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

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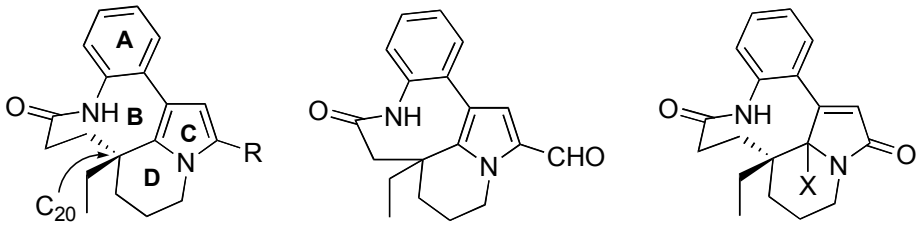
Dedicated to Professor Jim Coxon on the occasion of his 65th birthday

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 described[5] 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. reported[7] a third synthesis, of racemic material, in 2001 whilst we have recently disclosed[8] the first total synthesis of (±)-rhazinal [(±)-**1**] as well as its (non-natural) B-nor-congener (±)-**3** (which also acts as a spindle toxin). Herein we describe a modification of our approach[8] 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.



(–)-**1** R = CHO
(–)-**2** R = H

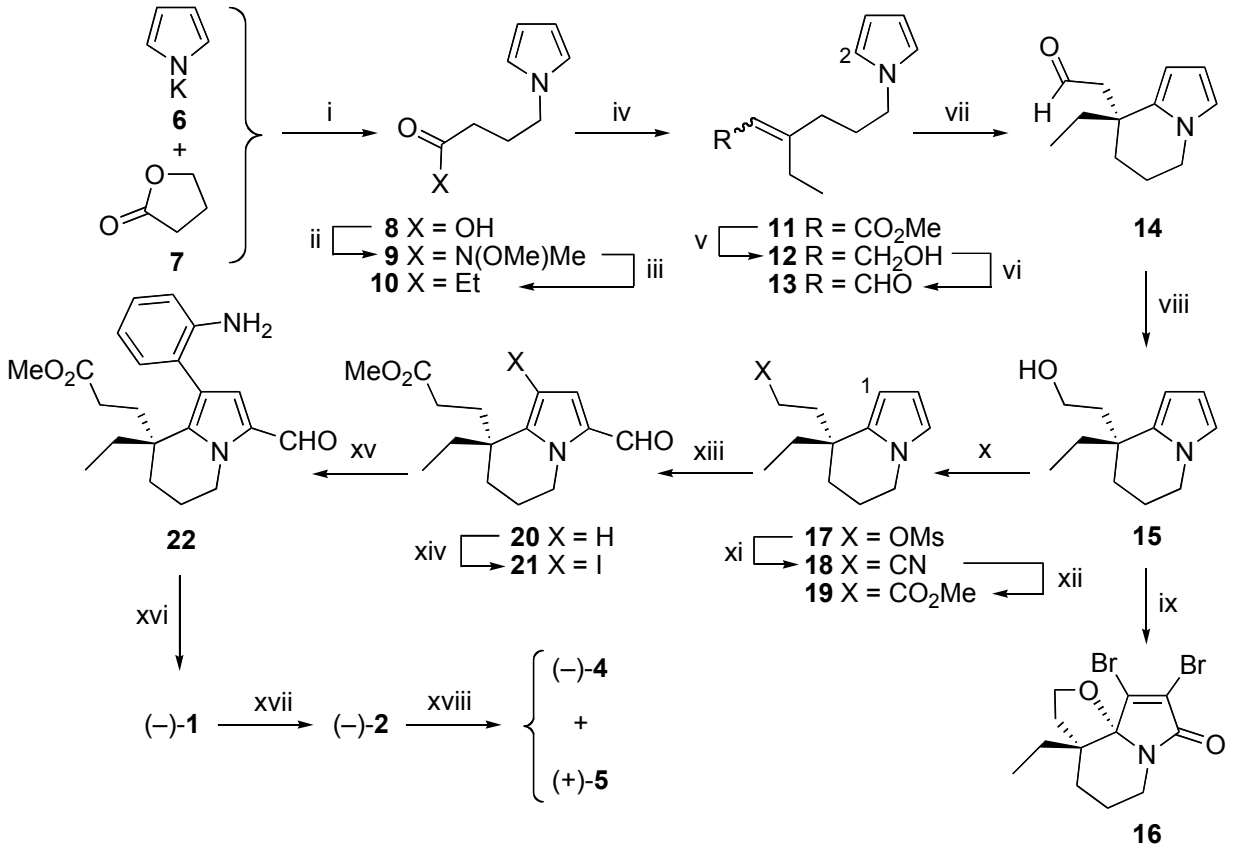
(±)-**3**

(–)-**4** X = β-OH
(+)-**5** X = α-OH

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 annulation 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 laboratories[12] have suggested that MacMillan's organocatalysts[13] 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**[8] in 60–90% yield. The latter species was converted into the corresponding Weinreb amide **9**[8] (87%), using a modification[15] 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 reported[8] 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**[8] 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.), 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) DIBAL-H (2.2 mole equiv.), THF, –78 to 18°C, 4 h; (vi) $BaMnO_4$ (8 mole equiv.), CH_2Cl_2, 18°C, 48 h; (vii) (5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monotrifluoroacetate (20 mole %), ca. 20 : 1 v/v THF–water, –20°C, 72 h; (viii) $NaBH_4$ (1.5 mole equiv.), 20 : 1 v/v THF–ethanol, 18°C, 2 h; (ix) Br_2 (2.2 mole equiv.), AcOH, 18°C, 2 h; (x) $MeSO_2Cl$ (2 mole equiv.), Et_3N (2 mole equiv.), CH_2Cl_2, 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 H_2O–MeOH, reflux, 16 h then aq. HCl; (b) DCC (2.2 mole equiv.), DMAP (ca. 10 mole %), 3 : 1 v/v CH_2Cl_2–MeOH, 18°C, 3 h; (xiii) DMF (12 mole equiv.), $POCl_3$ (1.1 mole equiv.), Et_2O, 0 to 18°C, 3.5 h; (xiv) I_2 (1.1 mole equiv.), $AgOCOCF_3$ (1.1 mole equiv.), $CHCl_3$, 0 to 18°C, 4.5 h; (xv) 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine (1 mole equiv.), $Pd(PPh_3)_4$ (cat.), 1 : 4 v/v MeOH–toluene, 2 M aq. Na_2CO_3 (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, CH_2Cl_2, 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 (5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monotrifluoroacetate (MacMillan's first generation organocatalyst[13a]) under previously specified conditions[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[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** → **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).

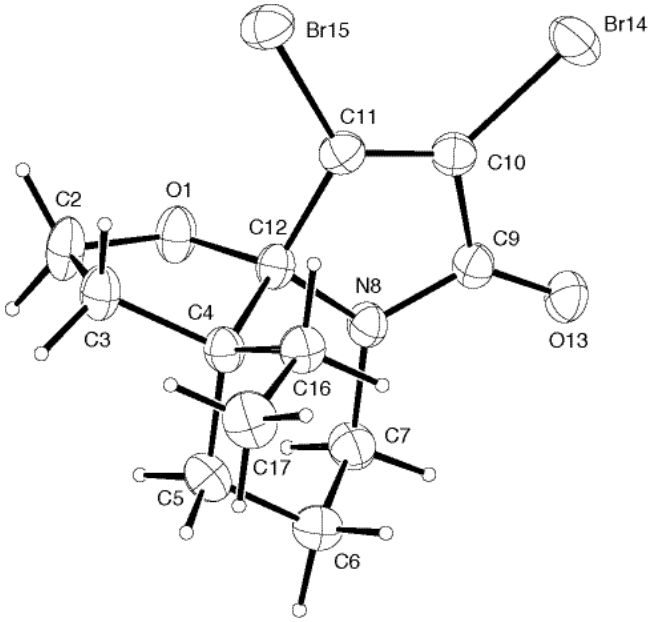


Figure 1. Anisotropic displacement ellipsoid plot of compound **16**. Ellipsoids show 50% probability levels. Hydrogen atoms are drawn as circles with small radii.

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[8] 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[18] 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[8] 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, $CHCl_3$), lit.[1] $[\alpha]_D$ –187 (*c* 0.2, $CHCl_3$)} is higher than that reported for the natural product (which has only been obtained as an oil) suggesting that the original samples[1] of (–)-rhazinal were not entirely pure. Nevertheless, the spectral data derived from the synthetic material matched those reported[1,8] 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**[8] 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.[19] 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[10] 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.[20] 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** → **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-(1*H*-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 *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_2O (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 *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: $M^{+\bullet}$, 193.1464, $C_{12}H_{19}NO$ requires $M^{+\bullet}$, 193.1467). ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ν_{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 ($M^{+\bullet}$, 55%), 176 (40), 162 (35), 94 (37), 81 (100), 80 (92), 67 (43), 53 (52), 41 (55).

(*E*)- and (*Z*)-3-Ethyl-6-(1*H*-pyrrol-1-yl)-2-hexenal (13). Freshly prepared barium manganate[22] (15.0 g, 58.5 mmol) was slowly added to a magnetically stirred solution of compound **12** (1.40 g, 7.25 mmol) in CH_2Cl_2 (200 mL) maintained at 18°C. After 48 h the reaction mixture was filtered through a pad of Celite™ and the solids thus retained washed with CH_2Cl_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 *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: $M^{+\bullet}$, 191.1312. $C_{12}H_{17}NO$ requires $M^{+\bullet}$, 191.1310). ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ν_{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 ($M^{+\bullet}$, 32%), 163 (75) 162 (100), 148 (45), 134 (63), 81(82).

(8*R*)-8-Ethyl-5,6,7,8-tetrahydro-8-indolizineethanal (14). A magnetically stirred mixture of (5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monotrifluoroacetate[13a] (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_2O (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: $M^{+\bullet}$, 191.1316. $C_{12}H_{17}NO$ requires $M^{+\bullet}$, 191.1310). ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ν_{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 ($M^{+\bullet}$, 60%), 163 (48), 162 (68) 149 (40), 148 (100), 134 (85), 133 (52), 118 (40), 80 (32), 41 (25).

(8*R*)-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 : 4 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_t 20.2 min (major enantiomer) and 33.4 min (minor enantiomer).

(3a*R*,10a*R*)-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_2O (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 ($MgSO_4$) 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 (Et_2O–benzene–cyclohexane) to provide the *title lactam* ***16*** (159 mg, 65% at 56% conversion) as white needles, mp 149–151°C, $[\alpha]_D$ –950 (*c* 0.3, $CHCl_3$) (Found: $M^{+\bullet}$, 362.9465. $C_{12}H_{15}{}^{79}Br_2NO_2$ requires $M^{+\bullet}$, 362.9470). ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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, 1024, 997, 944, 746 cm^{-1}; MS (EI, 70 eV) *m/z* 367, 365 and 363 ($M^{+\bullet}$, 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.

(8*R*)-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[8] 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.[8]

(8*R*)-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[8] 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.[8]

(8*R*)-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[8] 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.[8]

(8*R*)-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[8] 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]

(8*R*)-8-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 *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]

(8*R*)-1-(2'-Aminophenyl)-8-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 *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]

(–)-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, $CHCl_3$) {lit.[1] $[\alpha]_D$ –187 (*c* 0.2, $CHCl_3$)}. 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_t 12.7 min (major enantiomer) and 21.2 min (minor enantiomer).

(–)-Rhazinilam [(–)-2]. A magnetically stirred solution of (–)-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_2O 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, $CHCl_3$) {lit.[2] $[\alpha]_D$ –421 (*c* 1.0, $CHCl_3$)}. 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_t 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 CH_2Cl_2 (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 (R_f 0.3) afforded lactam (–)-**4** (21 mg, 28%) as an amorphous solid, mp 261–265°C (lit.[10] mp 263–264°C), $[\alpha]_D$ –300 (*c* 0.3, methanol) {lit.[23] $[\alpha]_D$ –519 (*c* 0.25, methanol)} (Found: $M^{+\bullet}$, 326.1632. $C_{19}H_{22}N_2O_3$ requires $M^{+\bullet}$, 326.1630). ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 ν_{max} (KBr) 3222, 2943, 1682, 1435, 1378, 1305, 1025, 1006, 898, 620 cm^{-1}; MS (EI, 70 eV) *m/z* 326 ($M^{+\bullet}$, 100%), 308 (15), 145 (60).

Concentration of fraction B (R_f 0.8) afforded lactam (+)-**5** (34 mg, 46%) as white needles, mp 67–69°C, $[\alpha]_D$ +147 (*c* 0.7, $CHCl_3$) {lit.[10] $[\alpha]_D$ +30 (*c* 0.65, $CHCl_3$)} (Found: $M^{+\bullet}$, 326.1636. $C_{19}H_{22}N_2O_3$ requires $M^{+\bullet}$, 326.1630). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, d, *J* = 7.8 Hz), 7.45 (1H, d, *J* = 7.8 Hz), 7.33 (1H, t, *J* = 7.8Hz), 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 173.8, 164.5, 148.9, 131.8, 124.6, 123.7, 121.8, 118.4, 116.2, 93.9, 44.8, 37.2, 34.4, 33.4, 30.7, 26.3, 17.0, 8.5; IR ν_{max} (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 ($M^{+\bullet}$, <1%), 308 (100), 280 (33), 279 (80), 251 (50), 156 (28).

Crystallographic Studies

Crystal data (for compound 16). $C_{12}H_{15}Br_2NO_2$, *M* = 365.06, *T* = 200(1) K, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 6.5483(1), *b* = 11.3888(2), *c* = 17.3544(3) Å, *V* = 1294.24(4) $Å^3$, D_x = 1.873 $Mg.m^{-3}$, 2966 unique data ($2\theta_{max}$ = 55°), 2598 with $I > 3.0\sigma(I)$; *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.[24] 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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