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Total synthesis of parvaquone and the serendipitous discovery of a novel chromium-mediated method for β-lactone formation

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Abstract

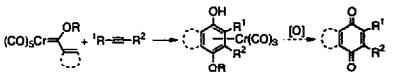
During attempts to synthesise the 2-hydroxy-1,4-naphthoquinone, parvaquone, **1**, a novel chromium-mediated method for the synthesis of functionalised β-lactones from propargyl alcohols has been discovered. Additionally, using both dry state and ultrasound conditions, the total synthesis of parvaquone (**1**) has been achieved; the most efficient techniques deliver this target compound in up to 46% overall yield over, as low as, two synthetic processes.

Keywords: Chromium carbene complexes; Dötz benzannulation; 2-Hydroxy-1,4-naphthoquinones; β-Lactones; Dry state techniques; Ultrasound techniques

1. Introduction

The Dötz annulation reaction [1–6], involving chromium carbene complexes, with a conjugated vinyl moiety, and alkynes, provides one of the most effective and regioselective synthetic methods for the efficient preparation of diversely substituted benzenoid systems (Scheme 1). Indeed, this reaction has frequently been used as the key transformation in the synthesis of natural products and other aromatic systems possessing an array of functionality and skeletal frameworks [1–5]; also, see refs. [4,5] in Ref. [7], ref. [6] in Ref. [8] and Ref. [9–11]. The only significant drawbacks with this methodology are that, under standard thermal conditions, reactions are often completed only following prolonged periods and low product yields are regularly encountered. More recently, we have reported [12,13] that the use of ultrasound techniques and dry state adsorption (DSA) methods, in conjunction with a standard oxidative work-up, both dramatically reduce reaction times and improve cyclisation yields in most cases tried. Furthermore, these techniques have now been utilised with equivalent and notable success by other workers [14].

In order to demonstrate the applicability of these modifications, we have recently initiated a number of routes towards targets of biological importance using the Dötz annulation as the key synthetic step. In particular, compounds containing the 2-hydroxy-1,4-naphthoquinone skeleton are known to display significant anti-protozoal activity [15] and, more recently, some analogues have displayed high levels of potency against sapsucking insects which are noted for their resistance to more conventional pesticides [16]. Amongst compounds of this general class, parvaquone (**1**) (originally marketed by Wellcome as Clexon) has been used as the first treatment for East Coast Fever (theileriosis), a disease, caused by a microscopic parasite *theileria parva*, which inflicts African cattle herds [17]. As the retrosynthesis in Scheme 2 shows, it was envisaged that use of the Dötz reaction would allow a facile and flexible synthesis of this target and analogous com-



$R^1 > R^2$

Scheme 1.

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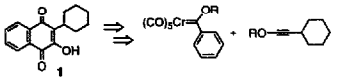


Scheme 2.

pounds and, additionally, illustrate the utility of our modified protocols.

2. Results and discussion

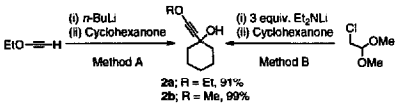
2.1. Preparation of alkoxy-substituted cyclohexylalkynes

In our planned strategy for the synthesis of parvaquone (**1**) (Scheme 2) a cyclohexylalkyne bearing alkoxy functionality was required. Using cyclohexanone as starting material, addition of acetylide anion led to the facile synthesis of this requisite class of compound by two complementary methods. As shown in Scheme 3, the first route (A; R = Et) involved formation of the lithium acetylide from ethoxyacetylene, whilst the alternative strategy (B; R = Me) generated the analogous methoxy reactive species from 2-chloroacetaldehyde dimethylacetal [18]. In both cases the addition product was obtained in high yield.

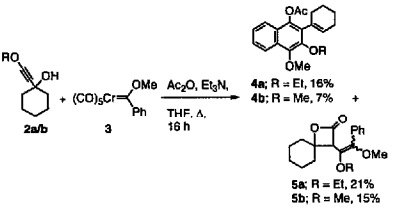
When our original synthetic strategy was considered, it was clear that substrates **2a** and **2b** both had hydroxyl functionality which would be superfluous to that required within the molecular skeleton of the current target **1**. Nonetheless, the ease of synthesis of both compounds, and the view that the unrequired groups would be more readily removed later in the synthesis, led us to attempt the key chromium-mediated annulation reaction with the propargylic alcohols as prepared.

2.2. Attempted benzannulation reactions and the discovery of chromium-mediated β-lactone formation

It is known that alkoxyalkynes tend to be poor substrates in the thermally induced Dötz cyclisation [19–21]. However, using triethylamine and acetic anhydride as reaction promoters, Yamashita and co-workers have developed conditions under which these and other sensitive substrates can be more successfully employed [22–28]. With this in mind, the well established Yamashita techniques were used for our initial cyclisation attempts. When either alkyne **2a/b** was heated with



Scheme 3.

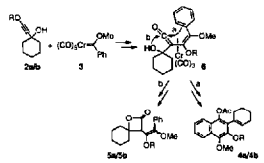


Scheme 4.

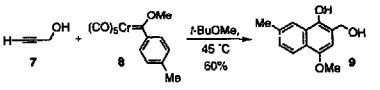
pentacarbonyl[phenyl(methoxy)carbene]chromium (**3**) [29], in the presence of Ac_2O and Et_3N, the expected acetylated Dötz product (with elimination of the tertiary hydroxyl group) **4a/b** was only the minor organic component of the reaction mixture. In each case, the major product was identified as the undesired but synthetically attractive β-lactone **5a/b** (Scheme 4).

These results were quite unexpected; yet, the synthetic outcomes can be explained by referring to one of the possible mechanistic pathways which are routinely cited, with considerable experimental evidence, for the benzannulation reaction [1,4,30–32]. Following loss of carbon monoxide from the carbene complex, alkyne complexation, chromacyclobutene formation and, subsequent ring opening, carbon monoxide insertion can lead to a precedented complexed vinyl ketene intermediate such as **6**. Indeed, a number of more stable vinyl ketene complexes have been isolated from reactions of chromium carbene complexes and alkynes [32–34]. In our case (Scheme 5), from this intermediate, electrocyclic ring closure (route a), followed by tautomerisation, acylation and demetallation will give the benzannulated product (with dehydration) **4a/b**. In contrast, intramolecular nucleophilic attack of the proximal hydroxy group onto the ketene carbonyl carbon (route b), followed by proton transfer, leads to the favoured β-lactone product **5a/b**.

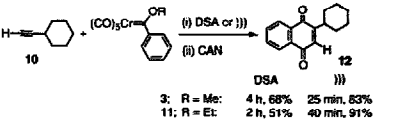
Despite this seemingly reasonable mechanistic rationalisation, on consideration of analogous reactions cited



Scheme 5.



Scheme 6.



Scheme 7.

in the literature, the formation of β-lactone products was still considered to be rather surprising. More specifically, Dötz and Sturm have shown [35] that when propargyl alcohol (**7**) is reacted thermally with the *p*-toluyl methoxy carbene complex **8** the sole product is the naphthol **9** resulting from the benzannulation process (Scheme 6). In contrast, when homopropargyl alcohol and higher acetylenic alcohol homologues are employed, cyclic ester formation competes with benzannulation and larger ring lactone products (γ- and above [1]) are known to form [37,30,35]. Additionally, trapping of proposed vinyl ketene intermediates by 'external' alcohols in an intermolecular fashion has been recorded on numerous occasions [22–24,30–32,38], although electrocyclic ring closure (benzannulation) at the vinyl ketene stage of the process is believed to be faster than the alcohol attack (esterification) in most cases [30,32] (see also the case for uncomplexed vinyl ketene intermediates [39]). However, in our examples, using the propargyl alcohols **2a/b**, the formation of the small ring ester products **5a/b** appears to be the favoured process and, indeed, this is believed to be the first recorded example of β-lactone formation by this technique. (It should be noted that, more usually, hydroxyl functionality in the position α to the alkyne is protected (α-alkynyl ethers), and these substrates are known to perform poorly in the Dötz cyclisation, see Ref. [40]; see also Refs. [11,20–24,26–28,34,41]. Furthermore, alkyne-tethered siloxycarbene complexes have been used as masked forms of propargyl and higher homologous alcohols in the intramolecular Dötz reaction; see Ref. [10].) Despite the yields of both products **5a/b** being low, this technique provides an extremely facile method for the formation of normally less accessible highly functionalised β-lactone products from readily available starting materials. (With respect to the enol ether double bond geometry in the β-lactone forming reaction (Scheme 4), when R = Et (**5a**) only one product is formed whereas when R = Me (**5b**) both isomers are observed.) Indeed, within our laboratory this general protocol is now being developed into a more efficient process for use with a range of propargylic alcohols to give β-lactones of varying functionalisation and will be the subject of a future preliminary publication [42].

[1] In a non-metal mediated process, intramolecular trapping of in situ generated ketenes has been shown to lead to formation of γ-lactones and larger ring species; see Ref. [36].

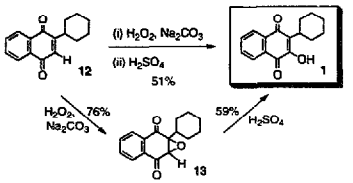
It should be noted at this stage that when our DSA techniques, known to be high yielding in previous Dötz annulation reactions, were applied to the propargylic substrates, neither benzannulation nor β-lactone products were formed. Instead, the only organic materials obtained (in low yields) were diene products, seemingly formed from the decarboxylation of β-lactones under the conditions employed [43].

2.3. Total synthesis of parvaquone

At this stage we returned our attention to the synthesis of our original target, parvaquone (**1**). From the outcome of our original cyclisation attempts and the resulting rationale for β-lactone formation, it was clear that the tertiary propargylic hydroxyl group, which we wrongly believed would be quiescent during benzannulation, should be removed in order to facilitate the desired Dötz cyclisation. All initial attempts at direct dehydroxylation of the alkoxy alkynes **2a/b** failed. Further endeavours, which utilised alkyne protection/activation with the $Co_2(CO)_6$ moiety and subsequent hydrido-dehydroxylation via the Nicholas carbocation [44], were also unsuccessful.

Our inability to gain ready access to the requisite dehyroxylated alkoxyalkyne(s) then inspired us to marginally modify the synthetic strategy for the preparation of the desired 2-hydroxy-1,4-naphthoquinone **1**. It was known that the non-alkoxylated alkyne, cyclohexylacetylene, **10**, was readily available [2] and that this substrate could be used in benzannulation reactions with a view to introducing the required 2-hydroxyl functionality at a later stage in the synthetic sequence. Reactions using both the methoxy and ethoxy carbene complexes, **3** and **11** respectively, were carried out with alkyne **10**, and a ceric ammonium nitrate (CAN) oxidative work-up employed in every case. As can be seen from Scheme 7, when our DSA conditions [12,13] were applied, the 1,4-naphthoquinone **12** was formed in good yields of 68% and 51% in 4 h and 2 h respectively. Furthermore,

[2] At the outset of this work cyclohexylacetylene **10** was available commercially from the Aldrich Chemical Co. Later, this item was discontinued and was not found to be available from any other source. Nonetheless, this alkyne **10** is readily available from cyclohexylcarbaldehyde using Corey–Fuchs based procedures [45] (see Section 4).



Scheme 8.

when our alternative sonication techniques ")))" were utilised [13] with both complexes, the same product **12** was realised in enhanced yields of 83% and 91% following remarkably short reaction times of 25–40 min. Under the more traditional and forcing thermal conditions (70 °C, n-Bu_2O), the alkyne **10** performed well in this cyclisation with complex **3**, giving a comparable yield (72%) to that of the dry state process but over a considerably longer reaction time of 14 h.

To complete our synthesis successfully, epoxidation of the quinone system in **12** was achieved using alkaline hydrogen peroxide to give **13** in 76% (Scheme 8). Subsequent treatment of this compound with concentrated sulfuric acid at room temperature afforded parvaquone (**1**), as a yellow crystalline solid, in 59% yield, with spectral data identical to that previously reported [46]. Alternatively, transformation of **12** to the desired 2-hydroxy-1,4-naphthoquinone **1** could be carried out more economically in one pot, without isolation of the epoxide **13**, in a 51% yield. Overall, using our most efficient processes, the anti-parasitic agent parvaquone (**1**) can be synthesised remarkably rapidly (approximately 3 h total reaction time) in 46% yield from readily available starting materials.

3. Conclusions

We have now shown that the 2-hydroxy-1,4-naphthoquinone **1** can be synthesised in a highly expeditious route of unprecedented economy using our modified Dötz reaction protocols; the key chromium carbene mediated cyclisations proceed in good to high yields in rapid reaction times and with greater overall efficiency than under more rigorous thermal conditions. The strategies and techniques outlined here should open up routes to a range of such compounds of high agrochemical and renewed pharmaceutical importance.

Additionally, during our synthetic endeavours we have serendipitously discovered a novel β-lactone forming reaction which further extends the scope and flexibility of chromium carbene complexes as applied to organic synthesis. We will report more extensively on this specific area in due course.

4. Experimental

4.1. General

All reagents were obtained from commercial suppliers and used without further purification, unless otherwise stated. Ether (Et_2O) and tetrahydrofuran (THF) were distilled from Na–benzophenone and methylene chloride (CH_2Cl_2) distilled from calcium hydride under a nitrogen atmosphere. All other solvents used were distilled prior to use. Petrol refers to petroleum ether (30–40 °C). Chromatographic purifications were performed on silica gel (230–400 mesh) by flash technique. All organometallic complexes were stored under nitrogen at, or below, −20 °C, and all reactions were performed under a nitrogen atmosphere unless otherwise stated. Sonication reactions were carried out using a Vibracell VC50 Titanium horn operating at 50 W/20 kHz.

^1H and ^{13}C NMR were run on a 250 MHz Bruker WM 250 and a 400 MHz Bruker WM 400 in $CDCl_3$ solutions. Chemical shifts are reported in parts per million downfield relative to tetramethylsilane (δ 0.00); coupling constants are reported in hertz; in 13C jmod, up (u) indicates C or CH_2 and down (d) indicates CH or CH_3. Infrared spectra were obtained on a Mattson 1000 or Nicolet Impact 400D FTIR spectrometer in CH_2Cl_2 solutions. High resolution mass spectrometry was performed on a Jeol Instruments JMS-AX505HA mass spectrometer system. Mass spectral data is reported as m/z (relative intensity).

4.2. Preparation of 1-(2-ethoxyethynyl)-1-cyclohexanol (2a) [18]

A solution of 50% w/w ethoxyacetylene–hexane (1.00 g, 7.14 mmol) in THF under nitrogen was cooled to −10 °C in an ice–salt bath. n-Butyllithium (2.86 ml, 2.5 M solution in hexanes, 7.14 mmol) was added dropwise over 5 min and the reaction stirred for 10 minutes at 0 °C. Cyclohexanone (466 mg, 4.76 mmol) in THF was added in one portion and the solution stirred for a further 45 min at 0 °C and for 30 min at room temperature. Solvent was removed in vacuo and the remaining oil treated with ammonium chloride solution (75 ml), extracted with ether (2 × 50 ml), dried over magnesium sulfate, filtered and purified by silica column chromatography (eluant: petrol–ether 2:1; $R_f = 0.7$) to give the desired compound **2a** (730 mg, 91%) as fine yellow crystals. ^1H NMR (250 MHz, $CDCl_3$): δ 4.11 (q, J = 7.1 Hz, 2H); 1.90–0.80 ppm (m, 14H). FTIR ν_{max} (CH_2Cl_2): 3591 (s, O–H stretch); 2953, 2877 (s, aliphatic C–H); 2263 cm^{-1} (w, C≡C).

4.3. Preparation of 1-(2-methoxyethynyl)-1-cyclohexanol (2b)

A stirred solution of diethylamine (2.37 ml, 22.9 mmol) in THF (90 ml) was treated with *n*-butyllithium (8.50 ml, 2.5 M solution in hexanes, 21.2 mmol) over a period of 5–10 min. The reaction mixture was allowed to stir for a further 10 min at 0 °C and then chloroacetaldehyde dimethylacetal (0.75 ml, 6.55 mmol) was slowly added. After 2 h, cyclohexanone (0.62 ml, 6.00 mmol) was added in one portion. The reaction mixture was stirred for a further 30 min at room temperature and then worked up by addition of mesyl chloride (0.54 ml, 7.00 mmol) and stirred for a further 30 min. The crude product was purified by silica column chromatography (eluant: dichloromethane; $R_f = 0.20$) to give the desired compound **2b** (920 mg, 99%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.87 (s, 3H); 2.35 (s, br, OH); 1.90–1.50 ppm (m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 95.1, 68.7, 65.9, 41.0, 40.8, 25.4, 23.6 ppm. FTIR υ_{max} (neat): 3525 (s, O–H stretch); 2928, 2876, (s, aliphatic C–H); 2263 cm^{-1} (w, C≡C). HRMS *m/z* calc. for $C_9H_{14}O_2$ (M^+): 154.0994. Found: 154.0987 (46); Calc. for $C_8H_{11}O_2$ ($M^+ - CH_3$): 139.0759. Found: 139.0760 (32).

4.4. Preparation of pentacarbonyl(methoxyphenylmethylene)chromium(0) (3) [29]

To a stirred suspension of chromium hexacarbonyl (2.15 g, 9.76 mmol) in dry ether (175 ml) at room temperature was added a solution of phenyllithium (5.7 ml, 1.7 M solution in hexanes, 9.69 mmol) in dry ether (25 ml) over 20 min. After 40 min the solvent was removed in vacuo and the resulting salt dissolved in nitrogen-saturated water. Trimethyloxonium tetrafluoroborate was added in portions until the solution became acidic; the aqueous layer was then extracted with ether. The solvent was removed in vacuo and chromatographic purification on silica gel (eluant: dichloromethane–petrol 1:9; $R_f = 0.40$) afforded complex **3** as fine, red needles (2.01 g, 66%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.53–7.38 (m, 3H); 7.32–7.21 (m, 2H); 4.72 ppm (s, 3H). FTIR υ_{max} (CH_2Cl_2): 2075, 1993, 1940 cm^{-1} (Cr–CO).

4.5. Reaction of alkyne 2a with carbene complex 3

Crystals of pentacarbonyl[phenyl(methoxy)carbene] chromium(0) (**3**) (152 mg, 0.487 mmol) and 1-(2-ethoxyethynyl)-1-cyclohexanol (**2a**) (96 mg, 0.570 mmol) were dissolved in THF. Acetic anhydride (0.09 ml, 0.954 mmol) and triethylamine (0.14 ml, 0.970 mmol) were added to the reaction mixture which was heated to reflux for 16 h. The solvent was removed in vacuo and the residue pre-absorbed onto silica and purified by chromatography (eluant: petrol–ether 5:1) to give 1-[2-(1-cyclohexenyl)-3-ethoxy-4-methoxy]naphthol acetate (**4a**) (27 mg, 16%; $R_f = 0.40$) and the β-lactone, 4-cyclohexanespiro-3-(1-ethoxy-2-methoxy-2-phenylethenyl)oxetan-2-one (**5a**) (33 mg, 21%; $R_f = 0.38$).

4.5.1. 1-[2-(1-Cyclohexenyl)-3-ethoxy-4-methoxy]naphthol acetate (4a)

^{1}H NMR (250 MHz, $CDCl_3$): δ 8.12 (dd, $J = 7.0$, 1.8 Hz, 1H); 7.68 (dd, $J = 7.3$, 1.5 Hz, 1H); 7.59–7.40 (m, 2H); 5.72 (s, br, 1H); 4.14 (q, $J = 7.1$ Hz, 2H); 4.02 (s, 3H); 2.38 (s, 3H); 2.30–0.80 ppm (m, 11H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 170.1, 146.5, 145.7, 139.8, 132.5, 131.7, 128.4, 127.4, 126.1, 125.7, 124.8, 122.0, 121.6, 69.8, 66.1, 29.1, 25.9, 23.5, 22.5, 20.9, 16.2 ppm. FTIR υ_{max} (CH_2Cl_2): 1778 (s, C=O); 1600 cm^{-1} (m, C=C). HRMS *m/z* calc. for $C_{21}H_{24}O_4$ (M^+): 340.1675. Found: 340.1698 (100).

4.5.2. 4-Cyclohexanespiro-3-(1-ethoxy-2-methoxy-2-phenylethenyl)oxetan-2-one (5a)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45–7.40 (m, 3H); 7.32–7.25 (m, 2H); 4.21 (dq, $J = 9.0$, 7.0 Hz, 1H); 4.05 (dq, $J = 9.1$, 7.0 Hz, 1H); 3.81 (s, 1H); 3.40 (s, 3H); 2.20–1.90 (m, 3H); 1.70–1.10 ppm (m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 169.3(u); 146.0(u); 134.1(u); 133.0(u); 129.7(d); 128.9(d); 128.6(d); 83.5(u); 69.0(u); 61.2(d); 57.3(d); 36.9(u); 31.1(u); 24.7(u); 22.8(u); 22.5(u); 15.8(d) ppm. FTIR υ_{max} (CH_2Cl_2): 2953, 2876 (s, aliphatic C–H); 1829 cm^{-1} (s, C=O). HRMS *m/z* calc. for $C_{19}H_{24}O_4$ (M^+): 316.1675. Found: 316.1668 (14). Calc. for $C_{18}H_{24}O_2$ ($M^+ - CO_2$): 272.1776. Found: 272.1770 (100).

4.6. Reaction of alkyne 2b with carbene complex 3

Crystals of pentacarbonyl[phenyl(methoxy)carbene] chromium(0) (**3**) (409 mg, 2.62 mmol) and 1-(2-methoxyethynyl)-1-cyclohexanol (**2b**) (316 mg, 2.05 mmol) were dissolved in THF. Acetic anhydride (0.24 ml, 2.62 mmol) and triethylamine (0.36 ml, 2.62 mmol) were added to the reaction mixture which was heated to reflux for 16 h. The solvent was removed in vacuo and the residue pre-absorbed onto silica and purified by chromatography (eluant: petrol–ether 6:1) to give 1-[2-(1-cyclohexenyl)-3,4-dimethoxy]naphthol acetate (**4b**) (29 mg, 7%; $R_f = 0.60$) and the β-lactone, 4-cyclohexanespiro-3-(1,2-dimethoxy-2-phenylethenyl)oxetan-2-one (**5b**) (58 mg, 15%; $R_f = 0.50$).

4.6.1. 1-[2-(1-Cyclohexenyl)-3,4-dimethoxy]naphthol acetate (4b)

^{1}H NMR (250 MHz, $CDCl_3$): δ 8.14–8.10 (m, 1H); 7.72–7.69 (m, 1H); 7.48–7.10 (m, 2H); 5.72 (s, br,

1H); 4.02 (s, 3H); 3.98 (s, 3H); 2.38 (s, 3H); 2.35–2.15 (m, 4H); 1.85–1.60 ppm (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 170.0, 147.3, 145.4, 139.8, 133.0, 132.3, 128.4, 128.1, 126.3, 125.9, 124.9, 121.9, 121.7, 61.5, 61.4, 29.1, 25.8, 23.4, 22.4, 20.9 ppm. FTIR ν_{max} (CH_2Cl_2): 1765 (s, C=O); 1603 cm^{-1} (m, C=C). HRMS m/z calc. for $C_{20}H_{22}O_4$ (M^+): 326.1518. Found: 326.1587 (50).

4.6.2. 4-Cyclohexanespiro-3-(1,2-dimethoxy-2-phenylethenyl)oxetan-2-one (5b)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.49–7.24 (m, 5H); 3.89 (s, 3H); 3.81 (s, 1H); 3.41 (s, 3H); 2.17–1.23 ppm (m, 10H). FTIR ν_{max} (CH_2Cl_2): 1825 (s, C=O); 1600 cm^{-1} (s, C=C). HRMS m/z calc. for $C_{18}H_{22}O_4$ (M^+): 302.1518. Found: 302.1515 (14). Calc. for $C_{17}H_{22}O_2$ ($M^+ - CO_2$) 258.1620. Found: 258.1624 (100).

4.7. Preparation of cyclohexylacetylene (10) [47]

Cyclohexylcarbaldehyde (0.569 g, 5.08 mmol) was dissolved in distilled dichloromethane (20 ml) with triphenylphoshine (4.32 g, 16.49 mmol, 3.3 equivalents) and cooled to 0 °C using an ice bath. Carbon tetrabromide (3.67 g, 11.05 mmol, 2.2 equivalents) in dichloromethane (15 ml) was added over 5 min causing the solution to become orange in colour. The reaction mixture was stirred at 0 °C for 1.5 h then petrol (200 ml) was added in one portion. This resulted in precipitation of triphenylphosphine oxide, which was removed by filtration through a pad of silica. Removal of the solvent in vacuo gave a slightly yellow oil which was then dissolved in THF (20 ml), cooled to −78 °C using an acetone–dry-ice bath and placed under a nitrogen atmosphere. *n*-Butyllithium (1.6 M solution in hexanes, 8.30 ml, 12.71 mmol, 2.5 equivalents) was added dropwise over 10 min causing the solution to become deep red in colour. The reaction mixture was stirred for 1 h at −78 °C and then allowed to warm to room temperature over 30 min. Water (50 ml) was added and the mixture was then extracted using ether (2 × 50 ml). The ethereal fractions were collected, dried over calcium sulfate then filtered. The solvent was removed in vacuo and the residual oil was purified by flash column chromatography (eluant: petrol; $R_f = 0.70$) to yield 0.374 g (68%) of product **10** as a clear oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.42–2.27 (m, 1H); 2.04 (d, $J = 2.4$ Hz, 1H); 1.85–1.66 (m, 4H); 1.56–1.26 ppm (m, 6H). FTIR ν_{max} (CH_2Cl_2): 3320 (s, alkyne C–H), 2939, 2857 (s, aliphatic C–H), 2120 cm^{-1} (w, alkyne C≡C).

4.8. Preparation of pentacarbonyl(ethoxyphenylmethylene)chromium(0) (11) [48]

To a stirred solution of bromobenzene (1.16 g, 7.39 mmol) in dry ether (30 ml) at 0 °C was added *n*-butyllithium (3.2 ml, 2.5 M solution in hexanes, 8.03 mmol) over 10 min. The mixture was stirred for a further 10 min and then transferred to a stirred suspension of chromium hexacarbonyl (1.13 g, 5.14 mmol) in dry THF (30 ml) at room temperature. After 2 h, solvent was removed in vacuo and the residue dissolved in degassed water (50 ml). Triethyloxonium tetrafluoroborate (1.01 g, 5.32 mmol) was added and the resultant red solution stirred at room temperature for 5 min. The solution was then extracted with ether, dried over magnesium sulfate, filtered and the solvent removed in vacuo. Chromatographic purification on silica gel (eluant: petrol; $R_f = 0.30$) afforded complex **3** as fine, red needles (0.951 g, 57%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.59–7.39 (m, 3H); 7.28–7.25 (m, 2H); 4.95 (q, $J = 7.0$ Hz, 2H); 1.68 ppm (t, $J = 7.0$ Hz, 3H). FTIR ν_{max} (CH_2Cl_2): 2062, 1945 cm^{-1} (s, Cr–CO).

4.9. Preparation of 2-cyclohexyl-1,4-naphthoquinone (12) [49,50]

4.9.1. Under dry state conditions with complex 3

Pentacarbonyl[phenyl(methoxy)carbene]chromium(0) (**3**) (260.3 mg, 0.834 mmol) and cyclohexylacetylene (**10**) (206.8 mg, 1.814 mmol, 2.2 equivalents) were stirred with silica (23.0 g, 10 g mmol^{-1} of alkyne) in ether (100 ml) for 5 min. Solvent was removed in vacuo at ice-bath temperature to reduce loss of the volatile alkyne. The resulting yellow powder was heated to 50 °C for 4 h under nitrogen. After 4 h the powder had become pale green and tlc (eluant: petrol) indicated that no starting complex remained. The powder was extracted with a 10:1 ether–methanol solvent system, the silica was removed by filtration and the solvent was removed in vacuo. The residual oil was dissolved in ether (40 ml) and CAN (3.61 g, 7.02 mmol, 8.4 equivalents) in water (20 ml) was added. The mixture was then stirred vigorously for 30 min at room temperature and then extracted with ether. The ethereal fractions were dried over magnesium sulfate, filtered and the solvent removed in vacuo. The crude material was purified using flash column chromatography (eluant: petrol–dichloromethane 2:1; $R_f = 0.50$) to afford 136.4 mg (68%) of **12** as yellow crystals. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.13–8.04 (m, 2H); 7.74–7.55 (m, 2H); 6.79 (d, $J = 1.0$ Hz, 1H); 2.96–2.87 (m, 1H); 1.96–1.16 ppm (m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 185.6, 184.8, 156.3, 133.6 (2 × C); 133.1, 132.6, 132.0, 126.8, 126.0, 36.8, 32.4, 26.5, 26.2 ppm. FTIR ν_{max} (CH_2Cl_2): 2935, 2853 (s, aliphatic C–H); 1666 (s, C=O); 1605 cm^{-1} (m, C=C).

4.9.2. Under ultrasound conditions with complex 3

Pentacarbonyl[phenyl(methoxy)carbene]chromium(0) (**3**) (74.1 mg, 0.236 mmol) and cyclohexylacetylene (**10**) (35.5 mg, 0.327 mmol, 1.4 equivalents) were dissolved

in THF (5 ml). The reaction mixture was sonicated for 25 min using an ultrasonic horn, after which time the solution had changed from a dark red colour to a dark green. Analysis by tlc (eluant: petrol) indicated no starting complex remaining and so THF was removed in vacuo and the residue redissolved in ether (25 ml). CAN (1.02 g, 1.86 mmol, 7.8 equivalents) in water (20 ml) was added and the mixture then stirred vigorously for 30 min at room temperature. The reaction mixture was then extracted with ether, dried over magnesium sulfate, filtered and solvent removed in vacuo. The material was purified using flash column chromatography (eluant: petrol–dichloromethane 2:1; $R_f = 0.50$) to afford 47.2 mg (83%) of **12** as a yellow crystalline solid.

4.9.3. Under dry state conditions with complex 11

Pentacarbonyl[phenyl(ethoxy)carbene]chromium(0) (**11**) (67.2 mg, 0.21 mmol) and cyclohexylacetylene (**10**) (42.0 mg, 0.39 mmol, 1.8 equivalents) were stirred with silica (3.9 g, 10 g $mmol^{-1}$ of alkyne) in ether (50 ml) for 10 min. Solvent was removed in vacuo at ice-bath temperature to reduce loss of the volatile alkyne. The resulting orange powder was heated to 60 °C for 2 h under nitrogen. After this time, the powder had become pale green and tlc (eluant: petrol) indicated that no starting complex remained. The powder was extracted with a 10:1 ether–methanol solvent system, the silica was removed by filtration and the solvent was removed in vacuo. The residual oil was dissolved in ether (30 ml) and CAN (1.00 g, 1.83 mmol, 8.5 equivalents) in water (30 ml) was added. The mixture was then stirred vigorously for 30 min at room temperature and then extracted with ether. Ethereal fractions were dried over magnesium sulfate, filtered and the solvent removed in vacuo. The crude material was purified using flash column chromatography (eluant: petrol–dichloromethane 2:1; $R_f = 0.50$) to afford 26.0 mg (51%) of the desired product **12** as yellow crystals.

4.9.4. Under ultrasound conditions with complex 11

Pentacarbonyl[phenyl(ethoxy)carbene]chromium(0) (**11**) (296.7 mg, 0.910 mmol) and cyclohexylacetylene (**10**) (196.6 mg, 1.820 mmol, 2.0 equivalents) were dissolved in THF (5 ml). The reaction mixture was sonicated for 40 min using the ultrasonic horn, after which time the solution had changed from dark red to black in colour. Analysis by tlc (eluant: petrol) indicated no starting complex remaining and so the THF was removed in vacuo and the residue redissolved in ether (30 ml). CAN (3.82 g, 6.97 mmol, 7.7 equivalents) in water (30 ml) was added and the mixture then stirred vigorously for 30 min at room temperature. The reaction mixture was then extracted with ether, dried over sodium sulfate, filtered and solvent removed in vacuo. The material was purified using flash column chromatography (eluant: petrol–dichloromethane 2:1; $R_f = 0.50$) to afford 199.7 mg (91%) of the desired product **12** as a yellow crystalline solid.

4.9.5. Under thermal conditions with complex 3

Pentacarbonyl[phenyl(methoxy)carbene]chromium(0) (**3**) (237.0 mg, 0.760 mmol) and cyclohexylacetylene (**10**) (152.8 mg, 1.344 mmol, 1.8 equivalents) were dissolved in di-*n*-butyl ether (5 ml). The reaction mixture was heated at 70 °C for 14 h and changed from a dark red colour to a murky green. Analysis by tlc (eluant: petrol) indicated no starting complex remaining and so di-*n*-butyl ether was removed in vacuo and the residue redissolved in ether (30 ml). CAN (3.31 g, 6.04 mmol, 8.0 equivalents) in water (30 ml) was added and the mixture then stirred vigorously for 30 min at room temperature. The reaction mixture was then extracted with ether, dried over magnesium sulfate, filtered and solvent removed in vacuo. The material was purified using flash column chromatography (eluant: petrol–dichloromethane 2:1; $R_f = 0.50$) to afford 131.4 mg (72%) of the desired product **12** as a yellow crystalline solid.

4.10. Preparation of 1a-cyclohexyl-1a,7a-dihydronaphth[2,3b]oxirene-2,7-dione (13) [50,51]

A solution of 2-cyclohexyl-1,4-naphthoquinone (**12**) (51.9 mg, 0.216 mmol) in warm ethanol (0.5 ml) was cooled until precipitation began to occur. At this point a solution of alkaline hydrogen peroxide (250 μl of 30% H_2O_2, 11.9 mg anhydrous sodium carbonate in water (100 μl)) was added in one portion. The mixture was stirred until the yellow colour disappeared (1 h) whereupon water (5 ml) was added causing precipitation of 42.2 mg (76%) of a white solid **13**. ^1H NMR (250 MHz, $CDCl_3$): δ 8.03–7.92 (m, 2H); 7.77–7.72 (m, 2H); 3.92 (s, 1H); 2.52 (tt, $J = 11.8$, 2.9 Hz, 1H); 1.81–1.08 ppm (m, 10H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 192.5, 191.7, 134.7, 134.4, 133.1, 131.8, 127.7, 126.8, 66.8, 58.3, 34.9, 29.3, 26.7, 26.3, 26.2, 26.0 ppm. FTIR ν_{max} (CH_2Cl_2): 3056 (m, epoxide C–H); 2936, 2861 (s, aliphatic C–H); 1696 (s, C=O); 1596 cm^{-1} (m, aromatic C=C). HRMS m/z calc. for $C_{16}H_{16}O_3$ (M^+): 256.1099. Found: 256.0941 (100).

4.11. Preparation of 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone, parvaquone (1) [46,50]

4.11.1. From 1a-cyclohexyl-1a,7a-dihydronaphth[2,3b]-oxirene-2,7-dione (13)

Crystals of 1a-cyclohexyl-1a,7a-dihydronaphth[2,3b]oxirene-2,7-dione (**13**) (31.5 mg, 0.123 mmol) were dissolved in concentrated sulfuric acid (250 μl) to give a bright red solution. This was stirred at room temperature for 15 min then water (3 ml) was added and the mixture extracted repeatedly with ether. Ethereal fractions were combined, dried over

magnesium sulphate, filtered and solvent removed in vacuo to give a brown oil which was purified chromatographically (eluant: petrol–ether 10:1; $R_f = 0.40$) to yield parvaquone (**1**) as a yellow crystalline solid (18.6 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, $J = 7.7$, 1.3 Hz, 1H); 8.05 (dd, $J = 7.5$, 1.4 Hz, 1H); 7.74 (td, $J = 7.6$, 1.4 Hz, 1H); 7.66 (td, $J = 7.5$, 1.3 Hz, 1H); 7.46 (s, disappears on treatment with D_2O, OH); 3.08 (tt, $J = 12.2$, 3.4 Hz, 1H); 2.03–1.93 (m, 2H); 1.87–1.23 ppm (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.8(u); 182.2(u); 153.0(u); 135.1(d); 133.4(u); 132.9(d); 129.4(u); 128.1(u); 127.1(d); 126.1(d); 32.5(d); 29.4(u); 27.0(u); 26.2(u) ppm. FTIR υ_{max} (CH_2Cl_2): 3680, 3595, 3520 (m, O–H); 2930, 2867 (s, aliphatic C–H); 1671 (s, C=O); 1596 cm^{-1} (m, C=C). HRMS m/z calc. for $C_{16}H_{16}O_3$ (M^+): 256.1099. Found: 256.1082 (100).

4.11.2. From 2-cyclohexyl-1,4-naphthoquinone (12)

A solution of 2-cyclohexyl-1,4-naphthoquinone (**12**) (54.6 mg, 0.228 mmol) in warm ethanol (0.5 ml) was cooled until precipitation began to occur. At this point a solution of alkaline hydrogen peroxide (350 µl of 30% H_2O_2, 31.4 mg anhydrous sodium carbonate in water (750 µl)) was added in one portion. The mixture was stirred until the yellow colour disappeared (90 min), whereupon water was added causing precipitation of a white solid. This was extracted with ether and solvent then removed in vacuo. The resultant oil was then dissolved in concentrated sulfuric acid (1 ml) causing a colour change to blood red. After stirring at room temperature for 1 h, water (3 ml) was added and the reaction mixture repeatedly extracted with ether. Ethereal fractions were combined, dried over magnesium sulfate, filtered and solvent removed in vacuo to give a brown oil which was purified chromatographically (eluant: petrol–ether 10:1; $R_f = 0.40$) to yield parvaquone (**1**) as a yellow crystalline solid (29.4 mg, 51%).

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