), 4.35 (2H, t, *J* 6), 6.02 (1H, d, *J* 4.2), 6.86 (1H, d, *J* 4.2), 9.41 (1H, s); δ_C 8.7, 19.5, 28.8, 33.3, 37.9, 44.3, 45.3, 51.4, 107.2, 124.4, 130.7, 145.5, 171.3, 178.7; *m/z* 249 (M$^{+\bullet}$, 45%), 220 (45), 176 (100) 160 (45), 132 (60).

Methyl (±)-8-ethyl-3-formyl-5,6,7,8-tetrahydro-1-iodoindolizin-8-acetate (33)

Iodine (92 mg, 0.36 mmol) was added to a magnetically stirred mixture of the pyrrole **32** (81 mg, 0.33 mmol) and silver trifluoroacetate (89 mg, 0.36 mmol) in chloroform (5 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction mixture was then warmed to 18 °C, stirred at this temperature for 4 h (whilst being protected from light), then treated with $Na_2S_2O_5$ (1 mL of a 20% w/v aqueous solution) and brine (5 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were dried, filtered and concentrated under reduced pressure to give the iodopyrrole **33** (105 mg, 75%) as a clear, colourless oil (Found: M$^{+\bullet}$, 375.0331. $C_{14}H_{18}INO_3$ requires M$^{+\bullet}$, 375.0331); ν_{max} 2961, 1732, 1661 cm^{-1}; δ_H 0.78 (3H, t, *J* 7.5), 1.74–2.18 (5H, complex m), 2.34 (1H, m), 2.70 (1H, d, *J* 15.4), 3.23 (1H, d, *J* 15.4), 3.60 (3H, s), 4.41 (2H, t, *J* 6), 7.03 (1H, s), 9.38 (1H, s); δ_C 8.7, 19.9, 29.0, 30.7, 38.7, 42.2, 46.2, 51.6, 58.6, 132.1, 133.1, 142.3, 171.4, 178.1; *m/z* 375 (M$^{+\bullet}$, 55%), 302 (75), 219 (100), 160 (25).

Methyl (±)-1-(2-aminophenyl)-8-ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-acetate (34)

Na_2CO_3 (1 mL of a 2 M aqueous solution) was added to a degassed and magnetically stirred solution of iodopyrrole **33** (52 mg, 0.14 mmol) and $Pd(PPh_3)_4$ (6 mg, 4 mole %) in toluene (2 mL), followed by a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine (67 mg, 0.34 mmol) in methanol (0.5 mL). The resulting mixture was heated at 80 °C for 2 h, then cooled, diluted with brine (5 mL) and extracted with ethyl acetate (2 × 10 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, 2 : 3 v/v ethyl acetate–hexane elution) gave, after concentration of the appropriate fractions, the amino-ester **34** (36 mg, 76%) as a clear, colourless oil (Found: M$^{+\bullet}$, 340.1792. $C_{20}H_{24}N_2O_3$ requires M$^{+\bullet}$, 340.1787); ν_{max} 3456, 3369, 1732, 1656, 1617 cm^{-1}; δ_H (C_6D_6, 2 : 1 mixture of rotamers) 0.60 (3H, m), 1.38–1.85 (6H, complex m), 2.28 (2/3H, d, *J* 15.5), 2.38 (1/3H, d, *J* 15.5), 2.72 (2/3H, d, *J* 15.5), 2.82 (1/3H, d, *J* 15.5), 3.28 (2H, s, OCH_3), 3.30 (2/3H, broad s), 3.31 (1H, s, OCH_3), 3.80 (4/3H, broad s), 4.40 (1/3H, m), 4.50 (4/3H, t, *J* 6.0), 4.64 (1/3H, m), 6.55 (2H, m), 6.85 (1H, m), 7.15–7.40 (2H, complex m), 9.55 (1/3H, s), 9.56 (2/3H, s); *m/z* 340 (M$^{+\bullet}$, 20%), 237 (30), 219 (70), 162 (60), 146 (50), 119 (100), 59 (70).

(±)-B-Norrhazinal (3)

Method A. Potassium hydroxide (2.25, 40 mmol) was added to a magnetically stirred solution of the amino-ester **34** (15 mg, 0.044 mmol) in ethanol (5 mL) maintained at 18 °C under a nitrogen atmosphere. After 48 h the reaction mixture was acidified to pH 5 (with 2 M aqueous HCl), then extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure to give a light yellow oil. This material was dissolved in THF (10 mL) and treated with the salt derived from 2-chloro-4,6-dimethoxytriazine (210 mg, 1.2 mmol) and *N*-methylmorpholine (40 mg, 0.4 mmol). The resulting solution was stirred for 2 h at 18 °C, then diluted with ethyl acetate (10 mL) and brine (5 mL). The separated aqueous phase was extracted with ethyl acetate (1 × 10 mL) and the combined organic extracts dried, filtered and concentrated under reduced pressure to give a light yellow oil. Subjection of this material to thin layer chromatography (silica gel, 7 : 3 v/v ethyl acetate–hexane elution) and extraction of the appropriate band gave (±)-B-norrhazinal (**3**) (7 mg, 74%) as a cream-coloured and crystalline solid, no mp but decomposition above 150 °C (crystals suitable for X-ray analysis were obtained from ether–hexane) (Found: M$^{+\bullet}$, 308.1523. $C_{19}H_{20}N_2O_2$ requires M$^{+\bullet}$, 308.1525); ν_{max} 3287, 1722, 1659 cm^{-1}; δ_H 0.68 (3H, t, *J* 7.5), 1.44–1.68 (3H, complex m), 1.87 (1H, dt, *J* 13.5 and 3.5), 1.94–2.03 (1H, complex m), 2.15 (1H, d, *J* 11.5), 2.40 (1H, td, *J* 13.5 and 3.6), 2.79 (1H, d, *J* 12.4), 4.08 (1H, m), 4.83 (1H, dd, *J* 14.3 and 6.0), 6.71 (1H, s), 7.13 (1H, m), 7.17 (1H, broad s), 7.28–7.42 (3H, complex m), 9.46 (1H, s); δ_C 8.1, 18.4, 28.3, 33.9, 38.3, 41.2, 45.3, 120.2, 125.2, 125.7, 127.6, 128.2, 131.1, 131.4, 134.8, 135.8, 143.2, 173.7, 179.0; *m/z* 308 (M$^{+\bullet}$, 56%), 279 (75), 251 (42), 237 (100).

Method B. Potassium *tert*-butoxide (40 mg, 0.37 mmol) was added to a solution of the amino-ester **34** (42 mg, 0.12 mmol) in *tert*-butanol (5 mL) and the resulting mixture stirred under a nitrogen atmosphere at 18 °C for 3 h. Water (5 mL) and NH_4Cl (5 mL of a saturated aqueous solution) were added to the resulting mixture, which was 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 to flash chromatography (silica gel, gradient elution with ether, then ethyl acetate elution) afforded two fractions A and B.

Concentration of fraction A afforded the amino-ester **34** (7 mg, 17% recovery), identical, in all respects, with an authentic sample.

Concentration of fraction B afforded (±)-B-norrhazinal (**3**) (22 mg, 78% at 83% conversion), identical, in all respects, with the material obtained by Method A.

Methyl (±)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-propionate (38)

DCC (206 mg, 1 mmol) was added to a magnetically stirred solution of the acid (100 mg, 0.45 mmol) derived from hydrolysis of nitrile **37**[40] and DMAP (5 mg, 0.04 mmol) in dichloromethane–methanol (4 mL of a 3 : 1 v/v mixture) maintained at 18 °C under a nitrogen atmosphere. After 3 h water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (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, ester **38** (75 mg, 72%) as a clear, colourless oil (Found: $M^{+\bullet}$, 235.1576. $C_{14}H_{21}NO_2$ requires $M^{+\bullet}$, 235.1572); ν_{max} 3097, 2948, 2876, 1738, 1195, 1170, 706 cm^{-1}; δ_H 0.84 (3H, t, *J* 7.5), 1.54–1.71 (4H, complex m), 1.86–2.00 (4H, complex m), 2.28 (2H, m), 3.63 (3H, s), 3.88 (2H, t, *J* 6.5), 5.85 (1H, d, *J* 3.5), 6.10 (1H, d, *J* 3.5), 6.45 (1H, bs); δ_C 8.5, 20.0, 29.7, 30.8, 33.1, 34.4, 37.3, 45.3, 51.5, 104.1, 107.1, 118.6, 134.6, 174.6; *m/z* 235 ($M^{+\bullet}$, 55%), 206 (80), 174 (50), 148 (100), 146 (48), 133 (35), 118 (30).

Methyl (±)-8-ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-propionate (39)

Phosphorus oxychloride (35 mg, 0.23 mmol) was added to a magnetically stirred solution of the pyrrole **38** (50 mg, 0.212 mmol) and DMF (0.2 mL, 2.58 mmol) in ether (5 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 0.5 h the ice-bath was removed and the reaction mixture stirred at 18 °C for 3 h, then treated with Na_2CO_3 (5 mL of a 2 M aqueous solution). Stirring was continued for 10 min, then diethyl ether (10 mL) was added and the organic phase separated. The aqueous phase was extracted with ether (1 × 10 mL) and the combined organic phases dried, filtered and concentrated under reduced pressure to give *pyrrole* ***39*** (44 mg, 78%) as a clear, colourless oil (Found: $M^{+\bullet}$, 263.1525. $C_{15}H_{21}NO_3$ requires $M^{+\bullet}$, 263.1521); ν_{max} (neat) 2926, 1738, 1659 cm^{-1}; δ_H 0.82 (3H, t, *J* 7.5), 1.67 (4H, m), 1.96 (4H, m), 2.20 (2H, m), 3.61 (3H, s), 3.43 (2H, m), 6.00 (1H, d, *J* 4), 6.87 (1H, d, *J* 4), 9.39 (1H, s); δ_C 8.5, 19.5, 28.8, 29.5, 33.2, 34.7, 38.0, 45.4, 51.7, 107.5, 124.5, 130.8, 146.0, 174.0, 178.5; *m/z* 263 ($M^{+\bullet}$, 50%), 234 (65), 176 (100), 174 (55), 146 (30).

Methyl (±)-8-ethyl-3-formyl-5,6,7,8-tetrahydro-1-iodoindolizin-8-propionate (40)

Iodine (46 mg, 0.18 mmol) was added to a magnetically stirred mixture of pyrrole **39** (44 mg, 0.167 mmol) and silver trifluoroacetate (40 mg, 0.18 mmol) in chloroform (5 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After addition was complete the ice-bath was removed and the reaction mixture stirred at 18 °C for 4 h with protection from light. $Na_2S_2O_5$ (1 mL of a 20% aqueous solution) and brine (5 mL) were added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried, filtered and concentrated under reduced pressure to give the iodopyrrole **40** (71 mg, quantitative) as a clear, colourless oil (Found: $M^{+\bullet}$, 389.0489. $C_{15}H_{20}INO_3$ requires $M^{+\bullet}$, 389.0488); ν_{max} (neat) 2950, 1736, 1661 cm^{-1}; δ_H 0.80 (3H, t, *J* 7.5), 1.58–1.98 (6H, complex m), 2.15 (3H, m), 2.60 (1H, m), 3.65 (3H, s), 4.30 (1H, m), 4.42 (1H, m), 7.03 (1H, s), 9.37 (1H, s); δ_C 8.6, 19.9, 28.4, 29.6, 31.1, 32.9, 39.5, 46.4, 51.7, 59.0, 132.2, 133.3, 143.0, 173.8, 178.0; *m/z* 389 ($M^{+\bullet}$, 60 %), 360 (15), 330 (10), 302 (100), 233 (95), 175 (15), 160 (15), 146 (15).

Methyl (±)-1-(2-aminophenyl)-8-ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-propionate (41)

Na_2CO_3 (1 mL of a 2 M aqueous solution), then a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzeneamine (20 mg, 0.093 mmol) in methanol (0.5 mL) were added to a degassed and magnetically stirred solution of iodopyrrole **40** (35 mg, 0.090 mmol) and $Pd(PPh_3)_4$ (5 mg) in toluene (2 mL) maintained under a nitrogen atmosphere. The resulting mixture was heated at 90 °C for 0.5 h, at which time further portions of the boronate ester (10 mg) and $Pd(PPh_3)_4$ (5 mg) were added. After a further 1 h of heating the reaction mixture was cooled, diluted with brine (5 mL) and extracted with diethyl ether (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 to flash chromatography (silica gel, diethyl ether elution) gave, after concentration of the appropriate fractions, the amino-ester **41** (20 mg, 64% yield) as a clear, colourless oil (Found: $M^{+\bullet}$, 354.1947. $C_{21}H_{26}N_2O_3$ requires $M^{+\bullet}$, 354.1943); ν_{max} 3465, 3368, 2951, 1732, 1657 cm^{-1}; δ_H (*ca.* 1 : 1 mixture of rotamers) 0.77 (3/2H, t, *J* 7.8), 0.80 (3/2H, t, *J* 7.8), 1.40–2.38 (12H, complex m), 3.59 (3/2H, s), 3.66 (3/2H, s), 4.24–4.60 (2H, complex m), 6.72 (2H, m), 6.80 (1H, d, *J* 3.3), 7.04 (1H, m), 7.14 (1H, dt, *J* 7.8 and 1.5), 9.42(8) (1/2H, s), 9.42(9) (1/2H, s); *m/z* 354 ($M^{+\bullet}$, 100%), 325 (50), 293 (15), 267 (65), 239 (45), 237 (30), 209 (25), 176 (20), 130 (10).

(±)-Rhazinal [(±)-1]

Potassium hydroxide (2.0 g, 35.6 mmol) was added to a magnetically stirred solution of the amino-ester **41** (13 mg, 0.036 mmol) in ethanol (3 mL) maintained at 18 °C under a nitrogen atmosphere. After 3 h the reaction mixture was acidified to pH 5 (with 2 M aqueous HCl) and extracted with dichloromethane (3 × 4 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure to give a light yellow oil. A solution of this material in dichloromethane (5 mL) was treated with EDCI (10 mg, 0.05 mmol) and DMAP (5 mg, 0.04 mmol), then stirred at 18 °C under a nitrogen atmosphere for 3 h. At this point water (2 mL) and HCl (2 drops of a 2 M aqueous solution) were added, and the separated aqueous phase was extracted with dichloromethane (2 × 3 mL). The combined organic extracts were then dried, filtered and concentrated under reduced pressure to give a light yellow oil. Subjection of this material to flash chromatography (silica gel, ethyl acetate elution) gave, after concentration of the appropriate fractions, (±)-rhazinal [(±)-**1**][1] (8 mg, 68% yield) as a white crystalline solid, mp 234–236 °C (crystals suitable for X-ray analysis were obtained from CH_2Cl_2–hexane) (Found: $M^{+\bullet}$, 322.1683. $C_{20}H_{22}N_2O_2$ requires $M^{+\bullet}$, 322.1681); ν_{max} 3180, 2919, 1660 cm^{-1}; δ_H 0.71 (3H, t, *J* 7.2), 1.24 (2H, m), 1.53 (2H, m), 1.76 (1H, td, *J* 13.5 and 3.3), 1.90–2.06 (2H, complex m), 2.19 (1H, m), 2.42 (1H, t, *J* 12.5), 2.46 (1H, t, *J* 10.5), 3.98 (1H, ddd, *J* 14.0, 12.0 and 1.8), 4.78 (1H, dd, *J* 14.0 and 5.5), 6.54 (1H, s), 6.80 (1H, bs), 7.24 (1H, d, *J* 7.8), 7.30–7.44 (3H, complex m), 9.39 (1H, s); δ_C 8.2, 18.5, 28.0, 29.8, 31.9, 36.5, 39.6, 46.3, 120.5, 125.6, 127.3, 127.7, 129.0, 130.1, 131.3, 137.5, 138.2, 141.3, 176.7, 178.8; *m/z* 322 ($M^{+\bullet}$, 30%), 293 (100), 265 (30), 237 (35).

X-Ray crystallographic analysis of compound (±)-1

$C_{20}H_{22}N_2O_2$, M_r = 322.41, T = 200.0(1) K, monoclinic, space group $P2_1/n$, Z = 4, a = 11.1081(3), b = 12.6796(4), c = 11.6659(4)Å, β = 101.2591(13)°, U = 1611.5 (1) Å^3, ρ_{calc} = 1.329 g cm^{-3}, $F(000)$ = 688, μ(MoKα) = 0.086 mm^{-1}, numerical absorption correction applied, 1493 unique data ($2\Theta_{max}$ = 40.0°), with 902 $I > 3\sigma I$); R = 0.097, R_w = 0.085, S = 0.835. The only crystals

ever obtained, even after exhaustive attempts at crystal growth, were very fine needles. The largest available had dimensions of 35 × 45 × 135 μm and was used in this experiment. No diffraction was observable above $\Theta = 20°$.

Images were measured on a Nonius Kappa CCD diffractometer[43] (graphite monochromator, $\lambda = 0.71073$ Å) and data extracted using the DENZO package.[44] Structure solution was by direct methods (SIR92)[45] and refinement was by full matrix least-squares on F using the CRYSTALS[46] program package. CCDC 195978. See http://www.rsc.org/suppdata/ob/b2/b209992f/ for crystallographic data in CIF or other electronic format.

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