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Total synthesis of monosporascone and dihydromonosporascone†

Kathryn A. Punch and Matthew J. Piggott*

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The first total synthesis of monosporascone is presented. The five-step synthesis developed includes a silver acetylide-acid chloride coupling, domino Diels–Alder-retro-Diels–Alder reaction, and an intramolecular Friedel–Crafts acylation, and provides the natural product in 57% yield overall. Selective reduction of monosporascone also afforded the related metabolite dihydromonosporascone.

Introduction

The naphtho[2,3-*c*]furandiones (isofuranonaphthoquinones) comprise a relatively small group of secondary metabolites, with a wide variety of biological activities, isolated from fungal, botanical, bacterial and insect sources. In 2005, when this class of compounds was comprehensively reviewed,[1] there were 17 natural products possessing the isofuranonaphthoquinone ring-system, and a similar number of partially reduced congeners. Since that time a single new member has been discovered: **1** (Fig. 1), which is moderately cytotoxic to a range of cancer cell lines and non-malignant human foreskin fibroblasts.[2]

Isofuranonaphthoquinones continue to attract the attention of synthetic chemists, with recent syntheses making use of silver(II) and manganese(III)-mediated radical cyclisation of 1,4-naphthoquinone derivatives;[3–5] a double conjugate addition of a hydroxymethyldihydronaphthoquinone monoketal to propiolate esters;[6] oxidative skeletal rearrangement of a naphtho[1,2-*b*]furan-5-ol, applied to the synthesis of bhimamycin B (**2**);[7] a sequence involving consecutive [2 + 2 + 2] alkyne cyclotrimerisation, Ullman, Claisen, and ring-closing metathesis reactions; and, in the synthesis of **1**, key Friedel–Crafts reactions.[8] Tsunoda and co-workers recently completed an efficient total synthesis of the cytotoxic aphid pigment furanaphin (**3**), in a total of eight steps and 23% yield, using a key boron trifluoride-acetic acid-mediated Fries rearrangement.[9]

In a continuation of our interest in naphtho[2,3-*c*]furandiones and related compounds,[1,10–14] we targeted monosporascone (**4**) for total synthesis (Scheme 1). Monosporascone and its dihydro derivative **5** were first isolated from the fungus

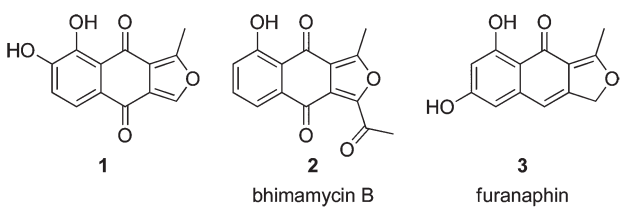
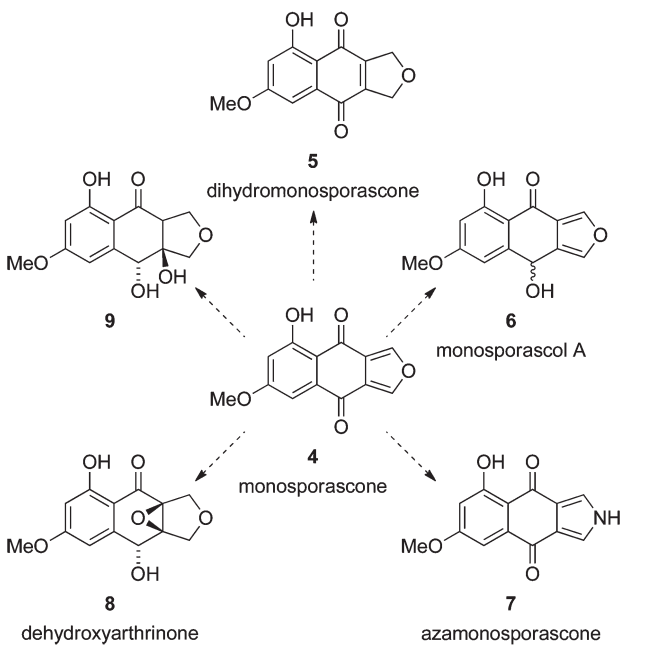


Fig. 1 Recently synthesised isofuranonaphthoquinone (**1**, **2**) and related (**3**) natural products.



Scheme 1 Monosporascone (**4**) could be a synthetic precursor to related natural products **5**,[15] **6**,[16] **7**,[16] **8**[16–18] and **9**.[17,18] Monosporascol A (**6**) is optically active, and presumably homochiral, but its configuration has not been determined.[16]

School of Chemistry and Biochemistry, The University of Western Australia, Perth, WA, Australia. E-mail: matthew.piggott@uwa.edu.au; Fax: +618 6488 1005; Tel: +618 6488 3170

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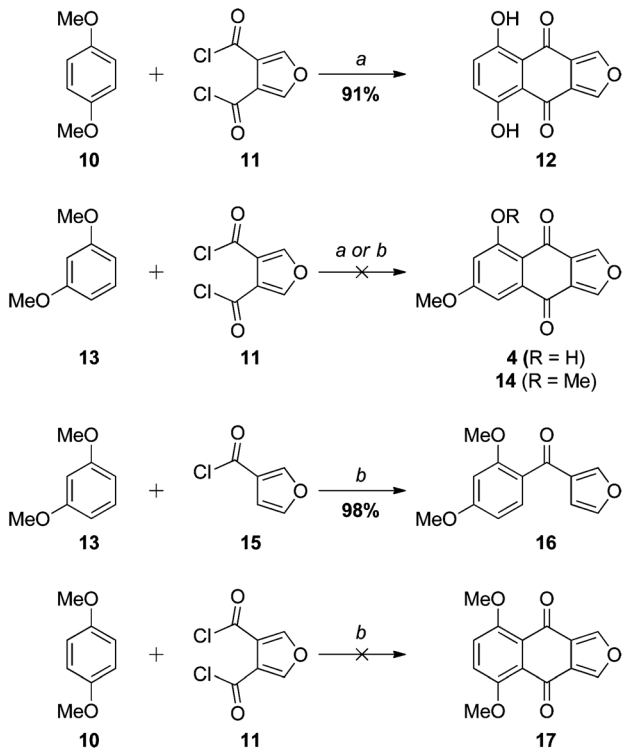
Gelasinospora pseudoreticulata, and hence originally named GP-A and GP-B, respectively.[15] Both compounds were shown to inhibit the pharmacotherapeutically important enzyme monoamine oxidase. Monosporascone (**4**) was named after the fungus it was subsequently isolated from – *Monosporascus cannonballus*[16] – the causative agent of root rot and vine decline in commercial melon species.

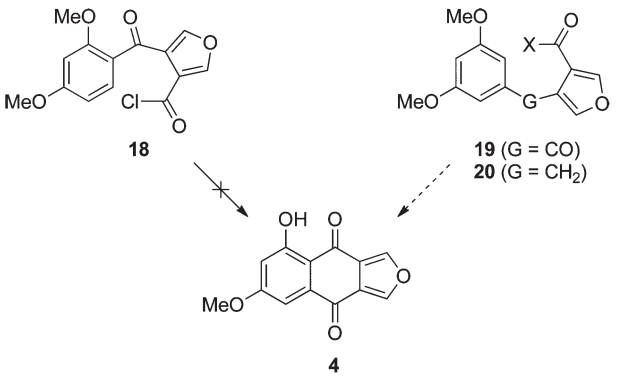
Monosporascone is the only known isofuranonaphthoquinone with oxygenation only at the 5- and 7-positions, and thus presents a unique synthetic challenge. In addition, there are a number of related biologically active metabolites with the same substitution pattern that could conceivably be derived from monosporascone (Scheme 1), in some cases very succinctly. These considerations were the impetus behind the work described herein.

Results and discussion

The initial approach to monosporascone was based on our previous synthesis of the 5,8-dihydroxy analogue **12** (Scheme 2). In that instance the double Friedel–Crafts acylation of hydroquinone dimethyl ether (**10**) with furan-3,4-dicarbonyl chloride (**11**),[19] with concomitant demethylation, provided **12** cleanly and in excellent yield.[10] Application of this methodology to resorcinol dimethyl ether (**13**) gave complex mixtures with $AlCl_3$ and no reaction with $SnCl_4$, with no sign of monosporascone (**4**) or its methyl ether **14** detected in any attempt. With $AlCl_3$ at least, presumably the first acylation at the doubly-activated 4-position of **13** proceeds as expected to give **18** (Scheme 3). This is supported by the reaction of **13** with 3-furoyl chloride (**15**), which in the presence of $SnCl_4$ gave **16** in excellent yield (Scheme 2). The site for subsequent cyclisation in **18**, however, is now strongly deactivated to electrophilic aromatic substitution by the *ortho*-carbonyl and further (weakly) deactivated by the two *meta*-methoxy groups. As a result cyclisation does not occur and side reactions ensue. With $SnCl_4$ as the Lewis acid, it is more difficult to explain why **15** reacts cleanly while **11** does not react at all. However, 1,4-dimethoxybenzene (**10**) was also unreactive with **11** under these conditions.



Scheme 2 Reagents and conditions: (a) $AlCl_3$, DCE (1,2-dichloroethane); (b) $SnCl_4$, DCM.

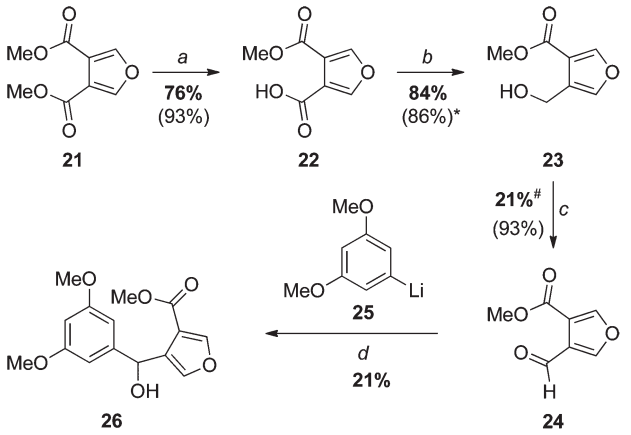


Scheme 3 Failed and revised approaches to monosporascone (**4**). X = OMe, OH or Cl.

In any case, the failure of this initial foray required a rethink. Since it appeared that cyclisation of putative intermediate **18** was not possible, we chose to investigate the reverse approach, where the initial event in the construction of the central ring was bond formation at C5 of resorcinol dimethyl ether (or a derivative), allowing cyclisation onto the position activated by both *ortho* and *para* methoxy groups (Scheme 3 right). Although the precedent in Scheme 2 suggested that this approach should work from ketone **19**, in parallel we also pursued the variant in which the furan is tethered by an activating alkyl bridge, as in **20**; that is, *via* the naphtho[2,3-*c*]furan-4(9*H*)-one, with the view to install the carbonyl group[20] of monosporascone at a later stage.

Approach 1: *via* a diarylmethane (33)

Our first approaches to monosporascone (see also the next section) sought to take advantage of available dimethyl furan-3,4-dicarboxylate (**21**) (Scheme 4), the precursor to acid chloride **11**. Thus, **21** was mono-saponified and chemoselective reduction of the carboxylic acid **22** with borane–dimethyl sulfide afforded the known primary alcohol **23**,[21] which was also previously made in low yield by direct partial reduction of the diester **21** with DIBAL.[22] Swern oxidation, as reported,[22] then provided the required 'semialdehyde' **24**. Addition of the aryllithium **25** generated from 1-bromo-3,5-dimethoxybenzene to this aldehyde gave the expected carbinol **26** in rather disappointing yield.

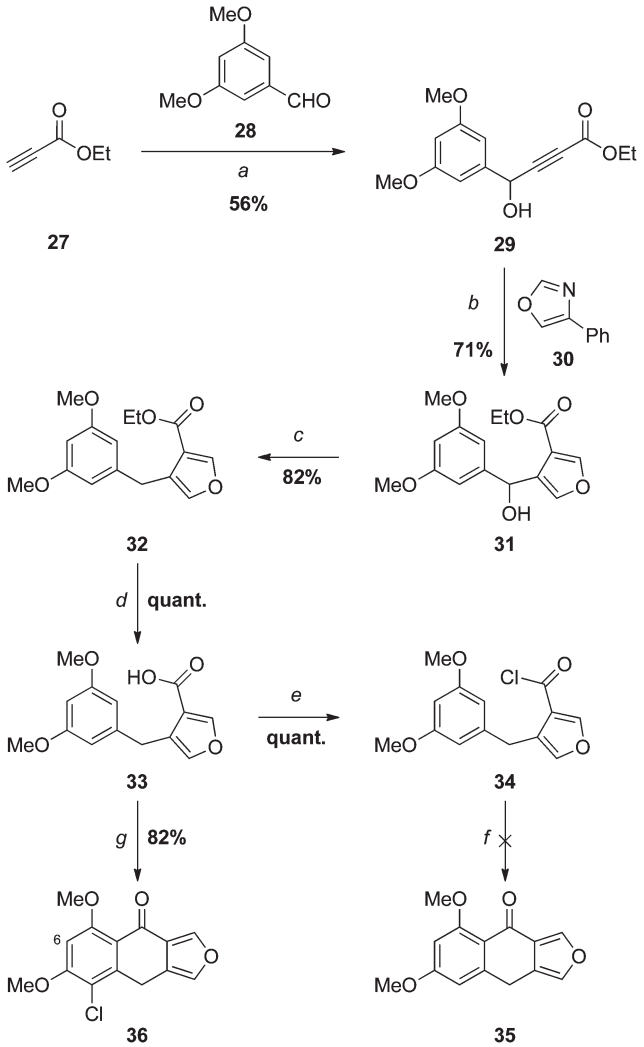


Scheme 4 Reagents and conditions: (a) 1. NaOH, MeOH, 2. H_3O^+; (b)* H_3B–SMe_2, THF; (c) DMSO, $(COCl)_2$, DCM; (d) 1. 3,5-dimethoxybromobenzene, BuLi, THF, 2. **24**. Literature yields are shown in brackets. *The reported procedure used H_3B–THF.[21] #We attribute no significance to the lower yield in our hands; the reaction was carried out only once.

Although the final step in Scheme 4 could almost certainly have been improved with further experimentation, the rather onerous synthesis of aldehyde **24** (six steps from furan and dimethyl acetylenedicarboxylate) led us to explore a more efficient route (Scheme 5).

Low temperature addition[13] of the lithium acetylide generated from ethyl propiolate (**27**) to 3,5-dimethoxybenzaldehyde (**28**) gave the expected secondary alcohol **29**, which underwent a domino Diels–Alder-retro-Diels–Alder reaction[13,23] with 4-phenyloxazole (**30**)[24] providing the 3,4-disubstituted furan **31**. Lewis or Brønsted acid-catalysed Friedel–Crafts ring closure at this juncture could, in principle, provide access to monosporascone (**4**) *via* racemic monosporascol A (**6**) (Scheme 1); however, we expected the benzylic alcohol to be incompatible with such conditions, and as such this was not attempted. Instead **31** was deoxygenated with trimethylsilyl iodide,[13,25] affording the diarylmethane **32** in excellent yield. Saponification then provided the carboxylic acid **33** quantitatively after acidification. Attempts to generate the corresponding acid chloride **34** with thionyl chloride led to complete degradation, even at low temperature. The reaction was successful with oxalyl chloride, however, and the acid chloride **34** was surprisingly stable, not hydrolysing during TLC, for example.

Based on the ^{1}H NMR spectrum of the crude product, the attempted intramolecular Friedel–Crafts acylation of **34** with $AlCl_3$ gave primarily what appeared to be a dialdehyde (although this was not properly identified), presumably arising from ring-opening of the furan. Surprisingly, based on precedent,[13] the use of the milder Lewis acid $SnCl_4$ with the isolated acid chloride **34** led to complete degradation, with no **35** detected. When this reaction was repeated with acid chloride generated *in situ* using PCl_5, cyclisation was successful, but accompanied by chlorination of the benzene ring, as apparent from the mass spectrum of the product **36**. Presumably the chlorinating agent is PCl_5, or perhaps Cl_2 arising from its disproportionation. The regioidentity of **36** was established by a 1D NOESY experiment: irradiation of H6 led to enhancements in the signals for both methoxy groups. The results described above suggest that chlorination, either before or after ring closure, is required to stabilise the product under the reaction conditions.

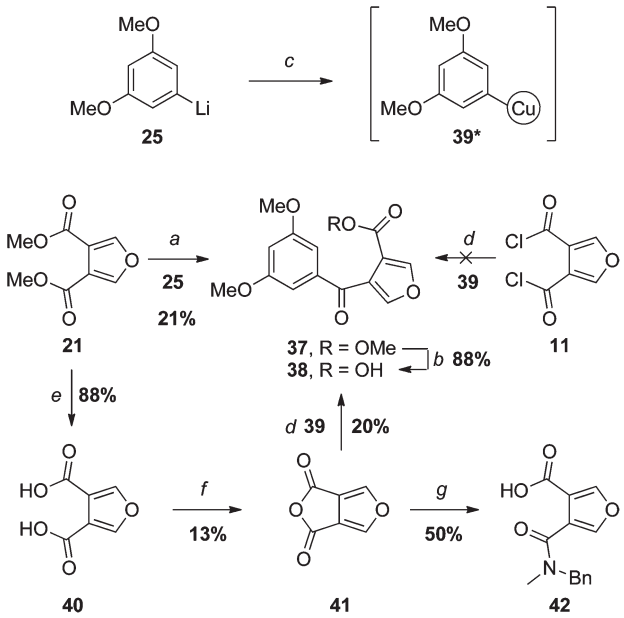


Scheme 5 Reagents and conditions: (a) 1. BuLi, THF, –100 °C, 2. **28**; (b) hydroquinone, 200 °C; (c) TMSCl, NaI, MeCN; (d) 1. NaOH, MeOH, 2. H_3O^+; (e) $(COCl)_2$, 0 °C (crude yield indicated); (f) $AlCl_3$, DCE, 0 °C or $SnCl_4$, PhH, 0 °C; (g) 1. PCl_5, PhH, reflux, 2. $SnCl_4$, 0 °C.

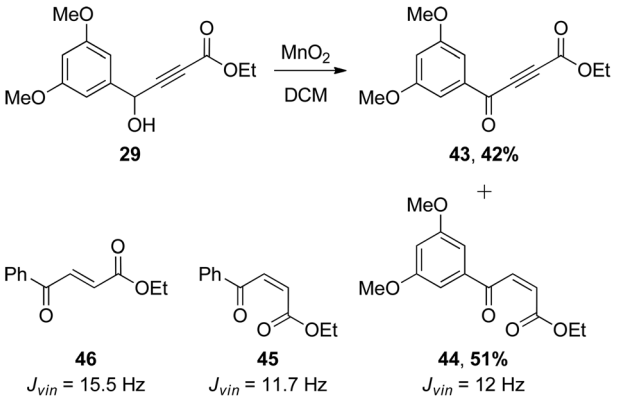
Our other endeavours (carried out in parallel) had born fruit at this time so, while it is probably possible to elaborate **36** to monosporascone through judicious redox transformations, we made no attempt at this task.

Approach 2: *via* a diarylketone (37)

Our first venture in this area mirrored the approach outlined in Scheme 4. Addition of one equivalent of aryllithium **25** to diester **21** did give the desired ketone **37**, but only in low yield and, not unexpectedly, accompanied by the corresponding tertiary alcohol arising from double addition (Scheme 6). An



Scheme 6 Reagents and conditions: (a) THF, −78 °C → RT (product is **37**); (b) LiOH, MeOH–H_2O, 0 °C; (c) CuCN·2LiCl, THF, −78 → −40 °C, *The structure of such organocuprates is poorly understood; (d) THF, −78 °C → RT, 2. H_3O^+ (product is **38**); (e)[19] 1. 20% NaOH, reflux, 2. H_3O^+; (f) Ac_2O, reflux; (g) xs BnNHMe, DCM.



Scheme 7 Reaction of **29** with MnO_2 gave the unexpected tautomerisation product **44**.

attempt to saponify the ester under standard conditions (NaOH, heat) lead to ring-opening of the furan, as apparent from the absence of relevant signals in the ^{1}H NMR spectrum of the crude product. The proclivity of isofuranonaphthoquinones to conjugate addition at the furan α-positions has been noted previously,[10] and presumably extends to other furans with electron-withdrawing groups at the β-positions. Fortunately, under milder conditions (LiOH, 0 °C), competing ring-opening was avoided, providing the carboxylic acid **38** in good yield after acidification.

An attempt was made to improve on the yield of the key carbonyl substitution reaction by use of an organocuprate intermediary **39**, generated by transmetallation of aryllithium **25** with CuCN/2LiCl.[26] However, reaction of one equivalent of **39** with bis-acid chloride **11**, followed by hydrolytic workup, failed to provide any of the expected keto-acid **38**, nor any other identifiable product.

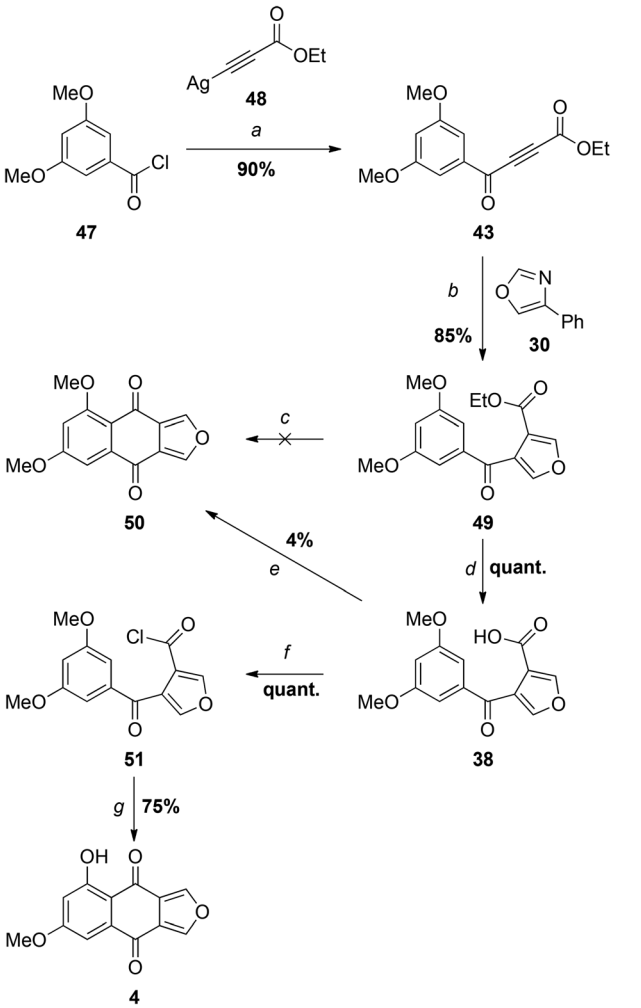
We also investigated the analogous reaction of novel bicyclic anhydride **41**, which, unlike the acid chloride **11**, can only undergo mono-substitution with an organocuprate. Anhydride **41** was prepared by dehydrative cyclisation of furan-3,4-dicarboxylic acid (**40**).[19] Whilst **41** passed elemental analysis, and the spectroscopic data supported the cyclic anhydride structure (*e.g.*, an IR absorption at 1780 cm^{-1}), we were initially thrown by the upfield ^{13}C NMR chemical shift of the carbonyl carbons (155.2 ppm). However, the carbonyl carbons of other strained anhydrides resonate at similar frequencies (*e.g.* malonic anhydride: 160.3 ppm[27]), and the mesomeric effect of the furan oxygen would be expected to further shield the carbonyl carbons in **41**. Nevertheless, to help confirm the structure, **41** was reacted with *N*-methylbenzylamine; indeed this gave rise to the expected amide **42**.

The reaction of organocuprate **39** with anhydride **41** did provide the desired keto-acid **38**, but unfortunately in no better yield than the aryllithium/ester substitution reaction (step a). Once again, the problems associated with monosubstitution of a furan-3,4-dicarboxylic acid derivative led us to consider an alternative approach in which the furan ring is constructed later in the synthesis. Specifically, we hoped to capitalise on the success of the successful cycloaddition–cycloreversion described in Scheme 5 but with the even better dienophile, keto-ester **43** (Scheme 7).

Since we had **29** in hand, the first synthesis of **43** was by oxidation of the benzylic/propargylic alcohol with MnO_2. To our surprise, the major product of this reaction was not that of oxidation, but tautomerisation – the alkene **44**. The *cis*-configuration of the product **44** is based on comparisons of the vicinal coupling constant of similar compounds in the literature. In isolation the value for **44** is equivocal at 12 Hz, but comparable to that for the phenyl ketone **45** (11.7 Hz)[28] and very different from the *trans*-isomer **46** (15.5 Hz).[29] Such *cis*-selective "redox isomerisation" has been reported previously using sodium carbonate as catalyst,[30] and presumably the slightly basic MnO_2 is responsible for this side-reaction in the current work. Indeed, when the MnO_2 was pre-washed with acid the formation of alkene **44** was diminished, but not completely avoided. The desired ynone **43** was also found to be light sensitive, decomposing under ambient conditions and complicating separation from the alkene. Fortunately a more direct and efficient synthesis[31] was achieved by the reaction of silver acetylide **48**[32] with acid chloride **47**[33] (Scheme 8), affording an excellent yield of **43**, which was used promptly in the next step.

As expected, the Diels–Alder-retro-Diels–Alder reaction of **43** with 4-phenyloxazole **30** proceeded at considerably lower temperature than that required for the less electron deficient dienophile **29** (see Scheme 5), giving furan **49** in excellent yield (Scheme 8).

Attempts to cyclise ester **49** directly with Eaton's reagent[34] or polyphosphoric acid (PPA)[35] led to no reaction or decompo-



Scheme 8 Reagents and conditions: (a) PhMe, 90 °C; (b) PhMe, reflux; (c) PPA 100 °C (n.r.), 140 °C (dec.); Eaton's reagent, 50 °C (n.r.); (d) LiOH, MeOH, H_2O, 0 °C; (e) 1. PCl_5, PhH, reflux, 2. $SnCl_4$, 0 °C; (f) $SOCl_2$; (g) $AlCl_3$, DCE.

sition at higher temperatures. Saponification of **49** provided the carboxylic acid **38**, but this was also unreactive with PPA[36] and Eaton's reagent, and partially decomposed with concentrated sulfuric acid.[37] Similarly, no cyclisation occurred in refluxing trifluoroacetic anhydride.[38] When the acid chloride **50** generated *in situ* using PCl_5 was treated with $SnCl_4$,[13] only a trace of monosporascone methyl ether (**14**) was isolated, the major product appearing (based on the ^{1}H NMR spectrum) to result from ring-opening of the furan. In direct contrast to the earlier observations with **33**/**34** (Scheme 5), reaction of **38** with oxalyl chloride resulted in multiple products but, with neat thionyl chloride, quantitatively provided the acid chloride **50**, which was stable enough to be fully characterised. To our great delight, treatment of this isolated acid chloride **50** with five equivalents of $AlCl_3$,[12] with an extended reaction period to allow selective demethylation of the *peri* methoxy group, then afforded monosporascone (**4**) in good yield. The NMR spectra of the synthetic product were virtually identical with those reported for the naturally-derived material.[15]

As proof of concept that monosporascone can be a synthetic precursor to the related natural products depicted in Scheme 1, **4** was subjected to reduction with zinc in acetic acid,[39] providing dihydromonosporascone (**5**) in modest (but unoptimised) yield. The ^{1}H NMR spectrum of this material also matched the data reported for the natural product.[15]

Conclusions

The first total synthesis of the isofuranonaphthoquinone natural product monosporascone (**4**) has been achieved in five linear steps and an overall yield of 57%, *via* a sequence of silver acetylide acylation, cycloaddition–cycloreversion and Friedel–Crafts acylation reactions. The brevity and efficiency of this route can provide quantities of monosporascone sufficient for further biological evaluation, and also elaboration to several biologically active natural products bearing the same framework and substitution pattern, as exemplified by the synthesis of dihydromonosporascone in one extra step.

Experimental

General details

Benzene, 1,2-dichloroethane (DCE) and dichloromethane (DCM) were distilled from CaH_2; tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl (all under inert gas). Acetonitrile was dried over activated 3A sieves overnight. RSF = rapid silica filtration.[26]

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained using Bruker AM-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C), Varian Gemini-400 (400 MHz, ^{1}H, 100 MHz, ^{13}C), Bruker AV500 (500 MHz, ^{1}H, 125.8 MHz, ^{13}C) and Bruker AV600 (600 MHz, ^{1}H, 150.9 MHz, ^{13}C) spectrometers. Chemical shifts are expressed in ppm relative to $CHCl_3$ (^{1}H, δ 7.26), $CDCl_3$ (^{13}C, δ 77.16), D_3CSOCD_2H (^{1}H, δ 2.50), $(D_3C)_2SO$ (^{13}C, δ 39.50), D_3CCOCD_2H (^{1}H, δ 2.05), $(D_3C)_2CO$ (^{13}C, δ 29.84), as appropriate; *J* values are given in hertz (Hz). Routine assignments of ^{13}C signals were made with the assistance of DEPT-135 and DEPT-90 experiments and full assignments of ^{1}H and ^{13}C signals were derived from HSQC and 1D and 2D NOESY experiments performed on either the Bruker AV500 or the Bruker AV600 spectrometers.

Mass spectra were recorded on a VG Autospec instrument using electron ionisation (EI+) or on a Waters GCT Premier Instrument with an Agilent 7890A GC using chemical ionization (CI, methane) and an Agilent DB-5MS column. Other general details are as reported previously.[40]

3-(2,4-Dimethoxybenzoyl)furan (16)

$SnCl_4$ (63 μL, 0.50 mmol) was added to a stirred solution of 1,3-dimethoxybenzene (**13**) (42 mg, 0.30 mmol) and 3-furoyl chloride (**15**) (40 mg 0.31 mmol) in anhydrous DCE (10 mL) under argon at 0 °C, whereupon the colourless solution slowly turned red. After 1 h the reaction mixture was allowed to warm

to room temperature and stirred for a further 4 h. The red solution was diluted with ice-cold 2 M HCl (75 mL), saturated with oxalic acid and stirred for 30 min. The resulting purple mixture was extracted with EtOAc (3 × 60 mL). The extract was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried and evaporated to yield a pale red oil (90 mg), which was subjected to rapid silica filtration. Elution with EtOAc–hexanes (1 : 9) gave **16** as a pale orange oil (70 mg, 98%). On a larger scale (10 mmol) the yield was lower (68%). Kugelrohr distillation (230° at 2 mm Hg) of a sample gave a pale yellow oil. R_f (1 : 9 EtOAc–hexanes): 0.15. IR (thin film) ν_{max} cm^{-1}: 1650 (C═O). ^1H NMR (300 MHz) δ 7.78 (dd, J = 1.5, 0.8 Hz, 1H, H2); 7.45–7.41 (m, 2H, H5/H6′); 6.82 (dd, J = 2.0, 0.8 Hz, 1H, H4); 6.53–6.49 (m, 2H, H5′/H3′); 3.86 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3). ^{13}C NMR (75.5 MHz) δ 188.3 (CO); 163.1 (ArO), 159.1 (ArO); 149.0 (C2); 143.6 (C5); 131.4 (C4); 128.4; 122.4; 109.8 (ArH); 104.2 (ArH); 98.9 (C3′), 55.6 (CH_3O); 55.5 (CH_3O). MS (EI) m/z 232 ($M^{\bullet+}$, 69%), 215 (39), 203 (100), 165 (41), 95 (47); HRMS observed: 232.0740, $C_{13}H_{12}O_4^{\bullet+}$ requires: 232.0736.

Methyl 4-[(3,5-dimethoxyphenyl)(hydroxy)methyl]-3-furoate (26)

A 1.1 M solution of BuLi in hexane (0.60 mL, 0.68 mmol) was added to a stirred solution of 1-bromo-3,5-dimethoxybenzene (146 mg, 0.670 mmol) in THF (2.5 mL) at 0 °C under argon. After stirring for 30 min, the solution of the aryllithium **25** was added dropwise to methyl 4-formyl-3-furoate (**24**)[22] (105 mg, 0.680 mmol) in THF (4.5 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature overnight, during which time the solution turned orange, then quenched with saturated NH_4Cl (5 mL) and extracted with ether (3 × 50 mL). The extract was washed with water (40 mL), dried and evaporated to yield a yellow oil (126 mg), which was subjected to RSF. Elution with EtOAc–hexanes (1 : 9) gave the **26** as a pale orange oil (34 mg, 21%). R_f (1 : 4 EtOAc–hexanes): 0.15. IR (thin film) ν_{max} cm^{-1}: 3431 br (OH), 1724 (C═O). ^1H NMR (300 MHz) δ 7.98 (d, J = 1.7 Hz, 1H, H2), 7.01 (dd, J = 1.7, 0.9 Hz, 1H, H5), 6.59 (d, J = 2.3 Hz, 2H, H2′/H6′), 6.39 (t, J = 2.3 Hz, 1H, H4′), 5.83 (sl. br s, 1H, C**H**OH), 4.85 (br s, 1H, OH), 3.85 (s, 3H, CO_2CH_3), 3.78 (s, 6H, OCH_3). ^{13}C NMR (75.5 MHz) δ 165.3 (C═O); 160.8 (ArO); 149.9 (C2); 144.1 (C1′); 142.3 (C5); 128.9 (C3), 117.5 (C4), 104.5 (C2′/C6′), 99.2 (C4′), 67.7 (CHOH), 55.5 (OCH_3), 52.2 (CO_2CH_3). MS (EI) m/z 292 ($M^{\bullet+}$, 40%), 276 (19), 139 (100), 123 (28); HRMS found: 292.0944; $C_{15}H_{16}O_6^{\bullet+}$ requires: 292.0947.

Ethyl 4-(3,5-dimethoxyphenyl)-4-hydroxybut-2-ynoate (29)

A 1.55 M solution of BuLi in cyclohexane (24.7 mL, 38.5 mmol) was added dropwise to a stirred solution of ethyl propiolate (4.1 g, 42 mmol) in anhydrous THF (80 mL) under argon at −100 °C. The solution was warmed to −80 °C over 30 min, then cooled again to −100 °C. The solution of lithium ethoxycarbonylacetylide thus formed was treated dropwise *via* cannula with a −40 °C solution of 3,5-dimethoxybenzaldehyde (**28**) (5.8 g, 35 mmol) in anhydrous THF (60 mL). The reaction mixture was allowed to warm to room temperature over 6.5 h and then quenched with AcOH (5 mL). The orange solution was partitioned between ether (200 mL) and saturated $NaHCO_3$ (100 mL). The ether extract was washed with saturated $NaHCO_3$ (2 × 50 mL), H_2O (50 mL) and brine (50 mL) then dried and evaporated to give a brown oil, which was subjected to RSF. Elution with EtOAc–hexanes (1 : 4) gave **29** as a yellow-orange solid (5.19 g, 56%), which crystallised from hexanes as a pale yellow solid, m.p. = 41–43 °C. R_f (EtOAc–hexanes 1 : 9) 0.2; IR ν_{max} cm^{-1}: br 3438 (OH), 2236 (C≡C), 1711 (C═O); ^1H NMR (400 MHz, $CDCl_3$) δ 6.67 (dd, $J_{2'/6',4'}$ = 2.0 Hz, $J_{2'/6',4}$ = 0.4 Hz, 2H, H2′/6′), 6.44 (t, $J_{4',2'/6'}$ = 2 Hz, 1H, H4′), 5.50 (br d, $J_{4,OH}$ = 6.4 Hz, 1H, H4), 4.24 (q, J = 7.2 Hz, 2H, OCH_2), 3.80 (s, 6H, 2 × OCH_3), 2.48 (br d, $J_{OH,4}$ = 6.4 Hz, 1H, OH), 1.31 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (C═O), 153.4 (C3′/5′), 140.9 (C1′), 104.7 (C2′/6′), 101.0 (C4′), 85.9 (C3), 70.0 (C2), 64.5 (C4), 62.4 (OCH_2), 55.6 (OCH_3), 14.1 (CH_3); MS (EI) m/z 264 ($M^{\bullet+}$, 100%), 191 (77), 166 (96), 165 (63); HRMS found: 264.0997; $C_{14}H_{16}O_5^{\bullet+}$ requires: 264.0998; Microanalysis found: C 63.7, H 6.0%; calculated for $C_{14}H_{16}O_5$: C 63.6, H 6.1%.

Ethyl 4-((3,5-dimethoxyphenyl)(hydroxy)methyl)-3-furoate (31)

Hydroquinone (5 mg) was added to a molten mixture of **29** (1.09 g, 4.12 mmol) and **30** (3.1 g, 21 mmol) under argon and the reaction mixture was heated at 200 °C for 90 min. TLC (EtOAc–hexanes 1 : 4) after this time showed no detectable starting material **29**. After cooling, the brown residue was subjected to RSF. Elution with EtOAc–hexanes 1 : 19 gave excess 4-phenyloxazole. Further elution with EtOAc–hexanes 1 : 4 gave **31** as a pale yellow oil (891 mg, 71%). R_f (EtOAc–hexanes 1 : 4) 0.3; IR ν_{max} cm^{-1}: br 3700–3200 (OH), 1715 (C═O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, $J_{2,5}$ = 1.6 Hz, 1H, H2), 7.00 (dd, $J_{5,2}$ = 1.6 Hz, $J_{5,CHOH}$ = 0.8 Hz, 1H, H5), 6.60 (d, $J_{2'/6',4'}$ = 2.4 Hz, 2H, H2′/6′), 6.40 (t, $J_{4',2'/6'}$ = 2.4 Hz, 1H, H4′), 5.82 (d, $J_{CH,OH}$ = 5.2 Hz, 1H, C**H**OH), 4.89 (d, $J_{OH,CH}$ = 5.2 Hz, 1H, OH), 4.32 (m, 2H, OCH_2), 3.78 (s, 6H, 2 × OCH_3), 1.34 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (C═O), 160.8 (C3′/5′), 149.9 (C2), 144.1 (C1′), 142.3 (C5), 129.0 (C3), 117.9 (C4), 104.6 (C2′/C6′), 99.9 (C4′), 67.7 (CHOH), 61.3 (CH_2O), 55.5 (CH_3O), 14.3 (CH_3); MS (EI) m/z 306 ($M^{\bullet+}$, 41%), 205 (28), 149 (46), 139 (100); HRMS found: 306.1105; $C_{16}H_{18}O_6^{\bullet+}$ requires: 306.1103.

Ethyl 4-(3,5-dimethoxybenzyl)-3-furoate (32)

TMSCl (1.54 mL, 12.2 mmol) was added to a solution of NaI (1.82 g, 12.2 mmol) in anhydrous MeCN (15 mL) under argon. The resulting yellow suspension was treated with a solution of **31** (625 mg, 2.04 mmol) in anhydrous MeCN (35 mL), whereupon a dark red solution formed immediately. After 10 min the reaction mixture was diluted with H_2O (100 mL) and extracted with ether (4 × 30 mL). The organic extract was washed with 5% aqueous sodium thiosulfate solution (2 × 50 mL) and brine (50 mL), dried and evaporated to give **32** as a pale yellow oil (487 mg, 82%), which required no further purification. R_f (EtOAc–hexanes 1 : 4) 0.6; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.98 (d, $J_{2,5}$ = 1.6 Hz, 1H, H2), 7.06 (m, 1H, H5), 6.40 (d, $J_{2'/6',4'}$ = 2.0 Hz, 2H, H2′/6′), 6.32 (t, $J_{4',2'/6'}$ = 2.0 Hz, 1H, H4′), 4.26 (q, J = 7.2 Hz, 2H, OCH_2), 3.94 (br s, 2H, CH_2), 3.76 (s, 6H, 2 × OCH_3), 1.30 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (C=O), 160.9 (C3′/5′), 149.1 (C2), 142.3 (C1′), 142.1 (C5), 124.7 (C3), 118.5 (C4), 107.0 (C2′/C6′), 98.3 (C4′), 60.3 (OCH_2), 55.4 (OCH_3), 30.7 (CH_2), 14.4 (CH_3); IR ν_{max} cm^{-1}: 1719 (C=O). MS (EI) m/z 290 ($M^{\bullet+}$, 100%), 245 (32), 244 (88), 215 (43); HRMS found: 290.1152; $C_{16}H_{18}O_5^{\bullet+}$ requires: 290.1154.

4-(3,5-Dimethoxybenzyl)-3-furoic acid (33)

Aqueous 20% (w/v) sodium hydroxide (4 mL) was added to a solution of **32** (95 mg, 0.33 mmol) in MeOH (4 mL) and a white precipitate formed immediately. Upon heating to reflux for 1 h this dissolved to give a colourless solution. After cooling, the reaction solution was poured into ice-cold 1 M HCl (40 mL), whereupon a white precipitate formed. The suspension was extracted with EtOAc (4 × 40 mL) and the organic extract was washed with H_2O (40 mL) and brine (40 mL), dried and concentrated to give **33** as a white solid (86 mg, quant.), which crystallised from EtOH as colourless needles, m.p. = 107–115 °C. R_f (EtOAc–hexanes 1 : 1) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, $J_{2,5}$ = 1.6 Hz, 1H, H2), 7.08 (dt [app. q], $J_{5,2}$ = $J_{5,CH2}$ = 1.5 Hz, 1H, H5), 6.42 (d, $J_{2'/6',4'}$ = 3 Hz, 2H, H2′/H6′), 6.34 (t, $J_{4',2'/6'}$ = 3 Hz, 1H, H4′), 3.94 (br s, 2H, CH_2), 3.77 (s, 6H, 2 × OCH_3), 1.65 (v br s, OH + H_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5 (C=O), 160.9 (C3′/5′), 150.6 (C2), 142.4 (C5), 142.0 (C1′), 125.1 (C3), 117.6 (C4), 107.1 (C2′/C6′), 98.4 (C4′), 55.4 (OCH_3), 30.6 (CH_2); IR ν_{max} cm^{-1}: br 3600–2400 (OH), 1687 (C=O); MS (EI) m/z 262 ($M^{\bullet+}$, 100%), 244 (30), 216 (20), 215 (21); HRMS found: 262.0839; $C_{14}H_{14}O_5^{\bullet+}$ requires: 262.0841; Microanalysis found: C 64.1, H 5.1%; calculated for $C_{14}H_{14}O_5$: C 64.1, H 5.4%.

4-(3,5-Dimethoxybenzyl)furan-3-carbonyl chloride (34)

Oxalyl chloride (0.5 mL) was added to **33** (27 mg, 0.10 mmol) under argon at 0 °C, whereupon a gas was immediately evolved. The reaction mixture was warmed to room temperature over 1 h and stirred in darkness overnight. Excess oxalyl chloride was evaporated under reduced pressure affording **34** as a brown oil (28 mg, quant.), which was used without purification in the following step. R_f (EtOAc–hexanes 1 : 9) 0.4; IR ν_{max} cm^{-1}: 1766 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, $J_{2,5}$ = 1.5 Hz, 1H, H2), 7.14 (m, 1H, H5), 6.37 (d, $J_{2'/6',4'}$ = 2 Hz, 2H, H2′/H6′), 6.34 (t, $J_{4',2'/6'}$ = 2 Hz, 1H, H4′), 3.87 (br s, 2H, CH_2), 3.77 (s, 6H, 2 × OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (C=O), 159.4 (C3′/5′), 154.5 (C2), 143.4 (C5), 140.9 (C1′), 125.1 (C3 or 4), 123.5 (C3 or 4), 107.1 (C2′/C6′), 98.6 (C4′), 55.4 (OCH_3), 30.4 (CH_2); MS (EI) m/z 282 (^{37}Cl $M^{\bullet+}$, 22%), 280 (^{35}Cl M, 66), 245 (100), 244 (66); HRMS found: 280.0507; $C_{14}H_{13}{}^{35}ClO_4^{\bullet+}$ requires: 280.0502.

8-Chloro-5,7-dimethoxynaphtho[2,3-*c*]furan-4(9*H*)-one (36)

Phosphorus pentachloride (150 mg, 0.72 mmol) was added to a stirred suspension of **33** (160 mg, 0.61 mmol) in anhydrous benzene (3 mL) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and then heated under reflux for 1 h. After cooling to room temperature, the reaction mixture was added dropwise to a stirred solution of $SnCl_4$ (87 μL, 0.75 mmol) in anhydrous benzene (3 mL) at 0 °C, whereupon an orange solution formed immediately. The reaction mixture was warmed slowly to room temperature and stirring was continued in the dark overnight. The benzene was evaporated and the residue was partitioned between 1 M HCl (50 mL) and EtOAc (15 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 × 20 mL). The combined organic phase was washed with saturated $NaHCO_3$ (2 × 20 mL), H_2O (20 mL) and brine (2 × 20 mL), dried and evaporated to give **36** as a yellow solid (140 mg, 82%). R_f (EtOAc–hexanes 1 : 4) 0.15; IR ν_{max} cm^{-1}: 1703 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, $J_{3,1}$ = 1.2 Hz, 1H, H3), 7.46 (m, 1H, H1), 6.49 (s, 1H, H6), 4.05 (br d, $J_{9,1}$ = 1.2 Hz, 2H, CH_2), 3.96 (s, 6H, 2 × OCH_3); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 179.9 (C=O), 162.2 (ArO), 159.1 (ArO), 144.1 (C1), 142.1 (C8a), 138.5 (C3), 124.0 (C3a), 119.8 (C9a), 117.0 (C4a or 8), 113.9 (C4a or 8), 95.1 (C6), 56.5 (OCH_3), 56.3 (OCH_3), 24.3 (CH_2); MS (EI) m/z 280 (^{37}Cl $M^{\bullet+}$, 32%), 278 (^{35}Cl $M^{\bullet+}$, 100), 249 (57), 213 (24); HRMS found: 278.0349; $C_{14}H_{11}{}^{35}ClO_4^{\bullet+}$ requires: 278.0346.

Methyl 4-(3,5-dimethoxybenzoyl)-3-furoate (37)

A 1.3 M solution of BuLi in hexanes (4.45 mL, 5.70 mmol) was added to a stirred solution of 1-bromo-3,5-dimethoxybenzene (1.30 g, 6.00 mmol) in anhydrous THF (25 mL) under argon at −78 °C. After stirring for 30 min, the solution of aryllithium **25** was added dropwise to dimethyl furan-3,4-dicarboxylate (**21**) (1.05 g, 5.68 mmol) in THF (40 mL) at −78°, whereupon the solution immediately turned orange. The reaction mixture was allowed to warm slowly to room temperature over 4.5 h then quenched with saturated NH_4Cl (5 mL). The reaction mixture was extracted with EtOAc (3 × 80 mL) and the extract was washed with brine (50 mL), dried and evaporated to yield a yellow oil (1.70 g), which was subjected to RSF. Elution with EtOAc–hexanes (1 : 9) gave **37** as a white solid (368 mg, 21%), which crystallised from hexanes as white chunky crystals, m.p. = 85–88 °C. R_f (EtOAc–hexanes 1 : 4): 0.2. IR (thin film) ν_{max} cm^{-1}: 1731 (O**C**=**O**); 1666 (C=O). ^{1}H NMR (300 MHz) δ 8.04 (d, J = 1.6 Hz, 1H, furyl), 7.72 (d, J = 1.7 Hz, 1H, furyl), 7.00 (d, J = 2.3 Hz, 2H, H2′/H6′), 6.67 (t, J = 2.3 Hz, 1H, H4′), 3.82 (s, 6H, 2 × OCH_3), 3.70 (s, CO_2CH_3). ^{13}C NMR (75.5 MHz) δ 183.3 (C=O), 162.2 (CO_2), 160.6 (ArO), 148.3 (α-furyl), 145.6 (α-furyl), 139.4 (C1′), 125.0 (β-furyl), 118.9 (β-furyl), 107.1 (C2′/C6′), 105.7 (C4′), 55.6 (OCH_3), 51.2 (CO_2CH_3); Microanalysis found: C 62.0, H 4.6%; calculated for $C_{15}H_{14}O_6$: C 62.1, H 4.9%.

4-(3,5-Dimethoxybenzoyl)-3-furoic acid (38)

Method A. LiOH (130 mg, 3.1 mmol) was added to a stirred suspension of **49** (180 mg, 0.60 mmol) in 3 : 1 MeOH–H_2O (8 mL) at 0 °C and the reaction mixture was stirred at 4 °C, in the dark, for 5 d. The reaction mixture was washed with ether

(30 mL) and carefully acidified (2 M HCl). The aqueous phase was extracted with EtOAc (4 × 50 mL) and the organic extract was evaporated to give **38** as a tan solid (166 mg; quant.), which crystallised from EtOH as very pale yellow needles, m.p. = 174–177 °C. R_f (EtOAc–Hex 2 : 3 + 3 drops AcOH) 0.45; IR ν_{max} cm^{-1}: 3500–2800 (OH), 1735 (OC=O), 1686 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 13.41 (v. br s, 1H, OH), 8.31 (d, $J_{2,5}$ = 1.5 Hz, 1H, H2), 8.06 (d, $J_{5,2}$ = 1.5 Hz, 1H, H5), 6.93 (d, $J_{2'/6',4'}$ = 2.5 Hz, 2H, H2′/6′), 6.74 (t, $J_{4',2'/6'}$ = 2.5 Hz, 1H, H4′), 3.86 (s, 6H, 2 × OCH_3); ^{13}C NMR (125.7 MHz; $CDCl_3$) δ 193.9 (C=O), 161.6 (CO_2H), 161.2 (C3′/5′), 154.0 (C2 or 5), 153.2 (C2 or 5), 138.9 (C1′), 122.6 (C3 or 4), 120.0 (C3 or 4), 107.4 (C2′/C6′), 105.9 (C4′), 55.9 (OCH_3); MS (EI) *m*/*z* 276 (M, 100%), 139 (42), 86 (18), 84 (28); HRMS found: 276.0629, $C_{14}H_{12}O_6^{\bullet+}$ requires: 276.0634; Microanalysis found: C 61.0, H 4.2%; calculated for $C_{14}H_{12}O_6$: C 60.9, H 4.4%.

The yield of the analogous reaction from **37** (10 mg, 0.035 mmol) was 88%.

Method B. A 2.0 M solution of BuLi in hexanes (125 μL, 0.251 mmol) was added to a solution of 1-bromo-3,5-dimethoxybenzene (49 mg, 0.24 mmol) in anhydrous THF (2 mL) at −78 °C under argon. After stirring for 30 min, the solution of the aryllithium **25** was added dropwise to a suspension of anhydrous CuCN (131 mg, 1.46 mmol) and LiCl (124 mg, 2.93 mmol) in anhydrous THF (3 mL) at −78°, whereupon the solution turned yellow. The reaction mixture was warmed to −40° for 20 min to ensure complete formation of the organocuprate, whereupon the solution turned blue. The solution was cooled to −78° and a solution of **41** (35 mg, 0.25 mmol) in anhydrous THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature over 6 h then quenched with 1 M HCl (2 mL), diluted with ether (30 mL) and extracted with saturated aqueous $NaHCO_3$ solution (3 × 20 mL) whereupon a white precipitate formed. The precipitate was filtered and the aqueous filtrate was carefully acidified (1 M HCl, 0 °C) then extracted with EtOAc (4 × 25 mL). The extract was dried and evaporated to give **38** as a yellow glassy solid (13 mg, 20%), spectroscopically identical with the material described above.

Furo[3,4-*c*]furan-1,3-dione (41)

A solution of 3,4-furandicarboxylic acid (**40**)[19] (279 mg, 1.80 mmol) in Ac_2O (5 mL) under N_2 was heated under reflux overnight, during which time the solution turned brown. The volatiles were evaporated and the crude product was subjected to Kuegelrohr distillation (170–210° at 1 mmHg) to give **41** as white crystals (35 mg, 13%), m.p. = 103–106°. R_f (EtOAc–hexanes 1 : 1): 0.1. IR (thin film) ν_{max} cm^{-1}: 1860 (antisym. C=O), 1798 (*sym*. C=O). ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 2H, furyl). ^{13}C NMR (75.5 MHz) δ 155.2 (C=O), 141.3 (CH), 121.6. Microanalysis found: C 52.3, H 1.5%; calculated for $C_6H_2O_4$: C 52.2, H 1.5%.

4-(Benzyl(methyl)carbamoyl)-3-furoic acid (42)

A solution of *N*-methylbenzylamine (2.0 mL, 15 mol) and **41** (15 mg, 0.11 mmol) in anhydrous DCM was stirred under nitrogen overnight. The reaction mixture was diluted with 1 M HCl (10 mL) then extracted with ether (3 × 20 mL). The extract was dried and evaporated to yield a yellow solid (12 mg), which was purified using preparative TLC. Elution with EtOAc–hexanes–AcOH (50 : 50 : 0.1) gave **42** as a white solid (12 mg, 50%), m.p. = 124–130 °C. R_f (EtOAc–hexanes 1 : 1 + 3 drops AcOH): 0.45. IR (thin film) ν_{max} cm^{-1}: 2750–3850 (OH), 1651 (br 2 × C=O). ^1H NMR (600 MHz, d_6-DMSO) major rotamer δ 8.33 (br s, 1H, furyl), 8.00 (s, 1H, furyl), 7.38 (d, J = 7.4 Hz, 2H, ArH), 7.35–7.30 (m, 3H, ArH), 4.65 (s, 2H, CH_2), 2.74 (s, 3H, CH_3); minor rotamer δ 8.29 (br s, 1H, furyl), 7.93 (s, 1H, furyl), 7.26 (app. t, 3H, ArH) 7.21 (d, J = 7.3 Hz, 2H, ArH), 4.38 (s, 2H, CH_2), 2.81 (s, 3H, CH_3).

MnO_2 oxidation of 29

MnO_2 (1.2 g, 14 mmol) was added to a stirred solution of **29** (740 mg, 2.8 mmol) in anhydrous CH_2Cl_2 (10 mL) under argon and the suspension was stirred for 72 h. Filtration of the reaction mixture followed by evaporation gave an orange oil, which was subjected to RSF. Elution with EtOAc–hexanes (1 : 9) gave **43** (323 mg, 42%) identical with the material described below. Further elution with EtOAc–hexanes (1 : 9) gave **(*Z*)-ethyl 4-(3,5-dimethoxyphenyl)-4-oxobut-2-enoate** (**44**) as a colourless oil (377 mg, 51%). R_f (EtOAc–hexanes 1 : 9) 0.30; IR ν_{max} cm^{-1}: 1721 (OC=O), 1672 (C=O). ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, $J_{2'/6',4'}$ = 2.5 Hz, 2H, H2′/6′), 6.84 (d, $J_{3,2}$ = 12 Hz, 1H, vinylic), 6.66 (t, $J_{4',2'/6'}$ = 2.5 Hz, 1H, H4′), 6.25 (d, $J_{2,3}$ = 12 Hz, 1H, vinylic), 4.07 (q, J = 7 Hz, 2H, OCH_2), 3.82 (s, 6H, 2 × OCH_3), 1.11 (t, J = 7 Hz, 3H, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 193.9 (C=O), 164.9 (CO_2), 161.1 (C3′/5′), 141.1 (vinylic), 137.9 (C1′), 126.3 (vinylic), 106.6 (C2′/6′), 106.3 (C4′), 61.3 (OCH_2), 55.7 (OCH_3), 13.9 (CH_3); MS (EI) *m*/*z* 264 ($M^{\bullet+}$, 38%), 191 (100), 137 (23), 122 (30); HRMS found: 264.1009; $C_{14}H_{16}O_5^{\bullet+}$ requires: 264.0998.

Ethyl 4-(3,5-dimethoxyphenyl)-4-oxobut-2-ynoate (43)

(3-Ethoxy-3-oxoprop-1-ynyl)silver (**48**)[32] (270 mg, 1.3 mmol) was added to a stirred solution of 3,5-dimethoxybenzoyl chloride (**47**)[33] (230 mg, 1.2 mmol) in anhydrous toluene (4 mL) under argon. The reaction mixture was stirred at 90 °C for 72 h at which point no starting material **47** was detectable by TLC (EtOAc–hexanes 1 : 9). After cooling, the reaction mixture was concentrated and subjected to RSF. Elution with EtOAc–hexanes (1 : 19) gave **43** as a bright yellow, light-sensitive solid (306 mg, 90%), which crystallised from hexanes as yellow needles, m.p. = 61–63 °C. R_f (EtOAc–hexanes 1 : 4) 0.55; IR ν_{max} cm^{-1}: 1719 (OC=O), 1650 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, $J_{2'/6',4'}$ = 2.4 Hz, 2H, H2′/6′), 6.74 (t, $J_{4',2'/6'}$ = 2.4 Hz, 1H, H4′), 4.34 (q, J = 7.2 Hz, 2H, OCH_2), 3.85 (s, 6H, 2 × OCH_3), 1.37 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0 (C=O), 161.2 (CO_2), 152.4 (C3′/5′), 137.6 (C1′), 107.9 (C4′), 107.5 (C2′/6′), 80.5 (C2 or 3), 79.9 (C2 or 3), 63.2 (OCH_2), 55.9 (OCH_3), 14.1 (CH_3); MS (EI) *m*/*z* 262 ($M^{\bullet+}$, 94%), 189 (38), 165 (40), 162 (100); HRMS found: 262.0844; $C_{14}H_{14}O_5^{\bullet+}$ requires: 262.0841; Microanalysis found: C 63.9, H 5.3%; calculated for $C_{14}H_{14}O_5$ C 64.1, H 5.4%.

Ethyl 4-(3,5-dimethoxybenzoyl)-3-furoate (49)

A solution of hydroquinone (13 mg), **43** (563 mg, 2.15 mmol) and 4-phenyloxazole **30**[24] (1.56 g, 10.8 mmol) in anhydrous toluene (40 mL) under argon was heated at 90 °C in the dark for 20 h. TLC (EtOAc–hexanes 1 : 9) after this time showed that the starting material **43** had been consumed. The solvent was evaporated and the residue was subjected to RSF. Elution with EtOAc–hexanes (1 : 19) gave excess phenyloxazole **30** followed by **49** as a colourless solid (554 mg, 85%), which crystallised from MeOH as white needles, m.p. = 55–56 °C. R_f (EtOAc–hexanes 1 : 4) 0.35; IR ν_{max} cm^{-1}: 1723 (OC═O), 1665 (C═O); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, $J_{2,5}$ = 1.5 Hz, 1H, H2), 7.72 (d, $J_{5,2}$ = 1.5 Hz, 1H, H5), 7.00 (d, $J_{2'/6',4'}$ = 2.5 Hz, 2H, H2′/6′), 6.67 (t, $J_{4',2'/6'}$ = 2.5 Hz, 1H, H4′), 4.14 (q, J = 7 Hz, 2H, OCH_2), 3.82 (s, 6H, 2 × OCH_3), 1.18 (t, J = 7 Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 188.9 (C═O), 162.1 (CO_2), 160.9 (C3′/5′), 148.4 (α-furyl), 145.9 (α-furyl), 139.9 (C1′), 125.3 (β-furyl), 119.6 (β-furyl), 107.4 (C2′/C6′), 105.9 (C4′), 61.1 (OCH_2), 55.8 (OCH_3), 14.0 (CH_3); MS (EI) m/z 304 ($M^{\bullet+}$, 100%), 260 (33), 259 (16), 139 (47); HRMS found: 304.0951; $C_{16}H_{16}O_6^{\bullet+}$ requires: 304.0947; Microanalysis found: C 63.1, H 5.3%; calculated for $C_{16}H_{16}O_6$ C 63.2, H 5.3%.

5,7-Dimethoxynaphtho[2,3-*c*]furan-4,9-dione (*monosporascone methyl ether*) (14)

PCl_5 (23 mg, 0.11 mmol) was added to a stirred solution of **38** (30 mg, 0.11 mmol) in anhydrous benzene (1 mL) under argon and the reaction mixture was heated under reflux. After 1 h, the reaction mixture was cooled to 0 °C and a solution of $SnCl_4$ (65 μL, 0.55 mmol) in anhydrous benzene (1 mL) was added, whereupon the solution turned yellow. The reaction mixture was stirred at room temperature for 24 h then quenched with ice-cold 2 M HCl (30 mL) and saturated with oxalic acid. The aqueous phase was extracted with EtOAc (4 × 20 mL) and the extract was dried and evaporated to yield an orange solid (10 mg). Purification by preparative TLC (EtOAc–hexanes 1 : 4 with 10 drops AcOH) gave **14** as an orange solid (1 mg, 4%), m.p. = 111–113°. R_f (1 : 4 EtOAc–hexanes + 3 drops AcOH): 0.2. IR (thin film) ν_{max} cm^{-1}: 1733 (C═O), 1667(C═O). ^1H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, J = 1.3 Hz, 1H, furyl), 8.11 (d, J = 1.3 Hz, 1H, furyl), 7.47 (d, J = 2.4 Hz, 1H, ArH), 6.79 (d, J 2.4 Hz, 1H, ArH), 3.99, (s, 3H, OCH_3), 3.98, 3H, s, OCH_3. ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 177.9 (CO), 174.5 (CO), 145.5 (α-furyl), 145.2 (α-furyl), 139.7, 136.5, 124.2, 104.6 (ArH), 103.8 (ArH), 56.5 (OCH_3), 55.9 (OCH_3). Three quaternary carbons were not observed due to the paucity of material available.

4-(3,5-Dimethoxybenzoyl)furan-3-carbonyl chloride (50)

$SOCl_2$ (500 μL) was added to **38** (36 mg, 0.13 mmol) at 0 °C under argon. The acid dissolved slowly (over 5 h) producing a pale yellow solution. After stirring overnight in the dark, excess thionyl chloride was evaporated under reduced pressure affording **50** as a brown oil, which was used without purification in the following step. R_f (EtOAc–hexanes 1 : 4) 0.25; IR ν_{max} cm^{-1}: 1773 (ClC═O), 1666 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, $J_{2,5}$ = 1.5 Hz, 1H, H2), 7.78 (d, $J_{5,2}$ = 1.5 Hz, 1H, H5), 6.99 (d, $J_{2'/6',4'}$ = 2 Hz, 2H, H2′/6′), 6.70 (t, $J_{4',2'/6'}$ = 2.5 Hz, 1H, H4′), 3.83 (s, 6H, 2 × CH_3O); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 187.1 (C═O), 161.1 (C3′/5′), 157.8 (ClCO), 153.5 (α-furyl), 147.4 (α-furyl), 139.1 (C1′), 124.8 (β-furyl), 124.0 (β-furyl), 107.6 (C2′/C6′) 106.2 (C4′), 55.8 (CH_3O); MS (EI) m/z 296 (^{37}Cl $M^{\bullet+}$, 12%), 294 (^{35}Cl $M^{\bullet+}$, 33), 259 (100), 229 (23); HRMS found: 294.0295; $C_{14}H_{11}{}^{35}ClO_5^{\bullet+}$ requires: 294.0289.

5-Hydroxy-7-methoxynaphtho[2,3-*c*]furan-4,9-dione, (*monosporascone*) (4)

Freshly sublimed $AlCl_3$ (68 mg, 0.51 mmol) was added to a stirred solution of **51** (30 mg, 0.10 mmol) in DCE (1 mL) under argon at 0 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued in the dark for 8 d, after which time the reaction mixture was diluted with ice-cold 2 M HCl (40 mL) and saturated with oxalic acid. The aqueous phase was extracted with EtOAc (3 × 60 mL) and the extract was evaporated to give a rust-coloured solid, which was subjected to RSF. Elution with (MeOH–DCM 1 : 99) gave monosporascone **1** (18 mg, 75%) as a bright yellow solid, which crystallised from hexanes–EtOAc as yellow-green crystals, m.p. = 226–240 °C [lit.[16] 205–215 °C (decomp.)]. R_f (MeOH–DCM 1 : 99) 0.65; IR ν_{max} cm^{-1}: 3700–2900 (OH), 1670 (C═O), 1628 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ 12.89 (s, 1H, OH), 8.20 (d, $J_{3,1}$ = 1.5 Hz, 1H, α-furyl), 8.19 (d, $J_{1,3}$ = 1.0 Hz, 1H, α-furyl), 7.37 (d, $J_{8,6}$ = 2.5 Hz, 1H, H8), 6.69 (d, $J_{6,8}$ = 2.5 Hz, 1H, H6), 3.93 (s, 3H, CH_3O); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 184.0 (C4), 178.7 (C9), 166.5 (C7), 166.3 (C5), 146.4 (α-furyl), 145.9 (α-furyl), 137.4 (C8a), 123.0 (C3a or C9a), 122.9 (C3a or C9a) 112.3 (C4a), 108.3 (C8), 106.8 (C6), 56.2 (CH_3O); MS (EI) m/z 244 ($M^{\bullet+}$, 59%), 88 (100), 83 (30), 81 (27); HRMS found: 244.0370; $C_{13}H_8O_5^{\bullet+}$ requires: 244.0372. The spectroscopic data matched those reported.[15]

5-Hydroxy-7-methoxy-1,3-dihydronaphtho[2,3-*c*]furan-4,9-dione (*dihydromonosporascone*) (5)

To a stirred solution of **1** (6 mg, 0.025 mmol) in anhydrous AcOH (2 mL) under argon was added zinc powder (140 mg) and the reaction mixture was heated to 100 °C for 2 h. The yellow solution was cooled and diluted with water (20 mL) then extracted with EtOAc (4 × 20 mL) and evaporated to give an orange oil. Preparative TLC (MeOH–DCM 1 : 99) gave three coloured bands, the middle one being **2**, which was recovered as a yellow solid (2 mg, 33%). ^1H NMR (500 MHz, $CDCl_3$) δ 12.06 (s, 1H, OH), 7.19 (d, $J_{8,6}$ = 2.5 Hz, 1H, H8), 6.64 (d, $J_{6,8}$ = 2.5 Hz, 1H, H6), 5.13 (d, $J_{1,3}$ = 2.5 Hz, 4H, 2 × H1, 2 × H3), 3.91 (s, 3H, CH_3O). The ^1H NMR spectrum matched the reported data.[15]

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