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DDQ induced oxidative cyclisations of 1,2-dihydronaptho[2,1-*b*]furans

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Abstract—The DDQ mediated oxidative cyclisation reactions of a series of dihydronaptho[2,1-*b*]furans were examined. In the presence of an acid catalyst, the reaction yielded polycyclic ethers and lactones in good to excellent yields.

1. Introduction

2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) is a common oxidant used in dehydrogenation reactions leading to aromatised products[1–3] and in the oxidation of aromatic and allylic alcohols to aldehydes and ketones.[4–6] DDQ can be used to generate benzylic and napthylic cations on suitably activated systems via hydride abstraction. The cations thus generated can undergo nucleophilic addition and intramolecular cyclisation reactions leading to oxygen containing heterocycles when the substrates are substituted with suitable latent nucleophiles.[7–9]

We have recently developed a route to 1,2-dihydronaptho[2,1-*b*]furans **3** utilising 1,2-dioxines **1** and stabilised phosphorus ylides.[10] We considered these products to be ideal substrates for DDQ induced oxidation due to the stabilising effect of the furan ring on the intermediate napthylic cation. The products generated in this previous study also contained an ester group that could act as the nucleophile for the intramolecular trapping of the napthylic cation. It was hypothesised that this ester or derivative thereof could participate in the reaction and give rise to novel cyclisation products. Some aryl-fused furofurans are found in nature such as psorofebrin[11,12] and platypodantherone[13] and we believed that by investigating DDQ induced oxidative cyclisations on dihydronapthofurans, we could develop a route to these types of compounds. We now report on the oxidative cyclisation reactions of a series of substituted 1,2-dihydronapthofurans facilitated by DDQ.

Keywords: DDQ; Dihydronapthofuran; Cyclisation.
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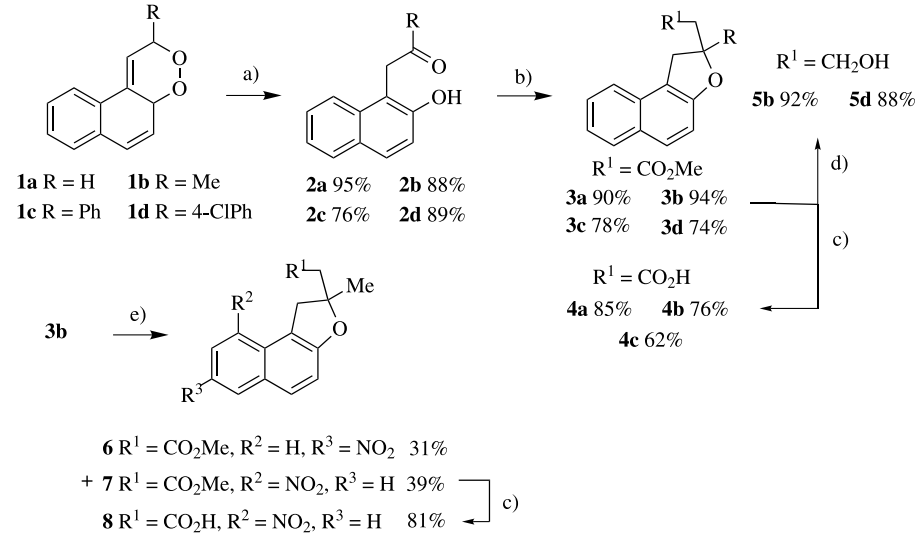
2. Results and discussion

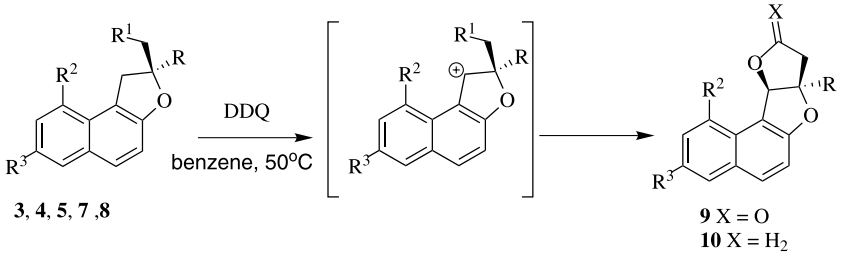
The synthesis of the starting dihydronapthofurans **3a–d** was achieved using our previously published procedure, Scheme 1.[10] Thus, Rose Bengal bis(triethylammonium) salt sensitised photooxidation of 1-vinylnapthalenes gave the 1,2-dioxines **1a–d**. These 1,2-dioxines underwent rearrangement when allowed to react with DABCO to afford the 1-(β-keto)-2-napthols **2a–d** in excellent yield. Reaction of the napthols **2a–d** with methyl(triphenylphosphoranylidene)acetate afforded the requisite dihydronapthofurans **3a–d** via a Wittig/oxy-Michael sequence.

Further functional group modifications were made on the dihydronapthofurans **3a–d** such that the scope of the oxidative cyclisation could be examined. Saponification of the esters **3a–c** afforded the acids **4a–c** and $LiAlH_4$ reduction of **3b** and **3d** gave the alcohols **5b** and **5d**, respectively. To the best of our knowledge, electrophilic aromatic substitution has not been examined on 1,2-dihydronaptho[2,1-*b*]furans, although the dehydrogenated naptho[2,1-*b*]furans are known to react primarily at the C6 position.[14] When **3b** was exposed to standard nitration conditions, electrophilic substitution occurred at both the C7 and C9 positions on the naphthalene skeleton to afford **6** and **7** in good overall yield. The identity of these isomers was determined using both COSY and ROESY 2D NMR techniques.

With a range of substrates in hand, the DDQ facilitated oxidative cyclisation reactions of napthofurans **3**, **4**, **5**, **7** and **8** were examined, Scheme 2 and Table 1. Initially, when the ester **3a** was heated to 50 °C in dry benzene in the presence of 1.1 equivalents of DDQ, no reaction was observed. To



Scheme 1. Key: (a) DABCO; (b) $Ph_3P{=}CHCO_2Me$; (c) KOH, $MeOH/H_2O$, 16 h; (d) $LiAlH_4$, THF, 16 h; (e) HNO_3, AcOH, 1 h.



Scheme 2.

enhance the reactivity of the DDQ, addition of an acid catalyst to the reaction medium was examined. In the presence of *p*-toluenesulfonic acid, the esters **3a–d** and **7** reacted with DDQ affording the furofuranones **9a–e** in good yield, entries 1–5. The dihydronapthofuran acids **4a–c** and **8** underwent smooth reaction to give the furofuranones **9a–c**,**e** without the need for an acid catalyst, entries 6–9. The yields obtained from the acids **4a–c** and **8** were virtually identical to the yields seen in the corresponding ester series **3a–c** and **7**.

Cyclisation of the alcohols **5b** and **5d** also proceeded smoothly to afford the furofurans **10b** and **10d** in the absence of an acid catalyst in excellent yield. The requirement for the acid catalyst in the ester series may be due to the reduced ability of the ester group, relative to the acid and alcohol groups, to stabilise the cation in the rate-determining cation-forming step. Oxidations involving DDQ are often performed in acidic solvents to activate DDQ towards hydride abstraction.[15]

The ^{1}H NMR data for the furolactones were consistent with the proposed structures. Each lactone exhibited a singlet at ca. δ 6.20 ppm due to the napthylic proton and an AB quartet at ca. δ 3.00 ppm. The lactone products exhibited characteristic IR absorptions at 1785 cm^{-1} and the stereochemistry of the products were confirmed when the X-ray structures of **9b** and **9e** were obtained, Figure 1.[16] The

Table 1. Oxidative cyclisations of 1,2-dihydronaptho[2,1-*b*]furans

Entry[a]	Starting material	R	R^1	R^2	R^3	Product	Yield (%)
1[b]	**3a**	H	CO_2Me	H	H	**9a**	40
2[b]	**3b**	Me	CO_2Me	H	H	**9b**	64
3[b]	**3c**	Ph	CO_2Me	H	H	**9c**	80
4[b]	**3d**	4-ClPh	CO_2Me	H	H	**9d**	85
5[b,c]	**7**	Me	CO_2Me	H	NO_2	**9e**	88
6	**4a**	H	CO_2H	H	H	**9a**	38
7	**4b**	Me	CO_2H	H	H	**9b**	81
8	**4c**	Ph	CO_2H	H	H	**9c**	71
9[c]	**8**	Me	CO_2H	H	NO_2	**9e**	91
10	**5b**	Me	CH_2OH	H	H	**10b**	81
11	**5d**	4-ClPh	CH_2OH	H	H	**10d**	87

[a] Reactions were performed in dry benzene at 50 °C for 1 h.
[b] Performed in the presence of a catalytic amount (2 mg) of *p*-toluenesulfonic acid.
[c] Reaction heated to reflux for 16 h.

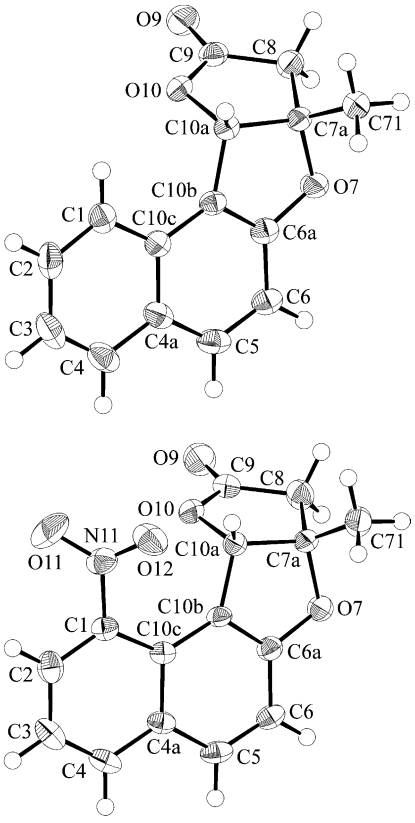


Figure 1. X-ray structures of **9b** and **9e**.

structure of **9e** also confirmed the substitution pattern obtained from the electrophilic aromatic substitution reaction of **3b**.

Mechanistically, the reaction proceeds via a two-step sequence with initial hydride abstraction by DDQ to give the napthyl cation and the $DDQH^-$ anion. The napthylic cation is trapped by the oxygen of the alcohol, acid or ester and then the $DDQH^-$ anion abstracts either a proton or methyl to yield the reduced $DDQH_2$ or DDQH(Me), respectively and the cyclisation product.

The oxidative cyclisation of a dihydrofuran with a nitrogen bearing arm was also examined, Scheme 3. The reaction of amide **11** afforded nitrile **12** and required two equivalents of DDQ for the reaction to achieve completion. This result suggests an oxygen transfer mechanism as depicted with a faster second hydride abstraction due to the stabilising effect of the α-oxygen atom. Nitrile **12** exhibited a resonance in the ^{1}H NMR attributed to the C1 carbonyl carbon at δ 197.3 ppm and an IR absorption at 2258 cm^{-1} corresponding to the nitrile moiety confirming the assigned structure.

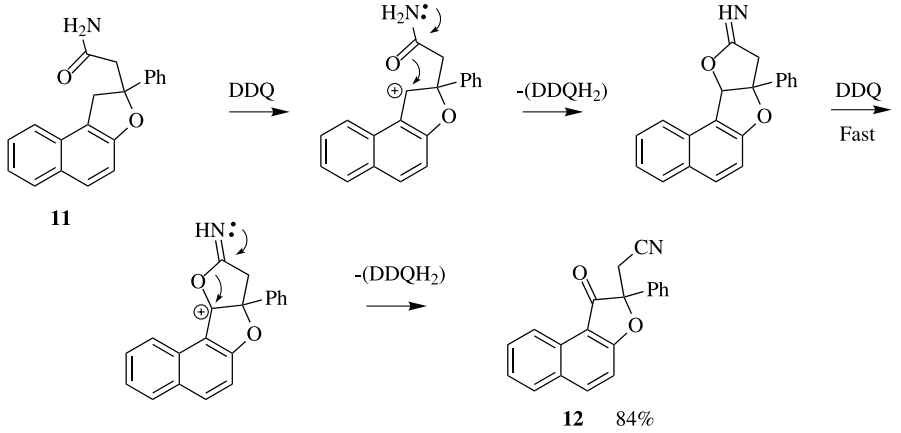
The oxidative cyclisation of dihydronapthofurans is a useful method for the construction of aryl furofuran ring systems, a ring structure found in natural products such as platypodantherone and psorofebrin. The naphthalene ring serves as a rigid template for the ether or lactone construction while stabilising the carbocation formation. Ring closures of this type could be used in the construction of arylfurofuranone natural products.

3. Experimental

3.1. General experimental

Solvents were dried by appropriate methods wherever needed. Benzene was dried by distillation over calcium hydride prior to use. Thin-layer chromatography (TLC) was performed using aluminium sheets silica gel 60 F_{254} (40× 80 mm) from Merck. Melting points were taken on a Reichert Thermovar Kofler apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FTIR spectrophotometer as nujol mulls unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian INOVA (600 MHz) or on a Varian Gemini 2000 instrument, TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as internal standards unless otherwise specified. Dihydrofurans **3a–d** and compounds **1d** and **2d** were prepared according to our previously reported procedure.[10]

3.1.1. (±) (2*R*,4a*R*)-2-(4-Chlorophenyl)-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine 1d. Light yellow solid; mp 78–82 °C; R_f 0.32 (30:70 CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.52 (dd, J=3.0, 3.0 Hz, 1H) 5.78 (dd, J=10.2, 2.4 Hz, 1H), 6.02 (dddd, J=3.0, 3.0, 3.0, 2.4 Hz, 1H), 6.15 (ddd, J=3.0, 3.0, 1.2 Hz, 1H), 6.45 (dd, J=10.2, 3.0 Hz, 1H), 7.08 (dd, J=7.8, 1.2 Hz, 1H),



Scheme 3.

7.22–7.28 (m, 2H), 7.32–7.34 (m, 2H), 7.38–7.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 80.9, 82.0, 119.3, 123.6, 124.1, 127.4, 128.6, 128.6, 129.2, 129.3, 129.9, 130.9, 132.2, 134.4, 136.3, 138.0; MS *m/z* (%) 296 (M^+, 20), 278 (57), 265 (32), 139 (100), 111 (31); HRMS calcd for $C_{18}H_{13}O_2^{35}Cl$: 296.0604; found: 296.0610.

3.1.2. 1-(4-Chlorophenyl)-2-(2-hydroxy-1-naphthalenyl)-1-ethanone 2d. White solid; mp 212–220 °C (decomposes); IR (Nujol) 3421, 1674, 1630, 1587, 1570, 1518 cm^{-1}; ^{1}H NMR ($CDCl_3$/d_6-DMSO, 300 MHz) δ 4.70 (s, 2H), 7.20–7.27 (m, 2H), 7.37–7.44 (m, 3H), 7.64–7.75 (m, 3H), 8.09–8.11 (m, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$/d_6-DMSO, 75 MHz) δ 35.9, 112.7, 117.9, 122.2, 122.4, 126.1, 128.1, 128.3, 128.4, 129.6, 133.6, 135.0, 138.8, 152.3, 197.3, (1 masked aromatic); MS *m/z* (%) 296 (M^+, 32), 157 (100), 139 (67), 128 (45); Anal. Calcd for $C_{18}H_{13}ClO_2$: C, 72.85; H, 4.42; Cl, 11.95; Found C, 72.64; H, 4.34; Cl, 12.18.

3.1.3. Methyl 2-[2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]acetate 3c. Colorless oil; R_f 0.46 (80:20 hexane/ethyl acetate); IR (CH_2Cl_2) 1738, 1633, 1601, 1579, 1522, 1494 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.13 (d, J=14.6 Hz, 1H), 3.16 (d, J=14.6 Hz, 1H), 3.48 (s, 3H), 3.77 (d, J=15.7 Hz, 1H), 4.14 (d, J=15.7 Hz, 1H), 7.26–7.50 (m, 6H), 7.58–7.62 (m, 3H), 7.72–7.75 (m, 1H), 7.81–7.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.2, 46.4, 51.6, 89.1, 112.0, 117.7, 122.7, 123.0, 124.8, 126.6, 127.5, 128.4, 128.7, 129.2, 129.4, 130.7, 144.8, 155.9, 169.9; EIMS *m/z* 318 (M^+, 32), 286 (22), 257 (2), 244 (100), 181 (11); HRMS calcd for $C_{21}H_{18}O_3$: 318.1256; found 318.1255.

3.1.4. Methyl 2-[2-(4-chlorophenyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]acetate 3d. Pale yellow viscous oil; R_f 0.49 (80:20 hexane/ethyl acetate); IR (neat) 1738, 1633, 1601, 1579, 1521 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.11 (d, J=14.9 Hz, 1H), 3.14 (d, J=14.9 Hz, 1H), 3.51 (s, 3H), 3.73 (d, J=15.6 Hz, 1H), 4.11 (d, J=15.6 Hz, 1H), 7.21–7.24 (m, 1H), 7.29–7.36 (m, 3H), 7.44–7.52 (m, 3H), 7.56–7.59 (m, 1H), 7.71–7.74 (m, 1H), 7.79–7.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 41.4, 46.2, 51.6, 89.2, 112.0, 117.4, 122.6, 123.1, 126.4, 126.8, 128.5, 128.7, 129.4, 129.5, 130.6, 133.4, 143.2, 155.7, 169.7; EIMS *m/z* 352 (M^+, 19), 291 (22), 278 (100), 181 (20); HRMS calcd for $C_{21}H_{17}O_3^{35}Cl$: 352.0866; found 352.0860.

3.2. General procedure for the hydrolysis of esters 3a–c and 7

3.2.1. 2-(1,2-Dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 4a. A solution of dihydrofuran **3a** (138 mg, 0.57 mmol) and potassium hydroxide (400 mg, excess) in methanol (10 ml) was stirred for 16 h. The solution was acidified with 1 *N* HCl and then extracted with CH_2Cl_2 (2×20 ml), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude acid was recrystallised from chloroform to give a white solid (110 mg, 85%); mp 138.5–139.5 °C; IR (CH_2Cl_2) 2760, 1693, 1631, 1599, 1577, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83 (dd, J=6.0, 16.2 Hz, 1H), 3.01 (dd, J=16.2, 7.2 Hz, 1H), 3.23 (dd, J=15.4, 6.9 Hz, 1H), 3.74 (dd, J=15.4, 9.6 Hz, 1H), 5.40 (dddd, J=6.0, 7.2, 6.9, 9.6 Hz, 1H), 7.11–7.14 (m, 1H), 7.30–7.35 (m, 1H), 7.45–7.51 (m, 1H), 7.57–7.60 (m, 1H), 7.68–7.71 (m, 1H), 7.80–7.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.3, 40.6, 79.1, 112.1, 117.6, 122.7, 123.1, 126.8, 128.8, 129.3, 129.4, 130.7, 156.4, 175.1; EIMS *m/z* 228 (M^+, 9), 168 (39), 69 (54), 55 (56), 41 (100); Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30; Found C, 73.40; H, 5.03.

3.2.2. 2-(2-Methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 4b. Recrystallised from *n*-heptane/dichloromethane; mp 124–126 °C; IR (Nujol) 1711, 1633, 1574, 1603, 2670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68 (s, 3H), 2.91 (s, 2H), 3.33 (d, J=15.9 Hz, 1H), 3.61 (d, J=15.9 Hz, 1H), 7.07–7.10 (m, 1H), 7.27–7.33 (m, 1H), 7.45–7.49 (m, 1H), 7.56–7.59 (m, 1H), 7.67–7.70 (m, 1H), 7.79–7.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 26.6, 40.4, 45.0, 86.7, 112.3, 117.8, 122.7, 122.9, 126.7, 128.7, 129.2, 129.3, 130.9, 155.5, 175.4; EIMS *m/z* 242 (M^+, 39), 144 (100), 105 (98), 77 (53); Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82; Found C, 74.15; H, 5.74.

3.2.3. 2-(2-Phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 4c. Recrystallised from hot dichloromethane/hexane (1:1); mp 154.5–155.5 °C; IR (Nujol) 1722, 1657, 1603, 1577, 1521, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.17 (d, J=15.5 Hz, 1H), 3.18 (d, J=15.5 Hz, 1H), 3.74 (d, J=15.9 Hz, 1H), 4.03 (d, J=15.9 Hz, 1H), 7.24–7.37 (m, 5H), 7.44–7.47 (m, 1H), 7.53–7.56 (m, 3H), 7.70–7.73 (m, 1H), 7.78–7.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.7, 45.9, 89.4, 112.1, 117.6, 122.7, 123.2, 124.8, 126.8, 127.7, 128.5, 128.7, 129.4, 129.6, 130.7, 144.2, 155.7, 173.6; EIMS *m/z* 304 (M^+, 64), 257 (28), 244 (100), 181 (15); Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30; Found C, 78.77; H, 5.44.

3.3. General procedure for the reduction of esters 3b,d

3.3.1. 2-(2-Methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)-1-ethanol 5b. To a stirred solution of dihydrofuran **3b** (206 mg, 0.805 mmol) in anhydrous THF (5 ml) was added $LiAlH_4$ (30 mg, 0.790 mmol) at ambient temperature. After 16 h the reaction was quenched with ethyl acetate (1 ml) and 1 *N* HCl (10 ml) added. The mixture was extracted with CH_2Cl_2 (2×20 ml), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography afforded a colorless oil (169 mg, 92%); R_f 0.24 (90:10 CH_2Cl_2/ethyl acetate); IR (CH_2Cl_2) 3614, 3566, 1632, 1599, 1586, 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.56 (s, 3H), 1.71 (br s, 1H), 2.09 (ddd, J=5.4, 6.2, 14.5 Hz, 1H), 2.19 (ddd, J=5.6, 7.4, 14.5 Hz, 1H), 3.28 (d, J=15.3 Hz, 1H), 3.43 (d, J=15.3 Hz, 1H), 3.86 (ddd, J=5.6, 6.2, 11.5 Hz, 1H), 3.95 (ddd, J=5.4, 7.4, 11.5 Hz, 1H) 7.06–7.07 (m, 1H), 7.29–7.32 (m, 1H), 7.45–7.48 (m, 1H), 7.55–7.57 (m, 1H), 7.68–7.69 (m, 1H), 7.80–7.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.9, 41.2, 43.4, 59.5, 89.8, 112.4, 118.1, 122.8, 123.0, 126.9, 128.9, 129.3, 129.4, 131.2, 155.9; EIMS *m/z* 228 (100), 209 (12), 195 (54), 183 (45); HRMS calcd for $C_{15}H_{16}O_2$: 228.1150; found 228.1158.

3.3.2. 2-[2-(4-Chlorophenyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]-1-ethanol 5d. Gummy colorless oil; R_f 0.25 (95:5 CH_2Cl_2/ethyl acetate); IR (CH_2Cl_2) 3683, 3608, 1633,

1603, 1579, 1522, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.94 (br s, 1H), 2.37 (ddd, $J=5.6$, 5.6, 14.7 Hz, 1H), 2.50 (ddd, $J=6.0$, 7.6, 14.7 Hz, 1H), 3.63–3.67 (m, 2H), 3.73 (ddd, $J=5.6$, 7.4, 11.4 Hz, 1H), 3.79 (d, $J=15.2$ Hz, 1H), 7.20–7.22 (m, 1H), 7.30–7.34 (m, 3H), 7.43–7.46 (m, 3H), 7.51–7.53 (m, 1H), 7.72–7.74 (m, 1H), 7.80–7.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.3, 44.2, 59.0, 91.7, 111.8, 117.2, 122.5, 123.1, 126.1, 126.7, 128.5, 128.6, 129.3, 129.4, 130.5, 133.0, 143.6, 155.5; EIMS *m/z* 324 (M^+, 100), 291 (81), 279 (49), 215 (27); Anal. Calcd for $C_{20}H_{17}O_2Cl$: C, 73.96; H, 5.28; Found C, 73.88; H, 5.33.

3.4. Reaction of methyl 2-(2-methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetate 3b with nitric acid

To a stirred solution of dihydronapthofuran **3b** (325 mg, 1.27 mmol) in glacial acetic acid (20 ml) cooled in an ice water bath was added nitric acid (4 ml, 50% in glacial acetic acid). The vessel was warmed to 30 °C and left to stir for 1 h at ambient temperature. The solution was poured onto ice water and the mixture extracted with dichloromethane (2× 20 ml). The organic phase was dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude residue was purified by flash chromatography (80:20 hexane/ethyl acetate) to give **6** (120 mg, 31%) and **7** (150 mg, 39%).

3.4.1. Methyl 2-(2-methyl-7-nitro-1,2-dihydronaphtho-[2,1-*b*]furan-2-yl)acetate 6. Yellow oil; R_f 0.33 (80:20 hexane/ethyl acetate); IR (CH_2Cl_2) 1738, 1626, 1603, 1537, 1506, 1338 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.67 (s, 3H), 2.86 (d, $J=15.3$ Hz, 1H), 2.89 (d, $J=15.3$ Hz, 1H), 3.33 (d, $J=16.2$ Hz, 1H), 3.66 (d, $J=16.2$ Hz, 1H), 3.66 (s, 3H), 7.19 (d, $J=8.7$ Hz, 1H), 7.60 (d, $J=9.1$ Hz, 1H), 7.85 (d, $J=8.7$ Hz, 1H), 8.21 (dd, $J=9.1$, 2.4 Hz, 1H), 8.74 (d, $J=2.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.9, 39.6, 44.8, 51.6, 88.1, 114.3, 119.0, 120.1, 123.7, 125.6, 127.2, 131.7, 133.6, 143.0, 159.1, 170.1; EIMS *m/z* 301 (M^+, 17), 227 (100), 181 (38), 152 (22); HRMS calcd for $C_{16}H_{15}NO_5$: 301.0950; found 301.0941.

3.4.2. Methyl 2-(2-methyl-9-nitro-1,2-dihydronaphtho-[2,1-*b*]furan-2-yl)acetate 7. Yellow orange oil; R_f 0.41 (80:20 hexane/ethyl acetate); IR (CH_2Cl_2) 1738, 1636, 1599, 1579, 1525, 1352 cm^{-1}; ^1H NMR (C_6D_6, 600 MHz) δ 1.27 (s, 3H), 2.37 (d, $J=15.0$ Hz, 1H), 2.39 (d, $J=15.0$ Hz, 1H), 3.09 (d, $J=16.2$ Hz, 1H), 3.18 (s, 3H), 3.48 (d, $J=16.2$ Hz, 1H), 6.60 (dd, $J=8.2$, 7.6 Hz, 1H), 6.93 (d, $J=8.8$ Hz, 1H), 7.17 (d, $J=8.8$ Hz, 1H), 7.25 (dd, $J=7.6$, 1.2 Hz, 1H), 7.31 (dd, $J=8.2$, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.6, 40.8, 44.8, 51.6, 87.3, 114.2, 114.7, 120.8, 122.6, 122.9, 130.4, 130.6, 133.4, 146.0, 159.0, 170.0; EIMS *m/z* 301 (M^+, 25), 284 (22), 267 (28), 227 (100), 181 (79), 152 (47). HRMS calcd for $C_{16}H_{15}NO_5$: 301.0950; found 301.0941.

3.4.3. 2-(2-Methyl-9-nitro-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 8. Yellow solid recrystallised from hot aqueous ethanol; mp 160–162 °C; IR (Nujol) 1709, 1624, 1595, 1576, 1522, 1500, 1331 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.64 (s, 3H), 2.82 (d, $J=15.3$ Hz, 1H), 2.84 (d, $J=15.3$ Hz, 1H), 3.17 (d, $J=16.2$ Hz, 1H), 3.41 (d, $J=16.2$ Hz, 1H), 7.23 (d, $J=8.8$ Hz, 1H), 7.32 (dd, $J=8.0$, 8.0 Hz, 1H), 7.80 (dd, $J=8.0$, 1.1 Hz, 1H), 7.81 (d, $J=$ 8.8 Hz, 1H), 7.99 (dd, $J=8.0$, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 26.4, 41.1, 44.6, 87.1, 114.4, 114.7, 121.0, 122.7, 123.1, 130.6, 130.8, 133.5, 146.1, 159.0, 174.0; EIMS *m/z* 287 (M^+, 53), 270 (57), 253 (53), 227 (85), 181 (100), 152 (72), 45 (90); Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88; Found C, 63.26; H, 4.69; N, 4.98.

3.5. General procedure for the reaction of esters 3a–d and 7 with DDQ

To a stirred solution of dihydronapthofuran (0.11 mmol) and DDQ (29 mg, 0.12 mmol) in dry benzene (8 ml) was added *p*-toluenesulphonic acid (2 mg, 0.01 mmol) dissolved in benzene (0.5 ml). The solution was heated to 50 °C for 1 h and then cooled and concentrated in vacuo to ca. 1 ml. The solution was filtered through a plug of cotton wool and the residue purified by flash chromatography.

3.6. General procedure for the reaction of acids 4a–c, 8 and alcohols 5b,d with DDQ

A stirred solution of dihydronapthofuran (0.11 mmol) and DDQ (29 mg, 0.12 mmol) in dry benzene (8 ml) was heated to 50 °C for 1 h and then cooled and concentrated in vacuo to ca. 1 ml. The solution was filtered through a plug of cotton wool and the residue purified by flash chromatography.

3.6.1. (±) (7a*R*,10a*R*)-7a,8,9,10a-Tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 9a. White solid; mp 205–207 °C (lit. 207–208 °C)[17]; R_f 0.58 (40:60 ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.05 (dd, $J=19.0$, 2.0 Hz, 1H), 3.17 (dd, $J=19.0$, 6.6 Hz, 1H), 5.56 (ddd, $J=2.0$, 6.6, 6.6 Hz, 1H), 6.46 (d, $J=6.6$ Hz, 1H), 7.12–7.15 (m, 1H), 7.38–7.43 (m, 1H), 7.55–7.60 (m, 1H), 7.83–7.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.5, 81.5, 83.4, 112.1, 115.1, 122.1, 124.1, 128.1, 128.7, 129.6, 130.6, 133.4, 159.2, 174.7.

3.6.2. (±) (7a*R*,10a*R*)-7a-Methyl-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 9b. White crystalline solid; mp 147–149 °C (CH_2Cl_2/hexane); R_f 0.39 (70:30 hexane/ethyl acetate); IR (CH_2Cl_2) 1780, 1635, 1601, 1585, 1525 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.73 (s, 3H), 2.93 (d, $J=18.9$ Hz, 1H), 3.22 (d, $J=18.9$ Hz, 1H), 6.06 (s, 1H), 7.09–7.12 (m, 1H), 7.37–7.42 (m, 1H); 7.54–7.59 (m, 1H), 7.83–7.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.5, 41.2, 88.0, 90.1, 112.4, 114.6, 122.2, 123.9, 128.0, 128.7, 129.5, 131.0, 133.4, 158.5, 174.4; EIMS *m/z* 240 (M^+, 12), 195 (17), 181 (39), 115 (23), 44 (100); Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found C, 75.08; H, 5.07.

3.6.3. (±) (7a*S*,10a*R*)-7a-Phenyl-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 9c. White solid; mp 171–172 °C; R_f 0.65 (70:30 hexane/ethyl acetate); IR (CH_2Cl_2) 1784, 1635, 1603, 1583, 1525, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.38 (d, $J=18.9$ Hz, 1H), 3.53 (d, $J=18.9$ Hz, 1H), 6.35 (s, 1H), 7.26–7.29 (m, 1H), 7.36–7.45 (m, 4H), 7.52–7.57 (m, 3H), 7.80–7.85 (m, 2H), 7.90–7.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.4, 89.7, 93.2, 112.1, 114.6, 122.2, 124.1, 124.5, 128.1, 128.7, 128.8, 129.0, 129.8, 130.8, 133.6, 139.6, 158.9, 174.0; EIMS *m/z*

302 (M^+, 14), 257 (100), 181 (49), 115 (42), 77 (60); Anal. Calcd for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67; Found C, 79.14; H, 4.83.

3.6.4. (±) (7a*S*,10a*R*)-7a-(4-Chlorophenyl)-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan-9-one 9d. White solid; mp 200–208 °C (decomposes); R_f 0.42 (80:20 hexane/ethyl acetate); IR (Nujol) 1785, 1636, 1582, 1526, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.33 (d, J= 19.2 Hz, 1H), 3.53 (d, J=19.2 Hz, 1H), 6.31 (s, 1H), 7.25–7.28 (m, 1H), 7.37–7.43 (m, 3H), 7.47–7.58 (m, 3H), 7.80–7.86 (m, 2H), 7.91–7.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.2, 89.5, 92.7, 112.0, 114.4, 122.2, 124.3, 125.9, 128.2, 128.8, 129.2, 129.9, 130.7, 133.7, 134.7, 138.1, 158.7, 173.6; EIMS *m/z* 336 (M^+, 46), 307 (59), 291 (100), 278 (38), 226 (26); Anal. Calcd for $C_{20}H_{13}O_3Cl$: C, 71.33; H, 3.89, Cl, 10.53. Found C, 71.05; H, 3.85; Cl, 10.27.

3.6.5. (±) (7a*R*,10a*R*)-7a-Methyl-1-nitro-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 9e. The general procedure was employed, however, the reaction mixture was refluxed overnight to give a yellow solid; mp 190–195 °C (sealed tube, decomposes); R_f 0.58 (40:60 ethyl acetate/hexane); IR (CH_2Cl_2) 1784, 1628, 1599, 1579, 1529 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.78 (s, 3H) 2.89 (d, J=19.2 Hz, 1H), 3.11 (d, J=19.2 Hz, 1H), 6.12 (s, 1H), 7.25 (d, J=8.7 Hz, 1H), 7.44 (dd, J=7.8, 7.8 Hz, 1H), 7.98 (d, J=8.7 Hz, 1H), 7.99 (dd, J=7.8, 1.2 Hz, 1H), 8.07 (dd, J=8.7, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.5, 41.0, 88.6, 90.1, 112.2, 114.7, 122.3, 122.9, 125.3, 131.1, 134.2, 134.6, 145.8, 161.6, 173.5; MS *m/z* (%): 285 (M^+, 100), 240 (8), 226 (64), 201 (48), 145 (65). HRMS, $C_{15}H_{11}NO_5Na$: calcd, 308.0535; found 308.0531.

3.6.6. (±) (7a*R*,10a*R*)-7a-Methyl-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan 10b. White solid; mp 63–65 °C; R_f 0.56 (80:20 hexane/ethyl acetate); IR (CH_2Cl_2) 1633, 1601, 1585, 1523 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.67 (s, 3H), 2.11 (ddd, J=13.2, 11.1, 7.5 Hz, 1H), 2.37 (ddd, J=1.9, 4.9, 13.2 Hz, 1H), 3.59 (ddd, J=4.9, 7.5, 11.1 Hz, 1H), 3.98 (ddd, J=1.9, 7.5, 7.5 Hz, 1H), 5.64 (s, 1H), 7.05–7.06 (m, 1H), 7.31–7.34 (m, 1H), 7.49–7.52 (m, 1H), 7.76–7.81 (m, 2H), 7.88–7.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 23.4, 40.8, 66.5, 87.4, 96.0, 112.1, 116.2, 122.3, 123.2, 127.3, 128.6, 129.4, 131.4, 131.7, 158.4; EIMS *m/z* 226 (M^+, 100), 195 (57), 181 (60), 171 (20); Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24; Found C, 79.52; H, 6.46.

3.6.7. (±) (7a*S*,10a*R*)-7a-(4-Chlorophenyl)-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan 10d. Gummy colorless oil; R_f 0.48 (15:85 ethyl acetate/hexane); IR (CH_2Cl_2) 3055, 1635, 1603, 1581, 1522, 1493 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.54 (ddd, J=7.3, 11.5, 13.5 Hz, 1H) 2.66 (ddd, J=1.3, 4.8, 13.5 Hz, 1H), 3.74 (ddd, J=4.8, 7.5, 8.0 Hz, 1H), 4.21 (ddd, J=1.3, 7.5, 8.0 Hz, 1H), 5.96 (s, 1H), 7.19–7.21 (m, 1H), 7.32–7.35 (m, 3H), 7.49–7.52 (m, 3H), 7.80–7.83 (m, 2H), 7.86–7.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.3, 67.2, 90.1, 98.4, 111.6, 115.7, 122.3, 123.5, 126.2, 127.5, 128.7, 128.7, 129.8, 131.2, 132.1, 133.6, 140.2, 158.6; EIMS *m/z* 323 (M^+, 100), 292 (97), 171 (40); Anal. Calcd for $C_{20}H_{15}O_2Cl$: C, 74.42; H, 4.68. Found C, 74.53; H, 4.68.

3.6.8. 2-(2-Phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetamide 11. To a stirred solution of acid **4c** (492 mg, 1.62 mmol) in dry CH_2Cl_2 (10 ml) was added thionyl chloride (1 ml). After 4 h the volatiles were removed under a stream of nitrogen. The residue was taken up in dry ether (25 ml), the vessel cooled to −78 °C and dry ammonia was condensed into the vessel for 5 min before the contents of the reaction were allowed to reach room temperature. Saturated NaCl (10 ml) was added to the mixture and the aqueous phase extracted with CH_2Cl_2 (2×20 ml). The organic phase was dried (Na_2SO_4), filtered and the solvent removed in vacuo. Purification by flash chromatography (florisil®, 70:30 CH_2Cl_2/ethyl acetate) gave a cream colored solid (352 mg, 76%); mp 155–158 °C; R_f 0.30 (70:30 CH_2Cl_2/ethyl acetate); IR (CH_2Cl_2) 3510, 3398, 1685, 1633, 1589, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15 (s, 2H), 3.70 (d, J=15.6 Hz, 1H), 3.90 (d, J=15.6 Hz, 1H), 5.28 (br s, 1H), 6.27 (br s, 1H), 7.24–7.57 (m, 9H), 7.75–7.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 42.9, 48.2, 89.9, 111.7, 117.7, 122.8, 123.4, 124.6, 126.9, 127.7, 128.7, 129.5, 129.7, 130.7, 144.1, 155.2, 171.2, (one masked aromatic); EIMS *m/z* 303 (M^+, 21), 278 (13), 244 (100), 215 (14); Anal. Calcd for $C_{20}H_{17}O_2N$: C, 79.19; H, 5.65; N, 4.62; Found C, 78.88; H, 5.75; N, 4.84.

3.6.9. (1-Oxo-2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methyl cyanide 12. Colorless oil; R_f 0.25 (25:75 ethyl acetate/hexane); IR (Nujol) 2258, 1704, 1632, 1586, 1529, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.20 (d, J= 16.8 Hz, 1H), 3.35 (d, J=16.8 Hz, 1H) 7.39–7.54 (m, 5H), 7.68–7.73 (m, 3H), 7.85–7.89 (m, 1H), 8.17–8.22 (m, 1H), 8.64–8.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.6, 87.1, 111.3, 113.5, 114.7, 123.2, 124.6, 125.9, 128.7, 129.0, 129.2, 129.3, 129.8, 130.3, 134.4, 141.2, 174.0, 197.3; EIMS *m/z* 299 (57), 259 (100), 231 (14), 126 (33); HRMS calcd for $C_{20}H_{13}O_2N$: 299.0946; found: 299.0954.

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16. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC (**9b**): 238027, (**9e**): 238026. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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