Enantioselective total syntheses of the alkaloids (−)-rhazinal, (−)-rhazinilam, (−)-leuconolam and (+)-epi-leuconolam

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Dedicated to Professor Jim Coxon on the occasion of his 65th birthday

Abstract
The title alkaloids, (−)-1, (−)-2, (−)-4 and (+)-5 respectively, have each been prepared from the enantiomerically enriched (74% ee) tetrahydroindolizine 14 which is itself obtained via an organocatalyzed and enantioselective intramolecular Michael addition reaction of the pyrrole 13 incorporating an N-tethered and β,β-disubstituted acrylaldehyde moiety.

Keywords: Enantioselective, (+)-epi-leuconolam, (−)-leuconolam, (−)-rhazinal, (−)-rhazinilam, total synthesis

Introduction
The alkaloid rhazinal [(−)-1],1 like its more well-known congener rhazinilam [(−)-2],2 is a potent spindle toxin by virtue of its capacity to disrupt the dynamic interconversion of tubulin and microtubules required for the normal mitotic division of cells.3 As such these compounds have been identified as novel leads for the development of new generation anti-cancer agents.4 The first total synthesis of rhazinilam was described5 by Smith et al. in 1973 with the second and thus far only enantioselective approach,6 due to Sames and co-workers, emerging almost twenty years later. Magnus et al. reported7 a third synthesis, of racemic material, in 2001 whilst we have recently disclosed8 the first total synthesis of (±)-rhazinal [(±)-1] as well as its (non-natural) β-nor-congener (±)-3 (which also acts as a spindle toxin). Herein we describe a modification of our approach8 that has culminated in enantioselective total syntheses of (−)-rhazinal [(−)-1] and (−)-rhazinilam [(−)-2] as well as the “biogenetically”9 and structurally related bis-lactams (−)-leuconolam [(−)-4]10 and (+)-epi-leuconolam [(+)-5].10 Compounds (−)-4 and (+)-5 have not, hitherto, been prepared by total synthesis.
Our earlier synthesis of (±)-rhazinal involved, as a key step, the Lewis-acid promoted intramolecular Michael addition of the C2 of pyrrole to an N-tethered acrylate incorporating an ethyl group at the β-position. The ensuing cyclization reaction resulted in annihilation of the rhazinal D-ring onto the pyrrole C-ring with simultaneous assembly of substituents about C20, the only quaternary and stereogenic centre associated with target 1. The central issue, therefore, in adapting this work to the construction of (−)-rhazinal [−]−1, as well as congeners (−)-2, (−)-4 and (+)-5, was to establish methods for effecting this type of intra-molecular Michael addition reaction in an enantioselective fashion. Whilst many useful methods are now available for promoting such processes in a catalytic manner,11 recent studies from these laboratories12 have suggested that MacMillan’s organocatalysts13 might provide a very effective means for achieving our objective. This has proven to be the case as demonstrated by the outcomes reported below.

Results and Discussion

The synthetic route to the substrate required for studying the proposed enantioselective Michael addition reaction is shown in the early parts of Scheme 1. Thus, as detailed previously,8 but reiterated here for the sake of completeness, reaction of potassium salt, 6, of pyrrole with γ-butyrolactone (7) under conditions defined by Li and Snyder,14 afforded, after acidic work up, the acid 8 in 60–90% yield. The latter species was converted into the corresponding Weinreb amide 9 (87%), using a modification15 of conditions defined by Mukaiyama and co-workers,16 and this was then reacted with ethyl magnesium bromide to give, after careful work up, the previously reported8 ethyl ketone 10 in 95% yield. HWE-type olefination of compound 10 using the anion derived from methyl diethylphosphonoacetate then gave the β,β-disubstituted acrylate 11 in 77% yield and as a ca. 1 : 1 mixture of E- and Z-isomers. Reduction of this material with DIBAL-H afforded, in 91% yield, the corresponding mixture of allylic alcohols 12 which was immediately oxidized, with barium manganate,17 to the targeted aldehyde 13 (76% yield of a ca. 1 : 1 mixture of E- and Z-isomers).
Scheme 1. Reagents and conditions: (i) (a) 160°C, 2 h then, (b) acidic work-up at 18°C; (ii) MeN(H)OMe·HCl (1.2 mole equiv.), Et₃N (1.2 mole equiv.), (2-pyridine-N-oxide)disulfide (1.5 mole equiv.), Bu₃P (1.5 mole equiv.), 18°C, 16 h; (iii) (a) EtMgBr (3 mole equiv.), Et₂O, 18°C, 1 h then, (b) 0.3 M aq. KHSO₄ (excess), −40°C, 0.1 h then, (c) NaHCO₃ (excess), −40°C to 18°C; (iv) NaH (2 mole equiv.), (EtO)₂POCH₂CO₂Me (2 mole equiv.), 18°C, 48 h; (v) DIBAL-H (2.2 mole equiv.), THF, −78 to 18°C, 4 h; (vi) BaMnO₄ (8 mole equiv.), CH₂Cl₂, 18°C, 48 h; (vii) (5S)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monotrifluoroacetate (20 mole %), ca. 20 : 1 v/v THF–water, −20°C, 72 h; (viii) NaBH₄ (1.5 mole equiv.), 20 : 1 v/v THF–ethanol, 18°C, 2 h; (ix) Br₂ (2.2 mole equiv.), AcOH, 18°C, 2 h; (x) MeSO₂Cl (2 mole equiv.), 0°C, 0.5 h; (xi) NaCN (20 mole equiv.), DMPU, 18°C, 24 h; (xii) (a) KOH (26 mole equiv.), 4 : 3 v/v H₂O–MeOH, reflux, 16 h then aq. HCl; (b) DCC (2.2 mole equiv.), DMAP (ca. 10 mole %), 3 : 1 v/v CH₂Cl₂–MeOH, 18°C, 3 h; (xiii) DMF (12 mole equiv.), POCl₃ (1.1 mole equiv.), Et₂O, 0 to 18°C, 3.5 h; (xiv) I₂ (1.1 mole equiv.), AgOCOCF₃ (1.1 mole equiv.), CHCl₃, 0 to 18°C, 4.5 h; (xv) 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine (1 mole equiv.), Pd(PPh₃)₄ (cat.), 1 : 4 v/v MeOH–toluene, 2 M aq. Na₂CO₃ (excess), MeOH, 90°C, 1.5 h; (xvi) (a) KOH (100 mole equiv.), ethanol, 18°C, 3 h then aq. HCl; (b) EDCI (1.4 mole equiv.), DMAP (1.1 mole equiv.), 18°C, 3 h; (xvii) chlorotris(triphenylphosphine)rhodium (1.1 mole equiv.), 1,4-dioxane, 100°C, 2 h; (xviii) PCC (2.6 mole equiv.), 4 Å molecular sieves, CH₂Cl₂, 18°C, 16 h.
With the previously unreported substrate 13 in hand the foreshadowed cyclization studies began. No effort was made to separate the constituent E- and Z-isomers because of the expectation that the derived iminium ions resulting from their reaction with the MacMillan organocatalyst would undergo rapid interconversion and/or cyclize to give the same enantiomeric form of the anticipated product, namely aldehyde 14. In the event, exposure of compound 13 to (5S)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monotrifluoroacetate (MacMillan’s first generation organocatalyst\textsuperscript{13a}) under previously specified conditions\textsuperscript{12,13a} resulted in the smooth production of the anticipated but rather unstable aldehyde 14 which was obtained in 81\% yield. The enantiomeric purity of this cyclization product was established through its reduction, with sodium borohydride, to the corresponding and completely stable alcohol 15 (84\%) which was subjected to chiral HPLC analysis on a Diacel ChiralPak AS-H column and using the previously reported\textsuperscript{8} racemic modification of this alcohol as a reference sample. By such means it was established that compound 15 had been obtained in 74\% ee. Since the enantioselectivity of the conversion 13 $\rightarrow$ 14 may be influenced by the rapidity, or otherwise, of proton loss from C2 (see structure 13) variations in the nature of the counterion associated with the MacMillan catalyst were investigated. Unfortunately, we have thus far been unable to improve the enantioselectivity of this reaction by such means. The assignment of the illustrated absolute configuration to the major enantiomeric form of compound 15 follows from its conversion, using bromine in acetic acid, into the dibrominated and crystalline lactam 16 (65\%) that was then subjected to X-ray analysis (see Figure 1 and Experimental Section).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{compound_16.pdf}
\caption{Anisotropic displacement ellipsoid plot of compound 16. Ellipsoids show 50\% probability levels. Hydrogen atoms are drawn as circles with small radii.}
\end{figure}
With highly enantiomERICALLY enriched samples of alcohol 15 now available by the means just outlined, the completion of the synthesis of (−)-rhazinal (1) was carried out in the same manner as described earlier for the preparation of the racemic material. Thus, the mesylate 17 (95%) derived from the alcohol was subjected to reaction with sodium cyanide in DMPU. The resulting nitrile 18 (91%) was then converted into the corresponding methyl ester 19 (63%) by reaction with KOH in aqueous methanol followed by acidic work up and reaction of the ensuing free-acid with DCC in methanol containing catalytic amounts of DMAP. Vilsmeier–Haack formylation of pyrrole 19 then afforded the aldehyde 20 (78%) which was subjected to electrophilic iodination using molecular iodine in the presence of silver (I) trifluoroacetate and thereby affording iodide 21 (quant.) in a completely regioselective manner. Suzuki–Miyaura cross-coupling of the last compound with the commercially available pinacolate ester of o-aminophenylboronic acid afforded the arylated pyrrole 22 (64%) which engaged in a simple two-step lactamization procedure to deliver synthetic (−)-rhazinal (1) (68%) in ca. 74% ee as judged by chiral HPLC analysis. The optical rotation of this crystalline material \([\alpha]_D^{−233} (c \ 0.1, \text{CHCl}_3)\), lit. \([\alpha]_D^{−187} (c \ 0.2, \text{CHCl}_3)\) is higher than that reported for the natural product (which has only been obtained as an oil) suggesting that the original samples of (−)-rhazinal were not entirely pure. Nevertheless, the spectral data derived from the synthetic material matched those reported previously.

Initial efforts to adapt the work detailed above to the synthesis of (−)-rhazinilam \([−−2]\), and thence (−)-leuconolam \([−−4]\) and (−)-epi-leuconolam \([−−5]\), involved efforts to iodinate the non-formylated pyrrole (±)-19 but this failed to deliver the required C1-halogenated derivative that could be used in the relevant cross-coupling reaction. Consequently, efforts turned to direct decarbonylation of (−)-rhazinal \([−−1]\) as the most obvious alternative for obtaining (−)-rhazinilam \([−−2]\). While decarbonylation is rarely used in total synthesis studies, there are several reagents available for this type of conversion. In the event, we found that simply heating compound (−)-1 with stoichiometric quantities of chlorotris(triphenylphosphine)rhodium (Wilkinson’s “catalyst”) in refluxing 1,4-dioxane afforded (−)-rhazinilam \([−−2]\) in 89% yield and 74% ee as judged by chiral HPLC analysis and optical rotation measurements. The remaining spectral data derived from this material matched those reported for the natural product. The conversion of (−)-rhazinilam \([−−2]\) into targets \([−−4]\) and \([−−5]\) proved equally straightforward and exploited our recently developed method for converting pyrroles into the corresponding maleimides. Thus, treatment of compound (−)-2 with an excess of PCC at 18°C and in the presence of 4 Å molecular sieves afforded a chromatographically separable mixture of (−)-leuconolam \([−−4]\) (28%) and (−)-epi-leuconolam \([−−5]\) (46%). We presume each of compounds (−)-4 and (−)-5 has been obtained in ca. 74% ee but we have not been able to separate them into their constituent enantiomers using the chiral HPLC columns mentioned earlier.

The success of conversion \(13 \rightarrow 14\) described above suggests that this type of process is likely to provide a useful means for the enantioselective assembly of quaternary carbon centres incorporated within polycyclic frameworks. It is also worth noting that the acquisition, in the
enantioselective manner detailed above, of the carboxylic acid precursor to ester 19 constitutes a formal total synthesis of the alkaloid (+)-aspidospermidine.\(^{21}\)

**Experimental Section**

**General Procedures.** General procedures followed during the course of the work detailed herein were similar to those reported elsewhere.\(^8\)

**Synthetic Studies**

\((E)\)- and \((Z)\)-3-Ethyl-6-(1H-pyrrol-1-yl)-2-hexen-1-ol (12). A magnetically stirred solution of ester 11\(^8\) (4.65 g, 21.0 mmol) in THF (150 mL) maintained at –78°C under nitrogen was treated, dropwise, with DIBAL-H (47.0 mL of a 1.0 M solution in hexane). The reaction mixture was allowed to warm to 18°C over \(\text{ca.} 4\) h then treated with ethyl acetate (50 mL). Stirring was continued for 10 minutes then potassium hydrogen sulfate (50 mL of a saturated aqueous solution) was added and the ensuing mixture diluted with Et\(_2\)O (150 mL) and water (50 mL). The separated aqueous phase was extracted with ethyl acetate (3 x 100 mL) and the combined organic phases washed with brine (2 x 80 mL) then dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to give a clear, colorless oil. Subjection of this material to flash chromatography (silica, 1 : 4 v/v ethyl acetate–hexane elution) and concentration of the appropriate fractions (\(R_f\) 0.3) afforded a \(\text{ca.} 1 : 1\) mixture of the \(E\) - and \(Z\)-isomers of the allylic alcohol 12 (3.69 g, 91%) as a clear, colorless oil (Found: M\(^+\), 193.1464, C\(_{12}\)H\(_{19}\)NO requires M\(^+\), 193.1467).\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.66 (2H, m), 6.15 (2H, m), 5.42 (1/2H, t, \(J = 6.9\) Hz), 5.36 (1/2H, t, \(J = 6.9\) Hz), 4.15 (1H, d, \(J = 6.9\) Hz), 4.06 (1H, t, \(J = 6.9\) Hz), 3.87 (2H, m), 2.06 (4H, m), 1.95–1.80 (2H, complex m), 1.32 (1H, s), 0.99 (3H, m); \(^{13}\)C NMR (300 MHz, CDCl\(_3\)) \(\delta\) 144.0, 143.9, 123.5, 123.1, 120.4, 120.3, 107.9, 107.8, 58.9, 49.1, 49.0, 33.2, 30.2, 29.4, 29.2, 27.3, 23.3, 13.6, 12.4; IR \(\nu_{\text{max}}\) (KBr, neat) 3351, 2964, 2933, 2874, 1664, 1500, 1448, 1360, 1281, 1089, 1066, 1006, 724, 618 cm\(^{-1}\); MS (EI, 70 eV) \(m/z\) 193 (M\(^+\), 55%), 176 (40), 162 (35), 94 (37), 81 (100), 80 (92), 67 (43), 53 (52), 41 (55).

\((E)\)- and \((Z)\)-3-Ethyl-6-(1H-pyrrol-1-yl)-2-hexenal (13). Freshly prepared barium manganate\(^{22}\) (1.40 g, 7.25 mmol) in CH\(_2\)Cl\(_2\) (200 mL) maintained at 18°C. After 48 h the reaction mixture was filtered through a pad of Celite\(^\text{TM}\) and the solids thus retained washed with CH\(_2\)Cl\(_2\) (2 x 100 mL). The combined filtrates were then concentrated under reduced pressure to afford a clear, red oil that was immediately subjected to flash-chromatography (silica, 1 : 9 v/v ethyl acetate–hexane elution). Concentration of the appropriate fractions (\(R_f\) 0.3) under reduced pressure then gave a \(\text{ca.} 1 : 1\) mixture of the \(E\)- and \(Z\)-isomers of the title compound 13 (1.05 g, 76%) as a clear, colorless oil (Found: M\(^+\), 191.1312. C\(_{12}\)H\(_{17}\)NO requires M\(^+\), 191.1310).\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.99 (1/2H, d, \(J = 8.1\) Hz), 9.81 (1/2H, d, \(J = 8.1\) Hz), 6.64 (2H, m), 6.16 (2H, m), 5.87 (1/2H, d, \(J = 8.1\) Hz), 3.93 (2H, m), 2.62–2.48 (2H, complex m), 2.28–2.15 (2H, complex m),...
2.05–1.92 (2H, complex m), 1.14 (3/2H, t, \(J = 7.8\) Hz), 1.07 (3/2H, t, \(J = 7.8\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 190.8, 190.7, 168.3, 126.6, 126.4, 120.4, 120.3, 108.4, 108.2, 48.9, 48.7, 34.3, 31.0, 30.6, 28.9, 28.4, 24.5, 14.3, 11.6; IR \(\nu_{\text{max}}\) (KBr, neat) 2969, 2937, 2877, 1671, 1628, 1500, 1460, 1403, 1359, 1282, 1189, 1157, 1125, 1090, 963, 859, 726, 618 cm\(^{-1}\); MS (EI, 70 eV) \(m/z\) 191 (M\(^+\)•, 32%), 163 (75), 162 (100), 149 (40), 134 (63), 118 (40), 80 (32), 41 (25).

**(8R)-8-Ethyl-5,6,7,8-tetrahydro-8-indolizineethanal (14).** A magnetically stirred mixture of (5S)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monotrifluoroacetate \(^{13}a\) (347 mg, 20 mole %) and water (1.8 mL) in THF (30 mL) was cooled to –20°C then treated, dropwise, with a solution of compound \(^{13}\) (1.00 g, 5.23 mmol) in THF (8.0 mL). After addition was complete the reaction mixture was stirred at –20°C for 72 h, quenched by dropwise addition of sodium bicarbonate (20 mL of a saturated aqueous solution) and then warmed to 18°C and treated with Et\(_2\)O (40 mL) and water (10 mL). The separated organic phase was washed with brine (1 x 10 mL) before being dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1 : 19 v/v ethyl acetate–hexane elution) and concentration of the appropriate fractions (\(R_f\) 0.3) afforded the title aldehyde \(^{14}\) (812 mg, 81%) as a clear, colorless and rather unstable oil (Found: M\(^+\)•, 191.1316. C\(_{12}\)H\(_{17}\)NO requires M\(^+\)•, 191.1310). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.64 (1H, t, \(J = 3.3\) Hz), 6.52 (1H, m), 6.14 (1H, m), 5.94 (1H, m), 3.92 (2H, m), 2.60 (2H, m), 2.05–1.80 (6H, complex m), 0.91 (3H, t, \(J = 7.5\) Hz); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 203.8, 133.6, 119.0, 107.5, 104.3, 53.2, 45.1, 36.9, 34.1, 31.2, 19.9, 8.5; IR \(\nu_{\text{max}}\) (KBr, neat) 3098, 2944, 2878, 2737, 1710, 1486, 1462, 1326, 1270, 1204, 1079, 954, 774, 710, 610 cm\(^{-1}\); MS (EI, 70 eV) \(m/z\) 191 (M\(^+\)•, 60%), 163 (48), 162 (68) 149 (40), 148 (100), 134 (85), 133 (52), 118 (40), 80 (32), 41 (25).

**(8R)-8-Ethyl-5,6,7,8-tetrahydro-8-indolizineethanol (15).** Sodium borohydride (238 mg, 6.3 mmol) was added in portions to a magnetically stirred solution of aldehyde \(^{14}\) (0.8 g, 4.19 mmol) and ethanol (0.5 mL) in THF (10 mL) maintained at 18°C under an atmosphere of nitrogen. After 2 h the reaction mixture was treated sequentially with potassium hydrogen sulfate (1.0 mL of a saturated aqueous solution), water (2.0 mL) and ethyl acetate (20 mL). The separated organic phase was dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to give a light-red oil. Subjection of this material to flash chromatography (silica, 1 : 19 v/v ethyl acetate–hexane elution) and concentration of the appropriate fractions (\(R_f\) 0.3) afforded the title compound \(^{15}\) (679 mg, 84%) as a clear, colorless oil, [\(\alpha\)\(_D\)] –11 (c 0.9, CHCl\(_3\)). The spectroscopic data derived from this material matched those reported\(^8\) previously for its racemic modification. Subjection of this material to chiral HPLC analysis [ChiralPak AS–H 250 x 4.6 (i.d.) mm 5-micron particle size analytical column, 5 : 95 v/v isopropanol–hexane elution, flow rate 0.9 mL/min] revealed that this material had been obtained in 70–75% ee: \(R\) 20.2 min (major enantiomer) and 33.4 min (minor enantiomer).

**(3aR,10aR)-9,10-Dibromo-3a-ethyl-2,3,3a,4,5,6-hexahydrofuro[3,2-h]indolizin-8-one (16).** A magnetically stirred solution of alcohol \(^{15}\) (235 mg, 1.2 mmol) in glacial acetic acid (5.0 mL) maintained at 18°C under a nitrogen atmosphere was treated, dropwise, with molecular bromine (428 mg, 2.64 mmol). The ensuing mixture was stirred at 18°C for 2 h then diluted with Et\(_2\)O (60
mL) and potassium carbonate (10 mL of a 10% w/v aqueous solution). The organic phase was separated, washed with potassium carbonate (3 x 10 mL of a 10% w/v aqueous solution) then dried (MgSO₄) filtered and concentrated under reduced pressure. The resultant yellow oil was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) and thus affording two fractions, A and B.

Concentration of fraction A ($R_f$ 0.4) afforded a white solid that was recrystallized (Et₂O–benzene–cyclohexane) to provide the title lactam 16 (159 mg, 65% at 56% conversion) as white needles, mp 149–151°C, [α]₀ –950 (c 0.3, CHCl₃) (Found: M⁺, 362.9465. C₁₂H₁₅Br₂NO₂ requires M⁺, 362.9470). $^1$H NMR (300 MHz, CDCl₃) δ 4.35–4.15 (3H, complex m), 2.90 (1H, tm, $J = 12.3$ Hz), 2.56 (1H, m), 1.92–1.80 (2H, complex m), 1.54–1.25 (5H, complex m), 0.89 (3H, t, $J = 7.5$ Hz); $^{13}$C NMR (75 MHz, CDCl₃) δ 161.9, 141.2, 121.6, 101.7, 66.8, 47.2, 37.5, 35.9, 28.5, 22.8, 20.6, 9.3; IR $ν_{max}$ (KBr, neat) 2953, 2901, 2876, 1708, 1607, 1406, 1288, 1135, 1070, 1040, 997, 944, 746 cm⁻¹; MS (EI, 70 eV) $m/z$ 367, 365 and 363 (M⁺, 7, 14 and 7% respectively), 286 and 284 (both 50), 258 and 256 (97 and 100 respectively).

Concentration of fraction B ($R_f$ 0.3) afforded the starting pyrrole 15 (104 mg, 44% recovery) as a clear, colorless oil and identical, in all respects, with authentic material.

(8R)-8-Ethyl-5,6,7,8-tetrahydro-8-indolizineethanol methanesulfonate (17). The enantiomerically enriched alcohol 15, obtained as described above, was converted into the corresponding mesylate under the same conditions used to prepare the racemic material. In this way the title mesylate 17 (95%) was obtained as a clear, colorless oil that was identical, as judged by $^1$H NMR, $^{13}$C NMR and IR spectroscopic as well as low resolution mass spectrometric analysis, with the racemic modification reported previously.

(8R)-8-Ethyl-5,6,7,8-tetrahydro-8-indolizinepropanenitrile (18). The enantiomerically enriched mesylate 17, obtained as described above, was treated with sodium cyanide in DMPU under the same conditions used in converting the racemic modification of this substrate into the corresponding nitrile. In this way the title nitrile 18 (91%) was obtained as a clear, colorless oil that was identical, as judged by $^1$H NMR, $^{13}$C NMR and IR spectroscopic as well as low resolution mass spectrometric analysis, with the racemic modification reported previously.

(8R)-8-Ethyl-5,6,7,8-tetrahydro-8-indolizinepropanoic acid methyl ester (19). The enantiomerically enriched nitrile 18, obtained as described above, was treated under the same conditions used in converting the racemic modification of this substrate into the corresponding ester. In this way the title compound 19 (63%) was obtained as a clear, colorless oil that was identical, as judged by $^1$H NMR, $^{13}$C NMR and IR spectroscopic as well as low resolution mass spectrometric analysis, with the racemic modification reported previously.

(8R)-8-Ethyl-3-formyl-5,6,7,8-tetrahydro-8-indolizinepropanoic acid methyl ester (20). The enantiomerically enriched ester 19, obtained as described above, was subjected to Vilsmeier–Haack formylation under the same conditions used in converting the racemic modification of this substrate into the corresponding C3-aldehyde. In this way compound 20 (78%) was obtained as a clear, colorless oil that was identical, as judged by $^1$H NMR, $^{13}$C NMR and IR spectroscopic
as well as low resolution mass spectrometric analysis, with the racemic modification reported previously.\(^8\)

\((8R)-8\text{-Ethyl-3-formyl-5,6,7,8-tetrahydro-1-iodo-8-indolizinepropanoic acid methyl ester}\) (21). The enantiomerically enriched ester 20, obtained as described above, was treated under the same iodination conditions\(^8\) used in converting the racemic modification of this substrate into the corresponding C1-iodide. In this way the \textit{title compound} 21 (quant.) was obtained as a clear, colorless oil that was identical, as judged by \(^1\)H NMR, \(^{13}\)C NMR and IR spectroscopic as well as low resolution mass spectrometric analysis, with the racemic modification reported previously.\(^8\)

\((8R)-1-(2'-\text{Aminophenyl})-8\text{-ethyl-3-formyl-5,6,7,8-tetrahydro-8-indolizinepropanoic acid methyl ester}\) (22). The enantiomerically enriched iodopyrrole 21, obtained as described above, was subjected to Suzuki–Miyaura cross-coupling with commercially available 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine under the same conditions\(^8\) used in converting the racemic modification of this substrate into the corresponding C1-arylated material. In this way the \textit{title compound} 22 (64\%) was obtained as a clear, colorless oil that was identical, as judged by \(^1\)H NMR, \(^{13}\)C NMR and IR spectroscopic as well as low resolution mass spectrometric analysis, with the racemic modification reported previously.\(^8\)

\textit{\((–)-Rhazinal\)} [(–)-1]. The enantiomerically enriched amino-ester 22, obtained as described above, was subjected to the same saponification/lactamisation sequence\(^8\) used in converting the racemic modification of this substrate into \((±\)-rhazinal. In this way the title compound \((–)-1\) (68\%) was obtained as a white crystalline solid, mp 229–232°C, \([\alpha]_D–233\ (c\ 0.1,\ \text{CHCl}_3)\) \{lit.\} \([\alpha]_D–187\ (c\ 0.2,\ \text{CHCl}_3)\}. The spectroscopic data derived from this material matched those reported\(^8\) previously for its racemic modification. Subjection of this material to chiral HPLC analysis [ChiralPak OD 250 x 4.6 (i.d.) mm analytical column, 1 : 4 v/v isopropanol–hexane elution, flow rate 1.0 mL/min] revealed that this material had been obtained in ca. 74\% ee: \(R\); 12.7 min (major enantiomer) and 21.2 min (minor enantiomer).

\textit{\((–)-Rhazinilam\)} [(–)-2]. A magnetically stirred solution of \((–)-\text{rhazinal}\) [(–)-1] (20 mg, 0.06 mmol), in degassed 1,4-dioxane (10 mL) was treated with Wilkinson’s “catalyst” [chlorotris(triphenylphosphine)rhodium (I)] (68 mg, 0.07 mmol) and the ensuing mixture heated at 150°C for 2 h then cooled to ca. 18°C and concentrated under reduced pressure to ca. one third of its original volume. The material thus obtained was diluted with ethanol (8 mL) and the resulting mixture filtered through a plug of Celite™ and the solids thus retained were washed with ethanol (2 mL). The combined filtrates were concentrated under reduced pressure and the resulting yellow oil subjected to flash chromatography (silica, Et\(_2\)O elution). Concentration of the appropriate fractions (\(R_f\) 0.4) afforded the title compound 2 (16 mg, 89\%) as a white crystalline solid, mp 210–212°C (lit.\(^6\) mp 213–215°C), \([\alpha]_D–294\ (c\ 1.0,\ \text{CHCl}_3)\) \{lit.\} \([\alpha]_D–421\ (c\ 1.0,\ \text{CHCl}_3)\}. The spectroscopic data derived from this material matched those reported\(^6\) previously for its racemic modification. Subjection of this material to chiral HPLC analysis [ChiralPak OD 250 x 4.6 (i.d.) mm 5-micron particle size analytical column, 1 : 9 v/v isopropanol–hexane elution, flow rate 1.0 mL/min] revealed that this material had been obtained in 70–75\% ee: \(R\); 11.3 min (major enantiomer) and 14.9 min (minor enantiomer).
(–)-Leuconolam [(–)-(4)] and (+)-epi-leuconolam [(+)-(5)]. A magnetically stirred solution of enantiomerically enriched rhazinilam [(–)-(2)] (68 mg, 0.23 mmol), powdered 4Å molecular sieves (215 mg) and PCC (130 mg, 0.60 mmol) in anhydrous CH₂Cl₂ (10 mL) was maintained at 18°C for 16 h, diluted with 10 : 2 : 1 v/v/v ethyl acetate–methanol–water (30 mL) then filtered through a small pad of Celite™ that was washed with 10 : 2 : 1 v/v/v ethyl acetate–methanol–water (10 mL). The combined filtrates were concentrated under reduced pressure to yield an orange residue that was subjected to flash chromatography (silica, 10 : 2 : 1 v/v/v ethyl acetate–methanol–water elution) and thus affording two fractions, A and B.

Concentration of fraction A (Rᵣ 0.3) afforded lactam (–)-(4) (21 mg, 28%) as an amorphous solid, mp 261–265°C (lit.¹⁰ mp 263–264°C), [α]D –300 (c 0.3, methanol) {lit.²³ [α]D –519 (c 0.25, methanol)} (Found: M⁺, 326.1632. C₁₉H₂₂N₂O₃ requires M⁺, 326.1630).

¹H NMR (300 MHz, CDCl₃) δ 7.88 (1H, d, J = 7.2 Hz), 7.51 (1H, broad s), 7.35 (2H, m), 7.18 (1H, d, J = 7.5 Hz), 5.77 (1H, s), 4.76 (1H, broad s), 4.00 (1H, d, J = 11.1 Hz), 2.92 (1H, m), 2.05 (2H, m), 1.85–1.05 (8H, complex m), 0.55 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 177.8, 166.7, 156.0, 135.2, 133.5, 129.9, 129.7, 128.6, 127.2, 126.5, 94.0, 45.3, 35.7, 32.5, 27.9, 25.8, 24.5, 20.1, 7.4; IR νmax (KBr) 3222, 2943, 1682, 1435, 1378, 1305, 1025, 1006, 898, 620 cm⁻¹; MS (EI, 70 eV) m/z 326 (M⁺, 100%), 308 (15), 145 (60).

Concentration of fraction B (Rᵣ 0.8) afforded lactam (+)-(5) (34 mg, 46%) as white needles, mp 67–69°C, [α]D +147 (c 0.7, CHCl₃) {lit.¹⁰ [α]D +30 (c 0.65, CHCl₃)} (Found: M⁺, 326.1636. C₁₉H₂₂N₂O₃ requires M⁺, 326.1630).

¹H NMR (300 MHz, CDCl₃) δ 8.16 (1H, d, J = 7.8 Hz), 7.45 (1H, d, J = 7.8 Hz), 7.33 (1H, t, J = 7.8 Hz), 7.11 (1H, t, J = 7.8 Hz), 6.21 (1H, s), 4.50 (1H, m), 3.27–3.00 (2H, complex m), 2.62 (1H, m), 2.05 (2H, m), 1.85–0.75 (8H, complex m), 0.75 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 176.3, 173.8, 164.5, 148.9, 131.8, 121.8, 118.4, 118.2, 116.2, 93.9, 44.8, 37.2, 34.4, 33.4, 30.7, 26.3, 17.0, 8.5; IR νmax (KBr) 2953, 2926, 2881, 1690, 1598, 1457, 1372, 1357, 1294, 1167, 1138, 1080, 919, 872, 759, 732 cm⁻¹; MS (EI, 70 eV) m/z 326 (M⁺, <1%), 308 (100), 280 (33), 279 (80), 251 (50), 156 (28).

Crystallographic Studies
Crystal data (for compound 16). C₁₂H₁₅Br₂NO₂, M = 365.06, T = 200(1) K, orthorhombic, space group P₂₁₂₁₂₁, Z = 4, a = 6.5483(1), b = 11.3888(2), c = 17.3544(3) Å, V = 1294.24(4) Å³, Dᵣ = 1.873 Mg.m⁻³, 2966 unique data (2θmax = 55°), 2598 with I > 3.0σ(I); R = 0.0170, Rw = 0.0178, S = 1.1185.

Structure Determination. Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO package.²⁵ Structure solution was by direct methods (SIR92).²⁵ The structure of compound 16 was refined using the CRYSTALS program package.²⁶ The absolute configuration was established by refinement of the Flack parameter, final value –0.02(1). Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC reference number 266300). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing...
data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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References and Footnotes

9. Compounds (−)−2, (−)−4 and (+)−5, at least, are artifacts of the isolation processes involved and the natural precursor is the unstable 5,21-dihydrorhazinilam.4,10 It has recently been suggested that compounds (−)−4 and/or (+)−5 are precursors to the novel tetracyclic dihydroindole alkaloid mersicarpine (Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. Tetrahedron Lett. 2004, 45, 5995).