

The Remarkable Effect of the 7-Substituent in the Diastereoselective Oxidative Rearrangement of Indoles: Asymmetric Synthesis of 3,3-Disubstituted Oxindoles

Mathilde Lachia, Cyril Poriel, Alexandra M. Z. Slawin and Christopher J. Moody

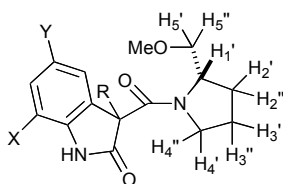
ELECTRONIC SUPPLEMENTARY INFORMATION

EXPERIMENTAL PROCEDURES AND X-RAY CRYSTAL STRUCTURES

General procedure for the chlorination and rearrangement

To a solution of the starting indole **7** (0.15 mmol) in dichloromethane (5 mL), protected from the light, was added *tert*-butyl hypochlorite (53 μ L, 0.45 mmol) in dichloromethane (1 mL). After 1 h, a further quantity of *tert*-butyl hypochlorite (30 μ L) in dichloromethane (1 mL) was added and the solution was stirred for 1 h. The solvents were removed under vacuum. The residue was taken up with dichloromethane (3 mL) and anhydrous ethanol (1.5 mL). Then, 500 μ L of a solution of acetyl chloride (500 μ L) and ethanol (9.5 mL) were added. The solution was stirred, protected from the light, overnight under N₂. The solvents were then removed and the residue was purified by flash chromatography over silica gel eluting with dichloromethane and ethyl acetate (7 : 3) to give the oxindole **8**.

In assigning HNMR spectra of oxindoles, the following numbering system is used. The use of H₅ cis/trans refers to the relative positions of the diastereotopic CH₂ protons with respect to H₁'.



(*R,S*)-2-Oxo-3-phenyl-1,3-dihydroindole-3-carboxylic acid (*S*)-2-methoxymethylpyrrolidinyl amide 8a

According to the general procedure, the title compound was obtained from the indole **7a** as a bright colourless solid (82%) as a mixture of diastereoisomers in a 1.3 : 1 ratio, mp 82 – 86 °C (light petroleum); (Found: M^+ , 350.1620. $C_{21}H_{22}N_2O_3$ requires 350.1630); ν_{\max} (KBr)/ cm^{-1} 3432 (NH), 3245, 2927, 1724 (C=O), 1617 (C=O), 1472, 1401, 1319, 1237, 1197, 1112; ν_H (300 MHz; $CDCl_3$) 8.91/8.90 (1 H, s, NH \square 2), 7.32-7.22 (7 H, m, ArH), 7.12-7.05 (1 H, d, J 7.5, ArH), 6.92-6.88 (1 H, m, ArH), 4.32 (1 H, m, H_1' \square 2), 3.61/3.59 (1 H, dd, J 9.4, 3.0, H_5'' *cis* \square 2), 3.47/3.41 (1 H, dd, J 9.4, 7.0, H_5' *trans* \square 2), 3.34/3.30 (3 H, s, OMe \square 2), 3.27-3.24 (0.5 H, m, H_{4a}''), 3.22-3.17 (0.5 H, m, H_{4b}''), 3.06-2.98 (0.5 H, m, H_{4b}'), 2.88-2.80 (0.5 H, m, H_{4a}'), 1.96-1.57 (4 H, m, $H_3'+H_3''$, $H_2'+H_2''$ \square 2); ν_C (75 MHz; $CDCl_3$) 176.1 (C), 166.6/165.5 (C), 141.2/140.8 (C), 137.5/137.0 (C), 129.2/129.1 (CH), 128.9/128.8 (CH), 128.6/128.4 (CH), 127.9/127.6 (CH), 127.8/127.7 (CH), 125.7/125.6 (CH), 122.9/122.8 (CH), 110.6/110.4 (C), 72/71.7 (CH_2), 66.5/66.3 (C), 59/58.9 (Me), 58.3 (CH), 47.5/47.3 (CH_2), 26.8/26.7 (CH_2), 24.7/24.6 (CH_2); m/z (FI) 351 (MH^+ , 21%), 350 (M^+ , 100), 280 (12), 127 (6).

(*S*)-7-Bromo-2-oxo-3-phenyl-1,3-dihydroindole-3-carboxylic acid (*S*)-2-methoxymethylpyrrolidinyl amide 8b

According to the general procedure, the title compound was obtained as a colourless solid (90%) from the indole **7b**. The title compound was obtained as a mixture of diastereoisomers (8 : 1). The major diastereoisomer was separated by crystallization from light petroleum and chloroform (9 : 1); mp 177 – 178 °C (from chloroform/light petroleum); $[\alpha]_D^{23}$ -75 (c 1.0, $CHCl_3$); (Found: MH^+ , 429.0790. $C_{21}H_{21}^{79}BrN_2O_3 + H$ requires 429.0814); ν_{\max} ($CHCl_3$)/ cm^{-1}

3422 (NH), 2982, 2931, 2881, 1731 (C=O), 1640 (C=O), 1454, 1398, 1308, 1137, 1112, 1068; δ_{H} (270 MHz; CDCl₃) 7.64 (1 H, s, NH), 7.42 (1 H, dd, *J* 8.2, 1.0, ArH), 7.36-7.30 (5 H, m, ArH), 7.21 (1 H, d, *J* 7.6, ArH), 7.00 (1 H, dd, *J* 8.0, 7.7, ArH), 4.32 (1 H, m, H₁'), 3.57 (1 H, dd, *J* 9.4, 3.2, H₅' *cis*), 3.42 (1 H, dd, *J* 9.4, 6.9, H₅' *trans*), 3.32 (3 H, s, OMe), 3.20-3.02 (2 H, m, H₄' , H₄''), 1.92-1.58 (4 H, m, H₂''+H₂' , H₃''+H₃''); δ_{C} (100 MHz; CDCl₃) 174.1 (C), 165.6 (C), 139.8 (C), 136.7 (C), 131.6 (CH), 130.7 (C), 128.9 (CH), 128.1 (CH), 127.3 (CH), 125.1 (CH), 124.1 (CH), 103.9 (C), 71.7 (CH₂), 67.9 (C), 58.9 (Me), 58.6 (CH), 47.9 (CH₂), 26.8 (CH₂), 24.7 (CH₂); *m/z* (ES) 453/451 (MNa⁺, 58/60%), 431/429 (MH⁺, 100/98%).

(S)-7-Bromo-3-(4-chlorophenyl)-2-oxo-1,3-dihydroindole-3-carboxylic acid (S)-2-methoxymethylpyrrolidinyl amide 8c

According to the general procedure, the *title compound* was obtained from the indole **7c** as a bright colourless solid (82%) as a mixture of diastereoisomers in a 9.5 : 1 ratio. The major isomer **8c** is separated from the mixture by crystallization in CDCl₃/hexanes, mp 92 – 96 °C (CDCl₃/hexanes); (Found: C, 54.1; H, 4.4; N, 5.6. C₂₁H₂₀BrClN₂O₃ requires C, 54.4; H, 4.35; N, 6.0%); (Found: MH⁺, 463.0406. C₂₁H₂₀⁷⁹Br³⁵ClN₂O₃ + H requires 463.0424); $[\alpha]_{\text{D}}^{27}$ -65 (*c* 0.15, CH₂Cl₂); ν_{max} (KBr)/cm⁻¹ 3431 (NH), 3217, 2926, 1731 (C=O), 1637 (C=O), 1618, 1491, 1473, 1450, 1400, 1311, 1240, 1162, 1185, 1125, 1094, 1015, 822, 770, 747; δ_{H} (300 MHz; CDCl₃) 7.87 (1 H, s, NH), 7.41 (1 H, d, *J* 8.1, ArH), 7.29-7.15 (5 H, m, ArH), 6.99 (1 H, dd, *J* 8.1, 7.7, ArH), 4.28 (1 H, m, H₁'), 3.47 (1 H, dd, *J* 9.4, 3, H₅' *cis*), 3.41 (1 H, dd, *J* 9.4, 6.9, H₅' *trans*), 3.26 (3 H, s, OMe), 3.26-3.13 (1 H, m, H₄''), 2.91-2.84 (1 H, m, H₄'), 1.91-1.61 (4 H, m, H₃''+H₃'', H₂''+H₂''); δ_{C} (75 MHz; CDCl₃) 162.7 (C), 134.3 (C), 133.1 (C), 132.5 (C), 130.5 (CH), 129.1 (CH), 129 (C), 127.3 (C), 126.5 (CH), 121.8 (CH), 119.3

(CH), 117.8 (C), 105.1 (C-Br), 72.4 (CH₂), 59 (Me), 56.6 (CH), 49.1 (CH₂), 27.2 (CH₂), 25 (CH₂); *m/z* (CI) 465/463 (MH⁺, 41/22%), 142 (100).

(*R,S*)-5-Bromo-2-oxo-3-phenyl-1,3-dihydroindole-3-carboxylic acid (*S*)-2-methoxymethylpyrrolidinyl amide 8d

According to the general procedure, the title compound was obtained as a colourless solid (93%) starting from the indole **7d**. The title compound was obtained as a 1.4 : 1 mixture of diastereoisomers, mp 95 – 100 °C (from light petroleum); (Found: C, 59.0; H, 5.0; N, 6.3. C₂₁H₂₁BrN₂O₃ requires C, 58.8; H, 4.9; N, 6.5%); (Found: MH⁺, 429.0796. C₂₁H₂₁⁷⁹BrN₂O₃ + H requires 429.0814); ν_{\max} (CHCl₃)/cm⁻¹ 3430 (NH), 1730 (C=O), 1632 (C=O), 1117; ν_{H} (400 MHz; CDCl₃) 8.37 (0.6 H, s, NH), 8.35 (0.4 H, s, NH), 7.40-7.29 (7 H, m, ArH), 6.77 (1 H, dd, *J* 10.6, 8.6, ArH), 4.33 (1 H, m, H₁'), 3.58-3.40 (2 H, m, H₅' + H₅''), 3.38 (1.73 H, s, OMe), 3.33 (1.27 H, s, OMe), 3.18-2.86 (2 H, m, H₄' + H₄''), 1.92-1.60 (4 H, m, H₂' + H₂'', H₃' + H₃''); ν_{C} (100 MHz; CDCl₃) 175.2 (C), 165.8 (C), 165.7 (C), 139.7 (C), 139.4 (C), 137.2 (C), 136.6 (C), 132.1 (C), 131.9 (CH), 131.7 (CH), 131.4 (C), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.4 (CH), 127.2 (CH), 126.6 (CH), 115.5 (C), 115.4 (C), 111.7 (CH), 111.6 (CH), 72.1 (C), 71.8 (C), 66.9 (CH₂), 66.7 (CH₂), 59.04 (CH), 59.01 (CH), 58.6 (Me), 58.5 (Me), 48.2 (CH₂), 48.0 (CH₂), 26.9 (CH₂), 26.8 (CH₂), 24.9 (CH₂), 24.8 (CH₂) ; *m/z* (ES) 431/429 (M⁺, 58/61%).

(*R,S*)-5-Bromo-3-(4-chlorophenyl)-2-oxo-1,3-dihydroindole-3-carboxylic acid (*S*)-2-methoxymethylpyrrolidinyl amide 8e

According to the general procedure, the title compound was obtained as a colourless solid (90%) starting from the indole **7e**. The title compound was obtained as a mixture of diastereoisomers (1.5 : 1), mp 95 – 97 °C (from chloroform/light petroleum); (Found: C, 54.7;

H, 4.4; N, 5.7. $C_{21}H_{20}BrClN_2O_3$ requires C, 54.4; H, 4.35; N, 6.0%); (Found: MH^+ , 463.0393. $C_{21}H_{20}^{79}Br^{35}ClN_2O_3 + H$ requires 463.0424); ν_{max} ($CHCl_3$)/ cm^{-1} 3430 (NH), 1733 (C=O), 1635 (C=O), 1395, 1095; ν_H (400 MHz; $CDCl_3$) 8.75 (0.60 H, s, NH), 8.74 (0.40 H, s, NH), 7.44-7.36 (2 H, m, ArH), 7.33-7.30 (2 H, m, ArH), 7.26-7.23 (2 H, m, ArH), 6.81 (0.60 H, d, J 8.3, ArH), 6.77 (0.40 H, d, J 8.3, ArH), 4.31 (1 H, m, H_1'), 3.56-3.47 (2 H, m, $H_5'+H_5''$), 3.36 (1.20 H, s, OMe), 3.32 (1.80 H, s, OMe), 3.28-3.18 (1H, m, H_4'), 3.00-2.94 (0.40 H, m, $H_4''b$), 2.88-2.82 (0.60 H, m, $H_4''a$), 1.92-1.60 (4 H, m, $H_2'+H_2''$, $H_3'+H_3''$); ν_C (100 MHz; $CDCl_3$) 175.1 (C), 175.0 (C), 165.5 (C), 165.4 (C), 140.1 (C), 139.7 (C), 135.6 (C), 134.9 (C), 134.3 (C), 134.1 (C), 132.3 (CH), 132.0 (CH), 131.1 (C), 130.4 (C), 129.2 (CH), 129.0 (CH), 128.86 (CH), 128.81 (CH), 128.75 (CH), 115.6 (C), 115.5 (C), 112.0 (CH), 111.9 (CH), 71.99 (CH₂), 71.73 (CH₂), 66.07 (C), 65.91 (C), 59.06 (CH), 59.01 (CH), 58.69 (Me), 58.60 (Me), 47.8 (CH₂), 47.6 (CH₂), 26.8 (CH₂), 24.87 (CH₂), 24.80 (CH₂); m/z (ES) 465/463 (MH^+ , 58/46 %).

(S)-7-Chloro-2-oxo-3-phenyl-1,3-dihydroindole-3-carboxylic acid (S)-2-methoxymethylpyrrolidinyl amide 8f

According to the general procedure, the title compound was obtained as a colourless solid (91%) starting from the indole **7f**. The compound was obtained as a mixture of diastereoisomers (6 : 1). The major diastereoisomer was separated by crystallization from $CDCl_3$ /hexane; mp 174 – 175 °C (from $CDCl_3$ /hexane); $[\alpha]_D^{21}$ -60.7 (c 1.1, $CHCl_3$); (Found: MH^+ , 385.1317. $C_{21}H_{21}^{35}ClN_2O_3 + H$ requires 385.1319); ν_{max} ($CHCl_3$)/ cm^{-1} 3425 (NH), 3197, 2938, 1731 (C=O), 1632 (C=O), 1457, 1393, 1305, 1133, 907; ν_H (400 MHz; $CDCl_3$) 8.12 (1 H, s, NH), 7.39-7.29 (5 H, ArH), 7.27 (1 H, dd, J 8.2, 1.0, ArH), 7.19 (1 H, d, J 7.4, ArH), 7.05 (1 H, dd, J 8.2, 7.6, ArH), 4.34 (1 H, m, H_1'), 3.58 (1 H, dd, J 9.2, 3.2, H_5' *cis*), 3.43 (1 H, dd, J 9.2, 6.8, H_5'' *trans*), 3.32 (3 H, s, OMe), 3.19 (1 H, dt, J 10.6, 6.7, H_4'), 3.09

(1 H, dt, J 10.6, 6.6, H_4''), 1.91-1.85 (2 H, m, H_2+H_2'), 1.82-1.55 (2 H, m, $H_3'+H_3''$); δ_C (100 MHz; $CDCl_3$) 174.7 (C), 165.6 (C), 138.4 (C), 136.9 (C), 131.0 (C), 128.99 (CH), 128.94 (CH), 128.2 (CH), 127.5 (CH), 124.7 (CH), 123.9 (CH), 115.4 (C), 71.8(CH₂), 67.7 (C), 59.1 (CH), 56.7 (Me), 48.0 (CH₂), 26.9 (CH₂), 24.8 (CH₂); m/z (ES⁺) 387/385 (MH⁺, 22/100).

(S)-7-Fluoro-2-oxo-3-phenyl-1,3-dihydroindole-3-carboxylic acid (S)-2-methoxymethylpyrrolidinyl amide 8g

According to the general procedure, the title compound was obtained as a colourless solid (95%) starting from the indole **7g**. The title compound was obtained as a 2 : 1 mixture of diastereoisomers. The major diastereoisomer was separated by crystallization from $CDCl_3$ /hexane; mp 195 – 196 °C (from $CDCl_3$ /hexane); $[\alpha]_D^{23}$ 15 (c 0.3, $CHCl_3$); (Found: MH⁺, 369.1607. $C_{21}H_{21}FN_2O_3 + H$ requires 369.1614); δ_{max} ($CHCl_3$)/ cm^{-1} 3431 (NH), 2927, 1736 (C=O), 1643 (C=O), 1491, 1467, 1384, 1305, 1112; δ_H (400 MHz; $CDCl_3$) 7.44 (1 H, s, NH), 7.37-7.31 (5 H, m, ArH), 7.09-7.06 (3 H, m, ArH), 4.34 (1 H, m, H_1'), 3.58 (1 H, dd, J 9.2, 3.2, H_5' *cis*), 3.43 (1 H, dd, J 9.2, 6.8, H_5'' *trans*), 3.32 (3 H, s, OMe), 3.21 (1 H, dt, J 10.7, 6.7, H_4'), 3.02 (1 H, dt, J 10.7, 6.7, H_4''), 1.91-1.87 (2 H, m, $H_2 H_2'$), 1.82-1.55 (2 H, m, $H_3'+H_3''$); δ_C (100 MHz; $CDCl_3$) 174.6 (C), 165.7 (C), 147.0 (C, d, J 243), 136.7 (C), 131.9 (C), 128.7 (CH), 128.1 (C), 128.0 (CH), 127.5 (CH), 123.4 (CH, d, J 6), 121.8 (CH, d, J 3), 115.9 (CH, d, J 17), 71.7 (CH₂), 66.7 (C, d, J 2), 58.9 (CH), 58.4 (Me), 47.8 (CH₂), 26.8 (CH₂), 24.7 (CH₂); m/z (ES) 369/370(M⁺, 23/100%), 142 (9%).

(S)-2-Oxo-3,7-diphenyl-1,3-dihydroindole-3-carboxylic acid (S)-2-methoxymethylpyrrolidinyl amide 8h

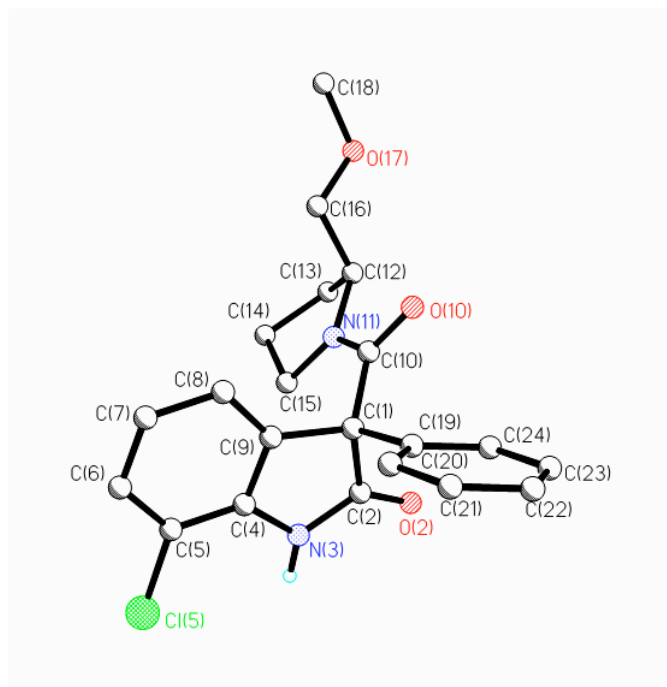
According to the general procedure, the title compound was obtained as a colourless solid (22 mg, 75%) starting from the indole **7h**. The title compound was obtained as a mixture of

diastereoisomers (11 : 1). The major diastereoisomer was separated by crystallization in hexane/ethyl acetate (9 : 1); mp 164 – 165 °C (from ethyl acetate/light petroleum); $[\alpha]_D^{23}$ -7 (c 0.3, CHCl₃); (Found: MH⁺, 427.2010. C₂₇H₂₆N₂O₃ + H requires 427.2022); ν_{\max} (CHCl₃)/cm⁻¹ 3427 (NH), 2929, 1727 (C=O), 1631 (C=O), 1458, 1392, 1302, 1095, 908; δ_{H} (400 MHz; CDCl₃) 7.66 (1 H, s, NH), 7.50-7.27 (12 H, m, ArH), 7.19 (1 H, t, *J* 7.6, ArH), 4.36 (1 H, m, H₁'), 3.59 (1 H, dd, *J* 9.2, 2.8, H₅' *cis*), 3.43 (1 H, dd, *J* 9.2, 6.8, H₅'' *trans*), 3.32 (3 H, s, OMe), 3.25-3.19 (1 H, m, H₄'), 3.05-3.00 (1 H, m, H₄''), 1.89-1.21 (4 H, m, H₂''+H₂' , H₃' +H₃''); δ_{C} (100 MHz; CDCl₃) 175.5 (C), 166.2 (C), 137.9 (C), 137.3 (C), 137.2 (C), 129.7 (C), 129.31 (CH), 129.28 (CH), 128.7 (CH), 128.0 (2 \square CH), 127.9 (CH), 127.6 (CH), 125.2 (CH), 124.5 (C), 123.3 (CH), 71.7 (CH₂), 66.7 (C), 58.9 (CH), 58.4 (Me), 47.7 (CH₂), 26.8 (CH₂), 24.7 (CH₂); *m/z* (ES) 449 (MNa⁺, 34%), 427 (MH⁺, 100%), 263 (6%).

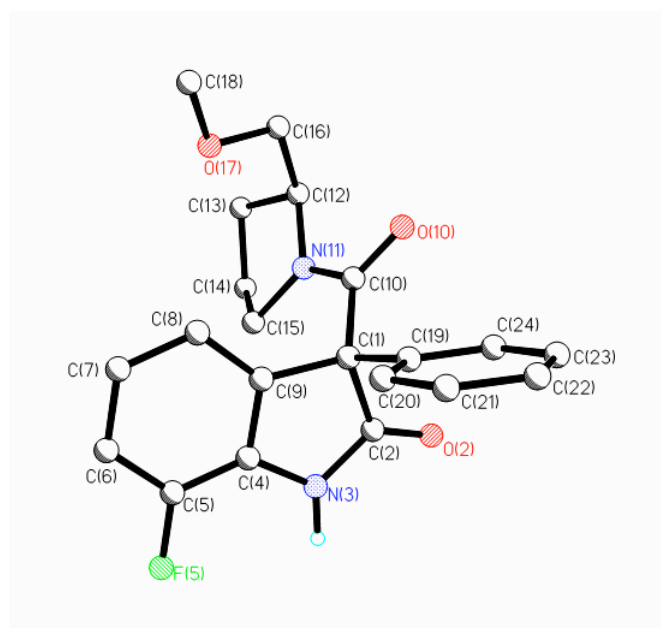
(S)-7-Bromo-3-methyl-2-oxo-1,3-dihydroindole-3-carboxylic acid (S)-2-methoxymethylpyrrolidinyl amide 8i

According to the general procedure, the title compound was obtained as a colourless solid (90%) starting from the indole **7i**. The title compound was obtained as a mixture of diastereoisomers (4 : 1). The major diastereoisomer was separated by crystallization from light petroleum and chloroform (9 : 1); mp 191 – 192 °C (from chloroform/light petroleum); $[\alpha]_D^{23}$ 117 (c 1.0, CHCl₃); (Found: MH⁺, 367.0633. C₁₆H₁₉⁷⁹BrN₂O₃ + H requires 367.0657); ν_{\max} (CHCl₃)/cm⁻¹ 3422 (NH), 2982, 2931, 2881, 1731 (C=O), 1640 (C=O), 1454, 1398, 1308, 1137, 1112, 1068; δ_{H} (270 MHz; CDCl₃) 8.04 (1 H, s, NH), 7.38 (1 H, dd, *J* 1.1, 9.2, ArH), 7.06 (1 H, d, *J* 7.3, ArH), 6.94 (1 H, t, *J* 7.3, ArH), 4.33-4.28 (1 H, m, H₁'), 3.50 (1 H, dd, *J* 9.3, 3.2, H₅' *cis*), 3.36-3.32 (4 H, m, *J* 9.2, 6.8, H₅'' *trans*, OMe), 3.29 (1 H, m, H₄'), 2.49 (1 H, m, H₄''), 1.89-1.73 (4 H, m, H₂''+H₂' , H₃' +H₃''), 1.67 (3 H, s, Me); δ_{C} (75 MHz; CDCl₃) 176.5 (C), 165.6 (C), 139.5 (C), 132.6 (C), 131.3 (CH), 124.6 (CH), 121.9 (CH),

102.8 (C), 71.6 (CH₂), 58.9 (Me), 58.2 (CH), 57.7 (C), 44.8 (CH₂), 26.7 (CH₂), 24.3 (Me);
m/z (ES+) 391/389 (MNa⁺, 66/66%), 369/367 (MH⁺, 98/100%), 263 (6%).



X-ray crystal structure of oxindole **8f**.



X-ray crystal structure of oxindole **8g**.

Crystal data

Full hemisphere of data collected, corrected for Lorentz and polarization and for absorption using multiple equivalent reflections. Refinements on F^2 using SHELXTL.

Compound 8f Rigaku MM007 high brilliance generator, confocal optics, Saturn 70 detector, colourless prism 0.08 x 0.08 x 0.08 mm, $C_{21}H_{21}Cl_1N_2O_3$, $M_r = 384.85$, orthorhombic, space group $P2(1)2(1)2(1)$, $a = 8.9714(7)$, $b = 14.1418(11)$, $c = 15.1487(12)$ Å, $V = 1921.9(3)$ Å³, $Z = 4$, $2\theta_{max} 50.7^\circ$, $MoK\alpha = 0.71073$ Å, $T = 93(2)$ K, $\rho_{calcd} = 1.330$ gcm⁻³, $\mu = 0.223$ mm⁻¹ (max, min transmission 1.00, 0.9016), 13683 reflections collected, 3381 unique [$R_{(int)} = 0.0198$], $R_1 = 0.0221$, $wR2 = 0.0554$ for 3349 observed reflections [$I > 2\sigma(I)$], max and min residual electron density 0.163, -0.159 e Å⁻³. Flack parameter -0.04(4).

Compound 8g Rigaku MM007 high brilliance generator, confocal optics, Mercury detector, colourless prism 0.05 x 0.05 x 0.05 mm, $C_{21}H_{21}F_1N_2O_3$, $M_r = 368.40$, orthorhombic, space group $P2(1)2(1)2(1)$, $a = 9.797(2)$, $b = 12.303(2)$, $c = 14.883(3)$ Å, $V = 1793.9(6)$ Å³, $Z = 4$, $2\theta_{max} 50.7^\circ$, $MoK\alpha = 0.71073$ Å, $T = 93(2)$ K, $\rho_{calcd} = 1.364$ gcm⁻³, $\mu = 0.099$ mm⁻¹ (max, min transmission 1.00, 0.8034), 11683 reflections collected, 3208 unique [$R_{(int)} = 0.0399$], $R_1 = 0.0369$, $wR2 = 0.0812$ for 2956 observed reflections [$I > 2\sigma(I)$], max and min residual electron density 0.143, -0.196 e Å⁻³. Flack parameter 0.3(8).

CCDC-609781-609784 contain the supplementary crystallographic data for this paper.

These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html

(or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge,
CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).CCDC.