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Synthesis of 5,8-dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one

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Abstract—The synthesis of the title compound, which shares its skeleton with a number of biologically active natural products, is described. The key steps are construction of a 3,4-disubstituted furan by a tandem Diels–Alder-retro-Diels–Alder reaction of an alkyne with 4-phenyloxazole, and an intramolecular Friedel–Crafts acylation.

1. Introduction

The naphtho[2,3-*c*]furan-4(9*H*)-ones, represented by the parent compound **1** (Fig. 1), comprise a small group of natural and synthetic products displaying diverse biological activity. The chemistry of this class of compounds and their more common congeners, the naphtho[2,3-*c*]furan-4,9-diones (**2**), has recently been comprehensively reviewed.[1]

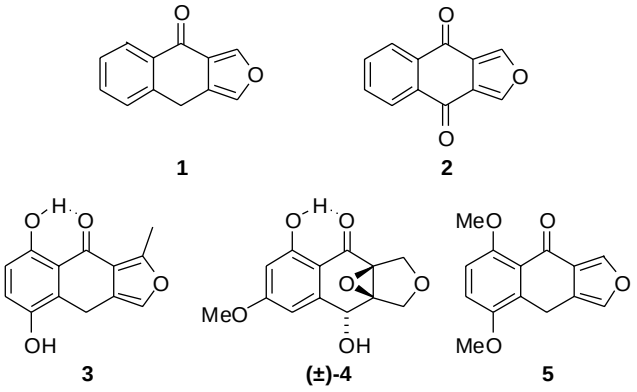

Figure 1.

Previous syntheses of natural products containing the naphtho[2,3-*c*]furan-4(9*H*)-one moiety include that of MS-444 (**3**), which involved a key Michael–Dieckmann annulation,[2] and racemic arthrinone [(±)-**4**] and co-occuring metabolites, which made use of a Dieckmann condensation (Fig. 1).[3] Herein, we detail studies of alternative synthetic approaches to the naphtho[2,3-*c*]furan-4(9*H*)-one ring system, culminating in the synthesis of 5,8-dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one (**5**).

2. Results and discussion

The *o*-quinonedimethide **7**, generated thermally from the protected benzocyclobutenol **6**,[†] reacts regiospecifically with α,β-unsaturated ketones **8** (R = sugar residues) to give Diels–Alder adducts **9** as mixtures of stereoisomers (Scheme 1).[17] We proposed that a similar reaction of **7** with an appropriate acetylenic dienophile (**10**) would afford the adduct **11**, which could, in principle, be elaborated to give the natural product 5-hydroxynaphtho[2,3-*c*]furan-4(9*H*)-one (**12**)[18] (Scheme 1).

As a model system for the route depicted above, and as a means to access the unknown parent naphtho[2,3-*c*]furan-4(9*H*)-one (**1**), we decided to examine the reaction of the acetylenic dienophile **15** with the TBS-protected benzocyclobutenol **17**.[17] The dienophile **15** was conveniently prepared by quenching the dilithium salt **14** of propargyl alcohol **13** with methyl chloroformate (Scheme 2). The methyl ketone **16** required for the synthesis of the natural product **12** was similarly obtained when **14** was quenched with acetic anhydride.

Thermal generation of the *o*-quinonedimethide **18** in the presence of the acetylenic dienophile **15** gave the expected adduct **19**, along with the naphthalene **20** resulting from transannular elimination of *t*-butyldimethylsilanol

Keywords: Naphtho[2,3-*c*]furan-4(9*H*)-ones; Tandem Diels–Alder–retro-Diels–Alder; Intramolecular Friedel–Crafts acylation; *o*-Quinonedimethide.
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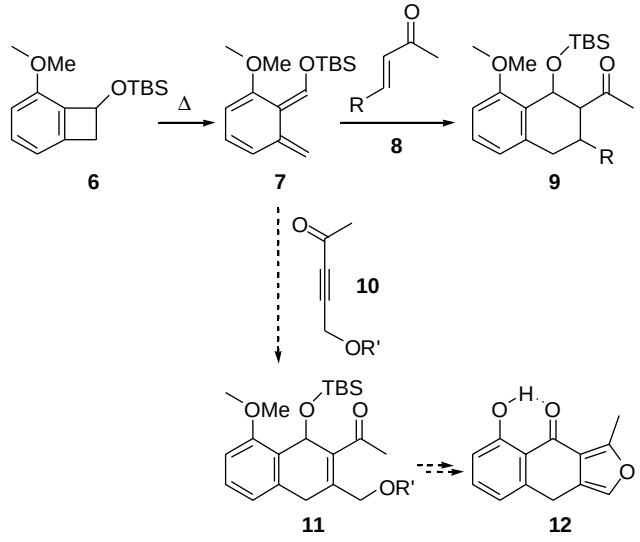
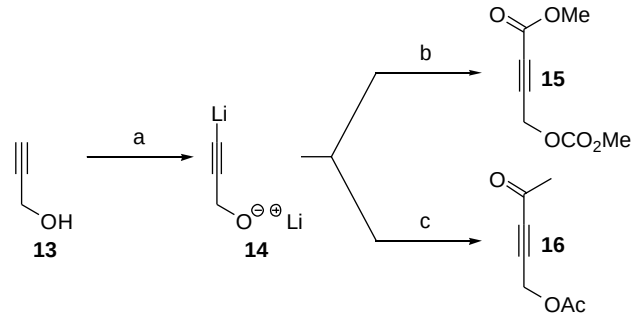
[†] The chemistry of benzocyclobutenes[4–10] and *o*-quinonedimethides[11–16] has been extensively reviewed.

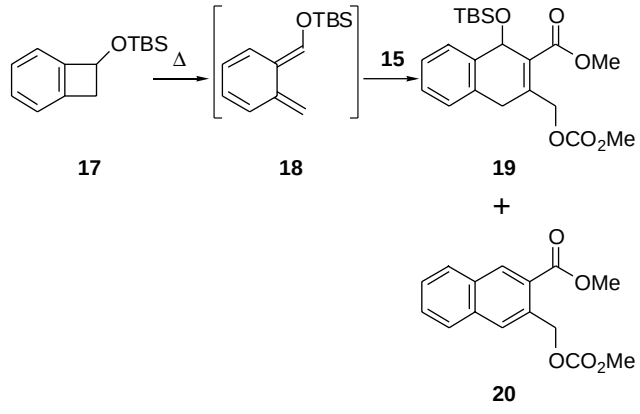


Scheme 1.



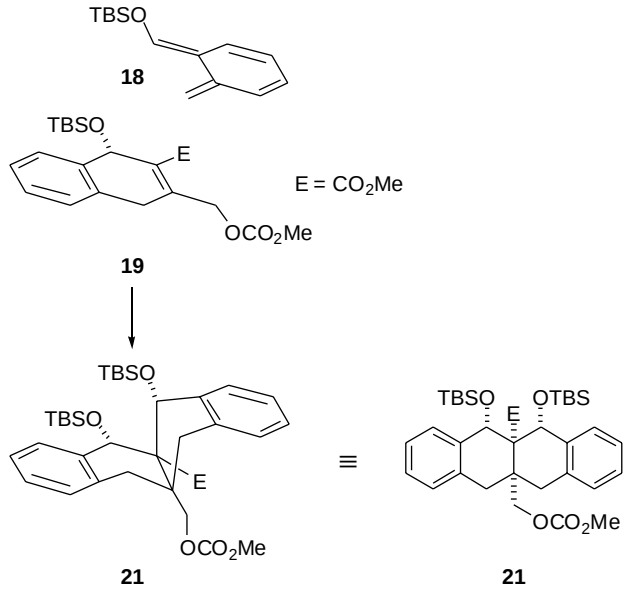
Scheme 2. Reagents and conditions: (a) *n*-BuLi, THF, −78°; (b) methyl chloroformate, 44%; (c) Ac_2O, 47%.

(Scheme 3). The ^{1}H NMR spectrum of **19** was obtained, but further characterisation was impossible due to the facile aromatisation. A similar elimination of methanol from the adducts of the methoxy substituted *o*-quinonedimethides with variously substituted acetylenes has been used intentionally for the regiospecific construction of substituted naphthalenes.[19]



Scheme 3. Reagents and conditions: PhMe, steam bath, 32 h, 54% (**19**), 26% (**20**).

On a separate occasion, the reaction of the *o*-quinonedimethide **18** with the dienophile **15** produced a small quantity of the product **21** arising from capture of a second molecule of **18** by the initial adduct **19** (Scheme 4). The ^{1}H NMR spectrum of **21** showed only one set of TBS signals implying a *cis* relationship of these groups. Given the preference for *endo* addition in Diels–Alder reactions, and the probable approach of the diene **18** *anti* to the bulky silyl group of the initial product **19**, the all *cis* configuration **21** is most likely for this product.

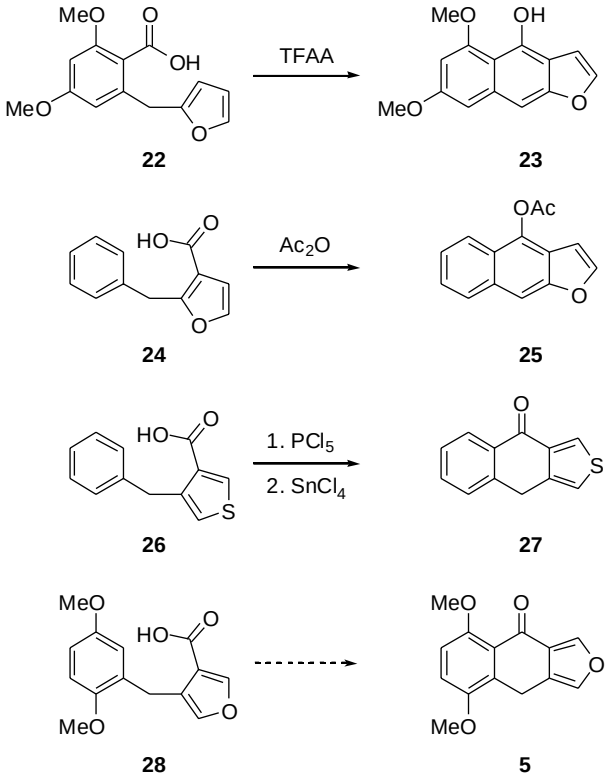


Scheme 4.

Unfortunately, attempts to elaborate **19** also resulted in aromatisation. For example, reduction with diisobutylaluminium hydride (DIBAL) gave only naphthalene-2,3-dimethanol[20] in 82% yield. Accordingly, the route was abandoned.

Several published routes to naphtho[2,3-*b*]furans have involved an intramolecular Friedel–Crafts acylation step late in the synthesis (Scheme 5). Both benzoic acids (**22**→**23**)[21] and furoic acids (**24**→**25**)[22,23] have been used. Although the intramolecular acylation concept has not been adapted to the synthesis of naphtho[2,3-*c*]furan-4(9*H*)-ones, it has been applied to the synthesis of naphtho[2,3-*c*]thiophene **27**.[24] Given these precedents, we were confident that the naphtho[2,3-*c*]furan-4(9*H*)-one skeleton would be accessible via an intramolecular Friedel–Crafts acylation. The furoic acid **28** was chosen to test this hypothesis.

We envisaged that the furoic acid **28** necessary for the intramolecular Friedel–Crafts acylation could be obtained via a tandem Diels–Alder-retro-Diels–Alder reaction[25,26] of the alkyne **31** and 4-phenyloxazole **34** (Scheme 6). However, lithiated ethyl propiolate (**29**)[27] failed to react with the benzyl bromide **30**,[28] even in the presence of HMPA,[29] presumably due to competing auto-condensation

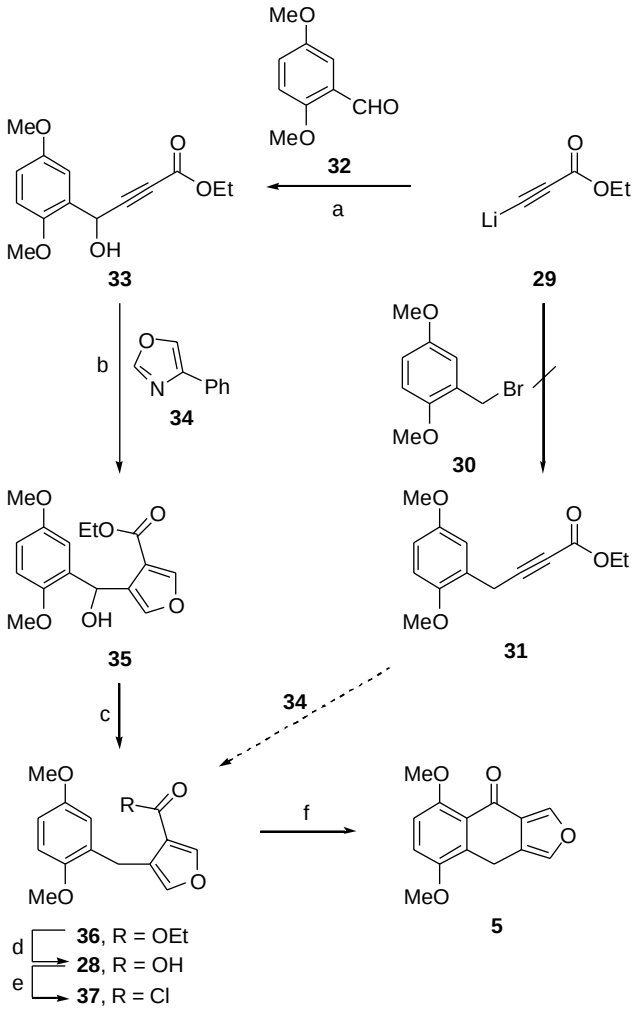


Scheme 5.

of **29**. The lithium acetylide did react smoothly with 2,5-dimethoxybenzaldehyde (**32**) and the resulting alcohol **33** underwent the expected cycloaddition–cycloreversion with 4-phenyloxazole (**34**) to give the furan **35**.

Hydrogenolysis of the benzylic alcohol **35** was complicated by concomitant reduction of the furan ring, while **35** failed to react with lithium in liquid ammonia[30] and decomposed with sodium borohydride/TFA.[31] Fortunately, with TMSI[22] the deoxygenation was complete within 10 min, giving a quantitative yield of the diarylmethane **36**. Hydrolysis of the ethyl ester then gave the target acid **28**.

Attempts to effect the cyclisation of **28** with TFAA, alone[23] or in conjunction with TFA,[32] were unsuccessful. Oxalyl chloride has been used to bring about the cyclisation of an activated aromatic acid,[33] but attempts with this reagent were also unsuccessful in the present case. The acid chloride **37** was resistant to cyclisation with graphite catalysis[33] in refluxing chlorobenzene and decomposed with aluminium chloride in 1,2-dichloroethane.[1] Stannic chloride is a milder reagent than aluminium chloride[34] and has been used with success in intramolecular Friedel–Crafts acylations involving furans.[35] An advantage of this Lewis acid is that when the acid chlorides are prepared with phosphorus pentachloride, it may be added directly to the reaction mixture, obviating the need for a purification step.[34] Accordingly, the acid **28** was converted into the acid chloride **37** with phosphorus pentachloride and the reaction mixture was transferred to a solution of stannic chloride in cold benzene. Obligingly, after workup, the



Scheme 6. Reagents and conditions: (a) 1. THF, −78°; 2. AcOH, −78°–rt, 71% (82% based on recovered **32**); (b) 200°, 72%; (c) NaI, TMSCl, MeCN, quant.; (d) 1. NaOH, MeOH, 2. H_3O^+, 97%; (e) PCl_5, PhH, Δ, (or $SOCl_2$, PhMe, Δ); (f) $SnCl_4$, 5°–rt, 89% from **28**.

cyclised product 5,8-dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one **5** was isolated in excellent yield.

3. Conclusion

5,8-Dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one **5**, which shares its skeleton with a number of biologically active natural products, was prepared in six steps and 44% overall yield. The synthesis includes construction of a 3,4-disubstituted furan by a tandem Diels–Alder-retro-Diels–Alder reaction of an alkyne with 4-phenyloxazole, and an intramolecular Friedel–Crafts acylation.

4. Experimental

4.1. General

All solvents were distilled prior to use; anhydrous solvents and reagents were distilled under N_2. MeCN, benzene, DCM, 1,2-dichloroethane and toluene were dried by

refluxing with calcium hydride. DMF, was dried over 4 Å molecular sieves. THF was distilled from potassium benzophenone ketyl. Propargyl alcohol and methyl chloroformate were dried over anhydrous K_2CO_3. Petrol denotes the hydrocarbon fraction distilling from 64–67 °C.

All reaction temperatures refer to bath temperatures. Kugelrohr distillation temperatures refer to the oven temperature. Organic extracts were dried over anhydrous $MgSO_4$ and then filtered. The concentrations of hexane solutions of *n*-BuLi were determined by titration against diphenylacetic acid in anhydrous THF.

Rapid silica filtration refers to chromatography on a short column of silica (BDH, for flash chromatography, 40–63 μm) in a sintered glass funnel, in which the eluent is sucked through the column under vacuum. Elutions were generally performed with increasing percentages of EtOAc in petrol up to the values shown in parentheses. Analytical TLC was performed on Whatman flexible plates (250 μL layer, Al Sil G/UV254). Spots were visualised under UV light and by staining with a 6% (w/v) solution of ceric sulfate in 2 M sulfuric acid followed by heating.

Melting points were measured on a Kofler hot stage melting point apparatus and are uncorrected. Microanalyses were performed by MHW laboratories (Arizona). Mass spectra were recorded on a VG Autospec instrument using a direct insertion probe and electron impact ionisation (EI) or fast atom bombardment (FAB) where indicated. Nuclear magnetic resonance (NMR) spectra were acquired on Gemini 200 (200 MHz, ^{1}H), Bruker AM300 (300 MHz, ^{1}H; 75.5 MHz, ^{13}C) and Bruker 500 (500 MHz, ^{1}H; 125 MHz, ^{13}C) instruments. Spectra were recorded in $CDCl_3$ unless otherwise indicated. Chemical shift values are expressed in ppm, relative to $CHCl_3$ (^{1}H, 7.26 ppm), $CDCl_3$ (^{13}C, 77.0 ppm), C_6D_5H (^{1}H, 7.15 ppm), C_6D_6 (^{13}C, 128.0 ppm), D_3CSOCD_2H (^{1}H, 2.49 ppm) or D_3CSOCD_3 (^{13}C, 39.5 ppm) as appropriate. Routine assignments of ^{13}C NMR spectra were made with the assistance of DEPT 135 and DEPT 90 experiments.

4.1.1. Methyl 4-[(methoxycarbonyl)oxy]but-2-ynoate (15). A 0.91 M hexane solution of *n*-BuLi (49 mL, 45 mmol) was added to a stirred solution of anhydrous propargyl alcohol (**13**) (1.3 mL, 22 mmol) in anhydrous THF (25 mL) at −78 °C under argon, whereupon a white precipitate formed. After 90 min the suspension was treated dropwise with a solution of methyl chloroformate (5.1 mL, 66 mmol) in anhydrous THF (25 mL). The reaction mixture was allowed to slowly warm to room temperature before being poured onto ice (500 mL), then extracted with ether (3×200 mL). The extract was washed with water (200 mL), dried and evaporated and the residue was subjected to rapid silica filtration. Elution with petrol gave **15** as pale yellow liquid (1.67 g, 44%); ^{1}H NMR (300 MHz) δ 4.81 (s, 2H, CH_2O), 3.79 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O). The spectrum was identical to that reported.[36]

4.1.2. 5-Acetoxy-3-pentyn-2-one (16). A 1.3 M hexane solution of *n*-BuLi (59.5 mL, 77.4 mmol) was added to a stirred solution of anhydrous propargyl alcohol (**13**) (2.2 mL, 39 mmol) in anhydrous THF (100 mL) at −78 °C under argon, whereupon a white precipitate formed. The suspension was diluted with anhydrous THF (100 mL) and then stirred for 1 h before being transferred via cannula to a dropping funnel. The cold suspension was added dropwise to a stirred solution of acetic anhydride (15 mL, 159 mmol) in anhydrous THF (10 mL) at −78 °C under argon. The reaction mixture was allowed to slowly warm to room temperature and stirring was continued overnight. The orange solution was poured into ice-cold saturated aqueous sodium bicarbonate (400 mL), then extracted with ether (3×200 mL). The extract was washed with brine (200 mL), dried and evaporated and the residue was subjected to rapid silica filtration. Elution with petrol gave several fractions, which were combined and distilled (Kugelrohr, 180 °C, 25 mmHg) to give **16** as a colourless liquid (2.486 g, 47%); ^{1}H NMR (300 MHz) δ 4.81 (s, 2H, CH_2O), 2.36 (s, 3H, CH_3), 2.12 (s, 3H, CH_3). This compound is known.[37]

4.1.3. 7-(*t*-Butyldimethylsilyloxy)bicyclo[4.2.0]octa-1,3,5-triene (17). A solution of bicyclo[4.2.0]octa-1,3,5-trien-7-ol[38] (0.75 g, 6.2 mmol), TBSCl (1.62 g, 10.7 mmol) and imidazole (1.12 g, 16.4 mmol) in anhydrous DMF (1.5 mL) was stirred for 6 h. The reaction mixture was diluted with water (50 mL) and extracted with ether (3× 20 mL). The extract was washed with 1 M HCl (20 mL) and water (2×20 mL), dried and evaporated to give a pale yellow liquid, which was subjected to rapid silica filtration. Elution with petrol gave **17** as a pale yellow liquid (1.21 g, 84%); ^{1}H NMR (500 MHz)[‡] δ 7.30–7.27 (m, 1H, Ar), 7.26–7.23 (m, 1H, Ar), 7.20–7.19 (m, 1H, Ar), 7.15–7.14 (m, 1H, Ar), 5.33 (br dd, $J_{7,8\text{-}trans}$=4.5 Hz, $J_{7,8\text{-}cis}$=2.0 Hz, 1H, H7), 3.57 (ddd [apparent br dd], J_{gem}=13.9 Hz, $J_{8\text{-}trans,7}$= 4.5 Hz, $J_{8\text{-}trans,6}$=0.4 Hz, 1H, H8-*trans*), 3.10 (ddd [apparent dt], J_{gem}=13.9 Hz, $J_{8\text{-}cis,7}$=2.0 Hz, $J_{8\text{-}cis,3}$= 0.6 Hz, 1H, H8-*cis*), 0.98 (s, 9H, *t*-Bu), 0.20 (s, 3H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$); ^{13}C NMR (125.8 MHz) δ 148.5 (Ar), 142.0 (Ar), 129.0 (ArH), 126.9 (ArH), 123.4 (ArH), 122.2 (ArH), 70.6 (C7), 42.3 (C8), 25.9 ($C[CH_3]_3$), 18.2 (SiC), −4.57 ($SiCH_3$), −4.64 ($SiCH_3$). This ether has been reported previously but no NMR data were published.[39]

4.1.4. Diels–Alder reaction of the *o*-quinonedimethide 18 and 15. A solution of **15** (0.26 g, 1.51 mmol) and **17** (0.34 g, 1.45 mmol) in anhydrous toluene (2 mL) under argon, was heated on a steam bath for 32 h. The toluene was evaporated and the residue was subjected to rapid silica filtration. Elution with EtOAc/petrol (1:99) gave the slightly impure methyl 1-(*t*-butyldimethylsilyloxy)-3-[(methoxycarbonyloxy)methyl]-1,4-dihydronaphthalene-2-carboxylate (**19**) as an unstable white solid (0.32 g, 54%), which crystallised from petrol, mp 63–64 °C; ^{1}H NMR (200 MHz) δ 7.35 (m, 1H, Ar), 7.23 (m, 3H, Ar), 5.77 (br s, 1H, H1), 5.33 (d, J_{gem}=14.4 Hz, 1H, OC*Ha*Hb), 5.19 (d, J_{gem}=14.4 Hz, 1H, OCHa*Hb*), 3.82 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 3.63 (br s, 2H, H4a/H4b), 0.74 (s, 9H, *t*-Bu), −0.04 (s, 3H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$). Further characterisation was impossible due to the facile elimination of *t*-butyldimethylsilanol.

[‡] The analysis of the spectrum was aided by a homonuclear decoupling experiment.

Further elution gave methyl 3-[(methoxycarbonyloxy)-methyl]naphthalene-2-carboxylate (**20**) as a white crystalline solid (0.10 g, 25%), which crystallised from petrol as colourless needles, mp 66–68 °C; (Found: C, 65.90, H, 5.08. $C_{15}H_{14}O_5$ requires C, 65.69, H, 5.15%); MS *m/z* 274 (M, 12%), 183 (100), 127 (16), 57 (23); ^{1}H NMR (300 MHz) δ 8.59 (s, 1H, H1), 7.95 (br s, 1H, H4), 7.93–7.85 (m, AB part of ABXY, 2H, Ar), 7.63–7.51 (m, XY part of ABXY, 2H, Ar), 5.73 (d, $J_{4,CH2}$=0.8 Hz, 2H, CH_2), 3.96 (s, 3H, CH_3O), 3.84 (s, 3H, CH_3O); ^{13}C NMR (75.5 MHz) δ 167.1 (CO_2), 155.6 (OCO_2), 134.7 (Ar), 132.8 (ArH), 132.6 (Ar), 131.9 (Ar), 128.8 (ArH), 128.6 (ArH), 127.8 (ArH), 127.7 (ArH), 127.0 (ArH), 125.9 (Ar), 68.2 (CH_2O), 54.9 (CH_3O), 52.2 (CH_3O).

On another occasion, a small amount of the double adduct, methyl 5α,5aα,6α,11aα-5,6-bis[(*t*-butyldimethylsilyl)oxy]-11a-[(methoxycarbonyl)methoxy]-5,5a,6,11,11a,12-hexahydronaphthacene-5a-carboxylate (**21**), was isolated by rapid silica filtration as a colourless oil (27 mg, 3%); ^{1}H NMR (300 MHz)[§] δ 7.01 (ddd, $J_{B,C}=J_{B,A}$=7.4 Hz, $J_{B,D}$=1.4 Hz, 2H, Ar [B]), 6.94 (ddd, $J_{C,B}$=7.4 Hz, $J_{C,D}$=7.4 Hz, $J_{C,A}$=1.0 Hz, 2H, Ar [C]), 6.85 (dd, $J_{A,B}$=7.4 Hz, $J_{A,C}$=1.0 Hz, 2H, Ar [A]), 6.82 (d, $J_{D,C}$=7.4 Hz, 2H, Ar [D]), 4.92 (s, 2H, H5/H6 or CH_2O), 4.77 (s, 2H, H5/H6 or CH_2O), 3.80 (s, 3H, CH_3O), 3.66 (s, 3H, CH_3O), 3.33 (d, J_{gem}=15.4 Hz, 2H, H11a/H12a), 2.59 (d, J_{gem}=15.4 Hz, 2H, H11b/H12b), 0.79 (s, 18H, *t*-Bu), 0.00 (s, 6H, $SiCH_3$), −0.31 (s, 6H, $SiCH_3$); ^{13}C NMR (75.5 MHz) δ 170.9 (CO_2), 155.8 (OCO_2), 136.6 (Ar), 136.2 (Ar), 127.9 (ArH), 127.8 (ArH), 127.3 (ArH), 125.4 (ArH), 75.6 (CH_2O), 74.7 (C5/C6), 62.1 (C5a), 54.6 (CH_3O), 51.4 (CH_3O), 41.2 (C11a), 38.3 (C11/C12), 25.8, (C[CH_3]$_3$), 18.1 (SiC), −4.3 ($SiCH_3$), −4.6 ($SiCH_3$).

4.1.5. Attempted reduction–deprotection of the Diels–Alder adduct (19). A stirred solution of **19** (100 mg, 0.25 mmol) in anhydrous DCM (15 mL) in an ice/salt bath under argon, was treated dropwise with a 1.2 M toluene solution of DIBAL (1.25 mL, 1.5 mmol). After 2 h the solution was allowed to warm to room temperature and the excess DIBAL was quenched with methanol (5 mL). Ice-cold 1 M HCl (50 mL) was added and the phases were separated. The aqueous layer was extracted with DCM (3×20 mL) and the combined organic solution was dried and evaporated to give naphthalene-2,3-dimethanol as a white solid (38 mg, 82%), which crystallised from DCM/petrol as colourless rhomboids, mp 160 °C (lit.[20] 160 °C); ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.47 (s, 2H, H1/H4), 7.43 (m, AA′ part of AA′BB′, 2H, Ar), 7.08 (m, BB′ part of AA′BB′, 2H, Ar), 4.77 (br t, J=5.0 Hz, 2H, OH), 4.45 (d, J=5.0 Hz, 4H, CH_2); ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 137.0 (Ar), 131.8 (Ar), 126.6 (ArH), 126.2 (ArH), 125.0 (ArH), 62.0 (CH_2). The ^{1}H NMR spectrum is somewhat different to that published at lower field.[20]

4.1.6. 2,5-Dimethoxybenzaldehyde (32). The methodology of Scarpatie et al. was used.[40] A solution of titanium tetrachloride (26 mL, 0.24 mol) in anhydrous DCM (45 mL) was added to a stirred solution of 1,4-dimethoxybenzene (13.82 g, 0.10 mol) in anhydrous DCM (200 mL) at 0 °C under argon, whereupon the colourless solution turned deep red. The reaction mixture was treated dropwise with a solution of dichloromethoxymethane (12.36, 0.14 mol) in anhydrous DCM (90 mL) over 1.5 h. The ice bath was removed and stirring was continued for 30 min before the reaction mixture was poured onto a mixture of ice (300 g) and concentrated HCl (8 mL). The biphasic mixture was stirred for 2 h, during which time the dark red organic layer turned green. The phases were separated and the aqueous layer was extracted with ether (2×200 mL). The combined organic solutions were washed with water (3×200 mL) and brine (200 mL), dried and evaporated to give essentially pure **32** as a green oil, which solidified on standing (16.57 g, 100%), and crystallised from ether as pale green microneedles, mp 48–50 °C (lit.[41] 53 °C); ^{1}H NMR (200 MHz) δ 10.37 (s, 1H, CHO), 7.25 (d, $J_{6,4}$=3.3 Hz, 1H, H6), 7.06 (m, 1H, H4), 6.87 (d, $J_{3,4}$=9.0 Hz, 1H, H3), 3.82 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O). The spectrum was similar to that reported.[42]

4.1.7. Ethyl 4-(2,5-dimethoxyphenyl)-4-hydroxy-2-butynoate (33). A 1.18 M solution of *n*-BuLi in hexane (8.5 mL, 10 mmol) was added dropwise to a stirred solution of ethyl propiolate (981 mg, 10 mmol) in anhydrous THF (20 mL) at −78 °C under argon. After 10 min a solution of **32** (1.662 g, 10.0 mmol) in anhydrous THF (20 mL) was added dropwise. Stirring was continued for 10 min and then for a further 10 min with the cryogenic bath removed. Acetic acid (2 mL, 35 mmol) was added and the reaction mixture was allowed to warm to room temperature before being partitioned between ether (100 mL) and saturated aqueous sodium bicarbonate (100 mL). The layers were separated and the aqueous phase was extracted with ether (2×50 mL). The combined ether solution was washed with saturated aqueous sodium bicarbonate (50 mL), water (50 mL) and brine (50 mL), dried and evaporated to give a red-brown oil, which was subjected to rapid silica filtration. Elution with EtOAc/petrol (1:19) gave unreacted **32** (233 mg). Further elution with EtOAc/petrol (1:4) gave **33** as a honey coloured oil (1.870 g, 71%, 82% based on recovered **32**); MS (FAB) *m/z* 264 (M, 80%), 247 (100), 175 (20), 165 (39); HRMS found: 247.0986. $[C_{14}H_{16}O_5–H_2O]^+$ requires 247.0970; ^{1}H NMR (300 MHz, C_6D_6)[¶] δ 7.07 (d, $J_{6',4'}$=3.1 Hz, 1H, H6′), 6.66 (dd, $J_{4',3'}$=8.9 Hz, $J_{4',6'}$=3.1 Hz, 1H, H4′), 6.34 (d, $J_{3',4'}$=8.9 Hz, 1H, H3′), 5.63 (br d, $J_{4,OH}$=7.1 Hz, 1H, H4), 3.81 (q, J=7.1 Hz, 2H, CH_2O), 3.29 (s, 3H, CH_3O), 3.19 (s, 3H, CH_3O), 2.92 (br d, $J_{OH,4}$=7.1 Hz, 1H, OH), 0.78 (t, J=7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, C_6D_6) δ 154.4 (C), 153.5 (C), 150.9 (C), 128.8 (C1′), 115.0 (ArH), 113.4 (ArH), 112.5 (ArH), 87.1 (C3), 77.3 (C2), 61.7 (CH_2O), 61.0 (C4), 55.6 (CH_3O), 55.2 (CH_3O), 13.7 (CH_3); IR ν_{max} br 3446 (OH), 2233 (C≡C), 1709 cm^{-1} (CO).

4.1.8. Ethyl 4-[(2,5-dimethoxyphenyl)(hydroxy)methyl]-3-furoate (35). A mixture of **33** (1.016 g, 3.8 mmol), 4-phenyloxazole (**34**)[41] (2.72 g, 18.7 mmol) and hydroquinone (5 mg) under argon, was stirred at 200 °C for 1.5 h,

[§] The designations A,B,C,D are meant only to represent the relationship of the Ar protons to each other as determined by the coupling constants. Thus, A and D correspond to H1/H10 and H4/H7; B and C correspond to H2/H9 and H3/H8, but not necessarily, respectively, as shown.

[¶] The ^{1}H NMR. spectrum in $CDCl_3$ was not first order.

after which time TLC showed the reaction to be complete. The reaction mixture was cooled and the crude product was subjected to rapid silica filtration. Elution with EtOA/petrol (1:19) gave excess **34**. Further elution with EtOAc/petrol (1:9) gave **35** as a yellow oil (844 mg, 72%); MS (FAB) *m/z* 306 (M, 83%), 290 (20), 289 (100), 229 (20), 153 (22); EI-HRMS ($M^{+\cdot}$) found: 306.1090. $C_{16}H_{18}O_6$ requires 306.1103; ^{1}H NMR (300 MHz) δ 7.97 (d, $J_{2,5}=1.7$ Hz, 1H, H2), 7.14 (m, 1H, H5, 6.88, dd, $J_{6',4'}=1.7$ Hz, $J_{6',3'}=1.0$ Hz, 1H, H6′), 6.80 (m [apparent d], 2H, H3′/H4′), 6.23 (s, 1H, CHOH), 4.92 (br s, 1H, OH), 4.32 (q, $J=7.1$ Hz, 2H, CH_2O), 3.76 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 1.33 (t, $J=7.1$ Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz) δ 164.8 (CO), 153.8 (ArO), 150.3 (ArO), 149.4 (C2), 142.0 (C5), 130.9 (Ar), 128.4 (Ar), 117.9 (Ar), 113.5 (ArH), 112.8 (ArH), 111.5 (ArH), 62.0 (CHOH), 61.0 (CH_2O), 56.0 (CH_3O), 55.7 (CH_3O), 14.1 (CH_3); IR ν_{max} br 3437 (OH), 1696 cm^{-1} (CO).

4.1.9. Ethyl 4-(2,5-dimethoxybenzyl)-3-furoate (36). TMSCl (4.2 mL, 33 mmol) was added to a stirred solution of NaI (5.00 g, 33 mmol) in anhydrous MeCN (40 mL) under argon, whereupon NaCl precipitated. A solution of **35** (1.702 g, mmol) in anhydrous MeCN (100 mL) was added dropwise to the suspension, whereupon iodine colour developed immediately. After 10 min the reaction mixture was diluted with water (500 mL) then extracted with ether (4×100 mL). The extract was washed with aqueous sodium thiosulfate solution (2×100 mL) and brine (100 mL), dried and evaporated to give essentially pure **36** as a yellow oil (1.61 g, 100%). Distillation under vacuum gave the analytical sample as a colourless oil; (Found: C, 66.45, H, 6.32. $C_{16}H_{18}O_5$ requires C, 66.20, H, 6.25%); MS *m/z* 167 (68%), 97 (100), 95 (26), 84 (26); ^{1}H NMR (300 MHz) δ 7.97 (d, $J_{2,5}=1.7$ Hz, 1H, H2), 7.01 (m, 1H, H5), 6.80 (d, $J_{3',4'}=8.6$ Hz, 1H, H3′), 6.76–6.70 (m, 2H, H4′/H6′), 4.27 (q, $J=7.1$ Hz, 2H, CH_2O), 3.97 (br s, 2H, CH_2), 3.78 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 1.29 (t, $J=7.1$ Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz) δ 163.6 (CO), 153.4 (ArO), 151.6 (ArO), 148.7 (C2), 142.1 (C5), 129.6 (Ar), 124.0 (Ar), 118.5 (Ar), 116.4 (ArH), 111.4 (ArH), 111.2 (ArH), 60.0 (CH_2O), 55.9 (CH_3O), 55.6 (CH_3O), 24.5 (CH_2), 14.1 (CH_3); IR ν_{max} 1720 cm^{-1} (CO).

4.1.10. 4-(2,5-Dimethoxybenzyl)-3-furoic acid (28). Aqueous sodium hydroxide (20% (w/v), 5 mL) was added to a solution of **36** (166 mg, 0.57 mmol) in methanol (5 mL), whereupon a white precipitate formed. The suspension was heated under reflux for 1 h and the solution, which formed was cooled and poured onto ice-cold 1 M HCl (50 mL), whereupon a white precipitate formed. The suspension was extracted with EtOAc (3×25 mL) and the extract was washed with water (25 mL) and brine (25 mL), dried and evaporated to give **28** as a white crystalline solid (146 mg, 97%), which crystallised from ether/petrol as colourless needles, mp 138–140 °C; (Found: C, 64.34, H, 5.49. $C_{14}H_{14}O_5$ requires C, 64.12, H, 5.38%); MS (FAB) *m/z* 263 (M+H, 24%), 262 (M, 20), 245 (14); ^{1}H NMR (300 MHz) δ 11.05 (br s, 1H, CO_2H), 8.09 (d, $J_{2,5}=1.7$ Hz, 1H, H2), 7.05 (m, 1H, H5), 6.83–6.80 (m, 2H, Ar), 6.75 (dd, $J_{4',3'}=8.9$ Hz, $J_{4',6'}=2.9$ Hz, 1H, H4′), 4.00 (br s, 2H, CH_2), 3.79 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O); ^{13}C NMR (75.5 MHz) δ 169.4 (CO), 153.4 (ArO), 151.6 (ArO), 150.2 (C2), 142.4 (C5), 129.3 (Ar), 124.4 (Ar), 117.7 (Ar), 116.4 (ArH), 111.7 (ArH), 111.4 (ArH), 55.9 (CH_3O), 55.5 (CH_3O), 24.4 (CH_2); IR ν_{max} v br 2400–3300 (OH), 1689 cm^{-1} (CO).

4.1.11. 5,8-Dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one (5). PCl_5 (0.86 g, 4.1 mmol) was added to a stirred suspension of **28** (0.899 g, 3.4 mmol) in partially frozen, anhydrous benzene (15 mL), in an ice bath under argon. The reaction mixture was allowed to warm to room temperature, and then heated under reflux for 1 h. The solution of 4-(2,5-dimethoxybenzyl)-3-furoyl chloride (**37**) was cooled to room temperature then added dropwise to a stirred solution of stannic chloride (0.5 mL, 4.25 mmol) in partially frozen, anhydrous benzene (15 mL), whereupon a red precipitate formed. The reaction mixture was allowed to slowly warm to room temperature and stirring in the dark was continued overnight. The benzene was evaporated and the residue was partitioned between 1 M HCl (300 mL) and EtOAc (80 mL). Oxalic acid was added to help break down the tin complex. The layers were separated and the aqueous phase was extracted with EtOAc (4×80 mL). The combined organic solution was washed with saturated aqueous sodium bicarbonate solution (2×80 mL), water (80 mL) and brine (2×80 mL), dried and evaporated to give **5** as a yellow solid (752 mg, 89%), which crystallised from EtOAc/petrol as an amorphous yellow solid, mp 140–143 °C; (Found: C, 68.61, H, 4.84. $C_{14}H_{12}O_4$ requires C, 68.85, H, 4.95%); MS (FAB) *m/z* 245 (M+H, 100), 244 (M, 38); ^{1}H NMR (300 MHz) δ 8.12 (d, $J_{3,1}=1.6$ Hz, 1H, H3), 7.45 (dt, $J_{1,3}=J_{1,9}=1.6$ Hz, 1H, H1), 7.04 (d, $J_{7,6}=9.1$ Hz, 1H, H7), 6.89 (d, $J_{6,7}=9.1$ Hz, 1H, H6), 3.96 (m [apparent br d], 2H, CH_2), 3.91 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O); ^{13}C NMR (75.5 MHz) δ 181.5 (CO), 155.3 (ArO), 150.5 (ArO), 144.1 (C3), 138.2 (C1), 132.0 (Ar), 124.5 (Ar), 123.0 (Ar), 120.5 (Ar), 115.0 (ArH), 110.7 (ArH), 56.6 (CH_3O), 55.8 (CH_3O), 19.6 (CH_2); IR ν_{max} 1667 cm^{-1} (CO).

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