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 µL, 0.45 mmol) in dichloromethane (1 mL). After 1 h, a further quantity of tert-butyl hypochlorite (30 µL) 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 µL of a solution of acetyl chloride (500 µL) 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$_2$O$_3$ requires 350.1630); $\bar{\nu}$$_{max}$ (KBr)/cm$^{-1}$ 3432 (NH), 3245, 2927, 1724 (C=O), 1617 (C=O), 1472, 1401, 1319, 1237, 1197, 1112; $\delta$ (300 MHz; CDCl$_3$) 8.91/8.90 (1 H, s, NH), 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$_1$'), 3.61/3.59 (1 H, dd, J 9.4, 3.0, H$_5$' cis $\gamma$ 2), 3.47/3.41 (1 H, dd, J 9.4, 7.0, H$_5$' trans $\gamma$ 2), 3.34/3.30 (3 H, s, OMe $\gamma$ 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$_2$' $\gamma$ 2); $\delta$ (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 (Fl) 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); $\bar{\nu}$$_{max}$ (CHCl$_3$)/cm$^{-1}$ 75 (c 1.0, CHCl$_3$); (Found: MH$^+$, 429.0790. C$_{21}$H$_{21}$BrN$_2$O$_3$ + H requires 429.0814); $\bar{\nu}$$_{max}$ (CHCl$_3$)/cm$^{-1}$...
(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. C₂₁H₂₀BrClN₂O₃ + H requires 463.0424); [α]D²⁷ -65 (c 0.15, CH₂Cl₂); \( n_{\text{max}} \) (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; [α]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, H₂’), 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, H₂’+H₃’+H₂’+H₂’); [α]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
(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. C_{21}H_{21}BrN_{2}O_{3} requires C, 58.8; H, 4.9; N, 6.5%); (Found: MH^+, 429.0796. C_{21}H_{21}^{79}BrN_{2}O_{3} + H requires 429.0814); \[^{1}H\]_{max} (CHCl\textsubscript{3})/cm\textsuperscript{-1} 3430 (NH), 1730 (C=O), 1632 (C=O), 1117; \[^{1}J\] (400 MHz; CDCl\textsubscript{3}) 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, H\textsubscript{1}'), 3.58-3.40 (2 H, m, H\textsubscript{5}'+H\textsubscript{5}''), 3.38 (1.73 H, s, OMe), 3.33 (1.27 H, s, OMe), 3.18-2.86 (2 H, m, H\textsubscript{4}'+H\textsubscript{4}''), 1.92-1.60 (4 H, m, H\textsubscript{2}'+H\textsubscript{2}'', H\textsubscript{3}'+H\textsubscript{3}''); \[^{13}C\] (100 MHz; CDCl\textsubscript{3}) 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 (CH\textsubscript{2}), 66.7 (CH\textsubscript{2}), 59.04 (CH), 59.01 (CH), 58.6 (Me), 58.5 (Me), 48.2 (CH\textsubscript{2}), 48.0 (CH\textsubscript{2}), 26.9 (CH\textsubscript{2}), 26.8 (CH\textsubscript{2}), 24.9 (CH\textsubscript{2}), 24.8 (CH\textsubscript{2}) ; 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;
(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 CDCl₃/hexane; mp 174 – 175 °C (from CDCl₃/hexane); $\delta$D²¹ -60.7 (c 1.1, CHCl₃); (Found: MH⁺, 385.1317. C$_{21}$H$_{21}$ClN$_{2}$O$_{3}$ + H requires 385.1319); $\sqrt{\text{max}}$ (CHCl₃)/cm⁻¹ 3425 (NH), 3197, 2938, 1731 (C=O), 1632 (C=O), 1457, 1393, 1305, 1133, 907; $\delta$I (400 MHz; CDCl₃) 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
(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 CDCl₃/hexane; mp 195 – 196 °C (from CDCl₃/hexane); [α]D²³ 15 (c 0.3, CHCl₃); (Found: MH⁺, 369.1607. C₂₁H₂₁FN₂O₃ + H requires 369.1614); \( \nu \)max (CHCl₃)/cm⁻¹ 3431 (NH), 2927, 1736 (C=O), 1491, 1467, 1384, 1305, 1112; \( \delta \)H (400 MHz; CDCl₃) 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, H₁’’), 3.58 (1 H, dd, J 9.2, 6.7, H₅’’ cis), 3.43 (1 H, dd, J 9.2, 6.8, H₅’’ trans), 3.32 (3 H, s, OMe), 3.21 (1 H, dt, J 10.7, 6.7, H₄’’), 3.02 (1 H, dt, J 10.7, 6.7, H₄’’), 1.91-1.87 (2 H, m, H₂, H₂’’), 1.82-1.55 (2 H, m, H₃’+H₃’’); \( \delta \)C (100 MHz; CDCl₃) 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); [$$\rho$$]$$^\text{23}_{D}$$ -7 (c 0.3, CHCl$_3$); (Found: MH$^+$, 427.2010. C$_{27}$H$_{26}$N$_2$O$_3$ + H requires 427.2022); $\max$ (CHCl$_3$)/cm$^{-1}$ 3427 (NH), 2929, 1727 (C=O), 1631 (C=O), 1458, 1392, 1302, 1095, 908; $\delta$ (400 MHz; CDCl$_3$) 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, H$_1'$), 3.59 (1 H, dd, $J$ 9.2, 2.8, H$_5'$ cis), 3.43 (1 H, dd, $J$ 9.2, 6.8, H$_5'$ trans), 3.32 (3 H, s, OMe), 3.25-3.19 (1 H, m, H$_4'$), 3.05.3.00 (1 H, m, H$_4''$), 1.89-1.21 (4 H, m, H$_2''$+H$_2'$, H$_3'$+H$_3'''$); $\delta$ (100 MHz; CDCl$_3$) 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 $\mu$CH), 127.9 (CH), 127.6 (CH), 125.2 (CH), 124.5 (C), 123.3 (CH), 71.7 (CH$_2$), 66.7 (C), 58.9 (CH), 58.4 (Me), 47.7 (CH$_2$), 26.8 (CH$_2$), 24.7 (CH$_2$); $m/z$ (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); [$$\rho$$]$$^\text{23}_{D}$$ 117 (c 1.0, CHCl$_3$); (Found: MH$^+$, 367.0633. C$_{16}$H$_{19}$BrN$_2$O$_3$ + H requires 367.0657); $\max$ (CHCl$_3$)/cm$^{-1}$ 3422 (NH), 2982, 2931, 2881, 1731 (C=O), 1640 (C=O), 1454, 1398, 1308, 1137, 1112, 1068; $\delta$ (270 MHz; CDCl$_3$) 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, H$_1'$), 3.50 (1 H, dd, $J$ 9.3, 3.2, H$_5'$ cis), 3.36-3.32 (4 H, m, J 9.2, 6.8, H$_5''$ trans, OMe), 3.29 (1 H, m, H$_4'$), 2.49 (1 H, m, H$_4''$), 1.89-1.73 (4 H, m, H$_2''$+H$_2'$, H$_3'$+H$_3'''$), 1.67 (3 H, s, Me); $\delta$ (75 MHz; CDCl$_3$) 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$_1$N$_2$O$_3$, $M_r = 384.85$, orthorhombic, space group P2(1)2(1)2(1), $a = 8.9714(7)$, $b = 14.1418(11)$, $c = 15.1487(12)$ Å, $V = 1921.9(3)$ Å$^3$, $Z = 4$, $2\theta_{\text{max}} = 50.7^\circ$, MoK$_\alpha\lambda = 0.71073$ Å, $T = 93(2)$ K, $\rho_{\text{calcd}} = 1.330$ gcm$^{-3}$, $\mu = 0.223$ mm$^{-1}$ (max, min transmission 1.00, 0.9016), 13683 reflections collected, 3381 unique [$R_{\text{int}} = 0.0198$], $R_1 = 0.0221$, $wR_2 = 0.0554$ 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$_1$N$_2$O$_3$, $M_r = 368.40$, orthorhombic, space group P2(1)2(1)2(1), $a = 9.797(2)$, $b = 12.303(2)$, $c = 14.883(3)$ Å, $V = 1793.9(6)$ Å$^3$, $Z = 4$, $2\theta_{\text{max}} = 50.7^\circ$, MoK$_\alpha\lambda = 0.71073$ Å, $T = 93(2)$ K, $\rho_{\text{calcd}} = 1.364$ gcm$^{-3}$, $\mu = 0.099$ mm$^{-1}$ (max, min transmission 1.00, 0.8034), 11683 reflections collected, 3208 unique [$R_{\text{int}} = 0.0399$], $R_1 = 0.0369$, $wR_2 = 0.0812$ 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](http://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.