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Divergent reactivity of phenol- and anisoletethered donor-acceptor α-diazoketones

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Divergent reactivity of phenol- and anisole-tethered donor-acceptor α-diazoketones

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ABSTRACT

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a-Diazocarbonyl compounds Anisole Buchner reaction Phenol Divergent reactivity The first study of the divergent reactivity of phenol/anisole-tethered donor-acceptor α diazoketones is described. Four distinct product classes were shown to be accessible from closely related α -diazoketone precursors, with the reaction outcome dependent on the nature of the oxygen substituent on the phenol/anisole ring and the catalyst used to decompose the diazo group. Anisole and TBS-protected derivatives selectively produce three products types (cyclopropanes, tetralones and 1,2-dicarbonyls) while phenols selectively produce spirocyclic dienones.

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1. Introduction

 α -Diazocarbonyl compounds are a versatile compound class able to undergo a variety of synthetic transformations to generate multiple products.^{1,2} Their diverse reactivity is well-known in the literature and is a consequence of the many reactive intermediates they can form, including carbenes, carbenoids, ylides and diazonium cations. An excellent review by Maguire, McKervey and co-workers details the importance of α -diazocarbonyl compounds in modern organic synthesis, and demonstrates their utility in a range of C-H insertion, cyclopropanation, cycloaddition and ylide-forming reactions.^{1d}

The versatile reactivity of α -diazocarbonyl compounds means that they are well-suited for use in diversity-oriented synthesis,³ especially for research focused on the synthesis of multiple product classes from the same starting material.^{4,5} Such processes are particularly useful if the chemoselectivity can be controlled, for example, by variation of the reaction conditions or reagents. In our groups,^{5a,6} we are interested in developing divergent reaction systems in which the outcome is controlled by the choice of catalyst. Such 'catalyst selective synthesis'7.8 has the power to significantly streamline the synthesis of diverse compounds, whilst also advancing our knowledge of the catalysis that underpins the divergent reactivity. An instructive example of the power of this approach was published by our groups in 2016, in which we demonstrated that by careful choice of catalyst and reaction conditions we could selectively generate six distinct products from single indolyl a-diazoketone precursors of the form 1 (Scheme 1A).^{5a} To the best of our knowledge, this represents the highest number of distinct products selectively accessible from a single precursor by varying the catalyst and reaction conditions reported date.



Scheme 1. Catalyst selective synthesis using α -diazoketones.

In this manuscript, we describe efforts to extend this catalyst selective synthesis approach to phenol-/anisole-tethered α -

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diazoketones of the form 3 (i.e. 'donor-acceptor' diazoketones,⁹ Scheme 1B). There were no reports concerning the reactions of diazo compounds of this type prior to this study,¹⁰ although we drew inspiration from earlier studies detailing the reactivity of related classes of phenol-tethered α-diazoketones. For example, one of the first published intramolecular cyclisation reactions of such a compound was reported by Mander et al. in 1974, in which either Brønsted or Lewis acids were used to promote the displacement of nitrogen from simple α -diazoketones of the form 8, leading to the formation of bridged tricyclic systems (e.g. $8 \rightarrow$ 9, Scheme 2A).¹¹ Iwata and co-workers later reported that similar transformations could be promoted with copper(I) chloride to generate spirocycles (e.g. $10 \rightarrow 11$, Scheme 2B);¹² indeed, Mander et al. had previously shown that spirocycles of this type could be prepared using BF₃.OEt₂ to promote the reaction, albeit with competing dienone-phenol rearrangement products being formed in some cases.¹³ Apart from these works, surprisingly little is known about the reactions of phenol-tethered α diazoketones, although Harada, Nemoto and co-workers recently published a powerful strategy for the conversion of structurally related α -diazoacetamides 12 into spirocyclic dienones 13 in high vield and enantiomeric excess using chiral silver(I) salts (Scheme 2C).¹⁴ Encouragingly for us, divergent reactivity was observed during initial catalyst screening in this study, with ring-annulated and C-H insertion products also observed to some degree when other catalysts were used.



Scheme 2. Use of related phenol-tethered α -diazocarbonyl compounds in the literature.

Compared to phenol-tethered systems, more is known about the reactivity of α -diazoketones tethered to anisoles, particularly in the well-established Buchner reaction (*e.g.* Scheme 3A).¹⁵ Various mechanistic and kinetic studies have been performed, most notably by McKervey and Maguire,¹⁶ with much of this work focused on the reactions of H-/Me-substituted α diazoketones. More recently, related reactions on α -diazoketones substituted with electron-withdrawing substituents have also emerged¹⁷ ('acceptor-acceptor' diazo compounds), for example, the anisole annulation method developed by Doyle and coworkers, depicted in Scheme 3B.^{17a} Notably, the reaction outcomes in these studies typically differ to those observed in the analogous phenol systems, in which spirocyclic products usually dominate.



Scheme 3. Use of related anisole-tethered α -diazocarbonyl compounds in the literature.

Our previous work in this area (Scheme 1A) focused on systems in which the diazo group is flanked on either side by both a ketone and an aromatic ring (see 1, Scheme 1); controlling the reactivity of such 'donor-acceptor' diazo systems⁹ is often easier than in less stabilised diazo systems, and it was decided to retain this feature in the current study (e.g. 3) in the hope that it would allow us to impart similar chemoselectivity to that achieved in our earlier work.^{5a} Our interest in these systems was further piqued by the fact that, to the best of our knowledge, there have been no reports concerning the reactions of any phenol/anisole-tethered α -diazoketones of this type (3) prior to this study.¹⁰ Thus, herein, we describe our initial catalyst-screening, reaction optimisation and provide mechanistic proposals for a new, catalyst-driven divergent reaction series, that enables cyclopropane, tetralone, 1,2-dicarbonyl and spirocyclic products (4-7) to be selectively prepared from structurally related α -diazoketone precursors of the form **3**.

2. Results and discussion

2.1. Anisole-tethered α -diazoketones

We initiated our study by treating anisole-tethered α diazoketone $\mathbf{3a}^{18}$ with a range of metal-based catalysts. The expectation was that by forming different metal carbenoid species, different reactive pathways would be accessed, resulting in the preparation of multiple products. Selected screening results are shown in Table 1, with details of the full screen included in the Supporting Information. All catalysts were tested at 10 mol% loading in CH₂Cl₂ (0.1 M) at RT unless stated, with the product ratios determined by integration of their unpurified ¹H NMR spectra. As expected, many of the conditions produced mixtures of products, although three major identifiable products were observed in most cases: these were subsequently isolated and the structures assigned as cyclopropane 4a, tetralone 5a and 1,2dicarbonyl **6a**. Other minor products were also observable by ${}^{1}H$ NMR spectroscopy in some cases, but these could not be obtained cleanly, hence the subsequent discussion is focused on the ratio of the three major products 4a-6a. Cyclopropane 4a, which was formed using the widest array of catalysts (via the Buchner reaction), was the major product produced using Rh(II), Cu(I) and Pd(II) catalysts (Table 1, entries 1-3), with Ag₂O producing this product with the highest purity of the catalysts screened (entry 4). Conversely, more Lewis acidic catalysts $Cu(OTf)_2$ and AgOTf furnished tetralone **5a** as the major product with good chemoselectivity (entries 5 and 6), whereas Pd(PhCN)₂Cl₂ unexpectedly formed 1,2-dicarbonyl **6a** as the major component (entry 7).

Table 1. Catalyst screening on diazoketone 3a^a CCEPTED M cyclopropane 4a and tetralone 5a required little additional

	[Catalyst] CH ₂ Cl ₂ , RT	h Ph OMe	Ph O Ph
3a	4a	5a	6a
Entry	Catalyst	3a : 4a : 5a	a : 6a ^b
1^c	Rh ₂ (OAc) ₄	15 : 65 : 0	: 20
2	CuCl	5 : 85 : 0	: 10
3	$Pd(OAc)_2$	0 : 80 : 0	: 20
4	Ag ₂ O	0 : 95 : 0	: 5
5	Cu(OTf) ₂	10 : 0 : 9 0) :0
6	AgOTf	0:0: 10) :0
7	Pd(PhCN) ₂ Cl ₂	0:0:15:	: 85 ^d

^{*a*} Reactions were performed with 0.1 mmol of diazoketone **3a** and 10 mol% catalyst in CH₂Cl₂ (0.1 M) under argon at RT for 16 h unless stated otherwise. ^{*b*} Product ratio was calculated using the ¹H NMR spectrum of the unpurified reaction mixture, rounded to nearest 5%. ^{*c*} 5 mol% catalyst used. ^d Other minor impurities (unidentified) were observed in this case.

Thus, these initial screening reactions uncovered three complementary metal-catalysed processes to access three distinct products. It is likely that products 4a and 5a are mechanistically related; Scheme 3 shows a proposed mechanistic pathway through which cyclopropane 4a could be converted into tetralone 5a. Presumably, following metal-mediated diazo decomposition, Buchner cyclopropanation of the electron-rich anisole ring takes place to form cyclopropane 4a which is in dynamic equilibrium with cyclohepatriene 4a' arising from reversible electrocyclic ring opening.¹⁹ Under certain conditions (e.g. Table 1, entries 1– 4) the cyclopropane/cyclohepatriene equilibrating mixture 4a/4a' is isolable, but under more acidic conditions (for example, in the presence of comparatively Lewis acidic catalysts such as $Cu(OTf)_2$ or AgOTf, see Table 1, entries 5 and 6) we propose that Lewis acid-mediated²⁰ ring expansion and tautomerisation ($4a \rightarrow$ 20 \rightarrow 5a) results in its conversion into tetralone $5a.^{\rm 16b,21}$ In support of this, it was observed that a purified sample of cyclopropane 4a can be converted into tetralone 5a smoothly upon treatment under our standard Ag(I)-mediated conditions (c.f. Table 1, entry 6).



Scheme 3. Buchner cyclisation and rearrangement.

Attention next turned to further optimising each of the three individual processes. Pleasingly, the selective formation of optimisation; changes to the reaction solvents and catalyst loadings were briefly examined, and optimal conditions were uncovered that enabled each product to be isolated in 83% and 79% yield respectively, using either 2 mol% Ag₂O or 10 mol% AgOTf, both in CH₂Cl₂ at room temperature (Scheme 4). We were also able to perform a subsequent Diels–Alder reaction on cyclopropane product **4a** with dimethyl acetylenedicarboxylate **21** to generate compound **22a** in good yield. This adds support to the notion that compound **4a** is norcaradiene-like in character.



Scheme 4. Formation of cyclopropane 4a and tetralone 5a.

In our initial catalyst screen, the most effective catalyst for the preparation of 1,2-dicarbonyl 6a was Ph(PhCN)₂Cl₂, but after further optimisation, we were unable to get full and clean conversion into this product, with unwanted side products (especially tetralone 5a) contaminating the desired product in all cases. Of course, this reaction is a formal oxidation process, but with no obvious oxidant present in the reaction, we reasoned that adventitious impurities (in particular oxygen and water), may be required for this transformation. However, changes to the solvent and reagent quantities failed to deliver an improved procedure; the addition of 1 equivalent of water, performing the reaction open to air and purging the reaction solvent with oxygen failed to improve the yield of this oxidation process. Pleasingly however, we found that we could access this third product more reliably using conditions originally reported by Toste et al; thus, 1,2diketone **6a** was isolated in 90% yield following treatment with a mixed Ag(I)/Au(I) catalyst system in the presence of diphenyl sulfoxide (Scheme 5)²²



Scheme 5. Synthesis of 1,2-dicarbonyl 6a.

2.2. Phenol-tethered α-diazoketones

Given that *para*-anisole derivatives have been successfully used²³ in dearomatising spirocyclisation²⁴ reactions to make spirocyclic dienones via other electrophilic activation modes, we were somewhat surprised that none of the catalysts tested on anisole **3a** delivered spirocycle **7**. However, based on precedent for the formation of spirocyclic dienones from related phenol derivatives,^{11-13, 25} we were optimistic that shifting focus to the analogous phenol-tethered α -diazoketone **3b** would facilitate access to this medicinally important compound class.²⁶ Thus, the

same metal catalysts previously used on anisole system **3a**, were tested on the new phenol substrate **3b**, with full screening results included in the Supporting Information. As we hoped, many of the catalysts screened delivered spirocycle **7** as the major product, along with 1,2-dicarbonyl **6a** and other unidentified minor impurities in some cases. The most effective catalyst at promoting spirocyclisation was Cu(OTf)₂; thus, the treatment of α -diazoketone **3b** with 5 mol% Cu(OTf)₂ for 3 h at RT in CH₂Cl₂ afforded spirocycle **7**, which was isolated in 70% yield (Scheme 6). The selective formation of this forth structural class nicely complements the anisole studies outlined above (Scheme 3–5).



Scheme 6. Synthesis of spirocyclic dienone 7.

2.3. Silyl-protected α-diazoketones

As shown above, each of products 4a-6a can be selectively obtained from anisole-tethered α -diazoketone 3a, while phenoltethered α -diazoketone **3b** delivers spirocycle **7** in good yield, but there is no crossover between the two series, meaning that the phenol analogues of anisole products 4a-6a, (i.e. 4b-6b) were inaccessible at this stage. To address this, it was decided to examine a third α -diazoketone starting material (3c) in which the tethered phenol is protected with a t-butyldimethylsilyl (TBS) group. The expectation here was that this compound 3c would react similarly to its anisole analogue 3a (to form TBS-protected products 4c-6c), and that subsequent desilylation would enable phenol derivatives **4b–6b** to be isolated. Thus, TBS-protected α diazoketone 3c was reacted under the optimised conditions for the preparation of 4a-6a (Scheme 7). First, the Ag₂O-catalysed conditions delivered the expected Buchner cyclopropane product 4c (as before, in dynamic equilibrium with its cyclohepatriene form) in good yield. Next, the AgOTf conditions also worked well, but proceeded with concomitant desilylation, affording phenol-tetralone 5b directly in 86% yield, with none of its TBSprotected analogue 5c observable. Finally, the oxidative conditions proceeded as expected, to deliver 1,2-diketone 6c in 61% yield, with the TBS group still in place.



Scheme 7. Divergent reactivity of α -diazoketone 3c.

At this point, all that remained was to test whether desilylation of products 4c and 6c could be achieved. Interestingly, treating cyclopropane 4c with TBAF in THF at -78 °C, did not lead to the

formation of its phenol analogue 4b, but instead promoted desilylation and rearrangement to form spirocycle 7 in 67% yield, presumably via the mechanism shown in Scheme 8. Thus, it appears that cyclopropane 4b is unstable with respect to collapse to spirocycle 7, which certainly helps to explain why we were unable to isolate any products other than 7 from the phenol-tethered α -diazoketone starting material 3b. Compound 4c is a good Diels–Alder substrate, reacting with dimethyl acetylenedicarboxylate 21 to form 22c in high yield, and subsequent TBS-cleavage with TBAF afforded its ketone derivative 22b in 85% yield.

The desilylation of **6c** was more challenging; a variety of deprotection conditions were tested on this substrate (TBAF at -78 °C and at RT, TFA, TiCl₄) but decomposition of starting material **6c** into a mixture of uncharacterisable products was commonly observed. The best conditions we uncovered involved reacting **6c** with BF₃·Et₂O in CH₂Cl₂ at RT; deprotected diketone **6b** was successfully formed using this method, although several impurities were still obtained during this reaction, hence the isolated yield (21%) is relatively low.



Scheme 8. Desilylation of 4c and 6c.

3. Conclusion

In conclusion, the first study of the divergent reactivity of phenol/anisole-tethered donor-acceptor α-diazoketones has been performed. In total, four distinct products classes have been shown to be accessible, with the reaction outcome dependent on the nature of the aromatic oxygen substituent and the catalyst used to activate the diazo group. Anisole and TBS derivatives 3a and **3c** were both able to selectively produce three products types (cyclopropanes, tetralones and 1.2-dicarbonyls **4–6**) while phenol derivative 3b produced only spirocycle 7, with this difference believed to be a consequence of the instability of the phenol Buchner cyclisation product 4b. These results are likely to be useful from a synthetic standpoint, especially in diversityoriented synthesis. Furthermore, the insight gleaned from studying a class of phenol/anisole-tethered $\alpha\text{-}diazoketones$ that has previously not been examined is expected to be of value to those interested in the study of diazo compounds and metal carbenoids, complementing the important studies of related systems summarised in the introduction.¹¹⁻¹⁷

4.1. General aspects

Except where stated, all reagents were purchased from commercial sources and used without further purification and all experimental procedures were carried out under an atmosphere of argon unless stated otherwise. Anhydrous CH2Cl2, toluene, MeCN and DMF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. ¹H NMR and ¹³C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δ_H 7.27 and δ_C 77.0 for CDCl_3 and δ_H 3.31 and δ_c 49.1 for CD_3OD were used as a reference. Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.5 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 Spectrometer as a thin film dispersed from either CH₂Cl₂ or CDCl₃. Mass spectra (highresolution) were obtained by the University of York Mass Spectrometry Service, using Electrospray Ionisation (ESI) or Liquid Injection Field Desorption Ionisation (LIFDI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on Merck silica gel 60F₂₅₄ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO₂), 35–70 µm, 60 Å, under a slight positive pressure, eluting with the specified solvent system.

4.2. General procedure A: Preparation of Weinreb amides

To a stirred solution of acid (1.00 mmol), MeNH(OMe)·HCl (107 mg, 1.10 mmol) and DIPEA (0.52 mL, 3.00 mmol) in CH₂Cl₂ (2.5 mL) was added T3P 50% in EtOAc (955 mg, 1.50 mmol). The solution was stirred at RT until completion was observed by TLC. The reaction mixture was poured into water (20 mL) and acidified using 10% aq. HCl (5 mL). The organics were collected and the aqueous extracted with EtOAc (3×30 mL). The organics were combined, washed with aq. 2 M NaOH (20 mL), brine (20 mL), dried over MgSO₄ and concentrated *in vacuo* to afford the Weinreb amide product.

4.3. Experimental procedures

4.3.1. N-Methoxy-3-(4-methoxyphenyl)-N-methylpropanamide

Synthesised using general procedure A with 3-(4-hydroxyphenyl)propanoic acid (7.00 g, 38.8 mmol), T3P 50% in EtOAc (37.0 g, 58.3 mmol), DIPEA (20.3 mL, 116 mmol) and MeNH(OMe)·HCl (4.20 g, 42.7 mmol) in CH₂Cl₂ (100 mL) at RT for 1 h. Afforded the title compound without further purification as a yellow oil (8.70 g, 100%); R_f 0.46 (1:1 hexane:EtOAc); $\delta_{\rm H}$ (400 MHz, CDCl₃) 2.71 (2H, t, *J* = 7.5 Hz), 2.91 (2H, t, *J* = 7.5 Hz), 3.18 (3H, s), 3.61 (3H, s), 6.84 (2H, d, *J* = 8.0), 7.15 (2H, d, *J* = 8.0 Hz); $\delta_{\rm C}$ (100 MHz, CDCl₃) 29.8, 32.1, 34.0, 55.2, 61.2, 113.8, 129.3, 133.4, 157.9, 173.7; HRMS (ESI⁺): Found: 246.1097; C₁₂H₁₇NNaO₃ (MNa⁺) Requires 246.1101, Found: 224.1277; C₁₂H₁₈NO₃ (MH⁺) Requires in the literature.²⁷

solution of N-methoxy-3-(4-methoxyphenyl)-N-To а methylpropanamide (2.00 g, 8.96 mmol) in THF (90 mL) at 0 °C under argon was added benzylmagnesium chloride (13.4 mL, 26.9 mmol, 2.0 M in THF) dropwise using a syringe pump. The resulting solution was warmed to RT and stirred for 1.5 h. The reaction was then cooled to 0 °C, quenched with sat. aq. NH₄Cl (20 mL), diluted with water (20 mL) and extracted with EtOAc (3 x 30 mL). The organics were combined, washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 8:2 hexane:EtOAc) to afford the title compound as a clear and colourless oil (1.76 g, 77%); $R_{\rm f}$ 0.70 (7:3 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 2908, 1712, 1512, 1245, 1178, 1033, 830, 735, 699; $\delta_{\rm H}$ (400 MHz, CDCl_3) 2.72– 2.78 (2H, m), 2.79-2.86 (2H, m), 3.67 (2H, s), 3.79 (3H, s), 6.81 (2H, d, J = 8.0 Hz), 7.06 (2H, d, J = 8.0 Hz), 7.18 (2H, d, J = 7.0 Hz)Hz), 7.25–7.36 (3H, m); δ_C (100 MHz, CDCl₃) 28.9, 43.7, 50.4, 55.2, 113.8, 127.0, 128.7, 129.2, 129.4, 132.9, 134.1, 157.9, 207.6; HRMS (ESI⁺): Found: 277.1189; $C_{17}H_{18}NaO_2$ (MNa⁺) Requires 277.1199.

4.3.3. 1-Diazo-4-(4-methoxyphenyl)-1-phenylbutan-2-one (3a)

To a solution of 4-(4-methoxyphenyl)-1-phenylbutan-2-one (977 mg, 3.84 mmol) and p-ABSA (1.11 g, 4.61 mmol) in MeCN (11.5 mL) at RT under argon was added DBU (0.8 mL, 5.38 mmol) dropwise. The resulting solution was stirred for 50 min before being concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc then 7:3 hexane:EtOAc with 3% Et₃N as a basic additive) to afford the title compound 3a as a yellow solid (797 mg, 74%); mp 79-81 °C; $R_f 0.73$ (7:3 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 3009, 2951, 2836, 2074, 1631, 1611, 1511, 1497, 1362, 1246, 1176, 1034, 821, 753; $\delta_{\rm H}$ (400 MHz, CDCl₃) 2.87 (2H, t, J = 7.5 Hz), 2.99 (2H, t, J = 7.5 Hz), 3.97 (3H, s), 6.84 (2H, d, J = 8.5 Hz), 7.13 (2H, d, J = 8.5 Hz), 7.27 (1H, t, J = 7.5 Hz), 7.41 (2H, dd, J = 7.5 Hz), 7.5 Hz),8.0, 7.5 Hz), 7.47 (2H, d, J = 8.0 Hz); $\delta_{\rm C}$ (100 MHz, CDCl₃) 29.8, 41.1, 55.2, 72.3, 113.9, 125.4, 126.1, 127.0, 129.0, 129.4, 132.7, 158.1, 192.0; HRMS (LIFDI⁺): Found: 280.1211; C₁₇H₁₆N₂O₂ (M⁺) Requires 280.1212.

4.3.4. 5-Methoxy-3a-phenyl-3a,3b-dihydro-1H-cyclopenta[1,3]cyclopropa[1,2]benzen-3(2H)-one (4a)

A flame-dried round-bottomed flask was charged with 1diazo-4-(4-methoxyphenyl)-1-phenylbutan-2-one **3a** (100 mg, 0.357 mmol) and Ag₂O (1.7 mg, 7.13 µmol) and purged with argon for 10 min. Anhydrous CH₂Cl₂ (3.6 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 22.5 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc) to afford the title compound 4a as a pale yellow oil (74.5 mg, 83%); R_f 0.33 (9:1 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 3028, 2934, 2829, 1745, 1715, 1647, 1489, 1446, 1416, 1219, 1167, 1109, 1020, 816, 756; δ_H (400 MHz, CDCl₃) 2.33-2.45 (1H, m), 2.55-2.67 (1H, m), 2.72-2.82 (1H, m), 2.83-2.95 (1H, m), 3.41 (3H, s), 5.07 (1H, br d, J = 8.5 Hz), 5.60 (1H, d, J = 8.0 Hz), 5.87 (1H, d, J = 8.5 Hz), 6.38 (1H, d, J = 8.0 Hz), 7.14–7.24 (5H, m); δ_{C} (100 MHz, CDCl₃) 27.4, 34.8, 54.6, 109.1, 115.5, 123.3, 126.9, 127.7, 128.5, 136.6, 157.2, 215.7; HRMS (ESI⁺): Found: 275.1040; $C_{17}H_{16}NaO_2$ (MNa⁺) Requires 275.1043, Found: 253.1222; C₁₇H₁₇O₂ (MH⁺) Requires 253.1223. Note: 1 ¹³C NMR signal was not observed, presumably due to peak broadening arising from the Buchner rearrangement.

4.3.5. (3bR,4R,7R,7aR)-Dimethyl 8-methoxy-3-oxo-3a-phenyl-2,3,3a,3b,4,7-hexahydro-1H-4,7-

ethenocyclopenta[1,3]cyclopropa[1,2]benzene-5.6 CEPTED MANS dicarboxylate (22a) hyd

A round-bottomed flask was charged with cyclopropane 4a (65 mg, 0.258 mmol) in toluene (0.5 mL) under argon. dimethyl acetylenedicarboxylate 21 (63 µL, 0.515 mmol) was added and the reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was then cooled to RT and concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (7:3 hexane:EtOAc) to afford the title compound 22a as a clear and colourless oil (83.4 mg, 82%); R_f 0.21 (7:3 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 2952, 1713, 1653, 1626, 1435, 1265, 1211, 1111, 1058, 1007, 915, 728; $\delta_{\rm H}$ (400 MHz, CDCl₃) 1.83 (1H, d, J = 4.0 Hz), 2.17–2.31 (2H, m), 2.36– 2.49 (5H, m), 3.80 (3H, s), 3.85 (3H, s), 4.09-4.13 (2H, m), 4.33 (1H, dd, J = 7.0, 3.0 Hz), 6.89–6.93 (1H, m), 7.12 (1H, d, J = 7.5 Hz), 7.15–7.23 (2H, m), 7.29–7.34 (1H, m); δ_{C} (100 MHz, CDCl₃) 27.1, 33.6, 35.4, 44.0, 44.7, 52.3, 52.4, 52.8, 54.6, 60.2, 99.1, 126.5, 127.3, 128.1, 130.1, 130.5, 133.7, 144.0, 152.9, 160.6, 165.0, 167.2, 211.8; HRMS (ESI⁺): Found: 417.1316; $C_{23}H_{22}NaO_6$ (MNa⁺) Requires 417.1309, Found: 395.1485; $C_{23}H_{23}O_6$ (MH⁺) Requires 395.1489.

4.3.6. 7-Methoxy-1-phenyl-3,4-dihydronaphthalen-2(1H)-one (5a)

A flame-dried round-bottomed flask was charged with 1diazo-4-(4-methoxyphenyl)-1-phenylbutan-2-one **3a** (100 mg, 0.357 mmol) and AgOTf (9.2 mg, 35.7 µmol) and purged with argon for 10 min. Anhydrous CH₂Cl₂ (3.6 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 16 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc) to afford the title compound 5a as a yellow oil (71.1 mg, 79%); $R_f 0.38$ (9:1 hexane:EtOAc); v_{max} (thin film)/cm⁻ 1 2940, 2844, 1714, 1611, 1502, 1450, 1260, 1156, 1037, 729; $\delta_{\rm H}$ $(400 \text{ MHz}, \text{CDCl}_3) 2.52-2.61 (1\text{H}, \text{m}), 2.72 (1\text{H}, \text{ddd}, J = 17.0,$ 6.5, 6.0 Hz), 2.93-3.11 (2H, m), 3.75 (3H, s), 4.72 (1H, s), 6.56 (1H, d, J = 2.5 Hz), 6.84 (1H, dd, J = 8.0, 2.5 Hz), 7.12 (2H, d, J = 7.5 Hz), 7.21 (1H, d, J = 8.0 Hz), 7.24–7.34 (3H, m); $\delta_{\rm C}$ (100 MHz, CDCl₃) 27.2, 37.2, 55.2, 59.9, 113.0, 114.6, 127.2, 128.56, 128.64, 128.8, 129.0, 137.3, 137.6, 158.7, 209.6; HRMS (ESI⁺): Found: 275.1044; C₁₇H₁₆NaO₂ (MNa⁺) Requires 275.1043, Found: 253.1232; C₁₇H₁₇O₂ (MH⁺) Requires 253.1223.

4.3.7. 4-(4-Methoxyphenyl)-1-phenylbutane-1,2-dione (6a)

To a solution of 1-diazo-4-(4-methoxyphenyl)-1-phenylbutan-2-one 3a (30.0 mg, 0.107 mmol) in CH₂Cl₂ (0.5 mL) was added diphenyl sulfoxide (86.6 mg, 0.428 mmol). This solution was then added to a premixed solution of Ph₃PAuCl (2.65 mg, 5.35 μ mol) and AgSbF₆ (1.84 mg, 5.35 μ mol) in CH₂Cl₂ (0.5 mL) cooled to 0 °C, the vial containing diazo solution was also rinsed with CH₂Cl₂ (0.2 mL). The reaction mixture was stirred at 0 °C for 2 h. The crude mixture was concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc) to afford the title compound 6a as a yellow oil (25.9 mg, 90%); R_f 0.32 (9:1 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 2934, 2836, 1711, 1670, 1596, 1449, 1245, 1177, 1033, 825, 689; $\delta_{\rm H}$ (400 MHz, CDCl₃) 3.00 (2H, t, J = 7.5Hz), 3.21 (2H, t, J = 7.5 Hz), 3.79 (3H, s), 6.83 (2H, d, J = 8.5 Hz), 7.15 (2 H, d, J = 8.5 Hz), 7.48 (2 H, dd, J = 7.5, 7.5 Hz), 7.64 (1 H, t, J = 7.5 Hz), 7.91 (2 H, d, J = 7.5 Hz); δ_{C} (100 MHz, CDCl₃) 28.0, 40.4, 55.2, 113.9, 128.7, 129.4, 130.2, 131.8, 132.1, 134.6, 158.1, 192.1, 202.4; HRMS (ESI⁺): Found: 291.0990; $C_{17}H_{16}NaO_3$ (MNa⁺) Requires 291.0992.

4.3.8. 3-(4-Hydroxyphenyl)-N-methoxy-N-methylpropanamide

A Synthesised using general procedure A with 3-(4-hydroxyphenyl)propanoic acid (7.00 g, 42.1 mmol), T3P 50% in EtOAc (40.2 g, 63.2 mmol), DIPEA (22.0 mL, 126 mmol) and MeNH(OMe)·HCl (4.50 g, 46.3 mmol) in CH₂Cl₂ (105 mL) at RT for 1 h. Afforded the title compound without further purification as a yellow oil (7.61 g, 86%); R_f 0.21 (1:1 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 3263, 2938, 1632, 1614, 1593, 1515, 1446, 1388, 1266, 1228, 1172, 987; $\delta_{\rm H}$ (400 MHz, CDCl₃) 2.72 (2H, t, *J* = 7.5 Hz), 2.90 (2H, t, *J* = 7.5 Hz), 3.19 (3H, s), 3.61 (3H, s), 5.85 (1H, br s), 6.77 (2H, d, *J* = 8.0), 7.08 (2H, d, *J* = 8.0 Hz); $\delta_{\rm C}$ (100 MHz, CDCl₃) 29.8, 32.2, 34.0, 61.2, 115.3, 129.5, 133.0, 154.3, 173.9; HRMS (ESI⁺): Found: 232.09591; C₁₁H₁₅NNaO₃ (MNa⁺) Requires 232.0944, Found: 210.1127; C₁₁H₁₆NO₃ (MH⁺) Requires 210.1125.

4.3.9. 4-(4-Hydroxyphenyl)-1-phenylbutan-2-one

To a solution of 3-(4-hydroxyphenyl)-N-methoxy-Nmethylpropanamide (1.53 g, 7.31 mmol) in THF (70 mL) at 0 °C under argon was added benzylmagnesium chloride (14.6 mL, 29.2 mmol, 2.0 M in THF) dropwise using a syringe pump. The resulting solution was warmed to RT and stirred for 2 h. The reaction was then cooled to 0 °C, quenched with sat. aq. NH₄Cl (20 mL), diluted with water (20 mL) and extracted with EtOAc (3 x 30 mL). The organics were combined, washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc then 3:2 hexane:EtOAc) to afford the title compound as a white solid (1.51 g, 86%); mp 112-114 °C; R_f 0.46 (6:4 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 3387, 3027, 2929, 1707, 1614, 1515, 1451, 1362, 1221, 833, 741, 699; $\delta_{\rm H}$ (400 MHz, CD₃OD) 2.68–2.81 (4H, m), 3.68 (2H, s), 6.66 (2H, d, J = 8.0 Hz), 6.93 (2H, d, J = 8.0 Hz), 7.11–7.17 (2H, m), 7.19–7.33 (3H, m); δ_C (100 MHz, CD₃OD) 30.2, 44.9, 51.0, 116.3, 128.0, 129.7, 130.4, 130.7, 133.2, 136.0, 156.8, 210.7; HRMS (ESI⁺): Found: 263.1034; C₁₆H₁₆NaO₂ (MNa⁺) Requires 263.1043.

4.3.10. 4-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-1-phenylbutan-2-one

To a solution of 4-(4-hydroxyphenyl)-1-phenylbutan-2-one (1.39 g, 5.77 mmol) in anyhrous DMF (11.5 mL) was added imidazole (590 mg, 8.66 mmol) at 0 °C. TBSCl (1.30 g, 8.66 mmol) was then added at 0 °C and then the reaction was warmed to RT and stirred for 2 h. The reaction mixture was then diluted with Et₂O (20 mL) and the organic layer was washed with water (3 x 30 mL). The organic layer was then washed with brine (20 mL), dried over MgSO4 and concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc) afforded the title compound as a white solid (1.53 g, 75%); mp 64–66 °C; $R_{\rm f}$ 0.51 (9:1 hexane:EtOAc); ν_{max} (thin film)/cm⁻¹ 2955, 2931, 2859, 1708, 1510, 1255, 910, 839, 779, 732; δ_H (400 MHz, CDCl₃) 0.19 (6H, s), 0.99 (9H, s), 2.71-2.77 (2H, m), 2.78–2.84 (2H, m), 3.66 (2H, s), 6.74 (2H, d, J = 8.0 Hz), 6.99 (2H, d, J = 8.0 Hz), 7.17 (2H, d, J = 7.5 Hz), 7.24-7.36 (3H, m); $\delta_{\rm C}$ (100 MHz, CDCl₃) -4.5, 18.2, 25.7, 29.0, 43.7, 50.4, 120.0, 127.0, 128.7, 129.2, 129.4, 133.5, 134.1, 153.9, 207.7; HRMS (ESI⁺): Found: 377.1905; C₂₂H₃₀NaO₂Si (MNa⁺) Requires 377.1907, Found: 355.2084; $C_{22}H_{31}O_2Si$ (MH⁺) Requires 355.2088.

4.3.11. 4-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2-one (**3***c*)

To a solution of 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1phenylbutan-2-one (150 mg, 0.423 mmol) and p-ABSA (122 mg, 0.508 mmol) in MeCN (1.5 mL) at RT under argon was added DBU (88.5 μ L, 0.592 mmol) dropwise. The resulting solution was stirred for 1 h before being concentrated in vacuo. The crude material was purified by column chromatography (9:1 hexane:EtOAc with 3% Et₃N as a basic additive) to afford the title compound **3c** as an orange oil (109 mg, 68%); $R_f 0.49$ (9:1 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 2955, 2929, 2857, 2067, 1648, 1509, 1497, 1252, 1204, 912, 838, 780, 1176, 1034, 821, 753; δ_H (400 MHz, CDCl₃) 0.19 (6H, s), 0.98 (9H, s), 2.86 (2H, t, J = 7.5 Hz), 2.97 (2H, t, J = 7.5 Hz), 6.76 (2H, d, J = 8.0 Hz), 7.06 (2H, d, J = 8.0 Hz), 7.24–7.29 (1H, m), 7.41 (2H, dd, J = 8.0, 7.5 Hz), 7.46 (2H, d, J = 8.0 Hz); δ_C (100 MHz, CDCl₃) –4.5, 18.2, 25.7, 30.1, 41.0, 72.4, 120.1, 124.1, 126.1, 127.1, 129.0, 129.3, 133.2, 154.1, 192.1; HRMS (ESI⁺): Found: 403.1816; C₂₂H₂₈N₂NaO₂Si (MNa⁺) Requires 403.1812.

4.3.12. 1-Diazo-4-(4-hydroxyphenyl)-1-phenylbutan-2-one (3b)

To a solution of 4-(4-((tert-butyldimethylsilyl)oxy)phenyl)-1diazo-1-phenylbutan-2-one 3c (785 mg, 2.06 mmol) in THF (4 mL) at 0 °C was added TBAF (3.09 mL, 3.09 mmol, 1 M solution in THF). The resulting solution was warmed to RT and stirred for 30 min. The reaction mixture was then diluted with Et₂O (10 mL) and washed with water (10 mL). The organic layer was dried over MgSO4 and concentrated in vacuo to afford the title compound 3b without further purification as a yellow solid (509 mg, 93%); mp 77–79 °C; R_f 0.63 (6:4 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 3361, 2077, 1612, 1515, 1497, 1448, 1370, 1205, 830, 756; $\delta_{\rm H}$ (400 MHz, CDCl₃) 2.86 (2H, t, J = 7.5 Hz), 2.97 (2H, t, J = 7.5 Hz), 4.70 (1H, br s), 6.76 (2H, d, J = 8.5 Hz), 7.08 (2H, d, J = 8.5 Hz), 7.24–7.29 (1H, m), 7.41 (2H, dd, J = 8.0, 7.5 Hz), 7.47 (2H, d, J = 7.5 Hz); δ_{C} (100 MHz, CDCl₃) 30.0, 41.1, 72.6, 115.4, 125.4, 126.2, 127.2, 129.0, 129.5, 132.5, 154.2, 192.4; HRMS (ESI⁺): Found: 289.0951; C₁₆H₁₄N₂NaO₂ (MNa⁺) Requires 289.0947.

4.3.13. 1-Phenylspiro[4.5]deca-6,9-diene-2,8-dione (7)

Method 1: A flame-dried round-bottomed flask was charged with 1-diazo-4-(4-hydroxyphenyl)-1-phenylbutan-2-one 3b (38 mg, 0.143 mmol) and Cu(OTf)₂ (2.6 mg, 7.14 µmol) and purged with argon for 10 min. Anhydrous CH₂Cl₂ (1.4 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 3 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (1:1 hexane:EtOAc) to afford the title compound 7 as a yellow solid (23.4 mg, 70%); mp 135–137 °C; R_f 0.21 (6:4 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 3035, 1746, 1663, 1622, 1499, 1135, 868, 700; $\delta_{\rm H}$ (400 MHz, CDCl₃) 2.17 (1H, ddd, J = 13.5, 8.5, 2.5 Hz), 2.32-2.42 (1H, m), 2.64-2.84 (2H, m), 3.75 (1H, s), 6.14 (1H, dd, J = 10.0, 2.0 Hz), 6.32 (1H, dd, J = 10.0, 2.0 Hz), 6.86 (1H, dd, J = 10.0, 3.0 Hz), 6.93–6.97 (2H, m), 7.00 (1H, dd, J = 10.0, 3.0 Hz), 7.21–7.29 (3H, m); $\delta_{\rm C}$ (100 MHz, CDCl₃) 31.4, 35.3, 51.4, 65.5, 127.9, 128.3, 129.4, 130.1, 130.5, 132.5, 147.5, 152.4, 185.3, 213.1; HRMS (ESI⁺): Found: 261.0875; $C_{16}H_{14}NaO_2$ (MNa⁺) Requires 261.0886, Found: 239.1057; C₁₆H₁₅O₂ (MH⁺) Requires 239.1067.

Method 2: To a solution of 5-((*tert*-butyldimethylsilyl)oxy)-3a-phenyl-3a,3b-dihydro-1H-

cyclopenta[1,3]cyclopropa[1,2]benzen-3(2H)-one **4c** (36.8 mg, 0.104 mmol) in THF (0.6 mL) at -78 °C was added TBAF (0.16 mL, 0.156 mmol, 1 M solution in THF) dropwise to afford an orange solution. The resulting solution was stirred at -78 °C for 3 h. The reaction mixture was then quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined, dried over MgSO₄ and concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (7:3 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the title compound **7** as a yellow solid (16.6 mg, 67%).

4.3.14. 5-((tert-Butyldimethylsilyl)oxy)-3a-phenyl-3a,3b-dihydro-1H-cyclopenta[1,3]cyclopropa[1,2]benzen-3(2H)-one (**4**c)

A A flame-dried round-bottomed flask was charged with 4-(4-((tert-butyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2one **3c** (150 mg, 0.394 mmol) and Ag₂O (4.57 mg, 19.7 μ mol) and purged with argon for 10 min. Anhydrous CH₂Cl₂ (3.9 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 16 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (10:1 hexane:EtOAc) to afford the title compound 4c as a yellow oil (110 mg, 79%); $R_{\rm f}$ 0.42 (9:1 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 2955, 2929, 2857, 1747, 1622, 1407, 1252, 1202, 1183, 1110, 900, 873, 837, 781, 749; $\delta_{\rm H}$ (400 MHz, CDCl₃) -0.36 (3H, s), -0.27 (3H, s), 0.77 (9H, s), 2.38 (1H, ddd, J = 18.0, 9.0, 6.5 Hz), 2.64 (1H, ddd, J = 18.0, 11.0, 7.0 Hz), 2.80–3.03 (2H, m), 5.41 (1H, d, J = 9.5 Hz), 5.76 (1H, d, *J* = 7.5 Hz), 5.98 (1H, d, *J* = 9.5 Hz), 6.41 (1H, d, *J* = 7.5 Hz), 7.11–7.21 (3H, m), 7.21–7.26 (2H, m); δ_C (100 MHz, CDCl₃) -5.4, -5.1, 17.8, 25.4, 27.3, 35.3, 56.9, 114.0, 116.1, 122.4, 123.8, 127.1, 127.74, 127.79, 137.4, 153.2, 216.0; HRMS (ESI⁺): Found: 353.1939; C₂₂H₂₉O₂Si (MH⁺) Requires 353.1931. Note: 1¹³C NMR signal was not observed, presumably due to peak broadening arising from the Buchner rearrangement.

4.3.15. 7-Hydroxy-1-phenyl-3,4-dihydronaphthalen-2(1H)-one (5b)

A flame-dried round-bottomed flask was charged with 4-(4-((tert-butyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2one 3c (150 mg, 0.394 mmol) and AgOTf (10.1 mg, 39.4 µmol) and purged with argon for 10 min. Anhydrous CH₂Cl₂ (3.9 mL) was degassed with argon for 20 min before adding to the diazo/catalyst mixture. The reaction mixture was then stirred at RT for 16 h before being concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (7:3 hexane:EtOAc) to afford the title compound **5b** as an orange oil (80.9 mg, 86%); R_f 0.38 (7:3 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 3372, 3027, 1704, 1612, 1587, 1493, 1450, 1342, 1297, 1232, 1153, 821; $\delta_{\rm H}$ (400 MHz, CDCl₃) 2.57 (1H, ddd, *J* = 17.0, 6.5, 6.5 Hz), 2.70 (1H, ddd, *J* = 17.0, 6.5, 6.5 Hz), 2.91–3.09 (2H, m), 4.66 (1H, s), 5.63 (1H, br s), 6.46 (1H, d, J = 2.5 Hz), 6.76 (1H, dd, J = 8.0, 2.5 Hz), 7.10 (2H, d, J = 7.0 Hz), 7.14 (1H, d, J = 8.0 Hz), 7.25–7.33 (3H, m); $\delta_{\rm C}$ (100 MHz, CDCl₃) 27.3, 37.3, 59.7, 114.5, 116.0, 127.3, 128.69, 128.71, 128.8, 129.1, 137.2, 137.7, 154.9, 210.5; HRMS (ESI⁺): Found: 261.0885; C₁₆H₁₄NaO₂ (MNa⁺) Requires 261.0886.

4.3.16. 4-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-1-phenylbutane-1,2-dione (**6**c)

A heterogeneous solution of Ph₃PAuCl (32.5 mg, 65.7 µmol) and AgSbF₆ (22.5 mg, 65.7 µmol) in CH₂Cl₂ (6 mL) was stirred for 5 min under air and cooled to 0 °C. A solution of 4-(4-((tertbutyldimethylsilyl)oxy)phenyl)-1-diazo-1-phenylbutan-2-one 3c (500 mg, 1.31 mmol) and diphenyl sulfoxide (1.06 g, 5.24 mol) in CH₂Cl₂ (6 mL) was then added to the catalyst mixture at 0 °C and the reaction mixture was stirred under air for 1.5 h. The reaction mixture was then concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (20:1 hexane:EtOAc) to afford the title compound $\hat{6c}$ as a yellow oil (294 mg, 61%); R_f 0.70 (9:1 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 2955, 2930, 2858, 1713, 1672, 1509, 1253, 912, 838, 781; $\delta_{\rm H}$ (400 MHz, CDCl₃) 0.18 (6H, s), 0.98 (9H, s), 2.98 (2H, t, J = 7.5 Hz), 3.21 (2H, t, J = 7.5 Hz), 6.76 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 7.48 (2H, dd, J = 7.5, 7.5 Hz), 7.64 (1H, t, J = 7.5 Hz), 7.91 (2H, d, J = 7.5 Hz); $\delta_{\rm C}$ (100 MHz, CDCl₃) -4.5, 18.2, 25.7, 28.1, 40.4, 120.1, 128.8, 129.3, 130.2, 131.8, 132.7, 134.6, 154.1, 192.1, 202.5; HRMS (ESI⁺): Found: 391.1705; $C_{22}H_{28}NaO_3Si$ (MNa⁺) Requires 391.1700.

4.3.17. (3bR,4S,7R,7aR)-Dimethyl 9-((tert- ACC butyldimethylsilyl)oxy)-3-oxo-3a-phenyl-2,3,3a,3b,4,7-

hexahydro-1H-4,7-

ethenocyclopenta[1,3]cyclopropa[1,2]benzene-5,6-dicarboxylate (22c)

A round-bottomed flask was charged with cyclopropane 4c (191 mg, 0.541 mmol) in toluene (1.1 mL) under argon and dimethyl acetylenedicarboxylate 21 (0.13 mL, 1.08 mmol) was added and the reaction mixture stirred at 80 °C for 30 h. The reaction mixture was then cooled to RT and concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (20:1 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the title compound 22c as a clear and colourless oil (220 mg, 82%); Rf 0.58 (6:4 hexane:EtOAc); v_{max} (thin film)/cm⁻¹ 2953, 2858, 1714, 1651, 1625, 1435, 1342, 1303, 1256, 1225, 1204, 1110, 1061, 913, 864, 839, 785; $\delta_{\rm H}$ (400 MHz, CDCl₃) -0.32 (3H, s), -0.19 (3H, s), 0.75 (9H, s), 1.80 (1H, d, J = 4.0 Hz), 2.13–2.33 (2H, m), 2.34–2.49 (2H, m), 3.81 (3H, s), 3.83 (3H, s), 3.91–3.95 (1H, m), 4.07 (1H, d, *J* = 6.5 Hz), 4.49 (1H, dd, J = 6.5, 3.0 Hz), 6.82 (1H, d, J = 7.5 Hz), 7.11– 7.22 (3H, m), 7.24–7.29 (1H, m); δ_{C} (100 MHz, CDCl3) –5.4, -4.7, 17.9, 25.4, 27.2, 34.0, 35.4, 44.7, 47.0, 52.3, 52.4, 52.9, 60.4, 106.9, 126.5, 127.5, 128.2, 130.0, 130.6, 133.8, 146.1, 151.0, 156.7, 165.7, 166.8, 212.2; HRMS (ESI⁺): Found: 517.2017; C₂₈H₃₄NaO₆Si (MNa⁺) Requires 517.2017, Found: 495.2195; C₂₈H₃₅O₆Si (MH⁺) Requires 495.2197.

4.3.18. (3bR,4S,7R,7aR)-Dimethyl 9-hydroxy-3-oxo-3a-phenyl-2,3,3a,3b,4,7-hexahydro-1H-4,7-

ethenocyclopenta[1,3]cyclopropa[1,2]benzene-5,6-dicarboxylate (22b)

A round-bottomed flask was charged with Diels-Alder adduct 22c (35 mg, 0.0708 mmol) in THF (0.5 mL) at -78 °C and TBAF (0.11 mL, 0.106 mmol, 1 M solution in THF) was added dropwise leading to the formation of a pale yellow milky solution. The reaction mixture was then stirred at -78 °C for 3 h. The reaction mixture was then quenched by the addition of water (2 mL) at -78 °C and extracted with EtOAc (3 x 5 mL). The organics were combined, dried over MgSO₄ and concentrated in vacuo to afford the crude product. The crude material was purified by column chromatography (9:1 hexane:EtOAc, then 1:1 hexane:EtOAc) to afford the title compound 22b as a clear and colourless oil (23 mg, 85%); Rf 0.66 (1:1 hexane:EtOAc); vmax (thin film)/cm⁻¹ 2953, 1718, 1626, 1435, 1333, 1270, 1218, 1115, 1064, 729, 718; $\delta_{\rm H}$ (400 MHz, CDCl₃) 1.82 (1H, dd, J = 19.0, 3.0Hz), 2.06-2.14 (2H, m), 2.24-2.36 (2H, m), 2.36-2.49 (2H, m), 3.72–3.75 (1H, m), 3.82 (3H, s), 3.87 (3H, s), 4.16 (1H, d, J = 4.0 Hz), 7.09 (1H, dd, J = 6.0, 2.0 Hz), 7.22–7.37 (4H, m); $\delta_{\rm C}$ (100 MHz, CDCl₃) 27.5, 33.1, 34.1, 37.2, 41.0, 47.6, 51.8, 52.7, 52.8, 57.7, 128.3, 128.7, 128.8, 131.2, 131.3, 132.5, 136.9, 150.5, 164.0, 166.4, 204.8, 211.1; HRMS (ESI⁺): Found: 403.1158; C₂₂H₂₀NaO₆ (MNa⁺) Requires 403.1152, Found: 381.1335; C₂₂H₂₁O₆ (MH⁺) Requires 381.1333.

4.3.19. 4-(4-Hydroxyphenyl)-1-phenylbutane-1,2-dione (6b)

A flame-dried round-bottomed flask was charged with 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-phenylbutane-1,2-dione **6c** (118 mg, 0.320 mmol) in anhydrous CH₂Cl₂ (3.2 mL) under argon. The solution was cooled to 0 °C and BF₃·Et₂O (0.4 mL, 3.20 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 1 h before warming to RT and stirring for another 4.5 h. The reaction mixture was then quenched by the addition of water (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The organics were combined, dried over MgSO₄ and concentrated in vacuo. The crude material was purified by column chromatography (8:2 hexane:EtOAc) to afford the title compound **6b** as a yellow oil (17.1 mg, 21%); R_f 0.27 (8:2

CCEPTED M. hexahe:EtOAc): V_{max} (thin film)/cm⁻¹ 3416, 3027, 2932, 1712,
1669, 1596, 1515, 1449, 1254; $\delta_{\rm H}$ (400 MHz, CDCl₃) 2.98 (2H, t,
J = 7.5 Hz), 3.20 (2H, t, J = 7.5 Hz), 4.90 (1H, br s), 6.76 (2H, d,
J = 8.0 Hz), 7.10 (2H, d, J = 8.0 Hz), 7.48 (2H, dd, J = 8.0, 7.5
Hz), 7.64 (1H, t, J = 7.5 Hz), 7.91 (2H, d, J = 7.5 Hz); $\delta_{\rm C}$ (100
MHz, CDCl₃) 28.0, 40.4, 115.3, 128.8, 129.6, 130.2, 131.8,
132.3, 134.6, 154.0, 192.1, 202.5; HRMS (ESI⁺): Found:
277.0837; C₁₆H₁₄NaO₃ (MNa⁺) Requires 277.0835.

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6. Dedication

In recognition of the many contributions of Sir Derek Barton, not least his memorable lectures on 'The Invention of Chemical Reactions'.

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