Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 12621–12628

Preparation of isobenzofurandiones by flash vacuum pyrolysis involving retro-Diels–Alder expulsion of ethylene and concomitant C–O cleavage of methoxy or ethylenedioxy groups

Riskiono Slamet and Dieter Wege*

Chemistry M313, School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia

Received 11 April 2007; revised 18 September 2007; accepted 4 October 2007
Available online 6 October 2007

Abstract—Flash vacuum pyrolysis (fvp) of a number of substrates, prepared by hydrogenating adducts derived from dimethoxy- or ethylenedioxy-substituted benzynes and furan, affords isobenzofurandiones through retro-Diels–Alder expulsion of ethylene and C–O bond cleavage of the methoxy or ethylenedioxy groups. The parent isobenzofuran-4,5-dione is reactive and undergoes two-fold conjugate addition of water to afford 3,4-dihydroxybenzene-1,2-dicarboxaldehyde.

1. Introduction

The chemistry of isobenzofuran **1** (Fig. 1) and its derivatives continues to attract considerable attention.[1,2] The parent compound **1** is highly reactive as it incorporates an *o*-xylylene structural moiety, which makes the system prone to 1,3-addition. The driving force for this is the generation of a benzenoid aromatic ring.[3,4] Various strategies, including the introduction of bulky substituents,[1c,2h] and the annulation of benzene rings to the *e*- and *f*-bonds of the six-membered ring, have been used to attenuate this reactivity; benzo-fusion to the *f*-bond increases the reactivity.[3–5]

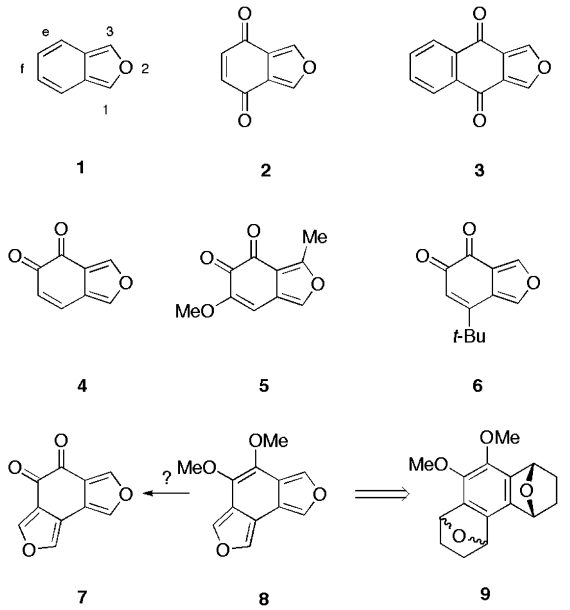


Figure 1. Some isobenzofurandiones and a possible route to **7**.

Isobenzofuran-4,7-dione **2** and isobenzofuran-4,5-dione **4** can be viewed as simple quinonoid derivatives of **1**. The *p*-quinone **2** has been known for some time,[6,7] and the related naphtho[2,3-*c*]furan-4,9-dione ring system **3** is present in a number of natural products.[8] The parent *o*-quinone **4** is currently unknown, but the derivative **5** (albidin, a mould metabolite)[9] and the sterically stabilised 7-*tert*-butylisobenzofuran-4,5-dione **6**[10] have been synthesised.

In an effort to extend the range of *o*-quinones related to isobenzofuran, we wondered if a difuran derivative such as **7** might be accessible through epoxidation and hydrolysis of the double enol ether **8**. This compound in turn should be available by the two-fold retro-Diels–Alder extrusion of ethylene from bridged diepoxide **9** induced by flash vacuum pyrolysis (fvp).[11–14] In this paper we report the results of such a study.

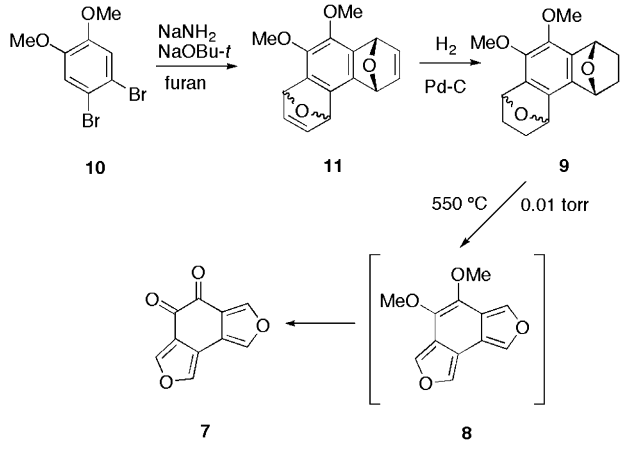
2. Results and discussion

The precursor **9** was prepared as shown in Scheme 1. Treatment of the dibromide **10** with sodium *tert*-butoxide and sodium amide (Caubère's base)[15] in the presence of furan gave

* Corresponding author. Tel.: +61 8 6488 3151; fax: +61 8 6488 1005; e-mail: dw@chem.uwa.edu.au

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.10.020

a mixture of *syn*- and *anti*-9,10-dimethoxy-1,4:5,8-tetrahydro-1,4:5,8-diepoxyphenanthrene (**11**) in 25% yield. Although the dehydrobromination of **10** and subsequent trapping by furan is undoubtedly a step-wise process, the dibromide **10** can be considered to have acted as a 'bisbenzyne' equivalent.[13,16] Hydrogenation of the diepoxytetrahydrophenanthrene **11** over palladium on charcoal then gave **9** in 97% yield.



Scheme 1. Preparation of the dione **7**.

Fvp of **9** at 550 °C/0.01 Torr directly gave yellow crystalline benzo[1,2-*c*:3,4-*c*′]difuran-4,5-dione **7** in 36% yield instead of the expected 4,5-dimethoxybenzo[1,2-*c*:3,4-*c*′]difuran **8** (Scheme 1). The ^{1}H NMR spectrum of the dione **7** showed two doublets at 7.74 and 8.26 ppm with J=1.2 Hz. The signal at 8.26 ppm arises from the 'outer' furyl protons since these possess some of the character of the β proton of an α,β-unsaturated carbonyl system, as well as experiencing *peri*-deshielding from the carbonyl groups (Fig. 2). For comparison, the chemical shifts of the furyl protons of benzo[1,2-*c*:3,4-*c*′]difuran **12**[13] are also shown.

The formation of the *o*-quinone **7** can be rationalised as shown in Scheme 2. Two-fold retro-Diels–Alder extrusion of ethylene from **9** gives compound **8**, which undergoes homolytic C–O cleavage of the methoxy groups to ultimately deliver **7**. The pyrolysis of aromatic methyl ethers in both the liquid and vapour phase is known to give some products derived from initial Me–O bond cleavage.[17–21] For example, the thermolysis of anisole **14** in a flow-system at atmospheric pressure yields phenol **15** (52%) as well as other products (Scheme 2).[17] It should be noted that in this case the reaction temperature is higher and the contact time within the hot zone is considerably greater than in our flash vacuum pyrolysis. However, in the thermolysis of *o*-dimethoxybenzene the *ortho*-methoxy group is known to lower the O–Me

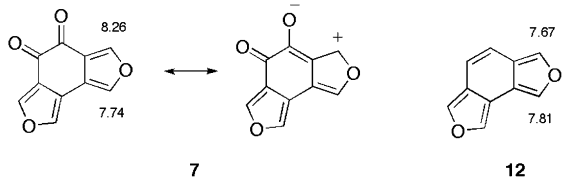
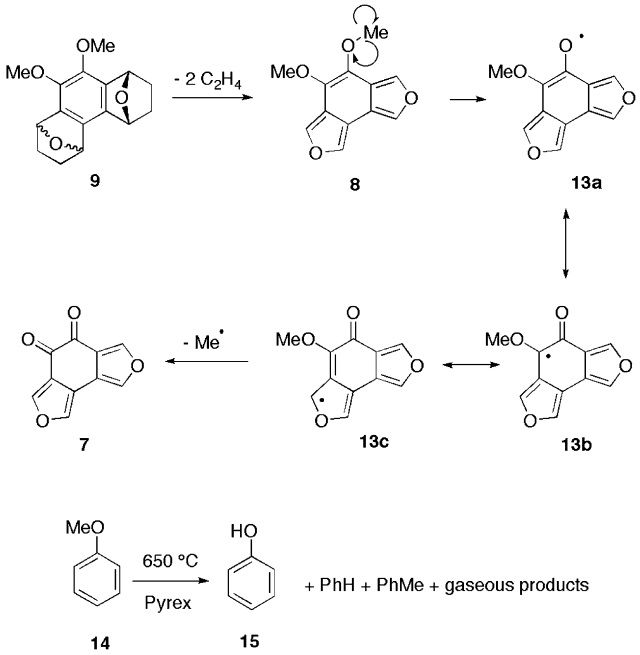


Figure 2. ^{1}H NMR ($CDCl_3$) chemical shifts of dione **7** and difuran **12**.

bond dissociation energy by about 16 kJ mol^{-1} due to additional resonance stabilisation of the phenoxy radical.[19,20] In our system for radical **13** such stabilisation can occur in contributing structures **13b** and **13c** due to electron-donation from the adjacent oxygen atoms. This additional stabilisation will lower the activation energy for Me–O bond cleavage and hence the isolation of **7** rather than **8** in the fvp of **9** under our conditions is not surprising.

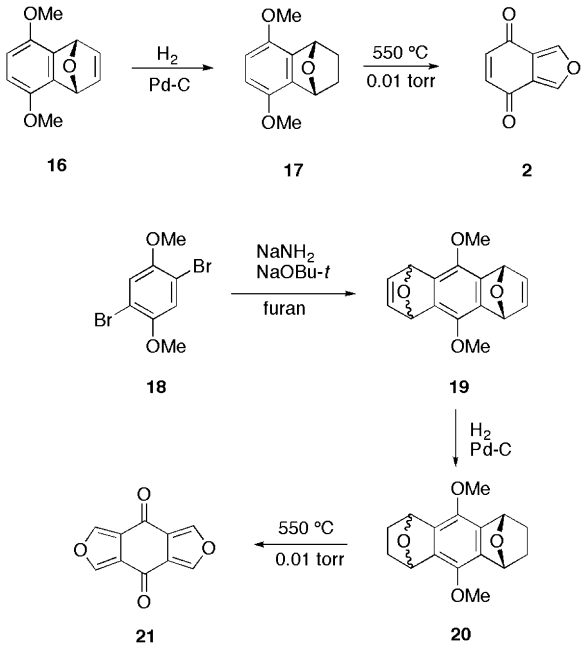


Scheme 2. Pathway for the formation of **7** and some products from the thermolysis of anisole **14**.[17]

If the proposal that the formation of the *o*-quinone **7** involves step-wise Me–O homolysis is correct, then the pyrolytic procedure should also be applicable to the generation of *p*-quinones incorporating an isobenzofuran moiety. This was confirmed by the synthesis of **2** and **21** by fvp of the appropriate precursors **17** and **20** (Scheme 3). We note that a previous approach to the difuran **21** was unsuccessful.[7]

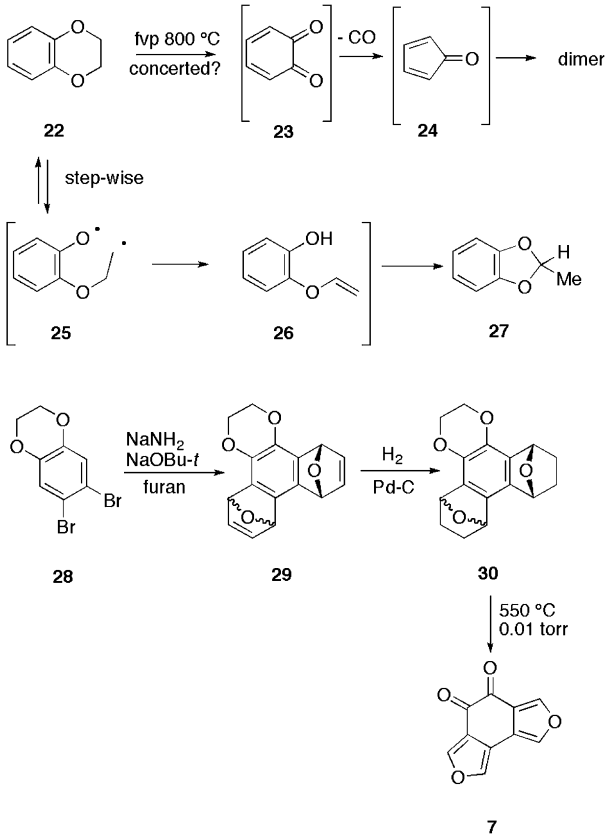
Wiersum has reported that fvp of **22**, the ethylenedioxy derivative of catechol, yields *o*-benzoquinone by loss of ethylene (Scheme 4), although the ultimate product of the reaction is the dimer of cyclopentadienone.[12,22,23] The expulsion of ethylene could be viewed as a concerted retro-Diels–Alder reaction, although Mulder and co-workers have proposed on the basis of kinetic and product studies that the reaction occurs via a step-wise pathway.[20] For example, thermolysis of **22** in the gas phase above 750 K in the presence of propene as a radical trap at atmospheric pressure gave, amongst other products, the dioxole **27**, apparently arising from diradical **25**. Irrespective of the mechanistic details, this led us to examine whether such a reaction would be advantageous for the preparation of isobenzofuran *o*-quinones.

The ethylenedioxy derivative **30** was prepared as shown in Scheme 4. Fvp of **30** afforded the quinone **7** in 63% yield. Although this is better than that observed (36%) in the thermolysis of the dimethoxy derivative **9** under similar



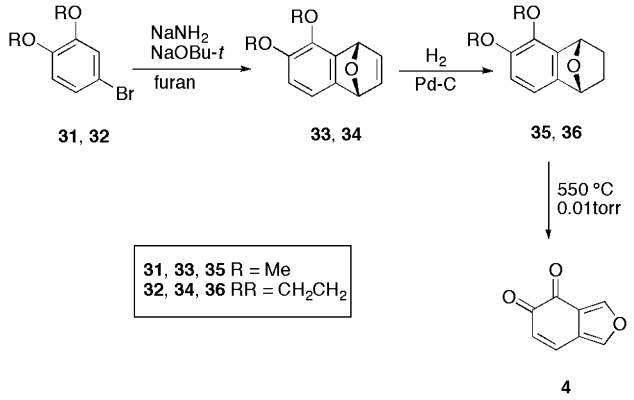
Scheme 3. Preparation of the *p*-quinones **2** and **21** by fvp.

conditions, we do not attach particular significance to this finding as in our experience yields can be variable due to pressure fluctuations or difficulties in vapourising substrates during fvp runs. A systematic study has shown that rigorous control of experimental conditions is often necessary to maximise yields in fvp reactions.[24]



Scheme 4. Some products of the thermolysis of **22**[12,20,22,23] and the preparation of dione **7** by fvp of ethylenedioxy derivative **30**.

Finally, we examined the pyrolytic approach to the synthesis of the parent isobenzofuran-4,5-dione **4** (Scheme 5). Fvp of both the dimethyl ether **35** and the ethylenedioxy derivative **36** provided **4** as a relatively unstable solid. Immediate measurement of the ^{1}H NMR spectrum revealed the chemical shifts and coupling constants shown in Figure 3. In particular, a long-range coupling constant through five bonds of 0.7 Hz was observed between H3 and H7. For comparison, the ^{1}H NMR data for the other known isobenzofuran-4,5-diones **5** and **6** are also shown.



Scheme 5. Formation of the parent isobenzofuran-4,5-dione **4** by fvp of **35** and **36**.

On brief standing, a solution of **4** in $CDCl_3$ developed new signals ascribable to the dihydroxy-dialdehyde **39** and the conversion of **4** into **39** was complete by the time the ^{13}C NMR spectrum was acquired. This conversion arises from a two-fold conjugate addition of water to the furanoid double bonds of **4**, presumably catalysed by traces of acid in the solvent (Scheme 6). This transformation also could be effected by stirring a solution of **4** with dilute hydrochloric acid. Thus the *o*-quinone **4** shows the properties characteristic of *o*- and *p*-quinonemethides (nucleophilic attack at C3 and C1, respectively). In the derivative **6** the bulky *tert*-butyl group provides steric protection against attack at C1, while in the natural product albidin **5** the methyl group hinders approach to C3, and the conjugative effect of the methoxy group reduces the electrophilicity of C1. The latter effect results in a 0.32 ppm upfield shift of the H1 resonance in albidin (7.33 ppm) compared to that within the parent quinone **4** (7.65 ppm).

In summary, we have provided a concise route to the isobenzofurandiones **2**, **4**, **7** and **21** by fvp of the appropriate precursors. There appears to be no significant advantage to the use of ethylenedioxy- over methoxy-substituted derivatives since the loss of ethylene from the former probably is not concerted.[20] Because of the relatively high temperature

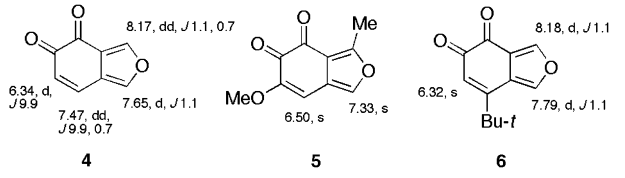
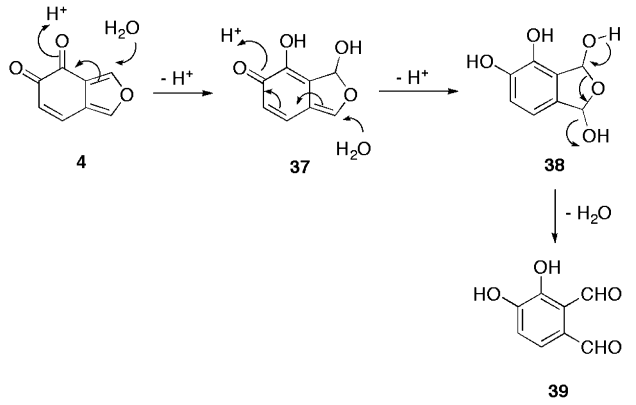


Figure 3. ^{1}H NMR chemical shifts ($CDCl_3$) of the isobenzofuran-4,5-diones **4**–**6**.



Scheme 6. Conversion of dione **4** into the dialdehyde **39**.

required, the pyrolytic route may well be limited to compounds possessing thermally robust substituents. Thus an attempt to prepare 7-*tert*-butylisobenzofuran-4,5-dione **6** (Fig. 1) by fvp of the appropriately *tert*-butyl-substituted dimethoxy derivative yielded a complex mixture, possibly as a result of competing benzylic C–C homolysis within the *tert*-butyl group.

3. Experimental

3.1. General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Microanalyses were performed by M.H.W. Laboratories (Phoenix, Arizona). NMR spectra were measured at 200 MHz (^{1}H) on a Varian Gemini, 300 MHz (^{1}H), 75.5 MHz (^{13}C) on a Bruker AM 300 spectrometer, and at 500 MHz (^{1}H), 126 MHz (^{13}C) on a Bruker ARX 500 spectrometer. ^{13}C assignments were made with the aid of DEPT experiments. Mass spectra were measured on a VG Autospec. mass spectrometer in the EI mode unless stated otherwise. Only molecular ion peaks, and peaks registering above 10% relative abundance in terms are reported. Infrared spectra were recorded using KBr discs with a Bio-Rad FTS45 FTIR spectrophotometer. Electronic spectra were recorded using a Milton Roy Array 3000 Spectrophotometer. Analytical thin layer chromatography (TLC) was carried out using Merck (Art. 554) silica gel 60 F_{254} precoated on aluminium sheets. The spots were first visualised using UV light (254 nm) and then spraying with 6% ceric sulfate in 2 M H_2SO_4 solution and heating for 30 s. Preparative radial chromatography was carried out using a Chromatotron Model 7924T (Harrison Research, Palo Alto, California) with Kieselgel 60 PF_{254} gipshaltig (Merk Art. 7749). Silica gel filtrations were performed using Fluka Kieselgel 60 as adsorbent packed dry under water aspirator vacuum on a sintered glass funnel. In both chromatographic techniques, increasing proportions of ethyl acetate in light petroleum were used as eluting solvents, unless stated otherwise. Fractions were monitored by TLC, and appropriate fractions were combined. Anhydrous tetrahydrofuran was obtained by distillation from benzophenone potassium ketyl. All reactions requiring anhydrous reagents were carried out under an inert atmosphere of nitrogen or argon. Light petroleum refers to the fraction bp 65–70 °C and organic extracts were dried over anhydrous magnesium sulfate. Flash vacuum pyrolysis were carried out by loading the substrate at the sealed end of a silica tube (500×10 mm) and placing the tube horizontally in a Thermolyne 21100 tube having a heating zone of 400 mm. The open end of the tube was connected to the vacuum system and the tube was cooled with solid dry ice near the exit. The substrate was heated slowly using a Kugelrohr oven to effect passage into the hot zone. The time required to vapourise each substrate is given for each fvp experiment.

3.1.1. 9,10-Dimethoxy-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-diepoxyphenanthrene (9). A solution of *tert*-butyl alcohol (5.50 g, 0.074 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise to a stirred suspension of sodium amide (7.87 g, 202 mmol) in anhydrous tetrahydrofuran (10 mL) under an argon atmosphere and was then used directly in the dehydrobromination. To the stirred complex base was added a solution of 1,2-dibromo-4,5-dimethoxybenzene (**10**) (2.00 g, 6.76 mmol) in dry furan (20 mL) and stirring was continued for 1.5 h. The reaction mixture was poured into ice-water and extracted with ether. The ether extract was washed successively with water, brine, dried and evaporated. The residue was submitted to rapid silica filtration. Elution with 5–30% ethyl acetate/light petroleum gave 9,10-dimethoxy-1,4,5,8-tetrahydro-1,4:5,8-diepoxyphenanthrene (**11**) (1.38 g, 75%) as a white crystalline solid, which crystallised from dichloromethane/petrol as prisms, mp 150–153 °C, consisting of one diastereomer on the basis of NMR spectroscopy. MS: *m*/*z* 270 (M, 15%), 269 (93), 244 (28), 227 (22), 213 (49), 199 (100), 183 (48), 171 (25), 153 (34), 139 (29), 127 (30), 115 (17), 102 (17). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 6H, OCH_3), 5.72 (narrow m, 2H, bridgehead), 6.85 (narrow m, 2H, vinyl), 6.97 (narrow m, 2H, vinyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 60.7 (OCH_3), 80.2 (CH), 80.6 (CH), 141.9 (CH), 141.6 (CH), 132.7 (C), 134.2 (C), 143.7 (C). The diepoxy compound **11** (700 mg, 2.59 mmol) in ethyl acetate (50 mL) was stirred with 10% palladium on charcoal (300 mg) under hydrogen until 2 equiv of gas were absorbed. The mixture was filtered through Celite, evaporated and the residue recrystallised from ethyl acetate/light petroleum to give the title compound **9** as colourless crystals (690 mg, 97%) mp 158–159 °C. MS: *m*/*z* 274 (M, 2%), 246 (10), 238 (100), 223 (77), 217 (12), 195 (61), 180 (43), 167 (14), 151 (30), 104 (15). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40–1.47 (m, 4H, CH_2CH_2), 1.98–2.05 (m, 4H, CH_2CH_2), 3.86 (s, 6H, OCH_3), 5.32–5.35 (narrow m, 2H, bridgehead), 5.57–5.59 (narrow m, 2H, bridgehead). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.7 (CH_2), 26.9 (CH_2), 60.7 (OCH_3), 77.0 (CH), 77.2 (CH), 131.9 (C), 135.2 (C), 143.3 (C). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.31, H, 6.43.

3.1.2. Benzo[1,2-*c*:3,4-*c*′] difuran-4,5-dione (7). The diepoxy compound **9** (50 mg, 0.182 mmol) was subjected to flash vacuum pyrolysis (fvp) over 2 h at 550 °C/0.01 Torr. The product was washed from the pyrolysis tube with chloroform and evaporated to give a yellow solid residue. Rapid silica filtration using ethyl acetate/light petroleum (5–30%) gave benzo[1,2-*c*:3,4-*c*′]difuran-4,5-dione (**7**) (14.3 mg, 36%), which was recrystallised from chloroform/light petroleum, mp>230 °C (dec). MS: *m*/*z* 189 (M+1, 10%), 188 (M, 100), 160 (31), 132 (47), 104 (25). ^{1}H NMR (500 MHz,

$CDCl_3$): δ 7.74 (d, *J* 1.2 Hz, 2H, H1, H8), 8.26 (d, *J* 1.2 Hz, H3, H6). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 114.3 (C), 123.0 (C), 138.3 (CH), 149.9 (CH), 176.9 (CO). UV ($CHCl_3$) λ_{max} nm/(log ε) 246 (3.88), 390 (3.31). IR (KBr) ν_{max}/cm^{-1} 3154 m, 3132 m, 2385 w, 2371 w, 1671 s, 1548 s, 1122 s, 1029 s, 867 m, 842 m, 595 m. Anal. Calcd for $C_{10}H_4O_4$: C, 63.83; H, 2.14. Found: C, 64.03; H, 2.14.

3.1.3. 5,8-Dimethoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalene (17). A solution of 5,8-dimethoxy-1,4-dihydro-1,4-epoxynaphthalene (**16**)[7] (250 mg, 1.22 mol) in ethyl acetate (20 mL) was hydrogenated over palladium on charcoal (100 mg) at room temperature. The required volume of hydrogen (28 mL) was absorbed. The catalyst was removed by filtration through Celite and the solution was evaporated to give a colourless oil, which crystallised on cooling. Recrystallisation from dichloromethane/light petroleum gave **17** as colourless prisms (238 mg, 92%), mp 78–79 °C. MS (FAB): *m/z* 208 (M+2, 8%), 207 (M+1, 51), 206 (M, 100), 190 (13), 189 (58), 179 (12), 178 (86), 163 (11.5). ^1H NMR (300 MHz, $CDCl_3$): δ 1.36–1.41 (m, 2H, CH_2CH_2), 2.01–2.06 (m, 2H, CH_2CH_2), 3.79 (s, 6H, OCH_3), 5.56–5.58 (m, 2H, bridgehead), 6.63 (s, 2H, aryl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.0 (CH_2), 56.1 (OCH_3), 77.4 (CH), 110.9 (CH), 134.7 (C), 146.4 (C). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.96; H, 6.86.

3.1.4. Isobenzofuran-4,7-dione (2). 5,8-Dimethoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalene (**17**) (85 mg, 0.41 mmol) was subjected to fvp over 20 min at 550 °C/0.01 Torr. The product was washed from the pyrolysis tube with chloroform. Radial chromatography using ethyl acetate/light petroleum 5–30% afforded the quinone **2** (21 mg, 34%) as brown prisms mp 141–142 °C (lit.[7] mp 140–142 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 6.84 (s, 2H, H5, H6), 8.09 (s, 2H, H1, H3), identical with the reported spectrum.[7]

3.1.5. 5,10-Dimethoxy-1,2,3,4,5,6,7,8,9-octahydro-1,4:5,8-diepoxyanthracene (20). A solution of *tert*-butyl alcohol (22 g, 0.074 mol) in anhydrous tetrahydrofuran (50 mL) was added dropwise to a stirred suspension of sodium amide (31.4 g, 0.806 mol) in anhydrous tetrahydrofuran (50 mL) at room temperature under argon. The complex base mixture was heated at 40–45 °C for 1.5 h and then allowed to cool to room temperature. To the stirred complex base was added a solution of 1,4-dibromo-2,5-dimethoxybenzene (8.0 g, 0.029 mol) in dry furan (80 mL). The stirring was continued overnight and the mixture was poured into ice-water and extracted with ether. The organic layers were washed with water, brine and dried. Evaporation under reduced pressure followed by rapid silica filtration of the residue using 5–40% ethyl acetate/light petroleum gave 9,10-dimethoxy-1,4,5,8-tetrahydro-1,4:5,8-diepoxyanthracene (**19**) as a crystalline solid, which recrystallised from dichloromethane/light petroleum as colourless plates (5.9 g, 54%), mp 209–211 °C (lit.[7] mp 203–223 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 3.84 (s, 6H, OCH_3), 5.84 (s, 4H, bridgehead), 7.04 (s, 4H, vinyl). A solution of **19** (1.00 g, 3.70 mmol) in ethyl acetate (150 mL) was hydrogenated over 10% palladium on charcoal (400 mg) until 2 equiv of gas were absorbed (165 mL). The solution was filtered through Celite. Evaporation under reduced pressure gave a crystalline residue, which was recrystallised from dichloromethane/light petroleum to give the title compound **20** as colourless plates (983 mg, 85%), mp 145–147 °C. MS: *m/z* 274 (M, 28%), 247 (14), 246 (100), 219 (10), 218 (78), 204 (10), 203 (89). ^1H NMR (500 MHz, $CDCl_3$): δ 1.37–1.40 (m, 4H, CH_2CH_2), 2.03–2.04 (m, 4H, CH_2CH_2), 3.88 (s, 6H, OCH_3), 5.57–5.58 (m, 4H, bridgehead). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 26.4 (CH_2), 26.5 (CH_2), 60.0 (CH), 60.1 (CH), 77.0 (OCH_3), 77.2 (OCH_3), 135.5 (C), 135.6 (C), 140.2 (C), 140.3 (C). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.99; H, 6.63.

3.1.6. Benzo[1,2-*c*:4,5-*c*′]difuran-4,8-dione (21). 5,10-Dimethoxy-1,2,3,4,5,6,7,8,9-octahydro-1,4:5,8-diepoxyanthracene (**20**) (50 mg, 0.182 mmol) was subjected to fvp over 2 h at 550 °C/0.01 Torr. The product was washed out with chloroform. Evaporation and recrystallisation from chloroform gave **20** as needles (20 mg, 58%), mp 212 °C (dec). MS: *m/z* 189 (M+1, 11%), 188 (M, 100), 160 (25), 132 (13), 123 (15). ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, furyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 125.3 (C), 145.9 (CH), 175.9 (CO). UV ($CHCl_3$): λ_{max} nm/(log ε) 233 (2.93), 306 (2.76). IR (KBr): ν_{max}/cm^{-1} 3495 s, 3414 s, 2924 w, 2379 w, 2374 w, 1678 s, 1536 m, 1412 w, 1385 m, 1129 m, 1020 w, 557 m, 742 m. Anal. Calcd for $C_{10}H_4O_4$: C, 63.83; H, 2.14. M^+ 188.0113. Found: C, 64.03; H, 2.20. M^+ 188.0109.

3.1.7. 6,7-Dibromo-2,3-dihydro-1,4-benzodioxin (28). To a solution of 2,3-dihydro-1,4-benzodioxin (12.8 g, 0.094 mol) in acetic acid (100 mL) was added dropwise a solution of bromine (9.7 mL, 0.198 mol) in acetic acid (100 mL) with stirring under a nitrogen atmosphere. The mixture was then heated for 4 h at 40–45 °C, poured into water and extracted with ether. The ether extract was washed with sodium hydroxide, water, brine and dried. Evaporation under reduced pressure gave a crystalline residue, which was recrystallised from ethanol to give 6,7-dibromo-2,3-dihydro-1,4-benzodioxin (**28**) (18.9 g, 68%) as colourless needles mp 139–140 °C (lit.[25] mp 138 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 4.24 (s, 4H, OCH_2CH_2O), 7.13 (s, 2H, aryl).

3.1.8. 2,3,5,8,9,12-Hexahydro-5,8:9,12-diepoxyphenanthro[9,10-*b*]-1,4-dioxin (29). A solution of *tert*-butyl alcohol (7.7 mL, 82 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise a stirred suspension of sodium amide (9.57 g, 245 mmol) in anhydrous tetrahydrofuran (30 mL) at room temperature under argon. The mixture was heated at 40–45 °C for 1.5 h and then allowed to cool to room temperature. To the stirred complex base was added a solution of 6,7-dibromo-2,3-dihydro-1,4-benzodioxin (**28**) (2.4 g, 8.16 mmol) in dry furan (50 mL). Stirring was continued for 4 h and then the reaction mixture was poured into ice-water and extracted with ether. The ether layers were washed with water, brine and dried. Evaporation of the solvent under reduced pressure gave a solid product, which was recrystallised from dichloromethane/light petroleum to give the title compound **29** as a mixture of diastereomers (1.1 g, 48%) as colourless plates. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.42; H, 4.70. Radial chromatography of 270 mg of this mixture using dichloromethane/light petroleum 30–90% gave diastereomer A (159 mg,

58%) as the more polar component and diastereomer B (107 mg, 40%) as the less polar component.

Diastereomer A: mp 170–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (s, 4H, OCH_2CH_2O), 5.70 (dd, *J* 1.8, 0.8 Hz, 2H, bridgehead), 5.75 (dd, *J* 1.8, 0.8 Hz, 2H, bridgehead), 6.84 (dd, *J* 5.6, 1.8 Hz, 2H, vinyl), 6.96 (dd, *J* 5.6, 1.8 Hz, 2H, vinyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 64.4 (CH_2), 79.3 (CH), 80.6 (CH), 130.3 (C), 133.3 (C), 136.4 (C), 142.0 (CH), 142.3 (CH).

Diastereomer B: mp 139–141 °C. MS *m/z* 268 (M, 100%), 242 (42), 239 (14), 216 (48), 214 (42), 212 (88), 211 (60), 188 (14), 158 (50), 156 (43), 155 (54), 128 (50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (s, 4H, OCH_2CH_2O), 5.65–5.66 (narrow m, 2H, bridgehead), 5.77–5.79 (narrow m, 2H, bridgehead), 6.93–6.98 (narrow m, 4H, vinyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 64.4 (CH_2), 79.5 (CH), 80.5 (CH), 130.0 (C), 133.7 (C), 136.5 (C), 141.7 (CH), 141.9 (CH).

3.1.9. 2,3,5,6,7,8,9,10,11,12-Decahydro-5,8:9,12-diepoxyphenanthro[9,10-*b*]-1,4-dioxin (30). A mixture of diastereomers of 2,3,5,8,9,12-hexahydro-5,8:9,12-diepoxyphenanthro-[9,10-*b*]-1,4-dioxin (**29**) (377 mg, 1.41 mmol) in ethyl acetate (100 mL) was stirred with 10% palladium on charcoal (150 mg) under hydrogen until 2 equiv of gas (63 mL) were absorbed. The mixture was filtered through the Celite, evaporated and the residue was recrystallised from dichloromethane/light petroleum to give the title compound **30** as colourless plates (367 mg, 96%), mp 200–203 °C. MS: *m/z* 272 (M, 13%), 244 (39), 217 (14), 216 (100), 188 (20), 160 (13). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35–1.46 (m, 4H, CH_2CH_2), 1.95–2.03 (m, 4H, CH_2CH_2), 4.23 and 4.24 (2×s, 4H, OCH_2CH_2O), 5.33–5.36 (m, 2H, bridgehead), 5.46–5.49 (m, 2H, bridgehead). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.3 (CH_2), 26.8 (CH_2), 64.5 (CH_2), 76.1 (CH), 76.4 (CH), 77.4 (CH), 77.5 (CH), 129.7 (C), 129.9 (C), 131.2 (C), 131.4 (C), 135.4 (C), 175.5 (C). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.37; H, 5.86.

3.1.10. Benzo[1,2-*c*:3,4-*c*′]difuran-4,5-dione (7). 2,3,5,6,7,8,9,10,11,12-Decahydro-5,8:9,12-diepoxyphenanthro[9,10-*b*]-1,4-dioxin (**30**) (57 mg, 0.21 mmol) was subjected to fvp over 2 h at 550 °C/0.01 Torr. The product was washed out with chloroform. Evaporation and rapid silica filtration using ethyl acetate/light petroleum (5–30%) gave the quinone **7** (25 mg, 63%), spectroscopically identical to the material prepared earlier.

3.1.11. 4-Bromo-1,2-dimethoxybenzene (31). Bromine (3.3 mL, 0.065 mmol) in acetic acid (50 mL) was added dropwise with stirring over 2 h to 1,2-dimethoxybenzene (9.0 g, 0.065 mmol) in acetic acid (20 mL) under nitrogen atmosphere at 5–10 °C. The mixture was kept at this temperature for 30 min and then overnight at room temperature, poured into water and extracted with light petroleum. The extract was washed with aqueous sodium hydroxide and then successively with water and brine. The dried solution was evaporated and distilled under reduced pressure to give **31** as a colourless oil (5.28 g, 63.8%), bp 100–104 °C/0.8 Torr (lit.[26] bp 69–70 °C/0.04 Torr). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.69 (d, *J* 8.8 Hz, 1H, H6), 6.93–7.01 (m, 2H, H3 and H5).

3.1.12. 5,6-Dimethoxy-1,4-dihydro-1,4-epoxynaphthalene (33). A solution of *tert*-butyl alcohol (6.5 mL, 0.069 mol) in anhydrous tetrahydrofuran (15 mL) was added dropwise to a stirred suspension of sodium amide (8.1 g, 0.21 mol) in anhydrous tetrahydrofuran (15 mL) under an argon atmosphere. To the complex base was added a solution of 4-bromo-1,2-dimethoxybenzene (**31**) (3.0 g, 0.016 mol) in dry furan (30 mL). Stirring was continued overnight, after which the reaction mixture was poured into ice-water and extracted with ether. The ether extracts were washed successively with water and brine. Evaporation of the dried extract under reduced pressure followed by rapid silica filtration using 3–25% ethyl acetate/light petroleum gave the adduct **33** as colourless prisms (1.08 g, 33%) mp 92–93 °C.

MS: *m/z* 205 (M+1, 14%), 204 (M, 100), 189 (62), 172 (13), 161 (30), 146 (12), 143 (17), 133 (12), 118 (13), 115 (23), 102 (13). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.62 (m, 1H, bridgehead), 6.02 (m, 1H, bridgehead), 6.40 (d, *J* 7.6 Hz, 1H, aryl), 6.83 (d, *J* 7.6 Hz, 1H, aryl), 6.98 (narrow, m, 2H, vinyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.2 (OCH_3), 60.4 (OCH_3), 81.2 (CH), 81.9 (CH), 107.2 (CH), 114.4 (CH), 136.6 (C), 141.4 (C), 141.7 (CH), 143.0 (CH), 143.8 (C), 149.7 (C). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.71; H, 6.05.

3.1.13. 5,6-Dimethoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalene (35). A solution of **33** (300 mg, 1.47 mmol) in ethyl acetate (50 mL) was hydrogenated over 10% palladium on charcoal (100 mg) at room temperature and pressure until the required volume of hydrogen (33 mL) had been absorbed. The catalyst was removed by filtration through Celite and the solution was evaporated under reduced pressure to give a colourless crystalline solid, which recrystallised from dichloromethane/light petroleum to give **35** (291 mg, 96%), mp 52–53 °C. MS: *m/z* 206 (M, 16%), 188 (20), 179 (11), 178 (100), 173 (14), 167 (13), 163 (53), 149 (51), 145 (11), 127 (11). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38–1.47 (m, 2H, CH_2CH_2), 2.03–2.06 (m, 2H, CH_2CH_2), 3.83 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.32–5.33 (br d, *J* 4.3 Hz, 1H, bridgehead), 5.69–5.70 (br d, *J* 4.3 Hz, 1H, bridgehead), 6.65 (d, *J* 7.8 Hz, 1H aryl), 6.83 (d, *J* 7.8 Hz, 1H, aryl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.0 (CH_2), 27.2 (CH_2), 56.3 (OCH_3), 60.3 (OCH_3), 77.6 (CH), 78.7 (CH), 110.1 (CH), 112.8 (CH), 135.3 (C), 139.8 (C), 141.9 (C), 150.5 (C). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.96; H, 6.86.

3.1.14. 6-Bromo-2,3-dihydro-1,4-benzodioxin (32). To a solution of 2,3-dihydro-1,4-benzodioxin (33.5 g, 0.246 mol) in acetic acid (100 mL) was added dropwise a solution of bromine (13 mL, 0.246 mol) in acetic acid (100 mL) with stirring under a nitrogen atmosphere. The mixture was then heated for 1.5 days at 40–45 °C and then poured into water and extracted with ether. The ether extract was washed with 5% sodium hydroxide, water, brine and dried. Evaporation under reduced pressure followed by distillation gave **32** as colourless oil (44.3 g, 87%), bp 115–120 °C/0.5 Torr (lit.[25] bp 275–276 °C/754 Torr). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.23 (s, 4H, OCH_2CH_2O), 6.71–7.02 (m, 3H, aryl).

3.1.15. 2,3,5,8-Tetrahydro-5,8-epoxynaphtho[1,2-*b*]-1,4-dioxin (34). A solution of *tert*-butyl alcohol (20 mL, 0.21 mol) in anhydrous tetrahydrofuran (50 mL) was added dropwise to a stirred suspension of sodium amide (24.5 g, 0.63 mol) in anhydrous tetrahydrofuran (50 mL) under an argon atmosphere. The complex base was heated at 40–45 °C for 1.5 h and then cooled to room temperature. To the stirred mixture was added a solution of 6-bromo-2,3-dihydro-1,4-benzodioxin (**32**) (9.0 g, 0.04 mol) in dry furan (100 mL). Stirring was continued for 0.5 h (TLC monitoring) and then the reaction mixture was poured into ice-water (400 mL) and extracted with dichloromethane (3×150 mL). The combined extracts were washed with water, brine and dried. The solvent was evaporated under reduced pressure and the residue was submitted to rapid silica filtration using 3–10% ethyl acetate/light petroleum to give the title compound **34** as a colourless oil (6.25 g, 74%), bp 150–160 °C/0.7 Torr (Kugelrohr). MS (FAB): *m*/*z* 203 (M+1, 100%), 202 (80), 201 (14), 192 (13). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22–4.27 (m, 4H, OCH_2CH_2O), 5.64–5.65 (narrow m, 2H, bridgehead), 6.45 (d, *J* 7.5 Hz, 1H, aryl), 6.74 (dd, *J* 7.5, 0.6 Hz, 1H, aryl), 7.03–7.04 (narrow m, 2H, vinyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 64.3 (CH_2), 64.5 (CH_2), 79.8 (CH), 82.4 (CH), 112.7 (CH), 113.4 (CH), 135.7 (C), 138.4 (C), 142.3 (CH), 142.4 (C), 142.7 (C), 143.4 (CH). Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.11; H, 5.00.

3.1.16. 2,3,5,6,7,8-Hexahydro-5,8-epoxynaphtho[1,2-*b*]-1,4-dioxin (36). A solution of 2,3,5,8-tetrahydro-5,8-epoxynaphtho[1,2-*b*]-1,4-dioxin (**34**) (306 mg, 1.57 mol) in methanol (100 mL) was flushed with argon and 10% palladium on charcoal (100 mg) was added. The mixture was stirred under hydrogen until 1 molar equivalent was absorbed. The solution was filtered through Celite and evaporated under reduced pressure to give a crystalline residue, which was recrystallised from ether/light petroleum to give **36** as colourless plates (298 mg, 96%), mp 84–86 °C. MS: *m*/*z* 204 (M, 5%), 186 (70), 131 (15), 130 (100), 120 (16), 102 (39). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32–1.47 (2H, CH_2CH_2), 1.96–2.20 (m, 2H, CH_2CH_2), 4.20–4.29 (m, 4H, OCH_2CH_2O), 5.31–5.32 (m, 1H, bridgehead), 5.52–5.54 (m, 1H, bridgehead), 6.62–6.74 (m, 2H, aryl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.1 (CH_2), 26.8 (CH_2), 64.2 (CH_2), 64.5 (CH_2), 76.4 (CH), 78.9 (CH), 111.4 (CH), 115.1 (CH), 132.9 (C), 136.6 (C), 139.8 (C), 142.6 (C). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.72; H, 6.10.

3.1.17. Isobenzofuran-4,5-dione (4)

(a) The epoxy compound **35** (99.3 mg, 0.481 mmol) was subjected to fvp at 550 °C/0.01 Torr over 2 h. The yellow product was dissolved in dichloromethane, filtered through a small plug of cotton wool and the solution concentrated by bubbling argon through it. Addition of light petroleum gave **4** as a yellow solid (62 mg, 87%), mp>300 °C due to decomposition during heating. The compound decomposed on standing. HRMS Calcd for $C_8H_4O_3$ M^+: 148.0160. Found M^+: 148.0158. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.34 (d, *J* 9.9 Hz, 1H, H6), 7.47 (dd, *J* 9.9, 0.7 Hz, 1H, H7), 7.65 (d, *J* 1.1 Hz, 1H, H1), 8.17 (dd, *J* 1.1, 0.7 Hz, 1H, H3). After ca. 3 h at room temperature the sample was shown by ^{1}H NMR analysis to consist of **4** (33%) and 3,4-dihydroxybenzene-1,2-dicarboxaldehyde (**39**) (67%). After 5 h the ^{13}C NMR spectrum was identical to that of dialdehyde **39** (see below).

(b) 2,3,5,6,7,8-Hexahydro-5,8-epoxynaphtho[1,2-*b*]-1,4-dioxin (**36**) (103 mg, 0.50 mmol) was subjected to fvp at 550 °C/0.01 Torr over 2 h. The yellow product was dissolved in dichloromethane. Evaporation under reduced pressure gave the crude product, which was subjected to rapid radial chromatography using 3–10% ethyl acetate/light petroleum to give **4** (54 mg, 72%).

3.1.18. 3,4-Dihydroxybenzene-1,2-dicarboxaldehyde (39) by acid-catalysed hydrolysis of isobenzofuran-4,5-dione (4). To a solution of freshly prepared isobenzofuran-4,5-dione (**4**) (37 mg, 0.25 mmol) in dichloromethane (5 mL) was added 3 drops aqueous 2 M hydrochloric acid and the mixture was stirred under argon for 2 days, during which the solution changed from yellow to colourless. The mixture was diluted with dichloromethane (10 mL), washed with water, brine and dried. Evaporation gave 3,4-dihydroxybenzene-1,2-dicarboxaldehyde (**39**) (39 mg, 94%) as colourless prisms, mp 152 °C (dec) after recrystallised from ether/light petroleum. MS: *m*/*z* 166 (M, 72%), 138 (31), 137 (100), 109 (27), 92 (11), 81 (23). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41 (br s, 1H, OH), 7.27 (d, *J* 8.1 Hz, 1H, aryl), 7.40 (d, *J* 8.1 Hz, 1H, aryl), 9.94 (s, 1H, CHO), 11.03 (s, 1H, CHO), 12.75 (br s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 117.4 (C), 118.7 (CH), 128.5 (C), 130.3 (CH), 150.4 (C), 151.0 (C), 192.0 (CHO), 198.3 (CHO). IR (KBr): ν_{max}/cm^{-1} 3999 br, 2373 w, 2341 w, 1664 s, 1642 m, 1574 m, 1446 m, 1392 m, 1302 m, 1214 m, 1012 m, 1001 m. HRMS Calcd for $C_8H_6O_4$ M^+: 166.0266. Found M^+: 166.0265.

References and notes

1. (a) For selected reviews see: Steel, P. G. *Science of Synthesis*; Thomas, J., Ed.; Thieme: Stuttgart, 2001; Vol. 10, p 87; (b) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1999**, *73*, 1; (c) Wege, D. *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich and London, 1998; Vol. 4, p 1; (d) Friedrichsen, W. *Methoden der Organischen Chemie*; Kreher, R., Ed.; Thieme: Stuttgart, 1994; Vol. E6b, p 163; (e) Rickborn, B. *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich and London, 1989; Vol. 1, p 1; (f) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093.
2. Some recent studies: (a) Rainbolt, J. E.; Miller, G. P. *J. Org. Chem.* **2007**, *72*, 3020; (b) Sander, M.; Jarrosson, T.; Chuang, S.-C.; Khan, S. I.; Ruben, Y. *J. Org. Chem.* **2007**, *72*, 2724; (c) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 12376; (d) Sygula, A.; Sygula, R.; Rabideau, P. W. *Org. Lett.* **2006**, *8*, 5909; (e) Chen, Y.-L.; Hau, C.-K.; Wang, H.; He, H.; Wong, M.-S.; Lee, A. W. M. *J. Org. Chem.* **2006**, *71*, 3512; (f) Nair, V.; Abhilash, K. G. *Synthesis* **2005**, 1967; (g) Payne, A. D.; Wege, D. *Org. Biomol. Chem.* **2003**, *1*, 383; (h) Siu-Hin, C.; Chung-Yan, Y.; Wong, H. N. C. *Tetrahedron* **2002**, *58*, 9413.
3. Moursounidis, J.; Wege, D. *Aust. J. Chem.* **1988**, *41*, 235.
4. Margetic, D.; Warrener, R. N.; Dibble, P. W. *J. Mol. Model.* **2004**, *10*, 87.

5. Tu, N. P. W.; Yip, J. C.; Dibble, P. W. *Synthesis* **1996**, 77.
6. Fumagalli, S. E.; Eugster, C. H. *Helv. Chim. Acta* **1971**, *54*, 959.
7. Cragg, G. L.; Giles, R. G. F.; Roos, G. H. P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1339.
8. Review: Piggott, M. J. *Tetrahedron* **2005**, *61*, 9929.
9. Structural elucidation: Grove, J. F.; Hitchcock, P. B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1145; synthesis: Tennant, S.; Wege, D. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2089.
10. Sims, C. G.; Wege, D. *Aust. J. Chem.* **1992**, *45*, 1983.
11. Wiersum, U. E.; Mijs, W. J. *J. Chem. Soc., Chem. Commun.* **1972**, 347.
12. Wiersum, U. E. *Aldrichimica Acta* **1981**, *14*, 53.
13. Stringer, M. B.; Wege, D. *Tetrahedron Lett.* **1980**, *21*, 3831.
14. Wiersum, U. E. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 365.
15. (a) Caubère, P.; Loubinoux, B. *Bull. Soc. Chim. Fr.* **1968**, 3857; (b) Caubère, P. *Acc. Chem. Res.* **1974**, *7*, 301.
16. Shahlai, K.; Acquaah, S. O.; Hart, H. *Org. Synth.* **1998**, *75*, 201.
17. Freidlin, L. Kh.; Balandin, A. A.; Nazarova, N. M. *Izvest. Akad. Nauk. SSSR, Otdel. Khim. Nauk.* **1949**, *1*, 102; *Chem. Abstr.* **1949**, *43*, 5758i.
18. Harrison, A. G.; Honnen, L. A.; Dauben, H. J., Jr.; Lossing, F. P. *J. Am. Chem. Soc.* **1960**, *82*, 5593.
19. Suryan, M. M.; Kafafi, S. A.; Stein, S. E. *J. Am. Chem. Soc.* **1989**, *111*, 1423.
20. Schraa, G.-J.; Arends, I. W. C.; Mulder, P. *J. Chem. Soc., Perkin Trans. 2* **1994**, 189.
21. Britt, P. F.; Buchanan, A. C., III; Cooney, M. J.; Martineau, D. R. *J. Org. Chem.* **2000**, *65*, 1376.
22. Wiersum, U. E. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 317.
23. Hageman, H. J.; Wiersum, U. E. *Chem. Ber.* **1973**, *9*, 206.
24. Duffy, E. F.; Foot, J. S.; McNab, H. M.; Milligan, A. A. *Org. Biomol. Chem.* **2004**, *2*, 2677.
25. Ghosh, B. N. *J. Chem. Soc.* **1915**, *107*, 1588.
26. Bruce, J. M. *J. Chem. Soc.* **1959**, 2366.