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Catalytic Bimetalic [Pd(0)/Ag(I) Heck-1,3-Dipolar Cycloaddition Cascade Reactions Accessing Spiro-oxindoles. Concomitant in situ generation of Azomethine Ylides and Dipolarophile.

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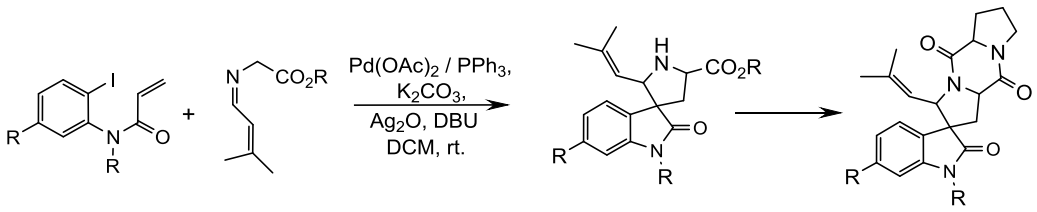

Catalytic Bimetallic [Pd(0)/Ag(I)] Heck-1,3-Dipolar Cycloaddition Cascade Reactions Accessing Spiro-oxindoles. Concomitant In situ Generation of Azomethine Ylides and Dipolarophiles.

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Abstract—

Spiro-oxindoles, epi-Spirotryprostatin A and its analogues were prepared from a tactical combination of cascade catalytic bimetallic Pd(0)/Ag(I), intramolecular Heck and subsequent imine → azomethine ylide → 1,3-Dipolar cycloaddition reactions. The cascade features *in situ* generation of azomethine ylides and dipolarophiles and produces two new rings together with three stereocentres in good to excellent yields.

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Keywords; Spirotryprostatins, spiro-oxindole, Heck reaction, Peterson olefination, imine, azomethine ylide, 1,3-dipolar cycloaddition cascade

1. Introduction.

The spiro-oxindole motif is an important structural feature within a range of bioactive indole alkaloids, such as the anti-cancer spirotryprostatins A **1** and B **2** which were isolated from *Aspergillus fumigatus*,[1] and the hemiterpene spiro-oxindole alkaloids[2,3a-c] elacomine **3a** and isoelacomine **3b** (Figure 1). Correspondingly, there has been significant interest in the development of efficient synthetic approaches to these systems.[4, 5] For instance, Danishefsky and co-workers have reported the synthesis of molecules **4** and **5** (Figure 1), which are potent analogues of the spirotryptostatins, showing significantly enhanced activity when compared to either spirotryprostatin A **1** and B **2** when tested against MDA MB-468 and MC57 human breast cancer cell lines.[5]

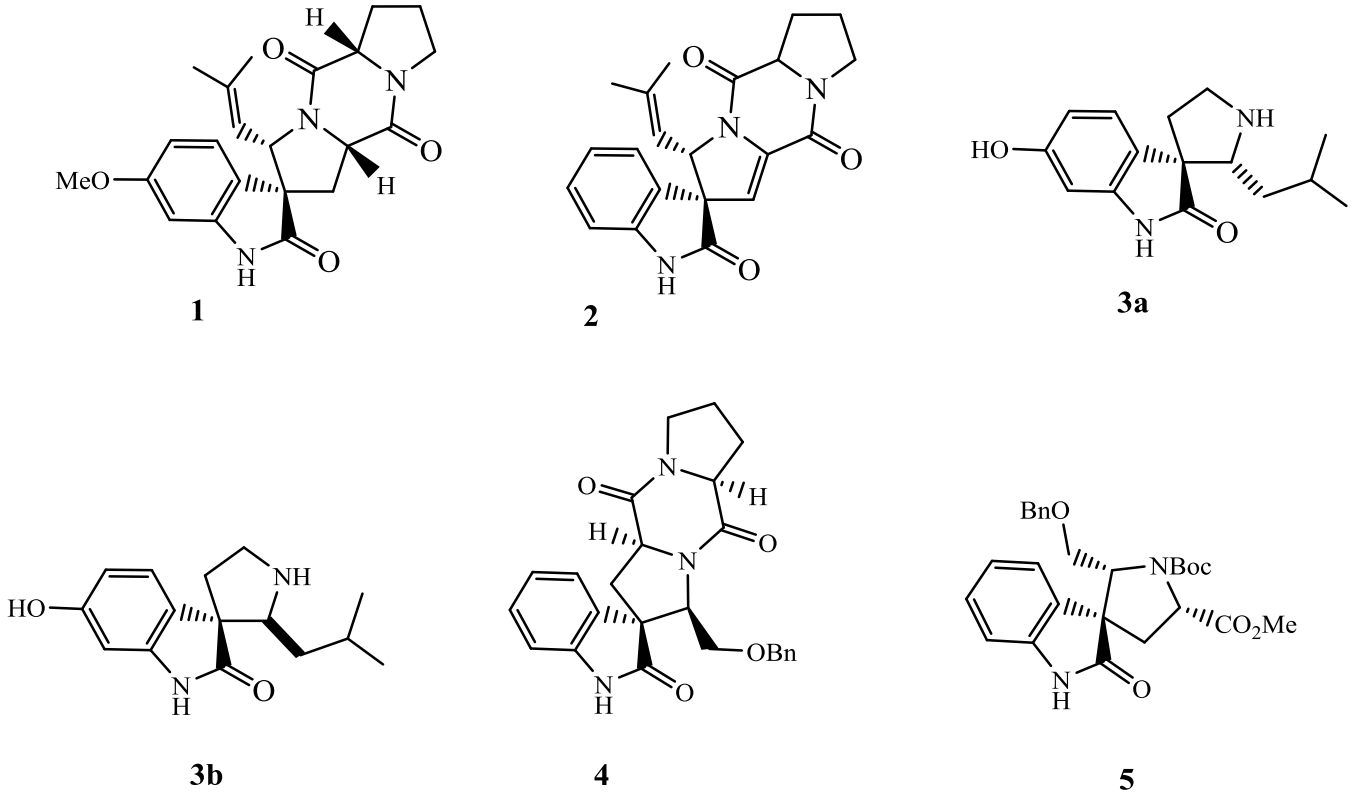
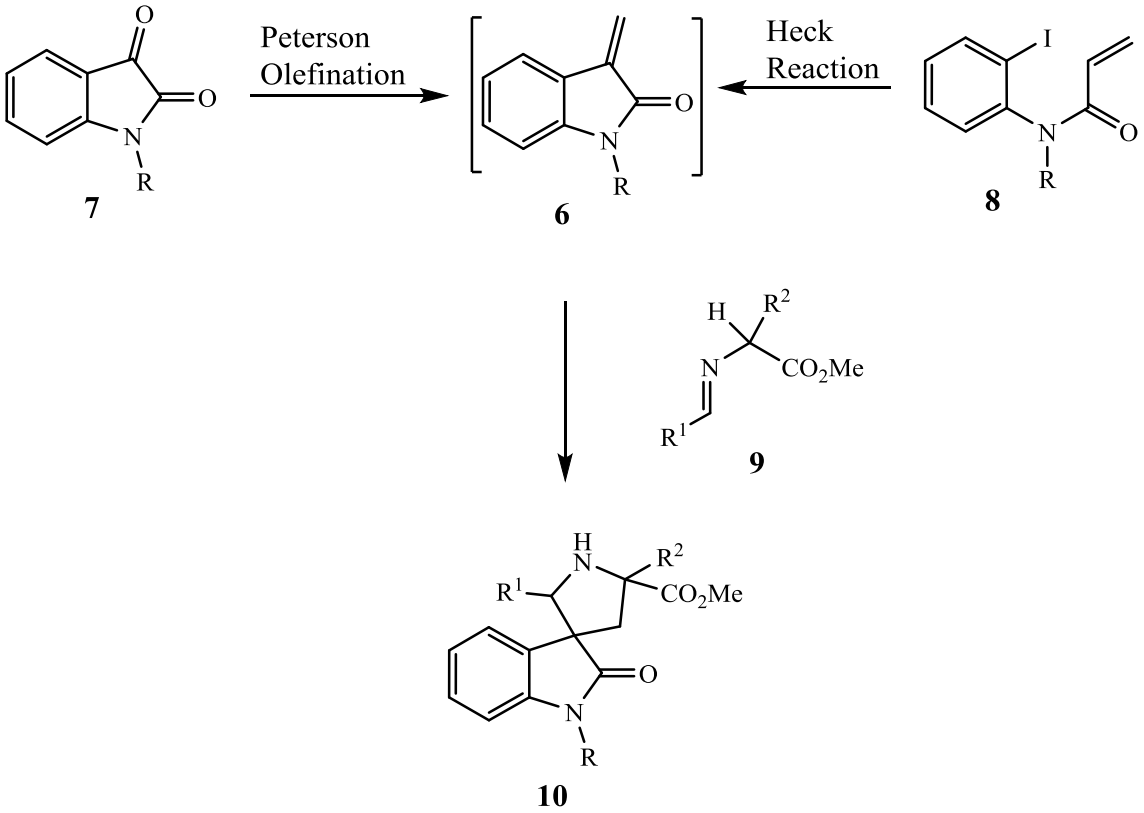


Figure 1. Some biologically active spiro-oxindoles

We have previously described a range of palladium-catalysed cyclisation and cycloaddition-based cascades which provide facile, stereo- and regiocontrolled access to a wide range of carbocyclic and heterocyclic systems including spiro- and bridged-ring heterocycles, *beta*-lactam analogues, isoquinolines, nucleosides, cyclopropyl diindolylmethanes, γ-carbolines AC190- analogues, and various other bioactive compounds.[6a-i] As part of this work, we have previously reported the combination of imine → azomethine ylide → cycloaddition with a Heck reaction[7] and in a preliminary communication we have reported[8] an alternative tactical combination of an intramolecular Heck reaction and a subsequent Ag(I) catalysed imine → azomethine ylide → cycloaddition cascade in order to access novel spiro-oxindoles. In the present paper, in addition to providing full details of our earlier findings, we report the extension of this work to the formation of novel spiro-oxindole analogues containing two new rings and three stereocentres, together with a synthesis of epi-spirotryprostatin A and its analogues, in good to excellent yields.

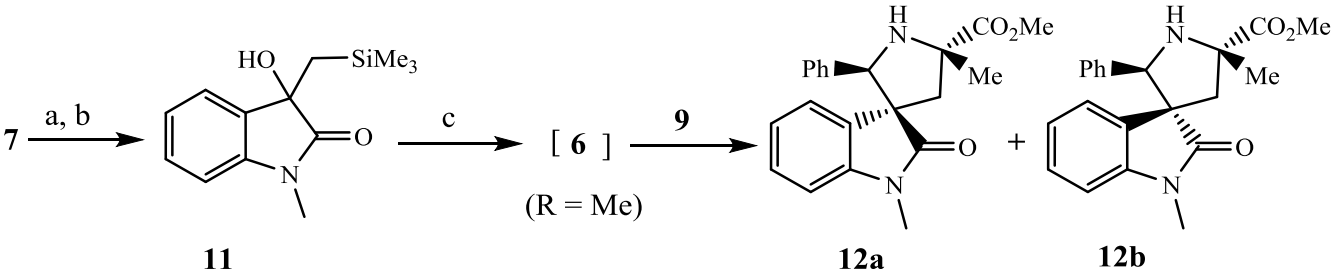
2. Results and Discussion

Two cascade approaches to spiro-oxindoles have been developed, both involving *in situ* formation and trapping of a 3-methylene oxindole dipolarophile moiety **6**, followed by cycloaddition with *in situ* generated azomethine ylides derived from imines **9** to form spiro-oxindoles **10** (Scheme 1).



Scheme 1. An approach to spiro-oxindoles **10** via cycloadditions of methylene oxindole **6**.

In the first approach, which is based upon a Peterson olefination route to methylene oxindole **6**, the spiro-oxindoles **12a/b** were obtained from a Peterson olefination - 1,3-dipolar cycloaddition cascade. Thus *N*-methyl isatin **7** (R = Me) was reacted with trimethylsilylmethyl magnesium chloride followed by addition of ammonium chloride solution to give β-hydroxysilane **11** in 92% yield. Reaction of **11** with imine **9** (R^1 = Ph, R^2 = Me), in the presence of KH, triethylamine and 10 mol% silver(I) oxide in toluene at 0 °C afforded spiro-oxindole **12a** and **12b** as a 2:1 mixture of stereoisomers, presumably via trapping of methylene intermediate **6** (Scheme 2).



Scheme 2. Synthesis of spiro-oxindoles **12**. a. Me_3SiCH_2MgCl, THF, 45 ° C, 4.5 h. b. NH_4Cl, H_2O c. KH, Et_3N, AgO, imine **9** (R^1 = Ph, R^2 = Me), toluene, 0-20 ° C, 16 h.

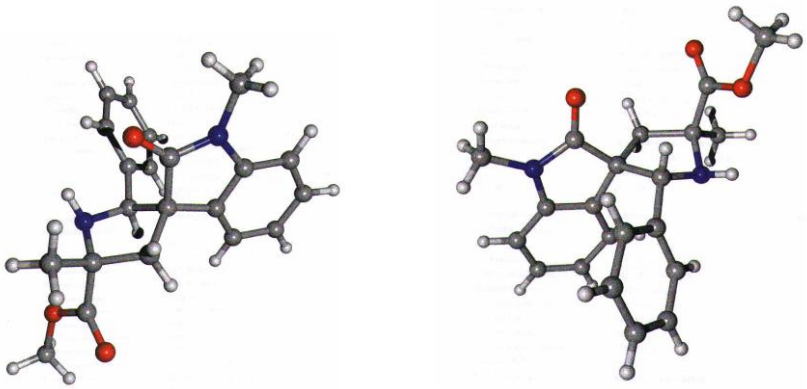


Figure 2. X-ray crystal structures of **12a** (left) and **12b** (right)

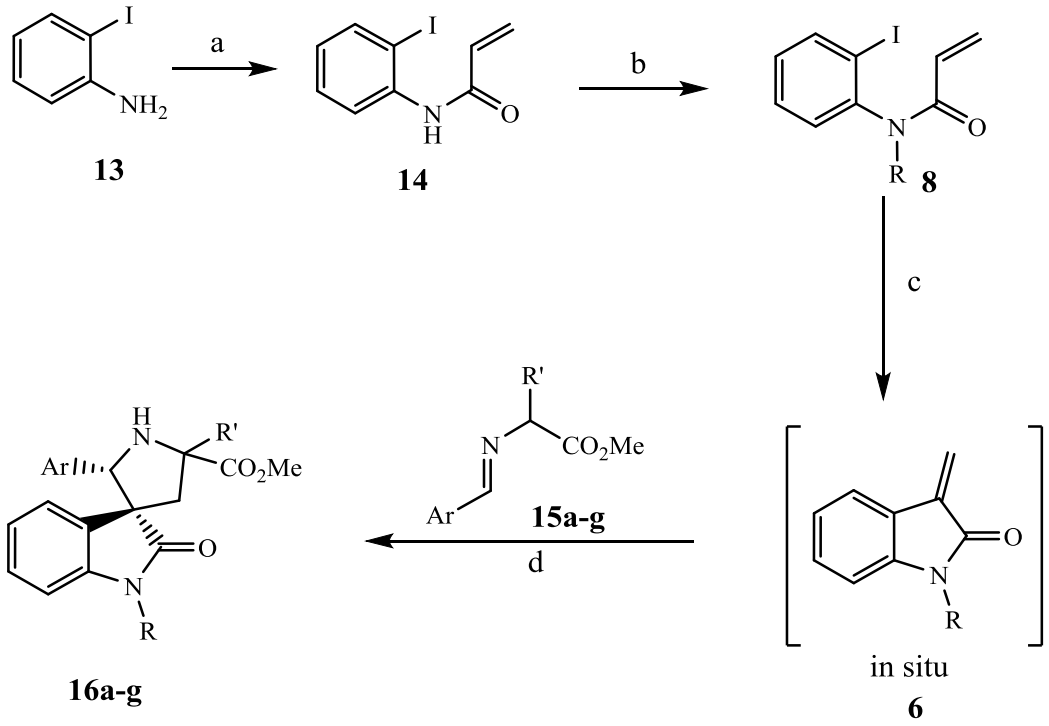
Syn-dipole. *Anti*-dipole

Figure 3. Possible structures of the *syn* and *anti* 1,3-dipoles derived from imines **9**.

The stereochemistry of the isomeric products was established unambiguously using single crystal X-ray analysis (Figure 2). The regiochemistry within both crystal structures was consistent with the expected regioselective nature of the reaction, confirming that both products arise from cycloaddition of

the *anti*-dipole (Figures 3) and the major product, **12a** arises *via* an *endo*-transition state, whilst the minor isomer **12b** arises *via* an *exo*-transition state.[9, 10]

In the second approach to the synthesis of the spiro-oxindoles, which is based upon a Heck cyclisation, compounds **16a-g** were obtained from the combination of a palladium-catalysed intramolecular Heck reaction and subsequent Ag(I) catalysed imine → azomethine ylide → 1,3-dipolar cycloaddition cascade reaction (Scheme 3)**.** The precursor **8** (R = Me) was prepared by reacting *o*-iodoaniline with acryloyl chloride in the presence of triethyl amine followed by *N*-methylation with methyl iodide in the presence of sodium hydride, to give **8** (R = Me) in 82% yield. This cascade process was performed with $Pd(OAc)_2/PPh_3$ for the intramolecular Heck reaction and a subsequent regiospecific *endo*-selective Ag(I) catalysed cycloaddition cascade gave spiro-oxindoles **16a-g** which comprised a ca. 4:1 to >9:1 mixture of two stereoisomers in good yields (Table 1). The structural characterisation of the products was made using both NMR spectroscopy and also *via* obtaining an X-ray crystal structure of compounds **16a** and **16b** (Figures 3 and 4).

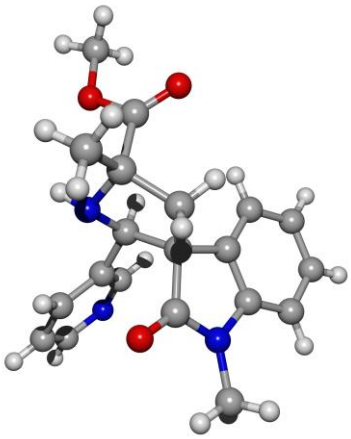


Scheme 3. a. CH_2=CHCOCl, Et_3N, DCM, rt. b. NaH, MeI, DMF, rt. c. $Pd(OAc)_2$/ PPh_3, K_2CO_3, d Imine (**15a-g),** Ag_2O, DBU, DCM, rt. (e) Isomer ratios determined from the ^{1}H NMR spectrum of the crude reaction mixture.

Table 1 Spiro-oxindoles and isomer ratios from intramolecular Heck–1,3-dipolar cycloaddition reaction[a].

Entry	Imine	Ar	R'	Spiro-oxindole (R = Me)	Yield (%)	Isomer Ratio[b]
1	**15a**		Me	**16a**	72	9.0:1
2	**15b**		CH_2OH	**16b**	68	>9:1
3	**15c**		CH_2Ph	**16c**	67	6.4:1
4	**15d**		4-OH-Bn	**16d**	68	5.4:1
5	**15e**		CH_2OH	**16e**	59	>9:1
6	**15f**		CH_2Ph	**16f**	62	7.8:1
7	**15g**		4-OH-Bn	**16g**	63	4.2:1

(a) All reactions were carried out in dichloromethane at room temperature over 18 h and employed 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 10 mol% Ag_2O and 1 mol. eq. DBU.
(b) Isomer ratios determined from the ^1H NMR spectra of the crude reaction mixtures



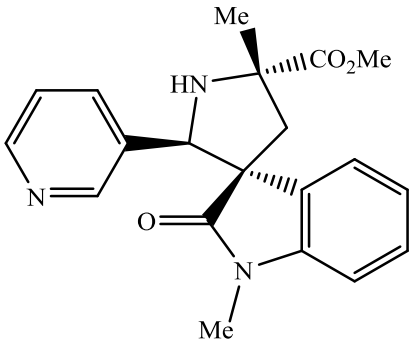


Figure 3: X-ray crystal structure of the major stereoisomer **16a**

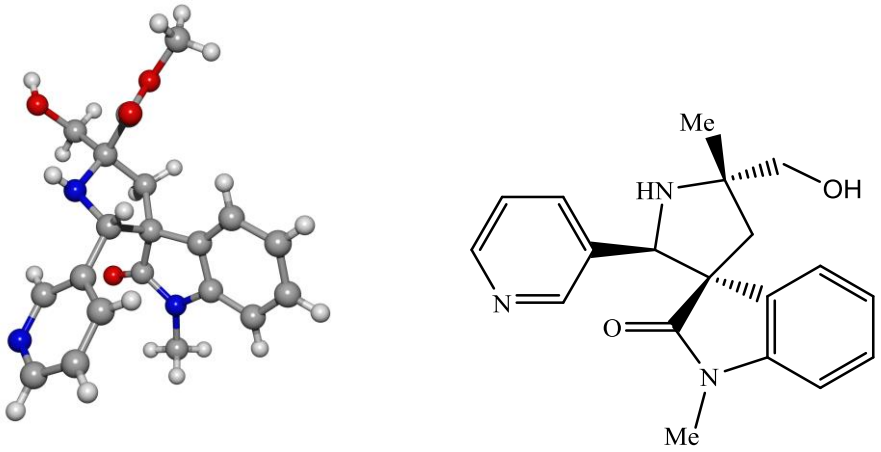
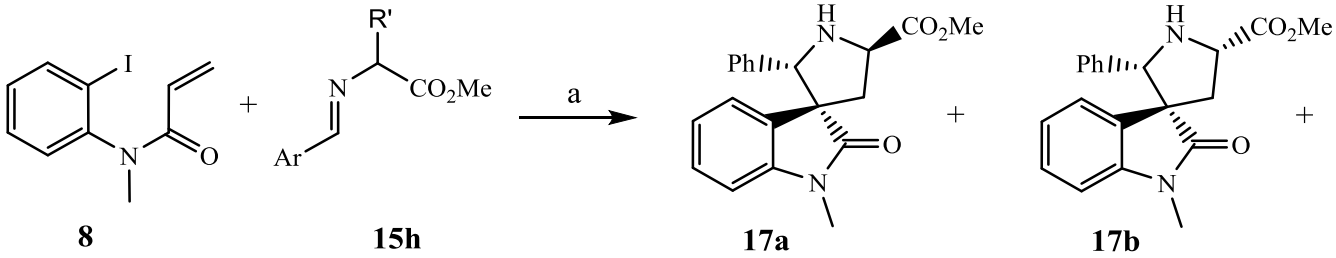


Figure 4: X-ray crystal structure of the major stereoisomer **16b**[8]

In the case of imine (**15h**, Ar = Ph, R' = H), derived from methyl glycinate, (Scheme 4), spiro-oxindoles **17a** and **17b** were obtained in a 1.2:1 isomer ratio. The stereochemistry of both products was determined using X-ray crystallographic analysis (Figure 5). It follows that the structure of the major isomer **17a** is consistent with resulting from cycloaddition of the *anti*-dipole, whilst the minor isomer **17b** resulted from the *syn*-dipole, by proceeding *via endo*-transition states respectively.



Scheme 4. a. $Pd(OAc)_2/PPh_3$, K_2CO_3; Ag_2O, DBU, CH_2Cl_2, rt. Isomer ratios determined from the ^1H NMR spectrum of the crude reaction mixture

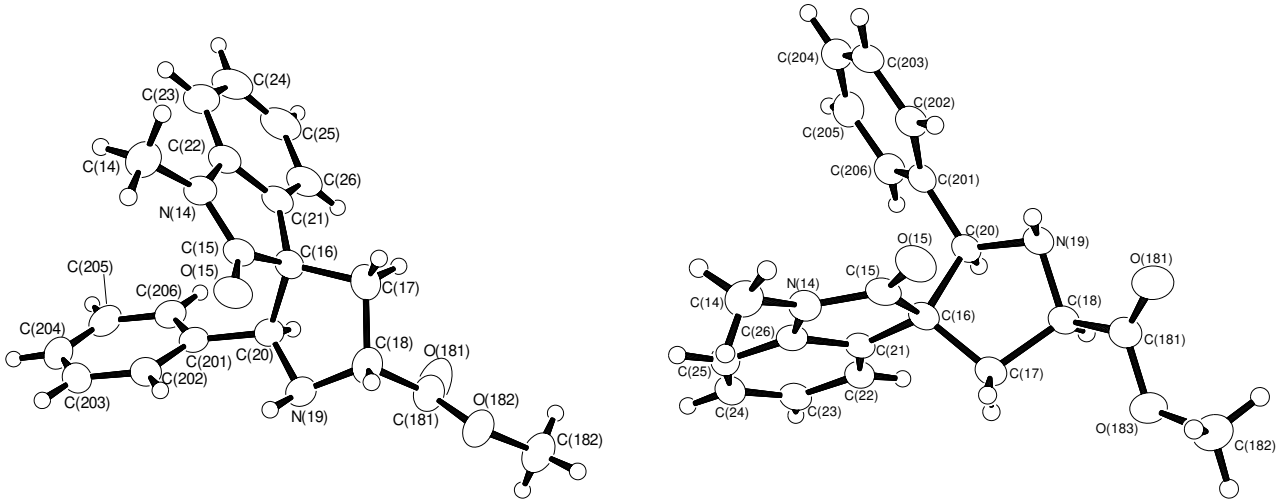
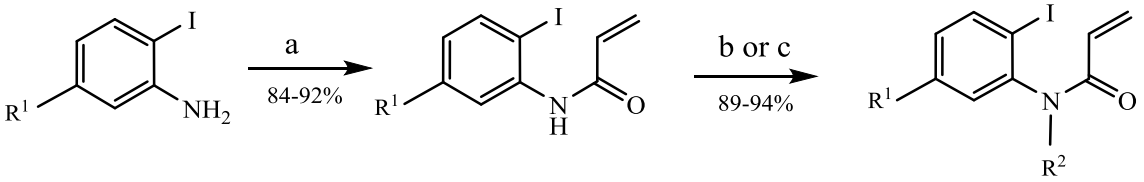


Figure 5: X-ray crystal structure of spirocycles **17a**[8] (left) and **17b**[8] (right)

Synthesis of *epi*-spirotryprostatin A and analogues:

In order to demonstrate the potential of our intramolecular Heck reaction-1,3-dipolar cycloaddition cascade, in the synthesis of biologically interesting molecules, we have utilized this approach to spiro-oxindoles in the synthesis of *epi*-spirotryprostatin A and analogues**.** The substrates **8a** and **8b** for access to *epi*-spirotryprostatin A and analogues were produced from readily available, inexpensive starting materials as outlined in Scheme 5. In the case of 2-iodo-5-methoxy-phenylamine (**13**, R^1 = OMe), this was prepared from 4-iodo nitroanisole. Thus the reaction of iodoaniline **13** with acryloyl chloride provided the acrylamide **14**, which was then methylated and/or Boc- protected by treatment with sodium hydride - methyl iodide and $(Boc)_2O$-DMAP respectively.



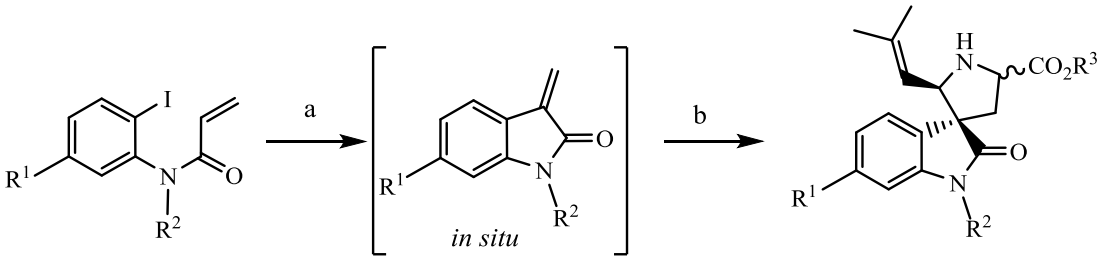
13

14 a. R^1 = H
b. R^1 = OMe

8 a. R^1 = H, R^2 = Me
b. R^1 = OMe, R^2 = Boc

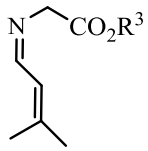
Scheme 5. Synthesis of Substrates **8**. a. Et_3N, CH_2=CHCOCl, CH_2Cl_2, rt. b. NaH, MeI, DMF, 0 ° C to rt. c. $(Boc)_2O$, DMAP, CH_3CN, rt

The key cyclisation reaction was developed as a one-pot cascade at room temperature (Scheme 6) in which the first step involved the Pd(0)-catalysed intramolecular Heck reaction with *in situ* generating dipolarophile **18a,b**, subsequent reaction of Ag(I)-catalysed imine → azomethine ylide → 1,3-dipolar cycloaddition led to the formation of the spiro-oxindoles **20-22** as a mixture of two stereoisomers with one predominating in a good yield. The configuration of both isomers was determined via comparison of the ^{1}H NMR spectra with the spectra obtained for the structurally similar compounds **17a,b** and for which, the stereochemistry was established using X-ray crystallography (see experimental section). In an analogous fashion to the reactions reported above, this sequence proceeded regiospecifically and the structure of the minor isomer is consistent with the product resulting from cycloaddition of the *syn*-dipole. The spiro-oxindoles **20a/b** were isolated in 45% yield as a 1.2:1 mixture of stereoisomers and the spiro-oxindoles **21a/b,** derived from glycine ethyl ester, were obtained in 63%, (as a 1.8:1 mixture of stereoisomers), and spiro-oxindoles **22a/b** in 52% yield as 2.1:1 mixture of stereoisomers.

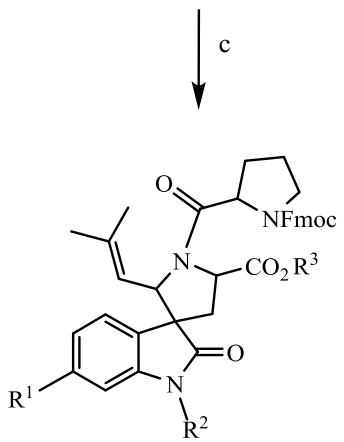


8a-b **18a-b** **20-22**

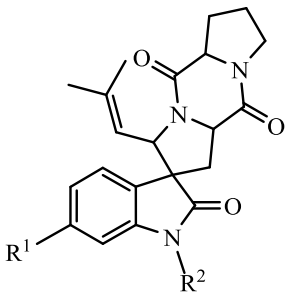
20. R^1 = H, R^2 = Me, R^3 = Me 45%
21. R^1 = H, R^2 = Me, R^3 = Et 63%
22. R^1 = OMe, R^2 = Boc, R^3 = Et 52%



19 a. R = Me
b. R = Et



23



24-25

24. R^1 = H, R^2 = Me 86%
25. R^1 = OMe, R^2 = H 70%

Scheme 6. a. 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3, K_2CO_3, b. imine (**19a-b),** 10 mol% of Ag_2O, DBU, DCM, 15-20 ^{o} C. c. Fmoc-L-ProCl, aq Na_2CO_3/CH_2Cl_2, rt. d. 20% piperidine, CH_2Cl_2, rt, (followed by TFA, Et_3SiH, CH_2Cl_2, rt in the case of **25**). Isomer ratios determined from the ^1H NMR spectra of the crude reaction mixtures.

Two-phase Schotten-Baumann acylation of relatively hindered amines **20-22** provided amides **23** as a mixture of stereoisomers. Deprotection of the Fmoc group in **23** triggered diketopiperazine cyclisation to yield **24** and **25** as a mixture of four diastereoisomer in 5:4:3.5:2 ratio in 86% and 70% yield respectively**.** This cyclisation yielded epimeric **24a,b** and **25a,b** and their diastereoisomers **24c,d** and **25c,d** (Figure 6). Molecule **25b** corresponds to 3-*epi*-spirotryprostatin A, and molecule **25b** corresponds to 18-*epi*-spirotryprostatin A. The stereochemistry of the products was assigned using n.O.e data (see experimental section), as well as comparison of these results with those from related studies.[1,4] Unequivocal proof was also obtained for one of the major isomer resulting in product **24b** via determination of the X-ray crystal structure (Figure 7).

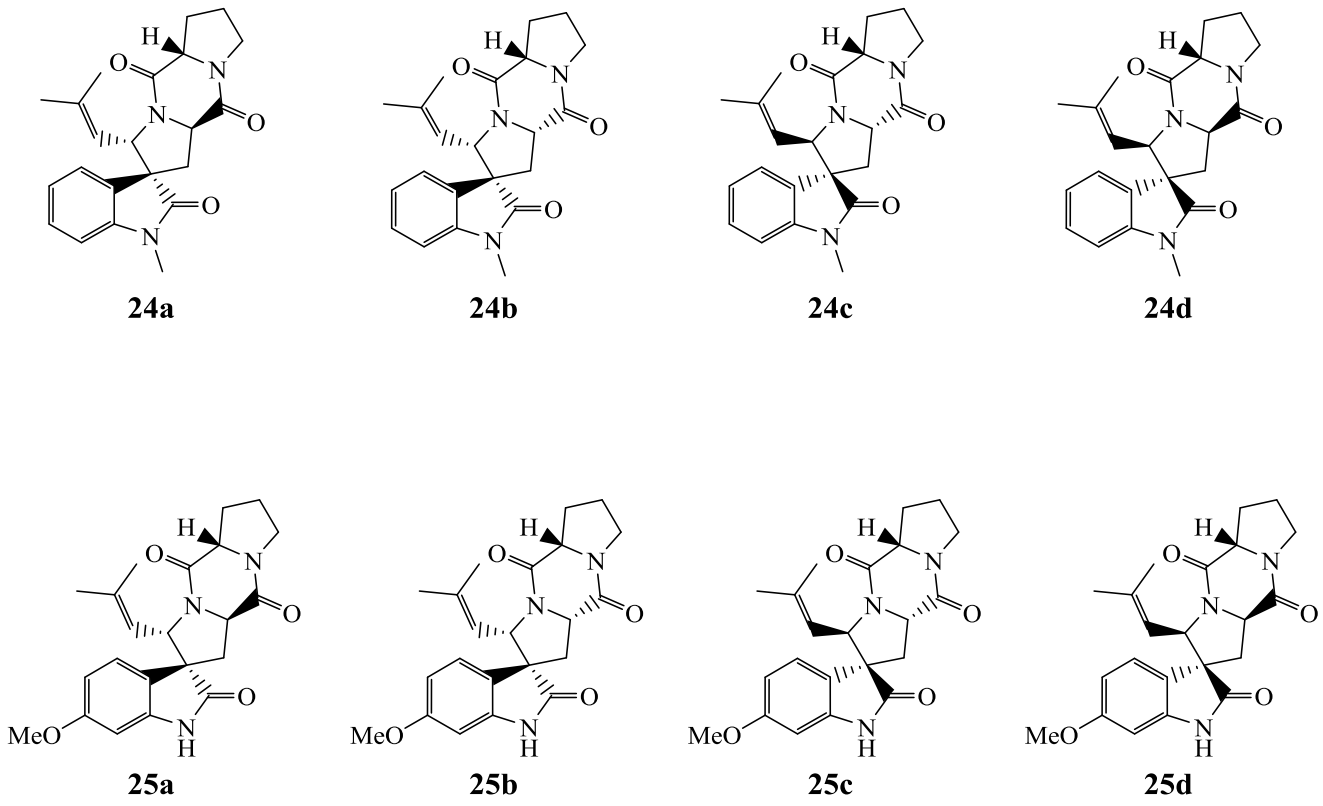


Figure 6. Structures of diastereoisomeric diketopiperazines

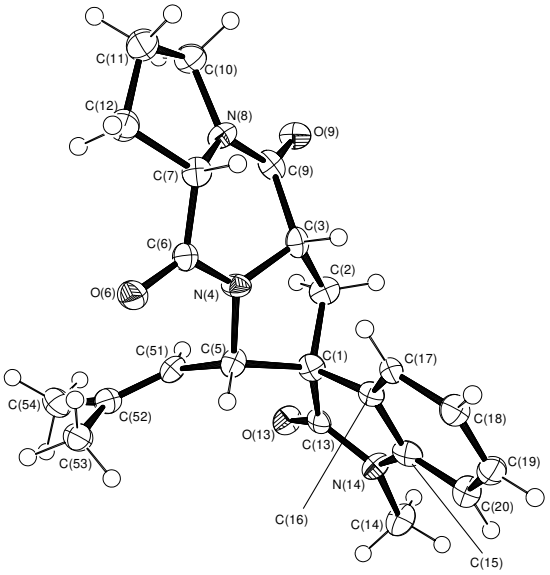


Figure 7. X-ray crystal structure of **24b (**for details see Supporting Information).

3. Conclusion.

The tactical combination of bimetallic Pd(0)/Ag(I) Heck-1,3-dipolar cycloaddition cascades offers an extremely simple and versatile route to a variety of structurally diverse spiro-oxindole-based systems. Furthermore, this approach is readily amenable to the production of complex biologically active systems as underlined by our facile synthesis of *epi*-spirotryprostatin A and its analogues as described above. It should be possible to apply this approach in a combinatorial fashion in order to create spiro-oxindoles with highly diverse functionality surrounding the core structure. Access to such diverse spiro-oxindole-based combinatorial libraries will be a valuable addition in the discovery of bioactive molecules.

4. Experimental Section

4.1. General information

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Mass spectra were recorded on a V.G.-AutoSpec instrument operating at 70 eV as electron impact (EI^+) spectra, and accurate molecular weights were determined using perfluorokerosine as an internal standard. Electrospray (ES^+) mass spectra were recorded using a Micro Mass LCT Time of Flight "KA111" instrument. Accurate molecular weights were recorded as ES^+ spectra using the EPSRC service. IR spectra were recorded using a Midac Prospect (Grams v3.2) instrument using a dichloromethane film on sodium chloride plates. Microanalyses were obtained using a Carlo-Erba Model 1106 instrument. Nuclear magnetic resonance spectra and decoupling experiments were determined at 500 MHz on a Bruker DRX500 instrument; at 300 MHz on either a General Electric QE300 instrument or a Bruker DPX300 instrument and at 250 MHz on a Bruker AC250 instrument. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker DPX300 instrument as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in $CDCl_3$ except where otherwise stated. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Specific optical rotations were measured in an Optical Activity Ltd., AA1000 polarimeter. THF was distilled from sodium-benzophenone ketyl. Toluene was dried over sodium wire. Dichloromethane was distilled from calcium hydride. All other commercially available reagents were used as received. Petroleum ether refers the fraction with b.p. 40-60 ºC unless otherwise specified. All reactions involving silver (I) salts were shielded from light by covering with aluminium foil and all air or moisture sensitive reactions were carried out under dry nitrogen.

The known compounds; *N-Methylisatin* **7**[11], *2-benzylideneamino-propionic acid methyl ester* 9[12] (R^1 =Ph, R^2 = Me)[12], *N-(2-iodo-phenyl)-acrylamide* ***14***[13], *N-(2-iodo-phenyl)-N-methyl-acrylamide* ***8***[13], *2-(pyridin-3-ylmethyleneamino)-propionic acid methyl ester* ***15a***[14], *3-phenyl-2-(pyridin-3-ylmethyleneamino)-propionic acid methyl ester* ***15c***[14], *2-benzylideneamino-3-hydroxy-propionic acid methyl ester* **15e**[15], *2-benzylideneamino-3-phenyl-propionic acid methyl ester* **15f**[16] and *2-benzylideneamino-3-(4-hydroxyphenyl)-propionic acid methyl ester* **15g**[17] were prepared according to published procedures. Novel compounds were prepared using the procedures given below.

4.2. Synthetic procedures and characterization data

*4.2.1. 3-Hydroxy-1-methyl-3-trimethylsilanyl-methyl-1,3-dihydro-indol-2-one **(11).*** A 1.0 M solution of trimethylsilylmethyl magnesium chloride (Me_3SiCH_2MgCI) in ether (3.00 mL, 3.00 mmol) was added dropwise to a solution of *N*-methylisatin **7** (0.49 g, 3.04 mmol) in THF (30 mL) over 5 min at room temperature. The resulting mixture was then heated to 45° C for 4.5 h, quenched using aqueous NH_4CI, and extracted with diethyl ether (3 x 30 mL). The organic phases were then dried over anhydrous $MgSO_4$, and the solvents evaporated *in vacuo.* The resulting solid was recrystallised from dichloromethane-hexane to give the *title compound* as orange needles (0.68 g, 92%); mp. 78-81 ºC; ^{1}H NMR (250 MHz): δ 7.06-6.88 (m, 4H, ArH), 3.29 (s, 3H, NCH_3), 1.58 (s, 2H, CH_2), 0.22 (s, 9H, $(CH_3)_3$; ^{13}C NMR: δ 179.6 (C=O), 144.1, 132.3, 130.9, 125.4, 124.4 and 109.7 (ArC), 76.9 (COH), 29.9 (CH_2), 27.5 (NCH_3) and 0.0 (3 x CH_3). υ_{max}: (cm^{-1}): 3055 (C-H), 1720 (C=O) and 1265 (C-Si); *m/z* (EI^+, %): 161 (M^+, 68), 133 (35), 104 (100), 91 (33), 78 (54), 63 (31) and 51 (30); HRMS: $[M+NH_4]^+$ $C_{13}H_{19}NO_2Si$ requires 267.1529; found 267.1530.

*4.2.2. 1,5'-Dimethyl-2-oxo-2'-phenyl-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-5'-carboxylic acid methyl ester **(12a/b).*** Potassium hydride (35% dispersion in oil, 0.20 g, 1.75 mmol) was added to a suspension of silver oxide (0.04 g, 0.18 mmol) in toluene (40 mL) at 0 °C. A solution containing the β-hydroxysilane **11** (0.45 g, 1.80 mmol), imine **9** (R^1 = Ph, R^2 = Me), (0.35 g, 1.80 mmol) and triethylamine (0.25 mL, 1.79 mmol) in toluene (10 mL) was then added dropwise over 10 min with stirring. The mixture was allowed to warm to room temperature, stirred for a further 16 h, then quenched by addition of saturated aqueous ammonium chloride and extracted with ether (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Purification using flash chromatography (3:2 v/v petroleum ether-ethyl acetate to ethyl acetate, gradient elution) produced a mixture of the stereoisomeric *products* (**12a**:**12b** = 2:1) as an off-white solid. Repeated flash column chromatography (1:1 v/v ethyl acetate-petroleum ether) afforded first **12b** (0.11 g, 9%), followed by **12a** (0.20 g, 17%). Spiro-oxindole **12b** crystallised from dichloromethane-petroleum ether as colourless prisms; mp. 145-147°C; Spirocycle **12a** crystallised from dichloromethane-petroleum ether as colourless prisms; mp. 96-99°C; Found (mixed isomers): C, 71.8; H, 6.45; N, 8.0, $C_{21}H_{22}N_2O_3$ requires C, 72.0; H, 6.30; N, 8.0 %. **12a:** ^{1}H NMR (300 MHz): **δ** 7.41-7.09 (m, 6H, PhH), 6.81 (d, 2H, J 7.3 Hz, PhH), 6.50 (d, 1H, J 7.7 Hz, PhH), 4.53 (s, 1H, CHPh), 3.85 (s, 3H, CO_2CH_3), 2.98 (d, 1H, J 13.9 Hz, $C\underline{H}_AH_B$ $_{pyrrolidine}$), 2.71 (s, 3H, NCH_3) 2.40 (d, 1H, J 13.9 Hz, $CH_A\underline{H}_B$ $_{pyrrolidine}$) and 1.80 (s, 3H, CH_3); ^{13}C NMR): δ 178.5 and 178.3 (C=O), 143.1, 138.1, 132.4, 127.9, 127.8, 127.6, 127.5, 126.8, 126.4, 125.6, 122.4 and 107.7 (ArC), 70.6 (CHPh), 64.6 ($\underline{C}CO_2CH_3$), 59.4 ($C_{spirocentre}$), 53.1 ($CO_2\underline{C}H_3$), 46.5 (CH_2 $_{pyrrolidine}$),

27.7 (CH_3) and 26.6 (NCH_3); **ν** (cm^{-1}): 3300 ($N\text{-}H_{stretch}$), 3055 ($C\text{-}H_{stretch}$), 1709 ($C{=}O_{ester}$ and $C{=}O_{oxindole}$) and 1612 ($C{=}C_{aromatic}$); **m/z** (EI^+, %): 350 (M^+, 12), 291 (19), 191 (82), 160 (21), 131 (100), and 90 (22). **12b: δ ^{1}H** (300 MHz): 7.47 (dd, 1H, J 7.4 and 0.6 Hz, PhH), 7.11-6.88 (m, 7H, PhH), 6.51 (d, 1H, J 7.7 Hz, PhH), 4.67 (s, 1H, CHPh), 3.84 (s, 3H, CO_2CH_3), 3.14 (d, 1H, J 13.9 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 3.10 (s, 3H, NCH_3) 2.14 (d, 1H, J 13.9 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$) and 1.67 (s, 3H, CH_3); ^{13}C NMR): δ 178.4 and 178.3 (C=O), 143.1, 138.1, 132.4, 128.0, 127.8, 127.6, 127.5, 126.8, 126.6, 125.6, 122.4 and 107.7 (ArC), 70.6 (CHPh), 64.6 ($\underline{C}CO_2CH_3$), 59.3 ($C_{spirocentre}$), 53.1 ($CO_2\underline{C}H_3$), 46.5 ($CH_{2\ pyrrolidine}$), 27.7 (CH_3) and 26.5 (NCH_3); **ν** (cm^{-1}): 3300 ($N\text{-}H_{stretch}$), 3055 ($C\text{-}H_{stretch}$), 1705 ($C{=}O_{ester}$ and $C{=}O_{oxindole}$) and 1613 ($C{=}O_{aromatic}$); *m/z* (EI^+, %): 350 (M^+, 9), 263 (14), 191 (74), 160 (35), 131 (100), 104 (33), and 73 (35).

4.2.3. 3-Hydroxy-2-(pyridin-3-ylmethyleneamino)-propionic acid methyl ester ***(15b)***. Stirring a solution of triethylamine (0.38 mL, 2.72 mmol), serine methyl ester hydrochloride (0.43 g, 2.75 mmol) and pyridine-3-carboxaldehyde (0.24 mL, 2.56 mmol) in dichloromethane (30 mL) over 48 h gave *the title imine* (0.23 g, 45%) as a yellow oil which was used without further purification. ^{1}H NMR (250 MHz): δ 8.87 (d, 1H, J 1.7 Hz, PyH), 8.60 (dd, 1H, J 4.8 and 1.7 Hz, PyH), 8.37 (s, 1H, N=CH), 8.11 (dt, 1H, J 7.9 and 1.7 Hz, PyH), 7.31 (dd, 1H, J 7.9 and 4.8 Hz, PyH), 4.21 (dd, 1H, J 9.1 and 4.5 Hz, $C\underline{H}CO_2CH_3$), 4.12-4.01 (m, 1H, CH_2OH) and 3.77 (s, 3H, CO_2CH_3).

4.2.4. 3-(4-Hydroxyphenyl)-2-(pyridin-3-ylmethyleneamino)-propionic acid methyl ester ***(15d)***. Obtained from triethylamine (0.38 mL, 2.72 mmol), tyrosine methyl ester hydrochloride (0.64 g, 2.75 mmol) and pyridine-3-carboxaldehyde (0.24 mL, 2.56 mmol) in dichloromethane (30 mL) over 72 h as a pale yellow oil (0.64 g, 90%) and was used without further purification. ^{1}H NMR (250 MHz): δ 8.75 (s, 1H, PyH), 8.61 (d, 1H, J 4.7 Hz, PyH), 8.13 (d, 1H, J 7.8 Hz, PyH), 7.89 (s, 1H, N=CH), 7.36 (dd, 1H, J 7.8 and 4.7 Hz, PyH), 6.95 (d, 2H, J 8.1 Hz, PhH), 6.71 (d, 2H, J 8.1 Hz, PhH), 4.15 (dd, 1H, J 9.2 and 4.5 Hz, $C\underline{H}CO_2CH_3$), 3.76 (s, 3H, CO_2CH_3), 3.28 (dd, 1H, J 13.6 and 4.5 Hz, $C\underline{H}_AH_BAr$) and 3.05 (dd, 1H, J 13.6 and 9.2 Hz, $CH_A\underline{H}_BAr$); *m/z* (ES^+, %): 285 ($[M+H]^+$, 89) and 179 (100).

4.3. General procedure for the synthesis of spiro-oxindoles ***(16a-g).***

The appropriate imine (1 mol. eq.) was added to a stirred solution of *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide **7** (1 mol. eq.), potassium carbonate (2 mol. eq.), and silver oxide (0.1 mol. eq.), in dichloromethane (45 mL/mmol) at room temperature. Palladium acetate (0.1 mol. eq.) and triphenylphosphine (0.2 mol. eq.) were then added followed by the dropwise addition of DBU (1 mol.

eq.). The resulting mixture was stirred at room temperature for 18 h, quenched by addition of saturated aqueous ammonium chloride and extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography.

4.3.1. 1,5'-Dimethyl-2-oxo-2'-pyridin-3-yl-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-5'-carboxylic acid methyl ester ***(16a).*** Obtained using the General Procedure from imine **15a** (0.33 g, 1.71 mmol), *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide (0.49 g, 1.71 mmol), potassium carbonate (0.47 g, 3.40 mmol), silver oxide (0.039 g, 0.17 mmol), palladium acetate (0.038 g, 0.17 mmol), triphenylphosphine (0.089 g, 0.34 mmol) and DBU (0.25 mL, 1.67 mmol) in dichloromethane (80 mL). The *title compound* was obtained as a mixture of stereoisomeric products (isomer ratio = 9:1). Purification by flash column chromatography (ethyl acetate to 95:5 v/v ethyl acetate-methanol gradient elution) afforded firstly **16a** (0.23 g, 39%) which crystallised from dichloromethane-petroleum ether as colourless prisms; mp. 97-99°C, followed by **16a** (0.21 g, 35%) as a pale yellow oil; Found (mixed isomers): C, 66.9; H, 5.90; N, 11.6. $C_{20}H_{21}N_3O_3.0.5H_2O$ requires C, 66.7; H, 6.15; N, 11.7 %; ν (mixed isomers) (cm^{-1}): 3395 (N-$H_{stretch}$), 2971-2872 (C-$H_{stretch}$), 1714 (C=O_{ester}), 1709 (C=$O_{oxindole}$) and 1614 (C=$C_{aromatic}$).

16a: ^{1}H NMR (300 MHz): δ 8.37 (d, 1H, J 3.7 Hz, ArH), 7.86 (s, 1H, ArH), 7.48-7.06 (m, 5H, ArH), 6.65 (d, 1H, J 7.6 Hz, ArH), 4.56 (s, 1H, CHPy), 3.87 (s, 3H, CO_2CH_3), 3.15 (s, br, 1H, NH), 2.97 (d, 1H, J 14.0 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 2.75 (s, 3H, NCH_3) 2.43 (d, 1H, J 14.0 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$) and 1.79 (s, 3H, CH_3); ^{13}C NMR: δ 178.2 and 177.4 (C=O), 149.4, 148.0, 143.8, 134.1, 131.9, 130.2, 128.9, 123.4, 123.1, 122.9 and 108.5 (ArC), 70.8 (CHPy), 66.6 ($\underline{C}CO_2CH_3$), 60.6 ($C_{spirocentre}$), 53.1 ($CO_2\underline{C}H_3$), 46.3 (CH_2), 25.9 (CH_3) and 25.6 (NCH_3); *m/z* (ES$^+$, %): 352 ([M+H]$^+$, 100).

16a': δ ^{1}H (300 MHz): 8.31 (d, 1H, J 4.7 Hz, ArH), 7.86 (s, 1H, ArH), 7.43-6.99 (m, 5H, ArH), 6.58 (d, 1H, J 7.6 Hz, ArH), 4.55 (s, 1H, CHPy), 3.81 (s, 3H, CO_2CH_3), 3.54 (s, br, 1H, NH), 2.91 (d, 1H, J 14.0 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 2.70 (s, 3H, NCH_3) 2.31 (d, 1H, J 14.0 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$) and 1.66 (s, 3H, CH_3); *m/z* (ES$^+$, %): 352 ([M+H]$^+$, 100).

4.3.2. 5'-Hydroxymethyl-1-methyl-2-oxo-2'-pyridin-3-yl-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-5'-carboxylic acid methyl ester ***(16b).*** Obtained using the General Procedure from imine **15b** (0.35 g, 1.68 mmol), *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide (0.49 g, 1.71 mmol), potassium carbonate (0.47 g, 3.40 mmol), silver oxide (0.039 g, 0.17 mmol), palladium acetate (0.038 g, 0.17 mmol), triphenylphosphine (0.089 g, 0.34 mmol) and DBU (0.25 mL, 1.67 mmol) in dichloromethane (80 mL). Purification of the

crude reaction product using flash column chromatography (ethyl acetate to 90:10 v/v ethyl acetate-methanol, gradient elution) gave the *title compound* as a mixture of stereoisomers (0.42 g, 68%: isomer ratio = > 9 : 1). Crystallisation from dichloromethane – petroleum ether afforded the major isomer as colourless prisms; mp. 117-119 °C; Found: C, 65.2; H, 5.80; N, 11.4. $C_{20}H_{21}N_3O_4$ requires: C, 65.4; H, 5.75; N, 11.4 %; ^{1}H NMR (250 MHz): δ 8.39-6.63 (m, 8H, ArH), 4.68 (s, 1H, CHPy), 4.03 (d, 1H, J 10.8 Hz, $C\underline{H}_AH_BOH$), 3.94 (d, 1H, J 10.8 Hz, $CH_A\underline{H}_BOH$), 3.88 (s, 3H, CO_2CH_3), 2.82 (d, 1H, J 13.1 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 2.73 (s, 3H, NCH_3) and 2.72 (d, 1H, J 13.1 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$); ^{13}C NMR: δ 177.9 and 176.3 (C=O), 149.6, 148.1, 143.7, 134.9, 132.4, 129.5, 129.3, 123.9, 123.4 and 108.7 (ArC), 70.0 (CHPy), 69.9 ($\underline{C}CO_2CH_3$), 66.5 (CH_2OH), 59.1 ($C_{spirocentre}$), 53.4 ($CO_2\underline{C}H_3$), 39.9 (CH_2) and 26.1 (NCH_3). ν (cm^{-1}): 3495 (O-$H_{stretch}$), 1732 (C=O_{ester}), 1705 (C=$O_{oxindole}$) and 1495, 1614 (C=$C_{aromatic}$). *m/z* (FAB$^+$, %): 368 ([M+H]$^+$, 100), 336 (21), 208 (10), 175 (4) and 149 (5).

4.3.3. 5'-Benzyl-1-methyl-2-oxo-2'-pyridin-3-yl-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-5'-carboxylic acid methyl ester ***(16c).*** Obtained using the General Procedure from imine **15c** (0.46 g, 1.71 mmol), *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide (0.49 g, 1.71 mmol), potassium carbonate (0.47 g, 3.40 mmol), silver oxide (0.039 g, 0.17 mmol), palladium acetate (0.038 g, 0.17 mmol), triphenylphosphine (0.089 g, 0.34 mmol) and DBU (0.25 mL, 1.67 mmol) in dichloromethane (80 mL). Purification of the crude reaction product using flash column chromatography (ethyl acetate) followed by crystallisation from dichloromethane – petroleum ether afforded the *title compound* (as a mixture of isomers) (0.49 g, 67%: isomer ratio = 6.4:1) as colourless prisms; mp. 124-152 °C; Found (mixed isomers): C, 72.9; H, 5.90; N, 9.7. $C_{26}H_{25}N_3O_3$ requires: C, 73.1; H, 5.90; N, 9.8 %; ν (mixed isomers) (cm^{-1}): 3500-3350 (N-$H_{stretch}$), 2950-2860 (C-$H_{stretch}$), 1720 (C=O_{ester}), 1714 (C=$O_{oxindole}$) and 1495, 1614 (C=$C_{aromatic}$); *m/z* (FAB$^+$, %) (mixed isomers): 428 ([M+H]$^+$, 100), 368 (11), 268 (15), 208 (10) and 91 (8).

16c: ^{1}H NMR (250 MHz): δ 8.39-6.61 (m, 13H, ArH), 4.52 (s, 1H, CHPy), 3.81 (s, 3H, CO_2CH_3), 3.57 (d, 1H, J 13.0 Hz, $C\underline{H}_AH_BPh$), 3.40 (d, 1H, J 13.0 Hz, $CH_A\underline{H}_BPh$), 2.85 (d, 1H, J 14.1 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 2.75 (s, 3H, NCH_3) and 2.68 (d, 1H, J 14.1 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$); ^{13}CNMR: δ 177.9 and 176.9 (C=O), 149.6, 148.4, 143.9, 137.3, 134.7, 132.9, 132.6, 132.4, 130.4, 130.0, 129.0, 128.8, 127.4, 123.4, 123.2, 123.1 and 108.4 (ArC), 70.8 (CHPy), 70.2 ($\underline{C}CO_2CH_3$), 59.6 ($C_{spirocentre}$), 52.9 ($CO_2\underline{C}H_3$), 46.0 (CH_2Ph), 45.1 (CH_2) and 26.1 (NCH_3).

16c': ^{1}H NMR (250 MHz): 8.39-6.58 (m, 13H, ArH), 4.90 (s, 1H, CHPy), 3.78 (s, 3H, CO_2CH_3), 3.28 (d, 1H, J 13.1 Hz, $C\underline{H}_AH_BPh$), 3.14 (d, 1H, J 13.1 Hz, $CH_A\underline{H}_BPh$), 3.12 (s, 3H, NCH_3), 2.99 (d, 1H, J 14.0 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$) and 2.58 (d, 1H, J 14.0 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$).

*4.3.4. 5'-(4-Hydroxybenzyl)-1-methyl-2-oxo-2'-pyridin-3-yl-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-5'-carboxylic acid methyl ester **(16d)*.** Obtained using the General Procedure from imine **15d** (0.48 g, 1.70 mmol), *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide (0.49 g, 1.71 mmol), potassium carbonate (0.47 g, 3.40 mmol), silver oxide (0.039 g, 0.17 mmol), palladium acetate (0.038 g, 0.17 mmol), triphenylphosphine (0.089 g, 0.34 mmol) and DBU (0.25 mL, 1.7 mmol) in dichloromethane (80 mL). Purification of the reaction product using flash column chromatography (ethyl acetate) produced the *title compound* as a mixture of stereoisomers (0.51 g, 68%: isomer ratio = 5.4 : 1). Crystallisation from dichloromethane – petroleum ether afforded the mixture of isomers as colourless prisms; mp. 195-212 °C; Found (mixed isomers): C, 70.2; H, 5.75; N, 9.5. $C_{26}H_{25}N_3O_4$ requires: C, 70.4; H, 5.70; N, 9.5 %; ν (mixed isomers) (cm^{-1}): 3610 ($O\text{-}H_{stretch}$), 2925-2840 ($C\text{-}H_{stretch}$), 1720 ($C{=}O_{ester}$), 1713 ($C{=}O_{oxindole}$) and 1495, 1613 ($C{=}C_{aromatic}$); *m/z* (FAB^+, %) (mixed isomers): 444 ($[M+H]^+$, 100), 384 (10), 336 (20), 284 (8) and 107 (9).

16d: ^{1}H NMR (250 MHz): δ 8.39-6.62 (m, 12H, ArH), 4.54 (s, 1H, CHPy), 3.81 (s, 3H, CO_2CH_3), 3.46 (d, 1H, J 13.1 Hz, $C\underline{H}_AH_BAr$), 3.32 (d, 1H, J 13.1 Hz, $CH_A\underline{H}_BAr$), 2.83 (d, 1H, J 14.1 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 2.76 (s, 3H, NCH_3) and 2.66 (d, 1H, J 14.1 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$); ^{13}C NMR: δ 177.9 and 177.1 (C=O), 155.9, 148.8, 131.6, 131.1, 131.0, 129.2, 129.0, 128.7, 128.5, 128.4, 128.0, 127.7, 127.2, 123.4, 123.1, 115.9 and 108.5 (ArC), 70.8 (CHPy), 70.3 ($\underline{C}CO_2CH_3$), 59.6 ($C_{spirocentre}$), 52.8 ($CO_2\underline{C}H_3$), 45.3 (CH_2Ph), 45.1 (CH_2) and 26.2 (NCH_3).

16d': δ ^{1}H (250 MHz): 8.37-6.55 (m, 12H, ArH), 4.90 (s, 1H, CHPy), 3.78 (s, 3H, CO_2CH_3), 3.14 (d, 1H, J 13.1 Hz, $C\underline{H}_AH_BAr$), 3.12 (s, 3H, NCH_3), 3.07 (d, 1H, J 13.1 Hz, $CH_A\underline{H}_BAr$), 2.93 (d, 1H, J 14.0 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$) and 2.58 (d, 1H, J 14.0 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$).

*4.3.5. 5'-Hydroxymethyl-1-methyl-2-oxo-2'-phenyl-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-5'-carboxylic acid methyl ester **(16e).*** Obtained by General Procedure from imine **15e** (0.35 g, 1.70 mmol), *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide (0.49 g, 1.71 mmol), potassium carbonate (0.47 g, 3.40 mmol), silver oxide (0.039 g, 0.17 mmol), palladium acetate (0.038 g, 0.17 mmol), triphenylphosphine (0.089 g, 0.34 mmol) and DBU (0.25 mL, 1.67 mmol) in dichloromethane (80 mL). Purification using flash column chromatography (3:1 v/v ethyl acetate-petroleum ether) produced a mixture of stereoisomeric *products* (0.37 g, 59%: isomer ratio = >9 : 1). Crystallisation from dichloromethane – petroleum ether afforded the major isomer as colourless prisms; mp. 85-86 °C; Found: C, 68.6; H, 6.10; N, 7.6. $C_{21}H_{22}N_2O_4$ requires: C, 68.9; H, 6.05; N, 7.7 %.

^{1}H NMR (300 MHz): δ 7.37-6.59 (m, 9H, ArH), 4.64 (s, 1H, CHPh), 3.98 (d, 1H, J 10.8 Hz, $C\underline{H}_AH_BOH$), 3.90 (d, 1H, J 10.8 Hz, $CH_A\underline{H}_BOH$), 3.87 (s, 3H, CO_2CH_3), 2.81 (d, 1H, J 14.6 Hz, $C\underline{H}_AH_B$

$_{pyrrolidine}$), 2.75 (d, 1H, J 14.6 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$) and 2.71 (s, 3H, NCH_3); ^{13}C NMR: δ 178.5 and 176.5 (C=O), 143.9, 139.1, 130.1, 129.0, 128.9, 128.4, 128.3, 128.0, 126.7, 123.2, 122.9 and 108.3 (ArC), 72.7 (CHPh), 69.7 ($\underline{C}CO_2CH_3$), 66.4 ($CO_2\underline{C}H_3$), 59.3 (CH_2OH), 53.2 ($C_{spirocentre}$), 39.8 (CH_2), and 26.0 (NCH_3); ν (cm^{-1}): 3500-3341 ($O\text{-}H_{stretch}$), 2950 ($C\text{-}H_{stretch}$), 1725 ($C{=}O_{ester}$), 1705 ($C{=}O_{oxindole}$) and 1495, 1613 ($C{=}C_{aromatic}$); m/z (FAB$^+$, %): 389 ([M+Na]$^+$, 15), 367 ([M+H]$^+$, 100), 207 (13) and 160 (10).

4.3.6. 5'-Benzyl-1-methyl-2-oxo-2'-phenyl-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-5'-carboxylic acid methyl ester ***(16f).*** Obtained by General Procedure from imine **15f** (0.45 g, 1.68 mmol), *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide (0.49 g, 1.71 mmol), potassium carbonate (0.47 g, 3.40 mmol), silver oxide (0.039 g, 0.17 mmol), palladium acetate (0.038 g, 0.17 mmol), triphenylphosphine (0.089 g, 0.34 mmol) and DBU (0.25 mL, 1.67 mmol) in dichloromethane (80 mL). Purification using flash column chromatography (3:2 v/v petroleum ether-ethyl acetate) afforded an inseparable mixture of stereoisomeric *products* (0.45 g; 62%; isomer ratio = 7.8 : 1). Crystallisation from dichloromethane – petroleum ether afforded the major isomer as pale yellow prisms; mp. 78-79 °C;
Found: C, 74.8; H, 6.25; N, 6.0. $C_{27}H_{26}N_2O_3.0.5H_2O$ requires: C, 74.5; H, 6.25; N, 6.3 %; ^{1}H NMR (300 MHz): δ 7.43-6.53 (m, 14H, ArH), 4.11 (s, 1H, CHPh), 3.82 (s, 3H, CO_2CH_3), 3.23 (d, 1H, J 13.1 Hz, $C\underline{H}_AH_BPh$), 3.11 (d, 1H, J 13.1 Hz, $CH_A\underline{H}_BPh$), 2.95 (d, 1H, J 14.0 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 2.71 (s, 3H, NCH_3) and 2.54 (d, 1H, J 14.0 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$); ^{13}CNMR: δ 178.0 and 175.9 (C=O), 144.3, 137.5, 131.2, 130.8, 130.3, 130.1, 129.4, 128.8, 128.7, 128.4, 128.2, 128.0, 127.9, 127.4, 126.4, 122.8, 122.2 and 108.2 (ArC), 73.7 (CHPh), 70.7 ($\underline{C}CO_2CH_3$), 60.8 ($C_{spirocentre}$), 52.9 ($CO_2\underline{C}H_3$), 47.0 (CH_2Ph), 45.1 (CH_2) and 25.8 (NCH_3); ν (cm^{-1}): 3300 ($N\text{-}H_{stretch}$), 2950 ($C\text{-}H_{stretch}$), 1730 ($C{=}O_{ester}$) 1705 ($C{=}O_{oxindole}$), and 1495, 1612 ($C{=}C_{aromatic}$); *m/z* (FAB$^+$, %): 427 ([M+H]$^+$, 100), 367 (11), 267 (30), 207 (13) and 91 (14).

4.3.7. 5'-(4-Hydroxybenzyl)-1-methyl-2-oxo-2'-phenyl-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-5'-carboxylic acid methyl ester ***(16g).*** Obtained by General Procedure from imine **15g** (0.48 g, 1.70 mmol), *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide (0.49 g, 1.71 mmol), potassium carbonate (0.47 g, 3.40 mmol), silver oxide (0.039 g, 0.17 mmol), palladium acetate (0.038 g, 0.17 mmol), triphenylphosphine (0.089 g, 0.34 mmol) and DBU (0.25 mL, 1.67 mmol) in dichloromethane (80 mL). Purification by flash column chromatography (11:6 v/v petroleum ether-ethyl acetate) produced a poorly separated mixture of stereoisomeric *products* (0.47 g, 63%: isomer ratio = 4.2 : 1) as a colourless oil; Found (mixed isomers): C, 73.4; H, 6.00; N, 6.1. $C_{27}H_{26}N_2O_4$ requires: C, 73.3; H, 5.90; N, 6.3 %; ν (mixed isomers) (cm^{-1}):

3640-3610 (O-$H_{stretch}$), 2950-2860 (C-$H_{stretch}$), 1725 (C=O_{ester}), 1705 (C=$O_{oxindole}$) and 1495, 1612 (C=$C_{aromatic}$); *m/z* (EI^+, %) (mixed isomers): 443 ($[M+H]^+$, 7), 335 (52), 283 (62), 223 (58), 107 (100) and 91 (24).

16g: ^{1}H NMR (300 MHz): δ 7.26-6.53 (m, 13H, ArH), 4.13 (s, 1H, CHPh), 3.80 (s, 3H, CO_2CH_3), 3.16 (d, 1H, J 13.2 Hz, C$\underline{H}_A$H$_B$Ar), 3.05 (d, 1H, J 13.2 Hz, CH$_A\underline{H}_B$Ar), 2.93 (d, 1H, J 14.0 Hz, C$\underline{H}_A$H$_B$ $_{pyrrolidine}$), 2.70 (s, 3H, NCH_3) and 2.54 (d, 1H, J 14.0 Hz, CH$_A\underline{H}_{B\ pyrrolidine}$); ^{13}CNMR: δ 178.3 and 176.1 (C=O), 155.7, 144.2, 135.5, 132.2, 129.4, 128.8, 128.7, 128.6, 128.3, 128.2, 127.9, 126.7, 126.3, 122.9, 122.3, 115.5 and 108.3 (ArC), 73.5 (CHPh), 70.7 ($\underline{C}CO_2CH_3$), 60.9 ($C_{spirocentre}$), 53.1 ($CO_2\underline{C}H_3$), 46.2 (CH_2Ph), 45.1 (CH_2) and 25.9 (NCH_3).

16g': ^{1}H NMR (300 MHz): δ 7.28-6.50 (m, 13H, ArH), 4.86 (s, 1H, CHPh), 3.78 (s, 3H, CO_2CH_3), 3.29 (s, 2H, CH_2Ar), 3.12 (s, 3H, NCH_3), 2.80 (d, 1H, J 14.0 Hz, C$\underline{H}_A$H$_{B\ pyrrolidine}$) and 2.65 (d, 1H, J 14.0 Hz, CH$_A\underline{H}_{B\ pyrrolidine}$).

4.3.8. 1-Methyl-2-oxo-2'-phenyl-1,2-dihydro-spiro[indole3,3'-pyrrolidine]-5'-carboxylic acid methyl ester (17a/b). Obtained by General Procedure from imine derived from methyl glycinate (**15**, R= H) (1.70 g, 19.08 mmol), *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide **8** (2.75 g, 9.58 mmol) potassium carbonate (2.66 g, 19.25 mmol), silver oxide (0.22 g, 0.96 mmol), palladium acetate (0.22 g, 0.96 mmol), triphenylphosphine (0.50 g, 1.92 mmol) and DBU (1.42 mL, 9.51 mmol) in dichloromethane (200 mL). Purification by flash column chromatography (3:2 v/v ether-petroleum ether to ether gradient elution) afforded first **(17a)** (0.83 g, 27%) which precipitated from dichloromethane-petroleum ether as colourless prisms, m.p. 79-80°C; followed by mixed isomers (0.57 g, 18%); followed by **(17b)** (0.69 g, 23%), which precipitated from dichloromethane-petroleum ether as colourless prisms; mp. 121-123 °C;

ν (mixed isomers) (cm^{-1}): 2950-2860 (C-$H_{stretch}$), 1743 (C=O_{ester}), 1705 (C=$O_{oxindole}$) and 1495,1614 (C=$C_{aromatic}$).

17a: ^{1}H NMR (300 MHz): δ 7.42 (d, 1H, J 7.1 Hz, PhH), 7.29-6.84 (m, 7H, PhH), 6.62 (d, 1H, J 7.6 Hz, PhH), 4.63 (s, 1H, CHPh), 4.56 (dd, 1H, J 8.7 and 6.2 Hz, C$\underline{H}CO_2CH_3$), 3.84 (s, 3H, CO_2CH_3), 2.76 (s, 3H, NCH_3), 2.71-2.80 (m, 1H, C$\underline{H}_A$H$_{B\ pyrrolidine}$) and 2.62 (dd, 1H, J 13.6 and 6.2 Hz, CH$_A\underline{H}_{B\ pyrrolidine}$); ^{13}C NMR: δ178.2 and 175.8 (C=O), 144.3, 135.7, 129.8, 128.8, 128.2, 128.1, 126.4, 126.2, 123.1, 122.8, 122.5 and 108.3 (ArC), 72.8 (CHPh), 60.6 ($\underline{C}HCO_2CH_3$), 59.5 ($C_{spirocentre}$), 52.8 ($CO_2\underline{C}H_3$), 39.7 ($CH_{2\ pyrrolidine}$) and 25.9 (NCH_3); Found: C, 71.4; H, 6.00; N, 8.2. $C_{20}H_{20}N_2O_3$ requires: C, 71.4; H, 6.00; N, 8.3 %.; *m/z* (EI^+, %): 336 (M^+, 15), 177 (56), 160 (33), 130 (26), 117 (100) and 90 (25).

17b: ^{1}H NMR (250 MHz): δ 7.37 (dd, 1H, J 7.3 and 0.8 Hz, PhH), 7.26 (dt, 1H, J 7.8 and 1.2 Hz, PhH), 7.17-7.04 (m, 4H, PhH), 6.85 (dd, 2H, J 7.6 and 1.2 Hz, PhH), 6.62 (d, 1H, J 7.7 Hz, PhH), 4.43 (s, 1H, CHPh), 4.32 (dd, 1H, J 9.7 and 5.8 Hz, C<u>H</u>CO_2CH_3), 3.87 (s, 3H, CO_2CH_3), 2.74 (s, 3H, NCH_3), 2.73 (dd, 1H, J 13.7 and 9.7 Hz, C<u>H</u>$_A$H$_{B\ pyrrolidine}$) and 2.64 (dd, 1H, J 13.7 and 5.8 Hz, CH$_A$<u>H</u>$_{B\ pyrrolidine}$); ^{13}C NMR: δ 177.8 and 173.0 (C=O), 144.0, 134.8, 129.8, 128.3, 127.8, 127.7, 125.8, 122.6, 122.0 and 107.9 (ArC), 74.1 (CHPh), 59.9 (<u>C</u>HCO_2CH_3), 59.0 ($C_{spirocentre}$), 52.5 (CO_2<u>C</u>H_3), 40.3 (CH_2) and 25.4 (NCH_3); Found: C, 71.3; H, 6.10; N, 8.5. $C_{20}H_{20}N_2O_3$ requires: C, 71.4; H, 6.00; N, 8.3 %; *m/z* (EI$^+$, %): 336 (M$^+$, 18), 177 (64), 160 (32), 130 (23), 117 (100) and 90 (24).

4.4. Synthesis of imines ***(19a** and **19b)***

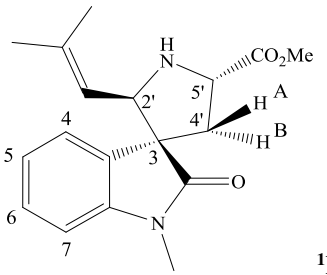
*4.4.1. (3-Methyl-but-2-enylideneamino)-acetic acid methyl ester (**19a**).* Prepared by adaptation of the literature procedure[18]. Glycine methyl ester hydrochloride (0.33 g, 2.65 mmol) and triethylamine (0.37 mL, 2.65 mmol) were stirred in THF (8 mL) at -20°C. 3, 3-Dimethyl acrylaldehyde (0.34 mL, 3.57 mmol) was then added, the mixture stirred for 2 h and was then allowed to stand for a further 1 h. Sodium carbonate (2 g) was added and the mixture was stirred for 2 h before being filtered, and the solvent removed *in vacuo*. The *product* (0.34 g, 82 %) was a pale yellow oil and was used directly in the next step without further purification; ^{1}H (300 MHz): δ 7.82 (d, 1H, J 9.4 Hz, C=NH), 5.67 (d, 1H, J 9.4 Hz, C<u>H</u>=C$(CH_3)_2$), 3.88 (s, 2H, C<u>H</u>$_2CO_2CH_3$), 3.29 (s, 3H, CO_2CH_3), 1.62 (s, 3H, CH_3) and 1.55 (s, 3H, CH_3); *m/z* (EI$^+$, %): 156 ([M+H]$^+$, 82), 96 (68), 58 (42) and 43 (100).

*4.4.1. (3-Methyl-but-2-enylideneamino)-acetic acid ethyl ester (**19b**)* Prepared by adaptation of the literature procedure[18]. Glycine ethyl ester hydrochloride (0.73 g, 5.30 mmol) and triethylamine (0.74 mL, 5.30 mmol) were stirred in THF (16 mL) at -20 °C. 3,3-Dimethyl acrylaldehyde (0.58 mL, 5.79 mmol) was then added, the mixture was stirred for 2 h and was then allowed to stand for a further 1 h. Sodium carbonate (2 g) was added and the mixture was stirred for 2 h before being filtered, and the solvent removed *in vacuo*. The *product* (0.64 g, 72 %) was a yellow oil and was used directly in the next step without further purification. ^{1}H NMR (300 MHz): δ 8.20 (d, 1H, J 9.4 Hz, C=NH), 6.08 (d, 1H, J 9.4 Hz, C<u>H</u>=C$(CH_3)_2$), 4.23 (s, 2H, CH_2CO), 4.16 (q, 2H, J 7.2 Hz, OC<u>H</u>$_2CH_3$), 1.94 (s, 3H, CH_3), 1.89 (s, 3H, CH_3) and 1.30 (t, 3H, J 7.2 Hz, CH_2C<u>H</u>$_3$). *m/z* (EI$^+$, %): 169 ([M+H]$^+$, 100), 154 (33) and 142 (58).

4.5.Synthesis of spiro-oxindoles ***(20-21).***

4.5.1. *1-Methyl-2'-(2-methyl-propenyl)-2-oxo-1,2-dihydro-spiro[indole-3,3'-pyrrolidine]-5'-carboxylic acid methyl ester* ***(20a/b).*** Imine **19a.** (0.29 g, 1.88 mmol) was added to a stirred solution of *N*-(2-iodo-phenyl)-*N*-methyl-acrylamide (0.45 g, 1.57 mmol), potassium carbonate (0.44 g, 3.14 mmol), and silver oxide (0.036 g, 0.16 mmol), in dichloromethane (100 mL) at 10°C. Palladium acetate (0.035 g, 0.16 mmol) and triphenylphosphine (0.083 g, 0.31 mmol) were then added followed by the dropwise addition of DBU (0.24 mL, 1.57 mmol). The resulting mixture was stirred for 18 h, quenched by addition of saturated aqueous ammonium chloride and extracted with dichloromethane (3 x 30 mL). The combined organic phases were dried (magnesium sulfate) and the solvent removed *in vacuo*. Purification by flash column chromatography (1:1 v/v ether-hexane) produced a poorly separated mixture of stereoisomeric *products* (0.22 g, 45%: isomer ratio 1.2:1) as a pale yellow oil. Subsequent second column chromatography (1:1 v/v ether-hexane to ether gradient elution) afforded the major isomer as a pale yellow oil; HRMS (mixed isomers): $[M+H]^+$ $C_{18}H_{22}N_2O_3$ requires 315.1708; found 315.1708; ν (mixed isomers) (cm^{-1}): 3055-2988 (C-$H_{stretch}$), 1729-1705 (br, C=O_{ester}, C=$O_{oxindole}$ and C=C_{alkene}) and 1614 (C=$C_{aromatic}$).

20a: ^{1}H NMR (300 MHz): δ 7.37 (d, 1H, J 7.4 Hz, PhH), 7.29 (t, 1H, J 7.7 Hz, PhH), 7.06 (t, 1H, J 7.4 Hz, PhH), 6.82 (d, 1H, J 7.7 Hz, PhH), 4.51 (d, 1H, J 8.9 Hz, CHC<u>H</u>=C), 4.41 (d, 1H, J 8.9 Hz, C<u>H</u>CH=C), 4.21 (dd, 1H, J 8.8 and 7.4 Hz, C<u>H</u>CO_2CH_3), 3.81 (s, 3H, CO_2CH_3), 3.19 (s, 3H, NCH_3), 2.61 (dd, 1H, J 13.1 and 7.4 Hz, C<u>H</u>$_A$H$_B$ pyrrolidine), 2.38 (dd, 1H, J 13.1 and 8.8 Hz, CH$_A$<u>H</u>$_B$ pyrrolidine) 1.57 (s, 3H, CH_3) and 1.45 (s, 3H, CH_3). ^{13}C NMR: δ 178.0 and 174.4 (C=O), 143.1, 138.5, 131.8, 123.9, 122.1, 119.9, 118.9 and 107.7 (ArC and C=C), 67.0 (<u>C</u>HCH=C), 63.9 (<u>C</u>CO_2CH_3), 58.9 (CH<u>C</u>H=C), 58.3 ($C_{spirocentre}$), 52.4 (CO_2<u>C</u>H_3), 40.7 (CH_2 pyrrolidine), 25.8 and 25.7 (CH_3) and 18.2 (NCH_3); *m/z* (EI^+, %): 314 (M^+, 12), 255 (13), 155 (100), 130 (28), 96 (42), 95 (92), 86 (40), 84 (65), 43 (31) and 32 (67).

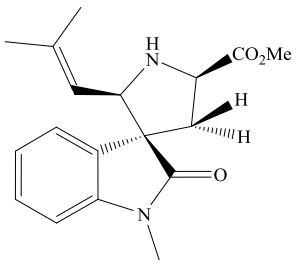


^{1}H NOE:

Proton Irradiated	Enhancement (%) H-5′	H-4′A	H-4′B	H-4	C<u>H</u>=C

H-5′	-	2.8	-	-	-
H-4′A	11.7	-	29.6	-	-
H-4′B		23.3	-	1.8	-
H-2′	-	-	-	-	1.0

20b: ^{1}H NMR (500 MHz): δ 7.30 (d, 1H, J 7.2 Hz, PhH), 7.19 (t, 1H, J 6.4 Hz, PhH), 7.03 (t, 1H, J 6.4 Hz, PhH), 6.80 (d, 1H, J 7.3 Hz, PhH), 4.53 (d, 1H, J 6.8 Hz, CHC<u>H</u>=C), 4.41 (d, 1H, J 6.8 Hz, C<u>H</u>CH=C), 4.24 (q, 2H, J 7.3 Hz, C<u>H</u>$_2$CH$_3$), 4.14 (dd, 1H, J 10.6 and 5.7 Hz, C<u>H</u>CO$_2$CH$_3$), 3.18 (s, 3H, NCH$_3$), 2.90 (dd, 1H, J 13.7 and 10.6 Hz, CH$_A$<u>H</u>$_B$ $_{\text{pyrrolidine}}$), 2.17 (dd, 1H, J 13.7 and 5.7 Hz, C<u>H</u>$_A$H$_B$ $_{\text{pyrrolidine}}$) 1.56 (s, 3H, CH$_3$), 1.44 (s, 3H, CH$_3$) and 1.30 (t, 3H, J 7.3 Hz, CH$_2$C<u>H</u>$_3$). ^{13}C NMR: δ 174.9 and 171.1 (C=O), 143.2, 137.5, 131.3, 127.9, 123.9, 123.1, 122.5 and 107.7 (ArC and C=C), 63.9 (<u>C</u>HCH=C), 61.3 (<u>C</u>H$_2$CH$_3$), 59.1 (<u>C</u>CO$_2$CH$_3$), 58.9 (CH<u>C</u>H=C), 58.2 (C$_{\text{spirocentre}}$), 38.7 (CH$_2$ $_{\text{pyrrolidine}}$), 25.9, 23.8, 18.6 and 14.2 (CH$_3$).



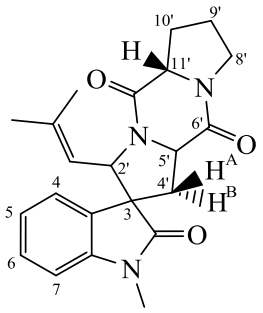
^{1}H NOE:

Proton Irradiated	Enhancement (%)				
	H-2′	H-4′A	H-4′B	H-5′	H-4
H-4′B	-	31.1	-	14.1	-
H-5′	1.0	-	2.2	-	1.0

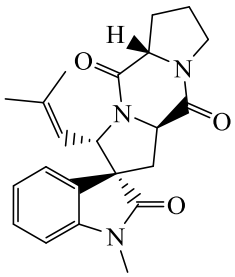
*4.6. Synthesis of Diketopiperazines **(24a-d).***

Spirocycle **20a/b** (0.15 g, 0.45 mmol) was dissolved in dichloromethane (5 mL) and Fmoc-L-Pro-Cl (0.21 g, 0.59 mmol) was added in one portion. After 2 min, aqueous Na$_2$CO$_3$ (1.37 mL, 1 M) was added and the mixture was stirred at room temperature for 12 h. The mixture was then extracted with dichloromethane (3 × 10 mL), dried (magnesium sulfate), and the solvent removed *in vacuo*. The residue was then stirred with piperidine (20% in dichloromethane) for 2 h, before being concentrated under reduced pressure and purified by flash column chromatography (1:1 v/v EtOAc-Hexane to 10% MeOH in EtOAc). The product was a colourless amorphous solid (0.30 g, 86%) and was isolated as a 5:4:3.5:2 diastereomeric mixture. HPLC separation and subsequent recrystallisation dichloromethane - hexane

afforded pure samples of the two major isomers and each of the minor isomers contaminated by each other; Found (mixed isomers): C, 69.2; H, 6.60; N, 11.0. $C_{22}H_{25}N_3O_3.0.125H_2O$ requires C, 69.3; H, 6.60; N, 11.0 %; ν (mixed isomers) (cm^{-1}): 2953 (C-$H_{stretch}$), 1747-1720 (br, C=O_{ester}, C=$O_{oxindole}$ and C=C_{alkene}) and 1611 (C=$C_{aromatic}$)*; m/z* (mixed isomers) (EI^+, %): 379 (M^+, 47), 220 (81), 205 (40), 192 (100), 160 (33), 123 (26), 95 (91), 70 (81) and 41 (18).



24a: Obtained as colourless needles; mp. 186-188 °C; $[\alpha]_D$ = -76.0 (c, 0.03, $CHCl_3$); ^{1}H NMR (500 MHz): δ 7.31 (t, 1H, J 7.7 Hz, PhH), 7.27 (d, 1H, J 6.9 Hz, PhH), 7.09 (t, 1H, J 6.9 Hz, PhH), 6.78 (d, 1H, J 7.7 Hz, PhH), 5.48 (d, 1H, J 9.8 Hz, CHC<u>H</u>=C), 4.55 (d, 1H, J 9.8 Hz, C<u>H</u>CH=C), 4.50 (t, 1H, J 8.1 Hz, NCH), 4.30 (dd, 1H, J 8.1 and 7.6 Hz, CHCO), 3.98 and 3.35 (m, 2 × 1H, 2 × $CH_{pyrrolidine}$), 3.14 (s, 3H, NCH_3), 2.71 (dd, 1H, J 13.2 and 7.6 Hz, CH_A<u>H</u>$_B$ $_{pyrrolidine}$), 2.65 (dd, 1H, J 13.2 and 8.1 Hz, C<u>H</u>$_A$$H_B$ $_{pyrrolidine}$), 2.33-1.76 (m, 4H, 4 × $CH_{pyrrolidine}$), 1.59 (s, 3H, CH_3) and 1.13 (s, 3H, CH_3); ^{13}C NMR: δ 177.1, 164.7 and 164.1 (C=O), 143.8, 135.7, 130.8, 128.9, 122.9, 122.6, 117.6 and 108.8 (ArC and C=C), 66.8 (<u>C</u>HCH=C), 61.5 and 60.4 (<u>C</u>HCO), 55.9 ($C_{spirocentre}$), 44.8, 37.9, 29.2 and 21.8 (CH_2 $_{pyrrolidine}$), 26.1, 25.7 and 17.8 (CH_3).

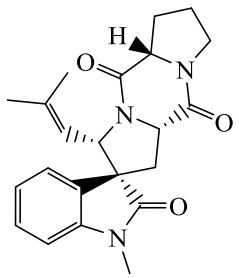


^{1}H NOE:

Proton Irradiated	Enhancement (%)				
	H-4	H-4′A	H-4′B	H-5′	H-7
H-4′A	-	-	25.7	-	-
H-4′B	-	25.0	-	12.0	-

H-5′	-	2.7	8.1	-	-
H-2′	7.5	-	-	-	1.6

24b: Obtained as colourless needles; mp. 189-191 °C; $[\alpha]_D$ = -70.6 (c, 0.03, $CHCl_3$); ^{1}H NMR (500 MHz): δ 7.29 (t, 1H, J 7.7 Hz, PhH), 7.18 (d, 1H, J 7.4 Hz, PhH), 7.07 (t, 1H, J 7.4 Hz, PhH), 6.82 (d, 1H, J 7.7 Hz, PhH), 5.24 (d, 1H, J 9.7 Hz, CHC<u>H</u>=C), 4.74 (d, 1H, J 9.7 Hz, C<u>H</u>CH=C), 4.56 (t, 1H, J 8.2 Hz, NCH), 4.25 (dd, 1H, J 8.5 and 8.0 Hz, CHCO), 3.75 and 3.55 (m, 2 × 1H, 2 × $CH_{pyrrolidine}$), 3.16 (s, 3H, NCH_3), 3.00 (dd, 1H, J 13.5 and 8.0 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 2.32 (dd, 1H, J 13.5 and 8.5 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$), 2.00-1.91 (m, 4H, 4 × $CH_{pyrrolidine}$), 1.65 (s, 3H, CH_3) and 1.36 (s, 3H, CH_3); ^{13}C NMR: δ 174.7, 166.9 and 165.9 (C=O), 143.3, 136.1, 131.2, 128.9, 122.7, 122.4, 119.1 and 108.2 (ArC and C=C), 64.1 (<u>C</u>HCH=C), 61.0 and 59.3 (<u>C</u>HCO), 55.7 ($C_{spirocentre}$), 45.2, 34.3, 27.7 and 23.6 ($CH_{2\ pyrrolidine}$), 26.3, 25.8 and 18.0 (CH_3); *m/z* (FAB$^+$, %): 380 ([M+H]$^+$, 100), 350 (5), 624 (10), 296 (7), 220 (15), 199 (10), 160 (7) and 70 (19).

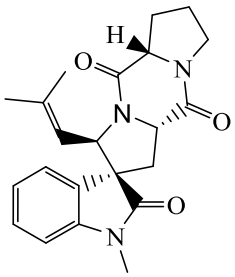


^{1}H NOE:

Proton Irradiated	Enhancement (%)				
	H-4	H-4′A	H-4′B	H-5′	H-11′
H-4′A	-	-	13.4	9.3	4.5
H-4′B	-	24.7	-	4.2	-
H-5′	9.7	7.7	-	-	6.7
H-11′	-	3.6	-	4.6	-
H-2′	5.2	4.8	-	-	-

24c: Obtained as a pale yellow solid (Contaminated with a trace of isomer **24d**); mp. 176-179 °C; $[\alpha]_D$ = -84.3 (c, 0.03, $CHCl_3$); ^{1}H NMR (500 MHz): δ 7.24 (t, 1H, J 7.6 Hz, PhH), 7.02 (d, 1H, J 7.3 Hz, PhH), 6.96 (t, 1H, J 7.3 Hz, PhH), 6.85 (d, 1H, J 7.6 Hz, PhH), 5.10-5.06 (m, 2H, CHC<u>H</u>=C and CHCO), 4.76 (d, 1H, J 9.2 Hz, C<u>H</u>CH=C), 4.30 (t, 1H, J 8.1 Hz, NCH), 3.66-3.54 (m, 2H, 2 × $CH_{pyrrolidine}$), 3.21 (s, 3H, NCH_3), 2.64 (dd, 1H, J 13.5 and 10.9 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 2.40 (dd, 1H, J 13.5 and 7.1 Hz, $CH_A\underline{H}_B$

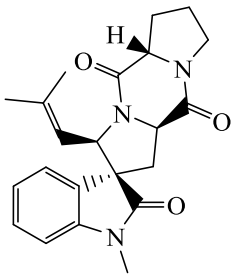
$_{pyrrolidine}$), 2.34-1.93 (m, 4H, 4 × $CH_{pyrrolidine}$), 1.61 (s, 3H, CH_3) and 1.10 (s, 3H, CH_3); ^{13}C NMR: δ 178.6, 167.1 and 166.9 (C=O), 143.8, 138.9, 138.1, 128.7, 126.2, 122.1, 121.5 and 107.8 (ArC and C=C), 61.1 (CHCH=C), 60.4 and 58.7 (CHCO), 55.7 ($C_{spirocentre}$), 45.2, 34.3, 27.5 and 23.7 (CH_2 $_{pyrrolidine}$), 26.5, 25.5 and 17.9 (CH_3).



^{1}H NOE:

Proton Irradiated	Enhancement (%)			
	H-4′A	H-4′B	H-5′	H-11′
H-4′A	-	8.5	8.9	3.7
H-4′B	17.0	-	6.1	-
H-5′	3.6	1.2	-	4.3
H-11′	-	-	5.4	-

24d: Obtained as a colourless amorphous solid (Contaminated with a trace of isomer **24c**); mp. 173-176 °C; $[\alpha]_D$ = -82.0 (c, 0.03, $CHCl_3$); ^1H NMR (500 MHz): δ 7.27 (t, 1H, J 6.4 Hz, PhH), 7.20 (d, 1H, J 6.4 Hz, PhH), 7.00 (t, 1H, J 7.8 Hz, PhH), 6.76 (d, 1H, J 7.8 Hz, PhH), 5.16 (d, 1H, J 9.8 Hz, CHCH=C), 4.80 (d, 1H, J 9.8 Hz, CHCH=C), 4.52 (t, 1H, J 8.1 Hz, NCH), 4.18 (dd, 1H, J 8.4 and 8.0 Hz, CHCO), 3.70 and 3.50 (m, 2 × 1H, 2 × $CH_{pyrrolidine}$), 3.10 (s, 3H, NCH_3), 3.00 (dd, 1H, J 13.5 and 8.0 Hz, CH_AH_B $_{pyrrolidine}$), 2.33 (dd, 1H, J 13.6 and 8.4 Hz, CH_AH_B $_{pyrrolidine}$), 2.05-1.95 (m, 4H, 4 × $CH_{pyrrolidine}$), 1.29 (s, 3H, CH_3) and 1.18 (s, 3H, CH_3).



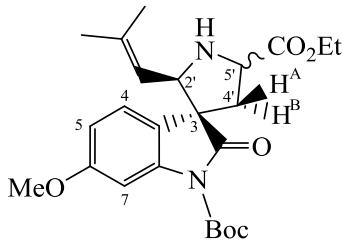
*4.7. Synthesis of N-(2-Iodo-5-methoxy-phenyl)-acrylamide **(14b).***

Triethylamine (3.5 mL, 25.09 mmol) was added dropwise over 10 min to a stirred solution of 2-iodo-5-methoxyaniline (5.8 g, 23.29 mmol) in dichloromethane (80 mL). Acryloyl chloride (2.1 mL, 25.98 mmol) was then added dropwise over 10 min (exotherm) and the mixture was stirred at room temperature for 15 h. It was then washed with brine (3 x 30 mL), dried (magnesium sulfate) and the solvent removed *in vacuo.* Purification by flash chromatography (1:1 ether-hexane) afforded the *product* (6.43 g, 92%), which crystallised from ether as colourless needles; mp. 77-79 °C; HRMS: $[M]^+$ $C_{10}H_{10}NO_2I$ requires 303.9834; found 303.9832. ^{1}H NMR (300 MHz): δ 8.05 (d, br, 1H, J 1.8 Hz, PhH), 7.63 (s, br, 1H, NH), 7.58 (d, 1H, J 8.8 Hz, PhH), 6.48 (dd, 1H, J 8.8 and 1.8 Hz, PhH), 6.43 (dd, 1H, J 16.8 and 1.4 Hz, CH=C$\underline{H}_{cis}$), 6.30 (dd, 1H, J 16.8 and 10.0 Hz, C$\underline{H}$=CH_2), 5.80 (dd, 1H, J 10.0 and 1.4 Hz, CH=C$\underline{H}_{trans}$) and 3.79 (s, 3H, OCH_3); ^{13}C NMR: δ 163.5 (C=O), 160.6, 138.8, 138.6, 131.3, 113.3, 106.8 and 76.5 (ArC and $\underline{C}$H=CH_2), 128.2 (CH_2) and 55.5 (OCH_3). ν (cm^{-1}): 2982 (C-$H_{stretch}$) and 1728 (C=O). *m/z* (EI^+, %): 303 (M^+, 10), 249 (10), 205 (6), 176 (100), 106 (13), 72 (10) and 55 (100).

4.8. Synthesis of Acryloyl-(2-iodo-5-methoxy-phenyl)-carbamic acid tert-butyl ester ***(8b).*** A solution of *N*-(2-iodo-5-methoxy-phenyl)-acrylamide (4.76 g, 15.72 mmol), Boc anhydride (3.77 g, 17.27 mmol) and DMAP (0.19 g, 1.56 mmol) in THF (80 mL) was stirred at room temperature for 15 h. It was then quenched by addition of saturated aqueous ammonium chloride and extracted with dichloromethane (3 x 30 mL), the combined organic phases were dried (magnesium sulfate) and the solvent was evaporated *in vacuo*. Purification by flash chromatography (1:2 v/v ether–petroleum ether) afforded the *product* (5.69 g, 90%), which crystallised from ether as colourless prisms; mp. 86-87 °C; Found: C, 44.5; H, 4.75; N, 3.5; I, 31.3. $C_{15}H_{18}NO_4I$ requires: C, 44.7; H, 4.50; N, 3.5; I, 31.5; HRMS: $[M]^+$ $C_{15}H_{18}NO_4I$ requires 403.0281; found 403.0287; ^{1}H NMR (300 MHz): δ 7.72 (d, 1H, J 8.8 Hz, ArH), 7.14 (dd, 1H, J 16.9 and 10.4 Hz, C$\underline{H}$=CH_2), 6.76 (d, 1H, J 2.9 Hz, ArH), 6.66 (dd, 1H, J 8.8 and 2.9 Hz, ArH), 6.44 (dd, 1H, J 16.9 and 1.4 Hz, CH=C$\underline{H}_{trans}$), 5.81 (dd, 1H, J 10.4 and 1.4 Hz, CH=C$\underline{H}_{cis}$), 3.78 (s, 3H, OCH_3) and 1.42 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ 161.2 and 158.6 (C=O), 149.5, 140.2, 137.4, 127.8, 113.9, 113.4 and 86.1 (ArC and $\underline{C}$H=CH_2), 128.7 (CH_2), 81.9 ($\underline{C}(CH_3)_3$), 53.6 (OCH_3) and 25.9 ($C(\underline{C}H_3)_3$). ν (cm^{-1}): 2982 (C-$H_{stretch}$), 1738 (br, C=O) and 1610 (C=$C_{aromatic}$); *m/z* (EI^+, %): 404 ($[M+H]^+$, 11), 348 (100), 326 (14), 304 (69), 177 (60) and 67 (11).

4.9. Synthesis of Spirooxindole ***(22a/b).*** Imine **19b** (0.21 g, 1.20 mmol) was added to a stirred solution of acrylamide **8b** (0.40 g, 1.00 mmol), potassium carbonate (0.28 g, 2.00 mmol), and silver oxide (0.022 g, 0.10 mmol), in dichloromethane (50 mL) at 10°C. Palladium acetate (0.022 g, 0.10 mmol) and

triphenylphosphine (0.052 g, 0.20 mmol) were then added followed by the dropwise addition of DBU (0.15 mL, 1.00 mmol). The resulting mixture was stirred for 18 h, quenched by addition of saturated aqueous ammonium chloride and extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (magnesium sulfate) and the solvent removed *in vacuo*. Purification by flash column chromatography (1:1 v/v ether-hexane) produced a poorly separated mixture of stereoisomeric *products* (0.23 g, 52%, isomer ratio 1.2:1) as a pale yellow oil; HRMS (mixed isomers): $[M]^+$ $C_{24}H_{32}N_2O_6$ requires 444.2260; found 444.2259; ν (mixed isomers) (cm^{-1}): 2953 (C-$H_{stretch}$), 1748-1709 (br, C=O_{ester}, C=$O_{oxindole}$ and C=C_{alkene}) and 1611 (C=$C_{aromatic}$); *m/z* (mixed isomers) (EI^+, %): 444 (M^+, 17), 371 (18), 344 (28), 262 (71), 169 (94), 132 (40), 95 (60) and 41 (100).



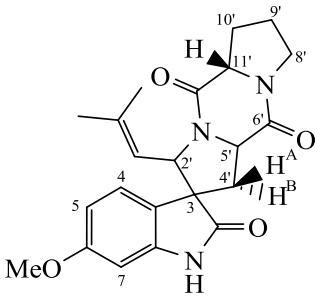
22a: ^{1}H NMR (300 MHz): δ 7.45 (m, 1H, PhH), 7.15 (m, 1H, PhH), 6.75 (m, 1H, PhH), 5.00 (d, 1H, J 8.4 Hz, CHC<u>H</u>=C), 4.45 (d, 1H, J 8.4 Hz, C<u>H</u>CH=C), 4.30-4.12 (m, 3H, C<u>H</u>$_2$CH$_3$ and C<u>H</u>CO$_2$CH$_3$), 3.98 (s, br, 1H, NH), 3.77 (s, 3H, OCH$_3$), 2.93 (m, 1H, C<u>H</u>$_A$H$_B$ pyrrolidine), 2.22 (m, 1H, CH$_A$<u>H</u>$_B$ pyrrolidine), 1.65 (s, 9H, C(CH$_3$)$_3$), 1.56 (s, 3H, CH$_3$), 1.42 (s, 3H, CH$_3$) and 1.31 (t, 3H, J 7.6 Hz, CH$_2$C<u>H</u>$_3$).

22b: ^{1}H NMR (300 MHz): δ 7.45 (m, 1H, PhH), 7.15 (m, 1H, PhH), 6.75 (m, 1H, PhH), 4.95 (d, 1H, J 8.4 Hz, CHC<u>H</u>=C), 4.45 (d, 1H, J 8.4 Hz, C<u>H</u>CH=C), 4.30-4.12 (m, 3H, C<u>H</u>$_2$CH$_3$ and C<u>H</u>CO$_2$CH$_3$), 3.77 (s, 3H, OCH$_3$), 2.93 (m, 1H, CH$_A$<u>H</u>$_B$ pyrrolidine), 2.22 (m, 1H, C<u>H</u>$_A$H$_B$ pyrrolidine), 1.65 (s, 9H, C(CH$_3$)$_3$), 1.56 (s, 3H, CH$_3$), 1.42 (s, 3H, CH$_3$) and 1.31 (t, 3H, J 7.6 Hz, CH$_2$C<u>H</u>$_3$).

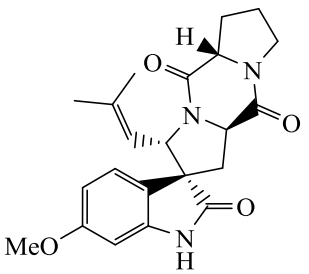
4.10. Synthesis of Diketopiperazines ***(25a-d)***

Spirocycle **22a/b** (0.20 g, 0.45 mmol) was dissolved in dichloromethane (5 mL) and Fmoc-L-Pro-Cl (0.21 g, 0.509 mmol) was added in one portion. After 2 min, aqueous sodium carbonate (1.37 mL, 1 M) was added and the mixture was stirred at room temperature for 12 h. The mixture was then extracted with dichloromethane (3 × 10 mL), dried (magnesium sulfate), and the solvent removed *in vacuo*. The residue was then stirred with piperidine (20% in dichloromethane) for 2 h, before being concentrated under reduced pressure and purified by flash column chromatography (1:1 v/v EtOAc-Hexane to 10% MeOH in EtOAc). The Boc-protected product was then stirred with Et_3SiH (1.2 mL) and TFA (6 mL) at

room temperature for 15 min. The solution was then diluted with dichloromethane and evaporated to dryness. Purification by flash column chromatography (5% MeOH in dichloromethane) afforded the product (0.125 g, 70%) as a pale yellow amorphous solid as a 5:4:3.5:2 diastereomeric mixture. HPLC separation and subsequent recrystallisation dichloromethane - hexane afforded pure samples of the two major isomers and each of the minor isomers contaminated by each other; Found (mixed isomers): C, 63.8; H, 6.30; N, 9.7. $C_{22}H_{25}N_3O_4.H_2O$ requires C, 63.9; H, 6.50; N, 10.0 %; HRMS (mixed isomers): $[M+H]^+$ $C_{22}H_{25}N_3O_4$ requires 396.1909; found 396.1923. ν (mixed isomers) (cm^{-1}): 3476 (N-H), 2954 (C-$H_{stretch}$), 1750-1709 (br, C=O_{ester}, C=$O_{oxindole}$ and C=C_{alkene}) and 1611 (C=$C_{aromatic}$). *m/z* (mixed isomers) (EI^+, %): 395 (M^+, 33), 220 (80), 192 (100), 95 (75), 70 (35) and 41 (26).

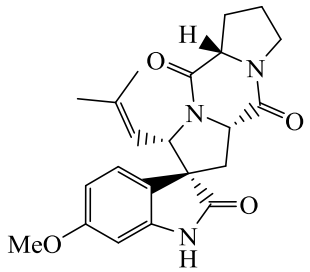


25a: Obtained as a pale yellow amorphous solid; mp. 122-126 °C; $[\alpha]_D$ = -31.0 (c, 0.1, $CHCl_3$); ^1H (500 MHz): δ 7.46 (s, br, 1H, NH), 6.93 (d, 1H, J 8.4 Hz, PhH), 6.52 (dd, 1H, J 8.4 and 2.3 Hz, PhH), 6.41 (d, 1H, J 2.3 Hz, PhH), 5.03 (d, 1H, J 9.8 Hz, CHC<u>H</u>=C), 5.01 (dd, 1H, J 10.4 and 6.4 Hz, CHCO), 4.78 (d, 1H, J 9.8 Hz, C<u>H</u>CH=C), 4.23 (dd, 1H, J 8.1 and 7.6 Hz, NCH), 3.79 (s, 3H, OCH_3), 3.61 and 3.59 (m, 2 × 1H, 2 × $CH_{pyrrolidine}$), 2.58 (dd, 1H, J 13.1 and 10.4 Hz, $CH_A\underline{H}_{B\ pyrrolidine}$), 2.41 (dd, 1H, J 13.1 and 6.4 Hz, $C\underline{H}_AH_{B\ pyrrolidine}$), 2.32-2.28 (m, 2H, 2 × $CH_{pyrrolidine}$), 2.07-1.97 (m, 2H, 2 × $CH_{pyrrolidine}$), 1.65 (s, 3H, CH_3) and 1.25 (s, 3H, CH_3); ^{13}C NMR: δ 180.6, 167.1 and 166.9 (C=O), 160.4, 141.6, 138.4, 127.3, 121.4, 118.8, 106.8 and 96.6 (ArC and C=C), 61.1 (<u>C</u>HCO), 60.2 (<u>C</u>HCH=C), 59.1 ($C_{spirocentre}$), 58.5 (<u>C</u>HCO), 55.5 (OCH_3), 45.2, 34.4, 27.5 and 23.7 ($CH_{2\ pyrrolidine}$), 25.5 and 18.0 (CH_3).



25b: Obtained as a pale yellow amorphous solid; mp. 139-141 °C; $[\alpha]_D$ = -52.0 (c, 0.1, $CHCl_3$); ^1H NMR (500 MHz): δ 7.85 (s, br, 1H, NH), 7.00 (d, 1H, J 8.3 Hz, PhH), 6.52 (dd, 1H, J 8.3 and 2.3 Hz,

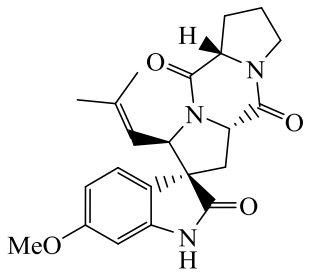
PhH), 6.47 (d, 1H, J 2.3 Hz, PhH), 5.22 (d, 1H, J 9.8 Hz, CHC<u>H</u>=C), 4.73 (d, 1H, J 9.8 Hz, C<u>H</u>CH=C), 4.55 (dd, 1H, J 8.2 and 7.2 Hz, CHCO), 4.23 (t, 1H, J 8.1 Hz, NCH), 3.80 (s, 3H, OCH_3), 3.65 and 3.59 (m, 2 × 1H, 2 × $CH_{pyrrolidine}$), 3.00 (dd, 1H, J 13.4 and 8.2 Hz, C<u>H</u>$_A$H$_B$ $_{pyrrolidine}$), 2.35 (dd, 1H, J 13.4 and 7.2 Hz, CH$_A$<u>H</u>$_B$ $_{pyrrolidine}$), 2.32-2.28 (m, 2H, 2 × $CH_{pyrrolidine}$), 2.01-1.97 (m, 2H, 2 × $CH_{pyrrolidine}$), 1.65 (s, 3H, CH_3) and 1.43 (s, 3H, CH_3). ^{13}C NMR: δ 176.9, 166.9 and 166.0 (C=O), 160.5, 141.4, 136.3, 123.1, 123.5, 119.3, 107.3 and 97.2 (ArC and C=C), 64.3 (<u>C</u>HCO), 61.1 (<u>C</u>HCH=C), 59.3 ($C_{spirocentre}$), 55.6 (<u>C</u>HCO), 55.4 (OCH_3), 45.3, 34.7, 27.8 and 23.6 ($CH_{2\ pyrrolidine}$), 25.9 and 18.2 (CH_3).



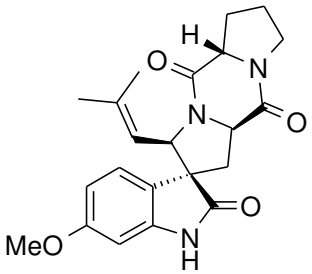
^{1}H NOE:

Proton Irradiated	Enhancement (%) H-4′A	H-4′B	H-5′	H-11′
H-4′A	-	10.7	4.4	4.4
H-4′B	17.9	-	-	-
H-5′	5.0	-	-	7.9
H-11′	10.1	-	4.5	-

25c: Obtained as a pale yellow amorphous solid; mp. 118-122 °C; $[\alpha]_D$ = -42.0 (c, 0.1, $CHCl_3$); ^{1}H NMR (500 MHz): δ 7.60 (s, br, 1H, NH), 7.13 (d, 1H, J 8.3 Hz, PhH), 6.57 (dd, 1H, J 8.3 and 2.4 Hz, PhH), 6.40 (d, 1H, J 2.4 Hz, PhH), 5.52 (d, 1H, J 9.6 Hz, CHC<u>H</u>=C), 4.45 (dd, 1H, J 10.0 and 8.0 Hz, CHCO), 4.22 (d, 1H, J 9.6 Hz, C<u>H</u>CH=C), 4.18 (m, 1H, NCH), 3.80 (s, 3H, OCH_3), 4.00 and 3.45 (m, 2 × 1H, 2 × $CH_{pyrrolidine}$), 2.68 (dd, 1H, J 13.2 and 10.0 Hz, C<u>H</u>$_A$H$_B$ $_{pyrrolidine}$), 2.50 (dd, 1H, J 13.2 and 8.0 Hz, CH$_A$<u>H</u>$_B$ $_{pyrrolidine}$), 2.41-2.20 (m, 2H, 2 × $CH_{pyrrolidine}$), 2.12-1.95 (m, 2H, 2 × $CH_{pyrrolidine}$), 1.60 (s, 3H, CH_3) and 1.18 (s, 3H, CH_3). ^{13}C NMR: δ 179.3, 164.6 and 164.2 (C=O), 160.6, 141.8, 135.8, 123.4, 122.5, 117.8, 107.4 and 97.2 (ArC and C=C), 66.7 (<u>C</u>HCO), 61.1 (<u>C</u>HCH=C), 59.3 ($C_{spirocentre}$), 55.8 (<u>C</u>HCO), 55.6 (OCH_3), 45.8, 38.5, 34.7 and 21.8 ($CH_{2\ pyrrolidine}$), 29.2 and 17.9 (CH_3).



25d: Obtained as a pale yellow amorphous solid; mp. 127-132 °C; $[\alpha]_D$ = -38.4 (c, 0.1, $CHCl_3$); *m/z* (%) (FAB): 396 (M+1, 100), 340 (13), 255 (118) and 192 (73). ^{1}H NMR (500 MHz): δ 7.40 (s, br, 1H, NH), 7.10 (d, 1H, J 8.3 Hz, PhH), 6.56 (dd, 1H, J 8.3 and 2.2 Hz, PhH), 6.41 (d, 1H, J 2.2 Hz, PhH), 5.15-5.03 (m, 2H, CHC<u>H</u>=C and CHCO), 4.84 (d, 1H, J 9.2 Hz, C<u>H</u>CH=C), 4.28 (t, 1H, J 7.8 Hz, NCH), 3.80 (s, 3H, OCH_3), 3.60-3.59 (m, 2 × 1H, 2 × $CH_{pyrrolidine}$), 2.58 (dd, 1H, J 13.4 and 10.3 Hz, $CH_A\underline{H}_B$ $_{pyrrolidine}$), 2.40-2.20 (m, 3H, C<u>H</u>$_A$H$_B$ $_{pyrrolidine}$ and 2 × $CH_{pyrrolidine}$), 2.06-2.03 (m, 2H, 2 × $CH_{pyrrolidine}$), 1.61 (s, 3H, CH_3) and 1.21 (s, 3H, CH_3). ^{13}C NMR: δ 179.4, 166.1 and 165.5 (C=O), 160.4, 141.9, 138.5, 125.8, 119.6, 119.1, 106.9 and 96.9 (ArC and C=C), 61.7 (<u>C</u>HCO), 60.1 (<u>C</u>HCH=C), 58.9 ($C_{spirocentre}$), 55.7 (<u>C</u>HCO), 54.2 (OCH_3), 45.7, 35.9, 27.8 and 23.2 ($CH_{2\ pyrrolidine}$), 25.5 and 18.1 (CH_3).



5. Crystallographic data

Crystallographic data for compound **12a:** CCDC 1572114 , **12b:** CCDC 1572115, **16a:** CCDC 1572113 and **24b:** CCDC 1572112 contain the supplementary crystallographic data have been deposited to the Cambridge Crystallographic Data Center. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/ conts/retrieving.html, or from the Cambridge Crystallographic Data Centre,12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

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