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

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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.2,4

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.

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

Scheme 1. Summary of the primary cyclobutenone rearrangement pathways.

Scheme 2. An anomalous rearrangement of arylcyclobutenone 9h to furanone 11h rather than the anticipated benzoquinone 10h.
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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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 tert-butyryl-cyclobutenones 9i, 9n and 9o and compared their thermolysis with the outcomes given by the corresponding methylcyclobutenones 9k, 9m and 9e (Scheme 3).\textsuperscript{14,15} As anticipated, the former all gave the corresponding 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\textsuperscript{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-pyridino-cyclobutenone 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.\textsuperscript{1,2,14,15}

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 cyclpentenediones 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 in high yield, they proved to be low yielding processes giving rise to complex product mixtures.\(^2\)

Importantly, protonolysis of 11q provided furanone 11p in quantitative yield while its treatment with NIS provided iodide 31.\(^26\) The trisopropylsilyl substituent was equally effective as a sterically buttress when neighboured by a dimethylamino residue, as evidenced by the conversion of arylcyclobutenone 9r to furanones 11r and 32.

![Scheme 7. Using a trisopropylsilyl group as a bulky proton and halogen surrogate to bias reactions toward furanone formation.](image)

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 trisopropylsilyl group, provides a means of directing rearrangements toward furanone formation.

The experimental section has no title; please leave this line here.

**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 Bruker AVIIIHD 500 spectrometer at 298 K using CDCl\(_3\) stored over dried K\(_2\)CO\(_3\) 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 positive pressure using silica gel with the stated solvent system. **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\(_2\)SO\(_4\). 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 9b-j, l, n, o, q and r (Schemes 8–10), 19c, 23g-j and 23r-t are provided below.

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

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

A solution of dimethylamine hydrochloride (67 mg, 0.82 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 (150 mg, 1.02 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/petrol) afforded the title compound (627 mg, 4.95 mmol) as a white solid.

**3-(Diethylamino)-4-methylcyclobutene-1,2-dione (34b).**

A solution of diethylamine hydrochloride (132 mg, 1.20 mmol) and triethylamine (0.10 mL, 1.20 mmol) in MeOH (40 mL) was added to a solution of 3-methoxy-4-methylcyclobutene-1,2-dione (150 mg, 1.02 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) (170 mg, 1.01 mmol, 85%) as a pale yellow oil.

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

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.

3-Methyl-4-(methyl(phenylamino)cyclobut-3-ene-1,2-dione (34e)

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-methyl-4-(methylamino)-cyclobutene-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 (34f) (170 mg, 1.01 mmol, 85%) as a pale yellow oil.

3-(Dibenzylationo)-4-methylcyclobutene-1,2-dione (34g)

To a solution of 3-methoxy-4-methylcyclobutene-1,2-dione (126 mg, 1.00 mmol) in MeOH (50 mL) was added dibenzylamine (0.10 mL, 1.00 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.

3-Methyl-4-(methyl(phenylamino)cyclobut-3-ene-1,2-dione (34h)

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) (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 (34d) (550 mg, 4.43 mmol, 89%) as a white solid.

3-Methyl-4-(methyl(phenylamino)cyclobut-3-ene-1,2-dione (34e)

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.
To a solution of 3-methylamino-4-methylcyclobutene-1,2-dione (9i) (1.9 M in Bu₂O, 4.6 mL, 8.7 mmol) dropwise. After 2 h, sat. NH₄Cl (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 MgSO₄ and concentrated under reduced pressure. Purification by recrystallization (Et₂O) afforded the title compound (280 mg, 1.58 mmol, 78%) as a yellow oil.

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


Scheme 9. Preparation of cyclobutrones 9l and o.

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

To a solution of 2-((tert-Butyl)-4-hydroxy-3-methoxy-4-phenylcyclobut-2-en-1-one (36b) (340 mg, 1.51 mmol) in THF (50 mL) at –78 °C was added MeLi (1.7 M in pentane, 2.0 mL, 3.4 mmol) dropwise. After 2 h sat. NH₄Cl (20 mL) was added and 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 MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (50–100% EtOAc/petrol) afforded the title product (390 mg, 1.58 mmol, 78%) as a yellow oil.

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


To a solution of 3-(tert-Butyl)-4-methoxycyclobut-3-ene-1,2-dione (36d) (340 mg, 2.02 mmol) in THF (50 mL) at –78 °C was added 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 by a further 20 min by sat. NH₄Cl (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 MgSO₄ and concentrated under reduced pressure and purified by column chromatography (50–100% EtOAc/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): 3398, 2952, 1745, 1630, 1448, 1365, 1187.

warmed to RT. The aqueous phase was separated and extracted with DCM (2 × 50 mL) then the organic phases were combined, dried over MgSO₄, 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.

H NMR (400 MHz, CDCl₃): δ = 2.29 (s, 3 H, CH₃), 1.25 (s, 9 H, C(CH₃)₃).

13C NMR (100 MHz, CDCl₃): δ = 20.2 (C), 200.1 (C), 198.3 (C), 196.0 (C), 35.5 (C), 27.1 (CH), 11.6 (CH₃).

MS (ESI+) m/z 153 [M⁺]⁺.


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 tetrahydrofuran 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 EtOAc (3 × 100 mL). The combined organic layers were washed with H₂O (3 × 300 mL), dried over MgSO₄, concentrated under reduced pressure and purified by column chromatography (10–30% EtOAc/petrol) to afford the title product 10i (145 mg, 0.72 mmol, 73%) as a dark red solid.

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

H NMR (400 MHz, CDCl₃): δ = 6.08 (dd, J = 7.7, 1.0 Hz, 1 H, ArH), 7.98 (dd, J = 7.6, 1.0 Hz, 1 H, ArH), 7.67 (td, J = 7.6, 1.3 Hz, 1 H, ArH), 7.57 (td, J = 7.6, 1.3 Hz, 1 H, ArH), 5.81 (br s, 1 H, OH), 3.24 (d, J = 5.0 Hz, 3 H, NCH₃), 2.28 (s, 3 H, CH₃).

MS (ESI+ m/z 202 [M⁺]⁺.

A solution of 2-(tert-butyl)-4-hydroxy-3-(methylamino)-4-phenylcyclobut-2-en-1-one 9n (200 mg, 0.82 mmol) in tetrahydrofuran (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% EtOAc/petrol) to afford the title compound 22c (119 mg, 0.48 mmol, 80%) as a yellow oil.

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


HRMS (ESI+): m/z = [M]+ calculated for C15H19O2: 231.1380; found: 231.1383.

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

To a solution of phenylacetylene (0.07 mL, 0.65 mmol) in THF (20 mL) at −78 °C was added tBuLi (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 (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. NH₄Cl (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 MgSO₄, 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.


3-(Dimethylamino)-4-hydroxy-3-methyl-5-(phenylethynyl)cyclobut-2-ene (26g)

Cyclobutene 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.
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 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 (120 mg, 0.45 mmol) in dioxane (10 mL) was heated under reflux and purified by column chromatography (5%–30% acetone/DCM) to afford the title compound 23h (73 mg, 0.27 mmol, 60%) as yellow solid.

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

HRMS (ESI+): m/z [MH]+ calcd for C_{17}H_{20}NO_{2}: 304.1332; found 304.1335.

3-(Dibenzylamino)-4-hydroxy-2-methyl-4-(phenylethynyl)cyclobut-2-en-1-one (23i)

Cyclobutene 23i (180 mg, 0.46 mmol) in dioxane (10 mL) was heated under reflux 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% EtO\_2/cyclohexane) to afford the title compound 26i (172 mg, 0.35 mmol, 71%) as yellow solid.


HRMS (ESI+): m/z [MH]+ calcd for C_{20}H_{18}NO_{2}: 328.1332; found 328.1336.

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

To a solution of phenylacetylene (0.07 mL, 0.65 mmol) in THF (20 mL) at −78 °C was added BuLi (2.4 M in hexanes, 0.18 mL, 0.43 mmol) dropwise. After 10 min the solution was added via cannula to a solution of 3-(dibenzylamino)-4-phenylcyclobutene-1,2-dione (161 mg, 0.96 mmol) in THF (40 mL) at −78 °C. After a further 2 h sat. NH\_4\Cl (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 26j (210 mg, 1.53 mmol, 77%) as yellow oil.


HRMS (ESI+): m/z [MH]+ calcd for C_{27}H_{24}NO_{2}: 394.1802; found 394.1803.
pressure and purified by column chromatography (10–70% EtOAc/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.

1H NMR (400 MHz, CDCl3): δ = 7.51–7.47 (m, 2 H, 2 × ArH), 7.40–7.30 (m, 8 H, 8 × ArH), 5.71 (s, 1 H, NH), 2.98 (s, 6 H, 2 × CH3).

13C NMR (100 MHz, CDCl3): δ = 137.2 (C), 129.5 (C), 119.0 (C), 119.2 (C), 112.8 (C), 127.1 (CH), 121.4 (CH).

IR (film): 2958, 1724, 1664, 1614, 1581, 1520, 1486, 1448, 1294.

1H NMR (400 MHz, CDCl3): δ = 4.86 (br, 1 H, CH2), 3.19 (s, 3 H, N(CH3)2), 3.13 (s, 3 H, N(CH3)2), 1.71 (s, 3 H, N(CH3)2), 0.11 (s, 9 H, Si(CH3)3).

13C NMR (100 MHz, CDCl3): δ = 185.0 (C), 170.1 (C), 113.8 (C), 88.8 (C), 81.1 (C), 75.8 (C), 39.6 (CH2), 39.1 (CH3), 21.5 (CH2), 20.6 (CH3), 13.3 (CH)2, 9.7 (CH3)2.


**3-(Dimethylamino)-4-hydroxy-2-methyl-4-[(trimethylsilyl)ethenyl]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 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 2-methylbut-1-en-3-yne (0.17 mL, 1.74 mmol) in THF (20 mL) at –78 °C. After a further 4 h sat. NH4Cl (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 MgSO4, concentrated under reduced pressure and purified by column chromatography (20–100% EtOAc/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.

1H NMR (400 MHz, CDCl3): δ = 4.86 (br, 1 H, CH), 3.19 (s, 3 H, N(CH3)2), 3.13 (s, 3 H, N(CH3)2), 1.71 (s, 3 H, N(CH3)2), 0.11 (s, 9 H, Si(CH3)3).

13C NMR (100 MHz, CDCl3): δ = 184.4 (C), 173.2 (C), 161.5 (C), 141.1 (C), 128.4 (CH), 127.8 (CH), 127.1 (CH), 121.4 (CH), 97.4 (CH), 87.0 (C), 81.7 (C), 41.7 (CH3).


**3-(Dimethylamino)-4-hydroxy-2-methyl-4-[(pent-1-ynyl)ethenyl]cyclobut-2-en-1-one (23t)**

To a solution of pent-1-yne (0.17 mL, 1.74 mmol) in THF (20 mL) at –78 °C was added 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. NH4Cl (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 MgSO4, concentrated under reduced pressure and purified by column chromatography (0–20% acetone/DCM) to afford the title compound 23t (210 mg, 1.01 mmol, 75%) as a yellow oil.

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

1H NMR (400 MHz, CDCl3): δ = 4.71 (s, 1 H, CH), 3.22 (s, 3 H, NCH3), 3.14 (s, 3 H, NCH3), 2.19 (t, J = 7.1 Hz, 2 H, CH2), 1.73 (s, 3 H, CH3), 1.51 (m, 2 H, CH2), 0.94 (t, J = 7.4 Hz, 3 H, CH3).

13C NMR (100 MHz, CDCl3): δ = 185.0 (C), 170.1 (C), 113.8 (C), 88.8 (C), 81.1 (C), 75.8 (C), 39.6 (CH2), 39.1 (CH3), 21.5 (CH2), 20.6 (CH3), 13.1 (CH3)2, 7.2 (CH)2.

HRMS (ESI+): m/z 208 [MH]+.

**3-(Dimethylamino)-4-hydroxy-2-methyl-4-[(3-methylbut-3-en-1-ynyl)cyclobut-2-en-1-one (23u)**

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

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% EtOAc/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.

[1H NMR (400 MHz, CDCl3): δ = 5.36 (s, 1 H, CH), 5.32 (s, 1 H, CH), 5.28 (m, 1 H, =CH)], 3.13 (s, 6 H, N(CH3)2), 1.95 (t, J = 7.3 Hz, 2 H, CH2), 1.86 (s, 3 H, CH3).

13C NMR (100 MHz, CDCl3): δ = 175.2 (C), 161.7 (C), 125.4 (C), 123.6 (CH2), 88.7 (C), 88.4 (C), 66.8 (CH), 40.8 (CH3), 22.8 (CH3), 9.7 (CH3).

MS (ESI+) m/z: 206 [M+H]+.

HRMS (ESI+): m/z [MH]+ calcd for C15H26NO2Si: 280.1727; found 280.1721.

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 (0.11 mL, 0.9 mmol) dropwise. After 2 h sat. NH4Cl (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 dried over MgSO4, concentrated under reduced pressure and purified by column chromatography (0–30% DCM/petrol) to afford the title compound 27 (310 mg, 1.11 mmol, 79%) as a yellow oil.

IR (solid): 2960, 1759, 1595, 1488, 1412, 1250, 1176, 1139, 1090.

[1H NMR (400 MHz, CDCl3): δ = 3.16 (s, 3 H, CH3), 3.13 (s, 3 H, CH3), 2.21 (t, J = 7.2 Hz, 2 H, CH2), 1.73 (s, 3 H, CH3), 1.53 (s, 6 H, N(CH3)2), 0.96 (t, J = 7.4 Hz, 3 H, CH3), 0.22 (s, 9 H, Si(CH3)3).

13C NMR (100 MHz, CDCl3): δ = 184.4 (C), 170.6 (C), 114.3 (C), 898 (C), 83.1 (C), 77.2 (C), 39.9 (CH3), 39.7 (CH2), 22.1 (CH3), 21.3 (CH3), 13.8 (CH3), 79 (CH1), 1.6 (CH3).

MS (ESI+) m/z: 280 [M+H]+.


Scheme 10. Preparation of cyclobutenones 9q and r.

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

To a solution of 3-(ethoxycarbonyl)cyclobut-3-ene-1,2-dione 39s (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.
5-Phenyl-4-(piperidin-1-yl)-3-(trisopropylsilyl)furan-2(5H)-one (11q)

Aminocyclobutene 9q (100 mg, 0.25 mmol) in diacane (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, 2838, 1659, 1578, 1452, 1243, 1256, 1181, 1023.

1H NMR (400 MHz, CDCl3): δ = 7.42-7.30 (m, 5 H, 5 × ArH), 5.70 (s, 1 H, OCH), 3.26 (dd, J = 13.1, 3.4 Hz, 2 H, 2 × NCH2), 3.17 (ddd, J = 13.0, 7.5, 3.7 Hz, 2 H, 2 × NCH2), 1.63 (sept, J = 7.8 Hz, 3 H, 3 × CH3), 1.51-1.45 (m, 2 H, CH2), 1.39-1.30 (m, 2 H, 2 × CH2), 1.18-1.14 (observed m, 2 H, 2 × CH2), 1.16 (d, J = 7.5 Hz, 18 H, 3 × CH2(CH3)).

13C NMR (100 MHz, CDCl3): δ = 177.5 (C), 177.4 (C), 137.1 (C), 129.2 (CH2), 129.1 (CH), 127.9 (CH), 86.3 (C), 80.7 (CH), 51.6 (CH2), 25.2 (CH2), 23.5 (CH3), 19.3 (CH2), 12.8 (CH).

HRMS (ESI+): m/z [M+Na+]+, 422, [M+H]+, 400; [MHI]+, 100%.

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

To silylfuranone 11q (53 mg, 0.13 mmol) in THF (5 mL) was added 2M HCl (2 mL). After 3 h, sat. NaHCO3 (10 mL) was added and the aqueous phase was separated and extracted with CHCl3 (3 × 20 mL). The organic phases were combined, dried over MgSO4, filtered and concentrated in vacuo. 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.

1H NMR (500 MHz, CDCl3): δ = 7.40-7.35 (m, 5 H, 5 × ArH), 5.75 (s, 1 H, OCH), 4.83 (s, 1 H, =CH), 3.34-3.18 (m, 2 H, 2 × NCH2), 2.98 (br, 2 H, 2 × NCH3) 1.66 (br s, 1 H, CH), 1.53 (br s, 3 H, 3 × CH3), 1.30 (br s, 1 H, CH), 0.92 (br s, 1 H, CH).

13C NMR (100 MHz, CDCl3): δ = 174.3 (C), 169.1 (C), 135.6 (C), 129.5 (CH), 129.1 (CH), 127.8 (CH), 82.5 (CH), 80.0 (CH), 48.9 (CH), 25.0 (CH2), 23.5 (CH3).

HRMS (ESI+): m/z [M+Na+]+, 266; [M+H]+, 244; [MHI]+, 100%.

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

A solution of silylfuranone 11q (60 mg, 0.15 mmol) and N-iodosuccinimide (50.7 mg, 0.23 mmol) in hexahloro propane (5 mL) was stirred at ~20 °C for 2 h then sat. NaHCO3 (5 mL) and sat. Na2SO3 (2 mL) were added. The aqueous phase was separated and extracted with CHCl3 (3 × 15 mL). The organic phases were combined, dried over MgSO4, 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 offwhite solid.

MP: 108-110 °C.

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

1H NMR (400 MHz, CDCl3): δ = 7.42-7.31 (m, 5 H, 5 × ArH), 5.81 (s, 1 H, OCH), 3.57 (ddd, J = 13.2, 7.3, 3.8 Hz, 2 H, 2 × NCH2), 3.48 (ddd, J = 13.1, 7.1, 3.6 Hz, 2 H, 2 × NCH3), 1.60-1.54 (m, 2 H, CH2), 1.50-1.41 (m, 2 H, 2 × CH), 1.37-1.30 (m, 2 H, 2 × CH2)
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 (32) (50.0 mg, 0.14 mmol) in THF (5 mL) was added to 2M HCl (2 mL). After 3 h, sat NaHCO₃ (10 mL) was added then the aqueous phase was separated and extracted with CHCl₃ (3 × 20 mL). The organic phases were combined, dried over MgSO₄, 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.

HRMS (ESI+): m/z [M+Na]+ calcd for C₂₁H₃₄NO₂Si: 360.2353; found 360.2353.

X-ray: see insert.

References


**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 aminocyclobutones 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 cyclobutones and their applications in target synthesis. It has included the development of a concise route to analogues of cibrassin in 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 focuses on natural products total synthesis; the synthesis of distorted aromatic ring systems and the development of reagentless cascade reaction sequence.