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A FORMAL SYNTHESIS OF (±)-ESEROLINE *VIA* AN AZAOXY-COPE REARRANGEMENT†

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Abstract - A novel synthesis of (±)-desoxyeseroline, from the crucial oxindole (**15**), obtained by a 3,3-sigmatropic rearrangement of the enolate derived from the hydroxamic acid derivative (**5**) followed by radical desulfurisation, has been described. The requisite C_2N fragment has been introduced through a Michael addition of nitroethylene to **15**.

(-)-Physostigmine (**1**), the major alkaloid of *Physostigma venenosum* (Balf.) seeds (Calabar beans),[1] is a highly potent acetylcholinesterase inhibitor and has been used medically in the treatment of glaucoma,[2] *myasthenia gravis*[3] and as an antidote against organophosphorous poisoning.[4] More recently the therapeutic properties shown by physostigmine (**1**)[5] towards Alzheimer's disease and the improved pharmacological activity exhibited by some analogues bearing different carbamate side chains[6] have prompted a renewed interest in the alkaloid. Furthermore (-)-eseroline (**2**), a major metabolite of (-)-physostigmine (**1**), is known to possess an analgesic effect similar to that of morphine.[7] As a consequence many syntheses, chiral or otherwise, of this class of compounds have been reported. Amongst them, the method of Julian,[8] developed more than 50 years ago, which involved the introduction of a ß-aminoethyl group equivalent at C-3 of 1,3-dimethyloxindole, (Scheme 1), still remains, in its essentials, an often used synthetic approach to **1** and its analogues.[9]

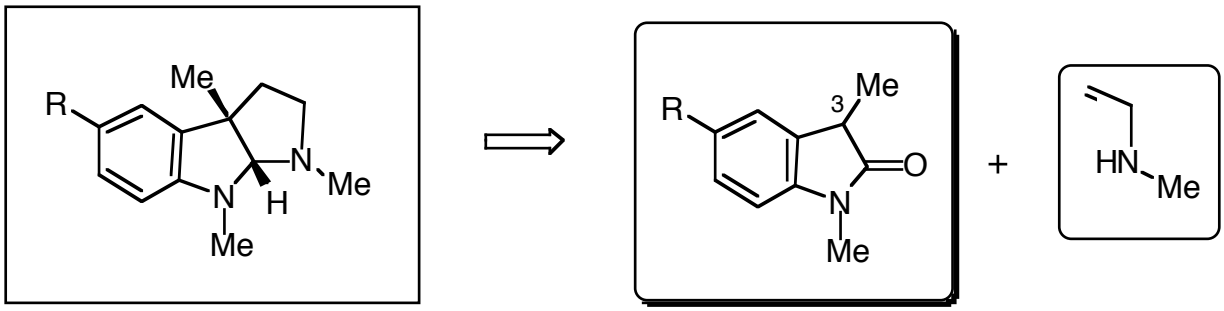
Herein we report a new formal synthesis of (±)-**1** *via* (±)-**3** involving a *N*-carbomethoxyoxindole as the starting material and describe our attempts to obtain the eseroline derivative [(±)-**2**] (R = OCO*t*Bu).

Results and Discussion

The requisite oxindole was readily prepared as follows: chemoselective acylation of *N*-phenylhydroxylamine with $ClCO_2Me$ furnished the hydroxamic acid (**4**) which was *O*-acylated (DCC, 4-DMAP) by 2-phenylsulfanylpropanoic acid[10] to **5** (Scheme 2).

† *Dedicated to Professor Alberto C. Ralha on the occasion of his 80th birthday.*

Similarly **6** gave the *tert*-butyl ester (**7**) which was converted into **8**.



1 R = OCONHMe (-)-physostigmine

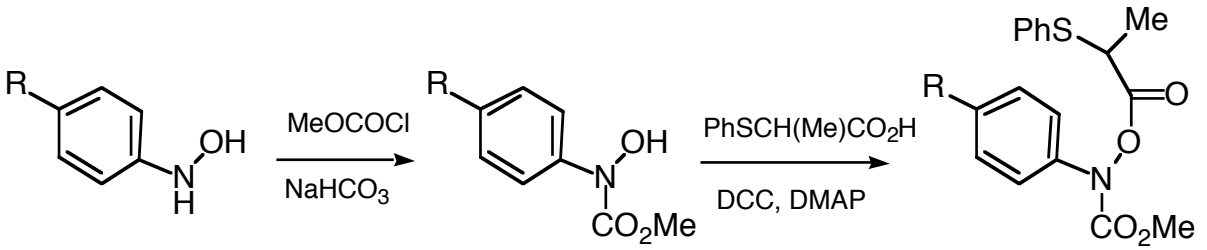
2 R = OH (-)-eseroline

3 R = H (-)-desoxyeseroline

Julian's oxindole

Scheme 1.

A 3,3-sigmatropic rearrangement[11] of the enolates derived from **5** and **8** was studied next for obtaining the precursors of the crucial oxindoles, extending a previously reported protocol.[12]



6 R = OCOBu-*t*

4 R = H
7 R = OCOBu-*t*

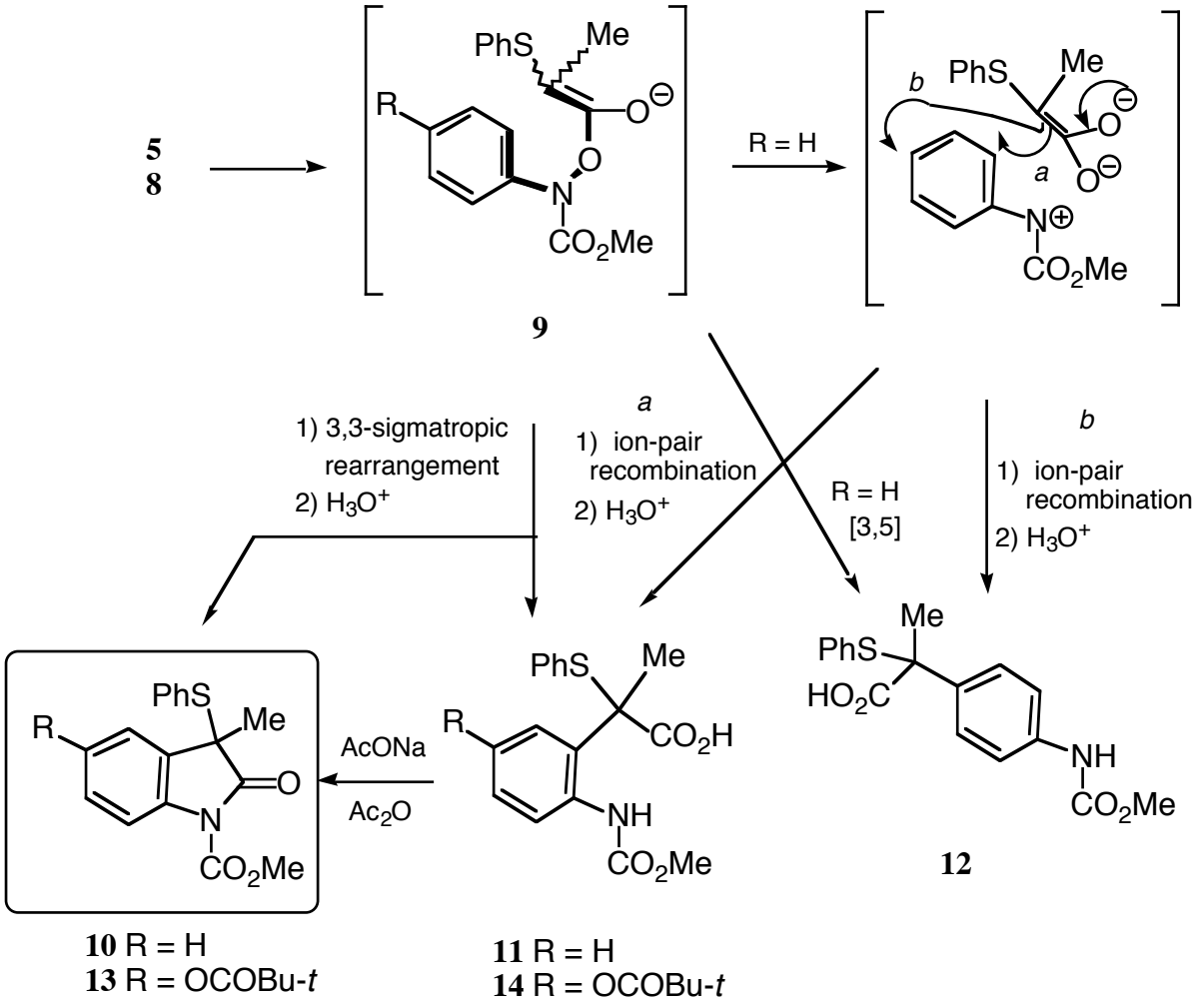
5 R = H
8 R = OCOBu-*t*

Scheme 2.

Although the enolate (**9**) (R=H) (Scheme 3) could be readily generated from **5**, at low temperature, with KH or lithium diisopropylamide, and a 3,3-sigmatropic rearrangement[13] achieved in satisfactory yield in the presence TMSCl, the best results were obtained with potassium bistrimethylsilylamide (KHMDS)[14] alone. The presence of the thioether functionality was also found to be crucial for the rearrangement to occur smoothly. A similar effect was first reported by Lythgoe for systems containing an all carbon framework.[15] The major products formed were isolated, after acidification, by chromatography and identified as the oxindole (**10**), the *o*-aminophenylacetic ester (**11**) and its *p*-isomer (**12**) (Scheme 3).[16]

However, for the subsequent reaction, such separation was unnecessary, since the crude product could be converted directly into **10**, by dehydration (Ac_2O, NaOAc), and purification effected at this stage. The oxindole (**13**) was similarly secured from **8** *via* **14**.

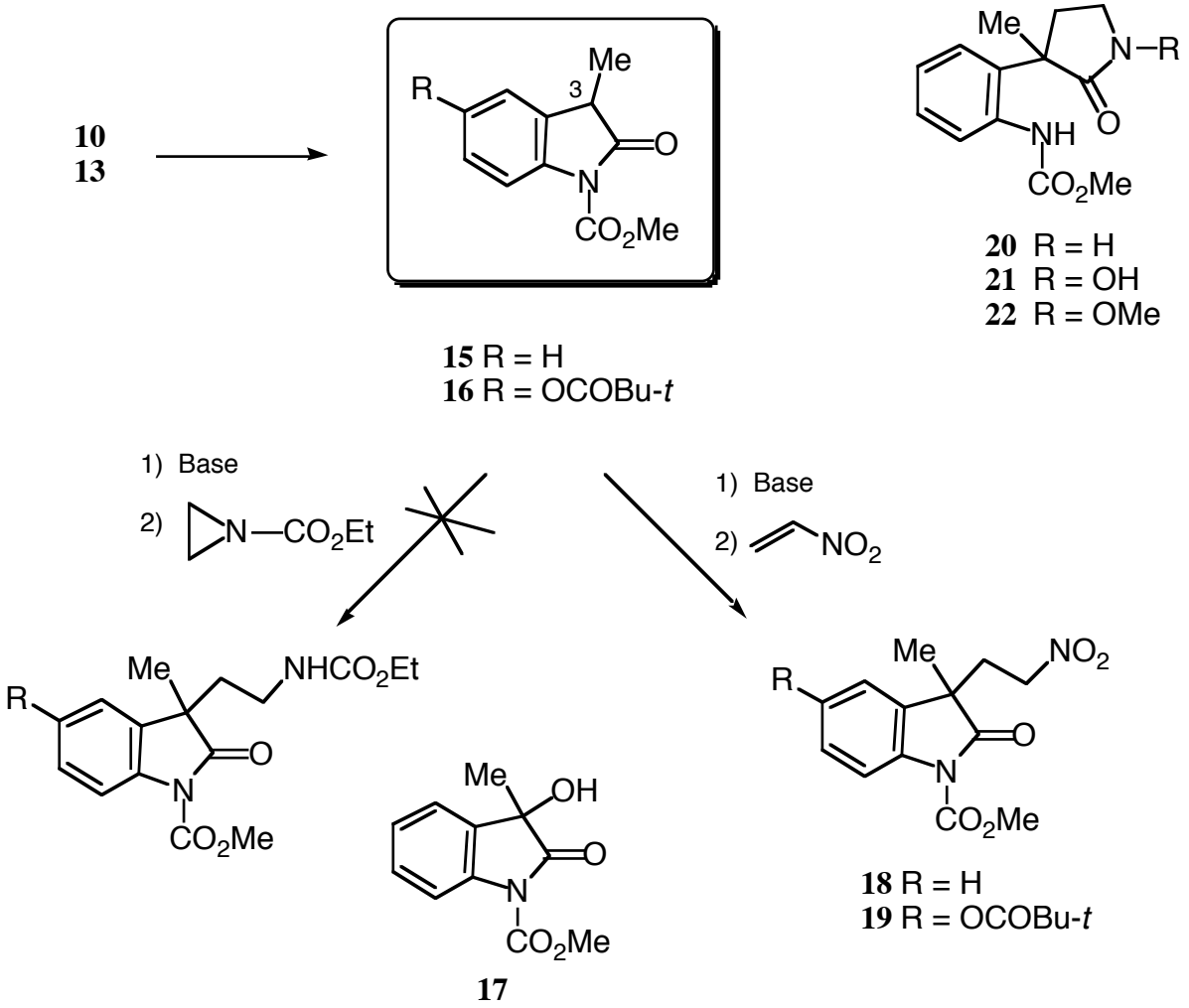
Stannyl hydride mediated desulfurisation of **10** and **13** occurred readily and the two oxindoles (**15**) and (**16**) were obtained in 78 and 79% yields respectively.



Scheme 3.

All our attempts to introduce the aminoethyl side chain at C-3, utilising the carbanion generated from **15** and its subsequent reaction with the electrophile *N*-carbethoxyaziridine,[17] failed[18] (Scheme 4). Instead, amongst a mixture of compounds formed, the hydroxyoxindole (**17**) (51%) was obtained probably from the reaction of the carbanion and the adventitious presence of oxygen in the system. However the same carbanion (derived from **15** and lithium tetramethylpiperidide, LTMP) in THF underwent alkylation with the more powerful electrophile nitroethylene,[19] to provide ß-nitroethyloxindole (**18**) in excellent yield. For reasons not clearly understood, a similar alkylation of **16** to **19** occurred, despite various conditions tried, with disappointingly low yield (14%).

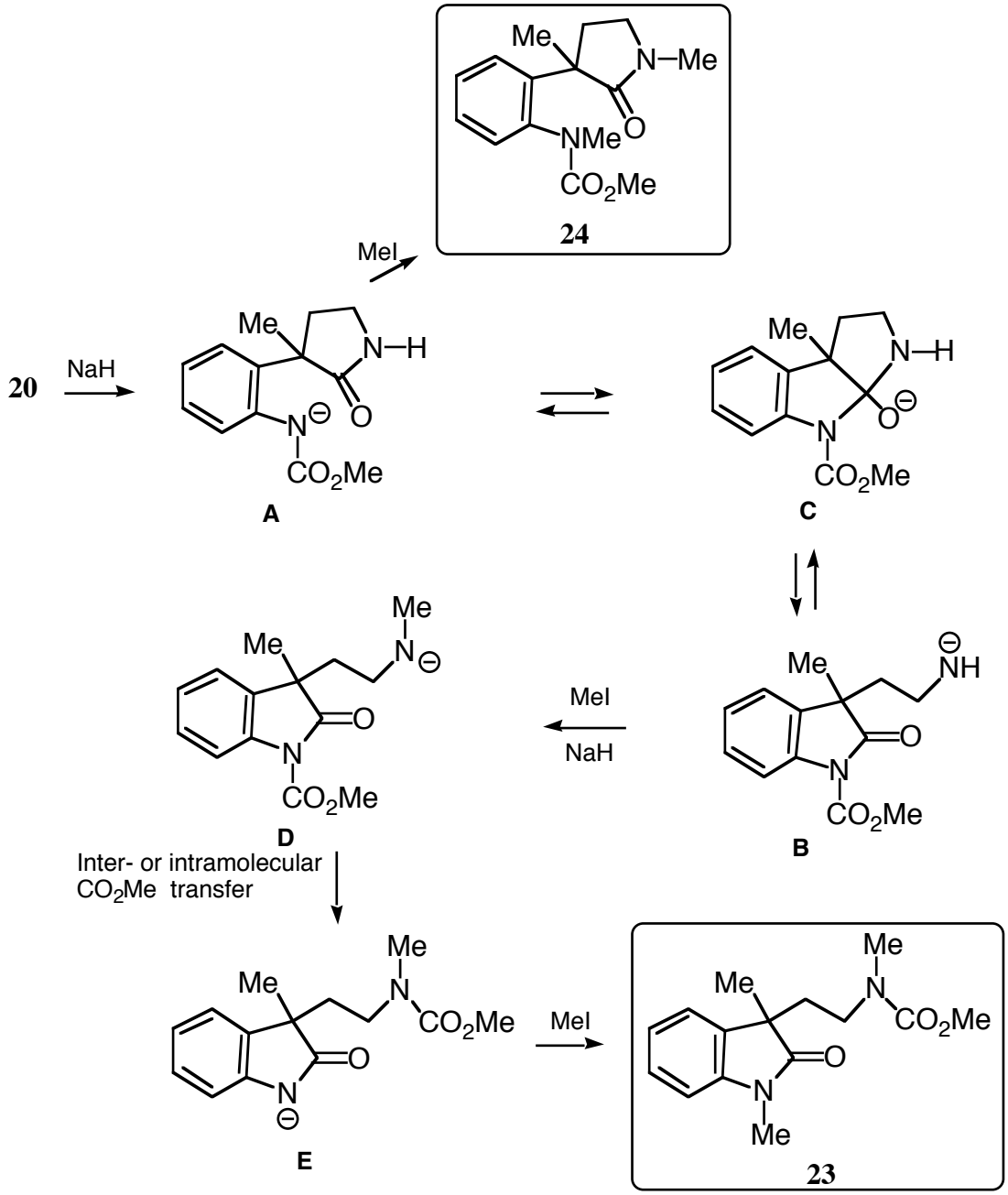
C-Alkylation of enolates, under phase transfer conditions, with chiral quaternary salts, especially those derived from *Cinchona* alkaloids, is a powerful method for the generation of chiral quaternary centres. Application of this procedure to oxindole (**15**) and nitroethylene in the presence of *N*-(4-trifluoromethyl-benzyl)cinchonium bromide,[9f] although successful in providing a modest chemical yield of **18** (~ 40%), proceeded with little or no optical induction under a variety of conditions (temp., conc., solvent). A probable reason for the failure could be due to the powerful electrophilic nature of nitroethylene, since it is known that in general the least reactive alkylating agent affords the highest chiral induction (with RCl > RBr > RI).[20] A similar result was obtained using lithium bis-[(*R*)-1-phenylethyl]amide.



Scheme 4.

Whilst catalytic reduction of **18** with Pd^0 provided a mixture of pyrrolidone (**20**) and the hydroxamic acid (**21**), characterised as its methyl ester (**22**), in 8 and 78% yields respectively, hydrogenation with Raney Ni furnished solely **20** in 76% yield. Direct reductive cyclisation of **20** with LAH did not lead to (±)-*nor*desoxyeseroline, possibly due to the presence of free NH groups forming insoluble lithium salts. Therefore **20** was subjected to the action of MeI (excess) in the presence of NaH (2 eq) (Scheme 5). The

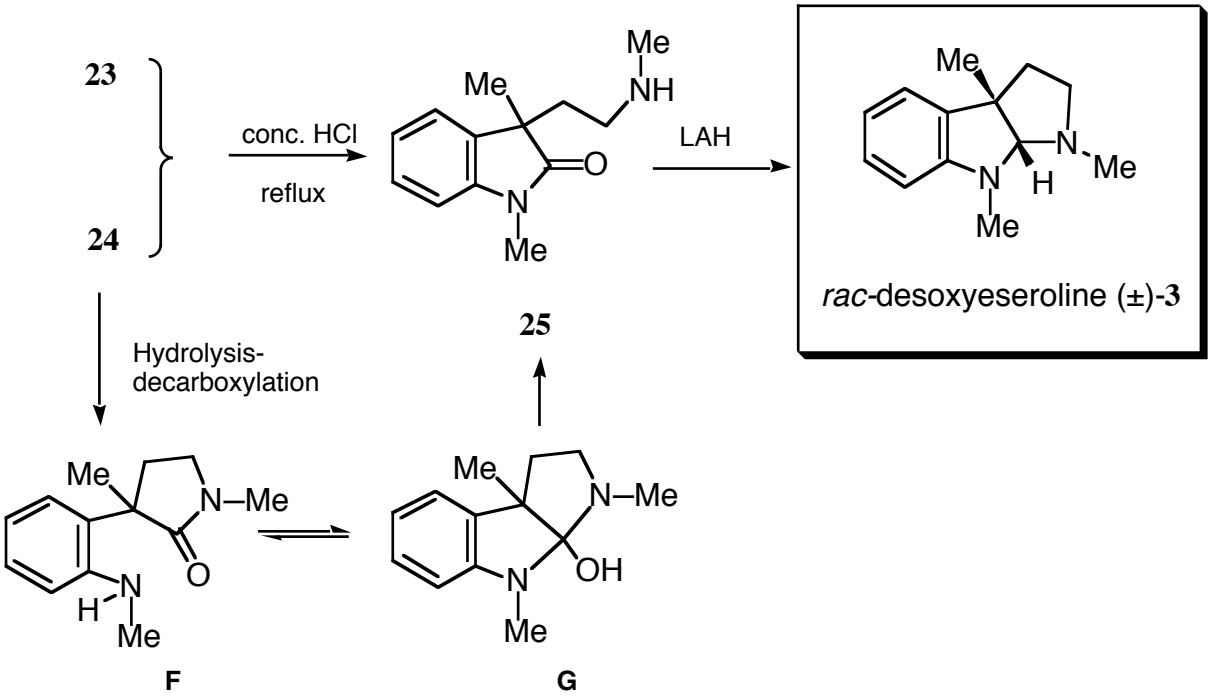
two isomeric urethanes, that were isolated from the reaction, were assigned structures (**23**) and (**24**) on the basis of their spectroscopic properties and MS spectral data. A possible mechanism for the formation of the oxindole (**23**) is shown: the deprotonated species (**A**), in equilibrium with **B** *via* **C**, is *N*-methylated to give **D**. Subsequently **D** undergoes either intra- or intermolecular acyl transfer to **E**, which in turn suffers *N*-alkylation to generate **23**.



Scheme 5.

Acid hydrolysis of either isomer (**23**) or (**24**) furnished the same oxindole (**25**) (Scheme 6), probably *via* **F** and **G**.

Reduction of **25** with LAH furnished (±)-desoxyeseroline [(±)-**3**]. The preparation of (±)-**3** constitutes in a formal sense a synthesis of (±)-physostigmine [(±)-**1**], since **3** has been converted *via* (-)-eseroline (**2**) into **1**.[21] In conclusion, a novel synthesis of (±)-desoxyeseroline [(±)-**3**] is disclosed, involving a formal 3,3-sigmatropic rearrangement of an appropriate *O*-acyl derivative of an hydroxamic acid. This approach can readily be adapted to produce differently 3-substituted oxindoles for production of analogues.



Scheme 6.

ACKNOWLEDGMENT

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EXPERIMENTAL

General: Solvents and reagents were purified and dried according to standard procedures. Hydrogenation reactions were carried out in a Parr 3911 hydrogenator, at room temperature. Elemental analyses were carried out with an automatic microanalyzer (Carlo Erba). For TLC, Merck silica gel 60 F_{254} plates were used. Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. NMR: Varian Unity 300 or Brucker ARX 400 spectrometers, using TMS as internal standard. All spectra were taken at 300 MHz in $CDCl_3$ solutions unless stated otherwise. EI-MS: Kratos MS 25 RS or Fisons TRIO 2000 spectrometers (70 eV). HR-MS: AutoSpecQ spectrometer. IR: Perkin Elmer 683 or Buck Scientific 500 spectrometers, in KBr, unless stated otherwise (wavenumbers in cm^{-1}).

***C*-Methoxy-*N*-phenylhydroxamic acid (4):** To an ice-cooled solution of *N*-phenylhydroxylamine[22a] (9.22 g, 84.6 mmol) in anhydrous Et_2O (125 mL), containing $NaHCO_3$ (9.0 g, 107.1 mmol), under

vigorous stirring, was added dropwise a solution of methyl chloroformate (6.6 mL, 85.4 mmol) in the same solvent (15 mL). The reaction mixture, after being stirred at rt for 2.5 h, was diluted with Et_2O and filtered to remove the inorganic salts, which were washed with Et_2O. The combined filtrates were washed with water, dried over anhydrous Na_2SO_4, and the solvent removed at reduce pressure to give **4** (13.42 g, 95%), as a slightly brownish solid: needles, mp 34-35 °C (Et_2O/*n*-hexane). IR: υ = 3210 (br, OH), 1676 (s, C=O). ^1H NMR: δ = 7.94 (br s, 1H, OH, exchangeable D_2O), 7.48 (m, 2H, ArH), 7.36 (m, 2H, ArH), 7.20 (m, 1H, ArH), 3.81 (s, 3H, OCH_3). EI-MS: *m/z* (%) 167 (15.0) [M^+], 151 (13.0), 119 (100.0). HR-MS: $C_8H_9NO_3$: calcd 167.0582; found: 167.0589.

***C*-Methoxy-*N*-phenyl-*O*-(2-phenylsulfanylpropanoyl)hydroxamic acid (5)**. A solution of DCC (20.6 g, 99.8 mmol) in anhydrous CH_2Cl_2 (70 mL) was added dropwise to a solution of **4** (15.85 g, 94.9 mmol), 2-phenylsulfanylpropanoic acid[10] (19.0 g, 104.4 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (2.35 g, 19.2 mmol), in the same solvent (250 mL), under vigorous stirring at rt. The reaction mixture, after being stirred for 3 h, was filtered under reduced pressure and the filtrate evaporated to dryness. Et_2O was added to the residue and the resulting mixture filtrated to remove the residual *N*,*N*-dicyclohexylurea. The filtrate was then washed, sequentially, with 5% aqueous $NaHCO_3$, 5% aqueous HCl and water. After drying over anhydrous Na_2SO_4, subsequent removal of the solvent at reduced pressure furnished **5** (26.7 g, 85%), as a viscous pale-yellow oil. IR (neat): υ = 1790 (s, NOCO), 1740 (s, COOMe). ^1H NMR: δ = 7.37-7.20 (m, 10H, ArH), 3.91 (q, *J* = 7.2 Hz, 1H, C*H*CH_3), 3.80 (s, 3H, OCH_3), 1.55 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$). EI-MS: *m/z* (%) 331 (1.9) [M^+], 151 (4.9), 137 (9.2), 119 (100.0). HR-MS: $C_{17}H_{17}NO_4S$: calcd 331.0878; found: 331.0889.

***N*-(4-Trimethylacetyloxyphenyl)hydroxylamine (6):** To 4-nitrophenyl trimethylacetate[23] (5.0 g, 22.4 mmol) in a EtOH/water mixture (4.3/1) (100 mL), containing ammonium chloride (2.0 g, 37.4 mmol), stirred vigorously at rt, was slowly added zinc (1.5 g, 22.9 mmol). The addition of zinc was carried out in such way that the reaction temperature did not exceed 60 °C. After being stirred for 1.5 h, the reaction mixture was filtered at reduced pressure and the filtrate extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and the residue recrystallized from benzene and petroleum ether to give **6** (1.39 g, 30%) as a pale-yellow solid: needles, mp 119-121 °C. IR: υ = 3290 (br, OH and NH), 1725 (s, C=O). ^1H NMR: δ = 7.01-6.94 (m, 4H, ArH), 6.78 (br s, 1H, NH or OH, exchangeable D_2O), 5.49 (br s, 1H, NH or OH, exchangeable D_2O), 1.35 [s, 9H, $C(CH_3)_3$].

***C*-Methoxy-*N*-(4-trimethylacetyloxyphenyl)hydroxamic acid (7):** Hydroxylamine (**6**) (2.45 g, 11.7 mmol) in anhydrous Et_2O (50 mL) was acylated with methyl chloroformate (0.91 mL, 11.8 mmol), in dry Et_2O (5 mL), in the presence of $NaHCO_3$ (1.18 g, 14.1 mmol), as described above for the preparation of **4** (1.5 h). Recrystallization of the crude product from Et_2O and petroleum ether afforded **7** (2.76 g, 88%), as a white solid: needles, mp 78-79 °C. IR: υ = 3390 (br, OH), 1740 (s, Me_3CCO), 1680 (s, COOMe). ^1H NMR δ = 7.67 (br s, 1H, OH, exchangeable D_2O), 7.46 (d, *J* = 8.8 Hz, 2H, ArH), 7.03 (d, *J* = 8.8 Hz, 2H, ArH), 3.81 (s, 3H, OCH_3), 1.35 [s, 9H, $C(CH_3)_3$]. EI-MS: *m/z* (%) 267 (8.3) [M^+], 251 (10.1), 219 (5.5), 183 (22.5), 167 (62.8), 135 (71.6), 107 (17.4), 57 (100.0). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24: Found: C, 58.36; H, 6.45; N, 5.11.

***C*-Methoxy-*N*-(4'-trimethylacetyloxyphenyl)-*O*-(2-phenylsulfanylpropanoyl)hydroxamic acid (8):** Compound (**7**) (3.48 g, 13.0 mmol) was condensed with 2-phenylsulfanylpropanoic acid (2.8 g, 15.4 mmol), in anhydrous CH_2Cl_2 (100 mL), in the presence of 4-DMAP (0.32 g, 2.6 mmol) and DCC (2.79 g, 13.5 mmol) in the same solvent (10 mL), as described above for the preparation of **5** (4 h). Recrystallization of the resulting residue from Et_2O and petroleum ether gave **8** (4.90 g, 87%), as a white solid: needles, mp 69.5-70.5 °C. IR: υ = 1800 (s, NOCO), 1755 (s, Me_3CCO), 1730 (s, COOMe). ^1H NMR: δ = 7.38-7.24 (m, 7H, ArH), 7.05 (d, *J* = 8.7 Hz, 2H, ArH), 3.88 (q, *J* = 7.4 Hz, 1H, C*H*CH_3), 3.78 (s, 3H, OCH_3), 1.54 (d, *J* = 7.4 Hz, 3H, $CHCH_3$), 1.36 [s, 9H, $C(CH_3)_3$]. EI-MS: *m/z* (%) 431 (14.1) [M^+], 278 (19.6), 267 (31.3), 251 (21.9), 219 (10.9), 183 (7.0), 167 (8.5), 137 (40.7), 135 (23.3), 109 (14.8), 57 (100.0). Anal. Calcd for $C_{22}H_{25}NO_6S$: C, 61.24; H, 5.84; N, 3.25: Found: C, 61.26; H, 5.81; N, 3.12.

Rearrangement of 5: To a suspension of KH (90.6 mmol, 10.38 g of a 35% dispersion, washed free of the mineral oil with anhydrous THF), in anhydrous THF (110 mL), stirred at rt under N_2 atmosphere, was slowly added bistrimethylsilylamine (19.1 mL, 90.6 mmol). The suspension, after having been stirred for 2 h, was cooled to – 80 °C and a solution of **5** (10.0 g, 30.2 mmol) in the same solvent (40 mL) was added dropwise. The reaction mixture was stirred for 1 h, while the temperature was allowed to rise slowly to rt, and then evaporated to dryness at reduced pressure. The residue was dissolved in a mixture of Et_2O and water, and the organic layer, after having been separated by decantation, extracted with 5% aqueous $NaHCO_3$. The combined aqueous layers were washed with Et_2O, acidified (pH ~ 1) with 5% HCl and extracted with Et_2O. The combined ethereal extracts were dried over anhydrous Na_2SO_4 and the solvent removed at reduced pressure to afford a 6/1 mixture of, respectively, acids (**11**) and (**12**) in 89% yield. Successive recrystallization of the crude mixture from Et_2O/*n*-hexane furnished **11** (6.5 g, 65%) as a white solid: mp 127 °C (decomp) (AcOEt/*n*-hexane). IR: υ = 3270 (br, OH and NH), 1730 (s, COOMe), 1660 (s, COOH). ^1H NMR (acetone d_6): δ = 8,00 (br s, 1H, NH or OH, exchangeable D_2O), 7.81 (d, *J* = 7.8 Hz, 1H, ArH), 7.38-7.26 (m, 2H, ArH), 7.19-7.14 (m, 2H, ArH), 7.08-7.05 (m, 2H, ArH), 6.91-6.80 (m, 2H, ArH), 3.72 (s, 3H, OCH_3), 1.91 (s, 3H, CCH_3). EI-MS: *m/z* (%) 313 (15.4) [M^+-H_2O], 204 (100.0). Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23: Found: C, 61.65; H, 5.16; N, 4.10.

The ethereal layers, containing the base insoluble products, were dried over anhydrous Na_2SO_4 and the residue subjected to preparative TLC (Et_2O/*n*-hexane - 1/1) to give oxindole (**10**) (0.19 g, 2%) as a white solid: mp 108.5-110.5 °C. IR: υ = 1775 (s, NCO), 1735 (s, COOMe). ^1H NMR: δ = 7.67-7.64 (m, 1H, ArH), 7.44-7.41 (m, 1H, ArH), 7.31-7.11 (m, 7H, ArH), 3.93 (s, 3H, OCH_3), 1.74 (s, 3H, CCH_3). EI-MS: *m/z* (%) 313 (14.3) [M^+], 204 (100.0). Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47: Found: C, 65.12; H, 4.78; N, 4.43. Acid (**12**) was isolated (0.77 g, 7%) from the crude mixture of the two isomeric acids after conversion of **11** into the corresponding oxindole (**10**) (as mentioned below), as a solid: mp 131 °C (decomp). IR: υ = 3170 (br, OH and NH), 1750 (s, COOMe), 1690 (s, COOH). ^1H NMR: δ = 9.18 (br s, 1H, OH, exchangeable D_2O), 7.61-7.58 (m, 2H, ArH), 7.49-7.29 (m, 7H, ArH), 6.38 (br s, 1H, NH, exchangeable D_2O), 3.70 (s, 3H, OCH_3), 1.44 (s, 3H, CCH_3). EI-MS: *m/z* (%) 299 (22.2) [M^+-MeOH], 286 (36.1), 256 (18.9), 222 (22.8), 221 (47.5), 118 (100.0). Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23: Found: C, 61.72; H, 5.14; N, 4.11.

Oxindole (10). The crude mixture of acids (**11**) and (**12**) (11.06 g, 33.4 mmol) and sodium acetate (270 mg, 3.3 mmol), in acetic anhydride (90 mL), was heated at 60-70 °C for 3 h, concentrated at reduced pressure and the residue treated, with stirring, with a saturated aqueous solution of $NaHCO_3$ until pH ~ 8. The mixture was then extracted with Et_2O and the combined organic layers washed, sequentially, with 5% aqueous $NaHCO_3$ and water. On drying over anhydrous Na_2SO_4, followed by evaporation under reduced pressure, crystallisation of the resulting solid from Et_2O/*n*-hexane gave **10** in 52% yield (5.43 g), which was identical with the sample obtained as mentioned above.

Rearrangement of 8: A solution of **8** (0.3 g, 0.7 mmol) in anhydrous THF (2 mL) was treated with a suspension of KHMDS (0.42 g, 2.13 mmol) in the same solvent (4 mL), as described above for **5** (13 h). Recrystallization of the resulting residue from CH_2Cl_2 and petroleum ether furnished acid **14** (0.21 g, 70%), as a solid: mp 142.0 °C (decomp). IR: υ = 3280 (br, OH and NH), 1755 (s, Me_3CCO), 1735 (s, COOMe), 1665 (s, COOH). ^{1}H NMR: δ = 7.92 (br s, 1H, NH or OH, exchangeable D_2O), 7.51-6.92 (m, 7H, ArH), 6.36 (s, 1H, ArH), 3.69 (s, 3H, OCH_3), 1.78 (s, 3H, CCH_3), 1.25 [s, 9H, $C(CH_3)_3$]. EI-MS: *m/z* (%) 413 (18.8) [M^+-H_2O], 304 (91.3), 246 (12.3), 220 (37.7), 161 (18.1), 133 (26.8), 110 (52.9), 77 (22.5), 57 (100.0). Acid (**14**) was further characterised as the methyl ester, readily obtained by treatment of an ethereal solution of the compound with excess ethereal solution of diazomethane,[22b] as a white solid: mp 112-113 °C (Et_2O/petroleum ether). IR: υ = 3310 (br, NH), 1750 (s, Me_3CCO), 1740 (s, COOMe), 1725 (s, NCOOMe). ^{1}H NMR: δ = 7.68-7.01 (m, 9H, ArH and NH), 6.41 (d, *J* = 2.4 Hz, 1H, ArH), 3.81 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 1.83 (s, 3H, CCH_3), 1.28 [s, 9H, $C(CH_3)_3$]. EI-MS: *m/z* (%) 445 (8.3) [M^+], 413 (100.0). HR-MS: $C_{23}H_{27}NO_6S$: calcd 445.1559; found: 445.1596.

Oxindole (13): Acid (**14**) (0.72 g, 1.67 mmol) was dehydrated with sodium acetate (13.8 mg, 0.17 mmol), in acetic anhydride (4 mL), as described for the crude mixture of acids (**11**) and (**12**) (2 h). Recrystallization of the residue from Et_2O yielded **13** (0.56 g, 81%), as a white solid: mp 106.0-107.5 °C. IR: υ = 1770 (s, NCO), 1750 (s, Me_3CCO), 1740 (s, COOMe). ^{1}H NMR (400 MHz): δ = 7.63 (d, *J* = 8.8 Hz, 1H, ArH), 7.30-7.23 (m, 3H, ArH), 7.18-7.13 (m, 3H, ArH), 6.92 (dd, *J* = 2.5, 8.8 Hz, 1H, ArH), 3.92 (s, 3H, OCH_3), 1.75 (s, 3H, CCH_3), 1.39 [s, 9H, $C(CH_3)_3$]. EI-MS: *m/z* (%) 413 (6.9) [M^+], 304 (63.4), 220 (15.8), 161 (5.7), 109 (11.7), 77 (7.9), 57 (100.0). Anal. Calcd for $C_{22}H_{23}NO_5S$: C, 63.90; H, 5.61; N, 3.39: Found: C, 64.29; H, 5.60; N, 3.27.

1-Methoxycarbonyl-3-methyloxindole (15): Compound (**10**) (2.84 g, 9.07 mmol) and *n*-Bu_3SnH (7.3 mL, 27.14 mmol) in anhydrous benzene (25 mL), under reflux, was treated (2 h 40 min), through a syringe pump, with a solution of AIBN (140 mg, 0.85 mmol) in the same solvent (4 mL). After the addition of the initiator was complete, reflux was continued for 40 min. The solvent was then removed at reduced pressure and the residue dissolved in a 1/1 mixture of acetonitrile and *n*-hexane. The acetonitrile layer, after being separated by decantation, was washed with *n*-hexane and evaporated to dryness. Recrystallization of the resulting residue from Et_2O/*n*-hexane furnished **15** (1.45 g, 78%), as a white solid: mp 75-76 °C.
IR: υ = 1760 (s, NCO), 1730 (s, COOMe). ^{1}H NMR: δ = 7.91 (d, *J* = 8.1 Hz, 1H, ArH), 7.36-7.17 (m, 3H, ArH), 4.02 (s, 3H, OCH_3), 3.61 (q, *J* = 7.7 Hz, 1H, C*H*CH_3, collapses to singlet by irradiation at the frequency of 1.54), 1.54 (d, *J* = 7.7 Hz, 1H, $CHCH_3$, collapses to singlet by irradiation at the frequency of

3.61). EI-MS: *m/z* (%) 205 (100.0) [M^+]. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.38: Found: C, 64.71; H, 5.40; N, 6.82.

1-Methoxycarbonyl-3-methyl-5-trimethylacetyloxyoxindole (16): Compound (**13**) (0.82 g, 1.99 mmol) was desulfurized with *n*-Bu_3SnH (1.6 mL, 5.95 mmol), in anhydrous benzene (25 mL), in the presence of AIBN (32 mg, 0.20 mmol) (solution in 7.5 mL of anhydrous benzene added to reaction mixture for 1.5 h), as described above (2 h). Recrystallization of the resulting residue from Et_2O/*n*-hexane yielded **16** (0.48 g, 79%), as a white solid: mp 122.5-124.0 °C. IR: υ = 1780 (s, NCO), 1750 (s, Me_3CCO), 1730 (s, COOMe). ^1H NMR: δ = 7.92 (d, *J* = 9.6 Hz, 1H, ArH), 7.02-6.98 (m, 2H, ArH), 4.02 (s, 3H, OCH_3), 3.62 (q, *J* = 7.6 Hz, 1H, C*H*CH_3), 1.54 (d, *J* = 7.6 Hz, 1H, CHC*H*$_3$), 1.37 [s, 9H, $C(CH_3)_3$]. EI-MS: *m/z* (%) 305 (9.7) [M^+], 221 (41.8), 162 (13.8), 146 (10.5), 119 (25.1), 57 (100.0). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59: Found: C, 62.57; H, 6.26; N, 4.43.

Reaction of 15 with *N*-ethoxycarbonylaziridine: To a solution of **15** (0.1 g, 0.49 mmol) and *N*-ethoxycarbonylaziridine[17] (260 mg, 2.26 mmol) in anhydrous THF (10 mL), cooled to -90°C, stirred under N_2 atmosphere, was added dropwise (1 h) a suspension of KHMDS (0.11 g, 0.57 mmol) in the same solvent (10 mL). The reaction mixture was then stirred for 5 h while the temperature was left to rise slowly to rt. The solvent was then removed at reduced pressure and the residue dissolved in a mixture of Et_2O and 5% aqueous HCl. The organic layer, obtained by decantion, was washed with water and dried over anhydrous Na_2SO_4. Removal of the solvent at reduced pressure left a dark residue which was subjected to preparative TLC (silica, Et_2O/*n*-hexane - 1/1) to give **3-hydroxy-1-methoxycarbonyl-3-methyloxindole** (**17**) (54.7 mg, 51%), as a colorless oil. IR: υ = 3450 (br, OH), 1780 (s, NCO), 1740 (s, COOMe). ^1H NMR: δ = 7.93 (d, *J* = 8.4 Hz, 1H, ArH), 7.47-7.36 (m, 2H, ArH), 7.27-7.22 (m, 1H, ArH), 4.02 (s, 3H, OCH_3), 2.90 (br s, 1H, OH, exchangeable D_2O), 1.64 (s, 3H, CCH_3). ^{13}C NMR: δ = 176.9 (C^2), 151.3 (*C*O_2Me), 138.3, 130.2, 130.1, 125.4, 123.5, 115.4, 73.5 (C^3), 54.0 (OCH_3), 25.8 (C^3-*C*H_3). EI-MS: *m/z* (%) 221 (100.0) [M^+]. HR-MS: $C_{11}H_{11}NO_4$: calcd 221.0688; found: 221.0698.

1-Methoxycarbonyl-3-methyl-3-(2'-nitroethyl)oxindole (18): To an ice-cooled solution of 2,2,6,6-tetramethylpiperidine (1.65 mL, 9.78 mmol) in anhydrous THF (30 mL), stirred under N_2 atmosphere, was added a 1.4 M solution of *n*-BuLi in *n*-hexane (7.0 mL, 9.8 mmol). After 30 min, the suspension was cooled to -80 °C and a solution of **15** (2.0 g, 9.76 mmol) in anhydrous THF (15 mL), followed by a solution of nitroethylene[19] (0.79 g, 10.8 mmol) in anhydrous benzene (6 mL), was added. The reaction mixture was stirred for 10 min, diluted with Et_2O and evaporated to dryness. The resulting residue was dissolved in a mixture of Et_2O and water, and the organic layer, after being separated by decantation, was washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent at reduced pressure, the residue obtained was recrystallized from Et_2O/*n*-hexane, to give **18** (2.25 g, 83%) as a white solid: mp 78-79.5 °C. IR: υ = 1765 (s, NCO), 1740 (s, COOMe), 1555 (s, NO_2), 1355 (s, NO_2). ^1H NMR: δ = 7.96 (d, *J* = 8.4 Hz, 1H, ArH), 7.41-7.34 (m, 1H, ArH), 7.28-7.22 (m, 2H, ArH), 4.34-4.24 (m, 1H, $CH_2CH_2NO_2$), 4.17-4.08 (m, 1H, $CH_2CH_2NO_2$), 4.04 (s, 3H, OCH_3), 2.74-2.64 (m, 1H, $CH_2CH_2NO_2$), 2.58-2.48 (m, 1H, $CH_2CH_2NO_2$), 1.50 (s, 3H, CCH_3). EI-MS: *m/z* (%) 278 (100.0) [M^+]. Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07: Found: C, 56.34; H, 5.05; N, 10.09.

1-Methoxycarbonyl-3-methyl-3-(2'-nitroethyl)-5-trimethylacetyloxyoxindole (19): Similarly **16** gave **19** (14%, after recrystallization from Et_2O and *n*-hexane), as a white solid: mp 124-125.5 °C. IR: υ = 1770 (s, NCO), 1750 (s, Me_3CCO), 1730 (s, COOMe), 1550 (s, NO_2), 1355 (m, NO_2). ^1H NMR: δ = 7.98 (d, *J* = 8.7 Hz, 1H, ArH), 7.06 (dd, *J* = 2.4, 8.7 Hz, 1H, ArH), 6.98 (d, *J* = 2.4 Hz, 1H, ArH), 4.35-4.10 (m, 2H, $CH_2CH_2NO_2$), 4.04 (s, 3H, OCH_3), 2.73-2.63 (m, 1H, $CH_2CH_2NO_2$), 2.54-2.43 (m, 1H, $CH_2CH_2NO_2$), 1.51 (s, 3H, CCH_3), 1.37 [s, 9H, $C(CH_3)_3$]. EI-MS: *m/z* (%) 378 (3.9) [M^+], 294 (33.8), 260 (3.2), 220 (3.6), 176 (12.5), 162 (5.7), 147 (3.8), 119 (3.1), 85 (10.1), 57 (100.0).

Reaction of 15 with nitroethylene in the presence of *N*-(4-trifluoromethylbenzyl)cinchonium bromide (4-CF_3BCNB): To an ice-cooled mixture of **15** (43.5 mg, 0.21 mmol) and 85% 4-CF_3BCNB (12 mg, 0.022 mmol) in toluene (2 mL), stirred vigorously under N_2 atmosphere, was added 25% aqueous NaOH (0.04 mL, 0.25 mmol) followed, 10 min later, by a solution of nitroethylene (81.6 mg, 1.12 mmol), in anhydrous benzene (0.6 mL) diluted in toluene (2 mL). After being stirred for 20 min, the reaction mixture was diluted with a mixture of Et_2O and water and acidified with 5% aqueous HCl. The organic layer, after being separated by decantation, was washed with water, dried over anhydrous Na_2SO_4 and the solvent removed a reduced pressure. The remaining residue was purified by preparative TLC (silica, Et_2O/*n*-hexane - 1/1) to give **18** (22.8 mg, 39%), as a white solid, which was identical with a sample previously isolated. The ^1H NMR spectrum of **18** in the presence of the shift reagent Eu(tfc)$_3$ (splitting of ArH doublet at d 7.69 into two doublets at δ 8.70 and 8.59) indicated *ee* ≈ 0.

Hydrogenation of 18. a) In the presence of PtO_2: A solution of **18** (0.4 g, 1.44 mmol) in EtOH (50 mL), containing 80% PtO_2 (41 mg, 0.14 mmol), was shaken under hydrogen pressure (45 Psi) for 26.5 h. After removal of the catalyst by filtration over celite, the filtrate was evaporated to dryness and the residue recrystallized from Et_2O and CH_2Cl_2 to give **1-hydroxy-3-(2'-methoxycarbonylamino)phenyl-3-methyl-2-pyrrolidone** (**21**) (0.30 g, 78%), as a white solid: mp 165 °C (decomp). IR: υ = 3240 (br, NH and OH), 1720 (s, COOMe), 1675 (s, NCO). ^1H NMR: δ = 9.17 (br s, 2H, NH and OH, exchangeable D_2O), 7.59 (br s, 1H, ArH), 7.31-7.25 (m, 2H, ArH), 7.13 (t, *J* = 7.5 Hz, 1H, ArH), 3.76-3.68 (m, 5H, OCH_3 and CH_2CH_2N), 2.68-2.58 (m, 1H, CH_2CH_2N), 2.07-1.99 (m, 1H, CH_2CH_2N), 1.53 (s, 3H, CCH_3). EI-MS: *m/z* (%) 264 (41.2) [M^+], 262 (48.4), 248 (19.6), 244 (44.0), 232 (50.8), 216 (48.0), 205 (31.8), 204 (52.0), 188 (45.2), 173 (43.8), 160 (36.4), 146 (91.2), 144 (77.6), 130 (100.0). HR-MS: $C_{13}H_{16}N_2O_4$: calcd 264.1110; found: 264.1108. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60: Found: C, 58.96; H, 6.11; N, 10.46. Evaporation of the mother-liquors from recrystallization of **21** left a residue which was purified by preparative TLC (silica, Et_2O/*n*-hexane - 3/1) to give **3-(2'-methoxycarbonylamino)phenyl-3-methyl-2-pyrrolidone** (**20**) (after recrystallization from Et_2O and CH_2Cl_2, 28 mg, 8%), as a white solid: mp 162 °C (decomp). IR: υ = 3280 (br, NH), 1715 (s, COOMe), 1690 (s, NCO). ^1H NMR: δ = 9.77 (br s, 1H, NH, exchangeable D_2O), 7.77 (br s, 1H, ArH), 7.31-7.26 (m, 2H, ArH), 7.10 (t, *J* = 7.5 Hz, 1H, ArH), 6.85 (br s, 1H, NH, exchangeable D_2O), 3.76 (s, 3H, OCH_3), 3.44-3.40 (m, 2H, CH_2CH_2N), 2.84-2.76 (m, 1H, CH_2CH_2N), 2.19-2.11 (m, 1H, CH_2CH_2N), 1.60 (s, 3H, CCH_3). ^{13}C NMR: δ = 182.0 (C^2), 155.1 (*C*OOMe), 137.2, 132.5, 128.1, 126.1, 125.7, 124.4, 52.2 (OCH_3), 47.6, 39.3, 36.6, 22.4. EI-MS: *m/z* (%) 248 (44.7) [M^+], 216 (30.7), 205 (100.0). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28: Found: C, 62.75; H, 6.49; N, 11.28. **b) In the**

presence of Raney-Ni: Compound (**18**) (0.289 g, 1.04 mmol) was dissolved in MeOH (30 mL) and hydrogenated in the presence of Raney-Ni[24] (~ 25 mg), as described previously with PtO_2. Recrystallization of the crude product from Et_2O and CH_2Cl_2 furnished **20** (196 mg, 76%), as a white solid, which was identical with a sample previously isolated.

1-Methoxy-3-(2'-methoxycarbonylamino)phenyl-3-methyl-2-pyrrolidone (22): To an ice-cooled suspension of KH (0.74 mmol, 85 mg of a 35% dispersion, washed free of oil with anhydrous THF) in anhydrous THF (4 mL), stirred under N_2 atmosphere, was added a solution of **21** (180.5 mg, 0.73 mmol) in the same solvent (2 mL). Once the evolution of H_2 has ceased, MeI (0.045 mL, 0.73 mmol) was added and the resulting mixture stirred for an additional 30 min at rt. The reaction mixture was then filtered at reduced pressure to remove the inorganic salt and the filtrate evaporated to dryness. Purification of the resulting residue by preparative TLC (silica, Et_2O) furnished **22** (145 mg, 71%, after recrystallization from Et_2O and CH_2Cl_2), as a white solid: mp 139.5-141.0 °C. IR: υ = 3170 (br, NH), 1700 (br and s, COOMe and NCO). ^{1}H NMR: δ = 9.49 (br s, 1H, NH, exchangeable D_2O), 7.76 (br d, *J* = 7.5 Hz, 1H, ArH), 7.33-7.26 (m, 2H, ArH), 7.16-7.10 (t, *J* = 7.5 Hz, 1H, ArH), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.70- 3.56 (m, 2H, CH_2CH_2N), 2.70-2.61 (m, 1H, CH_2CH_2N), 2.11-2.03 (m, 1H, CH_2CH_2N), 1.60 (s, 3H, CCH_3). EI-MS: *m/z* (%) 278 (2.5) [M^+], 246 (21.0), 216 (13.0), 204 (12.5), 173 (11.0), 172 (11.0), 159 (12.5), 146 (24.0), 130 (100.0). HR-MS: $C_{14}H_{18}N_2O_4$: calcd 278.1266; found: 278.1271.

Methylation of pyrrolidone (20): To an ice-cooled solution of **20** (0.48 g, 1.94 mmol) in anhydrous THF (12 mL), stirred under N_2 atmosphere, was added a 60% dispersion of NaH in mineral oil (165 mg, 4.13 mmol). After the evolution of gas has ceased, MeI (0.26 mL, 4.16 mmol) was added and the resulting mixture stirred at rt for 4 h 45 min. The reaction mixture was then filtrated over celite and the filtrate evaporated to dryness at reduced pressure. The residue was dissolved in CH_2Cl_2 and the solution washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent by evaporation at reduced pressure, the residue was subjected to preparative TLC (Et_2O) to afford **3-(2'-*N*-methoxycarbonylmethylamino)ethyl-1,3-dimethyloxindole** (**23**) (174 mg, 32%), as a 1/1 mixture of two conformers (^{1}H NMR)[25] (colorless oil). IR (neat): υ = 1705 (br and s, NCO and COOMe). ^{1}H NMR: δ = 7.31-7.19 (m, 2H, ArH), 7.09 (t, *J* = 7.2 Hz, 1H, ArH), 6.85 (br d, *J* = 7.2 Hz, 1H, ArH, changes to d at 50 °C), 3.58/3.55 (s/s, 3H, OCH_3, collapse to s at 50 °C), 3.21 (s, 3H, NCH_3), 3.18-2.78 (m, 2H, CH_2CH_2N, collapses to br s at 50 °C), 2.75/2.73 (s/s, 3H, NCH_3 collapse to s at 50 °C), 2.28-2.11 (m, 1H, CH_2CH_2N), 2.09-1.88 (m, 1H, CH_2CH_2N, collapses to br s at 50 °C), 1.37 (s, 3H, CCH_3). EI-MS: *m/z* (%) 276 (3.1) [M^+], 216 (4.7), 201 (7.6), 161 (100.0). HR-MS: $C_{15}H_{20}N_2O_3$: calcd 276.1473; found: 276.1487; and **3-(2'-*N*-methoxycarbonylmethylamino)phenyl-1,3-dimethyl-2-pyrrolidone** (**24**) (310 mg, 58%), as a 4.4/1 mixture of two conformers (^{1}H NMR, see ref.[25]), (colorless oil). IR: υ = 1700 (br and s, NCO and COOMe). ^{1}H NMR: δ = 7.51-7.47 (m, 1H, ArH), 7.43-7.26 (m, 2H, ArH), 7.07 (br s, 1H, ArH, changes to m at 50°C), 3.75/3.62 (br s/br s, 3H, OCH_3, collapse to br s at 50 °C), 3.50-3.23 (m, 2H, CH_2CH_2N), 3.21/3.06 (s/s, 3H, NCH_3), 2.95/2.93 (s/s, 3H, NCH_3), 2.80-1.85 (m, 2H, CH_2CH_2N, 1.60/1.58 (s/s, 3H, CCH_3). EI-MS: *m/z* (%) 276 (100.0) [M^+]. HR-MS: $C_{15}H_{20}N_2O_3$: calcd 276.1473; found: 276.1484.

1,3-Dimethyl-3-(2'-methylaminoethyl)oxindole (25). a) By hydrolysis of 24: To **24** (40 mg, 0.14 mmol) was added conc. HCl (2.5 mL) and the mixture heated under reflux for 15 h. The reaction mixture was cooled, diluted with water, washed with Et_2O, basified with $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. Recrystallization of the resulting residue from Et_2O/*n*-hexane furnished **25** (28.4 mg, 93%), as a white solid: mp 79-81 °C (lit.,[8b] mp 87 °C). IR (neat): υ = 3320 (br, NH), 1710 (s, C=O). ^1H NMR: δ = 7.29-7.25 (m, 1H, ArH), 7.19 (d, *J* = 7.5 Hz, 1H, ArH), 7.07 (t, *J* = 7.5 Hz, 1H, ArH), 6.85 (d, 1H, *J* = 7.5 Hz, ArH), 3.21 (s, 3H, NCH_3), 2.26 (s, 3H, NCH_3), 2.24-1.94 (m, 4H, CH_2CH_2), 1.37 (s, 3H, CCH_3). EI-MS: *m/z* (%) 218 (7.3) [M^+], 174 (6.4), 161 (27.5), 160 (30.3), 144 (11.9), 130 (17.4), 77 (19.3), 58 (100.0). HR-MS: $C_{13}H_{18}N_2O$: calcd 218.1419; found: 218.1449. **b) By hydrolysis of 23:** The hydrolysis of **23** (174.5 mg, 0.63 mmol) with conc. HCl (10 mL), carried out as above, furnished **25** (131 mg, 95%), which was identical with a sample prepared by method **a)**.

(±)-Desoxyeseroline [(±)-3]: To an ice-cooled solution of **25** (474 mg, 2.17 mmol) in anhydrous THF (10 mL), stirred under N_2 atmosphere, was added $LiAlH_4$ (161 mg, 4.24 mmol) and the suspension stirred at rt overnight. The mixture was then cooled in an ice bath and 5 N aqueous NaOH (5 mL) was slowly added. The resulting mixture was heated under reflux for 1 h and then extracted with boiling AcOEt. The combined organic layers were extracted with 10% aqueous HCl and the combined aqueous layers neutralized with 5 N aqueous NaOH. This mixture was extracted with $CHCl_3$ and the combined organic layers washed with water and dried. After removal of the solvent at reduced pressure, the residue was purified by column chromatography (Et_2O) to yield **(±)-3** (302.5 mg, 69%), as a yellowish oil. IR (neat): υ = 1605, 1495, 1450, 1345, 1300, 1255, 1120, 1035, 1020, 955, 735. ^1H NMR:[26] δ = 7.08 (dt, *J* = 1.1, 7.5 Hz, 1H, ArH), 7.00 (dd, *J* = 1.1, 7.5 Hz, 1H, ArH), 6.68 (dt, *J* = 1.1, 7.5 Hz, 1H, ArH), 6.42 (d, *J* = 7.5 Hz, 1H, ArH), 4.12 (s, 1H, NCHN), 2.95 (s, 3H, NCH_3), 2.77-2.59 (m, 2H, CH_2CH_2N), 2.55 (s, 3H, NCH_3), 1.99-1.95 (m, 2H, CH_2CH_2N), 1.44 (s, 3H, CCH_3). ^{13}C NMR: δ = 151.9, 136.6, 127.7, 122.2, 117.5, 106.6, 97.5 (C^{8a}), 53.2 (C^2), 52.7 (C^{3a}), 40.8 (C^3), 38.4 (C^8H_3), 36.5 (C^1H_3), 27.3 ($C^{3a}H_3$). EI-MS: 202 (100.0) [M^+]. HR-MS: $C_{13}H_{18}N_2$: calcd 202.1469; found: 202.1476. The picrate of **(±)-3**, obtained as yellow crystals, after recrystallization from EtOH, had: mp 182.5-184 °C (lit.,[8b] mp 179-180 °C). IR: υ = 1635, 1615, 1565 (s, NO_2), 1490, 1430, 1360, 1320 (s, NO_2), 1275, 1165, 1075, 1005, 910, 785, 740. ^1H NMR: δ = 11.30 (br s, 1H, NH), 8.93 (s, 2H, ArH), 7.24 (t, *J* = 7.2 Hz, 1H, ArH), 7.11 (d, *J* = 7.2 Hz, 1H, ArH), 6.92 (t, *J* = 7.2 Hz, 1H, ArH), 6.66 (d, *J* = 7.2 Hz, 1H, ArH), 5.16 (d, *J* = 3.0 Hz, 1H, NCHN), 3.71-3.65 (m, 1H, CH_2CH_2N), 3.19 (s, 3H, NCH_3), 2.83 (d, *J* = 4.5 Hz, 3H, NCH_3), 2.71-2.61 (m, 1H, CH_2CH_2N), 2.57-2.47 (m, 1H, CH_2CH_2N), 2.35-2.30 (m, 1H, CH_2CH_2N), 1.55 (s, 3H, CCH_3).

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