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The synthesis of 3-hydroxymethylfuro[3,2-*b*]naphtho[2,3-*d*]furan-5,10-dione, a novel metabolite isolated from *Crescentia cujete*

Linda B. Nielsen, Riskiono Slamet, Dieter Wege *

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

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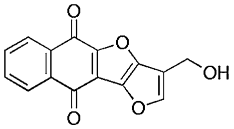
ABSTRACT

The title natural product **1**, which possesses a new ring skeleton, has been synthesised by a sequence in which the key steps involve a tandem intramolecular Diels–Alder/reverse Diels–Alder reaction sequence. Thus 3-(2-furyl)-1,4-dimethoxynaphthalen-2-ol was treated with ethyl 3-bromopropiolate, and without isolation, the resulting acetylenic ether was heated in the presence of 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine. Intramolecular addition of the pendant acetylenic chain to the furan ring followed by cycloaddition of the electron-deficient tetrazine and subsequent cycloreversion delivered ethyl 5,10-dimethoxyfuro[3,2-*b*]naphtho[2,3-*d*]furan-3-carboxylate, which has the ring system of the natural product. Functional group manipulation then provided **1**.

1. Introduction

The common tropical American tree *Crescentia cujete* has been an important source of folk medicine across Central America, the northern half of South America and the Caribbean,[1] with both extracts and pulp of the seeds, fruit, leaves and flowers being used to treat a variety of ailments. These include colds and other respiratory illnesses,[2–4] hypertension[5] and the haemorrhagic effect of venomous snake bites.[6] Like many other plant species used in traditional medicine, *C. cujete* has also attracted increasing interest as a source of novel and biologically active compounds, which could provide possible lead structures in the development of new pharmaceuticals.[7–10]

During an investigation into potentially useful anticancer agents from the wood of *C. cujete*, Kingston and co-workers isolated a series of nine related furo[*b*]-fused naphthoquinone derivatives.[7,8] Of particular interest are two tetracyclic naphthoquinones, which were isolated as red pigments and assigned structures 3-hydroxymethylfuro[3,2-*b*]naphtho[2,3-*d*]furan-5,10-dione (**1**) and 9-hydroxy-3-hydroxymethylfuro[3,2-*b*]naphtho[2,3-*d*]furan-5,10-dione (**2**) (Fig. 1) on the basis of extensive spectroscopic analysis.[7] Both compounds were found to be cytotoxic and **1** exhibited selective DNA-damaging activity in an assay involving a DNA repair-deficient strain of yeast,[7] suggesting that **1** may be useful in the development of new antitumour drugs. Kingston and co-workers have also noted that the planar structure of naphthoquinones **1** and **2** means that intercalation into DNA is likely to contribute to their mode of action for DNA damage.[11]



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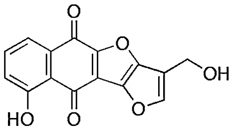

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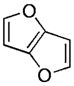
Figure 1. Two novel furo[3,2-*b*]naphtho[2,3-*d*]furan-5,10-diones isolated from *C. cujete*.[7]

As well as having potentially useful biological activity, naphthoquinones **1** and **2** are interesting in terms of their structure. The tetracyclic ring system, composed of a naphthoquinone ring fused to a fully aromatic furo[3,2-*b*]furan moiety, represents a new natural product skeleton. Synthetic compounds incorporating a fully aromatic furo[3,2-*b*]furan ring are also rare. The parent furo[3,2-*b*]furan (**3**) (Fig. 2) has not been synthesised to date, although it has been included in a number of computational studies on fused heterocycles.[12–15] Similarly, the benzo-fused and naphtho-fused compounds **4** and **5** have not been prepared. Only two reports



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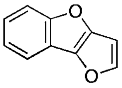

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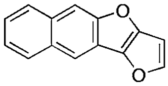

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Figure 2. Unknown parent compounds containing the furo[3,2-*b*]furan ring system.

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* Corresponding author. Fax: +61 8 6488 1005.
E-mail address: dwege@cyllene.uwa.edu.au (D. Wege).

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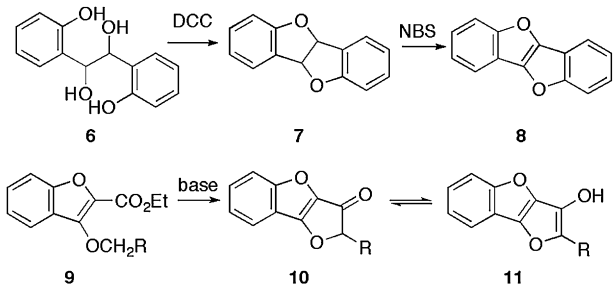
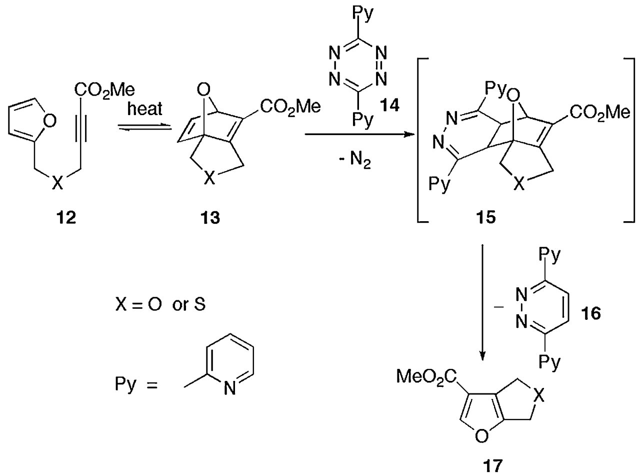
describing the preparation of several related benzo-fused derivatives have appeared.

Tolmach and co-workers have synthesised benzofuro[3,2-*b*]benzofuran (**8**) from 'hydrosalicyloin' **6** according to the route in Scheme 1.[16] The fused furofuran framework was constructed in the first step by a simple dehydrative cyclisation of **6** with dicyclohexylcarbodiimide (DCC). The resulting dihydro compound **7** was then treated with *N*-bromosuccinimide (NBS), which delivered the fully aromatic compound **8** via a bromination–dehydrobromination sequence in 32% yield. Vaidya and Agasimundin have achieved the synthesis of three related benzofuro[3,2-*b*]furan derivatives **10**/**11** via Dieckmann condensation of benzofuran **9**.[17] A positive ferric chloride colour test suggests that these compounds exist at least partially in the enol form **11**.



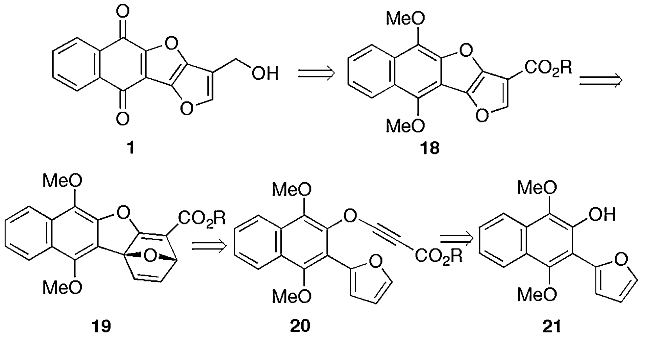
Scheme 1. Preparation of benzofuro[3,2-*b*]benzofuran (**8**)[16] and the benzofuro[3,2-*b*]furan derivatives **10**/**11**.[17]

In examining possible synthetic approaches to 3-hydroxymethylfuro[3,2-*b*]naphtho[2,3-*d*]furan-5,10-dione (**1**), we decided to adapt a pathway previously used in our laboratory to construct a number of thieno[3,4-*b*]furan and furo[3,4-*b*]furan derivatives by means of a tandem intramolecular Diels–Alder/retro Diels–Alder reaction sequence (Scheme 2).[18,19]



Scheme 2. Preparation of the thieno[3,4-*b*]furan and furo[3,4-*b*]furan derivatives **17**.[18,19]

When furans of general structure **12** possessing a pendant acetylenic ester moiety are heated in the presence of 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**14**), the intramolecular Diels–Alder adduct **13** is intercepted by the electron-deficient diene **14**. Loss of dinitrogen gives **15**, which undergoes cycloreversion to deliver **17**. Extension of this concept suggests that compound **20** would serve as a suitable precursor to the natural product **1** (Scheme 3), and this forms the basis of the work outlined in the current paper.



Scheme 3. Retrosynthetic analysis for the synthesis of **1**.

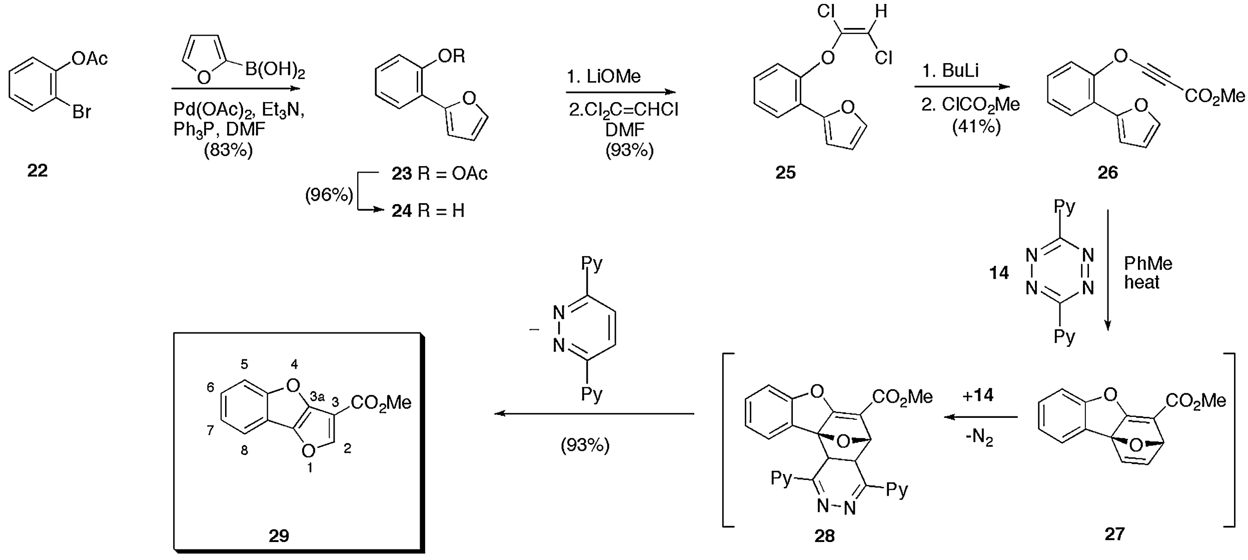
2. Results and discussion

Before embarking on the synthesis of the naphthalene derivative **20**, we investigated a simpler model system (Scheme 4). Treatment of 2-bromophenyl acetate (**22**) with 2-furanylboronic acid in the presence of $Pd(OAc)_2$ and PPh_3 gave the coupled product **23**, which on hydrolysis afforded 2-(2-furyl)phenol (**24**) in good overall yield. The reaction of the lithium salt of **24** with trichloroethylene in DMF[20] then provided the dichlorovinyl ether **25**. Treatment of **25** with 2 equiv of BuLi followed by addition of methyl chloroformate gave the acetylenic ester **26**.[21–23] When the latter was heated in refluxing toluene in the presence of 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**14**), the desired methyl furo[3,2-*b*]benzofuran-3-carboxylate (**29**) was isolated in 93% yield after simple chromatographic separation. This product had the expected spectroscopic properties and the carbon and proton resonances in the NMR spectra were assigned with the aid of 2D experiments (see Experimental).

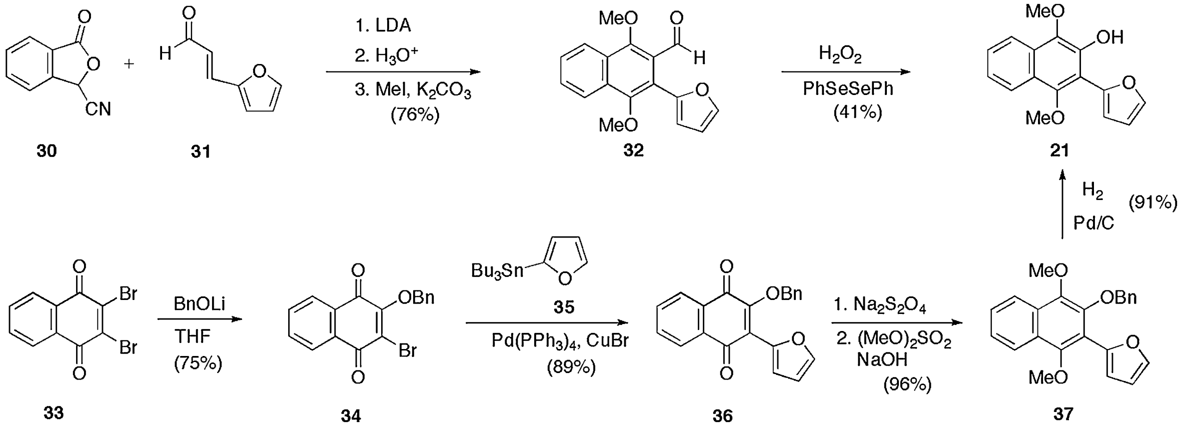
On the basis of these successful model reactions, attention was directed to the preparation of furyl-substituted naphthol **21** required for the synthesis of the natural product **1**. Our initial approach involved a Hauser–Kraus annulation,[24] as this would conceivably also permit the synthesis of the hydroxy-substituted derivative **2**. Thus addition of the anion derived from the cyanophthalide **30** to 3-(2-furyl)acrolein (**31**) followed by acidification and methylation provided the naphthaldehyde **32** in good yield (Scheme 5). However, the Baeyer–Villiger oxidation of **32** to give the naphthol **21** was not straightforward, presumably due to the presence of the electron-rich naphthalene and furan rings. The use of *m*-chloroperoxybenzoic acid afforded complex mixtures, but the action of hydrogen peroxide in the presence of diphenyl selenide[25] followed by hydrolysis gave **21** in modest yield.

A better route to **21** proceeded as follows. Treatment of 2,3-dibromonaphthoquinone (**33**) with 1 equiv of the lithium salt of benzyl alcohol in THF gave the benzyl ether **34** (Scheme 5). Stille coupling with 2-(tri-*n*-butylstannyl)furan (**35**) provided **36**, which was reduced and methylated to afford **37**. Finally, hydrogenolysis of the benzyl group gave **21**.

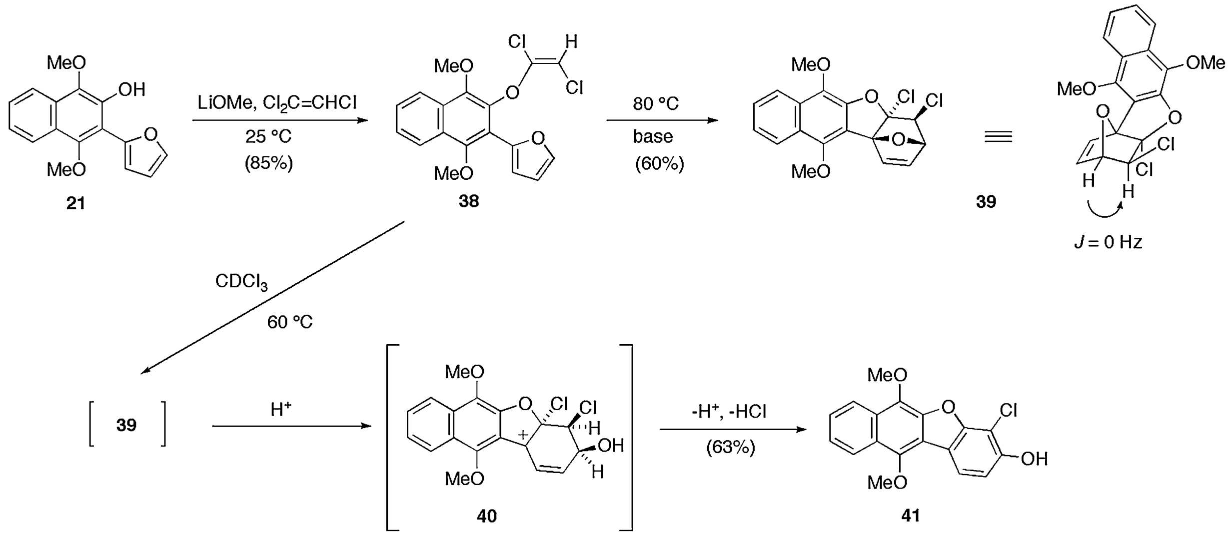
The preparation of the dichlorovinyl ether **38** was attempted under conditions used for the formation of the model compound **25** by treatment of the lithium salt of naphthol **21** with trichloroethylene in DMF at 80 °C. This afforded compound **39**, the intramolecular Diels–Alder adduct of **38** (Scheme 6). The structure of **39** was apparent from its spectroscopic properties, and the *exo*-orientation of the chloro substituent at C4 follows from the ^1H NMR spectrum, in which there is an absence of significant coupling between H4 and the bridgehead proton H3 within the 7-oxabicyclo[2.2.1]heptenyl moiety. The desired dichlorovinyl ether **38** could be obtained satisfactorily by carrying out the reaction at room temperature.



Scheme 4. Synthesis of the model compound **29**.



Scheme 5. Synthesis of the naphthol **21**.

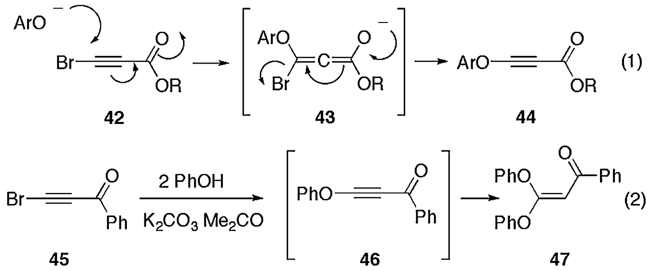


Scheme 6. Intramolecular Diels–Alder reaction of the dichlorovinyl ether **38**.

When the dichlorovinyl ether **38** was heated in $CDCl_3$ at 60 °C, adduct **39** was not detected and the ring-opened product **41** was formed instead, clearly as a result of acid-catalysed cleavage of the epoxy bridge within the strained ring system of **39** (Scheme 6).

With the appropriately substituted dichlorovinyl ether **38** in hand, we next attempted the construction of the acetylenic ester of general structure **20** required for the projected synthesis of **1** depicted in Scheme 3. Compound **38** was treated sequentially with BuLi and methyl or ethyl chloroformate under conditions, which were successful for the preparation of the model acetylenic ester **26** (Scheme 4). This gave a complex mixture from which no pure product could be isolated. The reaction was examined under various reaction conditions,[21,22] with similar outcomes. On some occasions evidence was obtained for competitive metallation and electrophilic capture at the α-position of the furan ring. The presence of the methoxy groups in **38** could also activate the *peri*-positions in the naphthalene system towards metallation, a feature not present in the model system. Because of this disappointing outcome, we reluctantly abandoned this approach to **20**.

In view of the ready availability of the bromopropiolates **42**,[26] we wondered whether the desired acetylenic ester **44** could be obtained by the simple substitution reaction as shown in (1) in Scheme 7. Such an approach to esters of this type does not appear to have been investigated before, presumably because of the high reactivity of the product towards further nucleophilic addition. For example, the acetylenic ether **46** resulting from the base-catalysed reaction of phenol and the bromoacetylenic ketone **45** was too reactive to be isolated and underwent further nucleophilic addition to deliver the ethylenic ether **47** in high yield.[27] However, we felt that this approach was worth examining since the pendant furan ring within **20** could potentially intercept the reactive alkyne moiety in competition with further nucleophilic addition.



Scheme 7. (1) A possible approach to compounds of structure **44** and (2) further nucleophilic addition to such activated alkynes.[27]

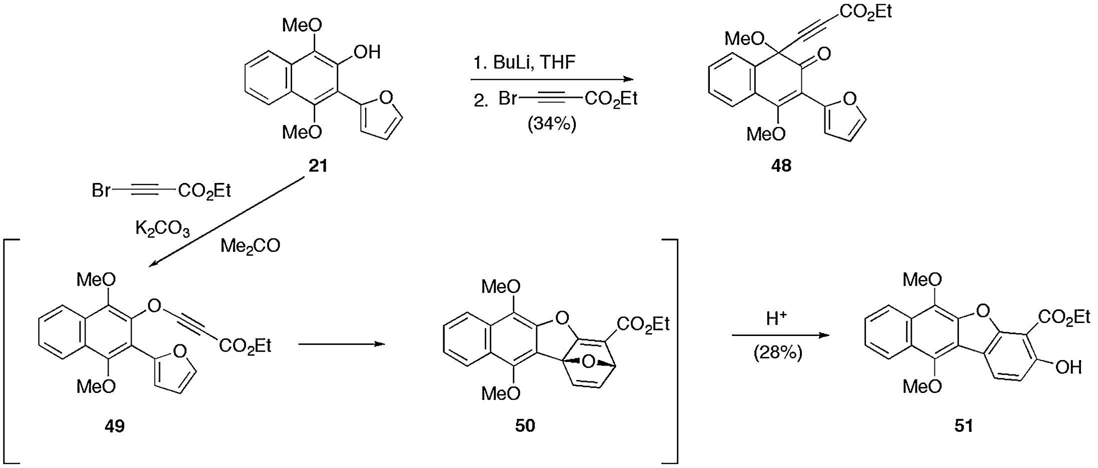
In an initial experiment, the lithium salt of **21** was treated with ethyl 3-bromopropiolate in THF. This gave a complex mixture from which a product isomeric with the desired compound **49** was isolated in 30% yield (Scheme 8). This product was assigned structure **48** on the basis of its spectroscopic properties. In particular, the ^{13}C NMR spectrum showed the presence of a ketonic carbonyl carbon at 190.7 ppm and the absence of a signal at ca. 90 ppm expected for the acetylenic ether carbon atom in **49** (in model compound **26** this resonance is at 88.7 ppm while in simple alkoxy acetylenic esters[22] the signal occurs at ca. 96 ppm). Compound **48** arises by C-alkynylation of the ambident naphthoxide derived from **21**, following a well-known outcome in the alkylation of 2-naphthols.[28,29]

When the naphthol **21** was treated with ethyl 3-bromopropiolate in the presence of K_2CO_3 in acetone under reflux, the phenolic ester **51** was isolated in 28% yield after chromatography of the complex reaction mixture (Scheme 8). Clearly the desired acetylenic ether **49** was formed under these conditions and underwent intramolecular Diels–Alder reaction to give **50**, which then suffered acid-catalysed ring opening, presumably during workup or chromatographic separation, by a pathway similar to that shown in Scheme 6 for adduct **39**.

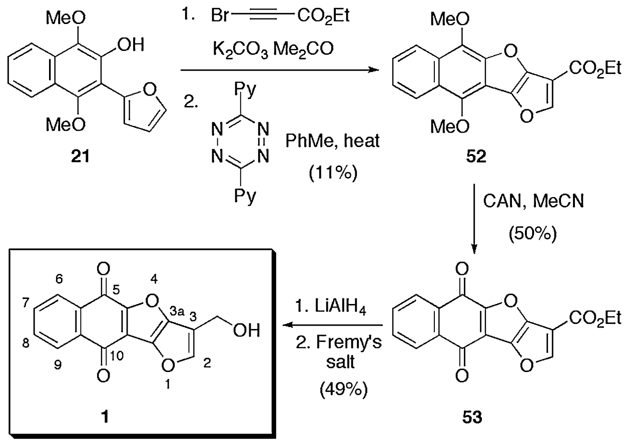
The apparent formation of the two required intermediates **49** and **50** was encouraging as it seemed that the synthesis of the furofuronaphthalene **52** might be achievable if the adduct **50** could be trapped with 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**14**) in the reaction mixture. Towards this end, a stirred suspension of the naphthol **21**, ethyl 3-bromopropiolate and K_2CO_3 in acetone was gently heated until **21** had been consumed. Without hydrolytic workup, the mixture was filtered, diluted with toluene and most of the acetone removed by distillation. The solution of the presumed adduct **50** was then subjected to the action of tetrazine **14** in refluxing toluene (Scheme 9). Gratifyingly, this afforded the target furofuronaphthalene **52**, albeit in only 11% yield. Attempts to increase this yield by varying the reaction conditions were unrewarding.

The remaining steps of the synthesis were carried out as shown in Scheme 9. Oxidative demethylation of **52** with ceric ammonium nitrate (CAN) gave quinone **53**. Reduction of the ester group with $LiAlH_4$ followed by re-oxidation of the resulting naphthalene-1,4-diol moiety with Fremy's salt delivered the target 3-hydroxymethylfuro[3,2-*b*]naphtho[2,3-*d*]furan-5,10-dione (**1**) as a red solid in 49% yield over two steps.

The NMR spectral properties of **1** are summarised in Table 1. It can be seen that there is excellent agreement between the data



Scheme 8. Formation of the undesired products **48** and **51**.



Scheme 9. Final steps in the synthesis of **1**.

reported[7] for the natural product and those observed for the synthetic material, except for the value for the ^{13}C chemical shift of the CH_2 group. We recorded the spectrum of synthetic **1** at three different concentrations and consistently observed the value of 52.3 ppm, ruling out any possible concentration dependence due to, for example, intermolecular hydrogen-bonding effects. We note that for the naturally occurring hydroxy derivative **2**, the reported chemical shift for the methylene carbon is 52.3 ppm,[7] a value identical to that observed by us for synthetic **1**. As the hydroxyl group in **2** is unlikely to interact with the distant CH_2 group, we conclude that the correct shift for this carbon atom in **1** is 52.3 ppm.

In summary, we have confirmed the nature of the novel ring skeleton of **1** by synthesis. The propensity of the naphthyl dichlorovinyl ether **38** to undergo facile intramolecular Diels–Alder addition (relative to the model ether **25**) may be a consequence of a buttressing effect due to the methoxy groups. These groups also appear to interfere with the metallation and further transformations of the dichlorovinyl moiety, which proceeded smoothly with the model ether **25**.

Table 1
Comparison of the NMR spectral data in $(CD_3)_2SO$ for natural[7] and synthetic 3-hydroxymethylfuro[3,2-*b*]naphtho[2,3-*d*]furan-5,10-dione (**1**)

Posn	Natural **1**		Synthetic **1**	
	δ_H[a]	δ_C[b]	δ_H[c]	δ_C[d]
2	8.18 (br s)	150.8	8.16 (t, 1.0)	150.8
3		116.5		116.5
3a		151.9		151.9
4a		153.3		153.3
5		173.0		173.0
5a		132.0		132.0
6	8.11 (m)	126.42	8.11 (m, $J_{6,7}$ 7.73, $J_{6,8}$ 1.24, $J_{6,9}$ 0.42)[e]	126.42
7	7.87 (m)	134.0	7.90 (m, $J_{6,7}$ 7.73, $J_{7,8}$ 7.27, $J_{7,9}$ 1.25)[e]	134.0
8	7.88 (m)	134.5	7.87 (m, $J_{8,9}$ 7.74, $J_{7,8}$ 7.27, $J_{6,8}$ 1.24)[e]	134.5
9	8.09 (m)	126.35	8.09 (m, $J_{8,9}$ 7.74, $J_{7,9}$ 1.25, $J_{6,9}$ 0.42)[e]	126.35
9a		132.2		132.2
10		179.1		179.2
10a		117.9		117.9
10b		141.2		141.2
CH_2	4.59 (d, 5.2)	54.5	4.58 (dd, 5.4, 1.0)	52.3
OH	5.51 (t, 5.2)		5.49 (t, 5.4)	

[a] 400 MHz.
[b] 100.57 MHz.
[c] 500 MHz.
[d] 125.75 MHz.
[e] Simulated using the program gNMR version 4.0 (Cherwell Scientific Publishing Limited).

3. Experimental

3.1. General

General details have been given previously.[30]

3.1.1. 2-(2-Furyl)phenol (**24**)

A mixture of 2-bromophenyl acetate (540 mg, 2.53 mmol), 2-furanylboronic acid (425 mg, 3.80 mmol), Et_3N (1.05 mL, 7.50 mmol), palladium acetate (117 mg, 0.757 mmol) and Ph_3P (40 mg, 1.53 mmol) in anhydrous DMF (10 mL) was heated at 100 °C under Ar for 3 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2. The solution was washed sequentially with aqueous NH_3 (10%), water, brine and was dried. Evaporation followed by radial chromatography using EtOAc/light petroleum (0–3%) gave 2-(2-furyl)phenyl acetate (**23**) (420 mg, 83%) as a colourless oil. δ_H (200 MHz, $CDCl_3$) 7.83 (1H, dd, *J* 5.8, 3.7, ArH), 7.49 (1H, d, *J* 1.8, furyl H), 7.35–7.26 (2H, m, ArH), 7.13 (1H, dd, *J* 6.0, 3.3, ArH), 6.68 (1H, d, *J* 3.4, furyl H), 6.49 (1H, dd, *J* 3.4, 1.8, furyl H). This spectrum is similar to that reported for **23** prepared by another route.[31] The foregoing acetate (303 mg, 1.50 mmol) and NaOH (60 mg, 1.5 mmol) in aqueous MeOH (1:1, 20 mL) was stirred under Ar at room temperature overnight. The MeOH was evaporated and the residue acidified with dilute HCl. Extraction with CH_2Cl_2 followed by radial chromatography eluting with EtOAc/light petroleum (0–7%) gave 2-(2-furyl)phenol (**24**) (208 mg, 86%) as pale yellow plates, mp 40–41 °C, after recrystallisation from CH_2Cl_2/light petroleum. EIMS *m*/*z* 161 (M+1, 30%), 160 (M, 100), 149 (19), 131 (11). δ_H (300 MHz, $CDCl_3$) 7.58 (1H, ddd, *J* 9.8, 7.2, 0.4, ArH), 7.52 (1H, dd, *J* 1.8, 0.7, furyl H), 7.23 (1H, ddd, *J* 9.8, 7.2, 1.7, ArH), 7.13 (1H, br, OH), 7.01–6.97 (1H, m, ArH), 6.75 (1H, dd, *J* 3.4, 0.7, furyl H), 6.54 (1H, dd *J* 3.4, 1.8, furyl H). δ_C (75.5 MHz, $CDCl_3$) 152.4 (C), 152.3 (C), 141.2 (CH), 129.1 (CH), 126.1 (CH), 120.5 (CH), 117.1 (CH), 116.5 (C), 111.7 (CH), 106.7 (CH). Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.75; H, 4.96.

3.1.2. (*E*)-1,2-Dichloroethenyl 2-(2-furyl)phenyl ether (**25**)

Methanolic LiOMe (2.50 mL of 1.5 M solution, 3.75 mmol) was added to a solution of 2-(2-furyl)phenol (**24**) (586 mg, 3.65 mmol) in MeOH (20 mL) under Ar. The MeOH was evaporated and the residue dissolved in DMF (20 mL), trichloroethylene (1.40 g, 11.1 mmol) was added, and the solution stirred at 80 °C for 14 h. The mixture was diluted with water and extracted thoroughly with light petroleum. The extract was washed sequentially with dilute NaOH and water, dried and then concentrated. Distillation gave (*E*)-1,2-dichloroethenyl 2-(2-furyl)phenyl ether (**25**) as a colourless liquid (780 mg, 93%) bp 190 °C/0.05 Torr (Kugelrohr). EIMS *m*/*z* 258 (M+4, 3%), 256 (M+2, 18), 254 (M, 30), 221 (43), 220 (20), 219 (100), 193 (15), 191 (46). δ_H (300 MHz, $CDCl_3$) 7.97–7.94 (1H, m, ArH), 7.53 (1H, dd, *J* 1.8, 0.7, furyl H), 7.29–7.25 (1H, m, ArH), 7.10–7.07 (1H, m, ArH), 6.98 (1H, dd, *J* 3.3, 0.7, furyl H), 6.55 (1H, dd, *J* 3.3, 1.7, furyl H), 6.04 (1H, s, vinyl H). δ_C (75.5 MHz, $CDCl_3$) 149.1 (C), 148.6 (C), 141.8 (CH), 139.5 (C), 127.8 (CH), 126.6 (CH), 124.7 (CH), 121.6 (C), 116.2 (CH), 111.9 (CH), 110.7 (CH), 103.8 (CH). Anal. Calcd for $C_{12}H_8Cl_2O_2$: C, 56.50; H, 3.16; Cl, 27.80. Found: C, 56.30; H, 3.22; Cl, 27.66.

3.1.3. Methyl 3-[2-(2-furyl)phenoxy]propynoate (**26**)

A solution of BuLi in hexane (3.0 mL of 0.80 M, 2.40 mmol) was added dropwise over 20 min to a stirred solution of 1,2-dichloroethenyl 2-(2-furyl)phenyl ether (**25**) (280 mg, 1.10 mmol) in ether (15 mL) at −78 °C. The mixture was allowed to warm to −10 °C, stirred for 10 min and then transferred via cannula to a solution of methyl chloroformate (1.16 g, 12.3 mmol) in ether at −78 °C. The mixture was stirred at −40 °C for 15 min and then added to phosphate buffer[22] (40 mL) and ether (75 mL). The organic layer was separated, dried, concentrated and the residue subjected to radial chromatography. Elution with EtOAc/light petroleum (0–20%) gave methyl 3-[2-(2-furyl)phenoxy]propynoate (**26**) (109 mg, 41%) as a colourless oil. EIMS *m*/*z* 242 (M, 33%), 211 (21), 210 (100), 182 (33), 126 (32), 77 (11). δ_H (300 MHz, $CDCl_3$) 7.89–7.86 (1H, m, ArH), 7.64–7.60 (1H, m, ArH), 7.51 (1H, dd, *J* 1.8, 0.7, furyl H), 7.34–7.25 (2H, m, ArH), 6.87 (1H, dd, *J* 3.4, 0.7, furyl H), 6.52 (1H, dd, *J* 3.5, 1.8, furyl H), 3.84 (3H, s, OCH_3). δ_C (75.5 MHz, $CDCl_3$) 154.6 (CO), 150.1 (C), 147.4 (C), 147.3 (CH), 142.3 (CH), 128.3 (CH), 126.7 (CH), 126.0 (CH), 120.0 (C), 114.8 (CH), 112.0 (CH), 111.1 (CH), 88.7 (C), 52.6 (OCH3), 41.1 (C). HRMS calcd for $C_{14}H_{10}O_4$ M^+: 242.0579, found: 242.0576.

3.1.4. *Methyl furo[3,2-b]benzofuran-3-carboxylate (**29**)*

A solution of methyl 3-[2-(2-furyl)phenoxy]propynoate (**26**) (50 mg, 0.21 mmol) and 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**14**) (49 mg, 0.21 mmol) in toluene (25 mL) was heated under reflux under Ar for 16 h. The solvent was evaporated and the residue subjected to radial chromatography. Elution with CH_2Cl_2/light petroleum (0–10%) gave methyl furo[3,2-*b*]benzofuran-3-carboxylate (**29**) (40 mg, 93%) as colourless needles mp 105–107 °C. EIMS *m*/*z* 216 (M, 100%), 185 (31), 158 (17), 157 (18), 149 (31), 101 (19), 86 (15), 84 (26). δ_H (500 MHz, $CDCl_3$) 8.11 (1H, s, furyl H2), 7.70–7.61 (2H, m, ArH5 and ArH8), 7.34–7.30 (2H, m, ArH6 and ArH7), 3.97 (3H, s, OCH_3). δ_C (125.75 MHz, $CDCl_3$) 161.9 (CO), 159.5 (C4a), 150.8 (C2), 145.5 (C8b), 143.8 (C3a), 124.3 (C6), 123.7 (C7), 117.2 (C8a), 117.5 (C5), 113.3 (C8), 109.9 (C3), 52.2 (OCH_3). ν_{max} (KBr)/cm^{-1} 1720 (C=O). Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.53; H, 3.87.

3.1.5. *3-(2-Furyl)-1,4-dimethoxynaphthalene-2-carboxaldehyde (**32**)*

A stirred solution of diisopropylamine (1.0 mL, 0.722 g, 7.71 mmol) in THF (20 mL) at −78 °C was treated dropwise with BuLi in hexane (5.20 mL of 1.5 M, 7.80 mmol) under Ar. To the mixture was then added over 20 min a solution of 3-cyanophthalide (**30**) (1.23 g, 7.73 mmol) in THF (50 mL). Stirring was continued for 45 min and then a solution of 3-(2-furyl)acrolein (**31**) (944 mg, 7.74 mmol) in THF (30 mL) was added. The mixture was allowed to warm to room temperature, stirred for 6 h and then acidified with HCl (1 M, 100 mL) and extracted thoroughly with EtOAc. The dried extract was evaporated and the residue dissolved in anhydrous acetone (100 mL) and treated with K_2CO_3 (4.0 g, 29 mmol) and MeI (7.0 mL, 16 g, 113 mmol) and refluxed under Ar for 18 h. The cooled mixture was filtered through Celite and the filtrate evaporated. The residue was subjected to silica gel filtration. Elution with CH_2Cl_2/light petroleum (0–5%) gave 3-(2-furyl)-1,4-dimethoxynaphthalene-2-carboxaldehyde (**32**) (1.65 g, 76%), mp 84–86 °C, after recrystallisation from Et_2O/light petroleum. EIMS *m*/*z* 282 (M, 77%), 267 (29), 240 (17), 239 (100), 224 (17), 223 (18), 139 (19). δ_H (300 MHz, $CDCl_3$) 10.20 (1H, s, CHO), 8.29–8.18 (2H, m, ArH), 7.75–7.56 (2H, m, ArH), 7.60 (1H, dd, *J* 1.8, 0.7, furyl H), 6.74 (1H, dd, *J* 3.3, 0.7, furyl H), 6.60 (1H, dd, *J* 3.3, 1.8, furyl H), 4.10 (3H, s, OCH_3), 3.71 (3H, s, OCH_3). δ_C (75.5 MHz, $CDCl_3$) 190.7 (CHO), 155.3 (C), 151.2 (C), 147.1 (C), 142.9 (CH), 131.3 (C), 129.2 (CH), 129.1 (C), 127.6 (CH), 125.1 (C), 123.9 (CH), 123.2 (CH), 118.9 (C), 111.7 (CH), 111.5 (CH), 65.0 (OCH_3), 61.9 (OCH_3). ν_{max} (KBr)/cm^{-1} 1695 (C=O). Anal. Calcd for $C_{17}H_{14}O_4$: C, 59.20; H, 3.86. Found: C, 59.42; H, 4.08.

3.1.6. *2-Benzyloxy-3-bromonaphthalene-1,4-dione (**34**)*

BuLi in hexane (1.6 M, 35 mL, 56 mmol) was added dropwise under Ar to a stirred solution of benzyl alcohol (7.41 g, 68.6 mmol) in anhydrous THF (180 mL) cooled in an ice bath. After 20 min the solution was treated with a slurry 2,3-dibromonaphthalene-1,4-dione (**33**)[32] (16.4 g, 52.0 mmol) in anhydrous THF (50 mL) and the resulting mixture was stirred for a further 1.5 h. The reaction mixture was quenched with a little ice, then diluted with water (500 mL) and extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with water, followed by brine, dried and concentrated to give a yellow residue, which was subjected to silica gel filtration. Elution with 5–30% EtOAc/light petroleum gave a yellow solid, which recrystallised from CH_2Cl_2/light petroleum to give 2-benzyloxy-3-bromonaphthalene-1,4-dione (**34**) as yellow needles (15.4 g, 75%), mp 103–104 °C. EIMS *m*/*z* 345 (M+3, 19%), 344 (M+2, 100), 343 (M+1, 19), 342 (M, 94), 265 (13), 264 (25), 255 (61), 254 (44), 253 (58). δ_H (300 MHz, $CDCl_3$) 8.10–8.04 (2H, m, ArH), 7.72–7.69 (2H, m, ArH), 7.49–7.46 (2H, m, ArH), 7.39–7.31 (3H, m, ArH), 5.64 (2H, s, OCH_2). δ_C (75.5 MHz, $CDCl_3$) 179.3 (CO), 178.5 (CO), 158.4 (C), 136.0 (C), 134.3 (CH), 138.8 (CH), 130.8 (C), 129.7 (C), 128.6 (CH), 128.2 (2×CH), 127.2 (CH), 126.9 (CH), 123.9 (C), 75.7 (OCH_2). ν_{max} (Nujol)/cm^{-1} 1669 (C=O). Anal. Calcd for $C_{17}H_{11}BrO_3$: C, 59.50; H, 3.23. Found: C, 59.35; H, 3.40.

3.1.7. *2-Benzyloxy-3-(2-furyl)naphthalene-1,4-dione (**36**)*

A mixture of 2-benzyloxy-3-bromonaphthalene-1,4-dione (**34**) (4.38 g, 12.8 mmol), 2-(tri-*n*-butylstannyl)furan[33] (5.61 g, 15.7 mmol), $Pd(PPh_3)_4$ (546 mg, 0.473 mmol) and CuBr (531 mg, 3.70 mmol) in dioxane (60 mL) was heated at reflux for 30 min under Ar. The reaction mixture was diluted with water (500 mL) and extracted with EtOAc (3×60 mL). The combined organic extracts were washed with water (60 mL), followed by brine (50 mL), dried and concentrated to give a red-brown residue, which crystallised from CH_2Cl_2/light petroleum to give 2-benzyloxy-3-(2-furyl)naphthalene-1,4-dione (**36**) as dark red plates (2.92 g), mp 141 °C. The mother liquor was concentrated under reduced pressure, adsorbed onto silica and subjected to silica gel filtration. Elution with 2.5–5% EtOAc/light petroleum gave a further portion of the title compound as a bright red solid (0.825 g, total yield 89%). EIMS *m*/*z* 330 (M, 42%), 302 (29), 241 (11), 240 (11), 183 (17), 127 (11), 91 (100). δ_H (300 MHz, $CDCl_3$) 8.13–8.05 (2H, m, ArH), 7.76–7.68 (2H, m, ArH), 7.61 (1H, dd, *J* 1.8, 0.7, furyl H), 7.47–7.41 (2H, m, ArH), 7.38–7.30 (3H, m, ArH), 7.22 (1H, dd, *J* 3.5, 0.7, furyl H), 6.56 (1H, dd, *J* 3.5, 1.8, furyl H), 5.42 (2H, s, OCH_2). δ_C (75.5 MHz, $CDCl_3$) 183.4 (CO), 181.5 (CO), 154.1 (C), 145.1 (C), 144.2 (CH), 136.4 (C), 133.9 (CH), 133.5 (CH), 132.1 (C), 131.2 (C), 128.4 (CH), 128.3 (CH), 126.6 (CH), 125.9 (CH), 123.3 (C), 117.9 (CH), 111.9 (CH), 75.6 (OCH_2). ν_{max} (Nujol)/cm^{-1} 1661 (C=O). Anal. Calcd for $C_{21}H_{14}O_4$: C, 76.36; H, 4.27. Found: C, 76.50; H, 4.33.

3.1.8. *2-Benzyloxy-3-(2-furyl)-1,4-dimethoxynaphthalene (**37**)*

A mixture of 2-benzyloxy-3-(2-furyl)naphthalene-1,4-dione (**36**) (1.71 g, 5.18 mmol), tetrabutylammonium bromide (109 mg, 0.295 mmol) and sodium dithionite (2.87 g, 16.5 mmol) in CH_2Cl_2 (45 mL) and H_2O (45 mL) was stirred vigorously under Ar. After 30 min the reaction mixture was treated sequentially with a solution of NaOH (2.31 g, 57.8 mmol) in H_2O (7 mL) and dimethyl sulfate (3.5 mL, 4.7 g, 37 mmol) and the resulting solution was left to stir for 17 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×40 mL). The combined organic extracts were washed with H_2O (40 mL), followed by brine (40 mL), dried and concentrated to give a light brown oil, which was subjected to silica gel filtration. Elution with 2.5% EtOAc/light petroleum gave 2-benzyloxy-3-(2-furyl)-1,4-dimethoxynaphthalene (**37**) (1.80 g, 96%) as a pale yellow oil. EIMS *m*/*z* 361 (M+1, 39%), 360 (M, 88), 345 (19), 269 (34), 242 (25), 241 (100), 226 (45), 211 (26), 183 (32), 127 (12), 91 (41). δ_H (300 MHz, $CDCl_3$) 8.20–8.17 (2H, m, ArH), 7.65 (1H, dd, *J* 1.8, 0.7, furyl H), 7.59–7.48 (2H, m, ArH), 7.39–7.30 (5H, m, ArH), 6.77 (1H, dd, *J* 3.3, 0.7, furyl H), 6.59 (1H, dd, *J* 3.3, 1.8, furyl H), 5.02 (2H, s, OCH_2), 4.08 (3H, s, OCH_3), 3.73 (3H, s, OCH_3). δ_C (75.5 MHz, $CDCl_3$) 150.9 (C), 146.8 (C), 145.9 (C), 144.3 (C), 142.2 (CH), 137.2 (C), 129.2 (C), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 126.7 (CH), 125.8 (C), 125.3 (CH), 122.6 (CH), 121.5 (CH), 117.2 (C), 111.6 (CH), 110.9 (CH), 75.4 (OCH_2), 61.7 (OCH_3), 61.3 (OCH_3). HRMS calcd for $C_{23}H_{20}O_4$ M^+: 360.1361, found: 360.1364.

*3.1.9. 3-(2-Furyl)-1,4-dimethoxynaphthalen-2-ol (**21**)*

(a) To a solution of 3-(2-furyl)-1,4-dimethoxynaphthalene-2-carboxaldehyde (**32**) (1.92 g, 6.80 mmol) in CH_2Cl_2 (80 mL) were added aqueous H_2O_2 (1.8 g of 35%) and diphenyl diselenide (88 mg, 0.28 mmol). The mixture was stirred under Ar at room temperature with periodic monitoring by ^{1}H NMR spectroscopy (the R_f values of the starting material and the product formate were identical). After 16 h the mixture was diluted with H_2O (100 mL) and the organic layer was separated and dried. Evaporation gave the crude formate, which was stirred for 2 h under Ar with a solution of NaOH (400 mg) in H_2O (40 mL) and MeOH (40 mL). The MeOH was evaporated and the residue acidified with dilute HCl and extracted with CH_2Cl_2 (3×50 mL), and the extract was dried and concentrated. The residue was subjected to radial chromatography. Elution with 0–5% EtOAc/light petroleum gave 3-(2-furyl)-1,4-dimethoxynaphthalen-2-ol (**21**) (750 mg, 41%) as a pale yellow oil possessing a strong blue fluorescence under 254 nm irradiation. EIMS *m*/*z* 270 (M, 100%), 255 (78), 241 (13), 212 (17), 199 (30), 183 (29), 149 (22), 128 (16), 139 (12). δ_H (300 MHz, $CDCl_3$) 8.11 (1H, d, *J* 8.4, ArH), 7.99 (1H, d, *J* 8.4, ArH), 7.65 (1H, dd, *J* 1.8, 0.7, furyl H) 7.56–7.32 (2H, m, ArH), 7.04 (1H, dd, *J* 3.3, 0.7, furyl H), 6.64 (1H, dd, *J* 3.3, 1.8, furyl H), 4.00 (3H, s, OCH_3), 3.78 (3H, s, OCH_3). δ_C (75.5 MHz, $CDCl_3$) 150.4 (C), 147.5 (C), 143.3 (C), 141.8 (CH), 137.0 (C), 128.2 (C), 127.0 (CH), 123.9 (CH), 123.4 (C), 122.9 (CH), 120.6 (CH), 112.0 (CH), 111.7 (C), 111.6 (CH), 61.5 (OCH_3), 61.2 (OCH_3). HRMS calcd for $C_{16}H_{14}O_4$ M^+: 270.0892, found: 270.0888.

(b) A solution of 2-benzyloxy-3-(2-furyl)-1,4-dimethoxynaphthalene (**37**) (1.86 g, 5.17 mmol) in EtOAc (50 mL) was hydrogenated in the presence of 10% Pd/C (280 mg) until TLC indicated that most of the starting material had been consumed (ca. 3.5 h). The reaction mixture was filtered through a plug of Celite and the filtrate was concentrated to give a yellow oil, which was subjected to silica gel filtration. Elution with 3% EtOAc/light petroleum returned starting material (157 mg) as a pale yellow oil. Further elution with 7.5% EtOAc/light petroleum afforded 3-(2-furyl)-1,4-dimethoxynaphthalen-2-ol (**21**) (1.27 g, 91%) as a yellow oil spectroscopically identical to the material prepared in (a).

*3.1.10. (E)-1,2-Dichloroethenyl 3-(2-furyl)-1,4-dimethoxynaphthalen-2-yl ether (**52**)*

BuLi in hexane (1.35 M, 1.2 mL, 1.6 mmol) was added dropwise to a stirred solution of 3-(2-furyl)-1,4-dimethoxynaphthalen-2-ol (**21**) (393 mg, 1.46 mmol) in anhydrous THF (7 mL) cooled in an ice bath under Ar. After 10 min the mixture was concentrated under reduced pressure and the resulting yellow residue was dissolved in DMF (10 mL). The reaction mixture was then treated with trichloroethylene (1.74 g, 13.2 mmol) and left to stir overnight. The mixture was diluted with water and extracted with 50% Et_2O/light petroleum (4×50 mL). The combined organic extracts were washed successively with dilute NaOH solution and H_2O, dried and concentrated to give a brown oil, which was subjected to silica gel filtration. Elution with 2% EtOAc/light petroleum afforded (*E*)-1,2-dichloroethenyl 3-(2-furyl)-1,4-dimethoxynaphthalen-2-yl ether (**38**) (454 mg, 85%) as a colourless oil, which crystallised on standing to afford plates mp 64–66 °C. EIMS *m*/*z* 368 (M+4, 15%), 367 (17), 366 (M+2, 77), 365 (24), 364 (M, 100), 351 (15), 349 (23), 331 (32), 329 (83), 313 (28), 301 (27), 285 (40), 281 (40), 183 (557), 152 (39), 139 (68). δ_H (300 MHz, $CDCl_3$) 8.26–8.09 (2H, m, ArH), 7.63 (1H, dd, *J* 1.8, 0.8, furyl H), 7.61–7.50 (2H, m, ArH), 6.82 (1H, d, *J* 0.8, furyl H), 6.59 (1H, dd, *J* 3.4, 1.8, furyl H), 5.56 (1H, s, vinyl H), 4.03 (3H, s, OCH_3), 3.75 (3H, s, OCH_3). δ_C (75.5 MHz, $CDCl_3$) 150.9 (C), 145.6 (C), 143.8 (C), 142.9 (CH), 141.3 (C), 128.4 (C), 127.4 (CH), 127.2 (C), 126.6 (C), 126.5 (CH), 123.0 (CH), 121.9 (CH), 112.4 (CH), 111.3 (C), 111.1 (CH), 94.9 (CH), 62.4 (OCH_3), 61.8 (OCH_3). HRMS calcd for $C_{18}H_{14}Cl_2O_4$ M^+: 364.0269, found: 364.0271.

*3.1.11. Intramolecular Diels–Alder reactions of (E)-1,2-dichloroethenyl 3-(2-furyl)-1,4-dimethoxynaphthalen-2-yl ether (**38**)*

(a) To a solution of 3-(2-furyl)-1,4-dimethoxynaphthalen-2-ol (**21**) (450 mg, 1.66 mmol) in MeOH (20 mL) was added methanolic LiOMe (1.2 mL of 1.58 M solution, 1.90 mmol) and the mixture was stirred under Ar for 10 min and the solvent was then evaporated. To the residue was added DMF (50 mL) and trichloroethylene (1.5 mL, 2.19 g, 16.7 mmol) and the solution was heated at 80 °C for 5 h. The cooled mixture was diluted with H_2O (300 mL) and extracted with light petroleum (3×75 mL). The extract was dried, concentrated and the residue subjected to radial chromatography. Elution with 0–3% EtOAc/light petroleum gave (3α,4α,4aβ,11bα)-4,4b-dichloro-6,11-dimethoxy-3,4,4a,11b-tetrahydro-3,11b-epoxybenzo[*b*]naphtho[2,3-*d*]furan (**39**) as a colourless solid (270 mg, 60%), which crystallised from CH_2Cl_2/light petroleum as prisms, mp100–101 °C. EIMS *m*/*z* 368 (M+4, 10%), 367 (12), 366 (M+2, 59), 365 (18), 364 (M, 93), 349 (26), 329 (100) and numerous peaks of intensity >10% at lower *m*/*z* values. δ_H (300 MHz, $CDCl_3$) 8.19–8.14 (2H, m, ArH), 7.56–7.53 (1H, m, ArH), 7.47–7.43 (1H, m, ArH), 7.88 (1H, d, *J* 5.7, vinyl H1), 6.71 (1H, dd, *J* 5.7, 1.9, vinyl H2), 5.15 (1H, d, *J* 1.9, bridgehead H2a), 4.41 (1H, s, chloromethine H3), 4.14 (3H, s, OCH_3), 4.03 (3H, s, OCH_3). δ_C (75.5 MHz, $CDCl_3$) 150.8 (C), 146.1 (C), 137.2 (CH), 135.6 (CH), 135.2 (C), 131.1 (C), 127.5 (CH), 125.4 (C), 124.9 (CH), 122.6 (CH), 121.9 (CH), 111.1 (C), 110.7 (C), 97.5 (C), 87.8 (CH), 64.5 (CH), 63.5 (OCH_3), 61.2 (OCH_3). Anal. Calcd for $C_{18}H_{14}Cl_2O_4$: C, 72.33; H, 5.00. Found: C, 72.50; H, 5.02.

(b) A solution of the ether **38** (48 mg) in $CDCl_3$ (1 mL) was heated at 60 °C with periodic monitoring of the ^{1}H NMR spectrum. Adduct **39** was not detected but a new product was formed slowly ($t_{1/2}$ ca. 65 h). After 115 h the mixture was subjected to radial chromatography. Elution with 2% EtOAc/light petroleum gave starting material (9 mg). Elution with 2–5% EtOAc/light petroleum afforded 4-chloro-6,11-dimethoxybenzo[*b*]naphtho[2,3-*d*]furan-3-ol (**41**) as a colourless solid (27 mg, 63%) possessing a blue fluorescence under 254 nm radiation. Recrystallisation from CH_2Cl_2/light petroleum gave **41** as plates, mp 196–197 °C. EIMS *m*/*z* 330 (M+2, 16%), 328 (M, 44), 315 (34), 314 (19), 313 (100), 300 (13), 298 (39), 86 (19). δ_H (600 MHz, $CDCl_3$) 8.36–8.34 (1H, m, ArH), 8.26–8.24 (1H, m, ArH), 7.97 (1H, d, *J* 8.3, ArH), 7.56–7.52 (2H, m, ArH), 7.09 (1H, d, *J* 8.3, ArH), 5.85 (1H, br s, OH), 4.38 (3H, s, OCH_3), 4.10 (3H, s, OCH_3). δ_C (150.9 MHz, $CDCl_3$) 153.4 (C), 152.1 (C), 144.7 (C), 143.6 (C), 135.2 (C), 126.7 (C), 125.4 (CH), 125.3 (C), 124.8 (CH), 122.3 (CH), 121.9 (CH), 121.6 (CH), 117.9 (C), 116.9 (C), 111.7 (CH), 103.4 (C), 61.6 (OCH_3), 61.3 (OCH_3). HRMS calcd for $C_{18}H_{13}ClO_4$ M^+: 328.0502, found: 328.0498.

*3.1.12. Attempted synthesis of ethyl 3-[3-(2-furyl)-1,4-dimethoxynaphthalen-2-yloxy]propynoate (**49**) by alkynylation of 3-(2-furyl)-1,4-dimethoxynaphthalen-2-ol (**21**)*

(a) BuLi in hexane (1.6 M, 0.65 mL, 1.0 mmol) was added dropwise under Ar to a stirred solution of 3-(2-furyl)-1,4-dimethoxynaphthalen-2-ol (**21**) (261 mg, 0.967 mmol) in anhydrous THF (8 mL) cooled in an ice bath. After 5 min the solution was treated with ethyl 3-bromopropiolate (184 mg, 1.04 mmol) in anhydrous THF (1 mL), then the ice bath was removed and the reaction mixture was left to stir at room temperature for a further 22 h. The mixture was diluted with H_2O (80 mL) and extracted with CH_2Cl_2

(3×40 mL). The combined organic extracts were washed with brine (30 mL), dried and concentrated to give a brown oil, which was subjected to radial chromatography. Elution with 10% EtOAc/light petroleum returned unreacted starting material (36 mg). Further elution with 20% EtOAc/petroleum gave ethyl 3-[3-(2-furyl)-1,4-dimethoxy-2-oxo-1,2-dihydronaphthalen-1-yl]propynoate (**48**) as a yellow oil (105 mg, 30%, 34% based on recovered starting material). EIMS *m*/*z*: 366 (M, 51%), 337 (29), 336 (46), 335 (100), 321 (23), 308 (16), 307 (69), 306 (34), 305 (16), 293 (45), 291 (17), 279 (22), 277 (26), 265 (24), 264 (18), 263 (38), 247 (19), 236 (19), 235 (48), 234 (15), 221 (15), 220 (40), 165 (17), 164 (20), 163 (35), 152 (19), 151 (21). δ_H (300 MHz, CDCl$_3$) 7.90–7.87 (1H, m, ArH), 7.80–7.77 (1H, m, ArH), 7.56–7.45 (3H, m, 2×ArH, 1×furyl H), 6.64 (1H, dd, *J* 3.3, 0.7, furyl H), 6.52 (1H, dd, *J* 3.3, 1.8, furyl H), 4.22 (2H, q, *J* 7.1, CH$_2$), 3.75 (3H, s, OCH$_3$), 3.48 (3H, s, OCH$_3$), 1.28 (3H, t, *J* 7.1, CH$_3$). δ_C (75.5 MHz, CDCl$_3$) 190.7 (ketone C=O), 165.7 (ester C=O), 152.8 (C), 144.5 (C), 142.6 (CH), 135.4 (C), 131.1 (CH), 129.7 (CH), 128.8 (C), 128.2 (CH), 125.5 (CH), 113.5 (CH), 111.5 (CH), 107.4 (C), 82.3 (C), 79.3 (C), 76.0 (C), 62.3 (CH$_2$), 60.5 (OCH$_3$), 54.5 (OCH$_3$), 13.9 (CH$_3$). ν_{max} (CH$_2$Cl$_2$)/cm^{-1} 1713 (C=O), 1676 (C=O), 2237 (alkyne). HRMS calcd for C$_{21}$H$_{18}$O$_6$ M$^+$: 366.1103, found: 366.1104.

(b) A suspension of 3-(2-furyl)-1,4-dimethoxynaphthalen-2-ol (**21**) (137 mg, 0.507 mmol), ethyl 3-bromopropiolate (93 mg, 0.52 mmol) and K$_2$CO$_3$ (175 mg,1.27 mmol) in acetone (2.5 mL) was stirred at room temperature for 2.5 h under Ar. TLC analysis indicated that starting material still remained so the reaction mixture was heated at 40 °C (bath) for 3 h, then allowed to cool to room temperature and left to stir for a further 16 h. The mixture was diluted with H$_2$O (40 mL) and extracted with CH$_2$Cl$_2$ (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried and concentrated to give a brown oil, which was subjected to radial chromatography. Elution with 2.5% EtOAc/light petroleum gave ethyl 3-hydroxy-6,11-dimethoxybenzo[*b*]naphtho[2,3-*d*]furan-2-carboxylate (**51**) as a white crystalline solid (52 mg, 28%), which recrystallised from CH$_2$Cl$_2$/petroleum as prisms, mp 154–155 °C. EIMS *m*/*z*: 366 (M, 41%), 351 (19), 320 (18), 306 (19), 305 (100), 290 (26). δ_H (500 MHz, CDCl$_3$) 11.55 (1H, s, OH), 8.36–8.34 (1H, m, ArH), 8.23–8.22 (2H, m, ArH), 7.54–7.51 (2H, m, ArH), 7.03 (1H, d, *J* 8.5, ArH), 4.57 (2H, q, *J* 7.2, OCH$_2$), 4.45 (3H, s, OCH$_3$), 4.09 (3H, s, OCH$_3$), 1.56 (3H, t, *J* 7.2, CH$_3$). δ_C (125.75 MHz, CDCl$_3$) 169.7 (C=O), 162.8 (C), 156.2 (C), 143.9 (C), 142.8 (C), 134.9 (C), 129.3 (CH), 126.1 (C), 125.2 (C), 125.1 (CH), 124.7 (CH), 122.4 (CH), 121.4 (CH), 117.2 (C), 115.2 (C), 113.1 (CH), 99.6 (C), 62.0 (OCH$_2$), 61.6 (OCH$_3$), 60.6 (OCH$_3$), 14.2 (CH$_3$). ν_{max} (CH$_2$Cl$_2$)/cm^{-1} 1670 (C=O). HRMS calcd for C$_{21}$H$_{18}$O$_6$ M$^+$: 366.1103, found: 366.1099.

*3.1.13. Ethyl 5,10-dimethoxyfuro[3,2-b]naphtho[2,3-d]furan-3-carboxylate (**52**)*

A stirred suspension of 3-(2-furyl)-1,4-dimethoxynaphthalen-2-ol (**21**) (193 mg, 0.715 mmol), ethyl 3-bromopropiolate (201 mg, 1.14 mmol) and K$_2$CO$_3$ (250 mg, 1.80 mmol) in acetone (5 mL) was heated at 40 °C (bath) under Ar until TLC indicated that the starting material had been consumed (ca. 3.5 h). The reaction mixture was filtered through a plug of Celite and washed through with a little acetone. The filtrate was diluted with toluene (5 mL) and most of the acetone was removed by distillation. Then the solution was treated with 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (169 mg, 0.716 mmol) and heated at reflux for 5.5 h under Ar. The resulting dark brown mixture was adsorbed onto silica and subjected to silica gel filtration. Elution with 1% EtOAc/light petroleum gave a number of fractions containing the impure title compound, which were combined and further subjected to radial chromatography. Elution with 2.5–5% EtOAc/light petroleum gave ethyl 5,10-dimethoxyfuro[3,2-*b*]naphtho[2,3-*d*]furan-3-carboxylate (**52**) as a pale pink crystalline solid (27 mg, 11%), which recrystallised from CH$_2$Cl$_2$/light petroleum as faint pink needles, mp 199–200 °C. EIMS *m*/*z*: 341 (M+1, 21%), 340 (M, 87), 326 (31), 325 (100), 297 (65). δ_H (500 MHz, CDCl$_3$) 8.33–8.31 (1H, m, ArH), 8.28–8.26 (1H, m, ArH), 8.10 (1H, s, furyl H), 7.54–7.47 (2H, m, ArH), 4.45 (2H, q, *J* 7.1, CH$_2$), 4.39 (3H, s, OCH$_3$), 4.30 (3H, s, OCH$_3$), 1.45 (3H, t, *J* 7.1, CH$_3$). δ_C (125.75 MHz, CDCl$_3$) 161.3 (C=O), 150.6 (CH, furyl), 148.7 (C), 146.2 (C), 142.3 (C), 141.5 (C), 134.4 (C), 125.6 (CH), 125.3 (C), 124.5 (CH), 123.1 (C), 122.3 (CH), 121.7 (CH), 110.4 (C), 106.0 (C), 61.6 (OCH$_3$), 61.2 (CH$_2$), 59.9 (OCH$_3$), 14.3 (CH$_3$). ν_{max} (CH$_2$Cl$_2$)/cm^{-1} 1724 (C=O). HRMS calcd for C$_{19}$H$_{16}$O$_6$ M$^+$: 340.0947, found: 340.0936.

*3.1.14. Ethyl 5,10-dioxofuro[3,2-b]naphtho[2,3-d]furan-3-carboxylate (**53**)*

A solution of ceric ammonium nitrate (149 mg, 0.272 mmol) in water (2 mL) was added dropwise under Ar to a stirred suspension of ethyl 5,10-dimethoxyfuro[3,2-*b*]naphtho[2,3-*d*]furan-3-carboxylate (**64**) (31 mg, 0.091 mmol) in CH$_3$CN (2 mL) cooled in an ice bath. The mixture was stirred vigorously for 10 min, then diluted with H$_2$O (20 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine, dried and concentrated to give a bright yellow solid, which was subjected to radial chromatography. Elution with 20–50% EtOAc/light petroleum gave the ethyl 5,10-dioxofuro[3,2-*b*]naphtho[2,3-*d*]furan-3-carboxylate (**53**) (14 mg, 50%), which recrystallised from dichloromethane/light petroleum as fine yellow needles, mp 219–220 °C. EIMS *m*/*z*: 311 (M+1, 20%), 310 (M, 100), 282 (33), 265 (33), 238 (20). δ_H (300 MHz, CDCl$_3$) 8.33 (1H, s, furyl), 8.27–8.20 (2H, m, ArH), 7.84–7.75 (2H, m, ArH), 4.44 (2H, q, *J* 7.1, CH$_2$), 1.43 (3H, t, *J* 7.1, CH$_3$). δ_C (75.5 MHz, CDCl$_3$) 178.9 (C=O), 173.5 (C=O), 160.0 (C=O), 156.0 (CH, furyl), 154.3 (C), 149.1 (C), 142.6 (C), 134.3 (CH), 133.9 (CH), 132.2 (C), 132.1 (C), 127.1 (CH), 126.0 (CH), 118.2 (C), 110.5 (C), 61.6 (CH$_2$), 14.2 (CH$_3$). ν_{max} (CH$_2$Cl$_2$)/cm^{-1} 1729 (C=O), 1674 (C=O). HRMS calcd for C$_{17}$H$_{10}$O$_6$ M$^+$: 310.0477, found: 310.0478.

*3.1.15. 3-Hydroxymethylfuro[3,2-b]naphtho[2,3-d]furan-5,10-dione (**1**)*

A solution of ethyl 5,10-dioxofuro[3,2-*b*]naphtho[2,3-*d*]furan-3-carboxylate (**53**) (12 mg, 0.039 mmol) in anhydrous THF (1.5 mL) was added to a suspension of LiAlH$_4$ (62 mg, 1.6 mmol) in anhydrous THF (1.5 mL) at 0 °C under Ar and the resulting mixture was stirred for 20 min. The reaction mixture was quenched with a little EtOAc and ice, then diluted with water (5 mL) and extracted with CHCl$_3$ (1×3 mL), followed by EtOAc (4×3 mL). The combined organic extracts were washed with brine and concentrated under reduced pressure. To the resulting brown residue were added Fremy's salt (40 mg, 0.15 mmol), Et$_2$O (3 mL) and an aqueous borax buffer solution (0.025 M sodium tetraborate, 2.7 mL; 0.1 M NaOH, 1.3 mL) and the resulting mixture was shaken vigorously for 20 min. The organic layer was separated and the aqueous layer was extracted with CHCl$_3$ (4×3 mL). The combined organic extracts were washed with brine, dried and concentrated to give a red residue, which was subjected to radial chromatography. Elution with 50–70% EtOAc/light petroleum afforded 3-hydroxymethylfuro[3,2-*b*]naphtho[2,3-*d*]furan-5,10-dione (**1**) as a red solid (5 mg, 49%), mp 204 °C onwards (sublimed and underwent crystal phase change), 240–241 °C (melted) (lit.[7] 217–218 °C). EIMS *m*/*z*: 269 (M+1, 22%), 268 (M, 100), 252 (17). The ^{1}H and ^{13}C NMR spectral data are given in Table 1. ν_{max} (KBr)/cm^{-1} 3485 (OH), 1672 (C=O), 1651 (C=O). HRMS calcd for C$_{15}$H$_8$O$_5$ M$^+$: 268.0372, found: 268.0368.

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