Direct Access to 1,4-dihydroxyanthraquinones: the Hauser Annulation Reexamined with *para*-Quinones

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Supporting information

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Supplementary information:

Preparation of quinones 9b, 9c, 9d, 9e, 23 and 27: 2-methoxybenzoquinone (**9d**), 2-chlorobenzoquinone¹ and o-quinol acetate² were prepared according to the literature procedures. For the preparation of 2-methyl-*p*-benzoquinone (**9b**), *ortho*-cresol was oxidised with PhI(OAc)₂ in dry methanol followed by acid-catalyzed hydrolysis to give the required quinone. Application of a similar route to 2,3-dimethylphenol provided 2,3-dimethylbenzoquinone (**9c**). 2-(1-Hydroxyethyl)-1,4-benzoquinone (**9e**) was prepared in 4 steps from hydroquinone, the last step being CAN-mediated oxidation of 2-(1-hydroxyethyl)-1,4-benzoquinol. Furanbenzoquinone (**23**) was prepared in 4 steps³, (i) mono O-allylation of catechol, (ii) Claisen rearrangement, (iii) I₂-catalysed cyclization and (iv) oxidation with Fremy's salt. 5-Hydroxy-5,6,7,8-tetrahydro naphthoquinone (**27**) was prepared from 5, 8- dimethoxy-1- tetralone in 2 steps, (i) NaBH₄ reduction, (ii) CAN mediated oxidation.

5,6,7,8-Tetrahydro-1,2-dihydroxynaphthalene (17): To a stirred solution of 5,6,7,8-tetrahydro-1,2-naphthol (**15**) (300 mg, 2.03 mmol) and RuCl₂(PPh₃)₃ (58.3 mg, 0.06 mmol) in ethyl acetate (3 mL) was added a 3.30 M solution of ^tBuOOH in dry benzene (3 mL, 8.1 mmol) dropwise at room temperature over a period of 1 h. After stirring for an additional 3 h, excess ^tBuOOH was destroyed by treatment with a solution of sodium bisulfite. The reaction mixture was extracted with ethyl acetate (3x 25 mL) and worked up in usual manner to give a white residue which was purified by column chromatography to give peroxy compound **16**²⁰ (410 mg, 85%). This was used for the next step without further purification.

A solution of TiCl₄ (2.07 mmol) in dry CH₂Cl₂ (4 mL) was dropwise added to a solution of **16** (410 mg, 1.73 mmol) in dry CH₂Cl₂ (4 mL) with stirring over a period of 30 min at -78 °C. After the mixture was stirred for an additional 1 h at room temperature, usual work-up with CH₂Cl₂ extraction followed by chromatography on silica gel gave 5,6,7,8-tetrahydro-1,2-dihydroxynaphthalene (**17**) (200 mg, 70%). ¹H NMR (200 MHz, CDCl₃): δ 6.52 (s, 2H), 2.65- 2.57 (m, 4H), 1.83- 1.68 (m, 4H).

5,6,7,8-Tetrahydro-1,4-naphthoquinone (18): To a solution of 5,6,7,8-tetrahydro-1,2-dihydroxynaphthalene (**17**) (100 mg, 0.60 mmol) in acetonitrile (2 mL), ceric ammonium nitrate (670 mg, 1.2 mmol) in water (4 mL) was added and the mixture stirred for 1 h. After completion of the reaction the mixture was extracted with ethyl acetate (3 x 25 mL). The combined extracts were subjected to usual work-up followed by chromatography on silica gel to give 5,6,7,8-tetrahydro-1,4-naphthoquinone (**18**) (60 mg, 61%). ¹H NMR (200 MHz, CDCl₃): δ 6.68 (s, 2H), 2.49- 2.33 (m, 4H), 1.72-1.63 (m, 4H).

References:

- (1) Carlson, W.; Miller, L. L. *J. Am. Chem. Soc.* **1985**, *107*, 479-485.
- (2) Quideau, S.; Pouysegu, L.; Oxoby, M.; Loony, M. A. *Tetrahedron* **2001**, *57*, 319-329.
- (3) Tapia, R. A. *Bioorg. Med. Chem.* **2003**, *11*, 2175-2182.

Characterisation data of products:

2-Methyl-*p*-benzoquinone (9b): ^1H NMR (200 MHz, CDCl_3): δ 6.77 (d, 1H, $J = 10.1$ Hz), 6.72 (dd, 1H, $J = 2$ Hz, 10 Hz), 6.60-6.62 (m, 1H), 3.36 (s, 6H), 1.91 (d, 3H, $J = 1.5$ Hz).

2,3-Dimethyl-*p*-benzoquinone (9c): ^1H NMR (200 MHz, CDCl_3): δ 6.62 (s, 2H), 2.02 (s, 6H) .

2-Methoxy-*p*-benzoquinone (9d): ^1H NMR (200 MHz, CDCl_3): δ 6.68 (s, 2H), 5.92 (s, 1H), 3.80 (s, 3H).

2-(2-hydroxyethyl)-*p*-benzoquinone (9e): ^1H NMR (200 MHz, CDCl_3): δ 6.79 (s, 1H), 6.75 (s, 2H), 4.85 (q, 1H, $J = 6.6$ Hz), 1.43 (d, 3H, $J = 6.6$ Hz).

1,4-Dihydroxyanthraquinone (10a): ^1H NMR (200 MHz, CDCl_3): 12.91 (s, 2H), 8.33-8.38 (m, 2H), 7.82-7.86 (m, 2H), 7.31 (d, 2H, $J = 11.4$ Hz).

2-Methyl-1,4-dihydroxyanthraquinone (10b): ^1H NMR (200 MHz, CDCl_3): δ 13.35 (s, 1H), 12.96 (s, 1H), 8.30-8.38 (m, 2H, 5), 7.78-7.86 (m, 2H), 7.16 (s, 1H), 2.37 (d, 3H, $J = 0.7$ Hz).

2,3-Dimethyl-1,4-dihydroxyanthraquinone (10c): ^1H NMR (200 MHz, CDCl_3): δ 13.62 (s, 2H), 8.32-8.36 (m, 2H), 7.79-7.83 (m, 2H), 2.33 (s, 6H).

2-Methoxy-1,4-dihydroxyanthraquinone (10d): ^1H NMR (200 MHz, CDCl_3): δ 13.57 (s, 1H), 13.48 (s, 1H), 8.39-8.33 (m, 2H), 7.86- 7.79 (m, 2H), 6.72 (s, 1H), 4.02 (s, 3H).

2-(2-hydroxyethyl)-1,4-dihydroxyanthraquinone (10e): ^1H NMR (200 MHz, CDCl_3): δ 13.46 (s, 1H), 12.89 (s, 1H), 8.35- 8.29 (m, 2H), 7.84- 7.78 (m, 2H), 7.48 (s, 1H), 5.21 (q, 1H, $J = 6.4$ Hz), 1.56 (d, 3H, $J = 6.4$ Hz).

6-Nitro-3-phenylthiophthalide (13): m. p. 115-117 $^{\circ}\text{C}$; IR (KBr) cm^{-1} : 1782 (s), 1610, 1528 (s), 1472, 1437, 1432, 1353, 1298, 1255, 1188 (m), 1049 (m), 998, 945, 882, 833,

731; ^1H NMR (200 MHz, CDCl_3): δ 8.60- 8.51 (m, 2H), 7.85 (d, 1H, $J = 8.8$ Hz), 7.49- 7.40 (m, 2H), 7.35-7.15 (m, 3H), 6.81 (s, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 166.6, 151.5, 149.2, 134.3, 129.6, 129.2, 129.0, 128.3, 127.7, 124.9, 120.7, 86.0.

6-Nitro-1,4-dihydroxyanthraquinone (14): ^1H NMR (200 MHz, CDCl_3): δ 12.77 (s, 1H), 12.75 (s, 1H), 9.17 (s, 1H), 8.62- 8.57 (m, 2H), 7.40 (s, 2H); HRMS m/e calcd. for $\text{C}_{14}\text{H}_8\text{NO}_6$ (MH) $^+$ 286.0349, found 286.0339.

7,8,9,10-Tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (19): ^1H NMR (200 MHz, CDCl_3): δ 13.57 (s, 2H), 8.38- 8.31 (m, 2H), 7.84- 7.77 (m, 2H), 2.81- 2.77 (m, 4H), 1.87- 1.80 (m, 4H).

6,11-dihydroxy-5,12-naphthacenedione (21): ^1H NMR (200 MHz, CDCl_3): δ 15.19 (s, 2H), 8.50- 8.45 (m, 4H), 7.86- 7.79 (m, 4H).

6,11-dimethoxy-5,12-naphthacenedione (22): ^1H NMR (200 MHz, CDCl_3): δ 8.46- 8.39 (m, 2H), 8.31- 8.24 (m, 2H), 7.79- 7.74 (m, 4H), 4.15 (s, 6H).

2,2-Dimethyl-2,3-dihydrofuranoquinone (23): ^1H NMR (200 MHz, CDCl_3): δ 6.62 (d, 1H, $J = 9.8$ Hz), 6.55 (d, 1H, $J = 9.6$ Hz), 2.86 (s, 2H), 1.54 (s, 6H).

6,7,11-Trihydroxy-5,12-naphthacenedione (26): ^1H NMR (200 MHz, CDCl_3): δ 15.36 (s, 1H), 14.27 (s, 1H), 12.43 (s, 1H), 8.60- 8.40 (m, 2H), 8.09- 7.90 (m, 1H), 7.89- 7.70 (m, 2H), 7.69- 7.59 (m, 1H), 7.42-7.30 (m, 1H); HRMS m/e calcd. for $\text{C}_{18}\text{H}_{11}\text{O}_5$ (MH) $^+$ 307.0606, found 307.0556.

5-Hydroxy-5,6,7,8-tetrahydronaphthoquinone(27): IR (KBr) cm^{-1} : 2944, 2362, 1652, 1301, 995, 838; ^1H NMR (200 MHz, CDCl_3): δ 6.78 (s, 2H), 4.80 (s, 1H), 2.62- 2.46 (m, 1H), 2.40-2.21 (m, 1H), 1.97- 1.70 (m, 4H); ^{13}C NMR (50 MHz, CDCl_3): δ 188.6, 187.5, 143.8, 141.1, 136.6, 136.3, 62.2, 29.2, 22.8, 16.9; HRMS m/e calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_3$ (MH) $^+$ 179.0708, found 179.0695.

6,7,11-Trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (28): m. p. 285-287 $^{\circ}\text{C}$; ^1H NMR (200 MHz, CDCl_3): δ 13.8, (s, 1H), 13.4 (s, 1H), 8.39- 8.30 (m, 2H), 7.88- 7.78 (m, 2H), 5.14 (s, 1H), 3.32- 2.87 (m, 1H), 2.69- 2.57 (m, 1H), 2.09- 1.78 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 186.8, 186.7, 156.9, 156.7, 140.4, 138.3, 134.4, 134.3, 133.5, 133.4, 127.0, 126.9, 110.5, 110.3, 62.6, 29.6, 23.9, 17.1; HRMS m/e calcd. for $\text{C}_{18}\text{H}_{11}\text{O}_5\text{Na}$ (MNa) $^+$ 333.0738, found 333.0719.

^{13}C NMR of 6-Chloro-7-methoxy-3-phenylthiophthalide (**11**)

DEPT-135 of 6-Chloro-7-methoxy-3-phenylthiophthalide (**11**)

^1H NMR of 5-Methoxy-6-chloro-1,4-dihydroxyanthraquinone (**12**)

^{13}C NMR of 5-Methoxy-6-chloro-1,4-dihydroxyanthraquinone (**12**)

DEPT-135 of 5-Methoxy-6-chloro-1,4-dihydroxyanthraquinone (**12**)

¹H NMR of 6-Nitro-1,4-dihydroxyanthraquinone (**14**)

^1H NMR of 7,8,9,10-Tetrahydro-6,11-dihydroxy-5,12-naphthacenedione (**19**)

^1H NMR of 6,11-dihydroxy-5,12-naphthacenedione (**21**)

^1H NMR of 2,3-Dihydro-2,2-dimethyl-4,11-dihydroxy anthra[2,3-*b*]furan-5,10-dione (**24**)

^{13}C NMR of 2,3-Dihydro-2,2-dimethyl-4,11-dihydroxy anthra[2,3-*b*]furan-5,10-dione
(24)

DEPT-135 of 2,3-Dihydro-2,2-dimethyl-4,11-dihydroxy anthra[2,3-*b*]furan-5,10-dione
(**24**)

^1H NMR of 6,7,11-Trihydroxy-5,12-naphthacenedione (**26**)

^1H NMR of 6,7,11-Trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (**28**)