Asymmetric Kita spirolactonisation catalysed by *anti*-dimethanoanthracene-based iodoarenes

Stephen J. Murray and Hasim Ibrahim*

Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

hasim.ibrahim@ucd.ie

Supporting Information

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General remarks
NMR spectra were recorded on Varian Inova 300 MHz, Varian Inova 400 MHz and Varian 500 MHz FT spectrometers at 30 °C with CDCl₃, MeOD or DMSO-d₆ as the solvent. Chemical shifts are reported in ppm relative to the residual solvent signal. High resolution mass spectra were measured on a Waters/Micromass GCT and Waters 2996 Photodiode Array Detector instrument. Infrared spectra were recorded on a Varian 3100 FT-IR spectrometer at room temperature. Melting points were recorded in open capillaries on a digital Barnsted Electro Thermal 9300 melting point apparatus and are uncorrected.

Materials
All reagents were obtained from commercial suppliers and used without further purification. All dry solvents were obtained from a dry solvent purification system. Thin Layer Chromatography was performed on Merck Aluminium sheets (silica gel 60 F₂₅₄). Detection was carried out by UV and by colouration with ceric ammonium molybdate (CAM). Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh). 1-Naphthols 6a-c and 6e,¹ and aldehyde (+)-3² were synthesised according to literature procedures. Iodoarenes 5 were considered light sensitive and were shielded from light by covering with aluminium foil.
3-(4-Cyano-1-hydroxynaphthalen-2-yl)propanoic acid 6d

![Chemical structure of 3-(4-Cyano-1-hydroxynaphthalen-2-yl)propanoic acid 6d]

To a solution of 4-cyano-1-naphthol (5.08 g, 30 mmol) and triethylorthoacrylate (6.0 mL, 48 mmol) in toluene (100 mL) was added pivalic acid (1.53 g, 15 mmol). The mixture was left to reflux for 24 h. After cooling, the reaction mixture was poured into 1N NaOH (30 mL), extracted with Et$_2$O (2 x 30 mL) and washed with brine. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and removed in vacuo. The residue was used directly in the next step without further purification. To a solution of this residue (30 mmol) in Et$_2$O (80 mL) was added 2N HCl (40 mL) and the resulting red solution was left to stir for 12 h. The mixture was extracted with EtOAc (2 x 30 mL) and washed with brine. The combined organic layers were dried over anhydrous MgSO$_4$ and concentrated in vacuo. This material was then dissolved in THF (30 mL) and MeOH (30 mL). After the addition of 2N NaOH (40 mL) the mixture was vigorously stirred at room temperature for 12 h. The reaction mixture was poured into 1N HCl (100 mL), extracted with EtOAc (2 x 30 mL) and washed with brine. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The oily residue was purified by flash column chromatography (SiO$_2$; pentane/EtOAc/AcOH, 79.5:19.5:1) to yield the title compound as a white powder (4.41 g, 61% overall yield). Mp: 182-185 °C; IR (KBr, cm$^{-1}$): 3370 (s), 3208 (s), 2242 (m), 1692 (s), 1595 (w), 1378 (w), 1241 (m), 870 (m); $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 2.59 (t, $J$ = 7.5 Hz, 2 H, CH$_2$), 3.02 (t, $J$ = 7.5 Hz, 2 H, CH$_2$), 7.63 (t, $J$ = 7.5 Hz, 1 H, ArH), 7.71 (t, $J$ = 7.2 Hz, 1 H, ArH), 7.95 (s, 1 H, ArH), 7.98 (d, $J$ = 8.2 Hz, 1 H, ArH), 8.37 (d, $J$ = 8.2 Hz, 1 H, ArH), 10.51 (brs, 1 H, OH), 12.17 (brs, 1 H, OH); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 25.3, 34.1, 99.4, 118.8, 122.2, 123.4, 124.5, 125.1, 126.8, 128.8, 132.7, 136.7, 155.4, 174.4; HRMS (ESI): C$_{14}$H$_{12}$NO$_3$ [M + H]$^+$ calculated: 242.0817, found: 242.0815.
General procedure for the catalytic asymmetric spirolactonisation of 1-naphthols

\[
\text{Ar}^*\text{I} (10 \text{ mol}%) \quad \text{mCPBA (1.5 equiv)}
\]
\[
\text{solvent, } -20^\circ \text{C, 19 h}
\]

\[
\text{mCPBA (184 mg, 0.75 mmol, 70% purity) was added to a stirred solution of Ar}^*\text{I 5 (0.05 mmol) and the appropriate 1-naphthol 6 (0.50 mmol) in the appropriate solvent (4 mL) at } -20 \degree \text{C. The mixture was allowed to stir at this temperature for 19 h at which point sat. aq NaHCO}_3 (5 \text{ mL}) was added to quench the reaction. The aqueous layer was extracted with CH}_2\text{Cl}_2 (3 \times 5 \text{ mL}) and the combined organic layers were washed with brine (5 \text{ mL}), dried over MgSO}_4 and concentrated } \textit{in vacuo} \text{ to yield the crude product. This material was purified by flash column chromatography (SiO}_2; \text{pentane/EtOAc, } 100:0 \rightarrow 80:20) \text{ to give the pure spirolactone 7.}
\]

\((+)-1'H,3H\text{-spiro[furan-2,2'-naphthalene]-1',5(4H)-dione (+)-7a}\)

According to the GP using 1-naphthol 6a in CHCl\textsubscript{3} at 0 °C, the title compound was obtained as a white powder (38 mg, 36%). Enantiomeric excess was determined by chiral HPLC analysis (Chiralpack IB, \textit{n}-heptane/EtOH, 98:2, 1.0 mL/min, 254 nm); \(t_\text{r}= 23.1 \text{ min (major); } t_\text{r} = 24.8 \text{ (minor): 40\% ee; } [\alpha]_{D}^{20} = +36.7 \text{ (c = 0.5, CHCl}_3). \) All analytical data are consistent with those reported in the literature.\(^1\)

\((+)-(R)-4'\text{-Bromo-1'H,3H\text{-spiro[furan-2,2'-naphthalene]-1',5(4H)-dione (+)-(R)-7b}\)

According to the GP using 1-naphthol 6b in CHCl\textsubscript{3}/MeNO\textsubscript{2} (2:1) at -20 °C, the title compound was obtained as a white powder (92 mg, 63%). Enantiomeric excess was determined by chiral HPLC analysis (Chiralpack IB, \textit{n}-heptane/EtOH, 95:5, 1.0 mL/min, 254 nm); (\(R\))-enantiomer, \(t_\text{r} = 22.6 \text{ min (major); (S)-enantiomer, } t_\text{r} = 23.9 \text{ (minor): 67\% ee; } [\alpha]_{D}^{20} = +42.9 \text{ (c = 0.5, CHCl}_3). \) All analytical data are consistent with those reported in the literature.\(^1\)
(+)-4'-Chloro-1'H,3H-spiro(furan-2,2'-naphthalene)-1',5(4H)-dione (+)-7c

According to the GP using 1-naphthol 6c in CHCl₃ at −20 °C, the title compound was obtained as a white powder (70 mg, 57%). Enantiomeric excess was determined by chiral HPLC analysis (Chiralpack AS-H, n-heptane/EtOH, 85:15, 1.0 mL/min, 254 nm); tᵣ = 16.9 min (minor); tᵣ = 23.7 (major): 42% ee; [α]D²⁰ = +30.7 (c = 1.0, CHCl₃). All analytical data are consistent with those reported in the literature.¹

(+)-4'-Cyano-1'H,3H-spiro[furan-2,2'-naphthalene]-1',5(4H)-dione (+)-7d

According to the GP using 1-naphthol 6d in CHCl₃/TFE (2:1) at −20 °C, the title compound was obtained as a white powder (52 mg, 44%). Enantiomeric excess was determined by chiral HPLC analysis (Chiralpack AS-H, n-heptane/EtOH, 75:25, 1.0 mL/min, 254 nm); tᵣ = 19.1 min (minor); tᵣ = 29.1 (major): 48% ee; [α]D²⁰ = +33.6 (c = 0.5, CHCl₃); Mp: 157-158 °C; IR (KBr, cm⁻¹): 3241 (m), 2251 (s), 1710, 1675, 1642 (m), 1534 (s), 1297 (s), 834 (m); ¹H NMR (500 MHz, MeOD): δ 2.43−2.49 (m, 1 H, CH₂), 2.51−2.58 (m, 1 H, CH₂), 2.69−2.76 (m, 1 H, CH₂), 2.80−2.89 (m, 1 H, CH₂), 7.30 (s, 1 H, C=CH), 7.70 (t, J = 8.1 Hz, 1 H, ArH), 7.76 (d, J = 7.4 Hz, 1 H, ArH), 7.93 (t, J = 8.1 Hz, 1 H, ArH), 8.16 (d, J = 7.4 Hz, 1 H, ArH); ¹³C NMR (125 MHz, MeOD): δ 26.9, 31.6, 84.4, 114.9, 115.9, 127.4, 128.3, 129.3, 132.0, 133.0, 137.5, 146.3, 178.0, 195.5; HRMS (ESI): C₁₄H₉NO₃Na [M + Na]⁺ calculated: 262.0480, found: 262.0471.

(+)-4'-Phenyl-1'H,3H-spiro[furan-2,2'-naphthalene]-1',5(4H)-dione (+)-7e

According to the GP using 1-naphthol 6e in CHCl₃ at −20 °C, the title compound was obtained as a white powder (89 mg, 62%). Enantiomeric excess was determined by chiral HPLC analysis (Chiralpack IB, n-heptane/EtOH, 96:4, 1.0 mL/min, 254 nm); tᵣ = 23.8 min (minor); tᵣ = 28.3 (major): 57% ee; [α]D²⁰ = +48.6 (c = 1.0, CHCl₃). All analytical data are consistent with those reported in the literature.¹
(+)-(1S,4R,5R,8S)-9-Methyl-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene

(+)-4

In a 100 mL glass insert, (+)-3 (2.19 g, 9.20 mmol) was dissolved in EtOAc (40 mL) and 10% Pd/C (0.40 g) was added to the mixture. The insert was placed in a Parr reactor which was pressurised with 50 bar of H_2. After stirring the reaction mixture for 12 h at room temperature, the reactor was slowly vented and the insert was removed and the mixture was set to one side for 10 min while the evolution of dissolved H_2 occurred. This mixture was then directly applied to a pad of silica gel and was eluted with EtOAc. Removal of the solvent in vacuo yielded the product as a white solid (2.05 g, 99%). [α]_D^{25} = +60 (c = 1, CHCl_3); Mp: 188-191 °C; IR (KBr, cm⁻¹): 2961 (s), 2863 (w), 1618 (w), 1110 (m); ^1H NMR (400 MHz, CDCl_3): δ 1.09–1.11 (m, 4 H, CH₂), 1.44-1.46 (m, 2 H, CHCHHCH), 1.68–1.71 (m, 2 H, CHCHHCH), 1.84–1.86 (m, 4 H, CH₂), 2.28 (s, 3 H, CH₃), 3.28 (brs, 2 H, CH), 3.42 (brs, 2 H, CH), 6.82 (s, 1 H, ArH); ^13C NMR (100 MHz, CDCl_3): δ 14.9, 26.7, 27.4, 41.4, 44.3, 49.1, 110.9, 122.4, 143.7, 145.0; HRMS (EI): C_{17}H_{20}[M]^+ calculated: 224.1565, found: 224.1562.

(−)-(1S,4R,5R,8S)-9-Methyl-10-iodo-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene (−)-5a

Arene (+)-4 (211 mg, 0.94 mmol) was dissolved in EtOAc (15 mL). To this solution (diacetoxy)iodobenzene (443 mg, 1.37 mmol) and iodine (210 mg, 1.74 mmol) were added. The purple solution was then heated to 70 °C and left for 12 h until TLC analysis (SiO₂; pentane) showed the starting material had been consumed. Sat. aq Na₂S₂O₃ (10 mL) was then added and the mixture stirred until the purple colour faded. The organic layer was washed with H₂O (2 x 10 mL), dried over MgSO₄ and concentrated in vacuo to yield the product as a white powder (231 mg, 70%). [α]_D^{25} = −66.5 (c = 1, CHCl_3); Mp: 125-127 °C; IR (KBr, cm⁻¹) 2921 (s), 2855 (m), 1423 (m), 1077 (m); ^1H NMR (300 MHz, CDCl₃): δ 1.06-1.16 (m, 4 H, CH₂), 1.43 (d, J = 9.0 Hz, 2 H, CHCHHCH), 1.71 (d, J = 9.0 Hz, 2 H, CHCHHCH), 1.81–1.94 (m, 4 H, CH₂), 2.21 (s, 3 H, CH₃), 3.39 (s, 2 H, CH), 3.59 (s, 2 H, CH); ^13C NMR (100 MHz, CDCl₃): δ 14.3, 26.2, 26.4, 43.2, 48.1, 48.3, 81.8, 122.5, 145.3, 148.3; HRMS (EI): C_{17}H_{19}I [M]^+ calculated: 350.0532, found: 350.0544.
(+)-(1S,4R,5R,8S)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene-9-ol

(+)-8

\[ \text{mCPBA} (1.72 \text{ g, } 6.9 \text{ mmol, } 70\% \text{ purity}) \text{ was added in one portion to a stirred solution of (+)-3 (200 mg, } 0.84 \text{ mmol) in CH}_2\text{Cl}_2 (20 \text{ mL}) \text{ at } 0 \text{ } ^\circ\text{C. The solution was allowed to reach room temperature and stirred for an additional 1 h. The mixture was diluted with Et}_2\text{O (45 mL) and washed with sat. aq Na}_2\text{SO}_3 (2 \times 15 \text{ mL}), \text{ sat. aq NaHCO}_3 (2 \times 15 \text{ mL}) \text{ and brine. After drying with MgSO}_4 \text{ the solvents were removed in vacuo to yield the crude formate. The residue was dissolved in MeOH (35 mL) and K}_2\text{CO}_3 (175 mg, } 1.2 \text{ mmol) was added. The mixture was left to stir at room temperature for 30 min, then diluted with Et}_2\text{O (40 mL). The organic layer was washed with H}_2\text{O (20 mL), brine (20 mL) and dried over MgSO}_4 \text{. The solvents were removed in vacuo to yield the title compound as a white solid. The product was sufficiently pure to be used in the next step but analytically pure (+)-8 was obtained after flash column chromatography (SiO}_2; \text{pentane/CH}_2\text{Cl}_2, 80:20) \text{ as a white solid (138 mg, } 73\%). \left[ \alpha \right]_{D}^{20} = +79.2 \text{ (c = 1, CHCl}_3); \text{Mp 139-140 } ^\circ\text{C; IR (KBr, cm}^{-1} \text{)} 3279 (s), 2962 (m), 1447 (w), 725 (m); ^1\text{H NMR (300 MHz, CDCl}_3): \delta 1.07-1.19 \text{ (m, 4 H, CH}_2\text{), 1.44-1.48 (m, 2 H, CHCH}_2\text{HCH), 1.68-1.72 (m, 2 H, CHCH}_2\text{HCH), 1.81-1.86 (m, 4 H, CH}_2\text{), 3.28 (bs, 2 H, CH), 3.48 (bs, 2 H, CH), 4.63 (bs, 1 H, OH), 6.64 (s, 1 H, ArH); } ^{13}\text{C NMR (100 MHz, CDCl}_3): \delta 26.9, 27.4, 39.3, 44.3, 49.3, 106.9, 130.1, 142.5, 147.9; \text{HRMS (ESI): C}_{16}\text{H}_{19}\text{O} \left[ \text{M} + \text{H}\right]^+ \text{ calculated: 227.1436, found: 227.1441.} \]

(+)-(1S,4R,5R,8S)-9-Methoxy-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene

(+)-9

2N NaOH (1.5 mL) was added to a solution of (+)-8 (100 mg, 0.44 mmol) in THF (3 mL). Dimethyl sulphate (0.4 mL, 531 mg, 2.57 mmol) was then added. After stirring the solution at room temperature for 5 min another aliquot of 2N NaOH (1.5 mL) was added at which point the reaction mixture was heated to reflux for 4 h. After cooling to room temperature, the aqueous layer was extracted with CH}_2\text{Cl}_2 (3 \times 10 \text{ mL}). The combined organic layers were washed with H}_2\text{O (10 mL), brine (10 mL) and dried over MgSO}_4 \text{. The organic layer was then concentrated in vacuo to yield the title compound as a white solid (98 mg, } 93\%). The product was sufficiently pure to be used directly in the next step, but an analytically pure sample was obtained following purification by flash column chromatography (SiO}_2; \text{pentane/CH}_2\text{Cl}_2, 1:1). \left[ \alpha \right]_{D}^{20} = +52.5 \text{ (c = 1, CHCl}_3); \text{Mp: 58-59 } ^\circ\text{C; IR (KBr, cm}^{-1} \text{)} 2955 (s), 2866 (s), 1572 (w), 1301 (s),
1058, 952 (m), 857 (m); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.05–1.20 (m, 4 H, CH$_2$), 1.42–1.44 (m, 2 H CHCHHCH$_2$), 1.64–1.71 (m, 2 H, CHCHHCH), 1.77–1.90 (m, 4 H, CH$_2$), 3.24 (brs, 2 H, OMe), 6.71 (s, 1 H, ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 27.2, 27.4, 40.6, 44.1, 49.2, 60.9, 109.1, 135.0, 147.5, 148.1; HRMS (ESI): C$_{17}$H$_{21}$O [M + H]$^+$ calculated: 241.1592, found: 241.1603.

$(-)-$(1S,4R,5R,8S)-9-Methoxy-10-iodo-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene $(-)-5b$

(+)-9 (50 mg, 0.21mmol) was added in one portion to a mixture of NIS (33 mg, 0.25 mmol) and trifluoroacetic acid (1.5 $\mu$L, 2 mg, 0.02 mmol) in MeCN (2.5 mL). The resulting mixture was stirred at room temperature for 12 h. Sat. aq Na$_2$S$_2$O$_3$ was added and the mixture was stirred vigorously for 10 min. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated in vacuo to yield the product as an off-white solid (60 mg, 79%). $[\alpha]_D^{20} = -37.5$ (c = 1, CHCl$_3$); Mp: 87-89 °C; IR (KBr, cm$^{-1}$) 2990 (m), 1589 (w), 1241 (s), 1072 (m), 732 (m); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.13–1.19 (m, 4 H, CH$_2$), 1.41–1.43 (m, 2 H CHCHHCH), 1.71–1.73 (m, 2 H, CHCHHCH), 1.82–1.92 (m, 4 H, CH$_2$) 3.39 (brs, 2 H, CH), 3.76 (brs, 2 H, CH) 3.86 (s, 3 H, OMe); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 25.1, 25.7, 41.1, 46.7, 47.2, 60.0, 76.7, 135.7, 146.7, 149.8; HRMS (EI): C$_{17}$H$_{19}$IO [M]$^+$ calculated: 366.0481, found: 366.0469.

References
HPLC traces

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I - 5a

\[ (-) - 5a \]
Crystal structure of (±)-9-iodo-anti-dimethanoanthracene

(thermal ellipsoids are drawn on the 50% probability level)

(a) Structure depicted in an angle similar to Figure 1 in the manuscript. (b) Front view along the arene plane. (c) Side-on view along the arene plane.