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PAPER

Enantioselective approach to functionalized quinolizidines: synthesis of (+)-julandine and (+)-cryptopleurine†

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An efficient synthesis of functionalized quinolizidines was developed from an enantiomerically enriched γ-nitroketone, which is easily prepared by an organocatalytic ketone–nitroalkene Michael addition. Oxidative ring expansion of the nitroketone followed by reductive ring-opening leads to a suitably functionalized nitrodiol which is an intermediate to the title compounds.

Introduction

The quinolizidine motif is a prominent structural unit in numerous alkaloids.[1] The structurally related phenanthroquinolizidine alkaloids[2] are also well known and these have attracted considerable interest due to their anticancer,[3] antiviral,[4] amoebicidal[5] and anti-inflammatory[6] activities. The synthesis of quinolizidines,[7] aryl-fused quinolizidines[8] and phenanthroquinolizidines[9] has therefore continued to engage synthetic chemists over the years. Herein, we describe a stereoselective synthesis of the secophenanthroquinolizidine alkaloid (+)-julandine (**1**),[10] an antimicrobial agent,[11] and the corresponding phenanthroquinolizidine (+)-cryptopleurine (**2**),[12] the enantiomer of which has antiviral,[13] amoebicidal[14] and anticancer[3] activity (Fig. 1). The synthesis of **1** and **2** is based on a γ-nitroketone precursor which is readily prepared by an organocatalytic ketone–nitroalkene Michael addition.

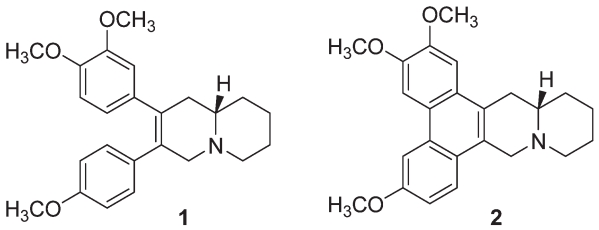

Fig. 1 (+)-Julandine (**1**) and (+)-cryptopleurine (**2**).

Results and discussion

The interest in quinolizidines is an outcome of our ongoing studies on the development and application of the organocatalytic ketone–nitroalkene Michael addition reaction.[15] This reaction has been extensively studied and although the development of new catalysts for the process continues at a significant pace, further application of the nitroketone Michael adducts has progressed relatively slowly.[16] It was therefore decided to examine the utility of a suitable γ-nitroketone in a general approach to the quinolizidine motif. The initial target of the investigation was the naturally occurring (+)-julandine, since only one enantioselective synthesis of the unnatural (–)-julandine has been reported.[10a] In addition, cryptopleurine can be obtained in one step by the oxidative cyclization of julandine[10e] and hence a route to julandine would also establish access to cryptopleurine.

Retrosynthetically, the 2,3-diaryl quinolizidine motif of julandine may be accessible by aryl cross-coupling from a 7-aryl indolizidinone such as A (Scheme 1) which derives from the functionalized piperidine B. This piperidine intermediate can be made from the reductive cyclization of the nitroketone C which can be obtained by the reductive opening of the lactone D. Ultimately, lactone D derives from a Baeyer–Villiger oxidation of the corresponding γ-nitroketone which leads us to the organocatalytic, ketone–nitroalkene Michael addition of an appropriate cyclic ketone and nitroalkene.

Accordingly, the organocatalytic Michael addition of cyclohexane-1,4-dione monoethylene ketal and 4-methoxy-β-nitrostyrene employing a chiral pyrrolidine-based triamine catalyst[15a,16j] provided the requisite γ-nitroketone **3** in good yield and stereoselectivity (er = 96 : 4, dr >19 : 1, Scheme 2). Baeyer–Villiger oxidation of **3** provided the corresponding lactone **4** which was reduced with sodium borohydride to the nitrodiol **5** (92%, 2 steps). The primary alcohol in **5** was then selectively acetylated to provide the corresponding acetate **6** (94%) which was converted to the nitroketone **7** by deketalization with iodine in acetone (90%).[17]

With the nitroketone **7** in hand, the construction of the quinolizidine framework was initiated. This process involved the preparation of a suitably substituted piperidine from **7** and then

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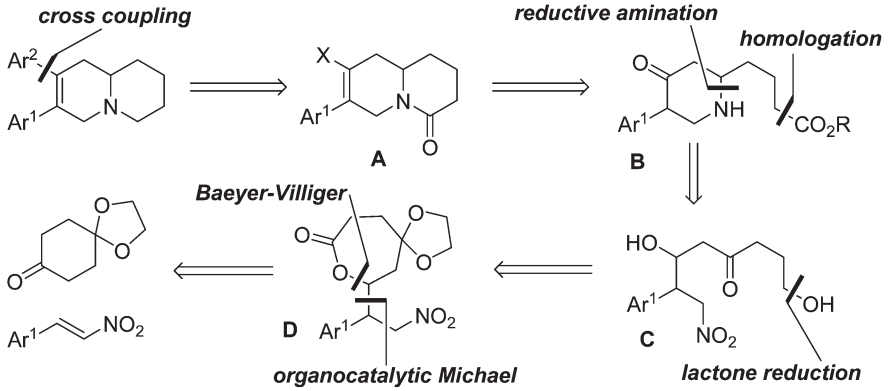
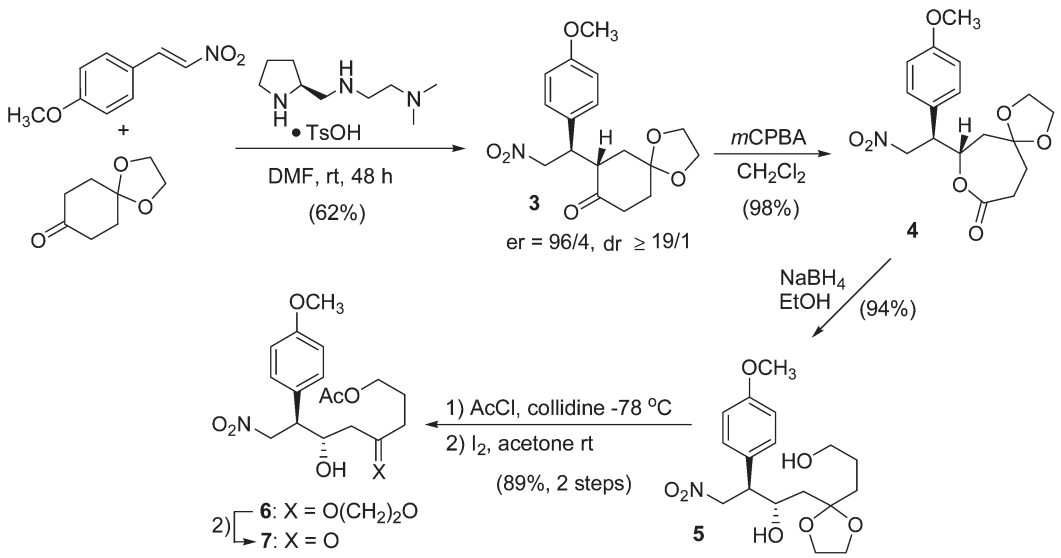


Scheme 1 Retrosynthetic analysis of the diaryl quinolizidine motif.



Scheme 2 Baeyer–Villiger oxidation of **3** and synthesis of nitroketone **7**.

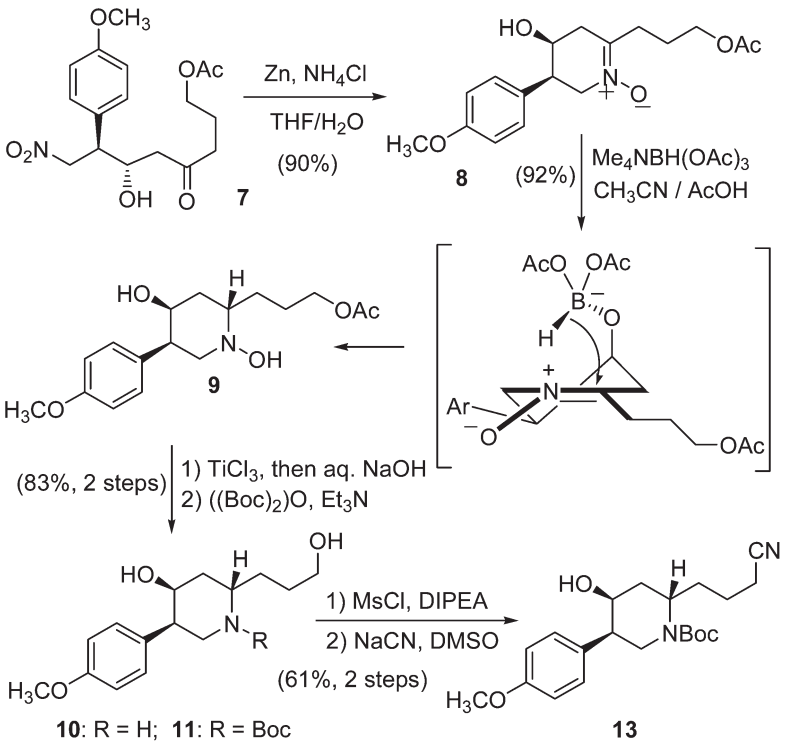
construction of the quinolizidine by cyclization. Reduction of the nitroketone with zinc in aq. ammonium chloride provided the nitrone **8**, presumably from the hydroxylamine derived from **7**. Reduction of the nitrone with tetramethylammonium triacetoxyborohydride provided the *N*-hydroxy piperidine **9** as a single diastereomer. The stereoselectivity of this reduction is presumably due to an intramolecular, hydroxyl-directed reduction of **8** (Scheme 3). Reduction of the N–O bond in **9** ($TiCl_3$ followed by aqueous NaOH[18]) provided the corresponding amino alcohol **10** which was protected to provide **11**.[19] Conversion of **11** into the quinolizidine motif required a one carbon homologation. This was achieved by conversion to the mesylate **12** and subsequent cyanation to provide **13**.

Conversion of **13** to the corresponding quinolizidinone **14** (Scheme 4) could be accomplished by hydrolysis of the nitrile to the acid, esterification with concommitant removal of the Boc group and subsequent cyclization of the aminoester (63% overall). The overall conversion of **13** to **14** could also be achieved in one step (30%) by treatment of **13** with HCl in methanol followed by basification of the crude product. However, the multi-step procedure proceeds with higher overall yield (63%) and is therefore the method of choice. Oxidation of **14** provided the keto lactam **15** which was then converted to the enol triflate **16**. This is the key intermediate for the target alkaloids.

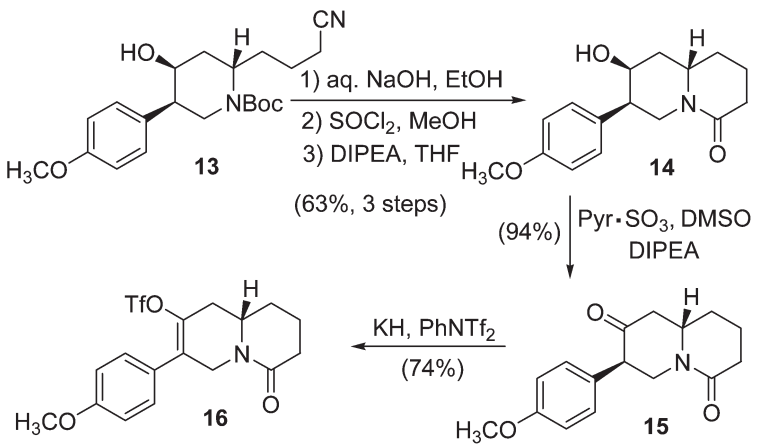
The conversion of **16** to (+)-julandine (**1**) was achieved by a Suzuki cross-coupling with 3,5-dimethoxyphenyl boronic acid to generate the lactam **17** followed by reduction with LAH to give **1** (73%, 2 steps). As expected, oxidative cyclization of **1** with thallium trifluoroacetate[10e] provided (+)-cryptopleurine (**2**, 62%, Scheme 5).

Conclusion

In conclusion, an efficient synthesis of functionalized quinolizidines was developed from a simple γ-nitroketone starting material which is readily available from the organocatalytic ketone–nitroalkene Michael addition reaction. The methodology was applied in the first total synthesis of the natural enantiomer of the diaryl quinolizidine alkaloid (+)-julandine and the structurally related phenanthroquinolizidine alkaloid (+)-cryptopleurine.



Scheme 3 Stereoselective reduction of nitrone **8** and synthesis of piperidine **13**.



Scheme 4 Synthesis of the quinolizidine framework from **13**.

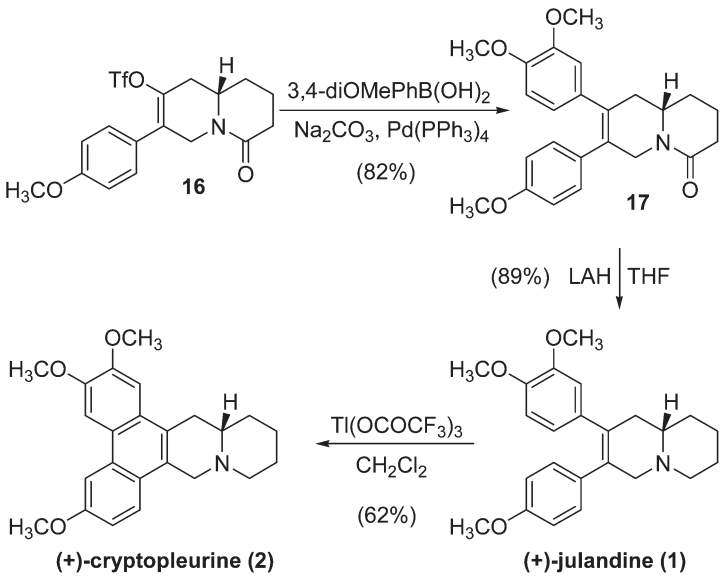
The synthetic strategy should be particularly amenable to the preparation of focused libraries of analogs of these alkaloids by judicious selection of the nitroalkene and the aryl component in the cross-coupling step. We are currently examining this possibility as well as other synthetic applications of nitroketones and nitrones related to **3** and **8** respectively.

Experimental section

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230–400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature.

(7*S*)-7-[(1*R*)-1-(4-Methoxyphenyl)-2-nitroethyl]-1,4-dioxaspiro-[4.5]decan-8-one (3)

To a solution of 1,4-cyclohexanedione monoethylene ketal (13.0 g, 83.7 mmol), N^1,N^1-dimethyl-N^2-(((*S*)-pyrrolidin-2-yl)-methyl)ethane-1,2-diamine[15a] (572 mg, 3.34 mmol) and *p*-toluene sulfonic acid monohydrate (634 mg, 3.34 mol) in



Scheme 5 Synthesis of (+)-julandine (**1**) and its conversion to (+)-cryptopleurine (**2**).

DMF (30 mL) was added 4-methoxy-β-nitrostyrene (3.00 g, 16.7 mmol) and the resulting solution was stirred at ambient temperature for 48 h. Ethyl acetate (100 mL) was added and the solution washed with water, aq. HCl (3N), dried (Na_2SO_4) and concentrated. The residue obtained was purified by flash chromatography on silica gel to provide 4.6 g of a solid. This was dissolved in ethyl acetate (23 mL) and precipitated by addition of hexanes (70 mL). The procedure was repeated once to provide 3.5 g (62%) of **3** with 96% ee. In repeated runs, **3** was obtained in 90–96% ee. Spectroscopic data for **3** is in agreement with that reported in the literature.[16j]

(*S*)-7-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro-[4.6]undecan-9-one (4)

To a solution of the nitroketone **3** (3.1 g, 9.24 mol) in anhydrous dichloromethane (60 mL) at ambient temperature, was added solid sodium phosphate heptahydrate (3.21 g, 12.0 mol) followed by *m*-chloro perbenzoic acid (~77%, 4.94 g, 28.7 mmol). The resulting white slurry was stirred vigorously for 16 h. Dichloromethane (100 mL) was added and the solution was washed with 5% aq. NaOH (2 × 60 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 3.20 g, (98%) of **4** as a white, solid foam. This material was pure by ^{1}H NMR (500 MHz) and was used in the next step without purification. Spectroscopic data for **4** is in agreement with that reported in the literature.[16j] $[\alpha]_D^{23}$ = +58.3 (*c* 1, $CHCl_3$).

(2*S*,3*R*)-1-(2-(3-Hydroxypropyl)-1,3-dioxolan-2-yl)-3-(4-methoxyphenyl)-4-nitrobutan-2-ol (5)

To a solution of the lactone **4** (2.85 g, 8.11 mmol) in ethanol (30 mL), was added sodium borohydride (0.46 g, 12.1 mmol). The mixture was stirred at room temperature for 3 h, then cooled to 0 °C and the solution was acidified (pH ~ 5) with aq. HCl (0.5 M). The acidic solution was extracted with EtOAc (2 × 50 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to provide 2.7 g (94%) of the diol **5** as a pale yellow gum. This material was pure by ^{1}H NMR and was used in the next step without purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc).

IR (neat): 3493, 2960, 2837, 1550, 1511, 1378, 1248, 1059 1028, 829 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, *J* = 8.6, Ar*H*), 6.85 (d, 2H, *J* = 8.6, Ar*H*), 5.06–5.02 (dd, 1H, *J* = 5.2, 12.7, CH_2NO$_2$), 4.61–4.57 (dd, 1H, *J* = 9.7, 12.7, CH_2NO$_2$), 4.05–3.99 (m, 1H, Ar–C*H*), 3.99–3.93 (m, 5H, CHO*H*, OCH_2CH_2O), 3.78 (s, 3H, OCH_3), 3.55 (t, 2H, *J* = 6.2, CH_2OH), 3.42–3.38 (td, 1H, *J* = 5.2, 9.5, C*H*OH), 1.70–1.57 (m, 4H, *CH*$_2$CHOH, CH_2C$_{ketal}$), 1.50–1.39 (m, 2H, CH_2CH$_2$OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2 (Ar*C*-OCH$_3$), 129.3 (ArC_{ipso}), 129.1 (2 × Ar*C*), 114.5 (2 × Ar*C*), 111.8 (O*C*O), 78.5 (*C*H$_2$NO$_2$), 70.1 (*C*HOH), 64.9 (O*C*H$_2$CH$_2$O), 64.6 (OCH$_2$*C*H$_2$O), 62.6 (*C*H$_2$OH), 55.3 (ArO*C*H$_3$), 50.3 (HO–CH*C*H$_2$), 40.3 (Ar–*C*HCH$_2$), 33.3 (CH$_2$*C*CH$_2$), 26.7 (*C*H$_2$CH$_2$OH); MS (API-ES): *m*/*z* 378 (M + Na); MALDI-TOF MS: 378.1611 (378.1529 calc. for $C_{17}H_{25}NO_7Na$ (M + Na)); $[\alpha]_D^{23}$ = + 40.5 (*c* 1, $CHCl_3$).

3-(2-((2*S*,3*R*)-2-Hydroxy-3-(4-methoxyphenyl)-4-nitrobutyl)-1,3-dioxolan-2-yl)propyl acetate (6)

A solution of the diol **5** (2.1 g, 5.9 mmol) in dry dichloromethane (35 mL) was cooled to −78 °C and acetyl chloride (0.50 mL, 7.09 mmol) and collidine (1.43 mL, 11.8 mmol) were added. The solution was stirred at −78 °C for 4 h and then diluted with dichloromethane (50 mL). The resulting solution was warmed to ambient temperature and washed with aq. HCl (0.5 M, 2 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 2.2 g (94%) of the acetate **6** as a pale yellow gum. This material was pure by ^{1}H NMR and was used in the next step without purification. An analytical sample was

obtained by flash chromatography on silica gel (EtOAc–hexanes, 6 : 4).

IR (neat): 3496, 2961, 1731, 1550, 1513, 1375, 1242, 1141, 1032, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, 2H, J = 8.7, Ar*H*), 6.85 (d, 2H, J = 8.7, Ar*H*), 5.06–5.02 (dd, 1H, J = 5.3, 12.7, CH_2NO$_2$), 4.61–4.57 (dd, 1H, J = 9.6, 12.7, CH_2NO$_2$), 3.99–3.92 (m, 8H, Ar–C*H*, CHO*H*, OCH_2CH_2O, CH_2OAc) 3.78 (s, 3H, ArOCH_3), 3.42–3.38 (td, 1H, J = 5.3, 9.5, C*H*OH), 2.03 (s, 3H, COCH_3) 1.67–1.64 (m, 3H, CHCH_2C$_{ketal}$, C$_{ketal}$CH_2), 1.50–1.46 (m, 3H, CHCH_2C$_{ketal}$, CH_2CH$_2$OAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6 (*C*(O)-CH$_3$), 159.7 (Ar*C*–OCH$_3$), 129.8 (Ar*C*$_{ipso}$), 129.6 (2 × Ar*C*), 115.0 (2 × Ar*C*), 112.0 (O*C*O), 79.0 (*C*H$_2$NO$_2$), 70.6 (*C*H$_2$OAc), 65.5 (*C*HOH) 65.2 (O*C*H$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 55.8 (O*C*H$_3$), 50.8 (CH*C*H$_2$C$_{ketal}$) 40.9 (Ar–*C*H), 33.8 (C$_{ketal}$*C*H$_2$CH$_2$), 23.5 (OC(O)*C*H$_3$) 21.5 (*C*H$_2$CH$_2$O); MS (API-ES, pos.): *m*/*z* 420.4 (M + Na); MALDI-TOF MS: 420.1704 (420.1634 calc. for $C_{19}H_{27}NO_8Na$ (M + Na)); $[\alpha]_D^{23}$ = +23.6 (*c* 0.5, $CHCl_3$).

(6*S*,7*R*)-6-Hydroxy-7-(4-methoxyphenyl)-8-nitro-4-oxooctyl acetate (7)

A solution of the ketal **6** (2.2 g, 5.5 mmol) and iodine (0.07 g, 0.55 mmol) in acetone (20 mL) was stirred at ambient temperature for 1 h. The acetone was removed under reduced pressure and the residue was diluted with dichloromethane. The resulting solution was washed successively with aqueous $Na_2S_2O_3$ (5% w/v, 2 × 25 mL) and brine (1 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide 1.85 g (95%) of the nitroketone **7** as a yellow solid. This material was pure by ^1H NMR and was used in the next step without purification. Mp: 77–80 °C; IR (neat): 3402, 2955, 1735, 1708, 1548, 1380, 1253, 1227, 1111, 1036, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.09 (d, 2H, J = 8.7, Ar*H*), 6.87 (d, 2H, J = 8.7, Ar*H*), 5.09–5.06 (dd, 1H, J = 5.1, 12.8, CH_2NO$_2$), 4.62–4.58 (dd, 1H, J = 9.8, 12.8, CH_2NO$_2$), 4.21–4.18 (m, 1H, ArC*H*), 4.03–4.01 (br t, 2H, J = 6.3, CH_2OAc), 3.79 (s, 3H, OCH_3), 3.49–3.44 (m, 2H, C*H*OH, CHO*H*), 2.43–2.37 (m, 4H, CH_2COCH_2) 2.01 (s, 3H, COCH_3), 1.86–1.82 (m, 2H, CH_2CH$_2$O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.6 (*C*O) 171.0 (O*C*(O)CH$_3$), 159.4 (Ar*C*–OCH$_3$), 129.0 (2 × Ar*C*), 128.6 (Ar*C*$_{ipso}$), 114.7 (2 × Ar*C*), 78.4 (*C*H$_2$NO$_2$), 69.6 (*C*HOH), 63.3 (*C*H$_2$OAc), 55.3 (O*C*H$_3$), 49.1 (*C*H$_2$C(O)), 46.8 (Ar*C*H), 39.7 (C(O)*C*H$_2$), 22.4 (*C*H$_2$CH$_2$CO), 20.9 (OC(O)*C*H$_3$); MS (API-ES, pos.): *m*/*z* 376 (M + Na); MALDI-TOF MS: 376.1443 (376.1372 calc. for $C_{17}H_{23}NO_7Na$ (M + Na).

(3*R*,4*S*)-4-Hydroxy-6-(3-acetoxypropyl)-3-(4-methoxyphenyl)-2,3,4,5-tetrahydropyridine-1-oxide (8)

A solution of NH_4Cl (0.297 g, 5.55 mmol) in water (5 mL) was added to a solution of the nitroketone **7** (1.96 g, 5.55 mmol) in THF (24 mL). Activated Zn powder (3.51 g, 55.5 mmol) was added and the mixture was stirred vigorously at room temperature under nitrogen for 3 h. The mixture was filtered through Celite, the residue was washed with THF, and the combined filtrates were concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL) and the solution was washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide 1.6 g (90%) of **8** as a pale yellow foam. This material was pure by ^1H NMR and was used in the next step without purification.

IR (neat): 2948, 1735, 1611, 1509, 1459, 1230, 1140, 1031, 826 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, 2H, J = 8.7, Ar*H*), 6.90 (d, 2H, J = 8.7, Ar*H*), 4.37–4.32 (apparent br t, 1H, J = 13.4, ArC*H*), 4.20–4.19 (br s, 1H, CHO*H*), 4.14–4.11 (t, 2H, J = 6.5, CH_2OAc), 3.94–3.90 (dd, 1H, J = 5.5, 14.9, CH_2N), 3.80 (s, 3H, OCH_3), 3.25–3.21 (m, 1H, CH_2N), 2.89–2.53 (m, 4H, CH_2C=N, C=NCH_2CH$_2$) 2.01 (s, 3H, COCH_3), 1.99–1.92 (m, 2H, CH_2CH$_2$OAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (*C*OCH$_3$), 159.0 (Ar*C*–OCH$_3$), 145.0 (*C*=NO), 129.4 (Ar*C*$_{ipso}$), 128.7 (2 × Ar*C*), 114.3 (2 × Ar*C*), 65.1 (*C*HOH), 63.8 (OCH_2), 57.5 (OCH_3), 55.2 (*C*H$_2$NO), 43.5 (Ar–*C*H), 37.6 (*C*H$_2$C=N), 28.1 (*C*H$_2$CH$_2$O), 23.5 (CO*C*H$_3$) 20.9 (N=C*C*H$_2$); MS (APCI, pos.): *m*/*z* 322.4 (M + 1); MALDI-TOF MS: 344.1557 (344.1474 calcd for $C_{17}H_{23}NO_5Na$ (M + Na)).

3-((2*R*,4*S*,5*S*)-4-Hydroxy-5-(4-methoxyphenyl)-*N*-hydroxypiperidin-2-yl)propyl acetate (9)

To a solution of tetramethylammonium borohydride (2.62 g, 9.96 mmol) in acetonitrile (14 mL) was added acetic acid (14 mL). The mixture was stirred at 0 °C for 5 min and a solution of the nitrone **8** (1.6 g, 4.98 mmol) in acetonitrile (6 mL) was added. The mixture was stirred at 0 °C for 1 h and then basified (pH ~ 8) with aqueous NaOH (5% solution). The mixture was extracted with dichloromethane (2 × 60 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to give 1.48 g (92%) of **9** as a brown gum. This material was pure by ^1H NMR and was used in the next step without purification. An analytical sample was obtained by flash chromatography on silica gel (CH_2Cl_2–MeOH, 98 : 2).

IR (neat): 3415, 2923, 1731, 1512, 1238, 1032, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, 2H, J = 8.7, Ar*H*), 6.88 (d, 2H, J = 8.7, Ar*H*), 4.10–4.07 (t, 2H, J = 6.7, OCH_2), 3.91 (br s, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 3.58–3.48 (m, 1H, NC*H*), 3.31–3.20 (m, 2H, NCH_2, CHO*H*), 3.03 (br d, J = 12.4, 1H, CH_2N), 2.86–2.82 (m, 1H, ArC*H*), 2.11–2.00 (m, 5H, COCH_3, CHCH_2CH), 1.74–1.55 (m, 2H, CH_2CH$_2$OAc), 1.50–1.42 (m, 2H, NCHCH_2); MS (APCI, pos.): *m*/*z* 324.2 (M + 1); HRMS (CI): *m*/*z* 324.1812 (324.1811 calc. for $C_{17}H_{26}NO_5$ (M + H)); $[\alpha]_D^{23}$ = +39.1 (*c* 0.7, $CHCl_3$).

(2*S*,4*S*,5*R*)-2-(3-Hydroxypropyl)-5-(4-methoxyphenyl)piperidin-4-ol (10)

To a stirred solution of the hydroxylamine **9** (0.9 g, 2.78 mmol) in methanol (20 mL) was added aq. $TiCl_3$ (15%, 3.77 mL, 3.70 mmol) at 0 °C and the mixture was stirred at 0 °C for 4 h. Aqueous NaOH (20% w/v, 27 mL) was added and the mixture was filtered to remove inorganic salts. The residue washed with methanol and the combined filtrates were concentrated under reduced pressure. The resulting aqueous solution was extracted with dichloromethane (3 × 40 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to provide 0.65 g

(88%) of the amino alcohol **10** as a yellow solid. This material was pure by ^{1}H NMR and was used in the next step without purification.

Mp: 138–140 °C; IR (neat): 3554, 2910, 2843, 1511, 1461, 1240, 1182, 1056, 1026, 817 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, 2H, J = 8.7, Ar*H*), 6.89 (d, 2H, J = 8.7, Ar*H*), 4.10 (d, 1H, J = 2.32, C*H*OH), 3.79 (s, 3H, OCH_3), 3.64–3.54 (m, 2H, CH_2OH), 3.38–3.35 (t, 1H, J = 12.5, NCH_2), 3.08–3.03 (m, 1H, NC*H*) 3.03–2.97 (dd, 1H, J = 4, 12.5, NCH_2), 2.79–2.74 (m, 1H, ArC*H*), 1.96–1.92 (dt, 1H, J = 13.8, 3.0, CHCH_2CH), 1.79–1.75 (m, 1H, CHCH_2CH), 1.65–1.57 (m, 3H, NCHCH_2, CH_2CH$_2$OH), 1.42–1.39 (m, 1H, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6 (Ar*C*–OCH$_3$), 132.8 (ArC_{ipso}), 128.8 (2 × Ar*C*), 114.2 (2 × Ar*C*), 69.3 (*C*HOH), 62.8 (*C*H$_2$OH), 55.3 (O*C*H$_3$), 49.8 (*C*HNH), 46.7 (*C*H$_2$NH), 44.1 (Ar–*C*H), 39.4 (CH*C*H$_2$CH), 35.6 (NHCH*C*H$_2$) 30.4 (*C*H$_2$CH$_2$OH); MS (APCI, pos.): *m*/*z* 266.2 (M + 1); MALDI-TOF MS: 266.1796 (266.1756 calc. for $C_{15}H_{24}NO_3$ (M + H)).

(2*S*,4*S*,5*R*)-*tert*-Butyl 4-hydroxy-2-(3-hydroxypropyl)-5-(4-methoxyphenyl)piperidine-1-carboxylate (11)

To a solution of the aminol **10** (0.85 g, 3.21 mmol) and triethylamine (0.54 mL, 3.84 mmol) in dry dichloromethane (10 mL) at 0 °C was slowly added a solution of the $(Boc)_2O$ (0.706 g, 3.24 mmol) in dichloromethane (5 mL). The mixture was stirred at ambient temperature for 16 h, saturated $NaHCO_3$ was added and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with aqueous HCl (0.5 M, 2 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 1.1 g (94%) of **11** as a pale yellow gum. This material was pure by ^{1}H NMR and was used in the next step without purification. An analytical sample was obtained by purification by flash chromatography on silica gel (EtOAc).

IR (neat): 3403, 2936, 1658, 1511, 1420, 1246, 1164, 1067, 823 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, 2H, J = 8.7, Ar*H*), 6.85 (d, 2H, J = 8.7, Ar*H*), 4.48–4.46 (br m, 1H, NC*H*), 4.33–4.30 (br dd, 1H, J = 3.4, 14.1 NCH_2), 4.21–4.14 (m, 1H, C*H*OH), 3.80 (s, 3H, OCH_3), 3.72–3.70 (m, 2H, CH_2OH), 3.37–3.33 (dd, 1H, J = 4.2, 14.1, NCH_2), 3.06 (br m, 1H, ArC*H*), 1.89–1.53 (m, 6H, CHCH_2CH, NCHCH_2, CH_2CH$_2$OH), 1.46 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8 (Ar*C*–OCH$_3$), 155.3 (*C*O$_2$^{t}Bu), 130.8 (2 × Ar*C*), 130.2 (ArC_{ipso}), 113.8 (2 × Ar*C*) 80.1 (*C*(CH$_3$)$_3$), 66.4 (*C*HOH), 62.6 (*C*H$_2$OH), 55.3 (O*C*H$_3$), 50.8 (N*C*H), 44.4 (*C*H$_2$N), 42.8 (Ar*C*H), 33.0 (CH*C*H$_2$CH), 29.3 (NCH*C*H$_2$), 28.5 (C(*C*H$_3$)$_3$), 27.6 (*C*H$_2$CH$_2$OH); MS (APCI, pos.): *m*/*z* 266.2 (M-Boc + 2); HRMS (CI): *m*/*z* 266.1751 (266.1756 calc. for $C_{15}H_{24}NO_3$ (M-Boc + 2H); $[\alpha]_D^{23}$ = +68.2 (*c* 1, $CHCl_3$).

3-((2*S*,4*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-4-hydroxy-5-(4-methoxyphenyl)piperidin-2-yl)propyl methanesulfonate (12)

To a stirred solution of **11** (1.1 g, 3.01 mmol) in dichloromethane (15 mL) was added DIPEA (0.53 mL) followed by methanesulfonyl chloride in dichloromethane (10 mL) over 15 min. at 0 °C. The mixture was stirred at 0 °C for 3 h. Cold water (10 mL) was added and the organic layer was separated, washed with water (3 × 25 mL), brine (1 × 25 mL) dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes–EtOAc, 2 : 8) to provide 0.85g (64%) of **12** as a white solid.

Mp: 140–144 °C; IR (neat): 3441, 2937, 1676, 1511, 1418, 1353, 1247, 1167, 915, 830 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, 2H, J = 8.7, Ar*H*), 6.85 (d, 2H, J = 8.7, Ar*H*), 4.46 (br m, 1H, NC*H*), 4.29–4.18 (m, 3H, NCH_2, OCH_2), 4.16–4.14 (m, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 3.36–3.30 (dd, 1H, J = 4.1, 14.2, NCH_2), 3.07–3.05 (m, 1H, ArC*H*), 3.02 (s, 3H, SO$_2$CH_3), 1.92–1.61 (m, 6H, CHCH_2CH, NCHCH_2, CH_2CH$_2$O), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8 (Ar*C*–OCH$_3$), 155.0 (*C*O$_2$^{t}Bu), 130.8 (2 × Ar*C*), 130.1 (ArC_{ipso}), 113.9 (2 × Ar*C*) 80.2 (*C*(CH$_3$)$_3$), 69.7 (*C*H$_2$O), 66.4 (*C*HOH), 55.3 (O*C*H$_3$), 50.4 (N*C*H), 44.4 (*C*H$_2$N), 42.8 (Ar*C*H), 37.4 (SO$_2$*C*H$_3$), 33.0 (CH*C*H$_2$CH), 28.5 (C(*C*H$_3$)$_3$), 27.2 (NCH*C*H$_2$), 26.3 (*C*H$_2$CH$_2$OMs); MS (APCI, pos.): *m*/*z* 344.1 (M-Boc + 2); HRMS (CI): *m*/*z* 344.1538 (344.1532 calc. for $C_{16}H_{26}NO_5S$ (M-Boc + 2H).

(2*S*,4*S*,5*R*)-*tert*-Butyl-2-(3-cyanopropyl)-4-hydroxy-5-(4-methoxyphenyl)piperidine-1-carboxylate (13)

To a solution of the mesylate **12** (0.82 g, 1.85 mmol) in anhydrous DMSO (15 mL), at ambient temperature, was added NaCN (18 g, 3.69 mmol). The mixture was stirred at 70 °C for 2 h and cooled to ambient temperature. Ethyl acetate (40 mL) was added and the mixture was washed with water (3 × 30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 0.65 g (95%) of **13** as a yellow solid. This material was pure by ^{1}H NMR and was used in the next step without purification.

IR (neat): 3447, 2934, 2248, 1678, 1511, 1416, 1246, 1162, 1113, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, 2H, J = 8.7, Ar*H*), 6.85 (d, 2H, J = 8.7, Ar*H*), 4.46 (br s, 1H, NC*H*), 4.33–4.30 (br dd, 1H, J = 2.2, 14.2, NCH_2), 4.19–4.13 (m, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 3.35–3.31 (dd, 1H, J = 4.0, 14.2, NCH_2), 3.07–3.05 (m, 1H, ArC*H*), 2.44 (t, 2H, J = 6.8, CH_2CN), 2.04–1.96 (m, 1H, CHCH_2CH), 1.80–1.77 (m, 1H, CHCH_2CH), 1.70–1.62 (m, 4H, NCHCH_2, CH_2CH$_2$CN), 1.46 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8 (Ar*C*–OCH$_3$), 155.0 (*C*O$_2$^{t}Bu), 130.7 (2 × Ar*C*), 130.0 (ArC_{ipso}), 119.5 (*C*N), 113.8 (2 × Ar*C*), 80.2 (*C*(CH$_3$)$_3$), 66.3 (*C*HOH), 55.3 (O*C*H$_3$), 50.0 (N*C*H), 44.4 (*C*H$_2$N), 42.8 (Ar–*C*H), 33.1 (CH*C*H$_2$CH), 30.2 (NCH*C*H$_2$), 28.4 (C(*C*H$_3$)$_3$), 22.5 (*C*H$_2$CH$_2$CN), 17.0 (*C*H$_2$CN); MS (APCI, pos.): *m*/*z* 275.3 (M-Boc + 2); HRMS (CI): *m*/*z* 375.2292 (375.2284 calc. for $C_{21}H_{31}N_2O_4$ (M + H); $[\alpha]_D^{23}$ = +27.0 (*c* 0.6, $CHCl_3$).

(7*R*,8*S*,9a*S*)-Hexahydro-8-hydroxy-7-(4-methoxyphenyl)-1*H*-quinolizin-4(6*H*)-one (14)

A solution of the nitrile **13** (0.61 g, 1.63 mmol) in aqueous NaOH (2 M, 6 mL) and ethanol (6 mL) was heated at 85 °C for 16 h. The ethanol was removed under reduced pressure and resulting solution was acidified (pH ~ 4) with aqueous HCl (0.5 M). The acidic solution was extracted with dichloromethane (2 × 50 mL) and the combined extracts were dried (Na_2SO_4) and

concentrated to provide 0.61 g (95%) of 4-((2*S*,4*S*,5*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxy-5-(4-methoxyphenyl)piperidin-2-yl)-butanoic acid (**13a**) as a brown solid. This material was pure by ^{1}H NMR and was used in the next step without purification.

Mp: 88–90 °C; IR (neat): 3423, 2933, 1666, 1511, 1418, 1245, 1160, 1033, 829, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, 2H, J = 7.9, Ar*H*), 6.84 (d, 2H, J = 7.9, Ar*H*), 4.42 (br s, 1H, NC*H*), 4.31 (br d, 1H, J = 13.9, NCH_2), 4.14–4.12 (br m, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 3.33–3.30 (br dd, 1H, J = 2.7, 13.9, NCH_2), 3.03 (br s, 1H, ArC*H*), 3.0–2.5 (br, CO_2H), 2.39 (br s, 2H, CH_2COOH), 1.79–1.61 (m, 6H, CHCH_2CH, NCHCH_2, CH_2CH$_2$COOH), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4 (*C*O_2H), 158.7 (Ar*C*–OCH$_3$ or *C*O_2^{t}Bu), 155.1 (Ar*C*–OCH$_3$ or *C*O_2^{t}Bu), 130.8 (2 × Ar*C*), 130.3 (ArC_{ipso}), 113.7 (2 × Ar*C*), 80.1 (*C*(CH$_3$)$_3$), 66.3 (*C*HOH), 55.2 (ArO*C*H$_3$), 50.7 (N*C*H), 44.2 (*C*H$_2$N), 42.8 (Ar–*C*H), 34.1 (*C*H$_2$CO$_2$H), 32.3 (CH*C*H$_2$CH), 30.2 (NCH*C*H$_2$), 28.4 (C(*C*H$_3$)$_3$), 21.8 (*C*H$_2$CH$_2$CO$_2$H); MS (APCI, pos.): *m*/*z* 294.2 (M-Boc + 2); HRMS (CI pos.): *m*/*z* 294.1711 (294.1705 calc. for $C_{16}H_{24}NO_4$ (M-Boc + 2H).

To a solution of the above acid (0.60 g, 1.53 mmol) in methanol (12 mL) at 0 °C was added $SOCl_2$ (0.51 mL, 7.02 mmol) and the mixture was stirred at ambient temperature for 16 h. The methanol was removed under reduced pressure, the residue was diluted with dichloromethane (25 mL) and the resulting solution was washed with water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide 0.43 g, (91%) of methyl 4-((2*S*,4*S*,5*R*)-4-hydroxy-5-(4-methoxyphenyl)piperidin-2-yl)butanoate (**13b**) as an off white solid. This material was pure by ^{1}H NMR and was used in the next step without purification.

IR (neat): 3123, 2940, 1727, 1610, 1510, 1433, 1240, 1168, 1030, 828 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, 2H, J = 8.6, Ar*H*), 6.87 (d, 2H, J = 8.6, Ar*H*), 4.08–4.07 (br m, 1H, C*H*OH), 3.79 (s, 3H, ArOCH_3), 3.67 (s, 3H, CO_2CH_3), 3.39–3.31 (t, 1H, J = 12.0, NCH_2), 3.00–2.91 (m, 2H, N*C*H, ArC*H*), 2.84–2.79 (m, 1H, NCH_2), 2.37–2.32 (t, 2H, J = 7.4, CH_2CO$_2$CH$_3$), 1.99–1.92 (dt, 1H, J = 2.9, 13.6, CHCH_2CH), 1.73–1.63 (m, 4H, CHCH_2CH, CH_2CH$_2$CO, CHN*H*), 1.49–1.35 (m, 2H, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (*C*O_2CH$_3$), 158.5 (Ar*C*–OCH$_3$), 133.3 (ArC_{ipso}), 128.8 (2 × Ar*C*), 114.1 (2 × Ar*C*), 69.3 (*C*HOH), 55.3 (ArO*C*H$_3$), 51.6 (CO$_2$*C*H$_3$), 49.4 (NH*C*H), 47.0 (*C*H$_2$N), 44.8 (Ar*C*H), 39.5 (CH*C*H$_2$CH), 36.4 (NHCH*C*H$_2$), 34.1 (*C*H$_2$CO$_2$CH$_3$), 21.4 (*C*H$_2$CH$_2$CO$_2$CH$_3$); MS (APCI, pos.): *m*/*z* 308.3 (M + 1); HRMS (CI): *m*/*z* 308.1861 (308.1862 calc. for $C_{17}H_{26}NO_4$ (M + H)).

To a solution of the above amino ester (0.38 g, 1.23 mmol) in THF (6 mL) was added diisopropylethylamine (752 μL, 4.31 mmol) and the solution was heated to reflux for 16 h. Additional diisopropylethylamine (0.25 mL, 1.43 mmol) was added and the mixture was refluxed for 2 h. The THF was removed under reduced pressure, the residue was dissolved in dichloromethane (30 mL) and the resulting solution was washed with aqueous HCl (0.5 M, 2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 246 mg (73%) of the lactam **14** as a pale yellow foam. This material was pure by ^{1}H NMR and was used in the next step without purification.

IR (neat): 3349, 2945, 1606, 1514, 1478, 1442, 1245, 1171, 1035, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, 2H, J = 8.7, Ar*H*), 6.89 (d, 2H, J = 8.7, Ar*H*), 4.77–4.74 (dd, 1H, J = 4.2, 12.8, NCH_2), 4.1 (br m, 1H, C*H*OH), 3.8 (s, 3H, OCH_3), 3.78–3.74 (m, 1H, NC*H*), 3.20–3.15 (t, 1H, J = 12.8, NCH_2), 2.85–2.81 (br m, 1H, ArC*H*), 2.48–2.40 (m, 1H, NCOCH_2), 2.38–2.31 (m, 1H, NCOCH_2), 2.02–1.97 (m, 2H, CHCH_2CH, CHO*H*), 1.86–1.82 (m, 1H, NCHCH_2CH$_2$), 1.74–1.68 (m, 3H, CHCH_2CH, COCH$_2$CH_2) 1.55–1.48 (m, 1H, CHCH_2CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (N*C*O), 158.7 (Ar*C*–OCH$_3$), 131.9 (ArC_{ipso}), 128.6 (2 × Ar*C*), 114.2 (2 × Ar*C*), 68.7 (*C*HOH), 55.3 (O*C*H$_3$), 50.0 (N*C*H), 45.3 (*C*H$_2$N), 40.3 (Ar–*C*H), 39.6 (CH*C*H$_2$CH), 33.0 (CO*C*H$_2$), 29.7 (NCH*C*H$_2$), 19.1 (*C*H$_2$CH$_2$CO); MS (APCI, pos.): *m*/*z* 276.5 (M + 1); HRMS (CI): *m*/*z* 275.1526 (275.1521 calc. for $C_{16}H_{21}NO_3$ (M+)).

(3*R*,9a*S*)-Hexahydro-3-(4-methoxyphenyl)-1*H*-quinolizine-2,6-dione (15)

To a stirred solution of the alcohol **14** (0.45 g, 1.63 mmol) in dichloromethane (15 mL) was added DMSO (8 mL) followed by DIPEA (2.4 mL) at 0 °C. Solid SO_3·pyridine (781 mg, 4.90 mmol) was added in small portions and the mixture was stirred at 0 °C for 1 h. Water (10 mL) was added and the mixture was diluted with dichloromethane (20 mL). The mixture was washed with water (2 × 30 mL) and the organic layer was dried (Na_2SO_4) and concentrated to provide 420 mg (94%) of **15** as a brown solid.

Mp: 88–90 °C; IR (neat): 2921, 1719, 1624, 1514, 1447, 1338, 1242, 1171, 1022, 826 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (d, 2H, J = 8.7, Ar*H*), 6.89 (d, 2H, J = 8.7, Ar*H*), 5.15–5.08 (dd, 1H, J = 12.7, 6.2, NCH_2), 3.85–3.82 (m, 1H, NC*H*) 3.79 (s, 3H, OCH_3), 3.67–3.61 (dd, 1H, J = 12.7, 6.2, NCH_2), 3.00–2.91 (t, 1H, J = 12.4, ArC*H*), 2.58–2.55 (m, 2H, COCH_2), 2.50–2.46 (m, 2H, NCOCH_2), 2.18–2.09 (m, 1H, NCHCH_2), 1.97–1.78 (m, 2H, COCH$_2$CH_2), 1.72–1.63 (m, 1H, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2 (*C*O), 169.4 (N*C*O), 159.0 (Ar*C*OCH$_3$),129.9 (2 × Ar*C*), 126.8 (Ar*C*), 114.1 (2 × Ar*C*), 56.0 (N*C*H), 55.4 (O*C*H$_3$), 55.3 (ArC*C*H), 48.3 (N*C*H$_2$), 47.7 (CO*C*H$_2$), 32.8 (NCO*C*H$_2$), 29.6 (COCH$_2$*C*H$_2$), 18.9 (NCH*C*H$_2$); MS (APCI pos.): *m*/*z* 274.1 (M + 1); HRMS (CI+): *m*/*z* 273.1371 (273.1365 calc. for $C_{16}H_{19}NO_3$, M$^+$).

(*S*)-4,6,7,8,9,9a-Hexahydro-3-(4-methoxyphenyl)-6-oxo-1*H*-quinolizin-2-yl trifluoromethanesulfonate (16)

To a suspension of KH (66 mg, 0.50 mmol) in THF (2 mL) was added the ketone **15** (136 mg, 0.50 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h and a solution of *N*-phenylbistrifluoromethanesulfonimide (195 mg, 0.55 mmol) in THF (2 mL) was added dropwise at 0 °C. The mixture was then stirred for 0.5 h at room temperature. Water (7 mL) was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a brown gum which was purified by flash chromatography on silica gel (EtOAc) to provide 150 mg (74%) of **16** as a yellow gum.

IR (neat): 2942, 1642, 1512, 1412, 1206, 1138, 1036, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, 2H, J = 8.8, Ar*H*), 6.91 (d, 2H, J = 8.8, Ar*H*), 5.28 (d, 1H, J = 18.4, NCH_2), 3.82 (s, 3H, OCH_3), 3.82–3.77 (m, 1H, NC*H*), 3.64 (d, 1H, J = 18.4, NCH_2), 2.79–2.72 (m, 1H, COCH_2), 2.52–2.49 (m, 1H, COCH_2), 2.49–2.43 (m, 2H, C═CCH_2) 2.20–2.11 (m, 1H, COCH$_2$CH_2), 1.99–1.89 (m, 1H, COCH$_2$CH_2), 1.81–1.61 (m, 2H, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (*C*═O), 160.0 (TfO*C*═C), 139.3 (Ar*C*OCH$_3$), 129.7 (2 × Ar*C*), 128.0 (Ar*C*), 124.8 (TfOC═*C*), 122.5 (q, J = 346.4, *C*F$_3$), 114.0 (2 × Ar*C*), 55.3 (O*C*H$_3$), 52.7 (N*C*H), 45.5 (N*C*H$_2$), 35.6 (C═C*C*H$_2$CH), 32.8 (CO*C*H$_2$), 28.3 (NCH*C*H$_2$), 18.2 (COCH$_2$*C*H$_2$); MS (APCI pos.): m/z 406.1 (M + 1); HRMS (CI+): m/z 405.0865 (405.0858 calc. for $C_{17}H_{18}NO_5SF_3$, M^+).

(*S*)-2,3,9,9a-Tetrahydro-8-(3,4-dimethoxyphenyl)-7-(4-methoxyphenyl)-1*H*-quinolizin-4(6*H*)-one (17)

To a stirred solution of the enol triflate **16** (150 mg, 0.37 mmol) and 3,4-dimethoxyphenyl boronic acid (74 mg, 0.41 mmol) in dioxane (6 mL) was added a degassed, aqueous solution of Na_2CO_3 (118 mg, 1.11 mmol, in 0.50 mL water) and the mixture was degassed with a stream of nitrogen for 15 min. $Pd(PPh_3)_4$ (21 mg, 0.019 mmol) was added and the mixture was heated with stirring at 85 °C for 90 min. The mixture was then cooled to ambient temperature, diluted with EtOAc (15 mL) and the resulting mixture was washed with water (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give a brown gum. This was purified by flash chromatography on silica gel (CH_2Cl_2–methanol, 98.5 : 1.5) to provide 120 mg (82%) of **17** as a white solid.

Mp: 94–101 °C; IR (neat): 2944, 1635, 1510, 1454, 1245, 1173, 1028, 824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.00 (d, 2H, J = 8.7, Ar*H*), 6.71–6.68 (m, 3H, Ar*H*), 6.62 (dd, 1H, J = 8.3, 2, Ar*H*), 6.43 (s, 1H, Ar*H*), 5.20 (d, 1H, J = 18.7 NCH_2), 3.81 (s, 3H, OCH_3), 3.81–3.79 (m, 1H, NC*H*), 3.73 (s, 3H, OCH_3), 3.72–3.68 (d, 1H, J = 18.7, NCH_2), 3.55 (s, 3H, OCH_3), 2.60–2.57 (m, 2H, C═CCH_2), 2.48–2.46 (t, 2H, J = 12.7, COCH_2), 2.16–2.11 (m, 1H, NCHCH_2) 1.91–1.88 (m, 1H, COCH$_2$CH_2), 1.81–1.72 (m, 2H, COCH$_2$CH_2, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4 (*C*═O), 158.4 (Ar*C*–OCH$_3$), 148.1 (Ar*C*–OCH$_3$), 147.5 (Ar*C*–OCH$_3$), 133.9 (Ar*C*C═C), 131.9 (C═*C*CH$_2$CH), 131.2 (C═*C*CH$_2$N), 131.1 (Ar*C*), 130.4 (2 × Ar*C*), 120.6 (Ar*C*H), 113.5 (2 × Ar*C*), 113.0 (Ar*C*), 110.6 (Ar*C*), 55.7 (N*C*H), 55.6 (O*C*H$_3$), 55.2 (O*C*H$_3$), 52.8 (O*C*H$_3$), 46.8 (N*C*H$_2$), 38.9 (C═C*C*H$_2$CH), 33.0 (CO*C*H$_2$), 28.7 (NCH*C*H$_2$), 18.5 (COCH$_2$*C*H$_2$); MS (APCI pos.): m/z 394.2 (M + 1); HRMS (CI+): m/z 394.2016 (394.2018 calc. for $C_{24}H_{28}NO_4$, M + H).

(*S*)-4,6,7,8,9,9a-Hexahydro-2-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-1*H*-quinolizine ((+)-julandine, 1)

To a suspension of $LiAlH_4$ (38 mg, 1 mmol) in dry THF (1.5 mL) at 0 °C was slowly added a solution of the lactam **17** (0.10 g, 0.25 mmol) in THF (2 mL). The mixture was stirred for an hour at 0 °C and then at ambient temperature for 24 h. It was then cooled to 0 °C and water (18 μL, 1 mmol), 1 N NaOH (1 mL) and water (48 μL), were added sequentially with vigorous stirring. The precipitated inorganic salts were filtered and washed with dichloromethane. The combined filtrates were dried (Na_2SO_4) and concentrated to give a yellow gum. This was purified by flash chromatography on silica gel ($CHCl_3$–MeOH, 99 : 1) to provide 63 mg (89%) of **1** as a pale yellow gum.

IR (neat): 2928, 1604, 1509, 1458 1242, 1172, 1029, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.98 (d, 2H, J = 8.6, Ar*H*), 6.69–6.67 (m, 4H, Ar*H*), 6.46 (br s, 1H, Ar*H*), 3.81 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.62–3.59 (br d, 1H, J = 16.5), 3.53 (s, 3H, OCH_3) 3.10–3.03 (m, 2H), 2.55–2.51 (br d, 1H, J = 18.1), 2.41–2.30 (m, 2H), 2.11–2.10 (m, 1H), 1.86–1.80 (m, 2H), 1.75–1.70 (br m, 2H), 1.36–1.35 (br m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 147.9, 147.2, 134.5, 133.2, 131.5, 131.3, 130.2, 120.5, 113.4, 113.0, 110.5, 62.8, 60.4, 57.9, 55.7, 55.6, 55.5, 55.2, 39.6, 33.3, 30.0, 25.9, 24.4; MS (APCI pos.): m/z 380.5 (M + 1); HRMS (CI+): m/z 379.2151 (379.2147 calc. for $C_{24}H_{29}NO_3$, M^+). $[\alpha]_D^{23}$ = +88.8° (c 0.5, $CHCl_3$, Lit.[10a] $[\alpha]_D^{26}$ = −71.6° (c 0.33, $CHCl_3$ for the *R*-enantiomer).

(*S*)-2,3,6-Trimethoxy-11,12,13,14,14a,15-hexahydro-9*H*-dibenzo-[*f*,*h*]pyrido[1,2-*b*]isoquinoline ((+)-cryptopleurine, 2)

A modification of the literature procedure was employed.[10e] To a stirred solution of **1** (65 mg, 0.17 mmol) in dichloromethane (10 mL) at ambient temperature was added thallium(III) trifluoroacetate (94 mg, 0.17 mmol) and the mixture was stirred for 30 min. The volatiles were removed under reduced pressure, water (5 mL) was added to the residue and the mixture was basified with saturated aqueous sodium carbonate. The mixture was then extracted with chloroform (2 × 15 mL). The combined extracts were dried and concentrated. The residue obtained was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 98 : 2) to give a yellow solid which was recrystallized from chloroform–acetone to give 40 mg (62%) of **2** as a white crystalline solid.

Mp: 190–194 °C (Lit.[20] mp. 197–198 °C (benzene); IR (neat): 2926, 1610, 1509, 1467, 1253, 1141, 1040, 846, 748, 632 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.9 (d, 1H J = 2.6), 7.26 (s, 1H), 7.20 (dd, 1H, J = 2.6, 9), 4.44 (d, 1H, J = 15.5), 4.10 (s, 3H), 4.06 (s, 3H), 4.01(s, 3H), 3.64 (d, 1H, J = 15.3), 3.28 (d, 1H, J = 10.8), 3.13–3.09 (dd, 1H, J = 4, 16.3), 2.92–2.86 (m, 1H), 2.43–2.39 (t, 1H, J = 10.3), 2.34–2.28 (td, 1H, J = 3.8, 11.5), 2.04 (d, 1H, J = 13.9), 1.89 (d, 1H, J = 12.3), 1.81–1.77 (m, 2H), 1.56–1.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 149.4, 148.3, 130.1, 126.5, 125.7, 124.5, 124.1, 123.7, 123.4, 114.8, 104.7, 103.9 (2 × Ar*C*), 57.6, 56.3, 56.2, 56.0, 55.9, 55.5, 34.8, 33.9, 26.0, 24.4; MS (APCI pos.): m/z 378.1 (M + 1); HRMS (CI+): m/z 377.1990 (377.1991 calc. for $C_{24}H_{29}NO_3$, M^+); $[\alpha]_D^{23}$ = +104.6° (c 0.55, $CHCl_3$); Lit.[12d] $[\alpha]_D^{23}$ = +106 ° (c 1, $CHCl_3$)).

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