Unusual rearrangements and cyclizations involving polycyclic indolic systems

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Abstract
During the course of experiments to explore and develop cyclization reactions of indolic systems, a number of unusual rearrangement reactions were discovered, and are reported in this paper. We describe routes to 4-substituted (methylsufanylmethyl)indole derivatives, and a simple route to a cyclopropanone derivative of a tetrahydro-β-carboline.

Keywords: Indole, Sommelet-Hauser rearrangement, Pictet-Spengler reaction, cyclopropanone

Introduction

There are an enormous number of important indolic natural products, containing a plethora of fused ring systems, as exemplified below (Figure 1). Our interest has been in using tryptophan as the chiral starting material for the synthesis of such compounds,[2] and in developing synthetic methods for accessing the polycyclic structures.[3]

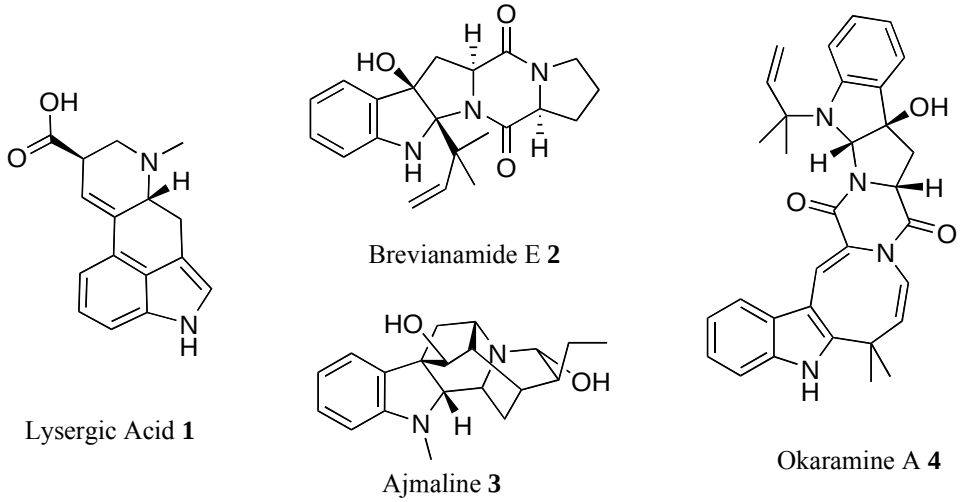


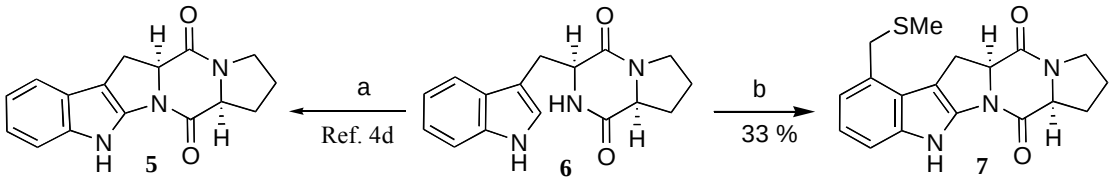
Figure 1

We describe herein some of our cyclization studies, which have led to unusual and unexpected rearrangements. The first of these is a Sommelet-Hauser rearrangement, observed during the attempted ring-closure to the [6.5.5] fused system found in brevianamide E (**2**) and okaramine A (**4**); the second is a cyclopropanone forming reaction, observed whilst attempting the preparation of the spiro-system found in ajmaline (**3**).

Results and Discussion

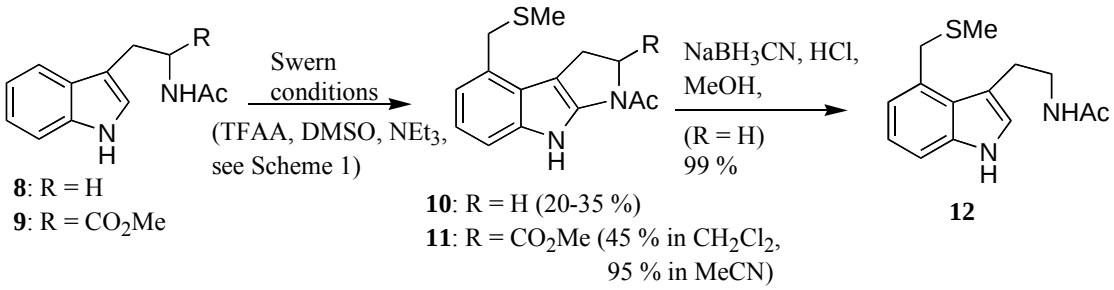
Section A. Methylsulfanylmethylation *via* Sommelet-Hauser rearrangements

A key reaction in the synthesis of brevianamide E (**2**) and okaramine A (**4**) would be a difficult oxidative cyclization, in which the indolic 2-position becomes bonded to nitrogen.[4] We decided to explore this process using the model cyclization of brevianamide F (**6**) (Scheme 1, a), for which we were able to confirm that the use of *t*-butyl hypochlorite proceeds in only about 30% yield.[4d] We had reasoned that treatment with Swern reagents[5] ought to achieve the desired cyclization, and we explored the same model cyclization (Scheme 1, b).[6] To our surprise, although the desired polycyclic skeleton was generated in 33% yield using trifluoroacetic anhydride as the Swern electrophile,[7] a methylsulfanylmethyl group was concurrently attached to the indole 4-position. Although unwanted for our work towards the brevianamides, accessing 4-substituted tryptophans is difficult, and such compounds are of importance for QSAR studies of tryptophyl peptides, or for the synthesis of natural products such as lysergic acid (**1**); we therefore sought to explore the scope and limitations of this chemistry, as well as an understanding of the mechanism of the reaction.



Scheme 1. Reagents and conditions: (a) Bu^tOCl, NEt_3, CH_2Cl_2, 0 ºC; (b) $(CF_3CO)_2O$, DMSO, CH_2Cl_2, -78 to 0 to -78 ºC; add NEt_3 and warm to RT.

Our first set of indole analogues were simple acyl derivatives of tryptamine **8** and tryptophan methyl ester **9**. We found that both of these reactions also proceeded with both cyclization and rearrangement, giving the 4-substituted products **10** and **11** in moderate yield, although the yield of the latter reaction was dramatically improved (to 95%) when the reaction was carried out in acetonitrile.



8: R = H
9: R = CO_2Me

10: R = H (20-35 %)
11: R = CO_2Me (45 % in CH_2Cl_2, 95 % in MeCN)

12

Scheme 2

The tryptophan derivative might be especially useful; for example, reduction with Raney nickel should generate the 4-methyltryptophan derivative, whilst other 4-substituted derivatives should be accessible using sulfide/sulfoxide chemistry, for incorporation into peptides. We were therefore pleased that reductive ring-opening of the tryptamine derivative **10** took place essentially quantitatively, thereby confirming that the ring-opening/unmasking can be easily achieved.

We next explored the range of indolic substrates suitable for the Sommelet-Hauser rearangement (Figure 2). Our choice was significantly guided by our proposed mechanism (see Scheme 3 below, and associated discussion), and we were therefore disappointed that only the three derivatives shown in Schemes 1 and 2 underwent the reaction.

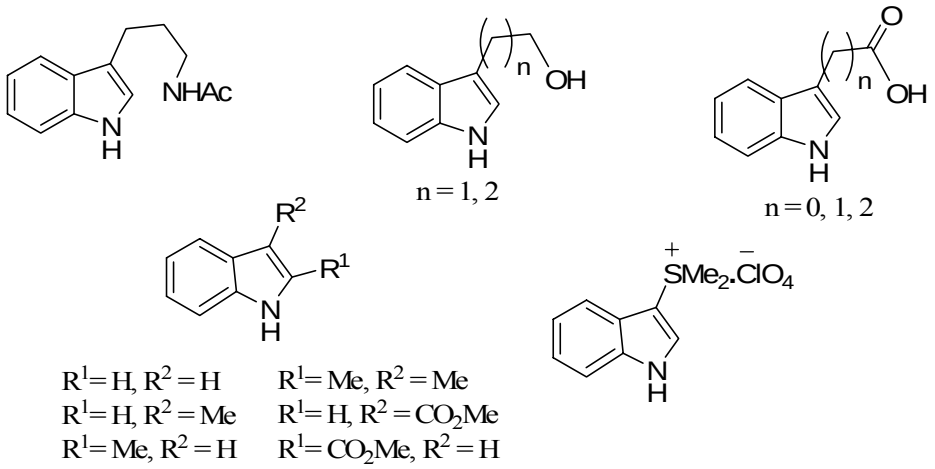
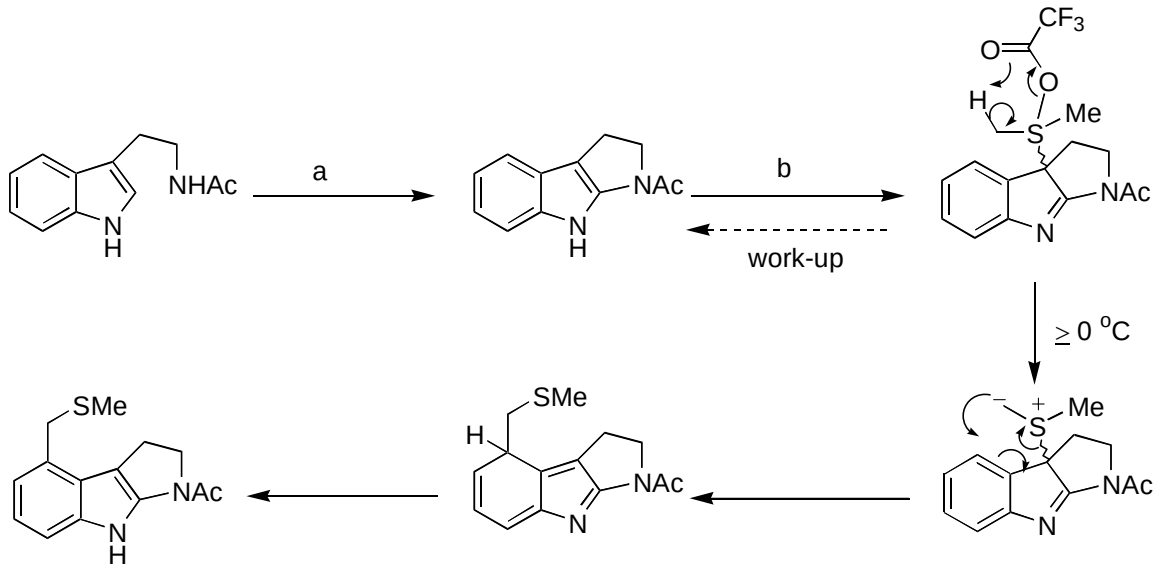


Figure 2. Substrates that failed to undergo the rearrangement.

Next we turned to the mechanism for this reaction, for which our proposal is shown in Scheme 3, in which a sulfonium intermediate is in equilibrium with an ylide, which can then undergo the Sommelet-Hauser rearrangement.[8]



Scheme 3. Proposed mechanism for Swern oxidation (DMSO/TFAA then ET_3N) (a) at low T or (b) with warming before basification.

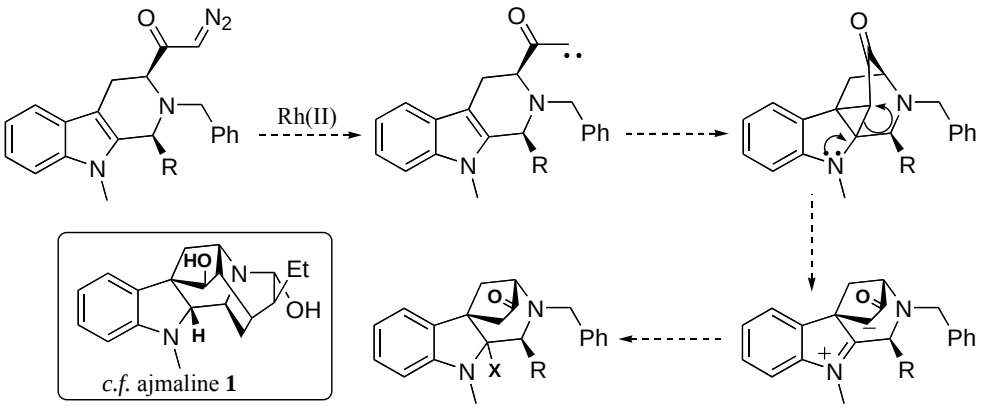
When the reaction was carried out entirely at low temperature, then the expected cyclization took place without introduction of the $MeSCH_2$ group; similarly, using only one equivalent of the Swern reagent, but allowing the reaction to warm up, also led to the simple cyclization product; finally, replacing trifluoroacetic anhydride with oxalyl chloride[9] also led to cyclization without rearrangement.

These results indicate that the [6.5.5] system must be pre-formed before the Sommelet-Hauser rearrangement can occur (in these systems, at least). Crucially, the Sommelet-Hauser rearrangement requires de-aromatization of the 'pyrrolic' indole ring before the [2,3] sigmatropic shift can occur, and it is noteworthy that the sulfonium salt (Figure 2, final entry) failed to undergo any reaction with triethylamine under our 'Swern' conditions. We had hoped that other heteroatoms tethered to the indole 3-position would be able to stabilise the key intermediates required for the Sommelet-Hauser rearrangement, but this turned out not to be the case. Although Swern *et al* have reported *ortho*-CH_2SMe insertion in the oxidation of an aniline derivative,[7b] our Swern-induced Sommelet-Hauser rearrangement for indolic systems has not been previously reported.

Section B. Cyclopropanone formation from a diazomethyl ketone

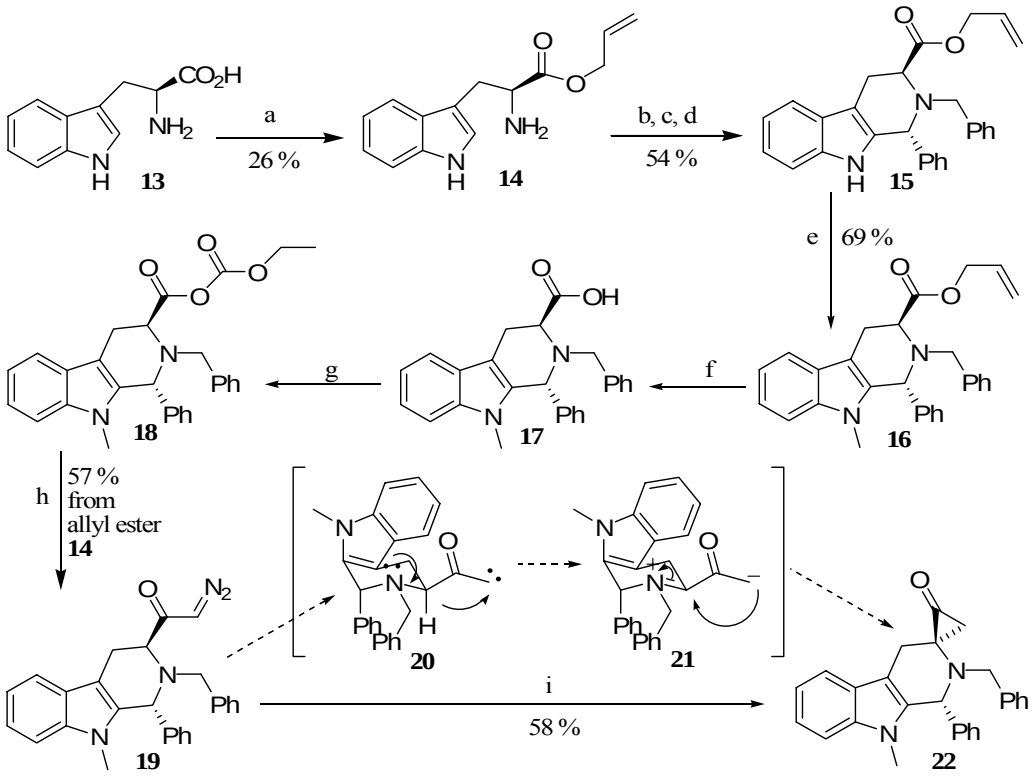
In work towards the [6.5.5.6] spiro system in ajmaline (**3**), we hoped to use a carbene insertion reaction, as outlined in Scheme 4.

We prepared the model diazoketone as shown in Scheme 5. Thus, allyl ester **14**[10] was benzylated, after which the *trans* specific Pictet-Spengler reaction[11] gave the tetrahydro-β-carboline **15**. After N^{in}-methylation, and palladium catalyzed deprotection of the ester, the diazoketone **19** was prepared via the mixed anhydride **18**.



Scheme 4. Planned route to key [6.5.6.5] spiro ring system of ajmaline.

Intriguingly, reaction with rhodium II acetate generated the cyclopropanone **22** instead of the desired spiro system, as a single diastereoisomer, for which the IR stretch at 1805 cm^{-1} and ^{13}C peak at 205 ppm were indicative of the strained ketone.



Scheme 5. Reagents and conditions; (a) allyl alcohol, AcCl, reflux, 18 h, (b) PhCHO, MeOH, 2 h, (c) $NaBH_4$, -30 ºC, 1 h, (d) PhCHO, $CHCl_3$, reflux, 18 h, (e) NaH, MeI, DMF, 0 ºC, (f) $Pd(Ph_3)_4$, CH_2Cl_2, morpholine, (g) ethyl chloroformate, Et_3N, CH_2Cl_2, -10 ºC, 1 h, (h) CH_2N_2, Et_2O, DCM 0 ºC, 1 h, RT, 72 h, (i) $Rh_2(OAc)_4$, CH_2Cl_2, 18h, RT.

If the mechanism we propose in Scheme 5 is correct, then the *trans* product shown would be expected, via pseudo-axial attack on the iminium intermediate in which the phenyl group is axial.[3b] As in the case of the Sommelet-Hauser rearrangement, the fine interplay of steric and electronic factors are probably prerequisites for the rearrangement/cyclization, involving hydride shift and subsequent ring closure. We are exploring the generality of this unusual reaction, and the possible synthetic utility of the resulting cyclopropanones.

Experimental Section

General Procedures. General procedures followed during the course of the work detailed herein were similar to those reported elsewhere.[2,3]

Synthetic studies

Section A

Preparation of brevianamide F (6).[4d] L-Proline methyl ester hydrochloride (1.39 g: 8.4 mmol) was dissolved in DMF (40 mL) and diisopropylethylamine (3 mL). To a DMF (60 mL) solution of *N*-Z-tryptophan (2.84 g: 8.4 mmol) and 1-hydroxybenzotriazole (1.25 g: 9.2 mmol) was added EDC (1.76 g: 9.2 mmol) in DMF (100 mL) at 0 ºC over 5 minutes. This was stirred at 0 ºC for 1 hour then at room temperature for half an hour. The DMF/DIPEA solution of L-proline was then added and the resultant solution stirred overnight. After this time the solvent was removed under vacuum and resultant oil dissolved in dichloromethane. This solution was washed with water (2 x 100 mL), saturated sodium bicarbonate solution (2 x 100 mL), citric acid solution (0.7 M: 2 x 100 mL) then water again before finally being dried over magnesium sulfate. The solution was filtered and the solvent removed under vacuum to give a crude white foam of the protected dipeptide Z-Trp-Pro-OMe (3.07 g: 80%) which was used in the next step without further purification.

The dipeptide (3.07 g: 6.8 mmol) was dissolved in methanol (100 mL) then the solvent removed under vacuum. This process was repeated twice before finally the starting material was dissolved in methanol (150 mL). To this solution was added palladium catalyst (Degussa type: 0.5 g). The solution was flushed three times with hydrogen before being left to stir overnight under a hydrogen atmosphere. After this time, the catalyst was removed by filtration and the solvent removed *in vacuo* to give the crude product as a colourless oil. The crude material was purified by flash chromatography eluting with 1:1 ethyl acetate/dichloromethane to yield the desired product **6** as a white solid (1.77 g: 92%): R_f 0.13 (1:99 methanol: dichloromethane); ν_{max}/cm^{-1} (KBr) 3288, 2923, 2872, 1674, 1653, 1429; δ_H (200 MHz, $CDCl_3$) 1.79-2.04 (3H, m, Pro-CH_2), 2.23-2.37 (1H, m, Pro-CH_2), 2.92 (1H, dd, *J* 15.1, 10.4 Hz, one of Trp-CH_2), 3.55-3.72 (3H, m, one of Trp-CH_2 and Pro-CH_2), 3.77 (1H, dd, *J* 3.7, 0.7 Hz, Pro-α-CH), 4.30 (1H, dd, *J* 10.4, 2.8

Hz, Trp-α-CH), 5.85 (1H, br s, NH), 7.04 (1H, d, *J* 2.2 Hz, CH), 7.12 (1H, ddd, *J* 7.7, 7.4, 1.2 Hz, CH), 7.21 (1H, ddd, *J* 7.7, 7.4, 1.5 Hz, CH), 7.37 (1H, dd, *J* 7.7, 1.5 Hz, CH), 7.58 (1H, dd, *J* 7.4, 1.2 Hz, CH), 8.62 (1H, br s, NH); δ_C (50 MHz, $CDCl_3$) 22.5 (CH_2), 26.7 (CH_2), 28.2 (CH_2), 45.3 (CH_2), 54.5 (CH), 59.1 (CH), 109.5 (3-C), 111.6 (7-CH), 118.4 (6-CH), 119.8 (4-CH), 122.6 (5-CH), 123.4 (2-CH), 126.6 (3a-C), 136.6 (7a-C), 165.5 (C=O), 169.3 (C=O); (Found: C, 67.88; H 5.99; N, 14.76 %. $C_{16}H_{17}N_3O_2$ requires C, 67.82; H, 6.05; N, 14.83 %).

(5a*S*,13a*S*)-7-(Methylsulfanylmethyl)-1,2,3,6,11,13a-hexahydro-13*H*-pyrrolo[1",2":4',5']-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-5(5a*H*),13-dione (7). To a solution of trifluoroacetic anhydride (566 μL: 4.0 mmol) in dichloromethane (20 mL) cooled to -78 ºC was added dimethylsulfoxide (568 μL: 8.0 mmol) in dichloromethane (2 mL). This solution was stirred at -78 ºC for 10 minutes before a solution of brevianamide F **6** (218.0 mg: 0.77 mmol) was added in dichloromethane (25 mL) *via* a canula. The reaction was stirred at -78 ºC for 1 hour before triethylamine (15 mL) was added. The reaction was stirred for a further 2.5 hours during which time it was allowed to warm to room temperature. At this time the reaction mixture was poured into a separating funnel containing brine (20 mL). The organic phase was collected and washed further with sodium hydrogencarbonate solution (2 x 20 mL) and brine (2 x 20 mL) before being collected and dried over $CaC1_2$. Upon filtration and removal of the solvent, the crude material was obtained as a yellow coloured foam. This was purified by flash chromatography eluting with 4:6 ethyl acetate and dichloromethane. The product **7** was isolated as a pale yellow coloured foam (72.1 mg: 33%). R_f 0.28 (1:1 ethyl acetate:dichloromethane); m.p. 116-120 ºC; ν_{max}/cm^{-1} (KBr) 3221, 2920, 1669, 1455, 1309, 1200, 747, 668; δ_H (200 MHz, $CDCl_3$) 1.89 (3H, s, S-CH_3), 1.89-2.05 (2H, m, Pro-CH_2), 2.13-2.41 (2H, m, Pro-CH_2), 3.29 (1H, dd, *J* 14.7, 10.1 Hz, Trp-CH_2), 3.57 (1H, dd, *J* 14.7, 7.7 Hz, Trp-CH_2), 3.54-3.62 (2H, m, Pro-CH_2), 3.90 (2H, s, Ar-CH_2-S), 4.23 (1H, dd, *J* 7.8, 7.5 Hz, Pro- CH), 5.12 (1H, dd, *J* 10.1, 7.7 Hz, Trp-CH), 6.92 (1H, d, *J* 7.7 Hz, CH), 7.04 (1H, t, *J* 7.7 Hz, CH), 7.32 (1H, d, *J* 7.7 Hz, CH), 9.47 (1H, br s, NH); δ_C (50 MHz, $CDCl_3$) 14.7 (SCH_3), 23.3 (CH_2), 26.3 (CH_2), 27.4 (CH_2), 34.9 (CH_2), 45.6 (CH_2), 59.9 (CH), 66.8 (CH), 102.0 (6a-C), 117.3 (10-CH), 120.3 (9-CH), 121.1 (7-C), 121.9 (8-CH), 123.7 (10a-C) 135.8 (6b-C), 139.3 (10a-C), 162.5 (C=O), 165.3 (C=O); HREI-MS *m/z* (M^+ $C_{18}H_{19}N_3O_2S$) calc. 341.1198, obs. 341.1159.

Methyl (3*S*)-1-acetyl-4-(methylsulfanylmethyl)-1,2,3,8-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (11). To a solution of trifluoroacetic anhydride (283 μL: 2.0 mmol) in dichloromethane (10 mL) cooled to -78 ºC was added dimethylsulfoxide (284 μL: 4.0 mmol) in dichloromethane (2 mL). This solution was stirred at -78 ºC for 10 minutes before a solution of *N*-acetyl tryptophan methyl ester (99.7 mg: 0.39 mmol) was added in dichloromethane (15 mL) *via* a canula. The reaction was stirred for 0.5 hours at – 78 ºC before allowing the solution to warm to 0ºC over 2 hours. The reaction was then cooled back to -78 ºC before triethylamine (7 mL) was added. The reaction was stirred for a further 2.5 hours during which time it was allowed to warm to room temperature. At this time the reaction mixture was poured into a separating funnel containing brine (20 mL). The organic phase was collected and washed further with

sodium hydrogencarbonate solution (2 x 20 mL) and brine (2 x 20 mL) before being collected and dried over $CaC1_2$. Upon filtration and removal of the solvent, the crude material was obtained as a yellow foam. This was purified by flash chromatography eluting with 4:6 ethyl acetate/ dichloromethane, and the product **11** was isolated as a pale yellow coloured foam (55.7 mg: 45 %). Running the reaction on a 500 mg scale of Ac-Trp-OMe, but replacing dichloromethane by acetonitrile, gave 580 mg (95%) of the same product. R_f 0.69 (1:1 ethyl acetate:dichloromethane): ν_{max}/cm^{-1} 3200, 2931, 1675, 1458, 1315, 1191; δ_H (100 MHz, $CDCl_3$) 1.94 (3H, s, CH_3), 2.13 (3H, s, CH_3), 3.31 (1H, dd, *J* 14.5, 3.1 Hz, CH_2), 3.67 (1H, dd, *J* 14.5, 10.2 Hz, CH_2), 3.83 (3H, s, CH_3), 3.91 (2H, s, Ar- CH_2), 5.23 (1H, dd, *J* 10.2, 3.1 Hz, CH), 6.96 (1H, d, *J* 7.6 Hz, CH), 7.06 (1H, dd, *J* 7.6, 7.4 Hz, CH), 7.26 (1H, d, *J* 7.4 Hz, CH), 9.00 (1H, br s, NH). δ_C (400 MHz, $CDCl_3$) 15.3 (q), 22.2 (q), 30.5 (t), 35.5 (t), 53.5 (q), 66.7 (d), 99.0 (s), 117.1 (d), 120.7 (d), 121.4 (s), 121.8 (d), 123.9 (s), 135.9 (s), 143.4 (s), 167.6 (s), 171.7 (s).

Preparation of 4-(methylsulfanylmethyl)tryptamine (12). To a stirred suspension of **11** (21 mg, 80.3 mmol) in MeOH (5 ml) under nitrogen was added solid $NaBH_3CN$ (6 mg, 0.1 mmol) followed by 2-3 drops of dilute 2M HCl. The solid rapidly dissolved to form a yellow solution. The reaction was followed by TLC and after 1 h the reaction mixture was evaporated to dryness. The residue was taken back up into dichloromethane, washed with saturated $NaHCO_3$ (2x), brine, dried ($MgSO_4$) and evaporated to dryness to afford 22 mg (99 %) of the reduction product **12** as a clear oil. ν_{max}/cm^{-1} (neat) 3401, 3285 (br), 2970, 2912, 2854, 1658; δ_H (400 MHz, $CDCl_3$)1.98 (3H, s), 2.14 (3H, s), 3.30 (2H, t, J 7 Hz), 3.68 (2H, q, J 7 Hz), 3.82 (2H, s), 5.24 (1H, s, br), 6.95 (1H, d, J 7 Hz), 7.03 (2H, m), 7.26 (1H, d, J 7 Hz), 9.56 (1H, s); δ_C (400 MHz, $CDCl_3$) 15.2 (q), 23.7 (q), 25.7 (t), 35.6 (t), 40.3 (t), 113.5 (s), 118.5 (d), 119.5 (d), 120.7 (s), 122.6 (d), 123.5 (d), 128.3 (s), 135.5 (s), 170.8 (s); HRMS (ES^+) *m/z* ($M+Na^+$ $C_{14}H_{18}N_2ONaS$) calc. 285.1038, obs. 285.1031.

Section B

L-Tryptophan allyl ester (14)

To L-tryptophan (15 g, 61 mmol) dissolved in allyl alcohol (150 ml), acetyl chloride was then added, and the resulting purple solution was maintained at reflux for 18 hr. It was then cooled to RT, and 10 % ammonia solution (250 ml) and CH_2Cl_2 (150 ml) were added. The phases were separated and the aqueous extracted with CH_2Cl_2 (2 x 250 ml). The combined organics were dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The product was purified by column chromatography using 50:50 $CHC1_3$: diethyl ether, giving 6.02 g (26 %) of the white solid **14**, which exhibited spectra in accordance with those already reported.[10]

Allyl (1*R*,3*S*)-1-phenyl-2-(phenylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (15). L-Tryptophan allyl ester (1.0 g, 4.1 mmol) was dissolved in dry methanol (15 ml), benzaldehyde (460 µl, 4.5 mmol) was then added and the resultant solution was stirred at

RT for 2 hr. The solution was then cooled to -30 ºC and sodium borohydride (77 mg, 2.1 mmol) was added portion-wise over 5 min. whilst maintaining the temperature at -30 ºC. The resultant mixture was then stirred at -30 ºC for 30 min, warmed to -10 ºC, AcOH (400 µl) was then added and the reaction mixture was warmed to RT. The solvent was removed in vacuo, the residue redissolved in CH_2Cl_2 (15 ml) and benzaldehyde (460 µl, 4.5 mmol) added. The resultant solution was then heated to reflux for 18 hr, cooled to RT and the solvent removed *in vacuo*. The product **15** was purified by column chromatography 3:2 CH_2C1_2: hexane, to give 904 mg (54 %) of a colourless oil: ν_{max}/cm^{-1} (neat) 3405, 3084, 3060, 3027, 2945, 2918, 2851, 1728, 1600, 1493, 1454, 1371, 1357, 1323, 1302, 1270, 1217, 1178, 1140, 1091, 1075, 1028, 1010, 971, 926, 747, 700; δ_H (400 MHz, $CDCl_3$) 7.42-7.10 (14H, m), 5.87 (1H, ddt, *J* 17.2, 10.5, 5.5 Hz), 5.52 (1H, s), 5.23 (1H, dq, *J* 17.2, 1.5 Hz), 5.18 (1H, dq, *J* 10.5, 1.5 Hz), 4.63 (1H, ddt, *J* 13.5, 5.5, 1.5 Hz), 4.54 (1H, ddt, *J* 13.5, 5.5, 1.5 Hz), 4.02 (1H, dd, *J* 5.0, 4.0 Hz), 3.96 (1H, d, *J* 13.8 Hz), 3.90 (1H, d, J 13.8 Hz), 3.33-3.22 (2H, m); δ_C (100 MHz, $CDCl_3$) 173.4, 142.8, 140.0, 137.1, 135.5, 132.6, 129.5, 129.3, 129.2, 129.0, 128.6, 127.7, 127.5, 122.2, 120.0, 118.8, 118.5, 111.5, 106.9, 65.4, 61.4, 56.7, 54.9, 25.0; HRMS (electrospray) *m/z* calc. $[M+H]^+$ ($C_{28}H_{27}N_2O_2$) 423.2073, obs. 423.2067.

Allyl (1*R*,3*S*)-9-methyl-1-phenyl-2-(phenylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (16). The allyl ester **15** (571 mg, 1.35 mmol) dissolved in dry DMF (15 ml) and cooled to 0 ºC. NaH (54 mg of a 60 % dispersion in mineral oil, 1.35 mmol) and iodomethane (92 µl, 1.48 mmol) were added and the resultant mixture stirred at 0 ºC for 2 hr and RT for 2 hr. The solvent was removed in vacuo, the residue redissolved in CH_2Cl_2 (15 ml) and washed with saturated sodium bicarbonate solution (30 ml). The phases were separated and the aqueous was washed with CH_2Cl_2 (2 x 15 ml). The combined organics were dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The product was purified by column chromatography using 3:2 CH_2C1_2: hexane, to give 409 mg (69 %) of a colourless oil. The product **16** displayed the following ^1H NMR data, but was used without further characterisation: ν_{max}/cm^{-1} (neat) 3057, 3027, 2933, 2847, 1732, 1647, 1492, 1470, 1454, 1372, 1262, 1216, 1172, 741, 700; δH (400 MHz, $CDCl_3$) 7.62 (1H, d, *J* 8.0 Hz), 7.41-7.14 (13H, m), 5.89 (1H, ddt, *J* 17.2, 10.5, 5.5 Hz), 5.27 (1H, dq, *J* 17.2, 1.5 Hz), 5.20 (1H, dq, *J* 10.5, 1.5 Hz), 5.19 (1H, s), 4.64 (1H, ddt, J 13.4, 5.5, 1.5 Hz), 4.56 (1H, ddt, *J* 13.4, 5.5, 1.5 Hz), 3.99 (1H, d, *J* 13.5 Hz), 3.96 (1H, dd, *J* 7.0, 6.0 Hz), 3.79 (1H, d, *J* 13.5 Hz), 3.31 (3H, s), 3.25 (2H, dd, *J* 9.0, 8.0 Hz); δ_C (100 MHz, $CDCl_3$) 173.2, 142.0, 140.2, 137.9, 135.4, 132.6, 129.9, 129.4, 128.8, 128.7, 128.1, 127.6, 126.9, 121.7, 119.5, 118.8, 118.5, 109.3, 107.5, 65.5, 59.9, 56.5, 53.7, 30.4, 23.5; HRMS (electrospray) *m/z* calc. $[M+H]^+$ ($C_{29}H_{29}N_2O_2$) 437.2229, obs. 437.2219.

(1*R*,3*S*)-9-Methyl-1-phenyl-2-(phenylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (17). The allyl ester **16** (204 mg, 4.7 mmol) was dissolved in THF (15 ml) and added via a syringe to $Pd(Ph_3)_4$ (53 mg, 0.47 mmol) under Ar. Morpholine (400 µl, 47 mmol) was added via syringe and the resultant mixture was stirred at RT for 10 min. The solvent was removed in vacuo, the residue redissolved in CH_2Cl_2 (15 ml) and washed with 2 M HCl solution

(2 x 15 ml). The phases were separated and the aqueous was washed with CH_2Cl_2 (2 x 15 ml). The combined organics were dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude product **17** was used immediately in the following reaction, and displayed: ν_{max}/cm^{-1} (neat): 3600-2800, 3057, 3031, 2936, 1699, 1471, 1456, 1406, 1311, 1244, 1217, 1189, 1103, 1000, 742, 698.

Ethoxyformic (1*R*,3*S*)-9-methyl-1-phenyl-2-(phenylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole-3-carboxylic anhydride (18). (1R,3S)-3-Carboxy-1-phenyl-2-phenylmethyl-1,2,3,4-tetrahydro-9-methylpyrido[3,4-b]indole was dissolved in CH_2Cl_2 (10 ml) and cooled to -10 ºC, ethyl chloroformate and Et_3N were then added and the resultant solution was stirred at -10 ºC for 1 h. The solvent was then removed *in vacuo* and the crude product **18** was then used immediately in the next reaction after limited characterisation: ν_{max}/cm^{-1} (neat): 2931, 2604, 2498, 2360, 2342, 1824, 1704, 1471, 1456, 1399, 1278, 1105, 1031, 997, 741, 700; δ_H (400 MHz, $CDCl_3$) 7.76-7.13 (14H, m), 5.17 (1H, s), 4.28 (2H, q, *J* 7.0 Hz), 4.09 (1H, dd, *J* 7.0, 6.0 Hz), 3.97 (1H, d, *J* 13.5 Hz), 3.80 (1H, d, *J* 13.5 Hz), 3.35-3.21 (2H, m), 3.29 (3H, s), 1.34 (3H, t, *J* 7.0 Hz).

(1*R*,3*S*)-3-Diazoacetyl-1-methyl-1-phenyl-2-(phenylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole (19). The anhydride **18** was dissolved in CH_2Cl_2 (10 ml) and cooled to -10 ºC. An alcohol free ethereal solution of diazomethane (20 ml) was then added via a flame polished pipette and the resultant solution was stirred at -10 ºC for 1 h and then RT for 72 h. The solvent was removed under a steady stream of compressed air. The product was purified by column chromatography using CH_2C1_2 as eluent, to give 112 mg (57 % from the allyl ester) of **19** as a pale yellow oil. The product displayed: ν_{max}/cm^{-1} (neat): 3031, 2920, 2106, 1742, 1700, 1652, 1471, 1395, 1343, 1314, 1282, 1212, 1185, 1106, 1031, 1006, 742, 699; δ_H (400 MHz, $CDCl_3$) 7.71 (1H, d, *J* 8.0 Hz), 7.51-7.20 (11H, m), 7.05 (2H, d, *J* 4.0 Hz), 5.97 (1H, s), 4.95 (1H, s), 3.84 (1H, d, *J* 13.5 Hz), 3.78 (1H, dd, *J* 11.0, 5.0 Hz), 3.64 (1H, d, *J* 13.5 Hz), 3.32 (3H, s), 3.27-3.06 (2H, m).

HRMS (electrospray) *m/z* calc. $[M+H-N_2]^+$ ($C_{27}H_{25}N_2O$) 393.1961, obs. 393.1968.

1-Methyl-1-phenyl-2-(phenylmethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-spiro-(2-oxocyclopropane) (22). To a stirred solution of rhodium(II) acetate (~0.1 mg) in CH_2Cl_2 (5 ml) under Ar was added over 2h using a syringe pump (1R, 3S)-3-diazoacetyl-1-phenyl-2-phenylmethyl-1,2,3,4-tetrahydro-9-methylpyrido[3,4-*b*]indole (112 mg, 2.67 mmol) in CH_2Cl_2 (10 ml). The resultant solution was allowed to stir at RT for 18 hr. The solvent was removed *in vacuo* and the product was purified by column chromatography using 3:2 CH_2Cl_2: hexane as eluent, to give 61 mg (58 %) of the cyclopropanone **22** as a colourless oil. The product displayed: ν_{max}/cm^{-1} (neat): 3058, 3028, 2920, 2849, 1805, 1495, 1466, 1455, 1378, 1260, 1169, 1029, 923; δ_H (400 MHz, $CDCl_3$) 7.45-6.97 (14H, m), 4.75 (1H, s), 4.12 (1H, d, *J* 13.0 Hz), 3.92 (1H, d, *J* 13.0 Hz), 3.86 (1H, d, *J* 15.0 Hz), 3.76 (1H, d, *J* 15.0 Hz), 3.37 (1H, d, *J* 15.0 Hz), 3.29 (1H, d, *J* 15.0 Hz), 3.24 (3H, s); δ_C (100 MHz, $CDCl_3$) 203.4, 142.8, 141.8, 138.7, 138.3, 129.2, 129.1, 128.9, 128.8, 127.9, 127.6, 124.2, 121.5, 119.8, 119.4, 109.4, 101.5, 72.1, 54.0, 49.9, 31.3, 31.2; HRMS (electrospray) *m/z* calc. $[M+H]^+$ ($C_{27}H_{25}N_2O$) 393.1961, obs. 393.1968.

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References and Notes

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