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Pictet–Spengler/Palladium Catalyzed Allenylation and Carbonylation Processes

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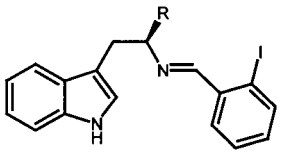
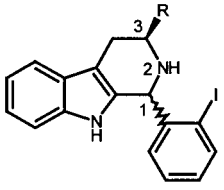
Abstract—The tactical combination of the Pictet–Spengler reaction with Pd catalyzed reactions with allene and with carbon monoxide provides rapid access to a range of tetrahydro-β-carboline and tetrahydroisoquinoline derivatives via intramolecular trapping of intermediate π-allyl– and acyl–palladium(II) complexes by the indolic or secondary amino moieties generating fused azepine and δ-lactam derivatives. Chiral tryptophan examples are also described.

We have previously reported[1] the combination of cascade imine→azomethine ylide→cycloaddition reactions with the Pictet–Spengler[2] reaction. This tactical combination provides rapid access to complex heterocycles with good regio- and stereo-selectivity. In this paper we report sequential Pictet–Spengler/palladium catalyzed allenylation and carbonylation sequences which allow rapid access to novel and complex heterocycles.



1 **a**. R= H

b. R= CO_2Me



2 **a**. R= H 81%

b. R= CO_2Me (R and Ar *trans*)

c. R= CO_2Me (R and Ar *cis*) 88%

Pictet–Spengler cyclization of imine (**1a**,**b**) proceeded smoothly in the presence of catalytic amount of *p*-toluenesulphonic acid in boiling toluene to give **2a** and **2b/2c** in excellent yield (81% and 88%, respectively).[3] In the case of **1b**, the product comprised a 1:1 *trans*/*cis* mixture of **2b** and **2c**. The stereochemistries of **2b** and **2c** were established by n.O.e studies (see Experimental). Partial racemization (~50%) occurred during this reaction.[4]

Pictet–Spengler products **2a**–**c** undergo palladium catalyzed allene insertion (allene 1 atm, toluene, 110°C, 16 h) to give **3a**–**c** in 77–92% yield (Scheme 1).[5] The catalyst system comprised 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Et_4NCl (1 mol equiv.) and K_2CO_3 (2 mol equiv.). The alternative product **4** arising from capture of the intermediate π-allyl species by the indole nitrogen atom was not observed.

The Pictet–Spengler products **2a**–**c** undergo palladium catalyzed carbonylation (CO 1 atm, toluene, 40 or 110°C, 16 h) to give **5a**–**c** in 67–93% yield. In this case catalyst system comprised 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and Et_3N (1.2 mol equiv.) (Scheme 2).[6]

The Pictet–Spengler cyclization of imines **6a**,**b** also proceeded smoothly to afford substituted tetrahydroisoquinoline derivatives **7a**–**c** in high yield with **6b** giving a 3:2 *trans*/*cis* mixture (61%) of **7b** and **7c**. The stereochemistries of **7b** and **7c** were established by n.O.e. studies (see Experimental).

The Pictet–Spengler products **7a**–**c** underwent palladium catalyzed allenylation and carbonylation processes under essentially similar conditions to the foregoing

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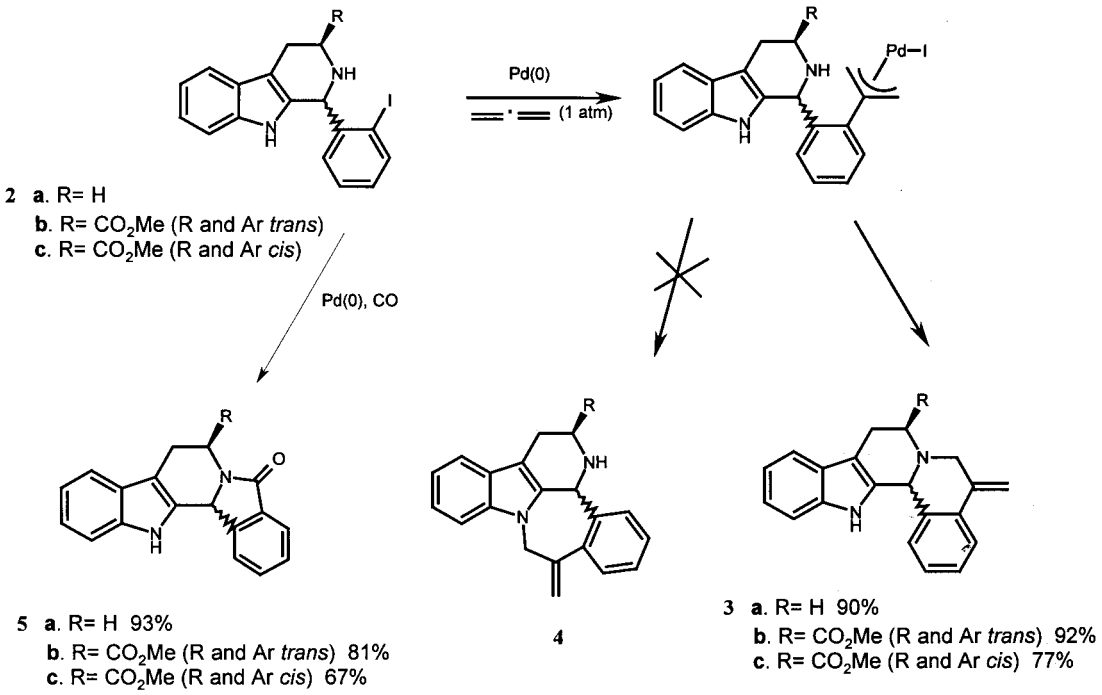


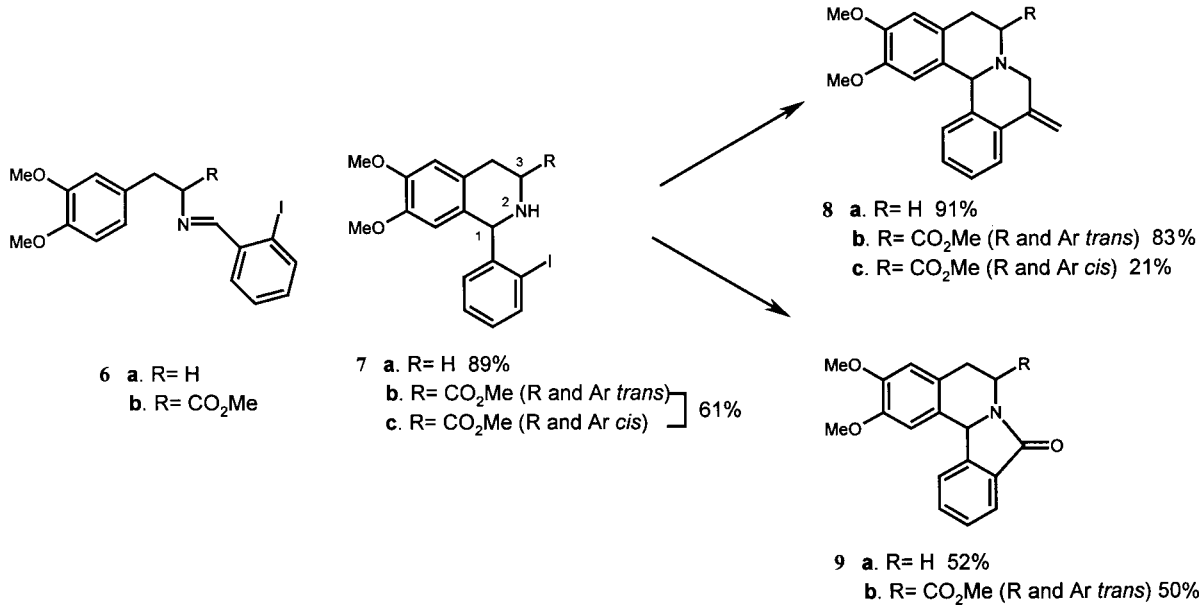
Scheme 1.

tetrahydro-β-carboline series to afford **8a–c** and **9a,b** in good yield, apart from **7c** which failed to undergo carbonylation under these conditions.

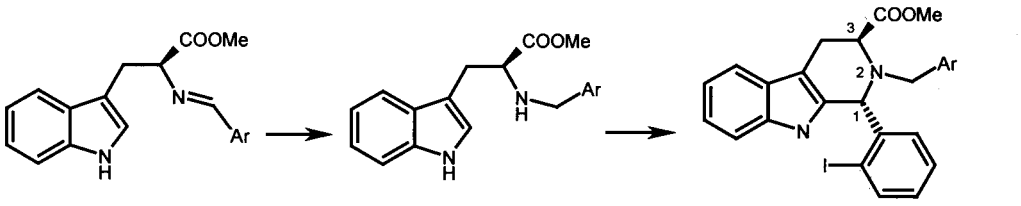
Finally we turned our attention to intercepting the π-allyl palladium intermediate with the indole nitrogen atom. To explore this process, amines **11a–d** were prepared in excellent yield by reduction of the corresponding imines **10a–d** using $NaB(OAc)_3H$ (Scheme 3).

The Pictet–Spengler reaction of **11a–d** with 2-iodobenzaldehyde afforded **12a–d** in 74–85% yield with exclusive formation of the *trans* diastereoisomers (n.O.e.).[7] There was no detectable racemization of **12a–d** by ^1H NMR in the presence of the chiral shift reagent tris(3-heptafluoropropylhydroxymethylene-(+)camphorato)europium (III).[8]

The palladium catalyzed reactions of enantiopure **12a–d** with allene (1 atm) under essentially similar conditions to those described above gave **13a–d** in good to excellent yield (Scheme 4).



Scheme 2.

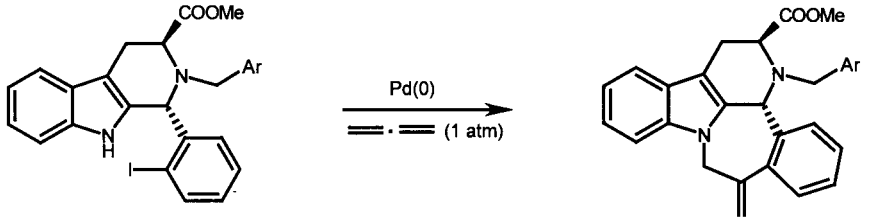


10 **a**. Ar= Phenyl
b. Ar= 2-Pyridyl
c. Ar= 2-Furyl
d. Ar= 2-Thienyl

11 **a**. Ar= Phenyl
b. Ar= 2-Pyridyl
c. Ar= 2-Furyl
d. Ar= 2-Thienyl

12 **a**. Ar= Phenyl 73%
b. Ar= 2-Pyridyl 55%
c. Ar= 2-Furyl 62%
d. Ar= 2-Thienyl 48%

Scheme 3.



13 **a**. Ar= Phenyl 73
b. Ar= 2-Pyridyl 55
c. Ar= 2-Furyl 62
d. Ar= 2-Thienyl 48

Scheme 4.

The stereochemistry of **13d** was confirmed by X-ray crystallography (Fig. 1).

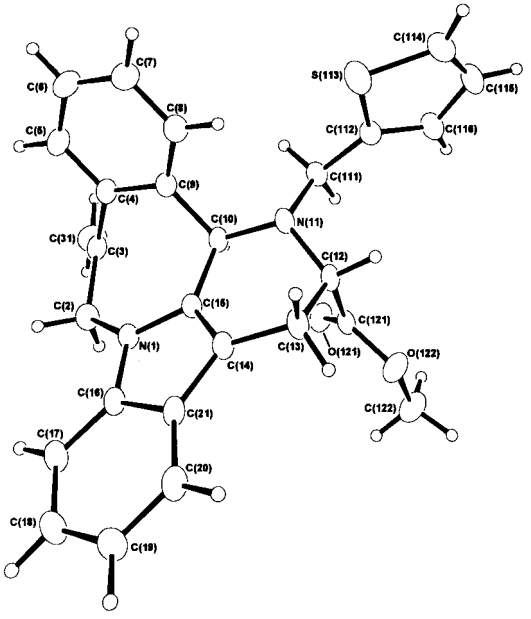


Figure 1. The X-ray crystal structure of **13d**.

Experimental

Melting points were obtained on a Reichert hot-stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba MOD 1106 instrument. Mass spectra were recorded on a V.G. Autospec using electron impact (EI) operating at 70 ev and accurate molecular weights were determined using perfluorokerosene as internal standard. Infrared spectra were recorded on a Nicolet Avatar 360 FI-IR instrument. Optical rotations were recorded on an AA100 Polarimeter. X-Ray analysis was performed on a Stoe STADI 4-circle machine. Nuclear magnetic resonance spectra were recorded at 300 MHz on a General Electric QE300 or Bruker DPX 300 instrument, at 250 MHz on a Bruker AC 250 instrument, at 400 MHz on a Bruker WP 400 instrument or at 500 MHz on a Bruker DRX 500 instrument. Deuterochloroform was used as the NMR solvent with tetramethylsilane as the internal standard. Chemical shifts are given in parts per million (δ) down field from tetramethylsilane and coupling constants are given in Hz. Solvents were purified according to standard procedures.[9] The term ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point

40–60°C. Flash chromatography employed silica gel 60 (230–400 mesh).

A. General procedure for preparation of imines

A mixture of amine (11 mmol), aldehyde (10 mmol) and anhydrous magnesium sulphate (2 g) in dry DCM (80 ml) was stirred at room temperature for 16 h. On completion of the reaction (NMR monitoring), the mixture was diluted with DCM (100 ml), washed with water (2×100 ml), dried ($MgSO_4$) and concentrated in vacuo to give imine which was used in the next step without further purification. N.B.: When the amine hydrochloride salt was used, triethylamine (1.21 g, 12 mmol) was added to the reaction mixture.

B. General procedure for reduction of imines to amines

A mixture of imine (8 mmol) and sodium triacetoxyborohydride (2.37 g, 11.2 mmol) in 1,2-dichloroethane (40 ml) was stirred at room temperature under N_2 for 24 h. On completion of the reaction (NMR monitoring), the mixture was quenched with saturated aqueous $NaHCO_3$ (100 ml) and DCM (150 ml) was added. The separated aqueous phase was extracted with ether (3×150 ml), the combined organic phase dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash column chromatography to afford the product.

C. General procedure for Pictet–Spengler reactions

(1). A mixture of imine (8 mmol) and *p*-toluenesulphonic acid monohydrate (0.152 g, 0.8 mmol) in toluene (80 ml) was stirred and boiled under reflux for 6–8 h. On completion of the reaction (NMR monitoring), the solvent was removed in vacuo and the residue purified by flash column chromatography to afford the product.

(2). A mixture of amine (6 mmol), 2-iodobenzaldehyde (1.39 g, 6 mmol) and *p*-toluenesulphonic acid monohydrate (0.114 g, 0.6 mmol) in toluene (80 ml) was stirred and boiled under reflux with a Dean–Stark apparatus for 16 h. The solvent was removed in vacuo and the residue purified by flash column chromatography to afford the product.

D. General procedure for carbonylation

A mixture of Pictet–Spengler product (1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol) and Et_3N (0.101 g, 1 mmol) in toluene (10 ml) was stirred and heated at 40–110°C for 16 h under a carbon monoxide balloon. The solvent was removed in vacuo, DCM (100 ml) added and the mixture washed with water (100 ml). The separated organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash column chromatography to afford the product.

E. General procedure for allenylation

A mixture of Pictet–Spengler product (1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) in toluene (10 ml) was stirred and heated at 110°C in a Schlenk tube under 1 atm of allene. On completion of the reaction (NMR monitoring), the tube was cooled, vented, the solvent removed in vacuo, DCM (100 ml) added and the mixture washed with water(100 ml). The separated organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash column chromatography.

[2-(1*H*-Indol-3-yl)ethyl]-(2-iodo-benzylidene)-amine 1a. Prepared by general procedure A from tryptamine (1.41 g, 8.8 mmol) and 2-iodobenzaldehyde (1.87 g, 8 mmol). Work up afforded **1a** (2.69 g, 90%) which crystallized from ethanol as pale orange prisms. Mp 121–123°C. (Found: C, 54.35; H, 4.05; N, 7.35; I, 34.05. $C_{17}H_{15}N_2I$ requires: C, 54.55; H, 4.05; N, 7.05; I, 33.9%); δ: 3.19 (t, 2H, J=7.2 Hz, $ArCH_2$), 4.00 (dt, 2H, J=1.3, 7.3 Hz, NCH_2), 7.04–7.40 (m, 6H, ArH), 7.68 (d, 1H, J=7.5 Hz, ArH), 7.83 (dd, 1H, J=1.1, 7.9 Hz, ArH), 7.96 (dd, 2H, J=1.7, 7.8 Hz, ArH and indole-NH) and 8.31 (s, 1H, N=CH); *m/z* (%): 374 (M^+, 9), 244 (4), 232 (14), 130 (100), 89 (9) and 77 (13).

[3-(1*H*-Indol-3-yl)ethyl]-2-(2-iodo-benzylideneamino)-propionic acid methyl ester 1b. Prepared by general procedure A from tryptophan methyl ester hydrochloride (2.24 g, 8.8 mmol) and 2-iodobenzaldehyde (1.87 g, 8 mmol). Work up afforded **1b** (3.28 g, 95%) as a pale yellow gum. δ: 3.26 (dd, 1H, J=8.8, 14.5 Hz, ArC*H*H), 3.57 (dd, 1H, J=4.9, 14.5 Hz, ArC*H*H), 3.78 (s, 3H, OCH_3), 4.39 (dd, 1H, J=4.8, 8.8 Hz, $NCHCO_2Me$), 6.96 (d, 1H, J=2.4 Hz, ArH), 7.04–7.20 (m, 3H, ArH), 7.31–7.67 (m, 2H, ArH), 7.75 (d, 1H, J=1.1 Hz, ArH), 7.78 (d, 1H, J=1.1 Hz, ArH), 7.98 (d, 1H, J=1.7 Hz, ArH), 8.00 (s, 1H, N=CH) and 8.03 (br, 1H, NH); *m/z* (%): 432 (M^+, 6), 232 (9), 130 (100) and 77 (6).

1-(2-Iodo-phenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline 2a. Prepared by general procedure C(1) from imine **1a** (2.99 g, 8 mmol) and *p*-toluenesulphonic acid monohydrate (0.152 g, 0.8 mmol) over 8 h. Flash chromatography eluting with 1:2 v/v ether–hexane afforded **2a** (2.42 g, 81%) which crystallized from ethyl acetate as pale yellow prisms. Mp 139–141°C. (Found: C, 54.85; H, 4.25; N, 7.2; I, 34.1. $C_{17}H_{15}N_2I$ requires: C, 54.55; H, 4.05; N, 7.5; I, 33.9%); δ: 2.01 (br, 1H, NH), 2.81–2.86 (m, 2H, $ArCH_2$), 3.06–3.19 (m, 2H, NCH_2), 5.45 (s, 1H, ArCHN), 6.94–7.22 (m, 6H, ArH), 7.53 (m, 1H, ArH) and 7.86–7.91 (m, 2H, ArH and indole-NH); *m/z* (%): 374 (M^+, 100), 345 (27), 245 (14), 218 (83), 171 (64), 123 (23) and 77 (7).

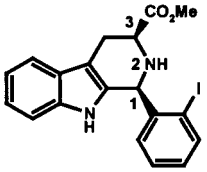
***trans*-1-(2-Iodo-phenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic acid methyl ester 2b and *cis*-1-(2-iodo-phenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic acid methyl ester 2c.** Prepared by general procedure C(1) from imine **1b** (4.32 g, 10 mmol) and *p*-toluenesulphonic acid monohydrate (0.190 g, 1.0 mmol) over 6 h. The product comprised a 1:1 mixture of **2b** and **2c** (^{1}H NMR).

cis isomer **2c**: Flash chromatography eluting with 3:1 v/v chloroform/hexane afforded **2c** (1.55 g, 37%) which crystallized from ether–petroleum ether as colorless needles. Mp 149–151°C. (Found: C, 52.95; H, 3.85; N, 6.2; I, 29.15. $C_{19}H_{17}N_2O_2I$ requires: C, 52.8; H, 3.95; N, 6.5; I, 29.35%); δ: 2.71 (br, 1H, NH), 3.02 (ddd, 1H, J=2.5,

11.1, 15.0 Hz, ArC*H*H), 3.24 (ddd, 1H, *J*=1.8, 4.1, 15.0 Hz, ArC*H*H), 3.81 (s, 3H, OCH_3), 4.00 (dd, 1H, *J*=4.1, 11.1 Hz, $NCHCO_2Me$), 5.64 (s, 1H, ArCHN), 7.03 (dt, 1H, *J*=1.8, 7.5 Hz, ArH), 7.10–7.16 (m, 2H, ArH), 7.21–7.33 (m, 3H, ArH) 7.53–7.55 (m, 2H, ArH and indole-NH) and 7.90 (dd, 1H, *J*=1.2, 8.0 Hz, ArH); *m/z* (%): 432 (M^+, 100), 373 (36), 305 (6), 229 (16) and 169 (21); ν_{max}: 3387, 1730, 1431 and 735 cm^{-1}.

n.O.e. (500 MHz): **Enhancement (%)**

		H_1	H_3
Proton	H_1	-	6.1
Irradiated	H_3	6.5	-

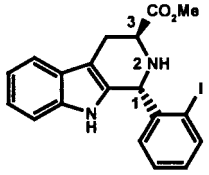


trans isomer **2b**: Continued flash chromatography eluting with 3:1 v/v chloroform/hexane afforded a mixture of **2b** and **2c** (0.376 g, 9%) followed by pure **2b** (1.77 g, 42%), which crystallized from ether–petroleum ether as colorless needles. Mp 149–151°C. (Found: C, 52.9; H, 3.8; N, 6.2; I, 29.25. $C_{19}H_{17}N_2O_2I$ requires: C, 52.8; H, 3.95; N, 6.5; I, 29.35%); δ: 2.84 (br, 1H, NH), 3.08 (ddd, 1H, *J*=1.5, 7.7, 15.3 Hz, ArC*H*H), 3.25 (ddd, 1H, *J*=1.1, 5.0, 15.3 Hz, ArC*H*H), 3.71 (s, 3H, OCH_3), 3.85 (dd, 1H, *J*=5.0, 7.7 Hz, $NCHCO_2Me$), 5.67 (s, 1H, ArCHN), 6.86 (dd, 1H *J*=1.7, 7.7 Hz, ArH), 6.97 (dt, 1H, *J*=1.7, 7.7 Hz, ArH), 7.10–7.24 (m, 4H, ArH), 7.55 (dd, 1H, *J*=1.5, 8.4 Hz, ArH), 7.72 (s, 1H, indole-NH) and 7.89 (dd, 1H, *J*=1.2, 7.9 Hz, ArH); *m/z* (%): 432 (M^+, 100), 373 (41), 305 (14), 245 (26) and 170 (6); ν_{max}: 3390, 1726, 1434 and 739 cm^{-1}.

n.O.e. (500 MHz):

Enhancement (%)

		H_1	H_3
Proton	H_1	-	0.5
Irradiated	H_3	0.9	-



Compound 3a. Prepared by general procedure E from **2a** (0.374 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 16 h. Flash chromatography eluting with 2:1 v/v ether–hexane afforded **3a** (0.270 g, 90%) which crystallized from chloroform as pale yellow prisms. Mp 203–205°C. (Found: C,83.6; H,6.5; N,9.9. $C_{20}H_{18}N_2$ requires: C, 83.9; H, 6.3; N, 9.8%); δ: 2.74 and 3.03 (2×m, 2×1H, Ar$CH_2$$CH_2$), 3.39–3.44 (m, 2H, Ar$CH_2$$CH_2$), 3.52 and 3.79 (2×d, 2×1H, *J*=13.3 Hz, NCH_2C), 5.06 and 5.41 (2×s, 2×1H, C=CH_2), 5.61 (s, 1H, ArCHN) and 7.05–7.82 (m, 8H, ArH); *m/z* (%): 286 (M^+, 100), 257 (48), 242 (17), 230 (12), 217 (10), 143 (27), 128 (21), 115 (18) and 77 (6).

Compound 3b. Prepared by general procedure E from **2b** (0.432, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 16 h. Flash chromatography eluting with 2:3 v/v ether–petroleum ether afforded **3b** (0.318 g, 92%) which crystallized from ether as pale yellow prisms. Mp 134–136°C. (Found: C, 76.65; H, 6.0; N, 7.9. $C_{22}H_{20}N_2O_2$ requires: C, 76.7; H, 5.85; N, 8.15%); δ: 3.25–3.29 (m, 2H, ArCH_2), 3.56 and 3.82 (2×d, 2×1H, *J*=13.4 Hz, NCH_2), 3.75 (s, 3H, OCH_3), 4.10 (dd, 1H, *J*=2.8, 6.3 Hz, $NCHCO_2Me$), 5.04 (s, 1H, C=C*H*H), 5.62 (s, 2H, C=C*H*H and ArCHN), 7.06–7.16 (m, 2H, ArH), 7.26–7.43 (m, 4H, ArH), 7.50 (d, 1H, *J*=8.3 Hz, ArH) and 7.74–7.77 (m, 2H, ArH and indole-NH); *m/z* (%): 344 (M^+, 81), 330 (6), 285 (100), 271 (15) and 142 (37); ν_{max}: 3398, 1738, 1454 and 731 cm^{-1}.

Compound 3c. Prepared by general procedure E from **2c** (0.432, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 16 h. Flash chromatography eluting with 1:2 v/v ether–petroleum ether afforded **3c** (0.266 g, 77%) as a pale yellow gum. (Found: C, 76.5; H, 5.75; N, 7.9. $C_{22}H_{20}N_2O_2$ requires: C, 76.7; H, 5.85; N, 8.15%); δ: 3.09–3.29 (m, 2H, ArCH_2), 3.25 and 3.64 (2×d, 2×1H, *J*=12.7 Hz, NCH_2), 3.87 (s, 3H, OCH_3), 4.25 (dd, 1H, *J*=5.4, 11.6 Hz, $NCHCO_2Me$), 5.06 and 5.61 (2×s, 2×1H, C=CH_2), 5.49 (s, 1H, ArCHN), 7.07–7.16 (m, 2H, ArH), 7.25 (m, 1H, ArH), 7.29–7.41 (m, 3H, ArH), 7.52 (dd, 1H, *J*=2.0, 6.2 Hz, ArH) 7.66 (br, 1H, NH) and 7.75 (d, 1H, *J*=7.7 Hz, ArH); *m/z* (%): 344 (M^+, 13), 285 (100), 271 (6), 257 (21) and 142 (11); ν_{max}: 2922, 2358, 1696 and 1454 cm^{-1}.

Compound 5a. Prepared by general procedure D from **2a** (0.374 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol) and Et_3N (0.101 g, 1 mmol) at 40°C. Flash chromatography eluting with 2:1 v/v ether–petroleum ether afforded **5a** (0.255 g, 93%) which crystallized from ether–petroleum ether as colorless plates. Mp 212–214°C. (Found: C, 78.7; H, 5.25; N, 10.0. $C_{18}H_{14}N_2O$ requires: C, 78.8; H, 5.15; N, 10.2%); δ: 2.84–3.06 (m, 2H, ArCH_2), 3.44 (m, 1H, NC*H*H), 4.88 (ddd, 1H, *J*=1.5, 5.6, 13.3 Hz, NC*H*H), 5.85 (s, 1H, ArCHN), 7.08–7.23 (m, 2H, ArH), 7.38 (m, 1H, ArH), 7.51 (t, 2H, *J*=8.0 Hz, ArH), 7.63 (dt, 1H, *J*=1.2, 7.5 Hz, ArH), 7.81 (dd, 1H, *J*=0.8, 7.5 Hz, ArH), 7.91 (dd, 1H, *J*=0.9, 8.4 Hz, ArH) and 8.32 (br, 1H, NH); *m/z*(%): 274 (M^+, 100), 245 (46), 217 (20), 189 (6), 128 (10) and 109 (21); ν_{max}: 3224, 1681 and 1313 cm^{-1}.

***trans*-7-Oxo-6,7,11b,12-tetrahydro-5*H*-6a, 12-diaza-indeno[1,2-*a*]fluorene-6-carboxylic acid methyl ester 5b.** Prepared by general procedure D from **2b** (0.432 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol) and Et_3N (0.101 g, 1 mmol) at 110°C. Flash chromatography eluting with 2:1 v/v ether–petroleum ether afforded **5b** (0.270 g, 81%) which crystallized from ether

as colorless rods. Mp 166–168 °C. (Found: C, 72.0; H, 4.9; N, 8.2. $C_{20}H_{16}N_2O_3$ requires: C, 72.3; H, 4.85; N, 8.45%); δ: 3.24 (ddd, 1H, *J*=2.4, 7.5, 16.0 Hz, ArCH*H*), 3.46 (d, 1H, *J*=16.0 Hz, ArCH*H*), 3.72 (s, 3H, OCH_3), 5.76 (d, 1H, *J*=7.0 Hz, $NCHCO_2Me$), 6.23 (s, 1H, ArCHN), 7.09–7.21 (m, 2H, ArH), 7.36 (d, 1H, *J*=7.9 Hz, ArH), 7.47–7.54 (m, 2H, ArH), 7.65 (dt, 1H, *J*=1.1, 7.5 Hz, ArH), 7.81 (d, 1H, *J*=7.6 Hz, ArH), 7.93 (d, 1H, *J*=7.5 Hz, ArH) and 8.31 (br, 1H, NH); *m/z* (%): 332 (M^+, 69), 304 (7), 273 (36), 271 (100) and 245 (37); ν_{max}: 3304, 1741, 1169, 1461 and 1197 cm^{-1}.

***cis*-7-Oxo-6,7,11b,12-tetrahydro-5*H*-6a,12-diaza-indeno-[1,2-*a*]fluorene-6-carboxylic acid methyl ester 5c.** Prepared by general procedure D from **2c** (0.216 g, 0.5 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), PPh_3 (0.026 g, 0.1 mmol) and Et_3N (0.051 g, 0.5 mmol) at 110 °C. Flash chromatography eluting with 2:1 v/v ether–petroleum ether afforded **5c** (0.111 g, 67%) which crystallized from ether–petroleum ether as colorless needles. Mp 180–182 °C. (Found: C, 72.1; H, 4.8; N, 8.2. $C_{20}H_{16}N_2O_3$ requires: C, 72.3; H, 4.85; N, 8.45%); δ: 3.24 (ddd, 1H, *J*=2.4, 7.5, 16.0 Hz, ArCH*H*), 3.46 (d, 1H, *J*=16.0 Hz, ArCH*H*), 3.72 (s, 3H, OCH_3), 5.77 (d, 1H, *J*=7.0 Hz, $NCHCO_2Me$), 6.24 (s, 1H, ArCHN), 7.08–7.21 (m, 2H, ArH), 7.35 (d, 1H, *J*=7.7 Hz, ArH), 7.47–7.53 (m, 2H, ArH), 7.63 (dd, 1H, *J*=1.1, 7.5 Hz, ArH), 7.84 (dd, 1H, *J*=0.7, 7.6 Hz, ArH), 7.92 (d, 1H, *J*=7.5 Hz, ArH) and 8.53 (br, 1H, NH); *m/z* (%): 332 (M^+, 46), 304 (6), 273 (28), 271 (100) and 245 (31); ν_{max}: 3308, 1677, 1465 and 727 cm^{-1}.

[2-(3,4-Dimethoxy-phenyl)-ethyl]-(2-iodo-benzylidene)-amine 6a. Prepared by general procedure A from 3,4-dimethoxy-phenethyl amine (1.09 g, 6 mmol) and 2-iodobenzaldehyde (1.39 g, 6 mmol). Work up afforded **6a** (2.37 g, 100%) which crystallized from benzene as colorless prisms, mp 70–72°C. (Found: C, 51.85; H, 4.7; N, 3.3; I, 31.9. $C_{17}H_{18}NO_2I$ requires: C, 51.65; H, 4.6; N, 3.55; I, 32.1%); δ: 2.98 (t, 2H, *J*=7.2 Hz, $ArCH_2$), 3.84 and 3.86 (2×s, 2×3H, $2\times OCH_3$), 3.87–3.95 (m, 2H, NCH_2), 6.75–7.40 (m, 5H, ArH), 7.82–7.96 (m, 2H, ArH) and 8.29 (s, 1H, N=CH); *m/z* (%): 395 (M^+, 27), 244 (45), 217 (11), 151 (100), 117 (69) and 90 (29).

3-(3,4-Dimethoxy-phenyl)-2-(2-iodo-benzylidene amino) propionic acid methyl ester 6b. Prepared by general procedure A from 3,4-dimethoxyphenylalanine methyl ester hydrochloride (3.03 g, 11 mmol), 2-iodobenzaldehyde (2.32 g, 10 mmol) and Et_3N (1.21 g, 12 mmol). Work up afforded **6b** (4.08 g, 90%) as a pale yellow gum. δ: 3.09 (dd, 1H, *J*=13.6, 9.2 Hz, ArC*H*H), 3.29 (dd, 1H, *J*=13.6, 4.6 Hz, ArC*H*H), 3.74, 3.78 and 3.82 (3×s, 3×3H, $3\times3OCH_3$), 4.24 (dd, 1H, *J*=9.3, 4.6 Hz, NCH), 6.66–6.79 (m, 3H, ArH), 7.12 (dt, 1H, *J*=1.4, 7.6 Hz, ArH), 7.35 (t, 1H, *J*=7.5 Hz, ArH), 7.79 (d, 1H, *J*=8.0 Hz, ArH) and 7.99–8.07 (m, 2H, ArH and N=CH); *m/z* (%): 453 (M^+, 14), 380 (8), 302 (17), 242 (13), 151 (100), 116 (11) and 77 (10).

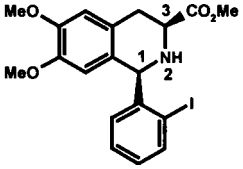
1-(2-Iodo-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline 7a. A mixture of imine **6a** (2.37 g, 6 mmol), trifluoroacetic acid (40 ml) and benzene (40 ml) was stirred and boiled under reflux for 12 h. The reaction mixture was reduced to 5 ml, quenched with saturated aqueous Na_2CO_3 (100 ml) and extracted with ether (3×150 ml). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 2:1 v/v ether–petroleum ether to afford **7a** (2.11 g, 89%) as a pale yellow gum. (Found: C, 51.55; H, 4.6; N, 3.45; I, 32.0. $C_{17}H_{18}NO_2I$ requires: C, 51.65; H, 4.6; N, 3.55; I, 32.1%); δ: 2.07 (br, 1H, NH), 2.81–2.89 (m, 2H, $ArCH_2$), 2.98–3.13 (m, 2H, NCH_2), 3.67 and 3.88 (2×s, 2×3H, $2\times OCH_3$), 5.37 (s, 1H, ArCHN), 6.24 and 6.65 (2×s, 2×1H, 2×ArH), 6.92–6.98 (m, 2H, ArH) and 7.23 and 7.88 (2×m, 2×1H, ArH); *m/z* (%): 395 (M^+, 23), 380 (11), 364 (8), 268 (6), 239 (7), 192 (100), 165 (10) and 77 (6); ν_{max}: 2934, 2829, 1517 and 1260 cm^{-1}.

***trans*-1-(2-Iodo-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester 7b and *cis*-1-(2-iodo-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methyl ester 7c.** Prepared by general procedure C(1) from imine **6b** (3.62 g, 8 mmol) and *p*-toluenesulphonic acid monohydrate (0.152 g, 0.8 mmol) over 8 h. The product comprised a 3:2 mixture of **7b** and **7c** (^1H NMR).

cis isomer **7c**: Flash chromatography eluting with 1:2 v/v ether–hexane afforded **7c** (0.88 g, 24%) which crystallized from ether as colorless prisms. Mp 113–115°C. (Found: C, 50.45; H, 4.55; N, 2.8; I, 28.05. $C_{19}H_{20}NO_4I$ requires: C, 50.35; H, 4.45; N, 3.1; I, 28.0%); δ: 3.06–3.12 (m, 2H, $ArCH_2$), 3.63, 3.78 and 3.87 (3×s, 3×3H, $3\times OCH_3$), 3.92 (m, 1H, $NCHCO_2Me$), 5.48 (s, 1H, ArCHN), 6.18 and 6.65 (2×s, 2×1H, ArH), 6.99 (m, 1H, ArH), 7.26–7.28 (m, 2H, ArH) and 7.87 (d, 1H, *J*=7.9 Hz, ArH); *m/z* (%): 453 (M^+, 12), 394 (100), 380 (21), 250 (45), 151 (23), 119 (17) and 77 (13); ν_{max}: 2948, 1734, 1514 and 1219 cm^{-1}.

n.O.e. (400 MHz):

		Enhancement (%)	
		H_1	H_3
Proton	H_1	-	9.2
Irradiated	H_3	11.2	-

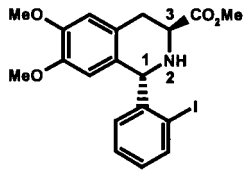


trans isomer **7b**: Continued flash chromatography eluting with 1:2 v/v ether–hexane afforded **7b** (1.33 g, 37%) which crystallized from ether as colorless needles. Mp 117–119°C. (Found: C, 50.35; H, 4.5; N, 2.85; I, 28.05. $C_{19}H_{20}NO_4I$ requires: C, 50.35; H, 4.45; N, 3.1; I, 28.0%); δ: 3.03 (dd, 1H, *J*=9.0, 15.9 Hz, $ArCH_2$), 3.16 (dd, 1H, *J*=4.7, 16.0 Hz, $ArCH_2$), 3.70, 3.73 and 3.89 (3×s, 3×3H, $3\times OCH_3$), 3.71 (m, 1H, $NCHCO_2Me$), 5.52 (s, 1H, ArCHN), 6.29 and 6.67 (2×s, 2×1H, ArH), 6.73 (dd, 1H, *J*=1.7, 7.7 Hz, ArH), 6.95 (dt, 1H, *J*=1.7, 7.7 Hz, ArH), 7.18 (dt, 1H, *J*=1.1, 7.5 Hz, ArH) and 7.90 (dd, 1H,

J=1.2, 7.9 Hz, ArH); *m/z* (%): 453 (M^+, 34), 394 (100), 326 (45), 250 (67), 190 (53), 119 (15) and 77 (12); ν_{max}: 2956, 1745, 1514 and 1223 cm^{-1}.

n.O.e. (400 MHz):

		Enhancement (%)	
		H_1	H_3
Proton	H_1	-	0
Irradiated	H_3	0	-



2,3-Dimethoxy-9-methylene-6,8,9,13b-tetrahydro-5*H*-isoquino[1,2-a]isoquinoline 8a. Prepared by general procedure E from **7a** (0.395 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 16 h. Flash chromatography eluting with ether afforded **8a** (0.279 g, 91%) which crystallized from ethyl acetate as colorless needles, mp 182–184°C. (Found: C, 77.9; H, 6.7; N, 4.45. $C_{20}H_{21}NO_2$ requires: C, 78.15; H, 6.9; N, 4.55%); δ: 2.76 and 2.94 (2×m, 2×1H, NCH_2CH_2), 2.92–2.98 (m, 2H, $ArCH_2$), 3.75 and 4.06 (2×d, 2×1H, J=15.2 Hz, NCH_2C), 3.86 (s, 6H, 2×OCH_3), 5.03 and 5.12 (2×s, 2×1H, C=CH_2), 5.67 (s, 1H, ArCHN), 6.44 and 6.75 (2×s, 2×1H, ArH), 7.12–7.25 (m, 3H, ArH) and 7.68–7.75 (m, 1H, ArH); *m/z* (%): 307 (M^+, 53), 306 (100), 292 (19), 232 (7), 189 (6), 165 (9), 115 (18) and 77 (10); ν_{max}: 2930, 1609, 1521 and 1225 cm^{-1}.

***trans*-2,3-Dimethoxy-9-methylene-6,8,9,13b-tetrahydro-5*H*-isoquino[1,2-*a*]isoquinoline-6-carboxylic acid methyl ester 8b.** Prepared by general procedure E from **7b** (0.453 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 16 h. Flash chromatography eluting with 3:2 v/v ether–petroleum ether afforded **8b** (0.302 g, 83%) which crystallized from ether as colorless needles, mp120–122°C. (Found: C, 72.1; H, 6.5; N, 3.55. $C_{20}H_{21}NO_2$ requires: C, 72.3; H, 6.35; N, 3.85%); δ: 2.84 and 3.00 (2×dd, 2×1H, J=6.8, 15.8 Hz, $ArCH_2$), 3.69–3.96 (m, 3H, NCH_2 and $NCHCO_2Me$), 3.73, 3.83 and 3.86 (3×s, 3×3H, 3×OCH_3), 5.02 and 5.23 (2×s, 2×1H, C=CH_2), 5.69 (s, 1H, ArCHN), 6.66 (s, 2H, ArH), 6.99 (d, 1H, J=7.4 Hz, ArH), 7.13–7.79 (m, 2H, ArH) and 7.71 (m, 1H, ArH); *m/z* (%): 365 (M^+, 15), 306 (100), 290 (9), 218 (6), 189 (16), 115 (19) and 77 (6); ν_{max}: 2953, 1742 and 1513 cm^{-1}.

***cis*-2,3-Dimethoxy-9-methylene-6,8,9,13b-tetrahydro-5*H*-isoquino[1,2-*a*]isoquinoline-6-carboxylic acid methyl ester 8c.** Prepared by general procedure E from **7b** (0.453 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 16 h. Flash chromatography eluting with 1:1 v/v ether–hexane afforded **8c** (0.075 g, 21%) which crystallized from ether–petroleum ether as colorless prisms, mp117–119°C. (Found (HRMS): 365.161140. $C_{20}H_{21}NO_2$ requires: 365.162708); δ: 2.94 and 3.30 (2×dd, 2×1H, J=5.8, 17.3 Hz, $ArCH_2$), 3.49–3.60 (m, 2H, NCH_2), 3.67, 3.83 and 3.86 (3×s, 3×3H, 3×OCH_3), 4.24 (dd, 1H, J=5.7, 12.4 Hz, $NCHCO_2Me$), 4.98 and 5.21 (2×s, 2×1H, C=CH_2), 5.61 (s, 1H, ArCHN), 6.62 and 6.66 (2×s, 2×1H, ArH), 7.28–7.32 (m, 3H, ArH) and 7.77 (dd, 1H, J=2.9, 5.4 Hz, ArH); *m/z* (%): 365 (M^+, 7), 306 (100), 205 (8), 149 (94), 115 (7) and 77 (5); ν_{max}: 2956, 1738, 1514 and 1241 cm^{-1}.

2,3-Dimethoxy-6,12b-dihydro-5*H*-isoindolo[1,2-*a*]isoquinolin-8-one 9a. Prepared by general procedure **D** from **7a** (0.395 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol) and Et_3N (0.101 g, 1 mmol) at 110°C over 16 h. Flash chromatography eluting with 4:1 v/v ether–petroleum ether afforded **9a** (0.153 g, 52%) which crystallized from ethyl acetate as colorless prisms, mp 164–166°C. (Found: C, 73.2; H, 5.95; N, 4.55. $C_{18}H_{17}NO_3$ requires: C, 73.2; H, 5.8; N, 4.75%); δ: 2.78 and 3.01 (2×m, 2×1H, $ArCH_2$), 3.42 and 4.05 (2×m, 2×1H, NCH_2), 3.85 and 3.49 (2×s, 2×3H, 2×OCH_3), 5.63 (s, 1H, ArCHN), 6.67 and 7.13 (2×s, 2×1H, ArH) and 7.41–7.89 (m, 4H, ArH); *m/z* (%): 295 (M^+, 75), 280 (28), 264 (100), 250 (17), 205 (29), 165 (10), 105 (9) and 77 (13); ν_{max}: 2934, 1690, 1513 and 1252 cm^{-1}.

***trans*-2,3-Dimethoxy-8-oxo-5,6,8,12b–tetrahydro-isoindolo[1,2-*a*]isoquinoline-6-carboxylic acid methyl ester 9b.** Prepared by general procedure D from **7b** (0.446 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol) and Et_3N (0.101 g, 1 mmol) at 110°C over 16 h. Flash chromatography eluting with 5:1 v/v ether–petroleum ether afforded **9b** (0.175 g, 50%) which crystallized from ether as pale yellow prisms, mp130–132°C. (Found: C, 67.9; H, 5.45; N, 3.7. $C_{20}H_{19}NO_5$ requires: C, 68.0; H, 5.5; N, 3.95%); δ: 3.13–3.32 (m, 2H, $ArCH_2$), 3.77, 3.86 and 3.92 (3×s, 3×3H, 3×OCH_3), 5.28 (t, 1H, J=5.8 Hz, $NCHCO_2Me$), 5.87 (s, 1H, ArCHN), 6.69 and 7.07 (2×s, 2×1H, ArH), 7.53 (t, 1H, J=7.4 Hz, ArH), 7.66 (t, 1H, J=7.5 Hz, ArH) and 7.63–7.93 (m, 2H, ArH); *m/z* (%): 353 (M^+, 13), 292 (100), 250 (13), 152 (16), 105 (8) and 77 (17); ν_{max}: 3401, 2961, 1696 and 1513 cm^{-1}.

2-(Benzylidene-amino)-3-(1*H*-indol-3-yl)-propionic acid methyl ester 10a.[10] Prepared by general procedure A from L-tryptophan methyl ester hydrochloride (2.80 g, 11 mmol), benzaldehyde (1.06 g, 10 mmol) and Et_3N (1.21 g, 12 mmol). Work up afforded **10a** (3.07 g, 96%) as a pale yellow gum. δ: 3.24 (dd, 1H, J=8.6, 14.3 Hz, $ArCH_2$), 3.55 (dd, 1H, J=4.9, 14.4 Hz, $ArCH_2$), 3.73 (s, 3H, OCH_3), 4.26 (dd, 1H, J=4.9, 8.6 Hz, CHN), 6.89 (d, 1H, J=2.1 Hz, ArH), 7.07–7.16 (m, 2H, ArH), 7.17–7.40 (m, 4H, ArH), 7.63–7.66 (m, 2H, ArH), 7.85 (s, 1H, N=CH) and 8.17 (br, 1H, NH); *m/z* (%): 306 (M^+, 7), 247 (5), 177 (5), 130 (100) and 77 (24).

3-(1*H*-Indol-3-yl)-2-(pyridin-2-ylmethyleneamino)propionic acid methyl ester 10b. Prepared by general procedure A from L-tryptophan methyl ester hydrochloride (2.80 g, 11 mmol), 2-pyridinecarboxaldehyde (1.07 g, 10 mmol) and Et_3N (1.21 g, 12 mmol). Work up afforded **10b** (2.94 g, 96%) as a pale yellow gum. δ: 3.28 (dd, 1H,

J=8.7, 14.5 Hz, $ArCH_2$), 3.64 (dd, 1H, J=5.0, 14.6 Hz, $ArCH_2$), 3.75 (s, 3H, OCH_3), 4.37 (dd, 1H, J=5.2, 8.3 Hz, CHN), 6.94–7.36 (m, 4H, ArH), 7.60–7.76 (m, 2H, ArH), 8.03–8.07 (m, 2H, ArH and N=CH), 8.18 (br, 1H, NH) and 8.58 (m, 1H, ArH); *m/z* (%): 307 (M^+, 7), 219 (7), 169 (8), 143 (3), 130 (100), 119 (34), 93 (15) and 77 (18).

2-(Furan-2-ylmethyleneamino)-3-(1*H*-indol-3-yl)-propionic acid methyl ester 10c. Prepared by general procedure A from L-tryptophan methyl ester hydrochloride (2.80 g, 11 mmol), 2-furaldehyde (0.96 g, 10 mmol) and Et_3N (1.21 g, 12 mmol). Work up afforded **10c** (2.90 g, 98%) as a pale yellow gum. δ: 3.24 (dd, 1H, J=8.8, 14.4 Hz, $ArCH_2$), 3.57 (dd, 1H, J=4.9, 14.4 Hz, $ArCH_2$), 3.74 (s, 3H, OCH_3), 4.22 (dd, 1H, J=4.9, 8.7 Hz, CHN), 6.41 (dd, 1H, J=1.7, 3.3 Hz, furan-H), 6.64 (d, 1H, J=3.4 Hz, furan-H), 6.93 (d, 1H, J=2.0 Hz, furan-H), 7.07–7.19 (m, 2H, ArH), 7.32 (d, 1H, J=7.6 Hz, ArH), 7.48 (s, 1H, ArH), 7.62–7.65 (m, 2H, ArH and N=CH) and 8.30 (br, 1H, NH); *m/z* (%): 296 (M^+, 2), 237 (2), 167 (5), 143 (3), 130 (100), 103 (11) and 77 (15).

3-(1*H*-Indol-3-yl)-2-(thiophen-2-ylmethyleneamino)propionic acid methyl ester 10d. Prepared by general procedure A from L-tryptophan methyl ester hydrochloride (2.80 g, 11 mmol), 2-thiophenecarboxaldehyde (1.12 g, 10 mmol) and Et_3N (1.21 g, 12 mmol). Work up afforded **10d** (2.81 g, 95%) as a pale yellow gum. δ: 3.24 (dd, 1H, J=8.8, 14.4 Hz, ArC*H*H), 3.54 (dd, 1H, J=4.8, 14.6 Hz, ArCH*H*), 3.73 (s, 3H, OCH_3), 4.21 (dd, 1H, J=4.8, 8.8 Hz, CHN), 6.94 (d, 1H, J=2.3 Hz, ArH), 7.00 (dd, 1H, J=3.7, 15.0 Hz, ArH), 7.07–7.39 (m, 5H, ArH), 7.65 (d, 1H, J=7.5 Hz, ArH), 7.94 (s, 1H, N=CH) and 8.12 (br, 1H, NH); *m/z* (%): 312 (M^+, 9), 250 (11), 183 (9), 130 (100), 103 (12) and 77 (24).

2-Benzyl-amino-3-(1*H*-Indol-3-yl)-propionic acid methyl ester 11a.[11] Prepared by general procedure B from imine **10a** (2.45 g, 8 mmol) and $Na(OAc)_3BH$ (2.37 g, 11.2 mmol). Work up afforded **11a** (2.22 g, 90%) as a pale yellow gum, which was purified by flash chromatography eluting with ether. $[\alpha]_D$=−8.8 (1.0, $CHCl_3$). δ: 1.84 (br, 1H, NH), 3.12–3.18 (m, 2H, $ArCH_2$), 3.62 (s, 3H, OCH_3), 3.64–3.83 (m, 3H, CHN and NCH_2), 7.02 (d, 1H, J=1.8 Hz, ArH), 7.07–7.23 (m, 5H, ArH), 7.29–7.38 (m, 2H, ArH), 7.52–7.70 (m, 2H, ArH) and 8.10 (br, 1H, indole-NH); *m/z* (%): 308 (M^+, 2), 249 (6), 178 (20), 130 (100) and 91 (78).

3-(1*H*-Indol-3-yl)-2-[(pyridin-2-ylmethyl)amino]-propionic acid methyl ester 11b. Prepared by general procedure B from imine **10b** (2.46 g, 8 mmol) and $Na(OAc)_3BH$ (2.37 g, 11.2 mmol). Work up afforded **11b** (2.84 g, 93%) as a pale yellow gum, which was purified by flash chromatography eluting with ether. $[\alpha]_D$=−20.0 (1.0, $CHCl_3$). (Found: C, 69.75; H, 6.45; N, 13.5. $C_{18}H_{19}N_3O_2$ requires: C, 69.9; H, 6.2; N,13.6%) δ: 3.12–3.29 (m, 2H, $ArCH_2$), 3.63 (s, 3H, OCH_3), 3.70 (m, 1H, CHN), 3.81 and 3.97 (2×d, 2×1H, J=14.3 Hz, NCH_2), 7.03–7.34 (m, 6H, ArH), 7.51–7.57 (m, 2H, ArH), 8.35 (br, 1H, indole-NH) and 8.45 (m, 1H, ArH); *m/z* (%): 309 (M^+, 1), 250 (6), 201 (10), 179 (64), 130 (100), 93 (55) and 77 (21); ν_{max}: 3175, 2945, 1735 and 1431 cm^{-1}.

2-[(Furan-2-ylmethyl)-amino]-3-(1*H*-indol-3-yl)-propionic acid methyl ester 11c. Prepared by general procedure B from imine **10c** (2.37 g, 8 mmol) and $Na(OAc)_3BH$ (2.37 g, 11.2 mmol). Work up afforded **11c** (2.33 g, 98%) which crystallized from ether as colorless needles. Mp 85–87°C, $[\alpha]_D$=−6.4 (1.0, $CHCl_3$). (Found: C, 68.7; H, 6.1; N, 9.1. $C_{17}H_{18}N_2O_3$ requires: C, 68.45; H, 6.1; N, 9.4%); δ: 1.88 (br, 1H, NH), 3.14–3.18 (m, 2H, $ArCH_2$), 3.61 (s, 3H, OCH_3), 3.65–3.82 (m, 3H, CHN and CH_2N), 6.08 (d, 1H, J=3.1 Hz, furan-H), 6.24 (dd, 1H, J=1.9, 3.0 Hz, furan-H), 7.00 (d, 1H, J=2.1 Hz, ArH), 7.06–7.34 (m, 5H, ArH), 7.55 (d, 1H, J=8.2, ArH) and 8.14 (br, 1H, indole-NH); *m/z* (%): 298 (M^+, 2), 239 (4), 168 (8), 130 (100), 103 (12), 81 (79) and 77 (15); ν_{max}: 3408, 1735, 1458 and 1213 cm^{-1}.

3-(1*H*-Indol-3-yl)-2-[(thiophen-2-ylmethyl)amino]-propionic acid methyl ester 11d. Prepared by general procedure B from imine **10d** (2.50 g, 8 mmol) and $Na(OAc)_3BH$ (2.37 g, 11.2 mmol). Work up afforded **11d** (2.26 g, 90%) which crystallized from ether–petrolum ether as colorless needles. Mp 71–73°C, $[\alpha]_D$=−12.8 (1.0, $CHCl_3$). (Found: C, 64.7; H, 5.9; N, 9.0; S, 10.3. $C_{17}H_{18}N_2O_2S$ requires: C, 64.95; H, 5.75; N, 8.9; S, 10.2%); δ: 2.02 (br, 1H, NH), 3.15–3.19 (m, 2H, $ArCH_2$), 3.63 (s, 3H, OCH_3), 3.71 (m, 1H, CHN), 3.85 (dd, 1H, J=0.6, 3.9 Hz, NCH_2), 4.04 (dd, 1H, J=0.7, 4.0 Hz, NCH_2), 6.82–6.91 (m, 2H, ArH), 7.01 (d, 1H, J=2.5 Hz, ArH) 7.09–7.33 (m, 4H, ArH), 7.58 (dd, 1H, J=0.5, 7.7 Hz, ArH) and 8.13 (br, 1H, indole-NH); *m/z* (%): 314 (M^+, 9), 255 (22), 184 (37), 130 (100), 97 (85) and 77 (48); ν_{max}: 3410, 2948, 1730, 1454 and 743 cm^{-1}.

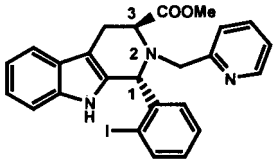
2-Benzyl-1-(2-iodo-phenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic acid methyl ester 12a. Prepared by general procedure C(2) from **11a** (1.85 g, 6 mmol), 2-iodobenzaldehyde (1.39 g, 6 mmol) and *p*-toluenesulphonic acid monohydrate (0.114 g, 0.6 mmol). Flash chromatography eluting with 1:12 v/v ether–hexane afforded **12a** (2.54 g, 81%) which crystallized from ether–hexane as pale yellow prisms. Mp 169–171°C. $[\alpha]_D$=−230.8 (1.0, $CHCl_3$). (Found: C, 59.75; H, 4.5; N, 5.1; I, 24.1. $C_{26}H_{23}N_2O_2I$ requires: C, 59.8; H, 4.45; N, 5.35; I, 24.3%); δ: 3.22–3.24 (m, 2H, $ArCH_2$), 3.62 (s, 3H, OCH_3), 3.77 and 4.00 (2×d, 2×1H, J=13.8 Hz, NCH_2), 3.96 (t, 1H, J=3.9 Hz, NCHCO2Me), 6.10 (s, 1H, ArCHN), 6.95–7.32 (m, 9H, ArH), 7.47–7.56 (m, 3H, ArH) and 7.89 (dd, 1H, J=1.1, 8.0 Hz, ArH); *m/z* (%): 522 (M^+, 23), 463 (51), 431 (100), 371 (9), 243 (17), 218 (67) and 91 (80); ν_{max}: 3440, 3058, 1731, 1459 and 734 cm^{-1}.

1-(2-Iodo-phenyl)-2-pyridin-2-ylmethyl-2,3,4,9-tetrahydro-1*H*–β-carboline-3-carboxylic acid methyl ester 12b. Prepared by general procedure C(2) from **11b** (1.85 g, 6 mmol), 2-iodobenzaldehyde (1.39 g, 6 mmol) and *p*-toluenesulphonic acid monohydrate (0.114 g, 0.6 mmol). Flash chromatography eluting with 3:2 v/v ether–hexane afforded **12b** (2.21 g, 74%) which crystallized from chloroform as pale yellow prisms. Mp 277–279°C. $[\alpha]_D$=−186.8 (1.0, $CHCl_3$). (Found: C, 57.25; H, 4.3; N, 7.8; I, 24.1. $C_{25}H_{22}N_3O_2I$ requires: C, 57.35; H, 4.25; N, 8.05; I, 24.25%); δ: 3.29–3.36 (m, 2H, $ArCH_2$), 3.61 (s, 3H, OCH_3), 3.86 and 4.22 (2×d, 2×1H, J=15.3 Hz,

NCH_2), 4.02 (t, 1H, J=4.1 Hz, NCHCO2Me), 6.15 (s, 1H, ArCHN), 6.93 (m, 1H, ArH), 7.04–7.68 (m, 9H, ArH), 7.84 (d, 1H, J=7.9 Hz, ArH) and 8.38 (m, 1H, ArH); *m/z* (%): 523 (M^+, 1), 431 (100), 371 (12), 243 (16), 217 (34), 169 (7) and 93 (77); ν_{max}: 3393, 2851, 1727, 1431 and 742 cm^{-1}.

n.O.e. (400 MHz):

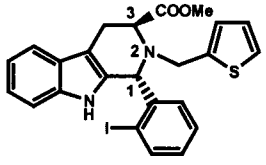
		Enhancement (%)	
		H_1	H_3
Proton	H_1	-	0
Irradiated	H_3	0	-



2-Furylmethyl-1-(2-iodo-phenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic acid methyl ester 12c. Prepared by general procedure C(2) from **11c** (1.79 g, 6 mmol), 2-iodobenzaldehyde (1.39 g, 6 mmol) and *p*-toluenesulphonic acid monohydrate (0.114 g, 0.6 mmol). Flash chromatography eluting with 1:15 v/v ether–hexane afforded **12c** (2.52 g, 82%) which crystallized from chloroform as colorless prisms. Mp 257–259°C. $[\alpha]_D$=−174.0 (1.0, $CHCl_3$). (Found: C, 56.2; H, 4.1; N, 5.2; I, 24.65. $C_{24}H_{21}N_2O_3I$ requires: C, 56.25; H, 4.1; N, 5.45; I, 24.75%); δ: 3.26–3.27 (m, 2H, $ArCH_2$), 3.63 (s, 3H, OCH_3), 3.69 (m, 1H, $NCHCO_2Me$), 4.03–4.09 (m, 2H, NCH_2), 6.03 (s, 1H, ArCHN), 6.14 (d, 1H, J=3.2 Hz, furan-H), 6.27 (dd, 1H, J=1.9, 3.1 Hz, furan-H), 6.95–7.57 (m, 8H, ArH and furan-H), 7.88 (dd, 1H, J=1.1, 8.0 Hz, ArH); *m/z* (%): 512 (M^+, 19), 453 (25), 431 (100), 371 (14), 309 (5), 243 (11), 218 (37), 128 (5) and 81 (47); ν_{max}: 3393, 2949,1731, 1459 and 739 cm^{-1}.

n.O.e. (400 MHz):

		Enhancement (%)	
		H_1	H_3
Proton	H_1	-	3.3
Irradiated	H_3	0	-



1-(2-Iodo-phenyl)-2-thienylmethyl-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylic acid methyl ester 12d. Prepared by general procedure C(2) from **11d** (1.88 g, 6 mmol), 2-iodobenzaldehyde (1.39 g, 6 mmol) and *p*-toluenesulphonic acid monohydrate (0.114 g, 0.6 mmol). Flash chromatography eluting with 1:15 v/v ether–petrolum ether afforded **12d** (2.69 g, 85%) which crystallized from ethyl acetate as colorless prisms. Mp 253–255°C. $[\alpha]_D$=−212.0 (1.0, $CHCl_3$). (Found: C, 54.8; H, 4.15; N, 5.05; S, 6.15. $C_{24}H_{21}N_2O_2SI$ requires: C, 54.55; H, 4.0; N, 5.3; S, 6.05%); δ: 3.27 (m, 2H, $ArCH_2$), 3.63 (s, 3H, OCH_3), 3.80 and 4.37 (2×d, 2×1H, J=14.7 Hz, NCH_2), 4.14 (t, 1H, J=4.0 Hz, $NCHCO_2Me$), 6.09 (s, 1H, ArCHN), 6.87–7.33 (m, 7H, ArH), 7.47–7.53 (m, 2H, ArH), 7.59 (dd, 1H, J=1.8, 7.8 Hz, ArH) and 7.88 (dd, 1H, J=1.2, 8.0 Hz, ArH); *m/z* (%): 528 (M^+, 11), 469 (15), 431 (64), 371 (9), 243 (13), 218 (11)and 97 (100); ν_{max}: 3440, 2948, 1727, 1459 and 739 cm^{-1}.

Compound 13a. Prepared by general procedure E from **12a** (0.522 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 40 h. Flash chromatography eluting with 1:12 v/v ether–petroleum ether afforded **12a** (0.317 g, 73%) which crystallized from ether–petrolum ether as colorless prisms. Mp 207–209°C. $[\alpha]_D$=−100.0 (1.0, $CHCl_3$). (Found: C, 80.1; H, 6.2; N, 6.2. $C_{29}H_{26}N_2O_2$ requires: C, 80.15; H, 6.05; N, 6.45%); δ: 3.06–3.27 (m, 2H, $ArCH_2CH$), 3.68 (s, 3H, OCH_3), 4.02–4.09 (m, 3H, $CH_2C{=}CH_2$ and $NCHCO_2Me$), 4.84 and 4.99 (2×d, 2×1H, J=14.3 Hz, NCH_2Ph), 5.29 and 5.51 (2×s, 2×1H, $C{=}CH_2$), 5.61 (s, 1H, ArCHN), 7.06–7.50 (m, 12H, ArH) and 7.95 (d, 1H, J=7.6 Hz, ArH); *m/z* (%): 434 (M^+, 20), 375 (22), 343 (100), 283 (27), 257 (44), 128 (7)and 91 (45); ν_{max}: 3058, 1735, 1450 and 735 cm^{-1}.

Compound 13b. Prepared by general procedure E from **12b** (0.523 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 40 h. Flash chromatography eluting with 1:1 v/v ether–petroleum ether afforded **13b** (0.241 g, 55%) as a pale yellow gum. $[\alpha]_D$=−118.4 (1.0, $CHCl_3$). (Found: C, 76.6; H, 5.85; N, 9.25. $C_{28}H_{25}N_3O_2{\cdot}(H_2O)_{1/4}$ requires: C, 76.55; H, 5.75; N, 9.55%; Found (HRMS): 435.194275. $C_{28}H_{25}N_3O_2$ requires: 435.194677); δ: 3.11–3.30 (m, 2H, $ArCH_2CH$), 3.70 (s, 3H, OCH_3), 4.08 and 4.23 (2×d, 2×1H, J=15.5 Hz, $CH_2C{=}CH_2$), 4.12 (t, 1H, J=5.8 Hz, $NCHCO_2Me$), 4.83 and 4.97 (2×d, 2×1H, J=14.3 Hz, NCH_2Py), 5.26 and 5.49 (2×s, 2×1H, $C{=}CH_2$), 5.60 (s, 1H, ArCHN), 7.04–7.34 (m, 8H, ArH), 7.48 (dd, 1H, J=0.9, 7.0 Hz, ArH), 7.68 (dt, 1H, J=1.7, 7.7 Hz, ArH), 7.77 (d, 1H, J=7.8 Hz, ArH), 7.90 (d, 1H, J=7.5 Hz, ArH) and 8.51 (m, 1H, ArH); *m/z* (%): 435 (M^+, 2), 376 (4), 343 (100), 283 (51), 256 (25), 119 (10) and 93 (50); ν_{max}: 2951, 1730, 1457 and 727 cm^{-1}.

Compound 13c. Prepared by general procedure E from **12c** (0.512 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 40 h. Flash chromatography eluting with 4:1 v/v ether–petroleum ether afforded **13c** (0.261 g, 62%) which crystallized from ethyl acetate as colorless prisms. Mp 224–226 °C. $[\alpha]_D$=−27.2 (1.0, $CHCl_3$). (Found: C, 75.8; H, 5.55; N, 6.55; $C_{27}H_{24}N_2O_3{\cdot}(H_2O)_{1/4}$ requires: C, 75.6; H, 5.75; N, 6.55%; Found (HRMS): 424.176689. $C_{27}H_{24}N_2O_3$ requires: 424.178693); δ: 3.06–3.23 (m, 2H, $ArCH_2CH$), 3.64 (s, 3H, OCH_3), 3.87–4.11 (m, 3H, $CH_2C{=}CH_2$ and $NCHCH_2$), 4.48 and 5.01 (2×d, 2×1H, J=14.2 Hz, furan-CH_2), 5.36 and 5.58 (2×s, 2×1H, $C{=}CH_2$), 5.75 (s, 1H, ArCHN), 6.30 (d, 1H, J=2.9 Hz, furan-H), 6.36 (d, 1H, J=1.2 Hz, furan-H), 7.03–7.45 (m, 8H, ArH and furan-H) and 7.94 (d, 1H, J=7.6 Hz, ArH); *m/z*

(%): 424 (M^+, 3), 343 (60), 283 (51), 257 (100), 128 (29) and 81 (92); ν_{max}: 3054, 1731 and 1454 cm^{-1}.

Compound 13d. Prepared by general procedure E from **12d** (0.528 g, 1 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol), PPh_3 (0.052 g, 0.2 mmol), Et_4NCl (0.166 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) over 40 h. Flash chromatography eluting with 1:10 v/v ether–petroleum ether afforded **13d** (0.212 g, 48%) which crystallized from ether–petrolum ether as colorless prisms. Mp 226–228°C. $[\alpha]_D=-124.4$ (1.0, $CHCl_3$). (Found: C, 73.55; H, 5.7; N, 6.1; S, 7.3. $C_{27}H_{24}N_2O_2S$ requires: C, 73.60; H, 5.50; N, 6.35; S, 7.3%); δ: 3.06–3.25 (m, 2H, ArCH_2CH), 3.67 (s, 3H, OCH_3), 4.11 and 4.28 (2×d, 2×1H, J=14.5 Hz, $CH_2C{=}CH_2$), 4.14 (t, 1H, J=5.1 Hz, $NCHCO_2Me$), 4.83 and 4.99 (2×d, 2×1H, J=14.2 Hz, NCH_2), 5.32 and 5.53 (2×s, 2×1H, $C{=}CH_2$), 5.69 (s, 1H, ArCHN), 6.94–7.47 (m, 10H, ArH) and 7.98 (d, 1H, J=7.4 Hz, ArH); m/z (%): 440 (M^+, 5), 381 (8), 343 (100), 257 (39), 128 (8) and 97 (83); ν_{max}: 2948, 1726, 1450 and 735 cm^{-1}.

Single crystal X-ray diffraction analysis of 13d

Crystallographic data were measured on a Stoe STADI 4-circle diffractometer using $\omega-\theta$ scans and CuKα radiation (λ=1.54184 Å). The structure was solved by direct methods using SHELXS-86[(2)12] and was refined by full-matrix least-squares (based on F^2) using SHELXL-93[(1).13] The weighting scheme used $w=[\sigma^2(F_o^2)+(0.0911P)^2+1.0092P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. Refinement included an isotropic extinction parameter, x, so that $F_c^{'}=kF_c[1+0.001*x*F_c^2*\lambda^{3]-1/4}$ where k is the overall scale factor. The residuals wR_2 and R_1, given below, are defined as $wR_2=(\sum[w(F_o-F_c^2)^2]/\sum[wF_o^4])^{1/2}$ and $R_1=\sum||F_o|-|F_c||/\sum|F_o|$.

Crystal data for 13d

$C_{27}H_{24}N_2O_2S$, 0.36×0.28×0.19 mm, M=440.54, triclinic, space group P-1, a=9.0602(3), b=11.4771(4), c=12.2957(3) Å, α=93.053(4)°, β=109.452(3)°, γ=108.441(3)°, V=1125.56(6) $Å^3$, Z=2, D_c=1.3 Mg m^{-3}, μ=1.49 mm^{-1}, $F(000)$=464, T=190 K.

Data collection

Graphite monochromated CuK_α radiation, λ=1.54184 Å, scan speeds 1.5–8.0° min^{-1}, ω scan widths 1.05°+α-doublet splitting, 7.74 $<2\theta<$128.92°; 3479 Unique data collected of which 2861 with $F_o>4.0\sigma(F_o)$ were considered 'observed'.

Structure refinement

Number of parameters=291, isotropic extinction parameter, x=0.007(1), goodness of fit, s=1.101; wR_2 (all data)=0.1678, R_1 ('observed' data)=0.0593.

A supplementary dataset, which includes hydrogen co-ordinates, all thermal parameters and complete sets of bond lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre and are available on request.

Acknowledgements

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