Steric Buttressing Changes Torquospecificity in Thermal Cyclobutenone Rearrangements Providing New Opportunities for 5*H*-Furanone Synthesis

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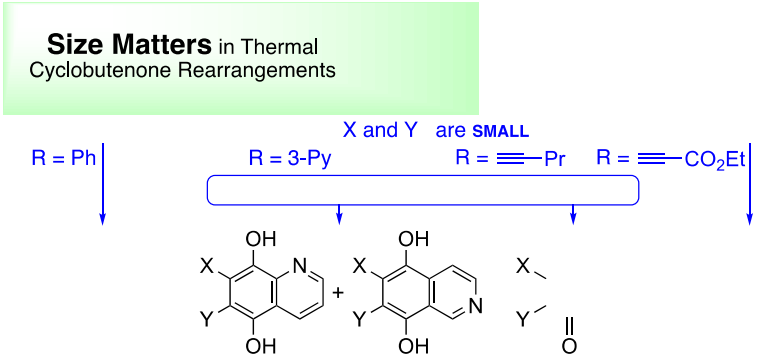
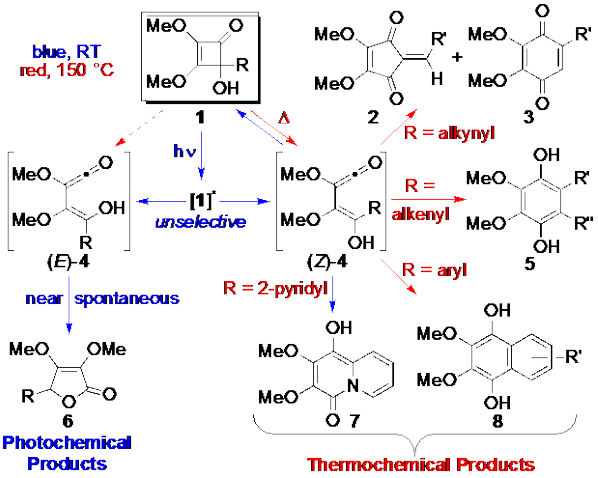


Received:
Accepted:
Published online:
DOI:

Abstract. Thermally induced rearrangements of 4-hydroxycyclobutenones are known to provide clean and reliable access to an array of useful carbocyclic and fused heterocyclic ring systems. Rarely, such reactions have been diverted to an alternative pathway leading to furanone formation. Herein we show that these switches in the course of the rearrangement occur when a substrate bears a bulky substituent and are due to adverse steric buttressing as the transition state for electrocyclisation is approached. We also show how the reaction provides new opportunities for furanone synthesis and how bulky proton and halogen surrogates can be used to divert classical rearrangement pathways toward furanone formation. Additionally, we show that classical rearrangement pathways can be promoted by the simple expedient of alcohol protection.

Key words Cyclobutenones, Rearrangement, Thermolysis, Flow Chemistry, Furanones, Steric Buttressing, Torquoselectivity.

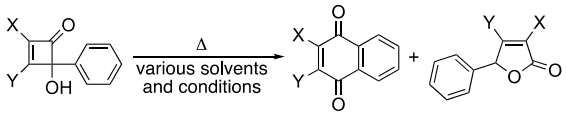
Cyclobutenone rearrangements triggered by heat and light have found widespread use in the preparation of carbocyclic and heterocyclic ring systems.[1-23] In common with many pericyclic reactions, different outcomes are usually given when rearrangements are triggered by heat and light.[1-3] Thus, while photochemical rearrangements of cyclobutenones akin to **1** generally give furanones **6** in high yield,[1-3] a host of products are possible from their thermochemical rearrangement (Scheme 1).[3–23] For the most part outcomes are dictated by the nature of the C4 residue and are highly predictable, as evidenced by their use as key steps in many target syntheses.[3-6]



Scheme 1. Summary of the primary cyclobutenone rearrangement pathways.

As interest in these reactions has grown, so has the number of reported anomalies. Most relate to thermochemical rearrangements that have been diverted from their usual course toward furanone formation.[2,7-10] Though largely viewed as oddities, such outcomes have generally been attributed to an opening of the cyclobutenone to a vinylketene akin to (*E*)-**4** due to steric or electronic factors,[2,8] or hydrogen bonding.[9]

We recently encountered such an anomaly when effecting the thermolysis of (dimethylamino)cyclobutenone **9h**. In stark contrast to all reported examples of phenylcyclobutenone rearrangements, *e.g.* **9a-g** → **10a-g** (Scheme 2), it gave furanone **11h** rather than the anticipated quinone **10h**.[6,10-17] Moreover, its lower homolog **9i** and phenylmethylamino analogue **9j** each followed the expected course, giving quinones **10i** and **10j** respectively.



9	X	Y	10	11
a[6,10]	OMe	OMe	73%	–
b[11]	O^{i}Pr	O^{i}Pr	40%	–
c[12]	O^{t}Bu	Me	78%	–
d[13]	CF_3	O^{i}Pr	73%	–
e[14,15]	Me	Me	87%	–
f[12,14]	Me	OMe	91%	–
g[16]	Me	Ph	90%	–
h	Me	**NMe_2**	–	**92%**
i	Me	NHMe	73%	–
j	Me	NPhMe	86%	–

Scheme 2. An anomalous rearrangement of arylcyclobutenone **9h** to furanone **11h** rather than the anticipated benzoquinone **10h**.

As uncertainty reduces confidence in a reaction and lessens its appeal in synthesis, we decided to determine the origin of this dichotomous behaviour. Computational analyses of cyclobutenone ring openings involving substrates akin to **9** have always shown them to be torquoselective processes. Indeed, all favour outward rotation of the hydroxyl group to vinylketene **17** over its inward rotation to geometric isomer **16** (typically by

~6 kcalmol^{-1}, Figure 1).[6,24] Preliminary DFT calculations (Supporting Information) on systems that exhibited anomalous behaviour confirmed this preference suggesting that the origin of the dichotomy lay further along the reaction co-ordinate.

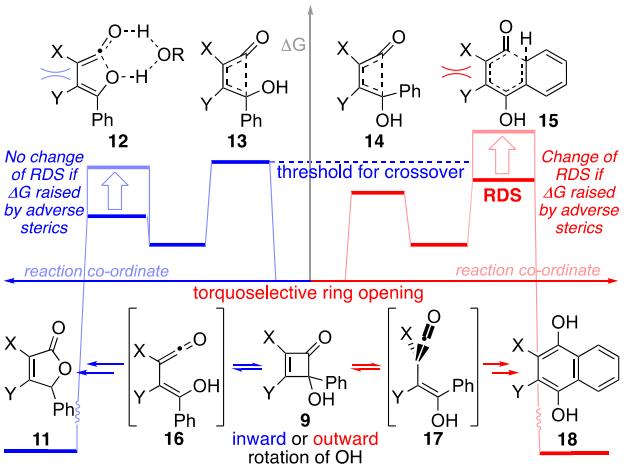
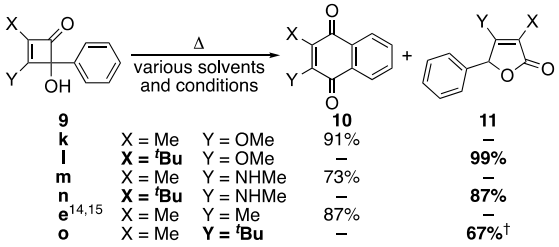


Figure 1. Understanding dichotomous reactivity in thermal cyclobutenone rearrangements.

A cursory analysis of known anomalies showed that all involved 2,3-disubstituted cyclobutenones. Additionally, comparison of these with analogues giving expected outcomes indicated that furanones were given when the cyclobutenone carried a bulky carbon or 3°-amine substituents. This observation led us to wonder whether steric buttressing might be involved.[25] In particular, for electrocyclic ring closure of vinylketene intermediate **17** to be realised (Figure 1), substituents X and Y must rotate toward one another in order to attain the transition state for cyclisation, **15**. When one or both of these substituents are bulky, the steric interaction between them will be severe, raising the activation energy significantly. Indeed, were this to be raised above that for opening of cyclobutenone **9** to the isomeric ketene **16**, the course of rearrangement would switch to favour furanone **11**.[2,6] Critically, while steric interactions between substituents X and Y would be expected to raise the activation energy for transition state **12** by a similar amount, this has no impact on the course of the reaction as it stays below the activation energy for transition state **15**.

For this hypothesis to provide a unified explanation for the anomalous outcomes in thermal cyclobutenone rearrangements we first needed to demonstrate that the influence of bulky carbon and 3°–amine substituents were comparable. To that end, we prepared *t*-butylcyclobutenones **9l, 9n** and **9o** and compared their thermolysis with the outcomes given by the corresponding methylcyclobutenones **9k, 9m** and **9e** (Scheme 3).[14,15] As anticipated, the former all gave the corresponding



Scheme 3. Dichotomous reactivity in the thermal rearrangements of *tert*-butyl-4-arylcyclobutenones. †**9o** contained 25% of a regioisomer.

furanone **11** while the latter gave the classic Moore rearrangement product **10**, following air oxidation.

Next, we used DFT calculations to determine the structures of vinylketene intermediates **17h-j** and **17o** in order to ascertain why the dimethylamino residue in **9h** mirrored the *tert*-butyl residue in **9o** rather than the methylamino and methylphenylamino residues in **9i** and **9j**. Calculations revealed that in all cases the amine residues would establish a hydrogen bond with the proximal hydroxyl group (Figure 2). This was weakest for the methylphenylamino analogue **17j** due to lone pair conjugation and its near planar geometry. By contrast, the methylamino and dimethylamino residues showed significant pyramidalization at nitrogen such that it approached sp^3 hybridisation in both **17h** and **17i**. Indeed, it seems that pyramidalization of the dimethylamino residue in **17h** ensures that it imparts a steric influence similar to that of the *tert*-butyl residue in **17o** to impede rotation of the ketene moiety toward the phenyl residue. By contrast, the amine residues in **17i** and **17j** offer little resistance to ketene rotation so can readily adopt the transition state **15** for electrocyclic ring closure.

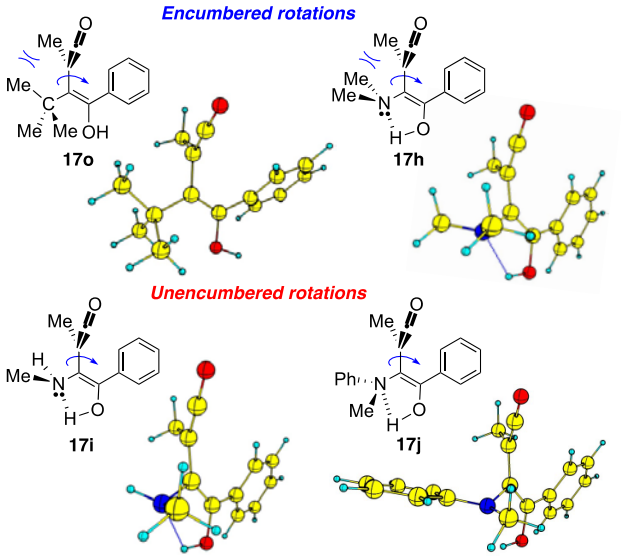
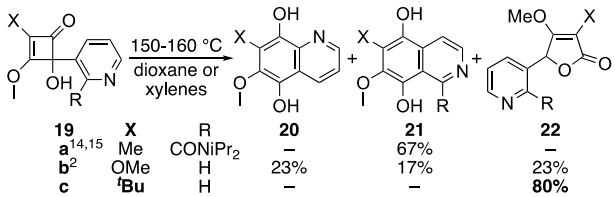


Figure 2. Understanding the reactivity of aminocyclobutenones **17h-j** and **17o**. Geometries calculated using B3LYP/6-311+g(d,p).

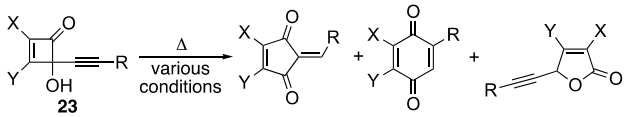
The buttressing effect was next examined with 3-pyridinocyclobutenone **19c**. As expected, while the reported thermal rearrangements of **19a** and **19b** each favoured electrocyclisation to the corresponding quinoline **20** and/or isoquinoline **21** (Scheme 4), the *tert*-butyl residue at C2 in cyclobutenone **19c** ensured that it gave furanone **22c** as the sole identified product.[2,14,15]



Scheme 4. Dichotomous rearrangements of pyridinocyclobutenones.

Having mimicked our earlier finding (Scheme 2), we next sought to extend our survey to alkynylcyclobutenones **23** where, to the

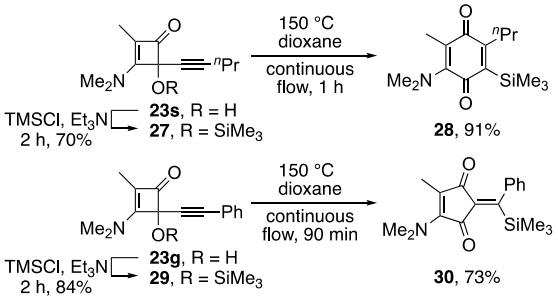
best of our knowledge, no precedent exists for their thermal rearrangement to furanones. Rather, reactions typically give cyclopentenediones akin to **24** or quinones akin to **25** (Scheme 5). Notably, while thermolysis of (methylamino)cyclobutenone **23f** gave a complex product mixture, the related (dimethylamino)cyclobutenones **23g-j** gave furanones **26g-j** respectively. Similarly, (dimethylamino)cyclobutenones **23r-t** gave furanones **26r-t** showing that the switch in reaction course was largely independent of the nature of the alkyne residue. Another point of interest came with our examination of the photochemical rearrangement of these aminocyclobuteneones. Though precedent suggested that these would give furanones **26** in high yield, they proved to be low yielding processes giving rise to complex product mixtures.[2]



	R	X	Y	24	25	26
a[18]	Ph	OMe	OMe	46%	21%	–
b[12]	Ph	O^{t}Bu	Me	83%	–	–
c[12]	Ph	Me	OMe	52%	40%	–
d[19]	Ph	Me	O^{t}Bu	36%	51%	–
e[18]	Ph	Ph	OEt	46%	–	–
f	Ph	Me	NHMe	complex product mixture		
g	Ph	Me	**NMe$_2$**	–	–	**49%**
h	Ph	Me	**NEt$_2$**	–	–	**60%**
i	Ph	Me	**NBn$_2$**	–	–	**67%**
j	Ph	Ph	**NMe$_2$**	–	–	**67%**
k[20]	H	Me	O^{i}Pr	–	85%	–
l[5]	SiMe$_3$	Me	O^{t}Bu	–	69%	–
m[5]	H	Me	O^{t}Bu	–	79%	–
n[16]	^{n}Bu	Me	Ph	–	80%	–
o[18,20]	H	OMe	OMe	–	72%	–
p[21]	CH$_2$SiMe$_3$	^{n}Bu	OMe	–	75%	–
q[22]	CD$_3$	OMe	OMe	–	55%	–
r	SiMe$_3$	Me	**NMe$_2$**	–	–	**67%**
s	^{n}Pr	Me	**NMe$_2$**	–	–	**83%**
t	^{i}Propenyl	Me	**NMe$_2$**	–	–	**73%**

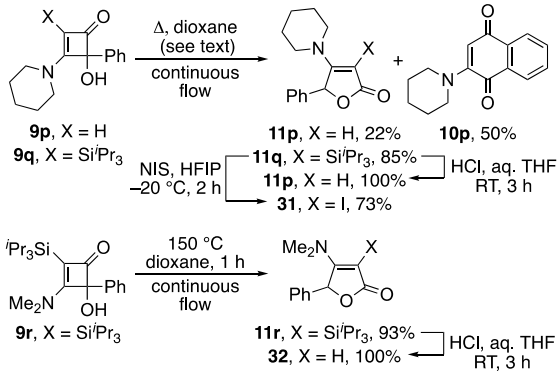
Scheme 5. Dichotomous rearrangements of alkynylcyclobutenones.

Having demonstrated the wide impact of steric buttressing on cyclobutenone rearrangements, we next sought a means of switching the course of such reactions back to classical rearrangement pathways. Protection of the C4 alcohol,[8,18,23] provided a simple means of shutting down furanone formation as exemplified by the rearrangements of trimethylsilyl ethers **27** to quinone **28** and **29** to cyclopentenedione **30** (Scheme 6).



Scheme 6. Shutting down furanone formation by alcohol protection.

We have also been able to bias reactions toward furanone formation by employing a triisopropylsilyl substituent as a bulky proton or halide surrogate (Scheme 7). Thus, while thermolysis of arylcyclobutenone **9p** for 3 h at 150 °C gave a mixture of furanone **11p** and benzoquinone **10p**, its triisopropylsilyl analogue **9q** gave furanone **11q** in 85% isolated yield following thermolysis at 150 °C for 1 h. Importantly, protonolysis of **11q** provided furanone **11p** in quantitative yield while its treatment with NIS provided iodide **31**.[26] The triisopropylsilyl substituent was equally effective as a steric buttress when neighboured by a dimethylamino residue, as evidenced by the conversion of arylcyclobutenone **9r** to furanones **11r** and **32**.



Scheme 7. Using a triisopropylsilyl group as a bulky proton and halogen surrogate to bias reactions toward furanone formation.

In summary, thermally induced rearrangements of 4-hydroxycyclobutenones are likely to give furanones when the alkene bears a bulky substituent. This switch away from the usual reaction course is due to adverse buttressing of substituents when the transition state for electrocyclisation is approached. Alcohol protection provides a means of shutting down furanone formation while the inclusion of a bulky proton or halogen surrogate, such as a triisopropylsilyl group, provides a means of directing rearrangements toward furanone formation.

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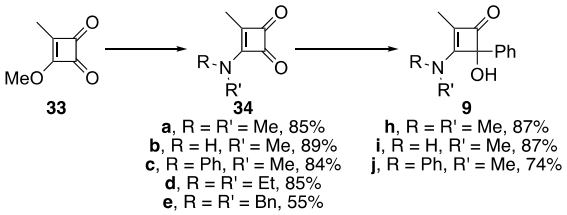
Melting points were recorded on an Electrothermal IA9100 digital melting point apparatus and are uncorrected. *Infrared Spectra* were recorded neat as thin films or as solid compressions using a Nicolet 380 Laboratory FT-IR spectrometer or a Nicolet iS5 Laboratory FT-IR spectrometer. *NMR Spectra* were recorded on a Bruker AVIIIHD 400 or a Bruker AVIIIHD 500 spectrometer at 298 K using $CDCl_3$ stored over dried K_2CO_3 to neutralise trace acidity unless stated otherwise. Assignments have been made on the basis of chemical shifts, coupling constants, DEPT-135, COSY, HMQC and comparison with literature values. *High Resolution Mass Spectrometry* was carried out using a MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a time of flight (TOF) analyser. Samples were introduced to the mass spectrometer via a Dionex Ultimate 3000 autosampler and uHPLC pump using a gradient of 20% to 100% acetonitrile (0.1% formic acid) over five minutes. Spectra were recorded using positive/negative ion electrospray ionization as specified and were calculated to four decimal places from the molecular formula. All samples were recorded by Ms. Julie Herniman at the University of Southampton. *Low Resolution Mass Spectrometry* was carried out using electrospray ionisation on a directly injected WATERS quadrupole MSD using ESI+ with MeOH/acetonitrile as solvent. *X-ray* data were recorded by Dr Mark Light at the UK National Crystallography Service, University of Southampton using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at 100 K.

Thin layer chromatography was carried out on Merck Silica Gel 60 Å F 254 0.2 mm plates, which were visualised under fluorescence UV (254 nm) followed by staining with iodine and/or aqueous 1% $KMnO_4$, methanolic H_2SO_4. Column chromatography was carried out under slight positive pressure using silica gel with the stated solvent system. *Reagents* that were commercially available were purchased and used without further purification unless stated otherwise. THF was distilled

from sodium benzophenone ketyl under argon. Toluene was distilled from sodium under argon. All air sensitive reactions were carried out under argon using flame or oven dried apparatus.

The Flow System used in this study was a Vapourtec R4/R2+ device. The R2 pumping module comes with a self-calibrating dual pumping system and an injection loop. The R4 reactor module can support four different temperature zones. The first three zones can be set at a temperature from ambient to 150 °C while the forth can reach 250 °C. In-line back pressure regulators (BPR) are incorporated into the system to prevent vaporisation of solvents when heated above their boiling points. Further details are provided in the Supporting Information.

Synthesis of starting materials. Details of the methods used to prepare cyclobutenones **9h-j**, **l**, **n**, **o, q** and **r** (Schemes 8–10), **19c**, **23g-j** and **23r-t** are provided below.



Scheme 8. Preparation of cyclobutenones **9h-j**.

3-(Dimethylamino)-4-methylcyclobutene-1,2-dione (34a)

A solution of dimethylamine hydrochloride (67 mg, 0.82 mmol) and triethylamine (0.12 mL, 0.82 mmol) in MeOH (10 mL) was added to a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **33** (103 mg, 0.82 mmol) in MeOH (40 mL). After 2 h at RT the solution was concentrated under reduced pressure and purified by column chromatography (0–5% MeOH/EtOAc) to afford the title compound **34a** (97 mg, 0.70 mmol, 85%) as a white solid.

MP: 128–129 °C (DCM/cyclohexane).

IR (solid): 2939, 1778, 1728, 1616, 1411, 1234, 1064.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (s, 3 H, NC**H**$_3$), 3.15 (s, 3 H, NC**H**$_3$), 2.22 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7 (**C**), 191.4 (**C**), 183.1 (**C**), 166.3 (**C**), 39.7 (**C**H$_3$), 38.9 (**C**H$_3$), 10.3 (**C**H$_3$).

MS (ESI+) *m/z* 162 $[M+Na]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_7H_{10}NO_2$: 140.0706; found 140.0706.

3-Methyl-4-(methylamino)-cyclobutene-1,2-dione (34b).

A solution of methylamine hydrochloride (440 mg, 6.52 mmol) and triethylamine (0.9 mL, 6.5 mmol) in MeOH (10 mL) was added to a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **33** (627 mg, 4.95 mmol) in MeOH (40 mL). After 2 h at RT the solution was concentrated under reduced pressure and purified by column chromatography (60–90% EtOAc/petrol) to afford the title compound **34b** (550 mg, 4.43 mmol, 89%) as a white solid.

MP: 178–179 °C.

IR (solid): 3138, 2952, 1702, 1587, 1506, 1475, 1397, 1255, 1174, 1150.

^{1}H NMR (400 MHz, D_2O): major rotamer δ = 3.18 (s, 3 H, C**H**$_3$), 2.31 (s, 3 H, C**H**$_3$); minor rotamer δ = 3.23 (s, 3 H, C**H**$_3$), 2.09 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, D_2O): major rotamer: δ = 194.4 (**C**), 192.2 (**C**), 184.5 (**C**), 189.3 (**C**), 30.5 (**C**H$_3$), 10.0 (**C**H$_3$); minor rotamer: δ = 194.1 (**C**), 192.6 (**C**), 185.1 (**C**), 168.3 (**C**), 30.9 (**C**H$_3$), 8.7 (**C**H$_3$).

MS (ESI+) *m/z* 126 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_6H_8NO_2$: 126.0550; found 126.0555.

3-Methyl-4-(methyl(phenyl)amino)cyclobut-3-ene-1,2-dione (34c).

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **33** (300 mg, 2.38 mmol) in MeOH (40 mL) was added *N*-methylaniline (0.26 mL, 2.4 mmol). The mixture was stirred at RT for 2 h then concentrated under reduced pressure. Purification by column chromatography (40–70% EtOAc)/petrol) afforded the title compound **36c** (401 mg, 1.99 mmol, 84%) as a white solid.

MP: 103–104 °C.

IR (solid): 2942, 1779, 1727, 1720, 1608, 1567, 1455, 1429, 1379, 1034.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.38 (m, 3 H, 3 × Ar**H**), 7.29–7.24 (m, 2 H, 2 × Ar**H**), 3.77 (s, 3 H, NC**H**$_3$), 1.63 (s, 3 H, C**H**$_3$) with an additional signal at δ 1.68 (s, C**H**$_3$) attributed to a minor rotamer.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1 (**C**), 192.9 (**C**), 183.2 (**C**), 169.5 (**C**), 142.2 (**C**), 129.8 (**C**H), 128.5 (**C**H), 125.1 (**C**H), 40.2 (**C**H$_3$), 10.7 (**C**H$_3$).

MS (ESI+) *m/z* 202 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{12}H_{12}NO_2$: 202.0863; found 202.0866.

3-(Diethylamino)-4-methylcyclobutene-1,2-dione (34d)[27]

A solution of diethylamine hydrochloride (132 mg, 1.20 mmol) and triethylamine (0.10 mL, 1.20 mmol) in MeOH (10 mL) was added to a solution of 3-methoxy-4-methylcyclobutene-1,2-dione **33** (150 mg, 1.20 mmol) in MeOH (40 mL). After 2 h at RT the solution was concentrated under reduced pressure and purified by column chromatography (20–60% acetone/cyclohexane) to afford the title compound **34d**[27] (170 mg, 1.01 mmol, 85%) as a pale yellow oil.

IR (film): 2973, 2939, 1774, 1727, 1581, 1438, 1365, 1296, 1211, 1061.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.64 (q, *J* = 7.2 Hz, 2 H, NC**H**$_2$), 3.36 (q, *J* = 7.2 Hz, 2 H, NC**H**$_2$), 2.15 (s, 3 H, C**H**$_3$), 1.18 (t, *J* = 7.3 Hz, 3 H, CH$_2$C**H**$_3$), 1.13 (t, *J* = 7.2 Hz, 3 H, CH$_2$C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8 (**C**), 191.3 (**C**), 182.0 (**C**), 165.7 (**C**), 44.4 (**C**H$_2$), 44.1 (**C**H$_2$), 14.4 (**C**H$_3$), 14.1 (**C**H$_3$), 10.2 (**C**H$_3$).

MS (ESI+) *m/z* 335 ($[2M+H]^+$), 168 ($[MH]^+$).

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_9H_{14}NO_2$: 168.1019; found 168.1019.

3-(Dibenzylamino)-4-methylcyclobut-3-ene-1,2-dione (34e)[28]

To a cooled (0 °C) solution of 3-methoxy-4-methylcyclobutene-1,2-dione (126 mg, 1.00 mmol) in MeOH (50 mL) was added dibenzylamine (0.10 mL, 1.0 mmol). After 2 h the solution was warmed to RT and after a further 2 h was concentrated under reduced pressure. Purification by column chromatography (EtOAc) afforded the title compound **42** (160 mg, 0.55 mmol, 55%) as a pale yellow oil.

IR (film): 2928, 2854, 1761, 1731, 1581, 1430, 1269, 1064.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.31 (m, 6 H, 6 × Ar**H**), 7.26–7.16 (m, 4 H, 4 × Ar**H**), 4.86 (s, 2 H, C**H**$_2$), 4.50 (s, 2 H, C**H**$_2$), 2.20 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0 (**C**), 191.8 (**C**), 183.7 (**C**), 167.3 (**C**), 134.8 (**C**), 134.6 (**C**), 129.4 (**C**H), 129.1 (**C**H), 128.7 (**C**H), 128.6 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 127.1 (**C**H), 52.4 (**C**H$_2$), 52.2 (**C**H$_2$), 10.8 (**C**H$_3$).

MS (ESI+) *m/z* 583 ($[2M+H]^+$), 292 ($[MH]^+$).

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{19}H_{18}NO_2$: 292.1332; found 292.1328.

3-(Dimethylamino)-4-hydroxy-2-methyl-4-phenylcyclobut-2-en-1-one (9h)

To a solution of 3-(dimethylamino)-4-methylcyclobut-3-ene-1,2-dione **34a** (140 mg, 1.01 mmol) in THF (50 mL) at –78 °C was added phenyllithium (1.9 M in Bu_2O, 0.69 mL, 1.31 mmol) dropwise. After 1 h, sat. NH_4Cl (20 mL) was added and the reaction mixture was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column

chromatography (Et_2O then 60% acetone/cyclohexane) afforded the title product **9h** (190 mg, 0.87 mmol, 87%) as a white solid.

MP: 154 °C dec.

IR: 3020, 1745, 1576, 1448, 1414, 1271, 1215, 1170, 1151, 1040.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2 H, Ar**H**), 7.29–7.25 (m, 2 H, Ar**H**), 7.20–7.17 (m, 1 H, Ar**H**), 5.67 (br s, 1 H, O**H**), 3.08 (s, 3 H, C**H**$_3$), 2.76 (s, 3 H, C**H**$_3$), 1.79 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.2 (**C**), 171.9 (**C**), 138.6 (**C**), 128.1 (**C**H), 127.2 (**C**H), 125.6 (**C**H), 114.3 (**C**), 90.7 (**C**), 39.9 (**C**H$_3$), 39.4 (**C**H$_3$), 7.4 (**C**H$_3$).

LRMS (ESI+) *m/z* 218 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{13}H_{16}NO_2$: 218.1176; found 218.1177.

4-Hydroxy-2-methyl-3-methylamino-4-phenylcyclobut-2-en-1-one (9i)

To a solution of 3-methylamino-4-methylcyclobutene-1,2-dione **34b** (434 mg, 3.58 mmol) in THF (50 mL) at –78 °C was added phenyllithium (1.9 M in Bu_2O, 4.6 mL, 8.7 mmol) dropwise. After 2 h, sat. NH_4Cl (20 mL) was added and the reaction mixture was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by recrystallization (Et_2O) afforded the title product **9i** (635 mg, 3.13 mmol, 87%) as an off-white solid.

MP: 187 °C dec.

IR: 3160, 2928, 2858, 1747, 1567, 1516, 1396, 1192, 1006.

^{1}H NMR (400 MHz, DMSO-d6): Major rotamer: δ = 7.84 (br, 1 H, N**H**), 7.40–7.21 (m, 5 H, 5 × Ar**H**), 6.37 (s, 1 H, O**H**), 2.63 (d, *J* = 4.9 Hz, 3 H, NC**H**$_3$), 1.56 (s, 3 H, C**H**$_3$); Minor rotamer: δ = 7.69 (br, 1 H, N**H**), 7.40–7.21 (m, 5 H, 5 × Ar**H**), 6.16 (s, 1 H, O**H**), 2.98 (d, *J* = 4.9 Hz, 3 H, NC**H**$_3$), 1.76 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, DMSO-d6): Major rotamer: δ = 186.4 (**C**), 172.3 (**C**), 139.9 (**C**), 128.0 (**C**H), 126.8 (**C**H), 125.3 (**C**H), 113.3 (**C**), 90.9 (**C**), 30.2 (**C**H$_3$), 6.2 (**C**H$_3$); Minor rotamer: δ = 187.6 (**C**), 172.0 (**C**), 138.6 (**C**), 127.8 (**C**H), 126.9 (**C**H), 125.3 (**C**H), 112.3 (**C**), 90.6 (**C**), 30.5 (**C**H$_3$), 7.0 (**C**H$_3$).

MS (ESI+) *m/z* 204 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{12}H_{14}NO_2$: 204.1023; found 204.1023.

4-Hydroxy-2-methyl-3-(methyl(phenyl)amino)-4-phenylcyclobut-2-en-1-one (9j)

To a solution of 3-(methyl(phenyl)amino)-4-methylcyclobut-3-ene-1,2-dione **34c** (303 mg, 1.51 mmol) in THF (50 mL) at –78 °C was added phenyllithium (1.9 M in Bu_2O, 1.1 mL, 2.1 mmol) dropwise. After 2 h, sat. NH_4Cl (20 mL) was added and the reaction mixture was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (Et_2O) afforded the title compound **9j** (309 mg, 1.11 mmol, 74%) as a white solid.

MP: 150 °C dec.

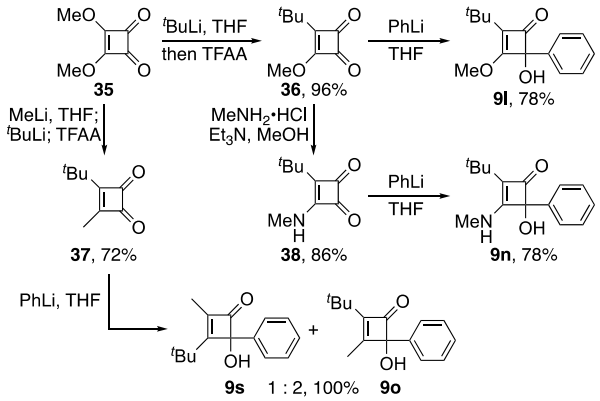
IR (solid): 3272, 2952, 1738, 1562, 1493, 1448, 1409, 1284, 1183, 1024.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (br, 2 H, 2 × Ar**H**), 7.45–7.37 (m, 4 H, 4 × Ar**H**), 7.35–7.28 (m, 4 H, 4 × Ar**H**), 5.36 (br s, 1 H, O**H**), 3.24 (s, 3 H, C**H**$_3$), 1.24 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.1 (**C**), 143.4 (**C**), 138.3 (**C**), 129.2 (**C**H), 128.4 (**C**H), 127.5 (**C**H), 127.4 (**C**H), 125.6 (**C**H), 125.5 (**C**H), 118.0 (**C**), 91.8 (**C**), 40.9 (**C**H$_3$), 7.6 (**C**H$_3$).

MS (ESI+) *m/z* 280 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{18}H_{18}NO_2$: 280.1332; found 280.1331.



Scheme 9. Preparation of cyclobutenones **9l**, **n** and **o**.

3-(*tert*-Butyl)-4-methoxycyclobut-3-ene-1,2-dione (36)[8,12,29]

To a solution of dimethyl squarate **35** (350 mg, 2.46 mmol) in THF (50 mL) at –78 °C was added ^{t}BuLi (1.7 M in pentane, 1.6 mL, 2.71 mmol) dropwise. After 30 min TFAA (0.41 mL, 2.95 mmol) was added dropwise followed after a further 20 min by sat. NH_4Cl (20 mL). The solution was warmed to RT then the aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (50–100% Et_2O/petrol) to afford 3-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **36** (398 mg, 2.37 mmol, 96%) as a yellow oil.

IR (film): 2971, 1790, 1761, 1735, 1585, 1481, 1398, 1356, 1217, 1049.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.38 (s, 3 H, OC**H**$_3$), 1.26 (s, 9 H, C(C**H**$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.0 (**C**), 194.5 (**C**), 194.4 (**C**), 190.8 (**C**), 60.9 (**C**H$_3$), 34.2 (**C**), 26.9 (**C**H$_3$).

MS (ESI+) *m/z* 169 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_9H_{13}O_3$: 169.0859; found 169.0858.

2-(*tert*-Butyl)-4-hydroxy-3-methoxy-4-phenylcyclobut-2-en-1-one (9l)

To a solution of 2-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **36** (340 mg, 2.02 mmol) in THF (50 mL) at –78 °C was added phenyllithium (1.9 M in Bu_2O, 1.3 mL, 2.5 mmol) dropwise. After 2 h sat. NH_4Cl (20 mL) was added then the reaction mixture was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (10–50% EtOAc/petrol) afforded the title product **9l** (390 mg, 1.58 mmol, 78%) as a yellow oil.

IR (film): 3398, 2952, 1745, 1630, 1448, 1365, 1187.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.44 (m, 2 H, 2 × Ar**H**), 7.40–7.34 (m, 2 H, 2 × Ar**H**), 7.32–7.29 (m, 1 H, Ar**H**), 5.41 (br s, 1 H, O**H**), 3.84 (s, 3 H, C**H**$_3$), 1.27 (s, 9 H, C(C**H**$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9 (**C**), 180.2 (**C**), 137.5 (**C**), 137.4 (**C**), 128.6 (**C**H), 127.8 (**C**H), 125.4 (**C**H), 92.1 (**C**), 59.5 (**C**H$_3$), 31.2 (**C**), 28.2 (**C**H$_3$).

MS (ESI+) *m/z* 247 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{15}H_{18}O_3$: 247.1329; found 247.1333.

3-(*tert*-Butyl)-4-methylcyclobut-3-ene-1,2-dione (37)[30]

To a solution of dimethyl squarate **35** (350 mg, 2.46 mmol) in THF (50 mL) at –78 °C was added MeLi (1.6 M in hexanes, 1.9 mL, 3.0 mmol) dropwise. After 1 h ^{t}BuLi (1.7 M in pentane, 2.0 mL, 3.4 mmol) was added dropwise followed after 30 min by TFAA (0.87 mL, 6.2 mmol). After a further 20 min sat. NH_4Cl (20 mL) was added and solution

warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–40% EtOAc/petrol) to afford the title compound **37** (270 mg, 1.77 mmol, 72%) as a brown oil.

IR (film): 2959, 1788, 1762, 1366, 1209, 1171, 1024.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, C**H**$_3$), 1.25 (s, 9 H, C(C**H**$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2 (**C**), 200.1 (**C**), 198.3 (**C**), 196.0 (**C**), 35.5 (**C**), 27.1 (**C**H$_3$), 11.6 (**C**H$_3$).

MS (ESI+) *m/z* 153 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_9H_{13}O_2$: 153.0910; found 153.0909.

3-(*tert*-Butyl)-4-(methylamino)cyclobutene-1,2-dione (38).

A solution of methylamine hydrochloride (216 mg, 3.20 mmol) and triethylamine (0.45 mL, 3.2 mmol) in MeOH (10 mL) was added to a solution of 3-(*tert*-butyl)-4-methoxycyclobutene-1,2-dione **36** (410 mg, 2.44 mmol) in MeOH (40 mL). After 2 h at RT the solution was concentrated under reduced pressure and purified by column chromatography (50–80% EtOAc/petrol) to afford the title compound **38** (350 mg, 2.09 mmol, 86%) as a white solid.

MP: 194–195 °C.

IR (solid): 3170, 2962, 1786, 1722, 1584, 1484, 1404, 1243, 1168.

^{1}H NMR (400 MHz, DMSO-d6): δ = 8.59 (br s, 1 H, N**H**), 3.15 (d, *J* = 4.9 Hz, 3 H, C**H**$_3$), 1.24 (s, 9 H, C(C**H**$_3$)$_3$) with an additional signal at δ 3.32 attributed to H_2O.

^{13}C NMR (100 MHz, DMSO-d6): δ = 195.6 (**C**), 189.5 (**C**), 181.4 (**C**), 178.0 (**C**), 33.3 (**C**H$_3$), 30.7 (**C**), 27.0 (**C**H$_3$).

MS (ESI+) *m/z* 168 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_9H_{14}NO_2$: 168.1019; found 168.1017.

2-(*tert*-Butyl)-4-hydroxy-3-(methylamino)-4-phenylcyclobut-2-en-1-one (9n)

To a solution of 3-(*tert*-butyl)-4-(methylamino)cyclobut-3-ene-1,2-dione **38** (300 mg, 1.79 mmol) in THF (50 mL) at –78 °C was added phenyllithium (1.9 M in Bu_2O, 2.4 mL, 4.6 mmol) dropwise. After 2 h sat. NH_4Cl (20 mL) was added and the reaction mixture was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by recrystallisation (Et_2O) afforded the title product **9n** (343 mg, 1.40 mmol, 78%) as a white solid.

MP: 175 °C dec.

IR (solid): 3310, 2955, 1737, 1537, 1394, 1265, 1141, 1032, 996.

^{1}H NMR (400 MHz, DMSO-d6): δ = 7.42 (s, 1 H, Ar**H**), 7.37–7.33 (m, 4 H, 3 × Ar**H** + N**H**), 7.24 (s, 1 H, Ar**H**), 6.36 (s, 1 H, O**H**), 2.59 (d, *J* = 4.8 Hz, 3 H, C**H**$_3$), 1.18 (s, 9 H, C(C**H**$_3$)$_3$) with an additional signal at δ 3.32 attributed to H_2O.

^{13}C NMR (100 MHz, DMSO-d6): δ = 184.9 (**C**), 168.9 (**C**), 140.2 (**C**), 128.1 (**C**H), 126.7 (**C**H), 125.9 (**C**), 125.2 (**C**H), 90.3 (**C**), 30.6 (**C**H$_3$), 30.5 (**C**), 28.6 (**C**H$_3$).

MS (ESI+) *m/z* 246 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{15}H_{20}NO_2$: 246.1489; found 246.1490.

4-(Dimethylamino)-3-methyl-5-phenylfuran-2(5*H*)-one (11h)

Cyclobutenone **9h** (100 mg, 0.46 mmol) in dioxane (10 mL) was heated at 180 °C in stainless steel tubing under continuous flow for a residence time of 2 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50-100% Et_2O/cyclohexane) to afford **11h** (92 mg, 0.41 mmol, 92%) as a yellow solid

MP: 148-149 °C.

IR (solid): 2925, 1720, 1608, 1489, 1406, 1313, 1296, 1078, 1016.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 3 H, 3 × Ar**H**), 7.29-7.25 (m, 2 H, 2 × Ar**H**), 5.56 (s, 1 H, C**H**), 2.86 (s, 6 H, N(C**H**$_3$)$_2$), 2.06 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7 (**C**), 163.8 (**C**), 135.8 (**C**), 129.2 (**C**H), 128.9 (**C**H), 127.7 (**C**H), 90.5 (**C**), 79.1 (**C**H), 40.7 (C**H**$_3$), 9.8 (**C**H$_3$).

MS (ESI+): *m/z* 218 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{13}H_{16}NO_2$: 218.1176; found 218.1177.

2-Methyl-3-(methylamino)naphthalene-1,4-dione (10i)[31]

A solution of 4-hydroxy-2-methyl-3-methylamino-4-phenylcyclobut-2-en-1-one **9i** (200 mg, 0.99 mmol) in tetraethylene glycol dimethyl ether (10 mL) was heated at 160 °C for 5 h under argon then cooled to RT and stirred for 1 h under air. Water (50 mL) was added and the reaction mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 300 mL), dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–30% Et_2O/petrol) to afford the title product **10i** (145 mg, 0.72 mmol, 73%) as a dark red solid.

MP: 128-129 °C. Lit.[4] 127–130 °C.

IR (solid): 3365, 2921, 1715, 1667, 1598, 1562, 1514, 1467, 1340.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 7.7, 1.0 Hz, 1 H, Ar**H**), 7.98 (dd, *J* = 7.6, 1.0 Hz, 1 H, Ar**H**), 7.67 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar**H**), 7.57 (td, *J* = 7.6, 1.3 Hz, 1 H, Ar**H**), 5.81 (br s, 1 H, O**H**), 3.24 (d, *J* = 5.0 Hz, 3 H, NC**H**$_3$), 2.28 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.6 (**C**), 182.5 (**C**), 146.9 (**C**), 134.3 (**C**H), 133.5 (**C**), 131.7 (**C**H), 130.2 (**C**), 126.2 (**C**H), 125.9 (**C**H), 112.0 (**C**), 32.9 (**C**H$_3$), 10.9 (**C**H$_3$).

MS (ESI+) *m/z* 202 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{12}H_{12}NO_2$: 202.0863; found 202.0861.

2-Methyl-3-(methyl(phenyl)amino)naphthalene-1,4-dione (10j)

Cyclobutenone **9j** (80 mg, 0.29 mmol) in dioxane (5 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–50% Et_2O/petrol) to afford **10j** (69 mg, 0.25 mmol, 86%) as a purple solid.

MP: 143–144 °C.

IR (solid): 2924, 1666, 1649, 1595, 1576, 1497, 1332, 1285, 1264.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (m, 1 H, Ar**H**), 8.06 (m, 1 H, Ar**H**), 7.76–7.70 (m, 2 H, 2 × Ar**H**), 7.27–7.24 (m, 2 H, 2 × Ar**H**), 6.87 (t, 1 H, *J* = 7.3 Hz, Ar**H**), 6.75 (d, *J* = 8.0 Hz, 2 H, Ar**H**), 3.32 (s, 3 H, C**H**$_3$), 2.06 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.7 (**C**), 182.0 (**C**), 148.9 (**C**), 147.1 (**C**), 141.6 (**C**), 133.6 (**C**H), 133.5 (**C**H), 132.4 (**C**), 132.1 (**C**), 129.2 (**C**H), 126.6 (**C**H), 126.3 (**C**H), 119.4 (**C**H), 114.6 (**C**H), 38.8 (**C**H$_3$), 12.9 (**C**H$_3$).

MS (ESI+) *m/z* 278 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{18}H_{16}NO_2$: 278.1176; found 278.1180.

3-(*tert*-Butyl)-4-methoxy-5-phenylfuran-2(5*H*)-one (11l)

Cyclobutenone **9l** (200 mg, 0.87 mmol) in dioxane (10 mL) was heated at 170 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (70-80% Et_2O/petrol) to afford the title compound **11l** (198 mg, 0.87 mmol, 99%) as a yellow solid.

MP: 113–114 °C.

IR (solid): 2954, 1737, 1643, 1456, 1348, 1303, 1241.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 3 H, 3 × Ar**H**), 7.33–7.30 (m, 2 H, 2 × Ar**H**), 5.70 (s, 1 H, C**H**), 3.56 (s, 3 H, C$\mathbf{H}_3$), 1.35 (s, 9 H, C(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (**C**), 171.9 (**C**), 134.2 (**C**), 129.8 (**C**H), 129.3 (**C**H), 127.7 (**C**H), 112.5 (**C**), 77.0 (**C**H), 57.5 (**C**H_3), 31.6 (**C**), 28.8 (**C**H_3).

MS (ESI+) *m/z* 247 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{15}H_{19}O_3$: 247.1329; found 247.1331.

3-(*tert*-Butyl)-4-(methylamino)-5-phenylfuran-2(5*H*)-one (11n)

A solution of 2-(*tert*-butyl)-4-hydroxy-3-(methylamino)-4-phenylcyclobut-2-en-1-one **9n** (200 mg, 0.82 mmol) in tetraethylene glycol dimethyl ether (10 mL) was heated at 180 °C under argon for 2 h then cooled to RT. Water (50 mL) was added and the reaction mixture was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O (3 × 300 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (10-30% Et_2O/petrol) afforded the title product **11n** (174 mg, 0.71 mmol, 87%) as a yellow oil

IR (film): 3400, 2953, 1715, 1603, 1455, 1396, 1307, 1036, 997.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.35 (m, 3 H, 3 × Ar**H**), 7.33-7.31 (m, 2 H, 2 × Ar**H**), 5.57 (s, 1 H, C**H**), 5.06 (br d, *J* = 4.0 Hz, 1 H, N**H**), 2.55 (d, *J* = 5.3 Hz, 3 H, C$\mathbf{H}_3$), 1.40 (s, 9 H, C(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4 (**C**), 162.7 (**C**), 135.7 (**C**), 129.4 (**C**H), 129.0 (**C**H), 127.8 (**C**), 101.7 (**C**H), 77.3 (**C**H), 31.7 (**C**), 31.1 (**C**H_3), 29.3 (**C**H_3).

MS (ESI+) *m/z* 246 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{15}H_{20}NO_2$: 246.1489; found 246.1495.

4-(*tert*-Butyl)-3-methyl-5-phenylfuran-2(5*H*)-one (11o)

An inseparable 2 : 1 mixture of 2-(*tert*-butyl)-4-hydroxy-3-methyl-4-phenylcyclobut-2-en-1-one **9o** and 3-(*tert*-butyl)-4-hydroxy-2-methyl-4-phenylcyclobut-2-en-1-one **9s** was dissolved in dioxane (10 mL) and heated at 170 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20-80% Et_2O/petrol) to afford **11o** (252 mg, 1.09 mmol, 67%) as a yellow oil.

IR (film): ν 2956, 1740, 1455, 1294, 1143, 1019 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 3 H, 3 × Ar**H**), 7.22–7.17 (m, 2 H, 2 × Ar**H**), 5.41 (s, 1 H, C**H**), 1.93 (s, 3 H, C$\mathbf{H}_3$), 1.40 (s, 9 H, C(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (**C**), 156.1 (**C**), 135.3 (**C**), 132.9 (**C**), 129.2 (**C**H), 128.9 (**C**H), 127.1 (**C**H), 84.5 (**C**H), 33.3 (**C**), 29.3 (**C**H_3), 14.0 (**C**H_3).

MS (ESI+) *m/z* 231 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{15}H_{19}O_2$: 231.1380; found 231.1383.

2-(*tert*-Butyl)-4-hydroxy-3-methoxy-4-(pyridin-3-yl)cyclobut-2-en-1-one (19c)

To a solution of 3-bromopyridine (0.3 mL, 3.1 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.5 M in hexanes, 1.25 mL, 3.13 mmol) dropwise. After 15 min the solution was added via cannula to a solution of 2-(*tert*-butyl)-4-methoxycyclobut-3-ene-1,2-dione **36** (403 mg, 2.40 mmol) in THF (50 mL) at –78 °C. After a further 1 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (20%–50% EtOAc/petrol) to afford the title compound **19c** (207 mg, 0.84 mmol, 35%) as a yellow oil.

IR (film): ν 2955, 1751, 1610, 1479, 1344, 1224, 1014.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 1.7 Hz, 1 H, Ar**H**), 8.45 (dd, *J* = 4.9, 1.6 Hz, 1 H, Ar**H**), 7.86 (dt, *J* = 8.0, 1.9 Hz, 1 H, Ar**H**), 7.71 (s, 1 H, O**H**), 7.31 (dd, *J* = 8.0, 4.9 Hz, 1 H, Ar**H**), 3.82 (s, 3 H, C$\mathbf{H}_3$), 1.13 (s, 9 H, C(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7 (**C**), 179.4 (**C**), 148.2 (**C**H), 146.4 (**C**H), 138.0 (**C**), 134.1 (**C**), 134.0 (**C**H), 123.6 (**C**H), 90.9 (**C**), 59.3 (**C**H_3), 31.1 (**C**), 28.0 (C(C$\mathbf{H}_3$)$_3$).

MS (ESI+) *m/z* 248 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{14}H_{18}NO_3$: 248.1281; found 248.1283.

3-(*tert*-Butyl)-4-methoxy-5-(pyridin-3-yl)furan-2(5*H*)-one (22c)

Cyclobutenone **19c** (150 mg, 0.61 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (60-100% Et_2O/petrol) to afford the title compound **22c** (119 mg, 0.48 mmol, 80%) as a yellow oil.

IR (film): 2954, 1743, 1645, 1457, 1342, 1245, 1032, 997.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (dd, 1 H, *J* = 4.8, 1.6 Hz, Ar**H**) , 8.61 (d, *J* = 1.8 Hz, 1 H, Ar**H**), 7.58 (dt, *J* = 8.0, 2.0 Hz, 1 H, Ar**H**), 7.35 (dd, *J* = 7.8, 4.8 Hz, 1 H, Ar**H**), 5.78 (s, 1 H, C**H**), 3.58 (s, 3 H, C$\mathbf{H}_3$), 1.32 (s, 9 H, C(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (**C**), 171.1 (**C**), 151.1 (**C**H), 149.5 (**C**H), 135.0 (**C**H), 130.4 (**C**), 124.3 (**C**H), 113.5 (**C**), 74.5 (**C**H), 57.7 (**C**H_3), 31.8 (**C**), 28.9 (**C**H_3).

MS (ESI+) m/z 248 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{14}H_{18}NO_3$: 248.1281; found 248.1280.

3-(Dimethylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-enone (23g)

To a solution of phenylacetylene (0.07 mL, 0.65 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexanes, 0.27 mL, 0.65 mmol) dropwise. After 10 min the solution was added via cannula to a solution of 3-dimethylamino-4-methylcyclobutene-1,2-dione **34a** (68 mg, 0.49 mmol) in THF (10 mL) at –78 °C. After a further 50 min sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (70%–100% EtOAc/hexane) to afford the title compound **23g** (83 mg, 0.34 mmol, 70%) as a white solid.

MP: 120 °C dec.

IR (solid): 3234, 2927, 1786, 1749, 1575, 1488, 1410, 1267, 1137, 1080.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.41 (m, 2 H, 2 × Ar**H**), 7.28–7.25 (m, 3 H, 3 × Ar**H**), 5.34 (br s, 1 H, O**H**), 3.29 (s, 3 H, NC$\mathbf{H}_3$), 3.17 (s, 3 H, NC$\mathbf{H}_3$), 1.77 (s, 3 H, C$\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.8 (**C**), 170.1 (**C**), 131.8 (**C**H), 128.4 (**C**H), 128.1 (**C**H), 122.3 (**C**), 114.5 (**C**), 87.9 (**C**), 85.1 (**C**), 81.6 (**C**), 40.1 (**C**H_3), 39.4 (**C**H_3), 7.7 (**C**H_3).

MS (ESI+) *m/z* 242 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{15}H_{16}NO_2$: 242.1176; found 242.1180.

4-(Dimethylamino)-3-methyl-5-(phenylethynyl)furan-2(5*H*)-one (26g)

Cyclobutenone **23g** (75 mg, 0.31 mmol) in dioxane (5 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (10–100% EtOAc/hexane) to afford the title compound **26g** (37 mg, 0.15 mmol, 49%) as a yellow oil.

IR (film): 2976, 1734, 1614, 1443, 1381, 1317, 1290, 1213, 1173, 1112.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 2 H, 2 × Ar**H**), 7.37–7.31 (m, 3 H, 3 × Ar**H**), 5.49 (s, 1 H, C**H**), 3.19 (s, 6 H, N(C$\mathbf{H}_3$)$_2$), 2.00 (s, 3 H, C$\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (**C**), 161.7 (**C**), 131.7 (**C**H), 129.1 (**C**H), 128.3 (**C**H), 121.4 (**C**), 88.9 (**C**), 87.2 (**C**), 81.9 (**C**), 67.0 (**C**H), 40.8 (**C**H_3), 9.8 (**C**H_3).

MS (ESI+) *m/z* 242 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{15}H_{16}NO_2$: 242.1176; found 242.1182.

3-(Diethylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (23h)

To a solution of phenylacetylene (0.14 mL, 1.25 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexanes, 0.53 mL, 1.27 mmol) dropwise. After 10 min the solution was added via cannula to a solution of 3-(diethylamino)-4-methylcyclobutene-1,2-dione **34d** (161 mg, 0.96 mmol) in THF (40 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5%–30% acetone/DCM) to afford the title compound **23h** (208 mg, 0.78 mmol, 81%) as a yellow oil.

IR (film): 3234, 2978, 1745, 1564, 1144, 1296, 1217, 1161, 1140, 1078.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.37 (m, 2 H, 2 × Ar**H**), 7.30–7.23 (m, 3 H, 3 × Ar**H**), 5.79 (s, 1 H, O**H**), 3.81 (dq, *J* = 14.3, 7.2 Hz, 1 H, NC**H**H), 3.61 (dq, *J* = 14.1, 7.1 Hz, 1 H, NCH**H**), 3.48–3.38 (m, 2 H, C$\mathbf{H}_2$), 1.77 (s, 3 H, C$\mathbf{H}_3$), 1.37 (t, *J* = 7.1 Hz, 3 H, C$\mathbf{H}_3$), 1.29 (t, *J* = 7.2 Hz, 3 H, C$\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9 (**C**), 169.7 (**C**), 131.7 (**C**H), 128.2 (**C**H), 127.9 (**C**H), 122.5 (**C**), 113.4 (**C**), 87.4 (**C**), 85.6 (**C**), 81.6 (**C**), 45.2 (**C**H_2), 43.3 (**C**H_2), 14.1 (**C**H_3), 13.9 (**C**H_3), 7.5 (**C**H_3).

MS (ESI+) *m/z* 539 ($[2M+H]^+$), 270 ($[MH]^+$).

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{17}H_{20}NO_2$: 270.1489; found 270.1487.

4-(Diethylamino)-3-methyl-5-(phenylethynyl)furan-2(5*H*)-one (26h)

Cyclobutenone **23h** (120 mg, 0.45 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–80% Et_2O/cyclohexane) to afford the title compound **26h** (73 mg, 0.27 mmol, 60%) as a yellow solid.

MP: 140 °C dec.

IR (solid): 2975, 2929, 1731, 1604, 1436, 1319, 1266, 1070, 1029.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.39 (m, 2 H, 2 × Ar**H**), 7.30–7.25 (m, 3 H, 3 × Ar**H**), 5.47 (s, 1H, C**H**), 3.53–3.34 (m, 4 H, 2 × C$\mathbf{H}_2$), 1.92 (s, 3 H, C$\mathbf{H}_3$), 1.21 (t, *J* = 7.1 Hz, 6 H, 2 × C$\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (**C**), 160.5 (**C**), 131.5 (**C**H), 128.9 (**C**H), 128.2 (**C**H), 121.3 (**C**), 87.3 (**C**), 86.7 (**C**), 82.5 (**C**), 66.7 (**C**H), 43.9 (**C**H_2) 14.0 (**C**H_3), 9.7 (**C**H_3).

MS (ESI+) *m/z* 270 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{17}H_{20}NO_2$: 270.1489; found 270.1486.

3-(Dibenzylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)-cyclobut-2-enone (23i)

To a solution of phenylacetylene (0.10 mL, 0.90 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexanes, 0.38 mL, 0.90 mmol) dropwise. After 10 min the solution was added via cannula to a solution of 3-(dibenzylamino)-4-methylcyclobutene-1,2-dione **34e**[10] (200 mg, 0.69 mmol) in THF (20 mL) at –78 °C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (5–30% acetone/cyclohexane) to afford the title compound **23i** (210 mg, 1.53 mmol, 77%) as a yellow oil.

IR (film): 2924, 2160, 2017, 1597, 1454, 1376, 1261, 1080, 1026.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.08 (m, 15 H, 15 × Ar**H**), 5.52 (s, 1 H, O**H**), 4.90–4.73 (m, 2 H, C$\mathbf{H}_2$), 4.55–4.36 (m, 2 H, C$\mathbf{H}_2$), 1.72 (s, 3 H, C$\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.2 (**C**), 170.9 (**C**), 135.4 (**C**), 135.0 (**C**), 131.8 (**C**H), 129.1 (**C**H), 128.8 (**C**H), 128.7 (**C**H), 128.5 (**C**H), 128.1 (**C**H), 128.0 (**C**H), 126.9 (**C**H), 122.2 (**C**), 114.7 (**C**), 88.6 (**C**), 85.2 (**C**), 82.2 (**C**), 53.8 (**C**H_2), 51.0 (**C**H_2), 7.6 (**C**H_3) with one coincident **C**H.

MS (ESI+) *m/z* 787 ($[2M+H]^+$), 394 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{27}H_{24}NO_2$: 394.1802; found 394.1803.

4-(Dibenzylamino)-3-methyl-5-(phenylethynyl)furan-2(5*H*)-one (26i)

Cyclobutenone **23i** (180 mg, 0.46 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (30–70% Et_2O/cyclohexane) to afford the title compound **26i** (122 mg, 0.31 mmol, 67%) as a yellow oil.

IR (film): 3031, 2919, 1735, 1616, 1493, 1431, 1288, 1076, 1041, 1014.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 11 H, 11 × Ar**H**), 7.24–7.19 (m, 4 H, 4 × Ar**H**), 5.60 (s, 1 H, C**H**), 4.81 (d, *J* = 16.5 Hz, 2 H, 2 × PhC**H**H), 4.44 (d, *J* = 16.5 Hz, 2 H, 2 × PhCH**H**), 1.92 (s, 3 H, C$\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0 (**C**), 161.5 (**C**), 136.4 (**C**), 131.7 (**C**H), 129.1 (**C**H), 129.0 (**C**H), 128.3 (**C**H), 127.8 (**C**H), 126.7 (**C**H), 121.2 (**C**), 90.1 (**C**), 87.9 (**C**), 82.2 (**C**), 67.3 (**C**H), 53.0 (**C**H_2), 9.9 (**C**H_3).

MS (ESI+) *m/z* 787 ($[2M+H]^+$), 394 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{27}H_{24}NO_2$: 394.1802; found 394.1813.

3-(Dimethylamino)-4-hydroxy-2-phenyl-4-(phenylethynyl)-cyclobut-2-enone (23j).

To a solution of phenylacetylene (0.07 mL, 0.65 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexanes, 0.27 mL, 0.65 mmol) dropwise. After 10 min the solution was added via cannula to a solution of 3-(dimethylamino)-4-phenylcyclobutene-1,2-dione (100 mg, 0.50 mmol) in THF (20 mL) at –78 °C. After a further 90 min sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL). The organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10-50% acetone/cyclohexane) to afford the title compound **23j** (131 mg, 0.42 mmol, 83%) as a yellow solid.

MP: 120 °C dec.

IR (solid): 3062, 2939, 1735, 1607, 1585, 1412, 1234, 1165, 1095, 1072.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.39 (4 H, m, 4 × Ar**H**), 7.35–7.21 (6 H, m, 6 × Ar**H**), 5.29 (1 H, s, O**H**), 3.42 (3 H, s, C$\mathbf{H}_3$), 3.12 (3 H, s, C$\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.5 (**C**), 167.4 (**C**), 131.9 (**C**H), 129.8 (**C**), 128.6 (**C**H), 128.5 (**C**H), 128.2 (**C**H), 128.1 (**C**H), 127.0 (**C**H), 122.2 (**C**), 118.2 (**C**), 88.5 (**C**), 84.6 (**C**), 82.1 (**C**), 41.1 (**C**H_3), 40.6 (**C**H_3).

MS (ESI+) *m/z* 607 ($[2M+H]^+$), 304 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{20}H_{18}NO_2$: 304.1332; found 304.1335.

4-(Dimethylamino)-3-phenyl-5-(phenylethynyl)furan-2(5*H*)-one (26j)

Cyclobutenone **23j** (150 mg, 0.50 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced

pressure and purified by column chromatography (10–70% Et_2O/cyclohexane) to afford the title compound **26j** (100 mg, 0.33 mmol, 67%) as a yellow solid.

MP: 140 °C dec.

IR (film): 2920, 2850, 1747, 1620, 1597, 1508, 1454, 1415, 1323, 1068.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 2 H, 2 × Ar**H**), 7.40–7.30 (m, 8 H, 8 × Ar**H**), 5.71 (s, 1 H, C**H**), 2.98 (s, 6 H, 2 × C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2 (**C**), 161.5 (**C**), 132.2 (**C**), 131.8 (**C**H), 131.0 (**C**H), 129.2 (**C**H), 128.4 (**C**H), 127.8 (**C**H), 127.1 (**C**H), 121.4 (**C**), 95.7 (**C**), 87.8 (**C**), 81.7 (**C**), 67.1 (**C**H), 41.7 (C**H**$_3$).

MS (ESI+) *m/z* 607 ([2M+H]$^+$), 304 [MH]$^+$.

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{20}H_{18}NO_2$: 304.1332; found 304.1334.

3-(Dimethylamino)-4-hydroxy-2-methyl-4-((trimethylsilyl)ethynyl) cyclobut-2-en-1-one (23r)

To a solution of ethynyltrimethylsilane (0.18 mL, 1.3 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexanes, 0.56 mL, 1.3 mmol) dropwise. After 15 min the solution was added via cannula to a solution of 3-dimethylamino-4-methylcyclobutene-1,2-dione **34a** (139 mg, 1.00 mmol) in THF (20 mL) at –78 °C. After a further 4 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (10–40% acetone/DCM) to afford the title compound **23r** (207 mg, 0.87 mmol, 87%) as a yellow solid.

MP: 147 °C dec.

IR (solid): 3240 (br), 2957, 1750, 1573, 1411, 1249, 1109, 841.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.86 (br s, 1 H, O**H**), 3.19 (s, 3 H, NC**H**$_3$), 3.13 (s, 3 H, NC**H**$_3$), 1.71 (s, 3 H, C**H**$_3$), 0.11 (s, 9 H, Si(C**H**$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.4 (**C**), 170.0 (**C**), 114.8 (**C**), 100.9 (**C**), 93.0 (**C**), 81.6 (**C**), 39.9 (**C**H$_3$), 39.4 (**C**H$_3$), 7.6 (**C**H$_3$), –0.33 (**C**H$_3$).

MS (ESI+) *m/z* 238 [MH]$^+$.

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{12}H_{20}NO_2Si$: 238.1258; found 238.1261.

4-(Dimethylamino)-3-methyl-5-((trimethylsilyl)ethynyl)furan-2(5*H*)-one (26r)

Cyclobutenone **23r** (120 mg, 0.50 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (50–80% Et_2O/cyclohexane) to afford the title compound **26r** (80 mg, 0.34 mmol, 67%) as a yellow oil.

IR (film): 2958, 1733, 1620, 1408, 1295, 1250, 1076, 1044.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.23 (s, 1H, C**H**), 3.12 (s, 6 H, N(C**H**$_3$)$_2$), 1.94 (s, 3 H, C**H**$_3$), 0.15 (s, 9 H, Si(C**H**$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (**C**), 161.5 (**C**), 97.4 (**C**), 93.3 (**C**), 88.6 (**C**), 66.8 (**C**H), 40.8 (**C**H$_3$), 9.8 (**C**H$_3$), –0.56 (Si(**C**H$_3$)$_3$).

MS (ESI+) *m/z* 238 [MH]$^+$.

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{12}H_{20}NO_2Si$: 238.1258; found 238.1258.

3-(Dimethylamino)-4-hydroxy-2-methyl-4-(pent-1-yn-1-yl)cyclobut-2-enone (23*s*)

To a solution of pent-1-yne (0.17 mL, 1.74 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.3 M in hexanes, 0.75 mL, 1.73 mmol) dropwise. After 10 min the solution was added via cannula to a solution of 3-dimethylamino-4-methylcyclobutene-1,2-dione **34a** (186 mg, 1.39 mmol) in THF (20 mL) at –78 °C. After a further 4 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–20% acetone/DCM) to afford the title compound **23s** (210 mg, 1.01 mmol, 75%) as a yellow oil.

IR (film): 3245, 2962, 1783, 1749, 1570, 1410, 1269, 1130, 1024.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (s, 1 H, O**H**), 3.22 (s, 3 H, NC**H**$_3$), 3.14 (s, 3 H, NC**H**$_3$), 2.19 (t, *J* = 7.1 Hz, 2 H, C**H**$_2$), 1.73 (s, 3 H, C**H**$_3$), 1.51 (m, 2 H, C**H**$_2$), 0.94 (t, *J* = 7.4 Hz, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.0 (**C**), 170.1 (**C**), 113.8 (**C**), 88.8 (**C**), 81.1 (**C**), 75.8 (**C**), 39.6 (**C**H$_3$), 39.1 (**C**H$_3$), 21.5 (**C**H$_2$), 20.6 (**C**H$_2$), 13.1 (**C**H$_3$), 7.2 (**C**H$_3$).

LRMS (ESI+) *m/z* 208 [MH]$^+$.

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{12}H_{18}NO_2$: 208.1332; found 208.1332.

4-(Dimethylamino)-3-methyl-5-(pent-1-yn-1-yl)furan-2(5*H*)-one (26*s*)

Cyclobutenone **23s** (120 mg, 0.58 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–100% Et_2O/cyclohexane) to afford the title compound **26s** (100 mg, 0.48 mmol, 83%) as a yellow oil.

IR (film): 2958, 2870, 1724, 1666, 1641, 1581, 1520, 1486, 1448, 1294.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.21 (s, 1 H, C**H**), 3.10 (s, 6 H, N(C**H**$_3$)$_2$), 2.17 (t, *J* = 7.0 Hz, 2 H, C**H**$_2$), 1.92 (s, 3 H, C**H**$_3$), 1.50 (app sext, *J* = 7.2 Hz, 2 H, C**H**$_2$), 0.93 (t, *J* = 7.3 Hz, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3 (**C**), 162.2 (**C**), 88.5 (**C**), 88.4 (**C**), 73.4 (**C**), 66.8 (**C**H), 40.7 (**C**H$_3$), 21.5 (**C**H$_2$), 20.6 (**C**H$_2$), 13.3 (**C**H$_3$), 9.7 (**C**H$_3$).

MS (ESI+) *m/z* 415 ([2M+H]$^+$), 208 [MH]$^+$.

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{12}H_{18}NO_2$: 208.1332; found 208.1330.

3-(Dimethylamino)-4-hydroxy-2-methyl-4-(3-methylbut-3-en-1-yn-1-yl)cyclobut-2-enone (23t)

To a solution of 2-methylbut-1-en-3-yne (0.17 mL, 1.74 mmol) in THF (20 mL) at –78 °C was added ^{n}BuLi (2.4 M in hexanes, 0.75 mL, 1.74 mmol) dropwise. After 10 min the solution was added via cannula to a solution of 3-dimethylamino-4-methylcyclobutene-1,2-dione **34a** (186 mg, 1.39 mmol) in THF (20 mL) at –78-°C. After a further 2 h sat. NH_4Cl (20 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–30% acetone/DCM) to afford the title compound **23t** (221 mg, 1.07 mmol, 80%) as a yellow oil.

IR (film): 3234, 2922, 1749, 1570, 1410, 1271, 1117, 1024.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.29 (m, 1 H, =C**H**H), 5.21 (m, 1 H, =CH**H**), 5.10 (s, 1 H, O**H**), 3.23 (s, 3 H, NC**H**$_3$), 3.16 (s, 3 H, NC**H**$_3$), 1.85 (s, 3 H, C**H**$_3$), 1.74 (s, 3 H, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.4 (**C**), 169.8 (**C**), 125.7 (**C**), 122.3 (**C**H$_2$), 114.1 (**C**), 88.8 (**C**), 83.6 (**C**), 81.2 (**C**), 39.7 (**C**H$_3$), 39.1 (**C**H$_3$), 22.8 (**C**H$_3$), 7.3 (**C**H$_3$).

MS (ESI+) *m/z* 411 ([2M+H]$^+$), 206 [MH]$^+$.

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{12}H_{16}NO_2$: 206.1176; found 206.1177.

4-(Dimethylamino)-3-methyl-5-(3-methylbut-3-en-1-yn-1-yl)furan-2(5*H*)-one (26t)

Cyclobutenone **23t** (210 mg, 1.02 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1.5 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (20–100% Et_2O/cyclohexane) to afford the title compound **26t** (153 mg, 0.75 mmol, 73%) as a yellow oil.

IR (film): 2960, 2931, 2871, 1726, 1605, 1404, 1296, 1084, 1031, 1014.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.36 (s, 1 H, C**H**), 5.32 (s, 1 H, =C**H**), 5.28 (m, 1 H, =C**H**H), 3.13 (s, 6 H, N(C$\mathbf{H}_3$)$_2$), 1.95 (s, 3 H, C$\mathbf{H}_3$), 1.86 (s, 3 H, C$\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (**C**), 161.7 (**C**), 125.4 (**C**), 123.6 (**C**H$_2$), 88.7 (**C**), 88.4 (**C**), 80.9 (**C**), 66.8 (**C**H), 40.8 (**C**H$_3$), 22.8 (**C**H$_3$), 9.7 (**C**H$_3$).

MS (ESI+) *m/z* 206 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{12}H_{16}NO_2$: 206.1176; found 206.1176.

3-(Dimethylamino)-2-methyl-4-(pent-1-yn-1-yl)-4-((trimethylsilyl)oxy)cyclobut-2-enone (27)

To a solution of aminocyclobutenone **23s** (330 mg, 1.59 mmol) and triethylamine (0.23 mL, 1.8 mmol) in THF (50 mL) at 0 °C was added TMSCl (0.23 mL, 1.8 mmol) dropwise. After 2 h sat. NH_4Cl (10 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–30% DCM/petrol) to afford the title compound **27** (310 mg, 1.11 mmol, 70%) as a yellow oil.

IR (film): 2956, 1759, 1597, 1488, 1412, 1250, 1176, 1139, 1090.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.16 (s, 3 H, C$\mathbf{H}_3$), 3.13 (s, 3 H, C$\mathbf{H}_3$), 2.21 (t, *J* = 7.2 Hz, 2 H, C$\mathbf{H}_2$), 1.73 (s, 3 H, C$\mathbf{H}_3$), 1.53 (sext, *J* = 7.2 Hz, 2 H, C$\mathbf{H}_2$), 0.96 (t, *J* = 7.4 Hz, 3 H, C$\mathbf{H}_3$), 0.22 (s, 9 H, Si(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.4 (**C**), 170.6 (**C**), 114.3 (**C**), 89.8 (**C**), 83.1 (**C**), 77.2 (**C**), 39.9 (**C**H$_3$), 39.7 (**C**H$_3$), 22.1 (**C**H$_2$), 21.3 (**C**H$_2$), 13.8 (**C**H$_3$), 7.9 (**C**H$_3$), 1.6 (**C**H$_3$).

MS (ESI+) *m/z* 280 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{15}H_{26}NO_2Si$: 280.1727; found 280.1732.

2-(Dimethylamino)-3-methyl-5-propyl-6-(trimethylsilyl)cyclohexa-2,5-diene-1,4-dione (28)

Aminocyclobutenone **27** (150 mg, 0.54 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (0–5% Et_2O/petrol) to afford the title compound **28** (137 mg, 0.49 mmol, 91%) as a dark red oil.

IR (film): 2950, 1709, 1655, 1610, 1594, 1572, 1398, 1296, 1245, 1093.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.98 (s, 6 H, N(C$\mathbf{H}_3$)$_2$), 2.47 (t, *J* = 8.1 Hz, 2 H, C$\mathbf{H}_2$), 1.97 (s, 3 H, C$\mathbf{H}_3$), 1.47–1.38 (m, 2 H, C$\mathbf{H}_2$), 0.97 (t, *J* = 7.3 Hz, 3 H, C$\mathbf{H}_3$), 0.29 (s, 9 H, Si(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.1 (**C**), 186.9 (**C**), 157.0 (**C**), 152.6 (**C**), 144.0 (**C**), 121.1 (**C**), 43.5 (**C**H$_3$), 31.4 (**C**H$_2$), 24.5 (**C**H$_2$), 14.4 (**C**H$_3$), 12.7 (**C**H$_3$), 1.2 (**C**H$_3$).

MS (ESI+) *m/z* 280 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{15}H_{26}NO_2Si$: 280.1727; found 280.1721.

3-(Dimethylamino)-2-methyl-4-(phenylethynyl)-4-((trimethylsilyl)oxy)cyclobut-2-enone (29)

To a solution of aminocyclobutenone **24c** (180 mg, 0.75 mmol) and triethylamine (0.10 mL, 0.9 mmol) in THF (50 mL) at 0 °C was added TMSCl (0.11 mL, 0.9 mmol) dropwise. After 2 h sat. NH_4Cl (10 mL) was added and the solution was warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (0–30% DCM/petrol) to afford the title compound **29** (200 mg, 0.63 mmol, 84%) as a yellow oil.

IR (film): 2962, 1761, 1597, 1412, 1248, 1211, 1130, 1049.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 2 H, 2 × Ar**H**), 7.28–7.24 (m, 3 H, 3 × Ar**H**), 3.19 (s, 3 H, C$\mathbf{H}_3$), 3.12 (s, 3 H, C$\mathbf{H}_3$), 1,73 (s, 3 H, C$\mathbf{H}_3$), 0.25 (s, 9 H, Si(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.1 (**C**), 169.6 (**C**), 131.5 (**C**H), 128.5 (**C**H), 128.2 (**C**H), 122.3 (**C**), 114.4 (**C**), 88.4 (**C**), 86.0 (**C**), 83.0 (**C**), 39.6 (**C**H$_3$), 39.4 (**C**H$_3$), 7.6 (**C**H$_3$), 1.2 (**C**H$_3$).

MS (ESI+) *m/z* 314 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{18}H_{24}NO_2Si$: 314.1571; found 314.1575.

(*Z*)-4-(Dimethylamino)-5-methyl-2-(phenyl(trimethylsilyl)methylene)cyclopent-4-ene-1,3-dione (30)

Aminocyclobutenone **29** (120 mg, 0.38 mmol) in dioxane (10 mL) was heated at 160 °C in stainless steel tubing under continuous flow for a residence time of 1.5 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (0–10% Et_2O/petrol) to afford the title compound **30** (87 mg, 0.28 mmol, 73%) as a yellow solid.

MP 153–155 °C (EtOAc/petrol).

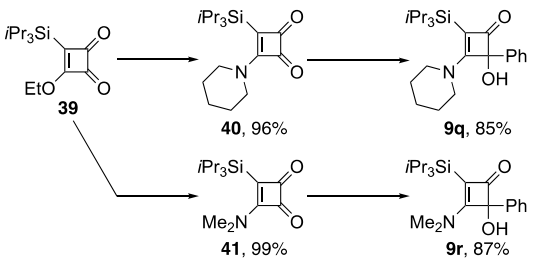
IR (solid): 2960, 1759, 1595, 1412, 1248, 1130, 1049.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.29 (m, 2 H, 2 × Ar**H**), 7.22 (m, 1 H, Ar**H**), 6.89–6.87 (m, 2 H, 2 × Ar**H**), 3.36 (s, 6 H, N(C$\mathbf{H}_3$)$_2$), 2.09 (s, 3 H, C$\mathbf{H}_3$), 0.12 (s, 9 H, Si(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.4 (**C**), 188.2 (**C**), 159.9 (**C**), 156.3 (**C**), 142.7 (**C**), 135.9 (**C**), 127.4 (**C**H), 127.1 (**C**), 125.7 (**C**H), 124.9 (**C**H), 41.9 (**C**H$_3$), 10.1 (**C**H$_3$), –0.5 (**C**H$_3$).

MS (ESI+) *m/z* 314 $[MH]^+$.

HRMS (ESI+): *m/z* $[MH]^+$ calcd for $C_{18}H_{24}NO_2Si$: 314.1571; found 314.1572.



Scheme 10. Preparation of cyclobutenones **9q** and **r**.

3-(Piperidin-1-yl)-4-(triisopropylsilyl)cyclobut-3-ene-1,2-dione (40)

To a solution of 3-ethoxy-4-(triisopropylsilyl)cyclobut-3-ene-1,2-dione **39**[32] (2.63 g, 9.30 mmol) in EtOH (120 mL) at 0 °C was added piperidine (1.3 mL, 13.3 mmol) dropwise over 5 min. The reaction mixture was allowed to warm to RT and after 50 min was concentrated under reduced pressure and purified by column chromatography (10–15% EtOAc/petrol) to afford the title compound **40** (2.75 g, 9.72 mmol, 96%) as a yellow solid.

MP: 114–115 °C.

IR (solid): 2942, 2864, 1759, 1724, 1587, 1463, 1454, 1272, 1091, 1022.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.02 (br s, 2 H, NC**H$_2$**), 3.46 (br s, 2 H, NC**H$_2$**), 1.73 (br, 6 H, 3 × C**H$_2$**), 1.50 (sept, *J* = 7.5 Hz, 3H, 3 × SiC**H**), 1.12 (d, *J* = 7.6 Hz, 18H, 6 × CHC**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9 (**C**), 194.4 (**C**), 186.4 (**C**), 167.3 (**C**), 51.4 (**C**H$_2$), 48.4 (**C**H$_2$), 26.1 (**C**H$_2$), 25.7 (**C**H$_2$), 23.5 (**C**H$_2$), 18.8 (**C**H$_3$), 12.3 (**C**H).

MS (ESI+) *m/z* 344 ([M+Na]$^+$, 46%), 322 ([MH]$^+$, 100%).

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{18}H_{32}NO_2Si$: 322.2197; found 322.2201.

4-Hydroxy-4-phenyl-3-(piperidin-1-yl)-2-(triisopropylsilyl)cyclobut-2-en-1-one (9q)

To a solution cyclobutenedione **40** (271 mg, 0.84 mmol) in THF (50 mL) at –78 °C was added PhLi (1.9 M in Bu_2O, 0.55 mL, 1.05 mmol) over 4 min. After 2 h sat. NH_4Cl (20 mL) was added and the reaction mixture was warmed to RT. The aqueous phase was separated and extracted with $CHCl_3$ (3 x 30 mL), then the organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10-50% EtOAc/petrol) afforded the title compound **9q** (286 mg, 0.71 mmol, 85%) as a white solid.

MP: 163–165 °C.

IR (solid): 3239, 2940, 2862, 1707, 1557, 1447, 1365, 1274, 1143, 1105.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.48 (m, 2 H, 2 × Ar**H**), 7.38–7.33 (m, 2 H, 2 × Ar**H**), 7.28–7.24 (m, 1 H, Ar**H**), 4.14 (s, 1 H, O**H**), 3.50–3.35 (m, 3 H, 2 × N**H**H + NH**H**), 3.22–3.17 (m, 1 H, NH**H**), 1.70–1.52 (m, 6 H, 3 × C**H$_2$**), 1.39 (sept, *J* = 7.5 Hz, 3 H, 3 × SiC**H**), 1.15 (d, *J* = 7.5 Hz, 9 H, 3 × C**H$_3$**), 1.12 (d, *J* = 7.5 Hz, 9 H, 3 × C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8 (**C**), 176.6 (**C**), 138.1 (**C**), 128.4 (**C**H), 127.3 (**C**H), 125.3 (**C**H), 112.1 (**C**), 92.4 (**C**), 49.9 (**C**H$_2$), 49.8 (**C**H$_2$), 25.6 (**C**H$_2$), 25.5 (**C**H$_2$), 23.3 (**C**H$_2$), 18.98 (**C**H$_3$), 18.95 (**C**H$_3$), 12.4 (**C**H).

191.2 (**C**), 178.4 (**C**), 137.9 (**C**), 128.5 (**C**H), 127.4 (**C**H), 125.4 (**C**H), 113.6 (**C**), 92.4 (**C**), 40.9 (**C**H$_3$), 40.5 (**C**H$_3$), 19.0 (**C**H$_3$), 18.9 (**C**H$_3$), 12.3 (**C**H).

MS (ESI+) *m/z* 422 ([M+Na]$^+$, 11%), 400 ([MH]$^+$, 100%).

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{24}H_{38}NO_2Si$: 400.2666; found 400.2670.

2-(Piperidin-1-yl)naphthalene-1,4-dione (10p)[33]

Aminocyclobutenone **9p** (100 mg, 0.25 mmol) was dissolved in dioxane (10 mL) with sonication then heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 3 h. The resulting solution was stirred under air for 1 h then concentrated under reduced pressure. Purification by column chromatography (5–10% EtOAc/petrol) afforded firstly the title compound **10p** (40.2 mg, 0.17 mmol, 50%) as a red oil then furanone **11p** (17.6 mg, 0.07 mmol, 22%) as a brown solid (data as reported later) and finally recovered starting material **9p** (6.1 mg, 0.03 mmol, 8%) as a yellow solid. Data for **10p**:

IR (film): 2936, 2855, 1674, 1633, 1593, 1557, 1339, 1303, 1242, 1127.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.6 Hz, 1 H, Ar**H**), 7.97 (d, *J* = 7.6 Hz, 1 H, Ar**H**), 7.67 (t, *J* = 7.6 Hz, 1 H, Ar**H**), 7.61 (t, *J* = 7.6 Hz, 1 H, Ar**H**), 6.01 (br s, 1 H, =C**H**), 3.48 (br s, 4 H, 2 × NC**H$_2$**), 1.71 (br s, 6 H, 3 × C**H$_2$**).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.5 (**C**), 183.3 (**C**), 154.1 (**C**), 133.7 (**C**H), 132.9 (**C**), 132.5 (**C**), 132.1 (**C**H), 126.5 (**C**H), 125.4 (**C**H) 110.3 (**C**H), 50.4 (**C**H$_2$), 25.7 (**C**H$_2$), 24.3 (**C**H$_2$).

MS (EI) *m/z* 241 ([M]$^{\bullet+}$, 100%).

5-Phenyl-4-(piperidin-1-yl)-3-(triisopropylsilyl)furan-2(5*H*)-one (11q)

Aminocyclobutenone **9q** (100 mg, 0.25 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (5–10% EtOAc/petrol) to afford the title compound **11q** (86 mg, 0.21 mmol, 85%) as a white solid.

MP: 166–169 °C.

IR (film): 2938, 2861, 1692, 1558, 1464, 1451, 1274, 1256, 1181, 1023.

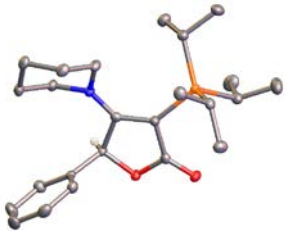
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 5 H, 5 × Ar**H**), 5.70 (s, 1 H, OC**H**), 3.26 (ddd, *J* = 13.1, 7.3, 3.4 Hz, 2 H, 2 × NC**H**H), 3.17 (ddd, *J* = 13.0, 7.5, 3.7 Hz, 2 H, 2 × NCH**H**), 1.63 (sept, *J* = 7.8 Hz, 3 H, 3 × SiC**H**), 1.51–1.45 (m, 2 H, C**H$_2$**), 1.39–1.30 (m, 2 H, 2 × C**H**H), 1.18–1.14 (obscured m, 2 H, 2 × CH**H**), 1.16 (d, *J* = 7.5 Hz, 18 H, 3 × CH(C**H$_3$**)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5 (**C**), 177.4 (**C**), 137.1 (**C**), 129.2 (**C**H), 129.1 (**C**H), 127.9 (**C**H), 86.3 (**C**), 80.7 (**C**H), 51.6 (**C**H$_2$), 25.2 (**C**H$_2$), 23.5 (**C**H$_2$), 19.3 (**C**H$_3$), 12.8 (**C**H).

MS (ESI+) *m/z* 422 ([M+Na]$^+$, 27%), 400 ([MH]$^+$, 100%).

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{24}H_{38}NO_2Si$: 400.2666; found 400.2671.

X-ray: see insert.



5-Phenyl-4-(piperidin-1-yl)furan-2(5*H*)-one (11p)

To silylfuranone **11q** (53 mg, 0.13 mmol) in THF (5 mL) was added 2M HCl (2 mL). After 3 h, sat. $NaHCO_3$ (10 mL) was added then the aqueous phase was separated and extracted with $CHCl_3$ (3 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (10-40% EtOAc/petrol) afforded the title compound **11p** (32 mg, 0.13 mmol, 100%) as a white solid.

MP: 163–164 °C.

IR (solid): 3109, 2919, 2850, 2812, 1713, 1608, 1439, 1314, 1175, 1003.

^{1}H NMR (500 MHz, T = 223 K, $CDCl_3$): δ = 7.40–7.35 (m, 5 H, 5 × Ar**H**), 5.75 (s, 1 H, OC**H**), 4.83 (s, 1 H, =C**H**), 3.34–3.18 (m, 2 H, 2 × NC**H**H), 2.98 (br, 2 H, 2 × NCH**H**) 1.66 (br s, 1 H, C**H**H), 1.53 (br s, 3 H, 3 × CH**H**), 1.30 (br s, 1 H, C**H**H), 0.92 (br s, 1 H, C**H**H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3 (**C**), 169.1 (**C**), 135.6 (**C**), 129.5 (**C**H), 129.1 (**C**H), 127.8 (**C**H), 82.5 (**C**H), 80.0 (**C**H), 48.9 (**C**H$_2$), 25.0 (**C**H$_2$), 23.5 (**C**H$_2$).

MS (ESI+) *m/z* 266 ([M+Na]$^+$, 7%), 244 ([MH]$^+$, 100%).

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{15}H_{18}NO_2$: 244.1334; found 244.1334.

3-Iodo-5-phenyl-4-(piperidin-1-yl)furan-2(5*H*)-one (31)

A solution of silylfuranone **11q** (60 mg, 0.15 mmol) and *N*-iodosuccinimide (50.7 mg, 0.23 mmol) in hexafluoroisopropanol (5 mL) was stirred at –20 °C for 2 h then sat. $NaHCO_3$ (5 mL) and sat. $Na_2S_2O_3$ (2 mL) were added. The aqueous phase was separated and extracted with $CHCl_3$ (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (0-20% EtOAc/petrol) afforded the title compound **31** (41 mg, 0.11 mmol, 73%) as an off white solid.

MP: 108–110 °C.

IR (solid): 2936, 2856, 1729, 1592, 1450, 1283, 1255, 1200, 1017.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.31 (m, 5 H, 5 × Ar**H**), 5.81 (s, 1 H, OC**H**), 3.57 (ddd, *J* = 13.2, 7.3, 3.8 Hz, 2 H, 2 × NC**H**H), 3.48 (ddd, *J* = 13.1, 7.1, 3.6 Hz, 2 H, 2 × NCH**H**), 1.60–1.54 (m, 2 H, C**H$_2$**), 1.50–1.41 (m, 2 H, 2 × C**H**H), 1.37–1.30 (m, 2 H, 2 × CH**H**).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9 (**C**), 165.1 (**C**), 135.4 (**C**), 129.8 (**C**H), 129.2 (**C**H), 127.8 (**C**H), 82.1 (**C**H), 49.5 (**C**H_2), 40.0 (**C**), 25.7 (**C**H_2), 23.7 (**C**H_2).

MS (ESI+) *m/z* 292 ([M+Na]$^+$, 21%), 370 ([MH]$^+$, 100%).

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{15}H_{17}INO_2$: 370.0298; found 370.0299.

3-(Dimethylamino)-4-(triisopropylsilyl)cyclobut-3-ene-1,2-dione (41)

Dimethylamine was bubbled through the solution 3-ethoxy-4-(triisopropylsilyl)cyclobut-3-ene-1,2-dione **39**[32] (413 mg, 1.46 mmol) in EtOH (30 mL) at 0 °C for 10 min. The reaction mixture was then warmed to RT and concentrated *in vacuo* to afford the title compound **40** (408 mg, 1.45 mmol, 99%) as a cream solid.

MP: 132–134 °C.

IR (solid): 2943, 2865, 1771, 1750, 1732, 1601, 1459, 1422, 1184, 1093.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.49 (s, 3 H, NC**H**$_3$), 3.16 (s, 3 H, NC**H**$_3$), 1.52 (sept, *J* = 7.5 Hz, 3 H, 3 × SiC**H**), 1.13 (d, *J* = 7.6 Hz, 18 H, Si(CH(C**H**$_3$)$_2$)$_3$.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3 (**C**), 194.0 (**C**), 188.5 (**C**), 168.1 (**C**), 42.0 (**C**H_3), 39.5 (**C**H_3), 18.8 (**C**H_3), 12.3 (**C**H).

MS (ESI+) *m/z* 304 ([M+Na]$^+$, 18%), 282 ([MH]$^+$, 100%).

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{15}H_{28}NO_2Si$: 282.1884; found 282.1890.

3-(Dimethylamino)-4-hydroxy-4-phenyl-2-(triisopropylsilyl)cyclobut-2-en-1-one (9r)

To a solution cyclobutenedione **41** (238 mg, 0.84 mmol) in THF (50 mL) at –78 °C was added PhLi (1.9 M in Bu_2O, 0.50 mL, 0.95 mmol) over 3 min. After 3 h sat. NH_4Cl (20 mL) was added and the reaction mixture was warmed to RT. The aqueous phase was separated and extracted with $CHCl_3$ (3 x 30 mL), then the organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10-50% EtOAc/petrol) afforded the title compound **9r** (264 mg, 0.74 mmol, 87%) as a white solid.

MP: 171–172 °C.

IR (solid): 3218, 2938, 2862, 1713, 1586, 1574, 1421, 1202, 1168.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.47 (m, 2 H, 2 × Ar**H**), 7.38–7.34 (m, 2 H, 2 × Ar**H**), 7.29–7.25 (m, 1 H, Ar**H**), 4.25 (s, 1 H, O**H**), 3.13 (s, 3 H, NC**H**$_3$), 2.92 (s, 3 H, NC**H**$_3$), 1.41 (sept, *J* = 7.5 Hz, 3 H, 3 × SiC**H**), 1.16 (d, *J* = 7.5 Hz, 9 H, 3 × C**H**$_3$), 1.13 (d, *J* = 7.5 Hz, 9 H, 3 × C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2 (**C**), 178.4 (**C**), 137.9 (**C**), 128.5 (**C**H), 127.4 (**C**H), 125.4 (**C**H), 113.6 (**C**), 92.4 (**C**), 40.9 (**C**H_3), 40.5 (**C**H_3), 19.0 (**C**H_3), 18.9 (**C**H_3), 12.3 (**C**H).

MS (ESI+) *m/z* 382 ([M+Na]$^+$, 13%), 360 ([MH]$^+$, 100%).

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{21}H_{34}NO_2Si$: 360.2353; found 360.2348.

5-Phenyl-4-(dimethylamino)-3-(triisopropylsilyl)furan-2(5*H*)-one (11r)

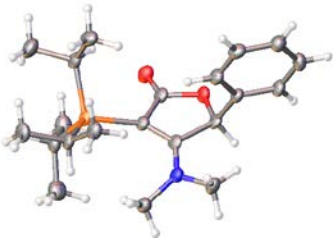
Aminocyclobutenone **9r** (100 mg, 0.28 mmol) in dioxane (10 mL) was heated at 150 °C in stainless steel tubing under continuous flow for a residence time of 1 h. The resulting solution was concentrated under reduced pressure and purified by column chromatography (5–10% EtOAc/petrol) to afford the title compound **11r** (93 mg, 0.26 mmol, 93%) as a white solid.

MP: 128–132 °C.

IR (solid): 2942, 2863, 1713, 1573, 1455, 1433, 1396, 1198, 1142, 1048.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 5 H, 5 × Ar**H**), 5.69 (s, 1 H, O**H**), 2.88 (br s, 6 H, N(C**H**$_3$)$_2$), 1.65 (sept, *J* = 7.8 Hz, 3 H, 3 × SiC**H**), 1.18 (d, *J* = 7.8 Hz, 18 H, 3 × CH(C**H**$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8 (**C**), 177.4 (**C**), 136.5 (**C**), 129.2 (**C**H), 129.1 (**C**H), 127.8 (**C**H), 86.3 (**C**), 80.9 (**C**H), 42.9 (**C**H_3), 19.3 (**C**H_3), 13.0 (**C**H).



MS (ESI+) *m/z* 382 ([M+Na]$^+$, 38%), 360 ([MH]$^+$, 100%).

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{21}H_{34}NO_2Si$: 360.2353; found 360.2361.

X-ray: see insert.

4-(Dimethylamino)-5-phenylfuran-2(5*H*)-one (32)[34]

To silylfuranone **11r** (50.0 mg, 0.14 mmol) in THF (5 mL) was added 2M HCl (2 mL). After 3 h, sat $NaHCO_3$ (10 mL) was added then the aqueous phase was separated and extracted with $CHCl_3$ (3 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (10-50% EtOAc/petrol) afforded the title compound **32** (28.5 mg, 0.14 mmol, 100%) as a pale brown solid.

MP: 130–134 °C

IR (film): 3126, 2919, 2857, 2812, 1712, 1607, 1454, 1414, 1323, 1306, 1266, 1163, 1155, 1064.

^{1}H NMR (500 MHz, T = 223 K, $CDCl_3$): δ = 7.41–7.32 (m, 5 H, 5 × Ar**H**), 5.76 (s, 1 H, O**H**), 4.79 (s, 1 H, =C**H**), 2.95 (s, 3 H, NC**H**$_3$), 2.68 (s, 3 H, NC**H**$_3$).

^{13}C NMR (125 MHz, T = 223 K, $CDCl_3$): δ = 174.6 (**C**), 170.1 (**C**), 134.4 (**C**), 129.6 (**C**H), 129.1 (**C**H), 127.7 (**C**H), 82.2 (**C**H), 80.0 (**C**H), 40.9 (**C**H_3), 39.6 (**C**H_3).

LRMS (ESI+) *m/z* 226 ([M+Na]$^+$, 10%), 204 ([MH]$^+$, 100%).

HRMS (ESI+): *m/z* [MH]$^+$ calcd for $C_{12}H_{14}NO_2$: 204.1019; found 204.1016.

Funding Information

The authors thank the ERDF for their partial support of this work via AI-Chem (InterReg IVa programme 4494/4196) and EPSRC for the equipment grant, reference EP/K039466/1.

Acknowledgment

The authors thank Professors R. L. Danheiser, T. T. Tidwell and A. D. Allen for advice on the synthesis of silylcyclobutenediones **9q** and **9r** and Mr A. A. Hussein for his advice in respect of DFT calculations.

Supporting Information

YES

Primary Data

NO

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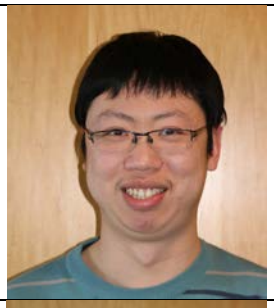
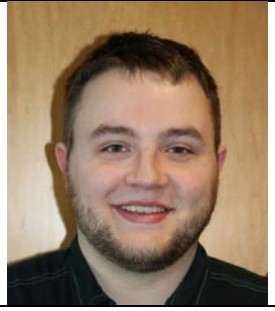
Biosketches



Wei Sun was born in Beijing, China. He was awarded a bachelor degree in Pharmacy from the Peking University in 2005. He then moved to the Beijing Institute for Drug Control where his focus was on microbiological testing and gene traceability. In 2013, he started his PhD at the University of Southampton under the supervision of Prof. D. C. Harrowven. His research program has focused on the rearrangements of aminocyclobutenones where his achievements included the development of a metal free C-H activation protocol for the rapid construction of saturated nitrogen heterocycles. As demonstrated herein, his work embraces flow chemistry and DFT calculations to achieve deeper mechanistic understanding.



Dharyl Wilson was born in the Medway, Kent. He was awarded an integrated MChem degree from the University of Southampton in 2014 which included a year-long placement at Expro Analytical Data Services. He then started his PhD at the University of Southampton under the supervision of Prof. D. C. Harrowven. His studies centre on the rearrangement chemistry of cyclobutenones and their applications in target synthesis. It has included the development of a concise route to analogues of cribrostatin 6 for biological evaluation and the development of a metal free C-H activation protocol for the rapid construction of saturated nitrogen heterocycles. His current studies are directed towards achieving the first total synthesis of alpkinidine.

David Harrowven was born in Norwich, England. He was awarded his PhD from the University of Southampton in 1989 for work directed towards the total synthesis of forskolin and conducted under the supervision of Prof. P. J. Kocienski, FRS. He then moved to a Postdoctoral Fellowship with Prof. G. Pattenden, FRS at the University of Nottingham which led to a Teaching Fellowship at that institution. In 1992 he moved to a lectureship at the University of Wales, Bangor before returning to Southampton as a lecturer in 1994. In 2005 he became Professor of Organic Chemistry at the University of Southampton. His work focusses on natural products total synthesis; the synthesis of distorted aromatic ring systems and the development of reagentless cascade reaction sequence.